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(Revision 11)

References

The hyperlinks in the document were last accessed online in June 2023.

1. Introduction

Altman, D. (2020). Practical Statistics for Medical Research (2nd ed.). Chapman & Hall.

Andrews, E., & Moore, N. (2014). Mann's Pharmacovigilance, Third Edition (3rd ed.). Wiley-Blackwell.

Ayad, A., & Hartzema, A. (2018). Post-Authorization Safety Studies of Medicinal Products: The PASS Book. Academic Press.

Begaud, B. (2000). Dictionary of Pharmacoepidemiology. Wiley.

Elseviers, M., Wettermark, B., & Almarsdóttir, A. B. (2016). Drug Utilization Research. Methods and Applications. Wiley-Blackwell.

Good pharmacovigilance practices | European Medicines Agency. (2022, April 26). European Medicines Agency. https://www.ema.europa.eu/en/human-regulatory/post-authorisation/pharmacovigilance/good-pharmacovigilance-practices

Hartzema, A. G., Tilson, H. H., & Chan, K. A. (2008). Pharmacoepidemiology and Therapeutic Risk Management. Harvey Whitney Books Company.

Hernan, M., & Robins, J. (2020). Causal Inference: What If. Chapman & Hall/CRC.

Hoffmann, W., Latza, U., Baumeister, S. E., Brünger, M., Buttmann-Schweiger, N., Hardt, J., Hoffmann, V., Karch, A., Richter, A., Schmidt, C. O., Schmidtmann, I., Swart, E., & van den Berg, N. (2019). Guidelines and recommendations for ensuring Good Epidemiological Practice (GEP): A guideline developed by the German Society for Epidemiology. European Journal of Epidemiology, 34(3), Art. 3. https://doi.org/10.1007/s10654-019-00500-x

IEA Good Epidemiology Practice (GEP). (2007). IEA.
https://ieaweb.org/IEAWeb/Content/IEA_Publications.aspx

ISPE Guidelines for Good Pharmacoepidemiology Practices (GPP)—International Society for Pharmacoepidemiology. (2022, April 25). ISPE.
https://www.pharmacoepi.org/resources/policies/guidelines-08027/

Lash, T., VanderWeele, T., Haneuse, S., & Rothman, K. (2020). Modern Epidemiology (4th ed.). Wolters Kluwer.

Parfrey, P., & Barret, B. (2015). Clinical epidemiology: Practice and methods (2nd ed.). Human Press.

Porta, M. (2014). A Dictionary of Epidemiology (6th ed.). Oxford University Press.

Scientific guidance on post-authorisation efficacy studies—EMA. (2016). European Medicines Agency.
https://www.ema.europa.eu/en/documents/scientific-guideline/scientific-guidance-post-authorisation-efficacy-studies-first-version_en.pdf

Strom, B., Kimmel, S. E., & Hennessy, S. (2019). Pharmacoepidemiology (6th ed.). Wiley-Blackwell.

Woodward, M. (2014). Epidemiology: Study Design and Data Analysis (3rd ed.). Chapman & Hall.

2. Formulating the research question and objectives and assessing study feasibility

Brown, P., Brunnhuber, K., Chalkidou, K., Chalmers, I., Clarke, M., Fenton, M., Forbes, C., Glanville, J., Hicks, N. J., Moody, J., Twaddle, S., Timimi, H., & Young, P. (2006). How to formulate research recommendations. BMJ : British Medical Journal, 333(7572), 804–806.
https://doi.org/10.1136/bmj.38987.492014.94

Criteria to select and prioritize health technologies for additional evidence generation.
https://www.eunethta.eu/wp-content/uploads/2018/01/Selection-prioritisation-criteria-1.pdf

European Medicines Agency. https://www.ema.europa.eu/en

Good pharmacovigilance practices. European Medicines Agency.
https://www.ema.europa.eu/en/human-regulatory/post-authorisation/pharmacovigilance/good-pharmacovigilance-practices

Gatto, N. M., Campbell, U. B., Rubinstein, E., Jaksa, A., Mattox, P., Mo, J., & Reynolds, R. F. (2022). The Structured Process to Identify Fit-For-Purpose Data: A Data Feasibility Assessment Framework. Clinical Pharmacology and Therapeutics, 111(1), 122–134. https://doi.org/10.1002/cpt.2466

Gatto, N. M., Reynolds, R. F., & Campbell, U. B. (2019). A Structured Preapproval and Postapproval Comparative Study Design Framework to Generate Valid and Transparent Real-World Evidence for Regulatory Decisions. Clinical Pharmacology and Therapeutics, 106(1), 103–115.
https://doi.org/10.1002/cpt.1480

Gatto, N. M., Vititoe, S. E., Rubinstein, E., Reynolds, R. F., & Campbell, U. B. (2023). A Structured Process to Identify Fit-for-Purpose Study Design and Data to Generate Valid and Transparent Real-World Evidence for Regulatory Uses. Clinical Pharmacology and Therapeutics, 113(6), 1235–1239.
https://doi.org/10.1002/cpt.2883

Guidelines for Good Pharmacoepidemiology Practices (GPP)—International Society for Pharmacoepidemiology. https://www.pharmacoepi.org/resources/policies/guidelines-08027/

The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
(ENCePP) Guide on Methodological Standards in Pharmacoepidemiology
EMA/228452/2023   Page 2/76

Jansen, E., Hines, P. A., Berntgen, M., & Brand, A. (2022). Strengthening the Interface of Evidence-Based Decision Making Across European Regulators and Health Technology Assessment Bodies. Value in Health: The Journal of the International Society for Pharmacoeconomics and Outcomes Research, 25(10), 1726–1735. https://doi.org/10.1016/j.jval.2022.01.026

Kloda, L., & Bartlett, J. C. (2014). Formulating Answerable Questions: Question Negotiation in Evidence-based Practice. Journal of the Canadian Health Libraries Association / Journal de l'Association Des Bibliothèques de La Santé Du Canada, 34(2), 55. https://doi.org/10.5596/c13-019

Lipowski, E. E. (2008). Developing great research questions. American Journal of Health-System Pharmacy, 65(17), 1667–1670. https://doi.org/10.2146/ajhp070276

Ritchey, M. E., & Girman, C. J. (2020). Evaluating the Feasibility of Electronic Health Records and Claims Data Sources for Specific Research Purposes. Therapeutic Innovation & Regulatory Science, 54(6), 1296–1302. https://doi.org/10.1007/s43441-020-00139-x

Rivera, D. R., Gokhale, M. N., Reynolds, M. W., Andrews, E. B., Chun, D., Haynes, K., Jonsson-Funk, M. L., Lynch, K. E., Lund, J. L., Strongman, H., Bhullar, H., & Raman, S. R. (2020). Linking electronic health data in pharmacoepidemiology: Appropriateness and feasibility. Pharmacoepidemiology and Drug Safety, 29(1), 18–29. https://doi.org/10.1002/pds.4918

Thabane, L., Thomas, T., Ye, C., & Paul, J. (2009). Posing the research question: Not so simple. Canadian Journal of Anaesthesia = Journal Canadien D'anesthesie, 56(1), 71–79. https://doi.org/10.1007/s12630-008-9007-4

Tully, M. P. (2014). Research: Articulating Questions, Generating Hypotheses, and Choosing Study Designs. The Canadian Journal of Hospital Pharmacy, 67(1), 31–34. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3952905/

Wang, S. V., Pinheiro, S., Hua, W., Arlett, P., Uyama, Y., Berlin, J. A., Bartels, D. B., Kahler, K. H., Bessette, L. G., & Schneeweiss, S. (2021). STaRT-RWE: Structured template for planning and reporting on the implementation of real world evidence studies. BMJ (Clinical Research Ed.), 372, m4856. https://doi.org/10.1136/bmj.m4856

Willame, C., Baril, L., van den Bosch, J., Ferreira, G. L. C., Williams, R., Rosillon, D., & Cohet, C. (2016). Importance of feasibility assessments before implementing non-interventional pharmacoepidemiologic studies of vaccines: Lessons learned and recommendations for future studies. Pharmacoepidemiology and Drug Safety, 25(12), 1397–1406. https://doi.org/10.1002/pds.4081

3. Development of the study protocol

Agency for Healthcare Research and Quality. https://www.ahrq.gov/

Beta ClinicalTrials.gov. https://clinicaltrials.gov/

Clinical Trial Regulation (EU) 536/2014, 158 OJ L (2014). http://data.europa.eu/eli/reg/2014/536/oj/eng

Commission Implementing Regulation (EU) No 520/2012. https://eur-lex.europa.eu/eli/reg_impl/2012/520/oj

Developing a Protocol for Observational Comparative Effectiveness Research: A User's Guide | Effective Health Care (EHC) Program. https://effectivehealthcare.ahrq.gov/products/observational-cer-protocol/research

Good pharmacovigilance practices. European Medicines Agency.
https://www.ema.europa.eu/en/human-regulatory/post-authorisation/pharmacovigilance/good-pharmacovigilance-practices

ENCePP Home Page. https://www.encepp.eu/standards_and_guidances/checkListProtocols.shtml

EU PAS Register. https://www.encepp.eu/encepp/studiesDatabase.jsp

Gatto, N. M., Wang, S. V., Murk, W., Mattox, P., Brookhart, M. A., Bate, A., Schneeweiss, S., & Rassen, J. A. (2022). Visualizations throughout pharmacoepidemiology study planning, implementation, and reporting. Pharmacoepidemiology and Drug Safety, 31(11), 1140–1152. https://doi.org/10.1002/pds.5529

Guidance for the format and content of the protocol of non-interventional post-authorisation safety studies.

Guidelines for Good Pharmacoepidemiology Practices (GPP)—International Society for Pharmacoepidemiology. https://www.pharmacoepi.org/resources/policies/guidelines-08027/

Open Science Forum https://osf.io/

Research, C. for D. E. and. (2020, April 29). Best Practices for Conducting and Reporting Pharmacoepidemiologic Safety Studies Using Electronic Healthcare Data Sets. U.S. Food and Drug Administration; FDA. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/best-practices-conducting-and-reporting-pharmacoepidemiologic-safety-studies-using-electronic

Schneeweiss, S., Rassen, J. A., Brown, J. S., Rothman, K. J., Happe, L., Arlett, P., Dal Pan, G., Goettsch, W., Murk, W., & Wang, S. V. (2019). Graphical Depiction of Longitudinal Study Designs in Health Care Databases. Annals of Internal Medicine, 170(6), 398–406. https://doi.org/10.7326/M18-3079

Wang, S. V., Pottegård, A., Crown, W., Arlett, P., Ashcroft, D. M., Benchimol, E. I., Berger, M. L., Crane, G., Goettsch, W., Hua, W., Kabadi, S., Kern, D. M., Kurz, X., Langan, S., Nonaka, T., Orsini, L., Perez-Gutthann, S., Pinheiro, S., Pratt, N., … Williams, R. J. (2023). HARmonized Protocol Template to Enhance Reproducibility of hypothesis evaluating real-world evidence studies on treatment effects: A good practices report of a joint ISPE/ISPOR task force. Pharmacoepidemiology and Drug Safety, 32(1), 44–55. https://doi.org/10.1002/pds.5507

Wang, S. V., & Schneeweiss, S. (2022). A Framework for Visualizing Study Designs and Data Observability in Electronic Health Record Data. Clinical Epidemiology, 14, 601–608. https://doi.org/10.2147/CLEP.S358583

4. Study design

4.1. Overview

Amrhein, V., Greenland, S., & McShane, B. (2019). Scientists rise up against statistical significance. Nature, 567(7748), 305–307. https://doi.org/10.1038/d41586-019-00857-9

Butler, A. M., Burcu, M., Christian, J. B., Tian, F., Andersen, K. M., Blumentals, W. A., Joynt Maddox, K. E., & Alexander, G. C. (2023). Noninterventional studies in the COVID-19 era: Methodological considerations for study design and analysis. Journal of Clinical Epidemiology, 153, 91–101. https://doi.org/10.1016/j.jclinepi.2022.11.011

The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
(ENCePP) Guide on Methodological Standards in Pharmacoepidemiology
EMA/228452/2023   Page 4/76

Causal analyses of existing databases: No power calculations required—PubMed. https://pubmed.ncbi.nlm.nih.gov/34461211/

Gatto, N. M., Wang, S. V., Murk, W., Mattox, P., Brookhart, M. A., Bate, A., Schneeweiss, S., & Rassen, J. A. (2022). Visualizations throughout pharmacoepidemiology study planning, implementation, and reporting. Pharmacoepidemiology and Drug Safety, 31(11), 1140–1152. https://doi.org/10.1002/pds.5529

Greenland, S., Senn, S. J., Rothman, K. J., Carlin, J. B., Poole, C., Goodman, S. N., & Altman, D. G. (2016). Statistical tests, P values, confidence intervals, and power: A guide to misinterpretations. European Journal of Epidemiology, 31, 337–350. https://doi.org/10.1007/s10654-016-0149-3

ICMJE | Recommendations | Preparing a Manuscript for Submission to a Medical Journal. https://icmje.org/recommendations/browse/manuscript-preparation/preparing-for-submission.html#two

It's time to talk about ditching statistical significance. (2019). Nature, 567(7748), 283–283. https://doi.org/10.1038/d41586-019-00874-8

Pottegård, A., Kurz, X., Moore, N., Christiansen, C. F., & Klungel, O. (2020). Considerations for pharmacoepidemiological analyses in the SARS-CoV-2 pandemic. Pharmacoepidemiology and Drug Safety, 29(8), 825–831. https://doi.org/10.1002/pds.5029

Renoux, C., Azoulay, L., & Suissa, S. (2021). Biases in Evaluating the Safety and Effectiveness of Drugs for the Treatment of COVID-19: Designing Real-World Evidence Studies. American Journal of Epidemiology, 190(8), 1452–1456. https://doi.org/10.1093/aje/kwab028

Song, J. W., & Chung, K. C. (2010). Observational studies: Cohort and case-control studies. Plastic and Reconstructive Surgery, 126(6), 2234–2242. https://doi.org/10.1097/PRS.0b013e3181f44abc

Wang, S. V., & Schneeweiss, S. (2022). A Framework for Visualizing Study Designs and Data Observability in Electronic Health Record Data. Clinical Epidemiology, 14, 601–608. https://doi.org/10.2147/CLEP.S358583

Wasserstein, R. L., & Lazar, N. A. (2016). The ASA Statement on p -Values: Context, Process, and Purpose. The American Statistician, 70(2), 129–133. https://doi.org/10.1080/00031305.2016.1154108

4.2. Types of study design

Avenue, 677 Huntington, Boston, & Ma 02115. (2012, October 19). Causal Inference: What If (the book). Miguel Hernan's Faculty Website. https://www.hsph.harvard.edu/miguel-hernan/causal-inference-book/

Burningham, Z., He, T., Teng, C.-C., Zhou, X., Nebeker, J., & Sauer, B. C. (2017). Evaluation of the Case-Crossover (CCO) Study Design for Adverse Drug Event Detection. Drug Safety, 40(9), 789–798. https://doi.org/10.1007/s40264-017-0540-3

Cadarette, S. M., Maclure, M., Delaney, J. A. C., Whitaker, H. J., Hayes, K. N., Wang, S. V., Tadrous, M., Gagne, J. J., Consiglio, G. P., & Hallas, J. (2021). Control yourself: ISPE-endorsed guidance in the application of self-controlled study designs in pharmacoepidemiology. Pharmacoepidemiology and Drug Safety, 30(6), 671–684. https://doi.org/10.1002/pds.5227

Collier, S., Harvey, C., Brewster, J., Bakerly, N. D., Elkhenini, H. F., Stanciu, R., Williams, C., Brereton, J., New, J. P., McCrae, J., McCorkindale, S., & Leather, D. (2017). Monitoring safety in a phase III real-

world effectiveness trial: Use of novel methodology in the Salford Lung Study. Pharmacoepidemiology and Drug Safety, 26(3), 344–352. https://doi.org/10.1002/pds.4118

Collins, R., Bowman, L., Landray, M., & Peto, R. (2020). The Magic of Randomization versus the Myth of Real-World Evidence. New England Journal of Medicine, 382(7), 674–678. https://doi.org/10.1056/NEJMsb1901642

Coutinho, J. M., Zuurbier, S. M., Aramideh, M., & Stam, J. (2012). The incidence of cerebral venous thrombosis: A cross-sectional study. Stroke, 43(12), 3375–3377. https://doi.org/10.1161/STROKEAHA.112.671453

Dagan, N., Barda, N., Kepten, E., Miron, O., Perchik, S., Katz, M. A., Hernán, M. A., Lipsitch, M., Reis, B., & Balicer, R. D. (2021). BNT162b2 mRNA Covid-19 Vaccine in a Nationwide Mass Vaccination Setting. New England Journal of Medicine, 384(15), 1412–1423. https://doi.org/10.1056/NEJMoa2101765

Dexamethasone in Hospitalized Patients with Covid-19 | NEJM. https://www.nejm.org/doi/10.1056/NEJMoa2021436

Dickerman, B. A., García-Albéniz, X., Logan, R. W., Denaxas, S., & Hernán, M. A. (2020). Emulating a target trial in case-control designs: An application to statins and colorectal cancer. International Journal of Epidemiology, 49(5), 1637–1646. https://doi.org/10.1093/ije/dyaa144

Dickerman, B. A., Gerlovin, H., Madenci, A. L., Kurgansky, K. E., Ferolito, B. R., Figueroa Muñiz, M. J., Gagnon, D. R., Gaziano, J. M., Cho, K., Casas, J. P., & Hernán, M. A. (2022). Comparative Effectiveness of BNT162b2 and mRNA-1273 Vaccines in U.S. Veterans. The New England Journal of Medicine, 386(2), 105–115. https://doi.org/10.1056/NEJMoa2115463

Effect of Discontinuing vs Continuing Angiotensin-Converting Enzyme Inhibitors and Angiotensin II Receptor Blockers on Days Alive and Out of the Hospital in Patients Admitted With COVID-19: A Randomized Clinical Trial | Critical Care Medicine | JAMA | JAMA Network. https://jamanetwork.com/journals/jama/fullarticle/2775280

Eworuke, E., Welch, E. C., Tobenkin, A., & Maro, J. C. (2019). Use of FDA's Sentinel System to Quantify Seizure Risk Immediately Following New Ranolazine Exposure. Drug Safety, 42(7), 897–906. https://doi.org/10.1007/s40264-019-00798-2

Farrington, C. P. (2004). Control without separate controls: Evaluation of vaccine safety using case-only methods. Vaccine, 22(15–16), 2064–2070. https://doi.org/10.1016/j.vaccine.2004.01.017

Farrington, C. P., Whitaker, H. J., & Hocine, M. N. (2009). Case series analysis for censored, perturbed, or curtailed post-event exposures. Biostatistics (Oxford, England), 10(1), 3–16. https://doi.org/10.1093/biostatistics/kxn013

Farrington, P., Whitaker, H., & Ghebremichael-Weldeselassie, Y. (2021). Self-Controlled Case Series Studies: A Modelling Guide with R. Chapman and Hall/CRC. https://www.routledge.com/Self-Controlled-Case-Series-Studies-A-Modelling-Guide-with-R/Farrington-Whitaker-Weldeselassie/p/book/9781032095530

Ford, I., & Norrie, J. (2016). Pragmatic Trials. New England Journal of Medicine, 375(5), 454–463. https://doi.org/10.1056/NEJMra1510059

Franklin, J. M., Glynn, R. J., Suissa, S., & Schneeweiss, S. (2020). Emulation Differences vs. Biases When Calibrating Real-World Evidence Findings Against Randomized Controlled Trials. Clinical Pharmacology and Therapeutics, 107(4), 735–737. https://doi.org/10.1002/cpt.1793

The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) Guide on Methodological Standards in Pharmacoepidemiology
EMA/228452/2023

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Fröbert, O., Lagerqvist, B., Olivecrona, G. K., Omerovic, E., Gudnason, T., Maeng, M., Aasa, M., Angerås, O., Calais, F., Danielewicz, M., Erlinge, D., Hellsten, L., Jensen, U., Johansson, A. C., Kåregren, A., Nilsson, J., Robertson, L., Sandhall, L., Sjögren, I., … James, S. K. (2013). Thrombus Aspiration during ST-Segment Elevation Myocardial Infarction. New England Journal of Medicine, 369(17), 1587–1597. https://doi.org/10.1056/NEJMoa1308789

García-Albéniz, X., Hsu, J., & Hernán, M. A. (2017). The value of explicitly emulating a target trial when using real world evidence: An application to colorectal cancer screening. European Journal of Epidemiology, 32(6), 495–500. https://doi.org/10.1007/s10654-017-0287-2

Girman, C. J., & Ritchey, M. E. (2021). Pragmatic Randomized Clinical Trials Using Primary Data Collection and Electronic Health Records (1st ed.).

Gould, M. K., Smith-Bindman, R., Kelly, K., Altman, D. E., Barjaktarevic, I., Creekmur, B., de Bie, E., Dyer, D. S., Mortani Barbosa, E. J., Mularski, R. A., Qi, L., Vaszar, L. T., Yu, S., & Miglioretti, D. L. (2019). Methods for the Watch the Spot Trial. A Pragmatic Trial of More- versus Less-Intensive Strategies for Active Surveillance of Small Pulmonary Nodules. Annals of the American Thoracic Society, 16(12), 1567–1576. https://doi.org/10.1513/AnnalsATS.201903-268SD

Greenland, S. (1996). Confounding and exposure trends in case-crossover and case-time-control designs. Epidemiology (Cambridge, Mass.), 7(3), 231–239. https://doi.org/10.1097/00001648-199605000-00003

Gulmez, S. E., Larrey, D., Pageaux, G.-P., Lignot, S., Lassalle, R., Jové, J., Gatta, A., McCormick, P. A., Metselaar, H. J., Monteiro, E., Thorburn, D., Bernal, W., Zouboulis-Vafiadis, I., de Vries, C., Perez-Gutthann, S., Sturkenboom, M., Bénichou, J., Montastruc, J.-L., Horsmans, Y., … Moore, N. (2013). Transplantation for Acute Liver Failure in Patients Exposed to NSAIDs or Paracetamol (Acetaminophen). Drug Safety, 36(2), 135–144. https://doi.org/10.1007/s40264-012-0013-7

Hallas, J. (1996). Evidence of depression provoked by cardiovascular medication: A prescription sequence symmetry analysis. Epidemiology (Cambridge, Mass.), 7(5), 478–484.

Hallas, J., Pottegård, A., Wang, S., Schneeweiss, S., & Gagne, J. J. (2016). Persistent User Bias in Case-Crossover Studies in Pharmacoepidemiology. American Journal of Epidemiology, 184(10), 761–769. https://doi.org/10.1093/aje/kww079

Harris, R. J., Hall, J. A., Zaidi, A., Andrews, N. J., & Dunbar, J. K. Impact of vaccination on household transmission of SARS-COV-2 in England. https://khub.net/documents/135939561/390853656/Impact+of+vaccination+on+household+transmission+of+SARS-COV-2+in+England.pdf/35bf4bb1-6ade-d3eb-a39e-9c9b25a8122a?t=1619551571214

Hernán, M. A. (2018). How to estimate the effect of treatment duration on survival outcomes using observational data. BMJ (Clinical Research Ed.), 360, k182. https://doi.org/10.1136/bmj.k182

Hernán, M. A., & Robins, J. M. (2016). Using Big Data to Emulate a Target Trial When a Randomized Trial Is Not Available. American Journal of Epidemiology, 183(8), 758–764. https://doi.org/10.1093/aje/kwv254

Hernán, M. A., Sauer, B. C., Hernández-Díaz, S., Platt, R., & Shrier, I. (2016). Specifying a target trial prevents immortal time bias and other self-inflicted injuries in observational analyses. Journal of Clinical Epidemiology, 79, 70–75. https://doi.org/10.1016/j.jclinepi.2016.04.014

Hernán, M. A., Wang, W., & Leaf, D. E. (2022). Target Trial Emulation: A Framework for Causal Inference From Observational Data. JAMA, 328(24), 2446–2447. https://doi.org/10.1001/jama.2022.21383

The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
(ENCePP) Guide on Methodological Standards in Pharmacoepidemiology
EMA/228452/2023   Page 7/76

Hernández-Díaz, S., Huybrechts, K. F., Chiu, Y.-H., Yland, J. J., Bateman, B. T., & Hernán, M. A. (2023). Emulating a Target Trial of Interventions Initiated During Pregnancy with Healthcare Databases: The Example of COVID-19 Vaccination. Epidemiology (Cambridge, Mass.), 34(2), 238–246. https://doi.org/10.1097/EDE.0000000000001562

Horby, P. W., Mafham, M., Bell, J. L., Linsell, L., Staplin, N., Emberson, J., Palfreeman, A., Raw, J., Elmahi, E., Prudon, B., Green, C., Carley, S., Chadwick, D., Davies, M., Wise, M. P., Baillie, J. K., Chappell, L. C., Faust, S. N., Jaki, T., … Landray, M. J. (2020). Lopinavir–ritonavir in patients admitted to hospital with COVID-19 (RECOVERY): A randomised, controlled, open-label, platform trial. The Lancet, 396(10259), 1345–1352. https://doi.org/10.1016/S0140-6736(20)32013-4

Ishani, A., Leatherman, S. M., Woods, P., Hau, C., Klint, A., Lew, R. A., Taylor, A. A., Glassman, P. A., Brophy, M. T., Fiore, L. D., Ferguson, R. E., & Cushman, W. C. (2022). Design of a pragmatic clinical trial embedded in the Electronic Health Record: The VA's Diuretic Comparison Project. Contemporary Clinical Trials, 116, 106754. https://doi.org/10.1016/j.cct.2022.106754

J, H., H, W., Ja, D., Sm, C., N, P., & M, M. (2021). The Use of Active Comparators in Self-Controlled Designs. American Journal of Epidemiology, 190(10). https://doi.org/10.1093/aje/kwab110

Join the PRINCIPLE Trial—PRINCIPLE Trial. https://www.principletrial.org

Kwakkenbos, L., Imran, M., McCall, S. J., McCord, K. A., Fröbert, O., Hemkens, L. G., Zwarenstein, M., Relton, C., Rice, D. B., Langan, S. M., Benchimol, E. I., Thabane, L., Campbell, M. K., Sampson, M., Erlinge, D., Verkooijen, H. M., Moher, D., Boutron, I., Ravaud, P., … Thombs, B. D. (2021). CONSORT extension for the reporting of randomised controlled trials conducted using cohorts and routinely collected data (CONSORT-ROUTINE): Checklist with explanation and elaboration. BMJ, 373, n857. https://doi.org/10.1136/bmj.n857

Lauer, M. S., & D'Agostino, R. B. (2013). The Randomized Registry Trial—The Next Disruptive Technology in Clinical Research? New England Journal of Medicine, 369(17), 1579–1581. https://doi.org/10.1056/NEJMp1310102

Leather, D. A., Jones, R., Woodcock, A., Vestbo, J., Jacques, L., & Thomas, M. (2020). Real-World Data and Randomised Controlled Trials: The Salford Lung Study. Advances in Therapy, 37(3), 977–997. https://doi.org/10.1007/s12325-019-01192-1

Lesko, S. M., & Mitchell, A. A. (1995). An assessment of the safety of pediatric ibuprofen. A practitioner-based randomized clinical trial. JAMA, 273(12), 929–933.

Levin, K. A. (2006). Study design VI - Ecological studies. Evidence-Based Dentistry, 7(4), 108. https://doi.org/10.1038/sj.ebd.6400454

Li, L., Kulldorff, M., Russek-Cohen, E., Kawai, A. T., & Hua, W. (2015). Quantifying the impact of time-varying baseline risk adjustment in the self-controlled risk interval design. Pharmacoepidemiology and Drug Safety, 24(12), 1304–1312. https://doi.org/10.1002/pds.3885

Loudon, K., Treweek, S., Sullivan, F., Donnan, P., Thorpe, K. E., & Zwarenstein, M. (2015). The PRECIS-2 tool: Designing trials that are fit for purpose. BMJ, 350, h2147. https://doi.org/10.1136/bmj.h2147

Lufkin, B., Lo, A.-C., Shangguan, S., Ngaiza, M., Wernecke, M., Choradia, N., Feinberg, L., Nelson, L., Simard, J., & Goodman, S. (2021). Master Protocol: Assessment of Risk of Safety Outcomes Following COVID-19 Vaccination. https://bestinitiative.org/wp-content/uploads/2021/04/COVID-19-Vaccine-Safety-Inferential-Draft-Master-Protocol.pdf

Maclure, M. (1991). The case-crossover design: A method for studying transient effects on the risk of acute events. American Journal of Epidemiology, 133(2), 144–153. https://doi.org/10.1093/oxfordjournals.aje.a115853

Maclure, M., Fireman, B., Nelson, J. C., Hua, W., Shoaibi, A., Paredes, A., & Madigan, D. (2012). When should case-only designs be used for safety monitoring of medical products? Pharmacoepidemiology and Drug Safety, 21 Suppl 1, 50–61. https://doi.org/10.1002/pds.2330

Matthews, A. A., Szummer, K., Dahabreh, I. J., Lindahl, B., Erlinge, D., Feychting, M., Jernberg, T., Berglund, A., & Hernán, M. A. (2021). Comparing Effect Estimates in Randomized Trials and Observational Studies From the Same Population: An Application to Percutaneous Coronary Intervention. Journal of the American Heart Association, 10(11), e020357. https://doi.org/10.1161/JAHA.120.020357

Mentz, R. J., Hernandez, A. F., Berdan, L. G., Rorick, T., O'Brien, E. C., Ibarra, J. C., Curtis, L. H., & Peterson, E. D. (2016). Good Clinical Practice Guidance and Pragmatic Clinical Trials. Circulation, 133(9), 872–880. https://doi.org/10.1161/CIRCULATIONAHA.115.019902

Moore, N., Gulmez, S. E., Larrey, D., Pageaux, G.-P., Lignot, S., Lassalle, R., Jové, J., Pariente, A., Blin, P., Bénichou, J., & Bégaud, B. (2013). Choice of the denominator in case population studies: Event rates for registration for liver transplantation after exposure to NSAIDs in the SALT study in France. Pharmacoepidemiology and Drug Safety, 22(2), 160–167. https://doi.org/10.1002/pds.3371

Morales, D. R., Conover, M. M., You, S. C., Pratt, N., Kostka, K., Duarte-Salles, T., Fernández-Bertolín, S., Aragón, M., DuVall, S. L., Lynch, K., Falconer, T., van Bochove, K., Sung, C., Matheny, M. E., Lambert, C. G., Nyberg, F., Alshammari, T. M., Williams, A. E., Park, R. W., … Suchard, M. A. (2021). Renin-angiotensin system blockers and susceptibility to COVID-19: An international, open science, cohort analysis. The Lancet. Digital Health, 3(2), e98–e114. https://doi.org/10.1016/S2589-7500(20)30289-2

Morgenstern, H. (1995). Ecologic studies in epidemiology: Concepts, principles, and methods. Annual Review of Public Health, 16, 61–81. https://doi.org/10.1146/annurev.pu.16.050195.000425

Peach, E. J., Pearce, F. A., Gibson, J., Cooper, A. J., Chen, L.-C., & Knaggs, R. D. (2021). Opioids and the Risk of Fracture: A Self-Controlled Case Series Study in the Clinical Practice Research Datalink. American Journal of Epidemiology, 190(7), 1324–1331. https://doi.org/10.1093/aje/kwab042

Petersen, I., Douglas, I., & Whitaker, H. (2016). Self controlled case series methods: An alternative to standard epidemiological study designs. BMJ, 354, i4515. https://doi.org/10.1136/bmj.i4515

Rao, S. V., Hess, C. N., Barham, B., Aberle, L. H., Anstrom, K. J., Patel, T. B., Jorgensen, J. P., Mazzaferri, E. L., Jolly, S. S., Jacobs, A., Newby, L. K., Gibson, C. M., Kong, D. F., Mehran, R., Waksman, R., Gilchrist, I. C., McCourt, B. J., Messenger, J. C., Peterson, E. D., … Krucoff, M. W. (2014). A Registry-Based Randomized Trial Comparing Radial and Femoral Approaches in Women Undergoing Percutaneous Coronary Intervention: The SAFE-PCI for Women (Study of Access Site for Enhancement of PCI for Women) Trial. JACC: Cardiovascular Interventions, 7(8), 857–867. https://doi.org/10.1016/j.jcin.2014.04.007

Sacristán, J. A., & Dilla, T. (2018). Pragmatic trials revisited: Applicability is about individualization. Journal of Clinical Epidemiology, 99, 164–166. https://doi.org/10.1016/j.jclinepi.2018.02.003

SELF-CONTROLLED CASE SERIES STUDIES. SELF-CONTROLLED CASE SERIES STUDIES. http://sccs-studies.info/

The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
(ENCePP) Guide on Methodological Standards in Pharmacoepidemiology
EMA/228452/2023
Page 9/76

Staa, T.-P. van, Goldacre, B., Gulliford, M., Cassell, J., Pirmohamed, M., Taweel, A., Delaney, B., & Smeeth, L. (2012). Pragmatic randomised trials using routine electronic health records: Putting them to the test. BMJ, 344, e55. https://doi.org/10.1136/bmj.e55

Strom, B. L., Eng, S. M., Faich, G., Reynolds, R. F., D'Agostino, R. B., Ruskin, J., & Kane, J. M. (2011). Comparative Mortality Associated With Ziprasidone and Olanzapine in Real-World Use Among 18,154 Patients With Schizophrenia: The Ziprasidone Observational Study of Cardiac Outcomes (ZODIAC). American Journal of Psychiatry, 168(2), 193–201. https://doi.org/10.1176/appi.ajp.2010.08040484

Suchard, M. A., Zorych, I., Simpson, S. E., Schuemie, M. J., Ryan, P. B., & Madigan, D. (2013). Empirical performance of the self-controlled case series design: Lessons for developing a risk identification and analysis system. Drug Safety, 36 Suppl 1, S83-93. https://doi.org/10.1007/s40264-013-0100-4

Suissa, S. (1995). The case-time-control design. Epidemiology (Cambridge, Mass.), 6(3), 248–253. https://doi.org/10.1097/00001648-199505000-00010

Théophile, H., Laporte, J.-R., Moore, N., Martin, K.-L., & Bégaud, B. (2011). The Case-Population Study Design. Drug Safety, 34(10), 861–868. https://doi.org/10.2165/11592140-000000000-00000

Théophile, H., Moore, N., Robinson, P., Bégaud, B., & Pariente, A. (2016). Vaccine Case-Population: A New Method for Vaccine Safety Surveillance. Drug Safety, 39(12), 1197–1209. https://doi.org/10.1007/s40264-016-0449-2

Thorpe, K. E., Zwarenstein, M., Oxman, A. D., Treweek, S., Furberg, C. D., Altman, D. G., Tunis, S., Bergel, E., Harvey, I., Magid, D. J., & Chalkidou, K. (2009). A pragmatic–explanatory continuum indicator summary (PRECIS): A tool to help trial designers. CMAJ, 180(10), E47–E57. https://doi.org/10.1503/cmaj.090523

van Staa, T.-P., Dyson, L., McCann, G., Padmanabhan, S., Belatri, R., Goldacre, B., Cassell, J., Pirmohamed, M., Torgerson, D., Ronaldson, S., Adamson, J., Taweel, A., Delaney, B., Mahmood, S., Baracaia, S., Round, T., Fox, R., Hunter, T., Gulliford, M., & Smeeth, L. (2014). The opportunities and challenges of pragmatic point-of-care randomised trials using routinely collected electronic records: Evaluations of two exemplar trials. Health Technology Assessment, 18(43), 1–146. https://doi.org/10.3310/hta18430

Wang, S., Linkletter, C., Maclure, M., Dore, D., Mor, V., Buka, S., & Wellenius, G. A. (2011). Future cases as present controls to adjust for exposure trend bias in case-only studies. Epidemiology (Cambridge, Mass.), 22(4), 568–574. https://doi.org/10.1097/EDE.0b013e31821d09cd

Wang, S. V., Schneeweiss, S., RCT-DUPLICATE Initiative, Franklin, J. M., Desai, R. J., Feldman, W., Garry, E. M., Glynn, R. J., Lin, K. J., Paik, J., Patorno, E., Suissa, S., D'Andrea, E., Jawaid, D., Lee, H., Pawar, A., Sreedhara, S. K., Tesfaye, H., Bessette, L. G., … Quinto, K. (2023). Emulation of Randomized Clinical Trials With Nonrandomized Database Analyses: Results of 32 Clinical Trials. JAMA, 329(16), 1376–1385. https://doi.org/10.1001/jama.2023.4221

Wang, X., & Cheng, Z. (2020). Cross-Sectional Studies: Strengths, Weaknesses, and Recommendations. Chest, 158(1S), S65–S71. https://doi.org/10.1016/j.chest.2020.03.012

Welcome—RECOVERY Trial. https://www.recoverytrial.net/

Weldeselassie, Y. G., Whitaker, H. J., & Farrington, C. P. (2011). Use of the self-controlled case-series method in vaccine safety studies: Review and recommendations for best practice. Epidemiology and Infection, 139(12), 1805–1817. https://doi.org/10.1017/S0950268811001531

The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
(ENCePP) Guide on Methodological Standards in Pharmacoepidemiology
EMA/228452/2023   Page 10/76

Whitaker, H. J., Farrington, C. P., Spiessens, B., & Musonda, P. (2006). Tutorial in biostatistics: The self-controlled case series method. Statistics in Medicine, 25(10), 1768–1797. https://doi.org/10.1002/sim.2302

Whitaker, H. J., Ghebremichael-Weldeselassie, Y., Douglas, I. J., Smeeth, L., & Farrington, C. P. (2018). Investigating the assumptions of the self-controlled case series method. Statistics in Medicine, 37(4), 643–658. https://doi.org/10.1002/sim.7536

Yu, L.-M., Bafadhel, M., Dorward, J., Hayward, G., Saville, B. R., Gbinigie, O., Van Hecke, O., Ogburn, E., Evans, P. H., Thomas, N. P. B., Patel, M. G., Richards, D., Berry, N., Detry, M. A., Saunders, C., Fitzgerald, M., Harris, V., Shanyinde, M., de Lusignan, S., … Butler, C. C. (2021). Inhaled budesonide for COVID-19 in people at high risk of complications in the community in the UK (PRINCIPLE): A randomised, controlled, open-label, adaptive platform trial. The Lancet, 398(10303), 843–855. https://doi.org/10.1016/S0140-6736(21)01744-X

Zuidgeest, M. G. P., Goetz, I., Groenwold, R. H. H., Irving, E., van Thiel, G. J. M. W., & Grobbee, D. E. (2017). Series: Pragmatic trials and real world evidence: Paper 1. Introduction. Journal of Clinical Epidemiology, 88, 7–13. https://doi.org/10.1016/j.jclinepi.2016.12.023

Zuidgeest, M. G. P., Goetz, I., Meinecke, A.-K., Boateng, D., Irving, E. A., van Thiel, G. J. M., Welsing, P. M. J., Oude-Rengerink, K., Grobbee, D. E., & www.imi-getreal.eu. (2022). The GetReal Trial Tool: Design, assess and discuss clinical drug trials in light of Real World Evidence generation. Journal of Clinical Epidemiology, 149, 244–253. https://doi.org/10.1016/j.jclinepi.2021.12.019

Zwarenstein, M., Treweek, S., Gagnier, J. J., Altman, D. G., Tunis, S., Haynes, B., Oxman, A. D., & Moher, D. (2008). Improving the reporting of pragmatic trials: An extension of the CONSORT statement. BMJ, 337, a2390. https://doi.org/10.1136/bmj.a2390

4.3. Specific aspects of study design

Altman, D. (2020). Practical Statistics for Medical Research (2nd ed.). Chapman & Hall.

Andrews, E., & Moore, N. (2014). Mann's Pharmacovigilance, Third Edition (3rd ed.). Wiley-Blackwell.

Ayad, A., & Hartzema, A. (2018). Post-Authorization Safety Studies of Medicinal Products: The PASS Book. Academic Press.

Begaud, B. (2000). Dictionary of Pharmacoepidemiology. Wiley.

Elseviers, M., Wettermark, B., & Almarsdóttir, A. B. (2016). Drug Utilization Research. Methods and Applications. Wiley-Blackwell.

Good pharmacovigilance practices | European Medicines Agency. (2022, April 26). European Medicines Agency. https://www.ema.europa.eu/en/human-regulatory/post-authorisation/pharmacovigilance/good-pharmacovigilance-practices

Hartzema, A. G., Tilson, H. H., & Chan, K. A. (2008). Pharmacoepidemiology and Therapeutic Risk Management. Harvey Whitney Books Company.

Hernan, M., & Robins, J. (2020). Causal Inference: What If. Chapman & Hall/CRC.

Hoffmann, W., Latza, U., Baumeister, S. E., Brünger, M., Buttmann-Schweiger, N., Hardt, J., Hoffmann, V., Karch, A., Richter, A., Schmidt, C. O., Schmidtmann, I., Swart, E., & van den Berg, N. (2019). Guidelines and recommendations for ensuring Good Epidemiological Practice (GEP): A guideline developed by the German Society for Epidemiology. European Journal of Epidemiology, 34(3), Art. 3. https://doi.org/10.1007/s10654-019-00500-x

The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
(ENCePP) Guide on Methodological Standards in Pharmacoepidemiology
EMA/228452/2023   Page 11/76

IEA Good Epidemiology Practice (GEP). (2007). IEA.
https://ieaweb.org/IEAWeb/Content/IEA_Publications.aspx

ISPE Guidelines for Good Pharmacoepidemiology Practices (GPP)—International Society for Pharmacoepidemiology. (2022, April 25). ISPE.
https://www.pharmacoepi.org/resources/policies/guidelines-08027/

Lash, T., VanderWeele, T., Haneuse, S., & Rothman, K. (2020). Modern Epidemiology (4th ed.). Wolters Kluwer.

Parfrey, P., & Barret, B. (2015). Clinical epidemiology: Practice and methods (2nd ed.). Human Press.

Porta, M. (2014). A Dictionary of Epidemiology (6th ed.). Oxford University Press.

Scientific guidance on post-authorisation efficacy studies—EMA. (2016). European Medicines Agency.
https://www.ema.europa.eu/en/documents/scientific-guideline/scientific-guidance-post-authorisation-efficacy-studies-first-version_en.pdf

Strom, B., Kimmel, S. E., & Hennessy, S. (2019). Pharmacoepidemiology (6th ed.). Wiley-Blackwell.

Understanding the Use of Negative Controls to Assess the Validity of Non-Interventional Studies of Treatment Using Real-World Evidence. Margolis Center for Health Policy.
https://healthpolicy.duke.edu/events/understanding-use-negative-controls-assess-validity-non-interventional-studies-treatment

Woodward, M. (2014). Epidemiology: Study Design and Data Analysis (3rd ed.). Chapman & Hall.

5. Definition and validation of drug exposure, outcomes and covariates

Banda, J. M., Seneviratne, M., Hernandez-Boussard, T., & Shah, N. H. (2018). Advances in Electronic Phenotyping: From Rule-Based Definitions to Machine Learning Models. *Annual Review of Biomedical Data Science*, *1*(1), 53–68. https://doi.org/10.1146/annurev-biodatasci-080917-013315

Brenner, H., & Gefeller, O. (1993). Use of the Positive Predictive Value to Correct for Disease Misclassification in Epidemiologic Studies. *American Journal of Epidemiology*, *138*(11), 1007–1015. https://doi.org/10.1093/oxfordjournals.aje.a116805

Brighton Collaboration – Home Page. Brighton Collaboration. https://brightoncollaboration.us/

Brunelli, S. M., Gagne, J. J., Huybrechts, K. F., Wang, S. V., Patrick, A. R., Rothman, K. J., & Seeger, J. D. (2013). Estimation using all available covariate information versus a fixed look-back window for dichotomous covariates. *Pharmacoepidemiology and Drug Safety*, *22*(5), 542–550. https://doi.org/10.1002/pds.3434

Carnahan, R. M., & Moores, K. G. (2012). Mini-Sentinel's systematic reviews of validated methods for identifying health outcomes using administrative and claims data: Methods and lessons learned. *Pharmacoepidemiology and Drug Safety*, *21*(S1), 82–89. https://doi.org/10.1002/pds.2321

ClinicalCodes Repository. https://clinicalcodes.rss.mhs.man.ac.uk/

Davé, S., & Petersen, I. (2009). Creating medical and drug code lists to identify cases in primary care databases. *Pharmacoepidemiology and Drug Safety*, *18*(8), 704–707. https://doi.org/10.1002/pds.1770

Elseviers, M., Wettermark, B., & Almarsdóttir, A. (2016). *Drug Utilization Research: Methods and Applications*. Wiley Blackwel.

Fox, M. P., Lash, T. L., & Bodnar, L. M. (2020). Common misconceptions about validation studies. *International Journal of Epidemiology*, *49*(4), 1392–1396. https://doi.org/10.1093/ije/dyaa090

Greenland, S. (1980). THE EFFECT OF MISCLASSIFICATION IN THE PRESENCE OF COVARIATES. *American Journal of Epidemiology*, *112*(4), 564–569. https://doi.org/10.1093/oxfordjournals.aje.a113025

Greenland, S. (1996). Basic methods for sensitivity analysis of biases. *International Journal of Epidemiology*, *25*(6), 1107–1116. https://pubmed.ncbi.nlm.nih.gov/9027513/

Hall, G. C., Lanes, S., Bollaerts, K., Zhou, X., Ferreira, G., & Gini, R. (2020). Outcome misclassification: Impact, usual practice in pharmacoepidemiology database studies and an online aid to correct biased estimates of risk ratio or cumulative incidence. *Pharmacoepidemiology and Drug Safety*, *29*(11), 1450–1455. https://doi.org/10.1002/pds.5109

Khan, N. F., Harrison, S. E., & Rose, P. W. (2010). Validity of diagnostic coding within the General Practice Research Database: A systematic review. *British Journal of General Practice*, *60*(572), e128–e136. https://doi.org/10.3399/bjgp10X483562

Lash, T. L., Fox, M. P., & Fink, A. K. (2009). *Applying quantitative bias analysis to epidemiologic data*. Springer-Verlag.

Lash, T. L., Fox, M. P., MacLehose, R. F., Maldonado, G., McCandless, L. C., & Greenland, S. (2014). Good practices for quantitative bias analysis. *International Journal of Epidemiology*, *43*(6), 1969–1985. https://doi.org/10.1093/ije/dyu149

Lee, W.-J., Lee, T. A., Pickard, A. S., Shoaibi, A., & Schumock, G. T. (2015). Using linked electronic data to validate algorithms for health outcomes in administrative databases. *Journal of Comparative Effectiveness Research*, *4*(4), 359–366. https://doi.org/10.2217/cer.15.14

Pottegård, A., Christensen, R. dePont, Houji, A., Christiansen, C. B., Paulsen, M. S., Thomsen, J. L., & Hallas, J. (2014). Primary non-adherence in general practice: A Danish register study. *European Journal of Clinical Pharmacology*, *70*(6), 757–763. https://doi.org/10.1007/s00228-014-1677-y

Pye, S. R., Sheppard, T., Joseph, R. M., Lunt, M., Girard, N., Haas, J. S., Bates, D. W., Buckeridge, D. L., van Staa, T. P., Tamblyn, R., & Dixon, W. G. (2018). Assumptions made when preparing drug exposure data for analysis have an impact on results: An unreported step in pharmacoepidemiology studies. *Pharmacoepidemiology and Drug Safety*, *27*(7), 781–788. https://doi.org/10.1002/pds.4440

Schneeweiss, S., & Avorn, J. (2005). A review of uses of health care utilization databases for epidemiologic research on therapeutics. *Journal of Clinical Epidemiology*, *58*(4), 323–337. https://doi.org/10.1016/j.jclinepi.2004.10.012

Yih, W. K. Quantitative Bias Analysis Methodology Development: Sequential Bias Adjustment for Outcome Misclassification. *Final Report*. https://www.sentinelinitiative.org/sites/default/files/Methods/Sentinel_Methods_Sequential_bias.pdf

Yland, J. J., Wesselink, A. K., Lash, T. L., & Fox, M. P. (2022). Misconceptions About the Direction of Bias From Nondifferential Misclassification. *American Journal of Epidemiology*, *191*(8), 1485–1495. https://doi.org/10.1093/aje/kwac035

6. Methods to address bias and confounding

6.1. Bias

Arana, A., Pottegård, A., Kuiper, J. G., Booth, H., Reutfors, J., Calingaert, B., Lund, L. C., Crellin, E., Schmitt-Egenolf, M., Kaye, J. A., Gembert, K., Rothman, K. J., Kieler, H., Dedman, D., Houben, E., Gutiérrez, L., Hallas, J., & Perez-Gutthann, S. (2021). Long-Term Risk of Skin Cancer and Lymphoma in Users of Topical Tacrolimus and Pimecrolimus: Final Results from the Extension of the Cohort Study Protopic Joint European Longitudinal Lymphoma and Skin Cancer Evaluation (JOELLE). Clinical Epidemiology, 13, 1141–1153. https://doi.org/10.2147/CLEP.S331287

Caniglia, E. C., Zash, R., Fennell, C., Diseko, M., Mayondi, G., Heintz, J., Mmalane, M., Makhema, J., Lockman, S., Mumford, S. L., Murray, E. J., Hernández-Díaz, S., & Shapiro, R. (2023). Emulating Target Trials to Avoid Immortal Time Bias—An Application to Antibiotic Initiation and Preterm Delivery. Epidemiology (Cambridge, Mass.), 34(3), 430–438. https://doi.org/10.1097/EDE.0000000000001601

Coughlin, S. S. (1990). Recall bias in epidemiologic studies. Journal of Clinical Epidemiology, 43(1), 87–91. https://doi.org/10.1016/0895-4356(90)90060-3

Gagne, J. J. (2017). New-user designs with conditional propensity scores: A unified complement to the traditional active comparator new-user approach. Pharmacoepidemiology and Drug Safety, 26(4), 469–471. https://doi.org/10.1002/pds.4189

Gerhard, T. (2008). Bias: Considerations for research practice. American Journal of Health-System Pharmacy: AJHP: Official Journal of the American Society of Health-System Pharmacists, 65(22), 2159–2168. https://doi.org/10.2146/ajhp070369

Griffith, G. J., Morris, T. T., Tudball, M. J., Herbert, A., Mancano, G., Pike, L., Sharp, G. C., Sterne, J., Palmer, T. M., Davey Smith, G., Tilling, K., Zuccolo, L., Davies, N. M., & Hemani, G. (2020). Collider bias undermines our understanding of COVID-19 disease risk and severity. Nature Communications, 11, 5749. https://doi.org/10.1038/s41467-020-19478-2

Horwitz, R. I., & Feinstein, A. R. (1978). Alternative Analytic Methods for Case-Control Studies of Estrogens and Endometrial Cancer. New England Journal of Medicine, 299(20), 1089–1094. https://doi.org/10.1056/NEJM197811162992001

Kaye, J. A., Margulis, A. V., Fortuny, J., McQuay, L. J., Plana, E., Bartsch, J. L., Bui, C. L., Perez-Gutthann, S., & Arana, A. (2017). Cancer Incidence after Initiation of Antimuscarinic Medications for Overactive Bladder in the United Kingdom: Evidence for Protopathic Bias. Pharmacotherapy, 37(6), 673–683. https://doi.org/10.1002/phar.1932

Kiri, V. A., & MacKenzie, G. (2009). RE: "IMMORTAL TIME BIAS IN PHARMACOEPIDEMIOLOGY". American Journal of Epidemiology, 170(5), 667–668. https://doi.org/10.1093/aje/kwp239

Ladapo, J. A., Blecker, S., Elashoff, M. R., Federspiel, J. J., Vieira, D. L., Sharma, G., Monane, M., Rosenberg, S., Phelps, C. E., & Douglas, P. S. Clinical Implications of Referral Bias in the Diagnostic Performance of Exercise Testing for Coronary Artery Disease. Journal of the American Heart Association, 2(6), e000505. https://doi.org/10.1161/JAHA.113.000505

Lévesque, L. E., Hanley, J. A., Kezouh, A., & Suissa, S. (2010). Problem of immortal time bias in cohort studies: Example using statins for preventing progression of diabetes. BMJ, 340, b5087. https://doi.org/10.1136/bmj.b5087

Lewis, M. A. (1999). The Transnational Study on Oral Contraceptives and the Health of Young Women. Methods, results, new analyses and the healthy user effect. Human Reproduction Update, 5(6), 707–720. https://doi.org/10.1093/humupd/5.6.707

The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
(ENCePP) Guide on Methodological Standards in Pharmacoepidemiology
EMA/228452/2023   Page 14/76

Lund, J. L., Richardson, D. B., & Stürmer, T. (2015). The active comparator, new user study design in pharmacoepidemiology: Historical foundations and contemporary application. Current Epidemiology Reports, 2(4), 221–228. https://doi.org/10.1007/s40471-015-0053-5

Menni, C., Klaser, K., May, A., Polidori, L., Capdevila, J., Louca, P., Sudre, C. H., Nguyen, L. H., Drew, D. A., Merino, J., Hu, C., Selvachandran, S., Antonelli, M., Murray, B., Canas, L. S., Molteni, E., Graham, M. S., Modat, M., Joshi, A. D., … Spector, T. D. (2021). Vaccine side-effects and SARS-CoV-2 infection after vaccination in users of the COVID Symptom Study app in the UK: A prospective observational study. The Lancet. Infectious Diseases, 21(7), 939–949. https://doi.org/10.1016/S1473-3099(21)00224-3

Metformin and the Risk of Cancer | Diabetes Care | American Diabetes Association. https://diabetesjournals.org/care/article/35/12/2665/38537/Metformin-and-the-Risk-of-CancerTime-related

Ray, W. A. (2003). Evaluating Medication Effects Outside of Clinical Trials: New-User Designs. American Journal of Epidemiology, 158(9), 915–920. https://doi.org/10.1093/aje/kwg231

Renoux, C., Azoulay, L., & Suissa, S. (2021a). Biases in Evaluating the Safety and Effectiveness of Drugs for the Treatment of COVID-19: Designing Real-World Evidence Studies. American Journal of

Salas, M., Hotman, A., & Stricker, B. H. (1999). Confounding by Indication: An Example of Variation in the Use of Epidemiologic Terminology. American Journal of Epidemiology, 149(11), 981–983. https://doi.org/10.1093/oxfordjournals.aje.a009758

Sharma, M., Nazareth, I., & Petersen, I. (2019). Observational studies of treatment effectiveness: Worthwhile or worthless? Clinical Epidemiology, 11, 35–42. https://doi.org/10.2147/CLEP.S178723

Shrank, W. H., Patrick, A. R., & Brookhart, M. A. (2011). Healthy user and related biases in observational studies of preventive interventions: A primer for physicians. Journal of General Internal Medicine, 26(5), 546–550. https://doi.org/10.1007/s11606-010-1609-1

Suissa, S. (2007). Immortal time bias in observational studies of drug effects. Pharmacoepidemiology and Drug Safety, 16(3), 241–249. https://doi.org/10.1002/pds.1357

Suissa, S. (2008a). Immeasurable Time Bias in Observational Studies of Drug Effects on Mortality. American Journal of Epidemiology, 168(3), 329–335. https://doi.org/10.1093/aje/kwn135

Suissa, S. (2008b). Immortal Time Bias in Pharmacoepidemiology. American Journal of Epidemiology, 167(4), 492–499. https://doi.org/10.1093/aje/kwm324

Suissa, S., Moodie, E. E. M., & Dell'Aniello, S. (2017). Prevalent new-user cohort designs for comparative drug effect studies by time-conditional propensity scores. Pharmacoepidemiology and Drug Safety, 26(4), 459–468. https://doi.org/10.1002/pds.4107

Surveillance Bias in Outcomes Reporting | Venous Thromboembolism | JAMA | JAMA Network. https://jamanetwork.com/journals/jama/fullarticle/900883

Zhou, Z., Rahme, E., Abrahamowicz, M., & Pilote, L. (2005). Survival Bias Associated with Time-to-Treatment Initiation in Drug Effectiveness Evaluation: A Comparison of Methods. American Journal of Epidemiology, 162(10), 1016–1023. https://doi.org/10.1093/aje/kwi307

6.2. Confounding

The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
(ENCePP) Guide on Methodological Standards in Pharmacoepidemiology
EMA/228452/2023   Page 15/76

Ali, M. S., Groenwold, R. H. H., Belitser, S. V., Pestman, W. R., Hoes, A. W., Roes, K. C. B., Boer, A. de, & Klungel, O. H. (2015). Reporting of covariate selection and balance assessment in propensity score analysis is suboptimal: A systematic review. Journal of Clinical Epidemiology, 68(2), 112–121. https://doi.org/10.1016/j.jclinepi.2014.08.011

Ali, M. S., Groenwold, R. H. H., Pestman, W. R., Belitser, S. V., Roes, K. C. B., Hoes, A. W., de Boer, A., & Klungel, O. H. (2014). Propensity score balance measures in pharmacoepidemiology: A simulation study. Pharmacoepidemiology and Drug Safety, 23(8), 802–811. https://doi.org/10.1002/pds.3574

Austin, P. C. (2011a). A Tutorial and Case Study in Propensity Score Analysis: An Application to Estimating the Effect of In-Hospital Smoking Cessation Counseling on Mortality. Multivariate Behavioral Research, 46(1), 119–151. https://doi.org/10.1080/00273171.2011.540480

Austin, P. C. (2011b). An Introduction to Propensity Score Methods for Reducing the Effects of Confounding in Observational Studies. Multivariate Behavioral Research, 46(3), 399–424. https://doi.org/10.1080/00273171.2011.568786

Belitser, S. V., Martens, E. P., Pestman, W. R., Groenwold, R. H. H., de Boer, A., & Klungel, O. H. (2011). Measuring balance and model selection in propensity score methods. Pharmacoepidemiology and Drug Safety, 20(11), 1115–1129. https://doi.org/10.1002/pds.2188

Brookhart, M. A., Rassen, J. A., & Schneeweiss, S. (2010). Instrumental variable methods in comparative safety and effectiveness research. Pharmacoepidemiology and Drug Safety, 19(6), 537–554. https://doi.org/10.1002/pds.1908

Brookhart, M. A., Schneeweiss, S., Rothman, K. J., Glynn, R. J., Avorn, J., & Stürmer, T. (2006). Variable selection for propensity score models. American Journal of Epidemiology, 163(12), 1149–1156. https://doi.org/10.1093/aje/kwj149

Brookhart, M. A., Wang, P., Solomon, D. H., & Schneeweiss, S. (2006). Evaluating short-term drug effects using a physician-specific prescribing preference as an instrumental variable. Epidemiology (Cambridge, Mass.), 17(3), 268–275. https://doi.org/10.1097/01.ede.0000193606.58671.c5

Cole, S. R., Hernán, M. A., Robins, J. M., Anastos, K., Chmiel, J., Detels, R., Ervin, C., Feldman, J., Greenblatt, R., Kingsley, L., Lai, S., Young, M., Cohen, M., & Muñoz, A. (2003). Effect of highly active antiretroviral therapy on time to acquired immunodeficiency syndrome or death using marginal structural models. American Journal of Epidemiology, 158(7), 687–694. https://doi.org/10.1093/aje/kwg206

Daniel, R. M., Cousens, S. N., De Stavola, B. L., Kenward, M. G., & Sterne, J. a. C. (2013). Methods for dealing with time-dependent confounding. Statistics in Medicine, 32(9), 1584–1618. https://doi.org/10.1002/sim.5686

Desai, R. J., Rothman, K. J., Bateman, B. T., Hernandez-Diaz, S., & Huybrechts, K. F. (2017). A Propensity-score-based Fine Stratification Approach for Confounding Adjustment When Exposure Is Infrequent. Epidemiology (Cambridge, Mass.), 28(2), 249–257. https://doi.org/10.1097/EDE.0000000000000595

Drugepi. https://www.drugepi.org/dope/software#Sensitivity

Franklin, J. M., Rassen, J. A., Ackermann, D., Bartels, D. B., & Schneeweiss, S. (2014). Metrics for covariate balance in cohort studies of causal effects. Statistics in Medicine, 33(10), 1685–1699. https://doi.org/10.1002/sim.6058

The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
(ENCePP) Guide on Methodological Standards in Pharmacoepidemiology
EMA/228452/2023   Page 16/76

Garabedian, L. F., Chu, P., Toh, S., Zaslavsky, A. M., & Soumerai, S. B. (2014). Potential bias of instrumental variable analyses for observational comparative effectiveness research. Annals of Internal Medicine, 161(2), 131–138. https://doi.org/10.7326/M13-1887

Glynn, R. J., Gagne, J. J., & Schneeweiss, S. (2012). Role of disease risk scores in comparative effectiveness research with emerging therapies. Pharmacoepidemiology and Drug Safety, 21 Suppl 2(Suppl 2), 138–147. https://doi.org/10.1002/pds.3231

Greenland, S. (2000). An introduction to instrumental variables for epidemiologists. International Journal of Epidemiology, 29(4), 722–729. https://doi.org/10.1093/ije/29.4.722

Grobbee, D. E., & Hoes, A. W. (1997). Confounding and indication for treatment in evaluation of drug treatment for hypertension. BMJ, 315(7116), 1151–1154. https://doi.org/10.1136/bmj.315.7116.1151

Groenwold, R. H. H., de Vries, F., de Boer, A., Pestman, W. R., Rutten, F. H., Hoes, A. W., & Klungel, O. H. (2011). Balance measures for propensity score methods: A clinical example on beta-agonist use and the risk of myocardial infarction. Pharmacoepidemiology and Drug Safety, 20(11), 1130–1137. https://doi.org/10.1002/pds.2251

Hernán, M. A., Brumback, B., & Robins, J. M. (2000). Marginal structural models to estimate the causal effect of zidovudine on the survival of HIV-positive men. Epidemiology (Cambridge, Mass.), 11(5), 561–570. https://doi.org/10.1097/00001648-200009000-00012

Ji, X., Small, D. S., Leonard, C. E., & Hennessy, S. (2017). The Trend-in-trend Research Design for Causal Inference. Epidemiology (Cambridge, Mass.), 28(4), 529–536. https://doi.org/10.1097/EDE.0000000000000579

Joffe, M. M., & Rosenbaum, P. R. (1999). Invited commentary: Propensity scores. American Journal of Epidemiology, 150(4), 327–333. https://doi.org/10.1093/oxfordjournals.aje.a010011

Karim, M. E., Petkau, J., Gustafson, P., Platt, R. W., & Tremlett, H. (2018). Comparison of Statistical Approaches Dealing with Time-dependent Confounding in Drug Effectiveness Studies. Statistical Methods in Medical Research, 27(6), 1709–1722. https://doi.org/10.1177/0962280216668554

Klungel, O. H., Martens, E. P., Psaty, B. M., Grobbee, D. E., Sullivan, S. D., Stricker, B. H. Ch., Leufkens, H. G. M., & de Boer, A. (2004). Methods to assess intended effects of drug treatment in observational studies are reviewed. Journal of Clinical Epidemiology, 57(12), 1223–1231. https://doi.org/10.1016/j.jclinepi.2004.03.011

Martens, E. P., Pestman, W. R., de Boer, A., Belitser, S. V., & Klungel, O. H. (2006). Instrumental variables: Application and limitations. Epidemiology (Cambridge, Mass.), 17(3), 260–267. https://doi.org/10.1097/01.ede.0000215160.88317.cb

McMahon, A. D. (2003). Approaches to combat with confounding by indication in observational studies of intended drug effects. Pharmacoepidemiology and Drug Safety, 12(7), 551–558. https://doi.org/10.1002/pds.883

MIETTINEN, O. S. (1976). STRATIFICATION BY A MULTIVARIATE CONFOUNDER SCORE. American Journal of Epidemiology, 104(6), 609–620. https://doi.org/10.1093/oxfordjournals.aje.a112339

Moodie, E. E. M., & Stephens, D. A. (2010). Using Directed Acyclic Graphs to detect limitations of traditional regression in longitudinal studies. International Journal of Public Health, 55(6), 701–703. https://doi.org/10.1007/s00038-010-0184-x

The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
(ENCePP) Guide on Methodological Standards in Pharmacoepidemiology
EMA/228452/2023   Page 17/76

Moving towards best practice when using inverse probability of treatment weighting (IPTW) using the propensity score to estimate causal treatment effects in observational studies—PubMed. https://pubmed.ncbi.nlm.nih.gov/26238958/

Rassen, J. A., Shelat, A. A., Franklin, J. M., Glynn, R. J., Solomon, D. H., & Schneeweiss, S. (2013). Matching by propensity score in cohort studies with three treatment groups. Epidemiology (Cambridge, Mass.), 24(3), 401–409. https://doi.org/10.1097/EDE.0b013e318289dedf

Rassen, J. A., Shelat, A. A., Myers, J., Glynn, R. J., Rothman, K. J., & Schneeweiss, S. (2012). One-to-many propensity score matching in cohort studies. Pharmacoepidemiology and Drug Safety, 21 Suppl 2, 69–80. https://doi.org/10.1002/pds.3263

Robins, J. M., Hernán, M. A., & Brumback, B. (2000). Marginal structural models and causal inference in epidemiology. Epidemiology (Cambridge, Mass.), 11(5), 550–560. https://doi.org/10.1097/00001648-200009000-00011

Salas, M., Hotman, A., & Stricker, B. H. (1999). Confounding by Indication: An Example of Variation in the Use of Epidemiologic Terminology. American Journal of Epidemiology, 149(11), 981–983. https://doi.org/10.1093/oxfordjournals.aje.a009758

Sanni Ali, M., Groenwold, R. H. H., Pestman, W. R., Belitser, S. V., Hoes, A. W., de Boer, A., & Klungel, O. H. (2013). Time-dependent propensity score and collider-stratification bias: An example of beta2-agonist use and the risk of coronary heart disease. European Journal of Epidemiology, 28(4), 291–299. https://doi.org/10.1007/s10654-013-9766-2

Schmidt, A. F., Klungel, O. H., Groenwold, R. H. H., & GetReal Consortium. (2016). Adjusting for Confounding in Early Postlaunch Settings: Going Beyond Logistic Regression Models. Epidemiology (Cambridge, Mass.), 27(1), 133–142. https://doi.org/10.1097/EDE.0000000000000388

Schneeweiss, S. (2006). Sensitivity analysis and external adjustment for unmeasured confounders in epidemiologic database studies of therapeutics. Pharmacoepidemiology and Drug Safety, 15(5), 291–303. https://doi.org/10.1002/pds.1200

Schneeweiss, S. (2018). Automated data-adaptive analytics for electronic healthcare data to study causal treatment effects. Clinical Epidemiology, 10, 771–788. https://doi.org/10.2147/CLEP.S166545

Schneeweiss, S., Rassen, J. A., Glynn, R. J., Avorn, J., Mogun, H., & Brookhart, M. A. (2009). High-dimensional propensity score adjustment in studies of treatment effects using health care claims data. Epidemiology (Cambridge, Mass.), 20(4), 512–522. https://doi.org/10.1097/EDE.0b013e3181a663cc

Simpson, C. R., Shi, T., Vasileiou, E., Katikireddi, S. V., Kerr, S., Moore, E., McCowan, C., Agrawal, U., Shah, S. A., Ritchie, L. D., Murray, J., Pan, J., Bradley, D. T., Stock, S. J., Wood, R., Chuter, A., Beggs, J., Stagg, H. R., Joy, M., … Sheikh, A. (2021). First-dose ChAdOx1 and BNT162b2 COVID-19 vaccines and thrombocytopenic, thromboembolic and hemorrhagic events in Scotland. Nature Medicine, 27(7), 1290–1297. https://doi.org/10.1038/s41591-021-01408-4

Stürmer, T., Rothman, K. J., Avorn, J., & Glynn, R. J. (2010). Treatment effects in the presence of unmeasured confounding: Dealing with observations in the tails of the propensity score distribution--a simulation study. American Journal of Epidemiology, 172(7), 843–854. https://doi.org/10.1093/aje/kwq198

Stürmer, T., Schneeweiss, S., Rothman, K. J., Avorn, J., & Glynn, R. J. (2007). Performance of propensity score calibration—A simulation study. American Journal of Epidemiology, 165(10), 1110–1118. https://doi.org/10.1093/aje/kwm074

The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) Guide on Methodological Standards in Pharmacoepidemiology
EMA/228452/2023

Page 18/76

Swanson, S. A., Robins, J. M., Miller, M., & Hernán, M. A. (2015). Selecting on Treatment: A Pervasive Form of Bias in Instrumental Variable Analyses. American Journal of Epidemiology, 181(3), 191–197. https://doi.org/10.1093/aje/kwu284

Tadrous, M., Gagne, J. J., Stürmer, T., & Cadarette, S. M. (2013). Disease Risk Score (DRS) as a Confounder Summary Method: Systematic Review and Recommendations. Pharmacoepidemiology and Drug Safety, 22(2), 122–129. https://doi.org/10.1002/pds.3377

Tannen, R. L., Weiner, M. G., & Xie, D. (2008). Replicated studies of two randomized trials of angiotensin- converting enzyme inhibitors: Further empiric validation of the 'prior event rate ratio' to adjust for unmeasured confounding by indication. Pharmacoepidemiology and Drug Safety, 17(7), 671–685. https://doi.org/10.1002/pds.1584

Uddin, M. J., Groenwold, R. H. H., de Boer, A., Belitser, S. V., Roes, K. C. B., Hoes, A. W., & Klungel, O. H. (2014). Performance of instrumental variable methods in cohort and nested case-control studies: A simulation study. Pharmacoepidemiology and Drug Safety, 23(2), 165–177. https://doi.org/10.1002/pds.3555

Uddin, M. J., Groenwold, R. H. H., van Staa, T. P., de Boer, A., Belitser, S. V., Hoes, A. W., Roes, K. C. B., & Klungel, O. H. (2015). Performance of prior event rate ratio adjustment method in pharmacoepidemiology: A simulation study. Pharmacoepidemiology and Drug Safety, 24(5), 468–477. https://doi.org/10.1002/pds.3724

Uddin, Md. J., Groenwold, R. H. H., de Boer, A., Afonso, A. S. M., Primatesta, P., Becker, C., Belitser, S. V., Hoes, A. W., Roes, K. C. B., & Klungel, O. H. (2016). Evaluating different physician's prescribing preference based instrumental variables in two primary care databases: A study of inhaled long-acting beta2-agonist use and the risk of myocardial infarction. Pharmacoepidemiology and Drug Safety, 25(S1), 132–141. https://doi.org/10.1002/pds.3860

Use of disease risk scores in pharmacoepidemiologic studies—Patrick G Arbogast, Wayne A Ray, 2009. https://journals.sagepub.com/doi/10.1177/0962280208092347

Williamson, E., Morley, R., Lucas, A., & Carpenter, J. (2012). Propensity scores: From naive enthusiasm to intuitive understanding. Statistical Methods in Medical Research, 21(3), 273–293. https://doi.org/10.1177/0962280210394483

Witteman, J. C., D'Agostino, R. B., Stijnen, T., Kannel, W. B., Cobb, J. C., de Ridder, M. A., Hofman, A., & Robins, J. M. (1998). G-estimation of causal effects: Isolated systolic hypertension and cardiovascular death in the Framingham Heart Study. American Journal of Epidemiology, 148(4), 390–401. https://doi.org/10.1093/oxfordjournals.aje.a009658

Wyss, R., Girman, C. J., LoCasale, R. J., Brookhart, A. M., & Stürmer, T. (2013). Variable selection for propensity score models when estimating treatment effects on multiple outcomes: A simulation study. Pharmacoepidemiology and Drug Safety, 22(1), 77–85. https://doi.org/10.1002/pds.3356

6.3. Missing data

Banda, J. M., Seneviratne, M., Hernandez-Boussard, T., & Shah, N. H. (2018). Advances in Electronic Phenotyping: From Rule-Based Definitions to Machine Learning Models. *Annual Review of Biomedical Data Science*, *1*(1), 53–68. https://doi.org/10.1146/annurev-biodatasci-080917-013315

Brenner, H., & Gefeller, O. (1993). Use of the Positive Predictive Value to Correct for Disease Misclassification in Epidemiologic Studies. *American Journal of Epidemiology*, *138*(11), 1007–1015. https://doi.org/10.1093/oxfordjournals.aje.a116805

The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
(ENCePP) Guide on Methodological Standards in Pharmacoepidemiology
EMA/228452/2023   Page 19/76

Brighton Collaboration – Home Page. Brighton Collaboration. https://brightoncollaboration.us/

Brunelli, S. M., Gagne, J. J., Huybrechts, K. F., Wang, S. V., Patrick, A. R., Rothman, K. J., & Seeger, J. D. (2013). Estimation using all available covariate information versus a fixed look-back window for dichotomous covariates. *Pharmacoepidemiology and Drug Safety*, *22*(5), 542–550. https://doi.org/10.1002/pds.3434

Carnahan, R. M., & Moores, K. G. (2012). Mini-Sentinel's systematic reviews of validated methods for identifying health outcomes using administrative and claims data: Methods and lessons learned. *Pharmacoepidemiology and Drug Safety*, *21*(S1), 82–89. https://doi.org/10.1002/pds.2321

ClinicalCodes Repository. https://clinicalcodes.rss.mhs.man.ac.uk/

Davé, S., & Petersen, I. (2009). Creating medical and drug code lists to identify cases in primary care databases. *Pharmacoepidemiology and Drug Safety*, *18*(8), 704–707. https://doi.org/10.1002/pds.1770

Elseviers, M., Wettermark, B., & Almarsdóttir, A. (2016). *Drug Utilization Research: Methods and Applications*. Wiley Blackwel.

Fox, M. P., Lash, T. L., & Bodnar, L. M. (2020). Common misconceptions about validation studies. *International Journal of Epidemiology*, *49*(4), 1392–1396. https://doi.org/10.1093/ije/dyaa090

GREENLAND, S. (1980). THE EFFECT OF MISCLASSIFICATION IN THE PRESENCE OF COVARIATES. *American Journal of Epidemiology*, *112*(4), 564–569. https://doi.org/10.1093/oxfordjournals.aje.a113025

Greenland, S. (1996). Basic methods for sensitivity analysis of biases. *International Journal of Epidemiology*, *25*(6), 1107–1116. https://pubmed.ncbi.nlm.nih.gov/9027513/

Hall, G. C., Lanes, S., Bollaerts, K., Zhou, X., Ferreira, G., & Gini, R. (2020). Outcome misclassification: Impact, usual practice in pharmacoepidemiology database studies and an online aid to correct biased estimates of risk ratio or cumulative incidence. *Pharmacoepidemiology and Drug Safety*, *29*(11), 1450–1455. https://doi.org/10.1002/pds.5109

Khan, N. F., Harrison, S. E., & Rose, P. W. (2010). Validity of diagnostic coding within the General Practice Research Database: A systematic review. *British Journal of General Practice*, *60*(572), e128–e136. https://doi.org/10.3399/bjgp10X483562

Lash, T. L., Fox, M. P., & Fink, A. K. (2009). *Applying quantitative bias analysis to epidemiologic data*. Springer-Verlag.

Lash, T. L., Fox, M. P., MacLehose, R. F., Maldonado, G., McCandless, L. C., & Greenland, S. (2014). Good practices for quantitative bias analysis. *International Journal of Epidemiology*, *43*(6), 1969–1985. https://doi.org/10.1093/ije/dyu149

Lee, W.-J., Lee, T. A., Pickard, A. S., Shoaibi, A., & Schumock, G. T. (2015). Using linked electronic data to validate algorithms for health outcomes in administrative databases. *Journal of Comparative Effectiveness Research*, *4*(4), 359–366. https://doi.org/10.2217/cer.15.14

Pottegård, A., Christensen, R. dePont, Houji, A., Christiansen, C. B., Paulsen, M. S., Thomsen, J. L., & Hallas, J. (2014). Primary non-adherence in general practice: A Danish register study. *European Journal of Clinical Pharmacology*, *70*(6), 757–763. https://doi.org/10.1007/s00228-014-1677-y

Pye, S. R., Sheppard, T., Joseph, R. M., Lunt, M., Girard, N., Haas, J. S., Bates, D. W., Buckeridge, D. L., van Staa, T. P., Tamblyn, R., & Dixon, W. G. (2018). Assumptions made when preparing drug

The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
(ENCePP) Guide on Methodological Standards in Pharmacoepidemiology
EMA/228452/2023   Page 20/76

exposure data for analysis have an impact on results: An unreported step in pharmacoepidemiology studies. *Pharmacoepidemiology and Drug Safety*, *27*(7), 781–788. https://doi.org/10.1002/pds.4440

Schneeweiss, S., & Avorn, J. (2005). A review of uses of health care utilization databases for epidemiologic research on therapeutics. *Journal of Clinical Epidemiology*, *58*(4), 323–337. https://doi.org/10.1016/j.jclinepi.2004.10.012

Yih, W. K. Quantitative Bias Analysis Methodology Development: Sequential Bias Adjustment for Outcome Misclassification. *Final Report*. https://www.sentinelinitiative.org/sites/default/files/Methods/Sentinel_Methods_Sequential_bias.pdf

Yland, J. J., Wesselink, A. K., Lash, T. L., & Fox, M. P. (2022). Misconceptions About the Direction of Bias From Nondifferential Misclassification. *American Journal of Epidemiology*, *191*(8), 1485–1495. https://doi.org/10.1093/aje/kwac035

Vach W, Blettner M. Missing data in epidemiological studies. In Armitage P, Colton T, eds. Encyclopedia of biostatistics. Wiley, 1998: 2641-2654.

6.4. Triangulation

Banda, J. M., Seneviratne, M., Hernandez-Boussard, T., & Shah, N. H. (2018). Advances in Electronic Phenotyping: From Rule-Based Definitions to Machine Learning Models. *Annual Review of Biomedical Data Science*, *1*(1), 53–68. https://doi.org/10.1146/annurev-biodatasci-080917-013315

Brenner, H., & Gefeller, O. (1993). Use of the Positive Predictive Value to Correct for Disease Misclassification in Epidemiologic Studies. *American Journal of Epidemiology*, *138*(11), 1007–1015. https://doi.org/10.1093/oxfordjournals.aje.a116805

Brighton Collaboration – Home Page. Brighton Collaboration. https://brightoncollaboration.us/

Brunelli, S. M., Gagne, J. J., Huybrechts, K. F., Wang, S. V., Patrick, A. R., Rothman, K. J., & Seeger, J. D. (2013). Estimation using all available covariate information versus a fixed look-back window for dichotomous covariates. *Pharmacoepidemiology and Drug Safety*, *22*(5), 542–550. https://doi.org/10.1002/pds.3434

Carnahan, R. M., & Moores, K. G. (2012). Mini-Sentinel's systematic reviews of validated methods for identifying health outcomes using administrative and claims data: Methods and lessons learned. *Pharmacoepidemiology and Drug Safety*, *21*(S1), 82–89. https://doi.org/10.1002/pds.2321

ClinicalCodes Repository. https://clinicalcodes.rss.mhs.man.ac.uk/

Davé, S., & Petersen, I. (2009). Creating medical and drug code lists to identify cases in primary care databases. *Pharmacoepidemiology and Drug Safety*, *18*(8), 704–707. https://doi.org/10.1002/pds.1770

Elseviers, M., Wettermark, B., & Almarsdóttir, A. (2016). *Drug Utilization Research: Methods and Applications*. Wiley Blackwel.

Fox, M. P., Lash, T. L., & Bodnar, L. M. (2020). Common misconceptions about validation studies. *International Journal of Epidemiology*, *49*(4), 1392–1396. https://doi.org/10.1093/ije/dyaa090

GREENLAND, S. (1980). THE EFFECT OF MISCLASSIFICATION IN THE PRESENCE OF COVARIATES. *American Journal of Epidemiology*, *112*(4), 564–569. https://doi.org/10.1093/oxfordjournals.aje.a113025

Greenland, S. (1996). Basic methods for sensitivity analysis of biases. *International Journal of Epidemiology*, *25*(6), 1107–1116. https://pubmed.ncbi.nlm.nih.gov/9027513/

Hall, G. C., Lanes, S., Bollaerts, K., Zhou, X., Ferreira, G., & Gini, R. (2020). Outcome misclassification: Impact, usual practice in pharmacoepidemiology database studies and an online aid to correct biased estimates of risk ratio or cumulative incidence. *Pharmacoepidemiology and Drug Safety*, *29*(11), 1450–1455. https://doi.org/10.1002/pds.5109

Khan, N. F., Harrison, S. E., & Rose, P. W. (2010). Validity of diagnostic coding within the General Practice Research Database: A systematic review. *British Journal of General Practice*, *60*(572), e128–e136. https://doi.org/10.3399/bjgp10X483562

Lash, T. L., Fox, M. P., & Fink, A. K. (2009). *Applying quantitative bias analysis to epidemiologic data*. Springer-Verlag.

Lash, T. L., Fox, M. P., MacLehose, R. F., Maldonado, G., McCandless, L. C., & Greenland, S. (2014). Good practices for quantitative bias analysis. *International Journal of Epidemiology*, *43*(6), 1969–1985. https://doi.org/10.1093/ije/dyu149

Lee, W.-J., Lee, T. A., Pickard, A. S., Shoaibi, A., & Schumock, G. T. (2015). Using linked electronic data to validate algorithms for health outcomes in administrative databases. *Journal of Comparative Effectiveness Research*, *4*(4), 359–366. https://doi.org/10.2217/cer.15.14

Pottegård, A., Christensen, R. dePont, Houji, A., Christiansen, C. B., Paulsen, M. S., Thomsen, J. L., & Hallas, J. (2014). Primary non-adherence in general practice: A Danish register study. *European Journal of Clinical Pharmacology*, *70*(6), 757–763. https://doi.org/10.1007/s00228-014-1677-y

Pye, S. R., Sheppard, T., Joseph, R. M., Lunt, M., Girard, N., Haas, J. S., Bates, D. W., Buckeridge, D. L., van Staa, T. P., Tamblyn, R., & Dixon, W. G. (2018). Assumptions made when preparing drug exposure data for analysis have an impact on results: An unreported step in pharmacoepidemiology studies. *Pharmacoepidemiology and Drug Safety*, *27*(7), 781–788. https://doi.org/10.1002/pds.4440

Schneeweiss, S., & Avorn, J. (2005). A review of uses of health care utilization databases for epidemiologic research on therapeutics. *Journal of Clinical Epidemiology*, *58*(4), 323–337. https://doi.org/10.1016/j.jclinepi.2004.10.012

Yih, W. K. Quantitative Bias Analysis Methodology Development: Sequential Bias Adjustment for Outcome Misclassification. *Final Report*. https://www.sentinelinitiative.org/sites/default/files/Methods/Sentinel_Methods_Sequential_bias.pdf

Yland, J. J., Wesselink, A. K., Lash, T. L., & Fox, M. P. (2022). Misconceptions About the Direction of Bias From Nondifferential Misclassification. *American Journal of Epidemiology*, *191*(8), 1485–1495. https://doi.org/10.1093/aje/kwac035

7. Effect measure modification and interaction

Altman, D. G., & Bland, J. M. (2003). Interaction revisited: The difference between two estimates. *BMJ*, *326*(7382), 219. https://doi.org/10.1136/bmj.326.7382.219

Bours, M. J. L. (2021). Tutorial: A nontechnical explanation of the counterfactual definition of effect modification and interaction. *Journal of Clinical Epidemiology*, *134*, 113–124. https://doi.org/10.1016/j.jclinepi.2021.01.022

Chandan, J. S., Zemedikun, D. T., Thayakaran, R., Byne, N., Dhalla, S., Acosta-Mena, D., Gokhale, K. M., Thomas, T., Sainsbury, C., Subramanian, A., Cooper, J., Anand, A., Okoth, K. O., Wang, J.,

The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
(ENCePP) Guide on Methodological Standards in Pharmacoepidemiology
EMA/228452/2023   Page 22/76

Adderley, N. J., Taverner, T., Denniston, A. K., Lord, J., Thomas, G. N., … Haroon, S. (2021). Nonsteroidal Antiinflammatory Drugs and Susceptibility to COVID-19. *Arthritis & Rheumatology*, *73*(5), 731–739. https://doi.org/10.1002/art.41593

Cohen, J. B., D'Agostino McGowan, L., Jensen, E. T., Rigdon, J., & South, A. M. (2021). Evaluating sources of bias in observational studies of angiotensin-converting enzyme inhibitor/angiotensin II receptor blocker use during COVID-19: Beyond confounding. *Journal of Hypertension*, *39*(4), 795. https://doi.org/10.1097/HJH.0000000000002706

Corraini, P., Olsen, M., Pedersen, L., Dekkers, O. M., & Vandenbroucke, J. P. (2017). Effect modification, interaction and mediation: An overview of theoretical insights for clinical investigators. *Clinical Epidemiology*, *9*, 331–338. https://doi.org/10.2147/CLEP.S129728

Hosmer, D. W., & Lemeshow, S. (1992). Confidence Interval Estimation of Interaction. *Epidemiology*, *3*(5), 452. https://journals.lww.com/epidem/Abstract/1992/09000/Confidence_Interval_Estimation_of_Interaction.12.aspx

Igelström, E., Craig, P., Lewsey, J., Lynch, J., Pearce, A., & Katikireddi, S. V. (2022). Causal inference and effect estimation using observational data. *Journal of Epidemiology and Community Health*, *76*(11), 960–966. https://doi.org/10.1136/jech-2022-219267

Karmakar, B., Heller, R., & Small, D. S. (2018). False discovery rate control for effect modification in observational studies. *Electronic Journal of Statistics*, *12*(2), 3232–3253. https://doi.org/10.1214/18-EJS1476

Knol, M. J., & VanderWeele, T. J. (2012). Recommendations for presenting analyses of effect modification and interaction. *International Journal of Epidemiology*, *41*(2), 514–520. https://doi.org/10.1093/ije/dyr218

Knol, M. J., VanderWeele, T. J., Groenwold, R. H. H., Klungel, O. H., Rovers, M. M., & Grobbee, D. E. (2011). Estimating measures of interaction on an additive scale for preventive exposures. *European Journal of Epidemiology*, *26*(6), 433–438. https://doi.org/10.1007/s10654-011-9554-9

Langan, S. M., Schmidt, S. A., Wing, K., Ehrenstein, V., Nicholls, S. G., Filion, K. B., Klungel, O., Petersen, I., Sorensen, H. T., Dixon, W. G., Guttmann, A., Harron, K., Hemkens, L. G., Moher, D., Schneeweiss, S., Smeeth, L., Sturkenboom, M., Elm, E. von, Wang, S. V., & Benchimol, E. I. (2018). The reporting of studies conducted using observational routinely collected health data statement for pharmacoepidemiology (RECORD-PE). *BMJ*, *363*, k3532. https://doi.org/10.1136/bmj.k3532

Moher, D., Hopewell, S., Schulz, K. F., Montori, V., Gøtzsche, P. C., Devereaux, P. J., Elbourne, D., Egger, M., & Altman, D. G. (2010). CONSORT 2010 Explanation and Elaboration: Updated guidelines for reporting parallel group randomised trials. *Journal of Clinical Epidemiology*, *63*(8), e1–e37. https://doi.org/10.1016/j.jclinepi.2010.03.004

Musgrove, R., Carr, M. J., Kapur, N., Chew-Graham, C. A., Mughal, F., Ashcroft, D. M., & Webb, R. T. (2022). Suicide and death by other causes among patients with a severe mental illness: Cohort study comparing risks among patients discharged from inpatient care v. those treated in the community. *Epidemiology and Psychiatric Sciences*, *31*, e32. https://doi.org/10.1017/S2045796022000075

Pradhan, R., Lu, S., Yin, H., Yu, O. H. Y., Ernst, P., Suissa, S., & Azoulay, L. (2022). Novel antihyperglycaemic drugs and prevention of chronic obstructive pulmonary disease exacerbations among patients with type 2 diabetes: Population based cohort study. *BMJ*, *379*, e071380. https://doi.org/10.1136/bmj-2022-071380

Spiegelman, D., & VanderWeele, T. J. (2017). Evaluating Public Health Interventions: 6. Modeling Ratios or Differences? Let the Data Tell Us. *American Journal of Public Health*, *107*(7), 1087–1091. https://doi.org/10.2105/AJPH.2017.303810

Tharmarajah, E., Buazon, A., Patel, V., Hannah, J. R., Adas, M., Allen, V. B., Bechman, K., Clarke, B. D., Nagra, D., Norton, S., Russell, M. D., Rutherford, A. I., Yates, M., & Galloway, J. B. (2021). IL-6 inhibition in the treatment of COVID-19: A meta-analysis and meta-regression. *Journal of Infection*, *82*(5), 178–185. https://doi.org/10.1016/j.jinf.2021.03.008

Vandenbroucke, J. P., von Elm, E., Altman, D. G., Gøtzsche, P. C., Mulrow, C. D., Pocock, S. J., Poole, C., Schlesselman, J. J., Egger, M., & Initiative, for the S. (2007). Strengthening the Reporting of Observational Studies in Epidemiology (STROBE): Explanation and Elaboration. *Epidemiology*, *18*(6), 805. https://doi.org/10.1097/EDE.0b013e3181577511

8. Approaches to data collection

8.1. Primary data collection

Abenhaim, L., Moride, Y., Brenot, F., Rich, S., Benichou, J., Kurz, X., Higenbottam, T., Oakley, C., Wouters, E., Aubier, M., Simonneau, G., & Bégaud, B. (1996). Appetite-Suppressant Drugs and the Risk of Primary Pulmonary Hypertension. New England Journal of Medicine, 335(9), 609–616. https://doi.org/10.1056/NEJM199608293350901

Artime, E., Qizilbash, N., Garrido-Estepa, M., Vora, P., Soriano-Gabarró, M., Asiimwe, A., & Pocock, S. (2019). Are risk minimization measures for approved drugs in Europe effective? A systematic review. Expert Opinion on Drug Safety, 18(5), 443–454. https://doi.org/10.1080/14740338.2019.1612875

Artime, E., Qizilbash, N., Herruzo, R., & Garrido-Estepa, M. (2020). Risk Minimisation Evaluation with Process Indicators and Behavioural or Health Outcomes in Europe: Systematic Review. Pharmaceutical Medicine, 34(6), 387–400. https://doi.org/10.1007/s40290-020-00361-w

Check, J., & Schutt, R. (2011). Research Methods in Education. Sage Publications.

Good pharmacovigilance practices [Text]. European Medicines Agency. https://www.ema.europa.eu/en/human-regulatory/post-authorisation/pharmacovigilance/good-pharmacovigilance-practices

EMA. (2018b, September 17). ICH E6 (R2) Good clinical practice—Scientific guideline - European Medicines Agency. https://www.ema.europa.eu/en/ich-e6-r2-good-clinical-practice-scientific-guideline

Fayers, P. M., & Machin, D. (2016). Quality of Life: The assessment, analysis and interpretation of patient-related outcomes (3rd ed.). Wiley.

FDA/CDER/"Rosenberg, L. M. (2019). REMS Assessment: Planning and Reporting Guidance for Industry.

Fischer, F., & Kleen, S. (2021). Possibilities, Problems, and Perspectives of Data Collection by Mobile Apps in Longitudinal Epidemiological Studies: Scoping Review. Journal of Medical Internet Research, 23(1), e17691. https://doi.org/10.2196/17691

Groves, R. M., Fowler, F. J., & Couper, M. P. (2009). Survey Methodology (2nd ed.). Wiley.

Kaufman, D. W., Rosenberg, L., & Mitchell, A. A. (2001). Signal generation and clarification: Use of case–control data. Pharmacoepidemiology and Drug Safety, 10(3), 197–203. https://doi.org/10.1002/pds.571

Kish, L. (1995). Survey Sampling. Wiley.

Menni, C., May, A., Polidori, L., Louca, P., Wolf, J., Capdevila, J., Hu, C., Ourselin, S., Steves, C. J., Valdes, A. M., & Spector, T. D. (2022). COVID-19 vaccine waning and effectiveness and side-effects of boosters: A prospective community study from the ZOE COVID Study. The Lancet Infectious Diseases, 22(7), 1002–1010. https://doi.org/10.1016/S1473-3099(22)00146-3

Regulation (EU) No 536/2014 of the European Parliament and of the Council of 16 April 2014 on clinical trials on medicinal products for human use. https://eur-lex.europa.eu/eli/reg/2014/536/oj/eng

Research, C. for D. E. and. (2020, May 5). Survey Methodologies to Assess REMS Goals That Relate to Knowledge. U.S. Food and Drug Administration; FDA. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/survey-methodologies-assess-rems-goals-relate-knowledge

Roujeau, J.-C., Kelly, J. P., Naldi, L., Rzany, B., Stern, R. S., Anderson, T., Auquier, A., Bastuji-Garin, S., Correia, O., Locati, F., Mockenhaupt, M., Paoletti, C., Shapiro, S., Shear, N., Schöpf, E., & Kaufman, D. W. (1995). Medication Use and the Risk of Stevens–Johnson Syndrome or Toxic Epidermal Necrolysis. New England Journal of Medicine, 333(24), 1600–1608. https://doi.org/10.1056/NEJM199512143332404

Shapiro, S. (1983). The design of a study of the drug etiology of agranulocytosis and aplastic anemia. European Journal of Clinical Pharmacology, 24(6), 833–836. https://doi.org/10.1007/BF00607096

Smith, M. Y., Russell, A., Bahri, P., Mol, P. G. M., Frise, S., Freeman, E., & Morrato, E. H. (2018). The RIMES Statement: A Checklist to Assess the Quality of Studies Evaluating Risk Minimization Programs for Medicinal Products. Drug Safety, 41(4), 389–401. https://doi.org/10.1007/s40264-017-0619-x

Standard Definitions—AAPOR. (2022, November 11). AAPOR. https://aapor.org/standards-and-ethics/standard-definitions/

8.2. Secondary use of data

Berger, M. L., Sox, H., Willke, R. J., Brixner, D. L., Eichler, H.-G., Goettsch, W., Madigan, D., Makady, A., Schneeweiss, S., Tarricone, R., Wang, S. V., Watkins, J., & Mullins, C. D. (2017). Good Practices for Real-World Data Studies of Treatment and/or Comparative Effectiveness: Recommendations from the Joint ISPOR-ISPE Special Task Force on Real-World Evidence in Health Care Decision Making. Value in Health, 20(8), 1003–1008. https://doi.org/10.1016/j.jval.2017.08.3019

Cave, A., Kurz, X., & Arlett, P. (2019). Real-World Data for Regulatory Decision Making: Challenges and Possible Solutions for Europe. Clinical Pharmacology & Therapeutics, 106(1), 36–39. https://doi.org/10.1002/cpt.1426

ENCePP Resources Database. https://www.encepp.eu/encepp/resourcesDatabase.jsp

Gatto, N. M., Campbell, U. B., Rubinstein, E., Jaksa, A., Mattox, P., Mo, J., & Reynolds, R. F. (2022). The Structured Process to Identify Fit-For-Purpose Data: A Data Feasibility Assessment Framework. Clinical Pharmacology & Therapeutics, 111(1), 122–134. https://doi.org/10.1002/cpt.2466

Gini, R., Sturkenboom, M. C. J., Sultana, J., Cave, A., Landi, A., Pacurariu, A., Roberto, G., Schink, T., Candore, G., Slattery, J., Trifirò, G., & the Working Group 3 of ENCePP (Inventory of EU data sources and methodological approaches for multisource studies). (2020). Different Strategies to Execute Multi-Database Studies for Medicines Surveillance in Real-World Setting: A Reflection on the European Model. Clinical Pharmacology & Therapeutics, 108(2), 228–235. https://doi.org/10.1002/cpt.1833

The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
(ENCePP) Guide on Methodological Standards in Pharmacoepidemiology
EMA/228452/2023   Page 25/76

Guidelines for Good Pharmacoepidemiology Practices (GPP)—International Society for Pharmacoepidemiology. (2022). ISPE. https://www.pharmacoepi.org/resources/policies/guidelines-08027/

Hall, G. C., Sauer, B., Bourke, A., Brown, J. S., Reynolds, M. W., & Casale, R. L. (2012). Guidelines for good database selection and use in pharmacoepidemiology research. Pharmacoepidemiology and Drug Safety, 21(1), 1–10. https://doi.org/10.1002/pds.2229

MHRA guidance on the use of real-world data in clinical studies to support regulatory decisions. (2022). MHRA. https://www.gov.uk/government/publications/mhra-guidance-on-the-use-of-real-world-data-in-clinical-studies-to-support-regulatory-decisions

Research, C. for D. E. (2020). Best Practices for Conducting and Reporting Pharmacoepidemiologic Safety Studies Using Electronic Healthcare Data Sets. FDA. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/best-practices-conducting-and-reporting-pharmacoepidemiologic-safety-studies-using-electronic

Research, C. for D. E. (2021). Considerations for the Use of Real-World Data and Real-World Evidence To Support Regulatory Decision-Making for Drug and Biological Products. FDA. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/considerations-use-real-world-data-and-real-world-evidence-support-regulatory-decision-making-drug

Research, C. for D. E. (2021, December 10). Real-World Data: Assessing Electronic Health Records and Medical Claims Data To Support Regulatory Decision-Making for Drug and Biological Products. U.S. Food and Drug Administration; FDA. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/real-world-data-assessing-electronic-health-records-and-medical-claims-data-support-regulatory

8.3. Patient registries

Bakker, E., Plueschke, K., Jonker, C. J., Kurz, X., Starokozhko, V., & Mol, P. G. M. (2023). Contribution of Real-World Evidence in European Medicines Agency's Regulatory Decision Making. Clinical Pharmacology & Therapeutics, 113(1), 135–151. https://doi.org/10.1002/cpt.2766

Charlton, R., & de Vries, C. Systematic overview of data sources for drug safety in pregnancy research. European Medicies Agency. https://www.encepp.eu/structure/documents/Data_sources_for_medicines_in_pregnancy_research.pdf

Doherty, D. A., Tong, S. Y. C., Reilly, J., Shrapnel, J., McDonald, S., Ahern, S., Harris, I., Tam, C. S., Brennan, A. L., Hodgson, C., Wilcox, L., Balagurunathan, A., Butcher, B. E., & Reid, C. M. (2023). Registry randomised trials: A methodological perspective. BMJ Open, 13(3), e068057. https://doi.org/10.1136/bmjopen-2022-068057

EHDEN Data Partners. Ehden.Eu. https://www.ehden.eu/datapartners/

Good pharmacovigilance practices – European Medicines Agency. https://www.ema.europa.eu/en/human-regulatory/post-authorisation/pharmacovigilance/good-pharmacovigilance-practices

Patient registries, European Medicines Agency. https://www.ema.europa.eu/en/human-regulatory/post-authorisation/patient-registries

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(ENCePP) Guide on Methodological Standards in Pharmacoepidemiology
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Scientific Advice Working Party – European Medicines Agency. https://www.ema.europa.eu/en/committees/working-parties-other-groups/chmp/scientific-advice-working-party

Regulatory science strategy – European Medicines Agency. https://www.ema.europa.eu/en/about-us/how-we-work/regulatory-science-strategy

Big data – European Medicines Agency. https://www.ema.europa.eu/en/about-us/how-we-work/big-data

Multi-stakeholder workshop: Patient experience data in medicines development and regulatory decision-making – European Medicines Agency. https://www.ema.europa.eu/en/events/multi-stakeholder-workshop-patient-experience-data-medicines-development-regulatory-decision-making

Emilsson, L., Lindahl, B., Köster, M., Lambe, M., & Ludvigsson, J. F. (2015). Review of 103 Swedish Healthcare Quality Registries. Journal of Internal Medicine, 277(1), 94–136. https://doi.org/10.1111/joim.12303

ENCePP Resource Database. https://www.encepp.eu/encepp/resourcesDatabase.jsp

EU PAS Register. https://www.encepp.eu/encepp/studiesDatabase.jsp

EUnetHTA Joint Action 3. https://www.eunethta.eu/ja3-archive/

EUROCAT. https://eu-rd-platform.jrc.ec.europa.eu

EUROmediCAT. https://www.euromedicat.eu/euromedisafe/euromedisafeinventory

European Platform on Rare Disease Registration. https://eu-rd-platform.jrc.ec.europa.eu

European Reference Networks (ERNs). (2023, March 8). https://health.ec.europa.eu/european-reference-networks/overview_en

Flynn, R., Plueschke, K., Quinten, C., Strassmann, V., Duijnhoven, R. G., Gordillo-Marañon, M., Rueckbeil, M., Cohet, C., & Kurz, X. (2022). Marketing Authorization Applications Made to the European Medicines Agency in 2018–2019: What was the Contribution of Real-World Evidence? Clinical Pharmacology & Therapeutics, 111(1), 90–97. https://doi.org/10.1002/cpt.2461

Furu, K., Kieler, H., Haglund, B., Engeland, A., Selmer, R., Stephansson, O., Valdimarsdottir, U. A., Zoega, H., Artama, M., Gissler, M., Malm, H., & Nørgaard, M. (2015). Selective serotonin reuptake inhibitors and venlafaxine in early pregnancy and risk of birth defects: Population based cohort study and sibling design. BMJ, 350, h1798. https://doi.org/10.1136/bmj.h1798

Guideline on registry-based studies, EMA. https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-registry-based-studies_en-0.pdf

Hogervorst, M. A., Pontén, J., Vreman, R. A., Mantel-Teeuwisse, A. K., & Goettsch, W. G. (2022). Real World Data in Health Technology Assessment of Complex Health Technologies. Frontiers in Pharmacology, 13, 837302. https://doi.org/10.3389/fphar.2022.837302

Informatics, O. H. D. S. and. The Book of OHDSI. https://ohdsi.github.io/TheBookOfOhdsi/

Karanatsios, B., Prang, K.-H., Verbunt, E., Yeung, J. M., Kelaher, M., & Gibbs, P. (2020). Defining key design elements of registry-based randomised controlled trials: A scoping review. Trials, 21(1), 552. https://doi.org/10.1186/s13063-020-04459-z

The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
(ENCePP) Guide on Methodological Standards in Pharmacoepidemiology
EMA/228452/2023
Page 27/76

Lauer, M. S., & D'Agostino, R. B. (2013). The Randomized Registry Trial—The Next Disruptive Technology in Clinical Research? New England Journal of Medicine, 369(17), 1579–1581. https://doi.org/10.1056/NEJMp1310102

Li, G., Sajobi, T. T., Menon, B. K., Korngut, L., Lowerison, M., James, M., Wilton, S. B., Williamson, T., Gill, S., Drogos, L. L., Smith, E. E., Vohra, S., Hill, M. D., & Thabane, L. (2016). Registry-based randomized controlled trials- what are the advantages, challenges, and areas for future research? Journal of Clinical Epidemiology, 80, 16–24. https://doi.org/10.1016/j.jclinepi.2016.08.003

McGettigan, P., Alonso Olmo, C., Plueschke, K., Castillon, M., Nogueras Zondag, D., Bahri, P., Kurz, X., & Mol, P. G. M. (2019). Patient Registries: An Underused Resource for Medicines Evaluation. Drug Safety, 42(11), 1343–1351. https://doi.org/10.1007/s40264-019-00848-9

Murphy, A., Bere, N., Vamvakas, S., & Mavris, M. (2022). The Added Value of Patient Engagement in Early Dialogue at EMA: Scientific Advice as a Case Study. Frontiers in Medicine, 8. https://www.frontiersin.org/articles/10.3389/fmed.2021.811855

Norwegian Patient Registry (Norsk pasientregister (NPR)). Helsedirektoratet. https://www.helsedirektoratet.no/tema/statistikk-registre-og-rapporter/helsedata-og-helseregistre/norsk-pasientregister-npr

Pacurariu, A., Plueschke, K., Olmo, C. A., & Kurz, X. (2018). Imposed registries within the European postmarketing surveillance system: Extended analysis and lessons learned for regulators. Pharmacoepidemiology and Drug Safety, 27(7), 823–826. https://doi.org/10.1002/pds.4449

PRINTO - Paediatric Rheumatology INternational Trials Organization. https://www.printo.it/projects/ongoing/15

Qualification opinion—The European Cystic Fibrosis Society Patient Registry (ECFSPR), EMA. https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/qualification-opinion-european-cystic-fibrosis-society-patient-registry-ecfspr_en.pdf

Registries for Evaluating Patient Outcomes: A User's Guide: 4th Edition | Effective Health Care (EHC) Program. https://effectivehealthcare.ahrq.gov/products/registries-guide-4th-edition/users-guide

REQueST Tool and its vision paper—EUnetHTA. (2019, October 10). https://www.eunethta.eu/request-tool-and-its-vision-paper/

Research, C. for D. E. (2020, May 15). Postapproval Pregnancy Safety Studies Guidance for Industry. U.S. Food and Drug Administration; FDA. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/postapproval-pregnancy-safety-studies-guidance-industry

Research, C. for D. E. (2021, November 29). Real-World Data: Assessing Registries to Support Regulatory Decision-Making for Drug and Biological Products Guidance for Industry. U.S. Food and Drug Administration; FDA. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/real-world-data-assessing-registries-support-regulatory-decision-making-drug-and-biological-products

RESERVED, I. U.-A. R. Orphanet. http://www.orpha.net/consor/www/cgi-bin/index.php?lng=EN

Schmidt, M., Schmidt, S. A. J., Sandegaard, J. L., Ehrenstein, V., Pedersen, L., & Sørensen, H. T. (2015). The Danish National Patient Registry: A review of content, data quality, and research potential. Clinical Epidemiology, 7, 449–490. https://doi.org/10.2147/CLEP.S91125

Swedish National Patient Register. (2022, January 14). Socialstyrelsen. https://www.socialstyrelsen.se/en/statistics-and-data/registers/national-patient-register/

Teixeira, M. M., Borges, F. C., Ferreira, P. S., Rocha, J., Sepodes, B., & Torre, C. (2022). A review of patient-reported outcomes used for regulatory approval of oncology medicinal products in the European Union between 2017 and 2020. Frontiers in Medicine, 9. https://www.frontiersin.org/articles/10.3389/fmed.2022.968272

8.4. Spontaneous reports

Note: Chapter 8.4 has not been updated for the 11th revision of the Guide

Al Dweik, R., Stacey, D., Kohen, D., & Yaya, S. (2017). Factors affecting patient reporting of adverse drug reactions: A systematic review. British Journal of Clinical Pharmacology, 83(4), 875–883. https://doi.org/10.1111/bcp.13159

Alvarez, Y., Hidalgo, A., Maignen, F., & Slattery, J. (2010). Validation of Statistical Signal Detection Procedures in EudraVigilance Post-Authorization Data. Drug Safety, 33(6), 475–487. https://doi.org/10.2165/11534410-000000000-00000

Aronson, J. K., & Hauben, M. (2006). Anecdotes that provide definitive evidence. BMJ, 333(7581), 1267–1269. https://doi.org/10.1136/bmj.39036.666389.94

Banovac, M., Candore, G., Slattery, J., Houÿez, F., Haerry, D., Genov, G., & Arlett, P. (2017). Patient Reporting in the EU: Analysis of EudraVigilance Data. Drug Safety, 40(7), 629–645. https://doi.org/10.1007/s40264-017-0534-1

Bate, A., Lindquist, M., & Edwards, I. r. (2008). The application of knowledge discovery in databases to post-marketing drug safety: Example of the WHO database. Fundamental & Clinical Pharmacology, 22(2), 127–140. https://doi.org/10.1111/j.1472-8206.2007.00552.x

Centre, U. M. VigiBase. Uppsala Monitoring Centre. https://who-umc.org/vigibase/

Detailed guide regarding the EudraVigilance data management activities by the European Medicines Agency Rev 1. https://www.ema.europa.eu/en/documents/other/detailed-guide-regarding-eudravigilance-data-management-activities-european-medicines-agency_en.pdf

EudraVigilance. (2018, September 17). European Medicines Agency. https://www.ema.europa.eu/en/human-regulatory/research-development/pharmacovigilance/eudravigilance

ICPE 2012 Abstracts. (2012). Pharmacoepidemiology and Drug Safety, 21(s3), 1–481. https://doi.org/10.1002/pds.3324

Inácio, P., Cavaco, A., & Airaksinen, M. (2017). The value of patient reporting to the pharmacovigilance system: A systematic review. British Journal of Clinical Pharmacology, 83(2), 227–246. https://doi.org/10.1111/bcp.13098

Kreimeyer, K., Menschik, D., Winiecki, S., Paul, W., Barash, F., Woo, E. J., Alimchandani, M., Arya, D., Zinderman, C., Forshee, R., & Botsis, T. (2017). Using Probabilistic Record Linkage of Structured and Unstructured Data to Identify Duplicate Cases in Spontaneous Adverse Event Reporting Systems. Drug Safety, 40(7), 571–582. https://doi.org/10.1007/s40264-017-0523-4

Pacurariu, A. C., Coloma, P. M., van Haren, A., Genov, G., Sturkenboom, M. C. J. M., & Straus, S. M. J. M. (2014). A Description of Signals During the First 18 Months of the EMA Pharmacovigilance Risk Assessment Committee. Drug Safety, 37(12), 1059–1066. https://doi.org/10.1007/s40264-014-0240-1

The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) Guide on Methodological Standards in Pharmacoepidemiology
EMA/228452/2023

Page 29/76

Postigo, R., Brosch, S., Slattery, J., van Haren, A., Dogné, J.-M., Kurz, X., Candore, G., Domergue, F., & Arlett, P. (2018). EudraVigilance Medicines Safety Database: Publicly Accessible Data for Research and Public Health Protection. Drug Safety, 41(7), 665–675. https://doi.org/10.1007/s40264-018-0647-1

Practical Aspects of Signal Detection in Pharmacovigilance: Report of CIOMS Working Group VIII • COUNCIL FOR INTERNATIONAL ORGANIZATIONS OF MEDICAL SCIENCES. (2010). CIOMS. https://cioms.ch/publications/product/practical-aspects-of-signal-detection-in-pharmacovigilance-report-of-cioms-working-group-viii/

Research, C. for B. E. and. (2021). VAERS Overview. FDA. https://www.fda.gov/vaccines-blood-biologics/vaccine-adverse-events/vaers-overview

Research, C. for D. E. and. (2019, May 22). Questions and Answers on FDA's Adverse Event Reporting System (FAERS). FDA. https://www.fda.gov/drugs/surveillance/questions-and-answers-fdas-adverse-event-reporting-system-faers

Tregunno, P. M., Fink, D. B., Fernandez-Fernandez, C., Lázaro-Bengoa, E., & Norén, G. N. (2014). Performance of Probabilistic Method to Detect Duplicate Individual Case Safety Reports. Drug Safety, 37(4), 249–258. https://doi.org/10.1007/s40264-014-0146-y

8.5. Social media

Audeh, B., Bellet, F., Beyens, M.-N., Lillo-Le Louët, A., & Bousquet, C. (2020). Use of Social Media for Pharmacovigilance Activities: Key Findings and Recommendations from the Vigi4Med Project. Drug Safety, 43(9), 835–851. https://doi.org/10.1007/s40264-020-00951-2

Bahri, P. (Ed.). (2020). Communicating about Risks and Safe Use of Medicines: Real Life and Applied Research. Springer. https://doi.org/10.1007/978-981-15-3013-5

Banerjee, A. K., & Ingate, S. (2012). Web-Based Patient-Reported Outcomes in Drug Safety and Risk Management. Drug Safety, 35(6), 437–446. https://doi.org/10.2165/11632390-000000000-00000

Bhattacharya, M., Snyder, S., Malin, M., Truffa, M. M., Marinic, S., Engelmann, R., & Raheja, R. R. (2017). Using Social Media Data in Routine Pharmacovigilance: A Pilot Study to Identify Safety Signals and Patient Perspectives. Pharmaceutical Medicine, 31(3), 167–174. https://doi.org/10.1007/s40290-017-0186-6

Brosch, S., de Ferran, A.-M., Newbould, V., Farkas, D., Lengsavath, M., & Tregunno, P. (2019). Establishing a Framework for the Use of Social Media in Pharmacovigilance in Europe. Drug Safety, 42(8), 921–930. https://doi.org/10.1007/s40264-019-00811-8

Caster, O., Dietrich, J., Kürzinger, M.-L., Lerch, M., Maskell, S., Norén, G. N., Tcherny-Lessenot, S., Vroman, B., Wisniewski, A., & van Stekelenborg, J. (2018). Assessment of the Utility of Social Media for Broad-Ranging Statistical Signal Detection in Pharmacovigilance: Results from the WEB-RADR Project. Drug Safety, 41(12), 1355–1369. https://doi.org/10.1007/s40264-018-0699-2

Cocos, A., Fiks, A. G., & Masino, A. J. (2017). Deep learning for pharmacovigilance: Recurrent neural network architectures for labeling adverse drug reactions in Twitter posts. Journal of the American Medical Informatics Association, 24(4), 813–821. https://doi.org/10.1093/jamia/ocw180

Coloma, P. M., Becker, B., Sturkenboom, M. C. J. M., van Mulligen, E. M., & Kors, J. A. (2015). Evaluating Social Media Networks in Medicines Safety Surveillance: Two Case Studies. Drug Safety, 38(10), 921–930. https://doi.org/10.1007/s40264-015-0333-5

Dasgupta, N., Winokur, C., & Pierce, C. (2020). Social Media Research. In P. Bahri (Ed.), Communicating about Risks and Safe Use of Medicines: Real Life and Applied Research (pp. 307–332). Springer. https://doi.org/10.1007/978-981-15-3013-5_11

EMA. (2018, September 17). Good pharmacovigilance practices. European Medicines Agency. https://www.ema.europa.eu/en/human-regulatory/post-authorisation/pharmacovigilance/good-pharmacovigilance-practices

ENISA. https://www.enisa.europa.eu

European Commission's Digital Single Market Glossary. Shaping Europe's Digital Future - European Commission. https://wayback.archive-it.org/12090/20210302044434/https://ec.europa.eu/digital-single-market/en/glossary

Gattepaille, L. M., Hedfors Vidlin, S., Bergvall, T., Pierce, C. E., & Ellenius, J. (2020). Prospective Evaluation of Adverse Event Recognition Systems in Twitter: Results from the Web-RADR Project. Drug Safety, 43(8), 797–808. https://doi.org/10.1007/s40264-020-00942-3

General Data Protection Regulation (GDPR) Compliance Guidelines. GDPR.Eu. https://gdpr.eu/

Martin, S., Kilich, E., Dada, S., Kummervold, P. E., Denny, C., Paterson, P., & Larson, H. J. (2020). "Vaccines for pregnant women…?! Absurd" – Mapping maternal vaccination discourse and stance on social media over six months. Vaccine, 38(42), 6627–6637. https://doi.org/10.1016/j.vaccine.2020.07.072

Note: Chapter 8.5 has not been updated for the 11th revision of the Guide

Opinion 1/2015 Mobile Health-Reconciling technological innovation with data protection—EDPS. https://edps.europa.eu/sites/edp/files/publication/15-05-21_mhealth_en_0.pdf

Powell, G. E., Seifert, H. A., Reblin, T., Burstein, P. J., Blowers, J., Menius, J. A., Painter, J. L., Thomas, M., Pierce, C. E., Rodriguez, H. W., Brownstein, J. S., Freifeld, C. C., Bell, H. G., & Dasgupta, N. (2016). Social Media Listening for Routine Post-Marketing Safety Surveillance. Drug Safety, 39(5), 443–454. https://doi.org/10.1007/s40264-015-0385-6

Sloane, R., Osanlou, O., Lewis, D., Bollegala, D., Maskell, S., & Pirmohamed, M. (2015). Social media and pharmacovigilance: A review of the opportunities and challenges. British Journal of Clinical Pharmacology, 80(4), 910–920. https://doi.org/10.1111/bcp.12717

Smartphone Secure Development Guidelines. [Report/Study]. ENISA. https://www.enisa.europa.eu/publications/smartphone-secure-development-guidelines-2016

van Stekelenborg, J., Ellenius, J., Maskell, S., Bergvall, T., Caster, O., Dasgupta, N., Dietrich, J., Gama, S., Lewis, D., Newbould, V., Brosch, S., Pierce, C. E., Powell, G., Ptaszyńska-Neophytou, A., Wiśniewski, A. F. Z., Tregunno, P., Norén, G. N., & Pirmohamed, M. (2019). Recommendations for the Use of Social Media in Pharmacovigilance: Lessons from IMI WEB-RADR. Drug Safety, 42(12), 1393–1407. https://doi.org/10.1007/s40264-019-00858-7

9. Research networks for multi-database studies

Arrhythmogenic potential of drugs | ARITMO Project | Fact Sheet | FP7 | CORDIS | European Commission. https://cordis.europa.eu/project/id/241679

Association of angiotensin converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARB) on coronavirus disease (COVID-19) incidence and complications. EU PAS Register. https://www.encepp.eu/encepp/viewResource.htm?id=35854

Background rates of Adverse Events of Special Interest for monitoring COVID-19 vaccines. EU PAS Register. https://www.encepp.eu/encepp/viewResource.htm?id=40361

Becker, B. F. H., Avillach, P., Romio, S., van Mulligen, E. M., Weibel, D., Sturkenboom, M. C. J. M., Kors, J. A., & Consortium, for the A. (2017). CodeMapper: Semiautomatic coding of case definitions. A contribution from the ADVANCE project. Pharmacoepidemiology and Drug Safety, 26(8), 998–1005. https://doi.org/10.1002/pds.4245

Bots, S. H., Riera-Arnau, J., Belitser, S. V., Messina, D., Aragón, M., Alsina, E., Douglas, I. J., Durán, C. E., García-Poza, P., Gini, R., Herings, R. M. C., Huerta, C., Sisay, M. M., Martín-Pérez, M., Martin, I., Overbeek, J. A., Paoletti, O., Pallejà-Millán, M., Schultze, A., … Sturkenboom, M. C. J. M. (2022). Myocarditis and pericarditis associated with SARS-CoV-2 vaccines: A population-based descriptive cohort and a nested self-controlled risk interval study using electronic health care data from four European countries. Frontiers in Pharmacology, 13, 1038043. https://doi.org/10.3389/fphar.2022.1038043

Brown, J. S., Mendelsohn, A. B., Nam, Y. H., Maro, J. C., Cocoros, N. M., Rodriguez-Watson, C., Lockhart, C. M., Platt, R., Ball, R., Dal Pan, G. J., & Toh, S. (2022). The US Food and Drug Administration Sentinel System: A national resource for a learning health system. Journal of the American Medical Informatics Association, 29(12), 2191–2200. https://doi.org/10.1093/jamia/ocac153

Burn, E., Duarte-Salles, T., Fernandez-Bertolin, S., Reyes, C., Kostka, K., Delmestri, A., Rijnbeek, P., Verhamme, K., & Prieto-Alhambra, D. (2022). Venous or arterial thrombosis and deaths among COVID-19 cases: A European network cohort study. The Lancet Infectious Diseases, 22(8), 1142–1152. https://doi.org/10.1016/S1473-3099(22)00223-7

Candore, G., Hedenmalm, K., Slattery, J., Cave, A., Kurz, X., & Arlett, P. (2020). Can We Rely on Results From IQVIA Medical Research Data UK Converted to the Observational Medical Outcome Partnership Common Data Model? Clinical Pharmacology & Therapeutics, 107(4), 915–925. https://doi.org/10.1002/cpt.1785

CNODES | Canadian Network for Observational Drug Effects Studies. CNODES. https://www.cnodes.ca/

Comment devenir pharmacien ? - Sos Nsaids Project. (2020, June 5). https://www.sos-nsaids-project.org/

ConcePTION. https://www.imi-conception.eu/

Data Analysis and Real World Interrogation Network (DARWIN EU®). DARWIN EU. https://darwin-eu.org/

DataQualityDashboard. (2023). [JavaScript]. Observational Health Data Sciences and Informatics. https://github.com/OHDSI/DataQualityDashboard (Original work published 2019)

Dedman, D., Cabecinha, M., Williams, R., Evans, S. J. W., Bhaskaran, K., & Douglas, I. J. (2020). Approaches for combining primary care electronic health record data from multiple sources: A systematic review of observational studies. BMJ Open, 10(10), e037405. https://doi.org/10.1136/bmjopen-2020-037405

Description of international collaboration in the area of medicines use and effects in COVID-19 affected pregnancies (CONSIGN-International). EU PAS Register. https://www.encepp.eu/encepp/viewResource.htm?id=40318

The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) Guide on Methodological Standards in Pharmacoepidemiology
EMA/228452/2023

Page 32/76

Monitoring of COVID-19 medicines. European Medicines Agency.
https://www.ema.europa.eu/en/human-regulatory/overview/public-health-threats/coronavirus-disease-covid-19/treatments-vaccines/monitoring-covid-19-medicines-0

EMIF. http://www.emif.eu/

ENCePP Resources Database. ENCePP. https://www.encepp.eu/encepp/resourcesDatabase.jsp

EUROmediCAT. https://www.euromedicat.eu/

European Health Data Evidence Network (EHDEN). https://www.ehden.eu/

European Health Data Space. https://health.ec.europa.eu/ehealth-digital-health-and-care/european-health-data-space_en

Exploring and understanding adverse drug reactions by integrative mining of clinical records and biomedical knowledge | EU-ADR Project | Fact Sheet | FP7 | CORDIS | European Commission.
https://cordis.europa.eu/project/id/215847

Flynn, R., Hedenmalm, K., Murray-Thomas, T., Pacurariu, A., Arlett, P., Shepherd, H., Myles, P., & Kurz, X. (2020). Ability of Primary Care Health Databases to Assess Medicinal Products Discussed by the European Union Pharmacovigilance Risk Assessment Committee. Clinical Pharmacology & Therapeutics, 107(4), 957–965. https://doi.org/10.1002/cpt.1775

Gedeborg, R., Igl, W., Svennblad, B., Wilén, P., Delcoigne, B., Michaëlsson, K., Ljung, R., & Feltelius, N. (2023). Federated analyses of multiple data sources in drug safety studies. Pharmacoepidemiology and Drug Safety, 32(3), 279–286. https://doi.org/10.1002/pds.5587

Gini, R., Schuemie, M., Brown, J., Ryan, P., Vacchi, E., Coppola, M., Cazzola, W., Coloma, P., Berni, R., Diallo, G., Oliveira, J., Avillach, P., Trifiro, G., Rijnbeek, P., Bellentani, M., Lei, J., Klazinga, N., & Sturkenboom, M. (2016). Data Extraction and Management in Networks of Observational Health Care Databases for Scientific Research: A Comparison of EU-ADR, OMOP, Mini-Sentinel and MATRICE Strategies (No. 1). 4(1), Art. 1. https://doi.org/10.13063/2327-9214.1189

Gini, R., Sturkenboom, M. C. J., Sultana, J., Cave, A., Landi, A., Pacurariu, A., Roberto, G., Schink, T., Candore, G., Slattery, J., Trifirò, G., & the Working Group 3 of ENCePP (Inventory of EU data sources and methodological approaches for multisource studies). (2020). Different Strategies to Execute Multi-Database Studies for Medicines Surveillance in Real-World Setting: A Reflection on the European Model. Clinical Pharmacology & Therapeutics, 108(2), 228–235. https://doi.org/10.1002/cpt.1833

Global Research in Paediatrics | GRIP Project | Fact Sheet | FP7 | CORDIS | European Commission.
https://cordis.europa.eu/project/id/261060

IMI Innovative Medicines Initiative. http://www.imi.europa.eu/

IMI Innovative Medicines Initiative | PROTECT | Pharmacoepidemiological research on outcomes of therapeutics by a European consortium. (2009, September 1). IMI Innovative Medicines Initiative.
http://www.imi.europa.eu/projects-results/project-factsheets/protect

Improving Consistency and Understanding of Discrepancies of Findings from Pharmacoepidemiological Studies: The IMI PROTECT Project. (2016). Pharmacoepidemiology and Drug Safety, 25(S1), Art. S1.
https://doi.org/10.1002/pds.3987

Izem, R., Huang, T.-Y., Hou, L., Pestine, E., Nguyen, M., & Maro, J. C. (2020). Quantifying how small variations in design elements affect risk in an incident cohort study in claims. Pharmacoepidemiology and Drug Safety, 29(1), 84–93. https://doi.org/10.1002/pds.4892

The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
(ENCePP) Guide on Methodological Standards in Pharmacoepidemiology
EMA/228452/2023   Page 33/76

Joint Action Towards the European Health Data Space – TEHDAS. Tehdas. https://tehdas.eu/

Kahn, M. G., Callahan, T. J., Barnard, J., Bauck, A. E., Brown, J., Davidson, B. N., Estiri, H., Goerg, C., Holve, E., Johnson, S. G., Liaw, S.-T., Hamilton-Lopez, M., Meeker, D., Ong, T. C., Ryan, P., Shang, N., Weiskopf, N. G., Weng, C., Zozus, M. N., & Schilling, L. (2016). A Harmonized Data Quality Assessment Terminology and Framework for the Secondary Use of Electronic Health Record Data. EGEMs, 4(1), 1244. https://doi.org/10.13063/2327-9214.1244

Klungel, O. H., Kurz, X., de Groot, M. C. H., Schlienger, R. G., Tcherny-Lessenot, S., Grimaldi, L., Ibáñez, L., Groenwold, R. H. H., & Reynolds, R. F. (2016). Multi-centre, multi-database studies with common protocols: Lessons learnt from the IMI PROTECT project. Pharmacoepidemiology and Drug Safety, 25(S1), 156–165. https://doi.org/10.1002/pds.3968

Kurz, X., Domergue, F., Slattery, J., Segec, A., Szmigiel, A., & Hidalgo-Simon, A. (2011). Safety monitoring of Influenza A/H1N1 pandemic vaccines in EudraVigilance. Vaccine, 29(26), 4378–4387. https://doi.org/10.1016/j.vaccine.2011.04.005

Lane, J. C. E., Weaver, J., Kostka, K., Duarte-Salles, T., Abrahao, M. T. F., Alghoul, H., Alser, O., Alshammari, T. M., Biedermann, P., Banda, J. M., Burn, E., Casajust, P., Conover, M. M., Culhane, A. C., Davydov, A., DuVall, S. L., Dymshyts, D., Fernandez-Bertolin, S., Fišter, K., … Prieto-Alhambra, D. (2020). Risk of hydroxychloroquine alone and in combination with azithromycin in the treatment of rheumatoid arthritis: A multinational, retrospective study. The Lancet Rheumatology, 2(11), e698–e711. https://doi.org/10.1016/S2665-9913(20)30276-9

Li, X., Burn, E., Duarte-Salles, T., Yin, C., Reich, C., Delmestri, A., Verhamme, K., Rijnbeek, P., Suchard, M. A., Li, K., Mosseveld, M., John, L. H., Mayer, M.-A., Ramirez-Anguita, J.-M., Cohet, C., Strauss, V., & Prieto-Alhambra, D. (2022). Comparative risk of thrombosis with thrombocytopenia syndrome or thromboembolic events associated with different covid-19 vaccines: International network cohort study from five European countries and the US. BMJ, 379, e071594. https://doi.org/10.1136/bmj-2022-071594

Li, X., Ostropolets, A., Makadia, R., Shoaibi, A., Rao, G., Sena, A. G., Martinez-Hernandez, E., Delmestri, A., Verhamme, K., Rijnbeek, P. R., Duarte-Salles, T., Suchard, M. A., Ryan, P. B., Hripcsak, G., & Prieto-Alhambra, D. (2021). Characterising the background incidence rates of adverse events of special interest for covid-19 vaccines in eight countries: Multinational network cohort study. BMJ, 373, n1435. https://doi.org/10.1136/bmj.n1435

OHDSI – Observational Health Data Sciences and Informatics. https://www.ohdsi.org/

Overhage, J. M., Ryan, P. B., Reich, C. G., Hartzema, A. G., & Stang, P. E. (2012). Validation of a common data model for active safety surveillance research. Journal of the American Medical Informatics Association, 19(1), 54–60. https://doi.org/10.1136/amiajnl-2011-000376

Platt, R., Carnahan, R. M., Brown, J. S., Chrischilles, E., Curtis, L. H., Hennessy, S., Nelson, J. C., Racoosin, J. A., Robb, M., Schneeweiss, S., Toh, S., & Weiner, M. G. (2012). The U.S. Food and Drug Administration's Mini-Sentinel program: Status and direction. Pharmacoepidemiology and Drug Safety, 21(S1), 1–8. https://doi.org/10.1002/pds.2343

Reilev, M., Jensen, P. B., Ranch, L. S., Egeberg, A., Furu, K., Gembert, K., Hagg, D., Haug, U., Karlstad, Ø., Reutfors, J., Schäfer, W., Schwartz, S., Smits, E., Holthius, E., Herings, R., Trifirò, G., Kirchmayer, U., Rosa, A. C., Belleudi, V., … Hallas, J. (2023). Methodology of the brodalumab assessment of hazards: A multicentre observational safety (BRAHMS) study. BMJ Open, 13(2), e066057. https://doi.org/10.1136/bmjopen-2022-066057

Research, C. for D. E. and. (2023, February 8). FDA's Sentinel Initiative. FDA; FDA. https://www.fda.gov/safety/fdas-sentinel-initiative

Russek, M., Quinten, C., de Jong, V. M. T., Cohet, C., & Kurz, X. (2023). Assessing heterogeneity of electronic health-care databases: A case study of background incidence rates of venous thromboembolism. Pharmacoepidemiology and Drug Safety. https://doi.org/10.1002/pds.5631

Safety Evaluation of Adverse Reactions in Diabetes | SAFEGUARD Project | Fact Sheet | FP7 | CORDIS | European Commission. https://cordis.europa.eu/project/id/282521

Schuemie, M. J., Ryan, P. B., Pratt, N., Chen, R., You, S. C., Krumholz, H. M., Madigan, D., Hripcsak, G., & Suchard, M. A. (2020). Large-scale evidence generation and evaluation across a network of databases (LEGEND): Assessing validity using hypertension as a case study. Journal of the American Medical Informatics Association, 27(8), 1268–1277. https://doi.org/10.1093/jamia/ocaa124

Slattery, J., & Kurz, X. (2020). Assessing strength of evidence for regulatory decision making in licensing: What proof do we need for observational studies of effectiveness? Pharmacoepidemiology and Drug Safety, 29(10), 1336–1340. https://doi.org/10.1002/pds.5005

Standardized Data: The OMOP Common Data Model. OHSDI. https://www.ohdsi.org/data-standardization/

Sultana, J., Giorgianni, F., Rea, F., Lucenteforte, E., Lombardi, N., Mugelli, A., Vannacci, A., Liperoti, R., Kirchmayer, U., Vitale, C., Chinellato, A., Roberto, G., Corrao, G., & Trifirò, G. (2019). All-cause mortality and antipsychotic use among elderly persons with high baseline cardiovascular and cerebrovascular risk: A multi-center retrospective cohort study in Italy. Expert Opinion on Drug Metabolism & Toxicology, 15(2), 179–188. https://doi.org/10.1080/17425255.2019.1561860

Systemic glucocorticoids in the treatment of COVID-19 and risks of adverse outcomes in COVID-19 patients in the primary and secondary care setting. EU PAS Register. https://www.encepp.eu/encepp/viewResource.htm?id=39816

Thurin, N. H., Pajouheshnia, R., Roberto, G., Dodd, C., Hyeraci, G., Bartolini, C., Paoletti, O., Nordeng, H., Wallach-Kildemoes, H., Ehrenstein, V., Dudukina, E., MacDonald, T., De Paoli, G., Loane, M., Damase-Michel, C., Beau, A.-B., Droz-Perroteau, C., Lassalle, R., Bergman, J., … Gini, R. (2022). From Inception to ConcePTION: Genesis of a Network to Support Better Monitoring and Communication of Medication Safety During Pregnancy and Breastfeeding. Clinical Pharmacology & Therapeutics, 111(1), 321–331. https://doi.org/10.1002/cpt.2476

Trifirò, G., Coloma, P. M., Rijnbeek, P. R., Romio, S., Mosseveld, B., Weibel, D., Bonhoeffer, J., Schuemie, M., van der Lei, J., & Sturkenboom, M. (2014). Combining multiple healthcare databases for postmarketing drug and vaccine safety surveillance: Why and how? Journal of Internal Medicine, 275(6), 551–561. https://doi.org/10.1111/joim.12159

VAC4EU. https://vac4eu.org/

vac4euorgdev. COVID-19 vaccine monitoring. VAC4EU. https://vac4eu.org/covid-19-vaccine-monitoring/

ADVANCE. VAC4EU. https://vac4eu.org/

Vaccine Safety Datalink (VSD) | VSD | Monitoring | Ensuring Safety | Vaccine Safety | CDC. (2022, October 28). CDC. https://www.cdc.gov/vaccinesafety/ensuringsafety/monitoring/vsd/index.html

van den Ham, H. A., Souverein, P. C., Klungel, O. H., Platt, R. W., Ernst, P., Dell'Aniello, S., Schmiedl, S., Grave, B., Rottenkolber, M., Huerta, C., Martín Merino, E., León-Muñoz, L. M., Montero, D.,

Andersen, M., Aakjær, M., De Bruin, M. L., & Gardarsdottir, H. (2021). Major bleeding in users of direct oral anticoagulants in atrial fibrillation: A pooled analysis of results from multiple population-based cohort studies. Pharmacoepidemiology and Drug Safety, 30(10), 1339–1352. https://doi.org/10.1002/pds.5317

Willame, C., Dodd, C., Durán, C. E., Elbers, R., Gini, R., Bartolini, C., Paoletti, O., Wang, L., Ehrenstein, V., Kahlert, J., Haug, U., Schink, T., Diez-Domingo, J., Mira-Iglesias, A., Carreras, J. J., Vergara-Hernández, C., Giaquinto, C., Barbieri, E., Stona, L., … Sturkenboom, M. (2023). Background rates of 41 adverse events of special interest for COVID-19 vaccines in 10 European healthcare databases—An ACCESS cohort study. Vaccine, 41(1), 251–262. https://doi.org/10.1016/j.vaccine.2022.11.031

Wood, A., Denholm, R., Hollings, S., Cooper, J., Ip, S., Walker, V., Denaxas, S., Akbari, A., Banerjee, A., Whiteley, W., Lai, A., Sterne, J., & Sudlow, C. (2021). Linked electronic health records for research on a nationwide cohort of more than 54 million people in England: Data resource. BMJ, 373, n826. https://doi.org/10.1136/bmj.n826

10. Systematic reviews and meta-analysis

Amani, B., Khanijahani, A., Amani, B., & Hashemi, P. Lopinavir/Ritonavir for COVID-19: A Systematic Review and Meta-Analysis. Journal of Pharmacy & Pharmaceutical Sciences, 24, 246–257. https://doi.org/10.18433/jpps31668

Bavishi, C., Whelton, P. K., Mancia, G., Corrao, G., & Messerli, F. H. Renin–angiotensin-system inhibitors and all-cause mortality in patients with COVID-19: A systematic review and meta-analysis of observational studies. Journal of Hypertension, 39(4), 784. https://doi.org/10.1097/HJH.0000000000002784

Chou, R., & Helfand, M. (2005). Challenges in Systematic Reviews That Assess Treatment Harms. Annals of Internal Medicine, 142(12_Part_2), 1090–1099. https://doi.org/10.7326/0003-4819-142-12_Part_2-200506211-00009

Henry, D., Lim, L. L.-Y., Rodriguez, L. A. G., Gutthann, S. P., Carson, J. L., Griffin, M., Savage, R., Logan, R., Moride, Y., Hawkey, C., Hill, S., & Fries, J. T. (1996). Variability in risk of gastrointestinal complications with individual non-steroidal anti-inflammatory drugs: Results of a collaborative meta-analysis. BMJ, 312(7046), 1563–1566. https://doi.org/10.1136/bmj.312.7046.1563

Hernández-Díaz, S., Bateman, B. T., Straub, L., Zhu, Y., Mogun, H., Fischer, M., & Huybrechts, K. F. (2021). Safety of Tenofovir Disoproxil Fumarate for Pregnant Women Facing the Coronavirus Disease 2019 Pandemic. American Journal of Epidemiology, 190(11), 2339–2349. https://doi.org/10.1093/aje/kwab109

NMA incorporating RWE – RWE Navigator. https://rwe-navigator.eu/use-real-world-evidence/summarise-and-synthesise-rwe/overview-of-evidence-synthesis-and-nma/nma-incorporating-rwe/

Overview of evidence synthesis and network meta-analysis – RWE Navigator. https://rwe-navigator.eu/use-real-world-evidence/summarise-and-synthesise-rwe/overview-of-evidence-synthesis-and-nma/

Sarri, G., Patorno, E., Yuan, H., Guo, J. (Jeff), Bennett, D., Wen, X., Zullo, A. R., Largent, J., Panaccio, M., Gokhale, M., Moga, D. C., Ali, M. S., & Debray, T. P. A. (2022). Framework for the synthesis of non-randomised studies and randomised controlled trials: A guidance on conducting a systematic

The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
(ENCePP) Guide on Methodological Standards in Pharmacoepidemiology
EMA/228452/2023   Page 36/76

review and meta-analysis for healthcare decision making. BMJ Evidence-Based Medicine, 27(2), 109–119. https://doi.org/10.1136/bmjebm-2020-111493

Working Group X – Meta-analysis • COUNCIL FOR INTERNATIONAL ORGANIZATIONS OF MEDICAL SCIENCES. COUNCIL FOR INTERNATIONAL ORGANIZATIONS OF MEDICAL SCIENCES. https://cioms.ch/working_groups/working-group-x/

11. Signal detection methodology and application

Note: Chapter 11 has not been updated for the 11th revision of the Guide

Bate, A., & Evans, S. J. W. (2009). Quantitative signal detection using spontaneous ADR reporting. Pharmacoepidemiology and Drug Safety, 18(6), 427–436. https://doi.org/10.1002/pds.1742

Bayer, S., Clark, C., Dang, O., Aberdeen, J., Brajovic, S., Swank, K., Hirschman, L., & Ball, R. (2021). ADE Eval: An Evaluation of Text Processing Systems for Adverse Event Extraction from Drug Labels for Pharmacovigilance. Drug Safety, 44(1), 83–94. https://doi.org/10.1007/s40264-020-00996-3

Berlin, C., Blanch, C., Lewis, D. J., Maladorno, D. D., Michel, C., Petrin, M., Sarp, S., & Close, P. (2012). Are all quantitative postmarketing signal detection methods equal? Performance characteristics of logistic regression and Multi-item Gamma Poisson Shrinker. Pharmacoepidemiology and Drug Safety, 21(6), 622–630. https://doi.org/10.1002/pds.2247

Candore, G., Juhlin, K., Manlik, K., Thakrar, B., Quarcoo, N., Seabroke, S., Wisniewski, A., & Slattery, J. (2015). Comparison of Statistical Signal Detection Methods Within and Across Spontaneous Reporting Databases. Drug Safety, 38(6), 577–587. https://doi.org/10.1007/s40264-015-0289-5

Caster, O., Aoki, Y., Gattepaille, L. M., & Grundmark, B. (2020). Disproportionality Analysis for Pharmacovigilance Signal Detection in Small Databases or Subsets: Recommendations for Limiting False-Positive Associations. Drug Safety, 43(5), 479–487. https://doi.org/10.1007/s40264-020-00911-w

Caster, O., Juhlin, K., Watson, S., & Norén, G. N. (2014). Improved Statistical Signal Detection in Pharmacovigilance by Combining Multiple Strength-of-Evidence Aspects in vigiRank. Drug Safety, 37(8), 617–628. https://doi.org/10.1007/s40264-014-0204-5

Caster, O., Norén, G. N., Madigan, D., & Bate, A. (2010). Large-scale regression-based pattern discovery: The example of screening the WHO global drug safety database. Statistical Analysis and Data Mining: The ASA Data Science Journal, 3(4), 197–208. https://doi.org/10.1002/sam.10078

Caster, O., Norén, G. N., Madigan, D., & Bate, A. (2013). Logistic Regression in Signal Detection: Another Piece Added to the Puzzle. Clinical Pharmacology & Therapeutics, 94(3), 312–312. https://doi.org/10.1038/clpt.2013.107

DuMouchel, W., & Harpaz, R. Regression-Adjusted GPS Algorithm (RGPS). 23.

DuMouchel, W., Yuen, N., Payvandi, N., Booth, W., Rut, A., & Fram, D. (2013). Automated Method for Detecting Increases in Frequency of Spontaneous Adverse Event Reports over Time. Journal of Biopharmaceutical Statistics, 23(1), 161–177. https://doi.org/10.1080/10543406.2013.736809

Good pharmacovigilance practices. European Medicines Agency. https://www.ema.europa.eu/en/human-regulatory/post-authorisation/pharmacovigilance/good-pharmacovigilance-practices

The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
(ENCePP) Guide on Methodological Standards in Pharmacoepidemiology
EMA/228452/2023   Page 37/76

Harpaz, R., DuMouchel, W., LePendu, P., Bauer-Mehren, A., Ryan, P., & Shah, N. H. (2013). Performance of Pharmacovigilance Signal Detection Algorithms for the FDA Adverse Event Reporting System. Clinical Pharmacology and Therapeutics, 93(6), 10.1038/clpt.2013.24. https://doi.org/10.1038/clpt.2013.24

Harpaz, R., DuMouchel, W., Schuemie, M., Bodenreider, O., Friedman, C., Horvitz, E., Ripple, A., Sorbello, A., White, R. W., Winnenburg, R., & Shah, N. H. (2017). Toward multimodal signal detection of adverse drug reactions. Journal of Biomedical Informatics, 76, 41–49. https://doi.org/10.1016/j.jbi.2017.10.013

Hauben, M., Madigan, D., Gerrits, C. M., Walsh, L., & Van Puijenbroek, E. P. (2005). The role of data mining in pharmacovigilance. Expert Opinion on Drug Safety, 4(5), 929–948. https://doi.org/10.1517/14740338.4.5.929

Juhlin, K., Karimi, G., Andér, M., Camilli, S., Dheda, M., Har, T. S., Isahak, R., Lee, S.-J., Vaughan, S., Caduff, P., & Norén, G. N. (2015). Using VigiBase to Identify Substandard Medicines: Detection Capacity and Key Prerequisites. Drug Safety, 38(4), 373–382. https://doi.org/10.1007/s40264-015-0271-2

Juhlin, K., Ye, X., Star, K., & Norén, G. N. (2013). Outlier removal to uncover patterns in adverse drug reaction surveillance – a simple unmasking strategy. Pharmacoepidemiology and Drug Safety, 22(10), 1119–1129. https://doi.org/10.1002/pds.3474

Kreimeyer, K., Dang, O., Spiker, J., Muñoz, M. A., Rosner, G., Ball, R., & Botsis, T. (2021). Feature engineering and machine learning for causality assessment in pharmacovigilance: Lessons learned from application to the FDA Adverse Event Reporting System. Computers in Biology and Medicine, 135, 104517. https://doi.org/10.1016/j.compbiomed.2021.104517

Low, Y. S., Caster, O., Bergvall, T., Fourches, D., Zang, X., Norén, G. N., Rusyn, I., Edwards, R., & Tropsha, A. (2016). Cheminformatics-aided pharmacovigilance: Application to Stevens-Johnson Syndrome. Journal of the American Medical Informatics Association, 23(5), 968–978. https://doi.org/10.1093/jamia/ocv127

Maignen, F., Hauben, M., Hung, E., Holle, L. V., & Dogne, J.-M. (2014). A conceptual approach to the masking effect of measures of disproportionality. Pharmacoepidemiology and Drug Safety, 23(2), 208–217. https://doi.org/10.1002/pds.3530

Maignen, F., Hauben, M., Hung, E., Van Holle, L., & Dogne, J.-M. (2014). Assessing the extent and impact of the masking effect of disproportionality analyses on two spontaneous reporting systems databases. Pharmacoepidemiology and Drug Safety, 23(2), 195–207. https://doi.org/10.1002/pds.3529

MedDRA - Medical Dictionary for Regulatory Activities. https://www.meddra.org/

Modern methods of pharmacovigilance: Detecting adverse effects of drugs | RCP Journals. https://www.rcpjournals.org/content/clinmedicine/9/5/486

Montastruc, J.-L., Rousseau, V., de Canecaude, C., Roussin, A., & Montastruc, F. (2020). Role of serotonin and norepinephrine transporters in antidepressant-induced arterial hypertension: A pharmacoepidemiological-pharmacodynamic study. European Journal of Clinical Pharmacology, 76(9), 1321–1327. https://doi.org/10.1007/s00228-020-02913-0

Muñoz, M. A., Dal Pan, G. J., Wei, Y.-J. J., Delcher, C., Xiao, H., Kortepeter, C. M., & Winterstein, A. G. (2020). Towards Automating Adverse Event Review: A Prediction Model for Case Report Utility. Drug Safety, 43(4), 329–338. https://doi.org/10.1007/s40264-019-00897-0

The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
(ENCePP) Guide on Methodological Standards in Pharmacoepidemiology
EMA/228452/2023   Page 38/76

Norén, G. N., Meldau, E.-L., & Chandler, R. E. (2021). Consensus clustering for case series identification and adverse event profiles in pharmacovigilance. Artificial Intelligence in Medicine, 122, 102199. https://doi.org/10.1016/j.artmed.2021.102199

OMOP Common Data Model – OHDSI. Observational Health Data Sciences and Informatics Community. https://www.ohdsi.org/data-standardization/the-common-data-model/

Pacurariu, A. C., Straus, S. M., Trifirò, G., Schuemie, M. J., Gini, R., Herings, R., Mazzaglia, G., Picelli, G., Scotti, L., Pedersen, L., Arlett, P., van der Lei, J., Sturkenboom, M. C., & Coloma, P. M. (2015). Useful Interplay Between Spontaneous ADR Reports and Electronic Healthcare Records in Signal Detection. Drug Safety, 38(12), 1201–1210. https://doi.org/10.1007/s40264-015-0341-5

Pinheiro, L. C., Candore, G., Zaccaria, C., Slattery, J., & Arlett, P. (2018). An algorithm to detect unexpected increases in frequency of reports of adverse events in EudraVigilance. Pharmacoepidemiology and Drug Safety, 27(1), 38–45. https://doi.org/10.1002/pds.4344

Practical Aspects of Signal Detection in Pharmacovigilance: Report of CIOMS Working Group VIII - COUNCIL FOR INTERNATIONAL ORGANIZATIONS OF MEDICAL SCIENCES (CIOMS). COUNCIL FOR INTERNATIONAL ORGANIZATIONS OF MEDICAL SCIENCES. https://cioms.ch/publications/product/practical-aspects-of-signal-detection-in-pharmacovigilance-report-of-cioms-working-group-viii/

PROTECT. PROTECT | IMI Innovative Medicines Initiative (europa.eu)

Research, C. for D. E. and. Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment. U.S. Food and Drug Administration; FDA. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/good-pharmacovigilance-practices-and-pharmacoepidemiologic-assessment

Research, C. for D. E. and. (2019, October 18). FDA's Sentinel Initiative. FDA. https://www.fda.gov/safety/fdas-sentinel-initiative

Salvo, F., Leborgne, F., Thiessard, F., Moore, N., Bégaud, B., & Pariente, A. (2013). A Potential Event-Competition Bias in Safety Signal Detection: Results from a Spontaneous Reporting Research Database in France. Drug Safety, 36(7), 565–572. https://doi.org/10.1007/s40264-013-0063-5

Scholl, J. H. G., van Hunsel, F. P. A. M., Hak, E., & van Puijenbroek, E. P. (2018). A prediction model-based algorithm for computer-assisted database screening of adverse drug reactions in the Netherlands. Pharmacoepidemiology and Drug Safety, 27(2), 199–205. https://doi.org/10.1002/pds.4364

Schotland, P., Racz, R., Jackson, D. B., Soldatos, T. G., Levin, R., Strauss, D. G., & Burkhart, K. (2021). Target Adverse Event Profiles for Predictive Safety in the Postmarket Setting. Clinical Pharmacology & Therapeutics, 109(5), 1232–1243. https://doi.org/10.1002/cpt.2074

Screening for adverse reactions in EudraVigilance—EMA. https://www.ema.europa.eu/en/documents/other/screening-adverse-reactions-eudravigilance_en.pdf

Seabroke, S., Candore, G., Juhlin, K., Quarcoo, N., Wisniewski, A., Arani, R., Painter, J., Tregunno, P., Norén, G. N., & Slattery, J. (2016). Performance of Stratified and Subgrouped Disproportionality Analyses in Spontaneous Databases. Drug Safety, 39(4), 355–364. https://doi.org/10.1007/s40264-015-0388-3

Summary of product characteristics. European Medicines Agency. https://www.ema.europa.eu/en/glossary/summary-product-characteristics

Stephenson, W. P., & Hauben, M. (2007). Data mining for signals in spontaneous reporting databases: Proceed with caution. Pharmacoepidemiology and Drug Safety, 16(4), 359–365. https://doi.org/10.1002/pds.1323

Tatonetti, N. P., Ye, P. P., Daneshjou, R., & Altman, R. B. (2012). Data-Driven Prediction of Drug Effects and Interactions. Science Translational Medicine, 4(125), 125ra31-125ra31. https://doi.org/10.1126/scitranslmed.3003377

Van Holle, L., & Bauchau, V. (2014). Use of Logistic Regression to Combine Two Causality Criteria for Signal Detection in Vaccine Spontaneous Report Data. Drug Safety, 37(12), 1047–1057. https://doi.org/10.1007/s40264-014-0237-9

Wisniewski, A. F. Z., Bate, A., Bousquet, C., Brueckner, A., Candore, G., Juhlin, K., Macia-Martinez, M. A., Manlik, K., Quarcoo, N., Seabroke, S., Slattery, J., Southworth, H., Thakrar, B., Tregunno, P., Van Holle, L., Kayser, M., & Norén, G. N. (2016). Good Signal Detection Practices: Evidence from IMI PROTECT. Drug Safety, 39(6), 469–490. https://doi.org/10.1007/s40264-016-0405-1

12. Statistical analysis plan

Ärzteblatt, D. Ä. G., Redaktion Deutsches. *Avoiding Bias in Observational Studies (09.10.2009)*. Deutsches Ärzteblatt. https://www.aerzteblatt.de/int/archive/article?id=66288

ICH E9 statistical principles for clinical trials—Scientific guideline [Text]. European Medicines Agency. https://www.ema.europa.eu/en/ich-e9-statistical-principles-clinical-trials-scientific-guideline

Hiemstra, B., Keus, F., Wetterslev, J., Gluud, C., & van der Horst, I. C. C. (2019). DEBATE-statistical analysis plans for observational studies. *BMC Medical Research Methodology*, *19*(1), 233. https://doi.org/10.1186/s12874-019-0879-5

Lash, T., VanderWeele, T., Haneuse, S., & Rothman, K. (2020). *Modern Epidemiology* (4th ed.). Wolters Kluwer.

Luijken, K., van Eekelen, R., Gardarsdottir, H., Groenwold, R. H. H., & van Geloven, N. (2023). Tell me what you want, what you really really want: Estimands in observational pharmacoepidemiologic comparative effectiveness and safety studies. *Pharmacoepidemiology and Drug Safety*, *32*(8), 863–872. https://doi.org/10.1002/pds.5620

Madsen, M. B., Skrede, S., Bruun, T., Arnell, P., Rosén, A., Nekludov, M., Karlsson, Y., Bergey, F., Saccenti, E., Martins dos Santos, V. a. P., Perner, A., Norrby-Teglund, A., & Hyldegaard, O. (2018). Necrotizing soft tissue infections – a multicentre, prospective observational study (INFECT): Protocol and statistical analysis plan. *Acta Anaesthesiologica Scandinavica*, *62*(2), 272–279. https://doi.org/10.1111/aas.13024

Rosenbaum, P. R. (2020). *Design of Observational Studies*. Springer Series in Statistics.

Thomas, L., & Peterson, E. D. (2012). The Value of Statistical Analysis Plans in Observational Research: Defining High-Quality Research From the Start. *JAMA*, *308*(8), 773–774. https://doi.org/10.1001/jama.2012.9502

Yuan, I., Topjian, A. A., Kurth, C. D., Kirschen, M. P., Ward, C. G., Zhang, B., & Mensinger, J. L. (2019). Guide to the statistical analysis plan. *Pediatric Anesthesia*, *29*(3), 237–242. https://doi.org/10.1111/pan.13576

13. Quality management

Aghazadeh-Attari, J., Mobaraki, K., Ahmadzadeh, J., Mansorian, B., & Mohebbi, I. (2018). Quality of observational studies in prestigious journals of occupational medicine and health based on Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement: A cross-sectional study. BMC Research Notes, 11(1), 266. https://doi.org/10.1186/s13104-018-3367-9

Blacketer, C., Defalco, F. J., Ryan, P. B., & Rijnbeek, P. R. (2021). Increasing trust in real-world evidence through evaluation of observational data quality. Journal of the American Medical Informatics Association, 28(10), 2251–2257. https://doi.org/10.1093/jamia/ocab132

Commission Implementing Regulation (EU) No 520/2012. https://eur-lex.europa.eu/eli/reg_impl/2012/520/oj

US National Patient-Centered Clinical Research Network. https://pcornet.org/data/

Determining Real-World Data's Fitness for Use and the Role of Reliability. Margolis Center for Health Policy. https://healthpolicy.duke.edu/publications/determining-real-world-datas-fitness-use-and-role-reliability

EFGCP - European Forum for Good Clinical Practice. https://efgcp.eu/

Good pharmacovigilance practices – European Medicines Agency. https://www.ema.europa.eu/en/human-regulatory/post-authorisation/pharmacovigilance/good-pharmacovigilance-practices

ICH E6 (R2) Good clinical practice—Scientific guideline. European Medicines Agency. https://www.ema.europa.eu/en/ich-e6-r2-good-clinical-practice-scientific-guideline

ICH E8 General considerations for clinical studies—Scientific guideline. European Medicines Agency. https://www.ema.europa.eu/en/ich-e8-general-considerations-clinical-studies-scientific-guideline

Joint Action Towards the European Health Data Space – TEHDAS. https://tehdas.eu/

Gatto, N. M., Campbell, U. B., Rubinstein, E., Jaksa, A., Mattox, P., Mo, J., & Reynolds, R. F. (2022). The Structured Process to Identify Fit-For-Purpose Data: A Data Feasibility Assessment Framework. Clinical Pharmacology & Therapeutics, 111(1), 122–134. https://doi.org/10.1002/cpt.2466

Gatto, N. M., Vititoe, S. E., Rubinstein, E., Reynolds, R. F., & Campbell, U. B. (2023). A Structured Process to Identify Fit-for-Purpose Study Design and Data to Generate Valid and Transparent Real-World Evidence for Regulatory Uses. Clinical Pharmacology & Therapeutics, 113(6), 1235–1239. https://doi.org/10.1002/cpt.2883

Ghadessi, M., Tang, R., Zhou, J., Liu, R., Wang, C., Toyoizumi, K., Mei, C., Zhang, L., Deng, C. Q., & Beckman, R. A. (2020). A roadmap to using historical controls in clinical trials – by Drug Information Association Adaptive Design Scientific Working Group (DIA-ADSWG). Orphanet Journal of Rare Diseases, 15(1), 69. https://doi.org/10.1186/s13023-020-1332-x

Guidelines for Good Pharmacoepidemiology Practices (GPP)—International Society for Pharmacoepidemiology. ISPE. https://www.pharmacoepi.org/resources/policies/guidelines-08027/

Herrett, E., Thomas, S. L., Schoonen, W. M., Smeeth, L., & Hall, A. J. (2010). Validation and validity of diagnoses in the General Practice Research Database: A systematic review. British Journal of Clinical Pharmacology, 69(1), 4–14. https://doi.org/10.1111/j.1365-2125.2009.03537.x

Hoffmann, W., Latza, U., Baumeister, S. E., Brünger, M., Buttmann-Schweiger, N., Hardt, J., Hoffmann, V., Karch, A., Richter, A., Schmidt, C. O., Schmidtmann, I., Swart, E., & van den Berg, N.

(2019). Guidelines and recommendations for ensuring Good Epidemiological Practice (GEP): A guideline developed by the German Society for Epidemiology. European Journal of Epidemiology, 34(3), 301–317. https://doi.org/10.1007/s10654-019-00500-x

Informatics, O. H. D. S. (2022). The Book of OHDSI. https://ohdsi.github.io/TheBookOfOhdsi/

Kahn, M. G., Callahan, T. J., Barnard, J., Bauck, A. E., Brown, J., Davidson, B. N., Estiri, H., Goerg, C., Holve, E., Johnson, S. G., Liaw, S.-T., Hamilton-Lopez, M., Meeker, D., Ong, T. C., Ryan, P., Shang, N., Weiskopf, N. G., Weng, C., Zozus, M. N., & Schilling, L. (2016). A Harmonized Data Quality Assessment Terminology and Framework for the Secondary Use of Electronic Health Record Data (No. 1). 4(1), Art. 1. https://doi.org/10.13063/2327-9214.1244

Kiran, D. R. (2016). Total Quality Management (1st ed.). BSP Books, Elsevier. https://shop.elsevier.com/books/total-quality-management/kiran/978-0-12-811035-5

TEHDAS develops data quality recommendations. Tehdas. https://tehdas.eu/results/tehdas-develops-data-quality-recommendations/

OHDSI – Observational Health Data Sciences and Informatics. https://www.ohdsi.org/

Publications. STROBE. https://www.strobe-statement.org/strobe-publications/

Registries for Evaluating Patient Outcomes: A User's Guide: 4th Edition | Effective Health Care (EHC) Program. https://effectivehealthcare.ahrq.gov/products/registries-guide-4th-edition/users-guide

Research, C. for D. E. and. (2020, April 29). Best Practices for Conducting and Reporting Pharmacoepidemiologic Safety Studies Using Electronic Healthcare Data Sets. U.S. Food and Drug Administration; FDA. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/best-practices-conducting-and-reporting-pharmacoepidemiologic-safety-studies-using-electronic

Sprenger, K., Nickerson, D., Meeker-O'Connell, A., & Morrison, B. W. (2013). Quality by Design in Clinical Trials: A Collaborative Pilot With FDA. Therapeutic Innovation & Regulatory Science, 47(2), 161–166. https://doi.org/10.1177/0092861512458909

Theobald, K., Capan, M., Herbold, M., Schinzel, S., & Hundt, F. (2009). Quality assurance in non-interventional studies. GMS German Medical Science, 7, Doc29. https://doi.org/10.3205/000088

What is a Quality Management System (QMS)? | ASQ. ASQ. https://asq.org/quality-resources/quality-management%20system

Ziemann, S., Paetzolt, I., Grüßer, L., Coburn, M., Rossaint, R., & Kowark, A. (2022). Poor reporting quality of observational clinical studies comparing treatments of COVID-19 – a retrospective cross-sectional study. BMC Medical Research Methodology, 22(1), 23. https://doi.org/10.1186/s12874-021-01501-9

14. Dissemination and communication of study results

Benchimol, E. I., Moher, D., Ehrenstein, V., & Langan, S. M. (2020). Retraction of COVID-19 Pharmacoepidemiology Research Could Have Been Avoided by Effective Use of Reporting Guidelines</p>. Clinical Epidemiology, 12, 1403–1420. https://doi.org/10.2147/CLEP.S288677

Good pharmacovigilance practices – European Medicines Agency. https://www.ema.europa.eu/en/human-regulatory/post-authorisation/pharmacovigilance/good-pharmacovigilance-practices

ENCePP Checklist for Study Protocols. ENCePP.
https://www.encepp.eu/standards_and_guidances/checkListProtocols.shtml

ENCePP Code of Conduct. ENCePP. https://www.encepp.eu/code_of_conduct/index.shtml

ENCePP Home Page. https://www.encepp.eu/standards_and_guidances/checkListProtocols.shtml

EU PAS Register. https://www.encepp.eu/encepp_studies/indexRegister.shtml

GRACE Principles—Good ReseArch for Comparative Effectiveness. https://www.graceprinciples.org/

Guidance for the format and content of the protocol of non-interventional post-authorisation safety
studies. https://www.ema.europa.eu/en/documents/other/guidance-format-content-protocol-non-
interventional-post-authorisation-safety-studies_en.pdf

Guidelines for Good Pharmacoepidemiology Practices (GPP)—International Society for
Pharmacoepidemiology. https://www.pharmacoepi.org/resources/policies/guidelines-08027/

Home—ClinicalTrials.gov. https://clinicaltrials.gov/

ICMJE. https://www.icmje.org/

ICMJE | Recommendations. https://www.icmje.org/recommendations/

IEA Good Epidemiology Practice (GEP). (2007). IEA.
https://ieaweb.org/IEAWeb/Content/IEA_Publications.aspx

Improving the reporting of pragmatic trials: An extension of the CONSORT statement | The BMJ.
https://www.bmj.com/content/337/bmj.a2390

Langan, S. M., Schmidt, S. A., Wing, K., Ehrenstein, V., Nicholls, S. G., Filion, K. B., Klungel, O.,
Petersen, I., Sorensen, H. T., Dixon, W. G., Guttmann, A., Harron, K., Hemkens, L. G., Moher, D.,
Schneeweiss, S., Smeeth, L., Sturkenboom, M., Elm, E. von, Wang, S. V., & Benchimol, E. I. (2018).
The reporting of studies conducted using observational routinely collected health data statement for
pharmacoepidemiology (RECORD-PE). BMJ, 363, k3532. https://doi.org/10.1136/bmj.k3532

Moher, D., Liberati, A., Tetzlaff, J., & Altman, D. G. (2009). Preferred reporting items for systematic
reviews and meta-analyses: The PRISMA statement. BMJ, 339, b2535.
https://doi.org/10.1136/bmj.b2535

Nicholls, S. G., Quach, P., Elm, E. von, Guttmann, A., Moher, D., Petersen, I., Sørensen, H. T.,
Smeeth, L., Langan, S. M., & Benchimol, E. I. (2015). The REporting of Studies Conducted Using
Observational Routinely-Collected Health Data (RECORD) Statement: Methods for Arriving at
Consensus and Developing Reporting Guidelines. PLOS ONE, 10(5), e0125620.
https://doi.org/10.1371/journal.pone.0125620

Open Sience Forum. https://osf.io/

Preprints & Conference Proceedings | Nature Portfolio. https://www.nature.com/nature-
portfolio/editorial-policies/preprints-and-conference-proceedings

Preprints with The Lancet. https://www.thelancet.com/preprints

PROSPERO - International prospective register of systematic reviews.
https://www.crd.york.ac.uk/PROSPERO/

STROBE. https://www.strobe-statement.org/strobe-publications/

The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
(ENCePP) Guide on Methodological Standards in Pharmacoepidemiology
EMA/228452/2023   Page 43/76

Research, C. for D. E. (2020, April 29). Best Practices for Conducting and Reporting Pharmacoepidemiologic Safety Studies Using Electronic Healthcare Data Sets. U.S. Food and Drug Administration; FDA. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/best-practices-conducting-and-reporting-pharmacoepidemiologic-safety-studies-using-electronic

Schneeweiss, S., Rassen, J. A., Brown, J. S., Rothman, K. J., Happe, L., Arlett, P., Dal Pan, G., Goettsch, W., Murk, W., & Wang, S. V. (2019). Graphical Depiction of Longitudinal Study Designs in Health Care Databases. Annals of Internal Medicine, 170(6), 398–406. https://doi.org/10.7326/M18-3079

Schulz, K. F., Altman, D. G., & Moher, D. (2010). CONSORT 2010 Statement: Updated guidelines for reporting parallel group randomised trials. BMJ, 340, c332. https://doi.org/10.1136/bmj.c332

STARD 2015 guidelines for reporting diagnostic accuracy studies: Explanation and elaboration | BMJ Open. https://bmjopen.bmj.com/content/6/11/e012799

Stroup, D. F., Berlin, J. A., Morton, S. C., Olkin, I., Williamson, G. D., Rennie, D., Moher, D., Becker, B. J., Sipe, T. A., Thacker, S. B., & for the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) Group. (2000). Meta-analysis of Observational Studies in EpidemiologyA Proposal for Reporting. JAMA, 283(15), 2008–2012. https://doi.org/10.1001/jama.283.15.2008

WMA - The World Medical Association-WMA Declaration of Helsinki – Ethical Principles for Medical Research Involving Human Subjects. https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/

15. Data protection and ethical aspects

15.1. Personal data protection in the European Union

Article 29 Working Party | European Data Protection Board. European Data Protection Board. https://edpb.europa.eu/about-edpb/more-about-edpb/article-29-working-party_en

Commission Directive 2005/28/EC. (2005). European Commission. http://data.europa.eu/eli/dir/2005/28/oj/eng

Commission Implementing Regulation (EU) No 520/2012—EC. https://eur-lex.europa.eu/eli/reg_impl/2012/520/oj

Data Privacy, Medical Record Confidentiality, and Research in the Interest of Public Health—International Society for Pharmacoepidemiology. ISPE. https://www.pharmacoepi.org/resources/policies/privacy/

Directive 2001/20/EC. https://ec.europa.eu/health/system/files/2016-11/dir_2001_20_en_0.pdf

EudraLex—EC. European Commission. https://ec.europa.eu/health/medicinal-products/eudralex_en

EDPB | European Data Protection Board. European Data Protection Board. https://edpb.europa.eu/edpb_en

EDPB Guidelines 3/2018 on the territorial scope of the GDPR. https://edpb.europa.eu/sites/default/files/files/file1/edpb_guidelines_3_2018_territorial_scope_after_public_consultation_en_1.pdf

ENCePP Home Page. https://www.encepp.eu/structure/index.shtml

European Data Protection Authorities. European Data Protection Board. https://edpb.europa.eu/about-edpb/about-edpb/members_en

General Data Protection Regulation (EU) 2016/679 (GDPR). https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32016R0679

Good pharmacovigilance practices. European Medicines Agency. https://www.ema.europa.eu/en/human-regulatory/post-authorisation/pharmacovigilance/good-pharmacovigilance-practices

Guidelines for Good Pharmacoepidemiology Practices (GPP)—International Society for Pharmacoepidemiology. ISPE. https://www.pharmacoepi.org/resources/policies/guidelines-08027/

Human medicines: Regulatory information. European Medicines Agency. https://www.ema.europa.eu/en/human-medicines-regulatory-information

Questions and Answers on the interplay between the Clinical Trials Regulation and the General Data Protection Regulation—EC. https://ec.europa.eu/health/system/files/2019-04/qa_clinicaltrials_gdpr_en_0.pdf

Regulation (EU) 2018/1725 (EUDPR). https://edps.europa.eu/sites/default/files/publication/regulation_eu_2018_1725_en.pdf

Regulation (EU) No 536/2014. https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32014R0536&rid=1

15.2. Scientific integrity and ethical conduct

Agency for Healthcare Research and Quality (AHRQ). https://www.ahrq.gov/

Council for International Organizations of Medical Sciences (CIOMS). (2016). International Ethical Guidelines for Health-related Research involving Humans. Council for International Organizations of Medical Sciences (CIOMS). https://doi.org/10.56759/rgxl7405

ENCePP Code of Conduct. https://www.encepp.eu/code_of_conduct/

EU PAS Register. https://www.encepp.eu/encepp/studiesDatabase.jsp

Guidelines for Good Pharmacoepidemiology Practices (GPP)—International Society for Pharmacoepidemiology. https://www.pharmacoepi.org/resources/policies/guidelines-08027/

HMA-EMA Joint Big Data Taskforce Phase II report: Evolving Data-Driven Regulation. https://www.ema.europa.eu/en/documents/other/hma-ema-joint-big-data-taskforce-phase-ii-report-evolving-data-driven-regulation_en.pdf

ICMJE https://www.icmje.org/

ICMJE | Recommendations. https://www.icmje.org/recommendations/

Kurz, X., Bauchau, V., Mahy, P., Glismann, S., van der Aa, L. M., & Simondon, F. (2017). The ADVANCE Code of Conduct for collaborative vaccine studies. Vaccine, 35(15), 1844–1855. https://doi.org/10.1016/j.vaccine.2017.02.039

Registries for Evaluating Patient Outcomes: A User's Guide: 4th Edition | Effective Health Care (EHC) Program. https://effectivehealthcare.ahrq.gov/products/registries-guide-4th-edition/users-guide

The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
(ENCePP) Guide on Methodological Standards in Pharmacoepidemiology
EMA/228452/2023   Page 45/76

WMA - The World Medical Association-WMA Declaration of Helsinki – Ethical Principles for Medical Research Involving Human Subjects. https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/

16. Specific topics

16.1. Comparative effectiveness research

Azzolina, D., Berchialla, P., Gregori, D., & Baldi, I. (2021). Prior Elicitation for Use in Clinical Trial Design and Analysis: A Literature Review. International Journal of Environmental Research and Public Health, 18(4), 1833. https://doi.org/10.3390/ijerph18041833

ClinicalTrials.gov. https://clinicaltrials.gov/

Cochrane Handbook for Systematic Reviews of Interventions. https://training.cochrane.org/handbook

COMET Initiative https://www.comet-initiative.org/

Crystal, S., Gaboda, D., Lucas, J., Gerhard, T., & Chakravarty, S. (2010). Assessing Medication Exposures and Outcomes in the Frail Elderly: Assessing Research Challenges in Nursing Home Pharmacotherapy. Medical Care, 48(6), S23. https://doi.org/10.1097/MLR.0b013e3181de9d10

D'Andrea, E., Vinals, L., Patorno, E., Franklin, J. M., Bennett, D., Largent, J. A., Moga, D. C., Yuan, H., Wen, X., Zullo, A. R., Debray, T. P. A., & Sarri, G. (2021). How well can we assess the validity of non-randomised studies of medications? A systematic review of assessment tools. BMJ Open, 11(3), e043961. https://doi.org/10.1136/bmjopen-2020-043961

Desai, R. J., Mahesri, M., Abdia, Y., Barberio, J., Tong, A., Zhang, D., Mavros, P., Kim, S. C., & Franklin, J. M. (2018). Association of Osteoporosis Medication Use After Hip Fracture With Prevention of Subsequent Nonvertebral Fractures: An Instrumental Variable Analysis. JAMA Network Open, 1(3), e180826. https://doi.org/10.1001/jamanetworkopen.2018.0826

Developing a Protocol for Observational Comparative Effectiveness Research: A User's Guide | Effective Health Care (EHC) Program. https://effectivehealthcare.ahrq.gov/products/observational-cer-protocol/research

Dickerman, B. A., Gerlovin, H., Madenci, A. L., Kurgansky, K. E., Ferolito, B. R., Figueroa Muñiz, M. J., Gagnon, D. R., Gaziano, J. M., Cho, K., Casas, J. P., & Hernán, M. A. (2022). Comparative Effectiveness of BNT162b2 and mRNA-1273 Vaccines in U.S. Veterans. New England Journal of Medicine, 386(2), 105–115. https://doi.org/10.1056/NEJMoa2115463

EU PAS Register. https://www.encepp.eu/encepp/studiesDatabase.jsp

Franklin, J. M., Glynn, R. J., Suissa, S., & Schneeweiss, S. (2020). Emulation Differences vs. Biases When Calibrating Real-World Evidence Findings Against Randomized Controlled Trials. Clinical Pharmacology & Therapeutics, 107(4), 735–737. https://doi.org/10.1002/cpt.1793

Franklin, J. M., Patorno, E., Desai, R. J., Glynn, R. J., Martin, D., Quinto, K., Pawar, A., Bessette, L. G., Lee, H., Garry, E. M., Gautam, N., & Schneeweiss, S. (2021). Emulating Randomized Clinical Trials With Nonrandomized Real-World Evidence Studies. Circulation, 143(10), 1002–1013. https://doi.org/10.1161/CIRCULATIONAHA.120.051718

Franklin, J. M., & Schneeweiss, S. (2017). When and How Can Real World Data Analyses Substitute for Randomized Controlled Trials? Clinical Pharmacology & Therapeutics, 102(6), 924–933. https://doi.org/10.1002/cpt.857

Ghadessi, M., Tang, R., Zhou, J., Liu, R., Wang, C., Toyoizumi, K., Mei, C., Zhang, L., Deng, C. Q., & Beckman, R. A. (2020). A roadmap to using historical controls in clinical trials – by Drug Information Association Adaptive Design Scientific Working Group (DIA-ADSWG). Orphanet Journal of Rare Diseases, 15, 69. https://doi.org/10.1186/s13023-020-1332-x

Goring, S., Taylor, A., Müller, K., Li, T. J. J., Korol, E. E., Levy, A. R., & Freemantle, N. (2019). Characteristics of non-randomised studies using comparisons with external controls submitted for regulatory approval in the USA and Europe: A systematic review. BMJ Open, 9(2), e024895. https://doi.org/10.1136/bmjopen-2018-024895

Gorst, S. L., Gargon, E., Clarke, M., Blazeby, J. M., Altman, D. G., & Williamson, P. R. (2016). Choosing Important Health Outcomes for Comparative Effectiveness Research: An Updated Review and User Survey. PLOS ONE, 11(1), e0146444. https://doi.org/10.1371/journal.pone.0146444

Guyatt, G. H., Oxman, A. D., Vist, G. E., Kunz, R., Falck-Ytter, Y., Alonso-Coello, P., & Schünemann, H. J. (2008). GRADE: An emerging consensus on rating quality of evidence and strength of recommendations. BMJ, 336(7650), 924–926. https://doi.org/10.1136/bmj.39489.470347.AD

Harker, J., & Kleijnen, J. (2012). What is a rapid review? A methodological exploration of rapid reviews in Health Technology Assessments. JBI Evidence Implementation, 10(4), 397. https://doi.org/10.1111/j.1744-1609.2012.00290.x

Hernán, M. A. (2018). How to estimate the effect of treatment duration on survival outcomes using observational data. BMJ, 360, k182. https://doi.org/10.1136/bmj.k182

Hernández-Díaz, S., Huybrechts, K. F., Chiu, Y.-H., Yland, J. J., Bateman, B. T., & Hernán, M. A. (2023). Emulating a Target Trial of Interventions Initiated During Pregnancy with Healthcare Databases: The Example of COVID-19 Vaccination. Epidemiology, 34(2), 238. https://doi.org/10.1097/EDE.0000000000001562

Huang, B., Qiu, T., Chen, C., Neace, A., Zhang, Y., Yue, X., Zahner, J., Adams, M., Seid, M., Lovell, D., Morgan, E., & Brunner, H. (2020). Comparative Effectiveness Research Using Electronic Health Records Data: Ensure Data Quality. SAGE Publications Ltd. https://doi.org/10.4135/9781529726480

In Defense of Pharmacoepidemiology—Embracing the Yin and Yang of Drug Research | NEJM. https://www.nejm.org/doi/full/10.1056/NEJMp0706892

Jahanshahi, M., Gregg, K., Davis, G., Ndu, A., Miller, V., Vockley, J., Ollivier, C., Franolic, T., & Sakai, S. (2021). The Use of External Controls in FDA Regulatory Decision Making. Therapeutic Innovation & Regulatory Science, 55(5), 1019–1035. https://doi.org/10.1007/s43441-021-00302-y

Johnson, E. S., Bartman, B. A., Briesacher, B. A., Fleming, N. S., Gerhard, T., Kornegay, C. J., Nourjah, P., Sauer, B., Schumock, G. T., Sedrakyan, A., Stürmer, T., West, S. L., & Schneeweiss, S. (2013). The incident user design in comparative effectiveness research. Pharmacoepidemiology and Drug Safety, 22(1), 1–6. https://doi.org/10.1002/pds.3334

Lessons Learned from Trial Replication Analyses: Findings from the DUPLICATE Demonstration Project. Margolis Center for Health Policy. https://healthpolicy.duke.edu/events/findings-duplicate-demonstration-project

Lumley, T. (2002). Network meta-analysis for indirect treatment comparisons. Statistics in Medicine, 21(16), 2313–2324. https://doi.org/10.1002/sim.1201

Muñoz, J., Hufstedler, H., Gustafson, P., Bärnighausen, T., De Jong, V. M. T., & Debray, T. P. A. (2023). Dealing with missing data using the Heckman selection model: Methods primer for

The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
(ENCePP) Guide on Methodological Standards in Pharmacoepidemiology
EMA/228452/2023   Page 47/76

epidemiologists. International Journal of Epidemiology, 52(1), 5–13. https://doi.org/10.1093/ije/dyac237

Overview of evidence synthesis and network meta-analysis – RWE Navigator. https://rwe-navigator.eu/use-real-world-evidence/summarise-and-synthesise-rwe/overview-of-evidence-synthesis-and-nma/

Perraillon, M. C., & Tina Shih, Y.-C. (2023). Causal Inference in Oncology Comparative Effectiveness Research Using Observational Data: Are Instrumental Variables Underutilized? Journal of Clinical Oncology, 41(13), 2319–2322. https://doi.org/10.1200/JCO.22.02853

Randomized, Controlled Trials, Observational Studies, and the Hierarchy of Research Designs | NEJM. https://www.nejm.org/doi/full/10.1056/NEJM200006223422507#t=article

Ray, W. A. (2003). Evaluating Medication Effects Outside of Clinical Trials: New-User Designs. American Journal of Epidemiology, 158(9), 915–920. https://doi.org/10.1093/aje/kwg231

Research, C. for D. E. and. (2023, January 31). Considerations for the Design and Conduct of Externally Controlled Trials for Drug and Biological Products. U.S. Food and Drug Administration; FDA. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/considerations-design-and-conduct-externally-controlled-trials-drug-and-biological-products

Rippin, G., Ballarini, N., Sanz, H., Largent, J., Quinten, C., & Pignatti, F. (2022). A Review of Causal Inference for External Comparator Arm Studies. Drug Safety, 45(8), 815–837. https://doi.org/10.1007/s40264-022-01206-y

RWE Navigator. https://rwe-navigator.eu/

Sarri, G., Patorno, E., Yuan, H., Guo, J. (Jeff), Bennett, D., Wen, X., Zullo, A. R., Largent, J., Panaccio, M., Gokhale, M., Moga, D. C., Ali, M. S., & Debray, T. P. A. (2022). Framework for the synthesis of non-randomised studies and randomised controlled trials: A guidance on conducting a systematic review and meta-analysis for healthcare decision making. BMJ Evidence-Based Medicine, 27(2), 109–119. https://doi.org/10.1136/bmjebm-2020-111493

Seeger, J. D., Davis, K. J., Iannacone, M. R., Zhou, W., Dreyer, N., Winterstein, A. G., Santanello, N., Gertz, B., & Berlin, J. A. (2020). Methods for external control groups for single arm trials or long-term uncontrolled extensions to randomized clinical trials. Pharmacoepidemiology and Drug Safety, 29(11), 1382–1392. https://doi.org/10.1002/pds.5141

Sox, H. C., & Goodman, S. N. (2012). The Methods of Comparative Effectiveness Research. Annual Review of Public Health, 33(1), 425–445. https://doi.org/10.1146/annurev-publhealth-031811-124610

The final version of HTA Core Model® and the Methodological Guidelines for Rapid REA of Pharmaceuticals is now available—EUnetHTA. (2013, March 8). https://www.eunethta.eu/the-final-version-of-hta-core-model-and-the-methodological-guidelines-for-rapid-rea-of-pharmaceuticals-is-now-available/

Valuck, R. J., Anderson, H. O., Libby, A. M., Brandt, E., Bryan, C., Allen, R. R., Staton, E. W., West, D. R., & Pace, W. D. (2012). Enhancing Electronic Health Record Measurement of Depression Severity and Suicide Ideation: A Distributed Ambulatory Research in Therapeutics Network (DARTNet) Study. The Journal of the American Board of Family Medicine, 25(5), 582–593. https://doi.org/10.3122/jabfm.2012.05.110053

Walker, J., Dormer, L., & Garner, P. (2023). Journal of Comparative Effectiveness Research welcoming the submission of study design protocols to foster transparency and trust in real-world evidence.

The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) Guide on Methodological Standards in Pharmacoepidemiology
EMA/228452/2023

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Journal of Comparative Effectiveness Research, 12(1), e220197. https://doi.org/10.2217/cer-2022-0197

Wang, S. V., Pottegård, A., Crown, W., Arlett, P., Ashcroft, D. M., Benchimol, E. I., Berger, M. L., Crane, G., Goettsch, W., Hua, W., Kabadi, S., Kern, D. M., Kurz, X., Langan, S., Nonaka, T., Orsini, L., Perez-Gutthann, S., Pinheiro, S., Pratt, N., … Williams, R. J. (2023). HARmonized Protocol Template to Enhance Reproducibility of hypothesis evaluating real-world evidence studies on treatment effects: A good practices report of a joint ISPE/ISPOR task force. Pharmacoepidemiology and Drug Safety, 32(1), 44–55. https://doi.org/10.1002/pds.5507

Wang, S. V., Schneeweiss, S., & RCT-DUPLICATE Initiative. (2023). Emulation of Randomized Clinical Trials With Nonrandomized Database Analyses: Results of 32 Clinical Trials. JAMA, 329(16), 1376–1385. https://doi.org/10.1001/jama.2023.4221

Yap, T. A., Jacobs, I., Baumfeld Andre, E., Lee, L. J., Beaupre, D., & Azoulay, L. (2022). Application of Real-World Data to External Control Groups in Oncology Clinical Trial Drug Development. Frontiers in Oncology, 11, 695936. https://doi.org/10.3389/fonc.2021.695936

16.2. Vaccine safety and effectiveness

ACCESS template protocol for safety of COVID-19 vaccines. EU PAS Register. https://www.encepp.eu/encepp/viewResource.htm?id=39362

ACCESS template protocols for effectiveness of COVID-19 vaccines. EU PAS Register. https://www.encepp.eu/encepp/viewResource.htm?id=39290

Ainslie, K. E. C., Shi, M., Haber, M., & Orenstein, W. A. (2019). A Dynamic Model for Evaluation of the Bias of Influenza Vaccine Effectiveness Estimates From Observational Studies. American Journal of Epidemiology, 188(2), 451–460. https://doi.org/10.1093/aje/kwy240

Alvergne, A., Kountourides, G., Argentieri, M. A., Agyen, L., Rogers, N., Knight, D., Sharp, G. C., Maybin, J. A., & Olszewska, Z. (2023). A retrospective case-control study on menstrual cycle changes following COVID-19 vaccination and disease. IScience, 26(4), 106401. https://doi.org/10.1016/j.isci.2023.106401

Analysis of relative effectiveness of high-dose versus standard-dose influenza vaccines using an instrumental variable method—PubMed. https://pubmed.ncbi.nlm.nih.gov/30745146/

Andrews, N. (2012). Epidemiological designs for vaccine safety assessment: Methods and pitfalls. Biologicals: Journal of the International Association of Biological Standardization, 40(5), 389–392. https://doi.org/10.1016/j.biologicals.2011.08.010

Andrews, N., Kent, A., Amin-Chowdhury, Z., Sheppard, C., Fry, N., Ramsay, M., & Ladhani, S. N. (2019). Effectiveness of the seven-valent and thirteen-valent pneumococcal conjugate vaccines in England: The indirect cohort design, 2006-2018. Vaccine, 37(32), 4491–4498. https://doi.org/10.1016/j.vaccine.2019.06.071

Andrews, N., Stowe, J., Thomas, S. L., Walker, J. L., & Miller, E. (2019). The risk of non-specific hospitalised infections following MMR vaccination given with and without inactivated vaccines in the second year of life. Comparative self-controlled case-series study in England. Vaccine, 37(36), 5211–5217. https://doi.org/10.1016/j.vaccine.2019.07.059

Andrews, N., Waight, P. A., Borrow, R., Ladhani, S., George, R. C., Slack, M. P. E., & Miller, E. (2011). Using the indirect cohort design to estimate the effectiveness of the seven valent pneumococcal

conjugate vaccine in England and Wales. PloS One, 6(12), e28435.
https://doi.org/10.1371/journal.pone.0028435

Background rates of Adverse Events of Special Interest for monitoring COVID-19 vaccines (2.0).
(2022). https://doi.org/10.5281/ZENODO.5255870

Baker, M. A., Baer, B., Kulldorff, M., Zichittella, L., Reindel, R., DeLuccia, S., Lipowicz, H., Freitas, K.,
Jin, R., & Yih, W. K. (2019). Kawasaki disease and 13-valent pneumococcal conjugate vaccination
among young children: A self-controlled risk interval and cohort study with null results. PLoS Medicine,
16(7), e1002844. https://doi.org/10.1371/journal.pmed.1002844

Baker, M. A., Lieu, T. A., Li, L., Hua, W., Qiang, Y., Kawai, A. T., Fireman, B. H., Martin, D. B., &
Nguyen, M. D. (2015). A vaccine study design selection framework for the postlicensure rapid
immunization safety monitoring program. American Journal of Epidemiology, 181(8), 608–618.
https://doi.org/10.1093/aje/kwu322

Baum, U., Sundman, J., Jääskeläinen, S., Nohynek, H., Puumalainen, T., & Jokinen, J. (2017).
Establishing and maintaining the National Vaccination Register in Finland. Euro Surveillance: Bulletin
Europeen Sur Les Maladies Transmissibles = European Communicable Disease Bulletin, 22(17), 30520.
https://doi.org/10.2807/1560-7917.ES.2017.22.17.30520

Beck, C. R., McKenzie, B. C., Hashim, A. B., Harris, R. C., University of Nottingham Influenza and the
ImmunoCompromised (UNIIC) Study Group, & Nguyen-Van-Tam, J. S. (2012). Influenza vaccination
for immunocompromised patients: Systematic review and meta-analysis by etiology. The Journal of
Infectious Diseases, 206(8), 1250–1259. https://doi.org/10.1093/infdis/jis487

Bias due to differential and non-differential disease- and exposure misclassification in studies of
vaccine effectiveness—PubMed. https://pubmed.ncbi.nlm.nih.gov/29906276/

Biggart, R., Finn, A., & Marlow, R. (2018). Lack of impact of rotavirus vaccination on childhood seizure
hospitalizations in England – An interrupted time series analysis. Vaccine, 36(31), 4589–4592.
https://doi.org/10.1016/j.vaccine.2018.06.029

Björk, J., Bonander, C., Moghaddassi, M., Rasmussen, M., Malmqvist, U., Kahn, F., & Inghammar, M.
(2022). Surveillance of COVID-19 vaccine effectiveness: A real-time case–control study in southern
Sweden. Epidemiology and Infection, 150, e59. https://doi.org/10.1017/S0950268822000425

Black, S. B., Law, B., Chen, R. T., Dekker, C. L., Sturkenboom, M., Huang, W.-T., Gurwith, M., &
Poland, G. (2021). The critical role of background rates of possible adverse events in the assessment
of COVID-19 vaccine safety. Vaccine, 39(19), 2712–2718.
https://doi.org/10.1016/j.vaccine.2021.03.016

Bollaerts, K., Biccler, J., Stuurman, A., Aponte, Z., Hartig-Merkel, W., & Rebry, G. Authors and
contributors table for this master protocol.

Bonaiuti, R. DRIVE. https://www.drive-eu.org/

Bots, S. H., Riera-Arnau, J., Belitser, S. V., Messina, D., Aragón, M., Alsina, E., Douglas, I. J., Durán,
C. E., García-Poza, P., Gini, R., Herings, R. M. C., Huerta, C., Sisay, M. M., Martín-Pérez, M., Martin, I.,
Overbeek, J. A., Paoletti, O., Pallejà-Millán, M., Schultze, A., … Sturkenboom, M. C. J. M. (2022).
Myocarditis and pericarditis associated with SARS-CoV-2 vaccines: A population-based descriptive
cohort and a nested self-controlled risk interval study using electronic health care data from four
European countries. Frontiers in Pharmacology, 13, 1038043.
https://doi.org/10.3389/fphar.2022.1038043

Brighton Collaboration – Home Page. Brighton Collaboration. https://brightoncollaboration.us/

The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
(ENCePP) Guide on Methodological Standards in Pharmacoepidemiology
EMA/228452/2023   Page 50/76

Broome, C. V., Facklam, R. R., & Fraser, D. W. (1980). Pneumococcal disease after pneumococcal vaccination: An alternative method to estimate the efficacy of pneumococcal vaccine. The New England Journal of Medicine, 303(10), 549–552. https://doi.org/10.1056/NEJM198009043031003

Brown, J. S., Kulldorff, M., Chan, K. A., Davis, R. L., Graham, D., Pettus, P. T., Andrade, S. E., Raebel, M. A., Herrinton, L., Roblin, D., Boudreau, D., Smith, D., Gurwitz, J. H., Gunter, M. J., & Platt, R. (2007). Early detection of adverse drug events within population-based health networks: Application of sequential testing methods. Pharmacoepidemiology and Drug Safety, 16(12), 1275–1284. https://doi.org/10.1002/pds.1509

Carvajal, A., Ortega, P. G., Sáinz, M., Velasco, V., Salado, I., Arias, L. H. M., Eiros, J. M., Rubio, A. P., & Castrodeza, J. (2011). Adverse events associated with pandemic influenza vaccines: Comparison of the results of a follow-up study with those coming from spontaneous reporting. Vaccine, 29(3), 519–522. https://doi.org/10.1016/j.vaccine.2010.10.067

Castilla, J., Beristain, X., Martínez-Artola, V., Navascués, A., García Cenoz, M., Alvarez, N., Polo, I., Mazón, A., Gil-Setas, A., & Barricarte, A. (2012). Effectiveness of rotavirus vaccines in preventing cases and hospitalizations due to rotavirus gastroenteritis in Navarre, Spain. Vaccine, 30(3), 539–543. https://doi.org/10.1016/j.vaccine.2011.11.071

Chodick, G., Tene, L., Patalon, T., Gazit, S., Ben Tov, A., Cohen, D., & Muhsen, K. (2021). Assessment of Effectiveness of 1 Dose of BNT162b2 Vaccine for SARS-CoV-2 Infection 13 to 24 Days After Immunization. JAMA Network Open, 4(6), e2115985. https://doi.org/10.1001/jamanetworkopen.2021.15985

Chrapkowska, C., Galanis, I., Kark, M., Lepp, T., Lindstrand, A., Roth, A., & Nilsson, A. (2020). Validation of the new Swedish vaccination register—Accuracy and completeness of register data. Vaccine, 38(25), 4104–4110. https://doi.org/10.1016/j.vaccine.2020.04.020

Chua, H., Feng, S., Lewnard, J. A., Sullivan, S. G., Blyth, C. C., Lipsitch, M., & Cowling, B. J. (2020). The use of test-negative controls to monitor vaccine effectiveness: A systematic review of methodology. Epidemiology (Cambridge, Mass.), 31(1), 43–64. https://doi.org/10.1097/EDE.0000000000001116

CIOMS Guide to Vaccine Safety Communication • COUNCIL FOR INTERNATIONAL ORGANIZATIONS OF MEDICAL SCIENCES. COUNCIL FOR INTERNATIONAL ORGANIZATIONS OF MEDICAL SCIENCES. https://cioms.ch/publications/product/cioms-guide-vaccine-safety-communication/

Core protocol for ECDC studies of COVID-19 vaccine effectiveness against hospitalisation with Severe Acute Respiratory Infection laboratory-confirmed with SARS-CoV-2, version 1.0. (2021, October 8). https://www.ecdc.europa.eu/en/publications-data/core-protocol-ecdc-studies-covid-19-vaccine-effectiveness-against-hospitalisation

Covid-19 Vaccine Effectiveness and the Test-Negative Design | NEJM. https://www.nejm.org/doi/full/10.1056/NEJMe2113151?query=recirc_curatedRelated_article

Crowcroft, N. S., & Klein, N. P. (2018). A framework for research on vaccine effectiveness. Vaccine, 36(48), 7286–7293. https://doi.org/10.1016/j.vaccine.2018.04.016

Dagan, N., Barda, N., Kepten, E., Miron, O., Perchik, S., Katz, M. A., Hernán, M. A., Lipsitch, M., Reis, B., & Balicer, R. D. (2021). BNT162b2 mRNA Covid-19 Vaccine in a Nationwide Mass Vaccination Setting. The New England Journal of Medicine, 384(15), 1412–1423. https://doi.org/10.1056/NEJMoa2101765

The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
(ENCePP) Guide on Methodological Standards in Pharmacoepidemiology
EMA/228452/2023   Page 51/76

de Bie, S., Verhamme, K. M. C., Straus, S. M. J. M., Stricker, B. H. C., & Sturkenboom, M. C. J. M. (2012). Vaccine-based subgroup analysis in VigiBase: Effect on sensitivity in paediatric signal detection. Drug Safety, 35(4), 335–346. https://doi.org/10.2165/11598120-000000000-00000

De Serres, G., Pilishvili, T., Link-Gelles, R., Reingold, A., Gershman, K., Petit, S., Farley, M. M., Harrison, L. H., Lynfield, R., Bennett, N. M., Baumbach, J., Thomas, A., Schaffner, W., Beall, B., Whitney, C., & Moore, M. (2012). Use of surveillance data to estimate the effectiveness of the 7-valent conjugate pneumococcal vaccine in children less than 5 years of age over a 9 year period. Vaccine, 30(27), 4067–4072. https://doi.org/10.1016/j.vaccine.2012.04.017

De Vito, C., Manzoli, L., Marzuillo, C., Anastasi, D., Boccia, A., & Villari, P. (2007). A systematic review evaluating the potential for bias and the methodological quality of meta-analyses in vaccinology. Vaccine, 25(52), 8794–8806. https://doi.org/10.1016/j.vaccine.2007.10.034

Definition and Application of Terms for Vaccine Pharmacovigilance. https://www.who.int/publications/m/item/9789290360834

Dhanda, S., Osborne, V., Lynn, E., & Shakir, S. (2022). Postmarketing studies: Can they provide a safety net for COVID-19 vaccines in the UK? BMJ Evidence-Based Medicine, 27(1), 1–6. https://doi.org/10.1136/bmjebm-2020-111507

Dickerman, B. A., Gerlovin, H., Madenci, A. L., Kurgansky, K. E., Ferolito, B. R., Figueroa Muñiz, M. J., Gagnon, D. R., Gaziano, J. M., Cho, K., Casas, J. P., & Hernán, M. A. (2022). Comparative Effectiveness of BNT162b2 and mRNA-1273 Vaccines in U.S. Veterans. The New England Journal of Medicine, 386(2), 105–115. https://doi.org/10.1056/NEJMoa2115463

Dieleman, J., Romio, S., Johansen, K., Weibel, D., Bonhoeffer, J., & Sturkenboom, M. (2011). Guillain-Barré syndrome and adjuvanted pandemic influenza A (H1N1) 2009 vaccine: Multinational case-control study in Europe. BMJ, 343, d3908. https://doi.org/10.1136/bmj.d3908

Dodd, C., Andrews, N., Petousis-Harris, H., Sturkenboom, M., Omer, S. B., & Black, S. (2021). Methodological frontiers in vaccine safety: Qualifying available evidence for rare events, use of distributed data networks to monitor vaccine safety issues, and monitoring the safety of pregnancy interventions. BMJ Global Health, 6(Suppl 2), e003540. https://doi.org/10.1136/bmjgh-2020-003540

Drolet, M., Bénard, É., Pérez, N., Brisson, M., & HPV Vaccination Impact Study Group. (2019). Population-level impact and herd effects following the introduction of human papillomavirus vaccination programmes: Updated systematic review and meta-analysis. Lancet (London, England), 394(10197), 497–509. https://doi.org/10.1016/S0140-6736(19)30298-3

Ebola ça Suffit Ring Vaccination Trial Consortium. (2015). The ring vaccination trial: A novel cluster randomised controlled trial design to evaluate vaccine efficacy and effectiveness during outbreaks, with special reference to Ebola. BMJ (Clinical Research Ed.), 351, h3740. https://doi.org/10.1136/bmj.h3740

Good pharmacovigilance practices European Medicines Agency. https://www.ema.europa.eu/en/human-regulatory/post-authorisation/pharmacovigilance/good-pharmacovigilance-practices

Escolano, S., Hill, C., & Tubert-Bitter, P. (2013). A new self-controlled case series method for analyzing spontaneous reports of adverse events after vaccination. American Journal of Epidemiology, 178(9), 1496–1504. https://doi.org/10.1093/aje/kwt128

European Centre for Disease Prevention and Control. https://www.ecdc.europa.eu/en European Centre for Disease Prevention and Control. Effectiveness of rotavirus vaccination: Generic study protocol for

retrospective case control studies based on computerised databases : technical document. Publications Office. https://data.europa.eu/doi/10.2900/64929

Evaluation of COVID-19 vaccine effectiveness. https://www.who.int/publications-detail-redirect/WHO-2019-nCoV-vaccine_effectiveness-measurement-2021.1

Evans, S. J. W. (2008). Stratification for spontaneous report databases. Drug Safety, 31(11), 1049–1052. https://doi.org/10.2165/00002018-200831110-00009

Farrington, C. P. (2004). Control without separate controls: Evaluation of vaccine safety using case-only methods. Vaccine, 22(15–16), 2064–2070. https://doi.org/10.1016/j.vaccine.2004.01.017

Farrington, C. P., Firth, M. J., Moulton, L. H., Ravn, H., Andersen, P. K., Evans, S., & Working Group on Non-specific Effects of Vaccines. (2009). Epidemiological studies of the non-specific effects of vaccines: II--methodological issues in the design and analysis of cohort studies. Tropical Medicine & International Health: TM & IH, 14(9), 977–985. https://doi.org/10.1111/j.1365-3156.2009.02302.x

Farrington, S. H., Kaatje Bollaerts, Paddy. (2021). Vaccination Programmes: Epidemiology, Monitoring, Evaluation. Routledge. https://doi.org/10.4324/9781315166414

Feikin, D. R., Higdon, M. M., Abu-Raddad, L. J., Andrews, N., Araos, R., Goldberg, Y., Groome, M. J., Huppert, A., O'Brien, K. L., Smith, P. G., Wilder-Smith, A., Zeger, S., Deloria Knoll, M., & Patel, M. K. (2022). Duration of effectiveness of vaccines against SARS-CoV-2 infection and COVID-19 disease: Results of a systematic review and meta-regression. Lancet (London, England), 399(10328), 924–944. https://doi.org/10.1016/S0140-6736(22)00152-0

Fell, D. B., Dimitris, M. C., Hutcheon, J. A., Ortiz, J. R., Platt, R. W., Regan, A. K., & Savitz, D. A. (2021). Guidance for design and analysis of observational studies of fetal and newborn outcomes following COVID-19 vaccination during pregnancy. Vaccine, 39(14), 1882–1886. https://doi.org/10.1016/j.vaccine.2021.02.070

Fine, P. E. M., Williams, T. N., Aaby, P., Källander, K., Moulton, L. H., Flanagan, K. L., Smith, P. G., Benn, C. S., & Working Group on Non-specific Effects of Vaccines. (2009). Epidemiological studies of the 'non-specific effects' of vaccines: I--data collection in observational studies. Tropical Medicine & International Health: TM & IH, 14(9), 969–976. https://doi.org/10.1111/j.1365-3156.2009.02301.x

Ghebremichael-Weldeselassie, Y., Jabagi, M. J., Botton, J., Bertrand, M., Baricault, B., Drouin, J., Weill, A., Zureik, M., Dray-Spira, R., & Farrington, P. (2022). A modified self-controlled case series method for event-dependent exposures and high event-related mortality, with application to COVID-19 vaccine safety. Statistics in Medicine, 41(10), 1735–1750. https://doi.org/10.1002/sim.9325

Glanz, J. M., McClure, D. L., Xu, S., Hambidge, S. J., Lee, M., Kolczak, M. S., Kleinman, K., Mullooly, J. P., & France, E. K. (2006). Four different study designs to evaluate vaccine safety were equally validated with contrasting limitations. Journal of Clinical Epidemiology, 59(8), 808–818. https://doi.org/10.1016/j.jclinepi.2005.11.012

Global Varicella Vaccine Effectiveness: A Meta-analysis | Pediatrics | American Academy of Pediatrics. https://publications.aap.org/pediatrics/article/137/3/e20153741/81443/Global-Varicella-Vaccine-Effectiveness-A-Meta?autologincheck=redirected

Gram, M. A., Nielsen, J., Schelde, A. B., Nielsen, K. F., Moustsen-Helms, I. R., Sørensen, A. K. B., Valentiner-Branth, P., & Emborg, H.-D. (2021). Vaccine effectiveness against SARS-CoV-2 infection, hospitalization, and death when combining a first dose ChAdOx1 vaccine with a subsequent mRNA vaccine in Denmark: A nationwide population-based cohort study. PLoS Medicine, 18(12), e1003874. https://doi.org/10.1371/journal.pmed.1003874

The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
(ENCePP) Guide on Methodological Standards in Pharmacoepidemiology
EMA/228452/2023   Page 53/76

Greenberg, J. A., Hohmann, S. F., Hall, J. B., Kress, J. P., & David, M. Z. (2016). Validation of a Method to Identify Immunocompromised Patients with Severe Sepsis in Administrative Databases. Annals of the American Thoracic Society, 13(2), 253–258. https://doi.org/10.1513/AnnalsATS.201507-415BC

Greene, S. K., Kulldorff, M., Lewis, E. M., Li, R., Yin, R., Weintraub, E. S., Fireman, B. H., Lieu, T. A., Nordin, J. D., Glanz, J. M., Baxter, R., Jacobsen, S. J., Broder, K. R., & Lee, G. M. (2010). Near real-time surveillance for influenza vaccine safety: Proof-of-concept in the Vaccine Safety Datalink Project. American Journal of Epidemiology, 171(2), 177–188. https://doi.org/10.1093/aje/kwp345

Guidance for the format and content of the protocol of non-interventional post-authorisation safety studies. https://www.ema.europa.eu/en/documents/other/guidance-format-content-protocol-non-interventional-post-authorisation-safety-studies_en.pdf

Halloran, M. E., Haber, M., Longini, I. M., Jr, & Struchiner, C. J. (1991). Direct and Indirect Effects in Vaccine Efficacy and Effectiveness. American Journal of Epidemiology, 133(4), 323–331. https://doi.org/10.1093/oxfordjournals.aje.a115884

Halloran, M. E., M. Longini, I., & J. Struchiner, C. (2010). Design and Analysis of Vaccine Studies. Springer. https://link.springer.com/book/10.1007/978-0-387-68636-3

Hanquet, G., Valenciano, M., Simondon, F., & Moren, A. (2013). Vaccine effects and impact of vaccination programmes in post-licensure studies. Vaccine, 31(48), 5634–5642. https://doi.org/10.1016/j.vaccine.2013.07.006

Harpaz, R., DuMouchel, W., Van Manen, R., Nip, A., Bright, S., Szarfman, A., Tonning, J., & Lerch, M. (2022). Signaling COVID-19 Vaccine Adverse Events. Drug Safety, 45(7), 765–780. https://doi.org/10.1007/s40264-022-01186-z

Harris, R. J., Hall, J. A., Zaidi, A., Andrews, N. J., Dunbar, J. K., & Dabrera, G. (2021). Effect of Vaccination on Household Transmission of SARS-CoV-2 in England. The New England Journal of Medicine, 385(8), 759–760. https://doi.org/10.1056/NEJMc2107717

Heffernan, J. M., & Keeling, M. J. (2009). Implications of vaccination and waning immunity. Proceedings of the Royal Society B: Biological Sciences, 276(1664), 2071–2080. https://doi.org/10.1098/rspb.2009.0057

Hennessy, S., Liu, Z., Tsai, T. F., Strom, B. L., Wan, C. M., Liu, H. L., Wu, T. X., Yu, H. J., Liu, Q. M., Karabatsos, N., Bilker, W. B., & Halstead, S. B. (1996). Effectiveness of live-attenuated Japanese encephalitis vaccine (SA14-14-2): A case-control study. Lancet (London, England), 347(9015), 1583–1586. https://doi.org/10.1016/s0140-6736(96)91075-2

Hocine, M. N., Farrington, C. P., Touzé, E., Whitaker, H. J., Fourrier, A., Moreau, T., & Tubert-Bitter, P. (2007). Hepatitis B vaccination and first central nervous system demyelinating events: Reanalysis of a case-control study using the self-controlled case series method. Vaccine, 25(31), 5938–5943. https://doi.org/10.1016/j.vaccine.2007.05.032

Hulme, W. J., Horne, E. M. F., Parker, E. P. K., Keogh, R. H., Williamson, E. J., Walker, V., Palmer, T. M., Curtis, H. J., Walker, A. J., Andrews, C. D., Mehrkar, A., Morley, J., MacKenna, B., Bacon, S. C. J., Goldacre, B., Hernán, M. A., & Sterne, J. A. C. (2023). Comparative effectiveness of BNT162b2 versus mRNA-1273 covid-19 vaccine boosting in England: Matched cohort study in OpenSAFELY-TPP. BMJ (Clinical Research Ed.), 380, e072808. https://doi.org/10.1136/bmj-2022-072808

The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
(ENCePP) Guide on Methodological Standards in Pharmacoepidemiology
EMA/228452/2023   Page 54/76

Hviid, A., Svanström, H., Scheller, N. M., Grönlund, O., Pasternak, B., & Arnheim-Dahlström, L. (2018). Human papillomavirus vaccination of adult women and risk of autoimmune and neurological diseases. Journal of Internal Medicine, 283(2), 154–165. https://doi.org/10.1111/joim.12694

Ignatova, G. L., Avdeev, S. N., & Antonov, V. N. (2021). Comparative effectiveness of pneumococcal vaccination with PPV23 and PCV13 in COPD patients over a 5-year follow-up cohort study. Scientific Reports, 11(1), 15948. https://doi.org/10.1038/s41598-021-95129-w

Impact and effectiveness of mRNA BNT162b2 vaccine against SARS-CoV-2 infections and COVID-19 cases, hospitalisations, and deaths following a nationwide vaccination campaign in Israel: An observational study using national surveillance data—PubMed. https://pubmed.ncbi.nlm.nih.gov/33964222/

Jackson, M. L., & Nelson, J. C. (2013). The test-negative design for estimating influenza vaccine effectiveness. Vaccine, 31(17), 2165–2168. https://doi.org/10.1016/j.vaccine.2013.02.053

Jefferson, T., Rivetti, D., Rivetti, A., Rudin, M., Di Pietrantonj, C., & Demicheli, V. (2005). Efficacy and effectiveness of influenza vaccines in elderly people: A systematic review. Lancet (London, England), 366(9492), 1165–1174. https://doi.org/10.1016/S0140-6736(05)67339-4

Kahn, R., Schrag, S. J., Verani, J. R., & Lipsitch, M. (2022). Identifying and Alleviating Bias Due to Differential Depletion of Susceptible People in Postmarketing Evaluations of COVID-19 Vaccines. American Journal of Epidemiology, 191(5), 800–811. https://doi.org/10.1093/aje/kwac015

Karlstad, Ø., Hovi, P., Husby, A., Härkänen, T., Selmer, R. M., Pihlström, N., Hansen, J. V., Nohynek, H., Gunnes, N., Sundström, A., Wohlfahrt, J., Nieminen, T. A., Grünewald, M., Gulseth, H. L., Hviid, A., & Ljung, R. (2022). SARS-CoV-2 Vaccination and Myocarditis in a Nordic Cohort Study of 23 Million Residents. JAMA Cardiology, 7(6), 600–612. https://doi.org/10.1001/jamacardio.2022.0583

Katsoularis, I., Fonseca-Rodríguez, O., Farrington, P., Lindmark, K., & Fors Connolly, A.-M. (2021). Risk of acute myocardial infarction and ischaemic stroke following COVID-19 in Sweden: A self-controlled case series and matched cohort study. Lancet (London, England), 398(10300), 599–607. https://doi.org/10.1016/S0140-6736(21)00896-5

Kerr, S., Joy, M., Torabi, F., Bedston, S., Akbari, A., Agrawal, U., Beggs, J., Bradley, D., Chuter, A., Docherty, A. B., Ford, D., Hobbs, R., Katikireddi, S. V., Lowthian, E., de Lusignan, S., Lyons, R., Marple, J., McCowan, C., McGagh, D., … Sheikh, A. (2022). First dose ChAdOx1 and BNT162b2 COVID-19 vaccinations and cerebral venous sinus thrombosis: A pooled self-controlled case series study of 11.6 million individuals in England, Scotland, and Wales. PLoS Medicine, 19(2), e1003927. https://doi.org/10.1371/journal.pmed.1003927

Klein, N. P. (2011). Vaccine safety in special populations. Human Vaccines, 7(2), 269–271. https://doi.org/10.4161/hv.7.2.13860

Kulldorff, M., Dashevsky, I., Avery, T. R., Chan, A. K., Davis, R. L., Graham, D., Platt, R., Andrade, S. E., Boudreau, D., Gunter, M. J., Herrinton, L. J., Pawloski, P. A., Raebel, M. A., Roblin, D., & Brown, J. S. (2013). Drug safety data mining with a tree-based scan statistic. Pharmacoepidemiology and Drug Safety, 22(5), 517–523. https://doi.org/10.1002/pds.3423

Lai, L. Y., Arshad, F., Areia, C., Alshammari, T. M., Alghoul, H., Casajust, P., Li, X., Dawoud, D., Nyberg, F., Pratt, N., Hripcsak, G., Suchard, M. A., Prieto-Alhambra, D., Ryan, P., & Schuemie, M. J. (2022). Current Approaches to Vaccine Safety Using Observational Data: A Rationale for the EUMAEUS (Evaluating Use of Methods for Adverse Events Under Surveillance-for Vaccines) Study Design. Frontiers in Pharmacology, 13, 837632. https://doi.org/10.3389/fphar.2022.837632

Layton, D., & Shakir, S. A. W. (2015). Specialist Cohort Event Monitoring studies: A new study method for risk management in pharmacovigilance. Drug Safety, 38(2), 153–163. https://doi.org/10.1007/s40264-014-0260-x

Leite, A., Andrews, N. J., & Thomas, S. L. (2016). Near real-time vaccine safety surveillance using electronic health records—A systematic review of the application of statistical methods. Pharmacoepidemiology and Drug Safety, 25(3), 225–237. https://doi.org/10.1002/pds.3966

Levi, M., Riera, M., Bollaerts, K., Stuurman, A., & Turunen, T. DRIVE, Core protocol for population-based database cohort-studies. https://www.drive-eu.org/wp-content/uploads/2018/12/DRIVE_D7.2_Core-protocol-for-population-based-database-cohort-studies_V1.1.pdf

Li, X., Lai, L. Y., Ostropolets, A., Arshad, F., Tan, E. H., Casajust, P., Alshammari, T. M., Duarte-Salles, T., Minty, E. P., Areia, C., Pratt, N., Ryan, P. B., Hripcsak, G., Suchard, M. A., Schuemie, M. J., & Prieto-Alhambra, D. (2021). Bias, Precision and Timeliness of Historical (Background) Rate Comparison Methods for Vaccine Safety Monitoring: An Empirical Multi-Database Analysis. Frontiers in Pharmacology, 12, 773875. https://doi.org/10.3389/fphar.2021.773875

Li, X., Ostropolets, A., Makadia, R., Shoaibi, A., Rao, G., Sena, A. G., Martinez-Hernandez, E., Delmestri, A., Verhamme, K., Rijnbeek, P. R., Duarte-Salles, T., Suchard, M. A., Ryan, P. B., Hripcsak, G., & Prieto-Alhambra, D. (2021). Characterising the background incidence rates of adverse events of special interest for covid-19 vaccines in eight countries: Multinational network cohort study. BMJ, 373, n1435. https://doi.org/10.1136/bmj.n1435

Lipsitch, M., Goldstein, E., Ray, G. T., & Fireman, B. (2019). Depletion-of-susceptibles bias in influenza vaccine waning studies: How to ensure robust results. Epidemiology and Infection, 147, e306. https://doi.org/10.1017/S0950268819001961

Lopez Bernal, J., Andrews, N., Gower, C., Robertson, C., Stowe, J., Tessier, E., Simmons, R., Cottrell, S., Roberts, R., O'Doherty, M., Brown, K., Cameron, C., Stockton, D., McMenamin, J., & Ramsay, M. (2021). Effectiveness of the Pfizer-BioNTech and Oxford-AstraZeneca vaccines on covid-19 related symptoms, hospital admissions, and mortality in older adults in England: Test negative case-control study. BMJ (Clinical Research Ed.), 373, n1088. https://doi.org/10.1136/bmj.n1088

Madewell, Z. J., Dean, N. E., Berlin, J. A., Coplan, P. M., Davis, K. J., Struchiner, C. J., & Halloran, M. E. (2021). Challenges of evaluating and modelling vaccination in emerging infectious diseases. Epidemics, 37, 100506. https://doi.org/10.1016/j.epidem.2021.100506

Mahaux, O., Bauchau, V., & Van Holle, L. (2016). Pharmacoepidemiological considerations in observed-to-expected analyses for vaccines. Pharmacoepidemiology and Drug Safety, 25(2), 215–222. https://doi.org/10.1002/pds.3918

Marshall, H. S., McMillan, M., Koehler, A. P., Lawrence, A., Sullivan, T. R., MacLennan, J. M., Maiden, M. C. J., Ladhani, S. N., Ramsay, M. E., Trotter, C., Borrow, R., Finn, A., Kahler, C. M., Whelan, J., Vadivelu, K., & Richmond, P. (2020). Meningococcal B Vaccine and Meningococcal Carriage in Adolescents in Australia. The New England Journal of Medicine, 382(4), 318–327. https://doi.org/10.1056/NEJMoa1900236

Martín Arias, L. H., Sanz, R., Sáinz, M., Treceño, C., & Carvajal, A. (2015). Guillain-Barré syndrome and influenza vaccines: A meta-analysis. Vaccine, 33(31), 3773–3778. https://doi.org/10.1016/j.vaccine.2015.05.013

The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
(ENCePP) Guide on Methodological Standards in Pharmacoepidemiology
EMA/228452/2023
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McClure, D. L., Glanz, J. M., Xu, S., Hambidge, S. J., Mullooly, J. P., & Baggs, J. (2008). Comparison of epidemiologic methods for active surveillance of vaccine safety. Vaccine, 26(26), 3341–3345. https://doi.org/10.1016/j.vaccine.2008.03.074

Menni, C., May, A., Polidori, L., Louca, P., Wolf, J., Capdevila, J., Hu, C., Ourselin, S., Steves, C. J., Valdes, A. M., & Spector, T. D. (2022). COVID-19 vaccine waning and effectiveness and side-effects of boosters: A prospective community study from the ZOE COVID Study. The Lancet. Infectious Diseases, 22(7), 1002–1010. https://doi.org/10.1016/S1473-3099(22)00146-3

Methods to account for measured and unmeasured confounders in influenza relative vaccine effectiveness studies: A brief review of the literature—PubMed. https://pubmed.ncbi.nlm.nih.gov/35545260/

Miller, E., Andrews, N., Stellitano, L., Stowe, J., Winstone, A. M., Shneerson, J., & Verity, C. (2013). Risk of narcolepsy in children and young people receiving AS03 adjuvanted pandemic A/H1N1 2009 influenza vaccine: Retrospective analysis. BMJ (Clinical Research Ed.), 346, f794. https://doi.org/10.1136/bmj.f794

Milman, O., Yelin, I., Aharony, N., Katz, R., Herzel, E., Ben-Tov, A., Kuint, J., Gazit, S., Chodick, G., Patalon, T., & Kishony, R. (2021). Community-level evidence for SARS-CoV-2 vaccine protection of unvaccinated individuals. Nature Medicine, 27(8), 1367–1369. https://doi.org/10.1038/s41591-021-01407-5

Murray, J., & Cohen, A. L. (2017). Infectious Disease Surveillance. International Encyclopedia of Public Health, 222–229. https://doi.org/10.1016/B978-0-12-803678-5.00517-8

Navar, A. M., Cosmatos, I., Purinton, S., Ramsey, J. L., Taylor, R. J., Sobel, R. E., Barlow, G., Dieck, G. S., Bulgrein, M. L., & Peterson, E. D. (2022). Using EHR data to identify coronavirus infections in hospitalized patients: Impact of case definitions on disease surveillance. International Journal of Medical Informatics, 166, 104842. https://doi.org/10.1016/j.ijmedinf.2022.104842

Nelson, J. C., Cook, A. J., Yu, O., Dominguez, C., Zhao, S., Greene, S. K., Fireman, B. H., Jacobsen, S. J., Weintraub, E. S., & Jackson, L. A. (2012). Challenges in the design and analysis of sequentially monitored postmarket safety surveillance evaluations using electronic observational health care data. Pharmacoepidemiology and Drug Safety, 21 Suppl 1, 62–71. https://doi.org/10.1002/pds.2324

O'Flanagan, D., Barret, A. S., Foley, M., Cotter, S., Bonner, C., Crowe, C., Lynch, B., Sweeney, B., Johnson, H., McCoy, B., & Purcell, E. (2014). Investigation of an association between onset of narcolepsy and vaccination with pandemic influenza vaccine, Ireland April 2009-December 2010. Euro Surveillance: Bulletin Europeen Sur Les Maladies Transmissibles = European Communicable Disease Bulletin, 19(17), 15–25.

Omersel, J., & Karas Kuželički, N. (2020). Vaccinomics and Adversomics in the Era of Precision Medicine: A Review Based on HBV, MMR, HPV, and COVID-19 Vaccines. Journal of Clinical Medicine, 9(11), 3561. https://doi.org/10.3390/jcm9113561

Ortiz, J. R., & Neuzil, K. M. (2022). The value of vaccine programme impact monitoring during the COVID-19 pandemic. Lancet (London, England), 399(10320), 119–121. https://doi.org/10.1016/S0140-6736(21)02322-9

Ostropolets, A., Li, X., Makadia, R., Rao, G., Rijnbeek, P. R., Duarte-Salles, T., Sena, A. G., Shaoibi, A., Suchard, M. A., Ryan, P. B., Prieto-Alhambra, D., & Hripcsak, G. (2022). Factors Influencing Background Incidence Rate Calculation: Systematic Empirical Evaluation Across an International Network of Observational Databases. Frontiers in Pharmacology, 13, 814198. https://doi.org/10.3389/fphar.2022.814198

The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
(ENCePP) Guide on Methodological Standards in Pharmacoepidemiology
EMA/228452/2023   Page 57/76

Panozzo, C. A., Said, M., Arya, D., Baxter, R., Dee, E. C., Fahey, K., Feibelmann, S., Fireman, B., Forshee, R. A., Izurieta, H., Jackson, L., Klein, N., Lu, Y., Menschik, D., Nordin, J., Pratt, D., Rodriguez, C., Selvam, N., & Shoaibi, A. Exploring the Feasibility of Conducting Vaccine Effectiveness Studies in Sentinel's PRISM Program. https://www.sentinelinitiative.org/sites/default/files/Methods/Sentinel_PRISM_Vaccine_Effectiveness_White_Paper.pdf

Patel, M. M., Jackson, M. L., & Ferdinands, J. (2020). Postlicensure Evaluation of COVID-19 Vaccines. JAMA, 324(19), 1939–1940. https://doi.org/10.1001/jama.2020.19328

Pebody, R. (2012). Vaccine registers—Experiences from Europe and elsewhere. Euro Surveillance: Bulletin Europeen Sur Les Maladies Transmissibles = European Communicable Disease Bulletin, 17(17), 20159. https://doi.org/10.2807/ese.17.17.20159-en

Pottegård, A., Lund, L. C., Karlstad, Ø., Dahl, J., Andersen, M., Hallas, J., Lidegaard, Ø., Tapia, G., Gulseth, H. L., Ruiz, P. L.-D., Watle, S. V., Mikkelsen, A. P., Pedersen, L., Sørensen, H. T., Thomsen, R. W., & Hviid, A. (2021). Arterial events, venous thromboembolism, thrombocytopenia, and bleeding after vaccination with Oxford-AstraZeneca ChAdOx1-S in Denmark and Norway: Population based cohort study. BMJ (Clinical Research Ed.), 373, n1114. https://doi.org/10.1136/bmj.n1114

Praet, N., Asante, K. P., Bozonnat, M.-C., Akité, E. J., Ansah, P. O., Baril, L., Boahen, O., Mendoza, Y. G., Haine, V., Kariuki, S., Lamy, M., Maleta, K., Mungwira, R., Ndeketa, L., Oduro, A., Ogutu, B., Olewe, F., Oneko, M., Orsini, M., … Pirçon, J.-Y. (2022). Assessing the safety, impact and effectiveness of RTS,S/AS01E malaria vaccine following its introduction in three sub-Saharan African countries: Methodological approaches and study set-up. Malaria Journal, 21(1), 132. https://doi.org/10.1186/s12936-022-04144-3

Prasad, S., Kalafat, E., Blakeway, H., Townsend, R., O'Brien, P., Morris, E., Draycott, T., Thangaratinam, S., Le Doare, K., Ladhani, S., von Dadelszen, P., Magee, L. A., Heath, P., & Khalil, A. (2022). Systematic review and meta-analysis of the effectiveness and perinatal outcomes of COVID-19 vaccination in pregnancy. Nature Communications, 13(1), 2414. https://doi.org/10.1038/s41467-022-30052-w

Protocol template to be used as template for observational study protocols for sentinel surveillance of adverse events of special interest (AESIs) after vaccination with COVID-19 vaccines. https://www.who.int/publications-detail-redirect/9789240029507

Prunas, O., Warren, J. L., Crawford, F. W., Gazit, S., Patalon, T., Weinberger, D. M., & Pitzer, V. E. (2022). Vaccination with BNT162b2 reduces transmission of SARS-CoV-2 to household contacts in Israel. Science (New York, N.Y.), 375(6585), 1151–1154. https://doi.org/10.1126/science.abl4292

Public health surveillance for COVID-19: Interim guidance. https://www.who.int/publications-detail-redirect/WHO-2019-nCoV-SurveillanceGuidance-2022.2

Raethke, M., van Hunsel, F., Thurin, N. H., Dureau-Pournin, C., Mentzer, D., Kovačić, B., Mirošević Skvrce, N., De Clercq, E., Sabbe, M., Trifirò, G., Luxi, N., Giovanazzi, A., Shakir, S., Klungel, O. H., Schmikli, S., & Sturkenboom, M. (2023). Cohort Event Monitoring of Adverse Reactions to COVID-19 Vaccines in Seven European Countries: Pooled Results on First Dose. Drug Safety, 46(4), 391–404. https://doi.org/10.1007/s40264-023-01281-9

Remschmidt, C., Rieck, T., Bödeker, B., & Wichmann, O. (2015). Application of the screening method to monitor influenza vaccine effectiveness among the elderly in Germany. BMC Infectious Diseases, 15(1), 137. https://doi.org/10.1186/s12879-015-0882-3

The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
(ENCePP) Guide on Methodological Standards in Pharmacoepidemiology
EMA/228452/2023   Page 58/76

Renoud, L., Khouri, C., Revol, B., Lepelley, M., Perez, J., Roustit, M., & Cracowski, J.-L. (2021). Association of Facial Paralysis With mRNA COVID-19 Vaccines: A Disproportionality Analysis Using the World Health Organization Pharmacovigilance Database. JAMA Internal Medicine, 181(9), 1243–1245. https://doi.org/10.1001/jamainternmed.2021.2219

Rodriguez-Nava, G., Egoryan, G., Trelles-Garcia, D. P., Yanez-Bello, M. A., & Murguia-Fuentes, R. (2021). Disproportionality analysis of anaphylactic reactions after vaccination with messenger RNA coronavirus disease 2019 vaccines in the United States. Annals of Allergy, Asthma & Immunology: Official Publication of the American College of Allergy, Asthma, & Immunology, 127(1), 139–140. https://doi.org/10.1016/j.anai.2021.04.004

Rondy, M., Issifou, D., Ibrahim, A. S., Maman, Z., Kadade, G., Omou, H., Fati, S., Kissling, E., Meyer, S., & Ronveaux, O. (2016). Vaccine Effectiveness of Polysaccharide Vaccines Against Clinical Meningitis—Niamey, Niger, June 2015. PLoS Currents, 8, ecurrents.outbreaks.5d6e9c1d071a2088109c242771b68886. https://doi.org/10.1371/currents.outbreaks.5d6e9c1d071a2088109c242771b68886

Rondy, M., Launay, O., Puig-Barberà, J., Gefenaite, G., Castilla, J., de Gaetano Donati, K., Galtier, F., Hak, E., Guevara, M., Costanzo, S., European hospital IVE network, & Moren, A. (2015). 2012/13 influenza vaccine effectiveness against hospitalised influenza A(H1N1)pdm09, A(H3N2) and B: Estimates from a European network of hospitals. Euro Surveillance: Bulletin Europeen Sur Les Maladies Transmissibles = European Communicable Disease Bulletin, 20(2), 21011. https://doi.org/10.2807/1560-7917.es2015.20.2.21011

Rosillon, D., Willame, C., Tavares Da Silva, F., Guignard, A., Caterina, S., Welby, S., & Struyf, F. (2020). Meta-analysis of the risk of autoimmune thyroiditis, Guillain-Barré syndrome, and inflammatory bowel disease following vaccination with AS04-adjuvanted human papillomavirus 16/18 vaccine. Pharmacoepidemiology and Drug Safety, 29(9), 1159–1167. https://doi.org/10.1002/pds.5063

Safety of COVID-19 vaccination and acute neurological events: A self-controlled case series in England using the OpenSAFELY platform—PubMed. https://pubmed.ncbi.nlm.nih.gov/35715350/

Schnitzer, M. E. (2022). Estimands and Estimation of COVID-19 Vaccine Effectiveness Under the Test-Negative Design: Connections to Causal Inference. Epidemiology (Cambridge, Mass.), 33(3), 325–333. https://doi.org/10.1097/EDE.0000000000001470

Seabroke, S., Candore, G., Juhlin, K., Quarcoo, N., Wisniewski, A., Arani, R., Painter, J., Tregunno, P., Norén, G. N., & Slattery, J. (2016). Performance of Stratified and Subgrouped Disproportionality Analyses in Spontaneous Databases. Drug Safety, 39(4), 355–364. https://doi.org/10.1007/s40264-015-0388-3

Simpson, C. R., Shi, T., Vasileiou, E., Katikireddi, S. V., Kerr, S., Moore, E., McCowan, C., Agrawal, U., Shah, S. A., Ritchie, L. D., Murray, J., Pan, J., Bradley, D. T., Stock, S. J., Wood, R., Chuter, A., Beggs, J., Stagg, H. R., Joy, M., … Sheikh, A. (2021). First-dose ChAdOx1 and BNT162b2 COVID-19 vaccines and thrombocytopenic, thromboembolic and hemorrhagic events in Scotland. Nature Medicine, 27(7), 1290–1297. https://doi.org/10.1038/s41591-021-01408-4

Singanayagam, A., Hakki, S., Dunning, J., Madon, K. J., Crone, M. A., Koycheva, A., Derqui-Fernandez, N., Barnett, J. L., Whitfield, M. G., Varro, R., Charlett, A., Kundu, R., Fenn, J., Cutajar, J., Quinn, V., Conibear, E., Barclay, W., Freemont, P. S., Taylor, G. P., … ATACCC Study Investigators. (2022). Community transmission and viral load kinetics of the SARS-CoV-2 delta (B.1.617.2) variant in vaccinated and unvaccinated individuals in the UK: A prospective, longitudinal, cohort study. The Lancet. Infectious Diseases, 22(2), 183–195. https://doi.org/10.1016/S1473-3099(21)00648-4

The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) Guide on Methodological Standards in Pharmacoepidemiology
EMA/228452/2023

Page 59/76

Sullivan, S. G., Tchetgen Tchetgen, E. J., & Cowling, B. J. (2016). Theoretical Basis of the Test-Negative Study Design for Assessment of Influenza Vaccine Effectiveness. American Journal of Epidemiology, 184(5), 345–353. https://doi.org/10.1093/aje/kww064

Tavares-Da-Silva, F., Co, M. M., Dessart, C., Hervé, C., López-Fauqued, M., Mahaux, O., Van Holle, L., & Stegmann, J.-U. (2020). Review of the initial post-marketing safety surveillance for the recombinant zoster vaccine. Vaccine, 38(18), 3489–3500. https://doi.org/10.1016/j.vaccine.2019.11.058

Théophile, H., Moore, N., Robinson, P., Bégaud, B., & Pariente, A. (2016). Vaccine Case-Population: A New Method for Vaccine Safety Surveillance. Drug Safety, 39(12), 1197–1209. https://doi.org/10.1007/s40264-016-0449-2

Tokars, J. I., Lewis, P., DeStefano, F., Wise, M., Viray, M., Morgan, O., Gargiullo, P., & Vellozzi, C. (2012). The risk of Guillain-Barré syndrome associated with influenza A (H1N1) 2009 monovalent vaccine and 2009-2010 seasonal influenza vaccines: Results from self-controlled analyses. Pharmacoepidemiology and Drug Safety, 21(5), 546–552. https://doi.org/10.1002/pds.3220

U, H., K, H., I, C., & Sr, B. (2017). Guide to active vaccine safety surveillance: Report of CIOMS working group on vaccine safety - executive summary. Vaccine, 35(32). https://doi.org/10.1016/j.vaccine.2017.06.033

Use of population based background rates of disease to assess vaccine safety in childhood and mass immunisation in Denmark: Nationwide population based cohort study—PMC. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3444137/

Vaccine Safety Basics. OpenWHO. https://openwho.org/courses/vaccine-safety-basics

van der Boom, M. D. X., van Eekeren, R., & van Hunsel, F. P. A. M. (2023). Observed-over-Expected analysis as additional method for pharmacovigilance signal detection in large-scaled spontaneous adverse event reporting. Pharmacoepidemiology and Drug Safety, 32(7), 783–794. https://doi.org/10.1002/pds.5610

Van Holle, L., & Bauchau, V. (2013). Optimization of a quantitative signal detection algorithm for spontaneous reports of adverse events post immunization. Pharmacoepidemiology and Drug Safety, 22(5), 477–487. https://doi.org/10.1002/pds.3392

Vandenbroucke, J. P., & Pearce, N. (2019). Test-Negative Designs: Differences and Commonalities with Other Case-Control Studies with 'Other Patient' Controls. Epidemiology (Cambridge, Mass.), 30(6), 838–844. https://doi.org/10.1097/EDE.0000000000001088

VEMisclassification. https://apps.p-95.com/VEMisclassification/

Verani, J. R., Baqui, A. H., Broome, C. V., Cherian, T., Cohen, C., Farrar, J. L., Feikin, D. R., Groome, M. J., Hajjeh, R. A., Johnson, H. L., Madhi, S. A., Mulholland, K., O'Brien, K. L., Parashar, U. D., Patel, M. M., Rodrigues, L. C., Santosham, M., Scott, J. A., Smith, P. G., … Zell, E. R. (2017a). Case-control vaccine effectiveness studies: Data collection, analysis and reporting results. Vaccine, 35(25), 3303–3308. https://doi.org/10.1016/j.vaccine.2017.04.035

Verani, J. R., Baqui, A. H., Broome, C. V., Cherian, T., Cohen, C., Farrar, J. L., Feikin, D. R., Groome, M. J., Hajjeh, R. A., Johnson, H. L., Madhi, S. A., Mulholland, K., O'Brien, K. L., Parashar, U. D., Patel, M. M., Rodrigues, L. C., Santosham, M., Scott, J. A., Smith, P. G., … Zell, E. R. (2017b). Case-control vaccine effectiveness studies: Preparation, design, and enrollment of cases and controls. Vaccine, 35(25), 3295–3302. https://doi.org/10.1016/j.vaccine.2017.04.037

Voss, E. A., Shoaibi, A., Yin Hui Lai, L., Blacketer, C., Alshammari, T., Makadia, R., Haynes, K., Sena, A. G., Rao, G., van Sandijk, S., Fraboulet, C., Boyer, L., Le Carrour, T., Horban, S., Morales, D. R.,

The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) Guide on Methodological Standards in Pharmacoepidemiology
EMA/228452/2023

Page 60/76

Martínez Roldán, J., Ramírez-Anguita, J. M., Mayer, M. A., de Wilde, M., … Ryan, P. B. (2023). Contextualising adverse events of special interest to characterise the baseline incidence rates in 24 million patients with COVID-19 across 26 databases: A multinational retrospective cohort study. EClinicalMedicine, 58, 101932. https://doi.org/10.1016/j.eclinm.2023.101932

Watt, A. E., Sherry, N. L., Andersson, P., Lane, C. R., Johnson, S., Wilmot, M., Horan, K., Sait, M., Ballard, S. A., Crachi, C., Beck, D. J., Marshall, C., Kainer, M. A., Stuart, R., McGrath, C., Kwong, J. C., Bass, P., Kelley, P. G., Crowe, A., … Howden, B. P. (2022). State-wide genomic epidemiology investigations of COVID-19 in healthcare workers in 2020 Victoria, Australia: Qualitative thematic analysis to provide insights for future pandemic preparedness. The Lancet Regional Health. Western Pacific, 25, 100487. https://doi.org/10.1016/j.lanwpc.2022.100487

Whitaker, J. A., Ovsyannikova, I. G., & Poland, G. A. (2015). Adversomics: A new paradigm for vaccine safety and design. Expert Review of Vaccines, 14(7), 935–947. https://doi.org/10.1586/14760584.2015.1038249

WHO Coronavirus (COVID-19) Dashboard. https://covid19.who.int

Wijnans, L., Dodd, C. N., Weibel, D., & Sturkenboom, M. (2017). Bell's palsy and influenza(H1N1)pdm09 containing vaccines: A self-controlled case series. PloS One, 12(5), e0175539. https://doi.org/10.1371/journal.pone.0175539

Willame, C., Dodd, C., van der Aa, L., Picelli, G., Emborg, H.-D., Kahlert, J., Gini, R., Huerta, C., Martín-Merino, E., McGee, C., de Lusignan, S., Roberto, G., Villa, M., Weibel, D., Titievsky, L., & Sturkenboom, M. C. J. M. (2021). Incidence Rates of Autoimmune Diseases in European Healthcare Databases: A Contribution of the ADVANCE Project. Drug Safety, 44(3), 383–395. https://doi.org/10.1007/s40264-020-01031-1

Woo, E. J., Ball, R., Burwen, D. R., & Braun, M. M. (2008). Effects of stratification on data mining in the US Vaccine Adverse Event Reporting System (VAERS). Drug Safety, 31(8), 667–674. https://doi.org/10.2165/00002018-200831080-00003

World Health Organization. (2017). Evaluation of influenza vaccine effectiveness: A guide to the design and interpretation of observational studies. World Health Organization. https://apps.who.int/iris/handle/10665/255203

World Health Organization. Quality Assurance and Safety of Medicines Team. (2006). The safety of medicines in public health programmes: Pharmacovigilance, an essential tool. World Health Organization. https://apps.who.int/iris/handle/10665/43384

Xie, J., Feng, S., Li, X., Gea-Mallorquí, E., Prats-Uribe, A., & Prieto-Alhambra, D. (2022). Comparative effectiveness of the BNT162b2 and ChAdOx1 vaccines against Covid-19 in people over 50. Nature Communications, 13(1), 1519. https://doi.org/10.1038/s41467-022-29159-x

Xie, J., Prats-Uribe, A., Gordillo-Marañón, M., Strauss, V. Y., Gill, D., & Prieto-Alhambra, D. (2022). Genetic risk and incident venous thromboembolism in middle-aged and older adults following COVID-19 vaccination. Journal of Thrombosis and Haemostasis: JTH, 20(12), 2887–2895. https://doi.org/10.1111/jth.15879

Yanni, E. A., Ferreira, G., Guennec, M., El Hahi, Y., El Ghachi, A., Haguinet, F., Espie, E., & Bianco, V. (2018). Burden of herpes zoster in 16 selected immunocompromised populations in England: A cohort study in the Clinical Practice Research Datalink 2000–2012. BMJ Open, 8(6), e020528. https://doi.org/10.1136/bmjopen-2017-020528

Yih, W. K., Daley, M. F., Duffy, J., Fireman, B., McClure, D., Nelson, J., Qian, L., Smith, N., Vazquez-Benitez, G., Weintraub, E., Williams, J. T. B., Xu, S., & Maro, J. C. (2023). A broad assessment of covid-19 vaccine safety using tree-based data-mining in the vaccine safety datalink. Vaccine, 41(3), 826–835. https://doi.org/10.1016/j.vaccine.2022.12.026

Yih, W. K., Kulldorff, M., Dashevsky, I., & Maro, J. C. (2021). A Broad Safety Assessment of the 9-Valent Human Papillomavirus Vaccine. American Journal of Epidemiology, 190(7), 1253–1259. https://doi.org/10.1093/aje/kwab022

Yih, W. K., Kulldorff, M., Fireman, B. H., Shui, I. M., Lewis, E. M., Klein, N. P., Baggs, J., Weintraub, E. S., Belongia, E. A., Naleway, A., Gee, J., Platt, R., & Lieu, T. A. (2011). Active surveillance for adverse events: The experience of the Vaccine Safety Datalink project. Pediatrics, 127 Suppl 1, S54-64. https://doi.org/10.1542/peds.2010-1722I

16.3. Design, implementation and analysis of pharmacogenetic studies

Alshabeeb, M. A., Deneer, V. H. M., Khan, A., & Asselbergs, F. W. (2019). Use of Pharmacogenetic Drugs by the Dutch Population. Frontiers in Genetics, 10. https://www.frontiersin.org/articles/10.3389/fgene.2019.00567

Avram, M., Stika, C., Rasmussen-Torvik, L., Ciolino, J., Pinheiro, E., George Jr, A., & Wisner, K. (2016). Rationale and design for an investigation to optimize selective serotonin reuptake inhibitor treatment for pregnant women with depression. Clinical Pharmacology & Therapeutics, 100(1), 31–33. https://doi.org/10.1002/cpt.375

Bozkurt, Ö., Verschuren, W. M. M., van Wieren-de Wijer, B. M. A., Knol, M. J., de Boer, A., Grobbee, D. E., Geerlings, M. I., Heerdink, E. R., & Klungel, O. H. (2008). Genetic variation in the renin-angiotensin system modifies the beneficial effects of ACE inhibitors on the risk of diabetes mellitus among hypertensives. Journal of Human Hypertension, 22(11), Art. 11. https://doi.org/10.1038/jhh.2008.62

Brouwer, J. M. J. L., Nijenhuis, M., Soree, B., Guchelaar, H.-J., Swen, J. J., van Schaik, R. H. N., Weide, J. van der, Rongen, G. A. P. J. M., Buunk, A.-M., de Boer-Veger, N. J., Houwink, E. J. F., van Westrhenen, R., Wilffert, B., Deneer, V. H. M., & Mulder, H. (2022). Dutch Pharmacogenetics Working Group (DPWG) guideline for the gene-drug interaction between CYP2C19 and CYP2D6 and SSRIs. European Journal of Human Genetics, 30(10), Art. 10. https://doi.org/10.1038/s41431-021-01004-7

Carbamazepine-Induced Toxic Effects and HLA-B*1502 Screening in Taiwan | NEJM. https://www.nejm.org/doi/full/10.1056/NEJMoa1009717

Carleton, B., Poole, R., Smith, M., Leeder, J., Ghannadan, R., Ross, C., Phillips, M., & Hayden, M. (2009). Adverse drug reaction active surveillance: Developing a national network in Canada's children's hospitals. Pharmacoepidemiology and Drug Safety, 18(8), 713–721. https://doi.org/10.1002/pds.1772

Carr, D. F., O'Meara, H., Jorgensen, A. L., Campbell, J., Hobbs, M., McCann, G., van Staa, T., & Pirmohamed, M. (2013). SLCO1B1 Genetic Variant Associated With Statin-Induced Myopathy: A Proof-of-Concept Study Using the Clinical Practice Research Datalink. Clinical Pharmacology & Therapeutics, 94(6), 695–701. https://doi.org/10.1038/clpt.2013.161

Cavallari, L., Beitelshees, A., Blake, K., Dressler, L., Duarte, J., Elsey, A., Eichmeyer, J., Empey, P., Franciosi, J., Hicks, J., Holmes, A., Jeng, L., Lee, C., Lima, J., Limdi, N., Modlin, J., Obeng, A., Petry, N., Pratt, Vm., … Johnson, J. (2017). The IGNITE Pharmacogenetics Working Group: An Opportunity

for Building Evidence with Pharmacogenetic Implementation in a Real-World Setting. Clinical and Translational Science, 10(3), 143–146. https://doi.org/10.1111/cts.12456

Chambliss, A. B., & Chan, D. W. (2016). Precision medicine: From pharmacogenomics to pharmacoproteomics. Clinical Proteomics, 13(1), 25. https://doi.org/10.1186/s12014-016-9127-8

Chan, H. T., Chin, Y. M., & Low, S.-K. (2019). The Roles of Common Variation and Somatic Mutation in Cancer Pharmacogenomics. Oncology and Therapy, 7(1), 1–32. https://doi.org/10.1007/s40487-018-0090-6

Chaplin, M., Kirkham, J. J., Dwan, K., Sloan, D. J., Davies, G., & Jorgensen, A. L. (2020). STrengthening the Reporting Of Pharmacogenetic Studies: Development of the STROPS guideline. PLOS Medicine, 17(9), e1003344. https://doi.org/10.1371/journal.pmed.1003344

COVID-19 Host Genetics Initiative. https://www.covid19hg.org/

Covid-19 Vaccine Effectiveness against the Omicron (B.1.1.529) Variant | NEJM. https://www.nejm.org/doi/full/10.1056/NEJMoa2119451?query=featured_home

CPIC. https://cpicpgx.org/

CPNDS | The Canadian Pharmacogenomics Network for Drug Safety. https://cpnds.ubc.ca/

Dennis, J., Hawken, S., Krewski, D., Birkett, N., Gheorghe, M., Frei, J., McKeown-Eyssen, G., & Little, J. (2011). Bias in the case-only design applied to studies of gene–environment and gene–gene interaction: A systematic review and meta-analysis. International Journal of Epidemiology, 40(5), 1329–1341. https://doi.org/10.1093/ije/dyr088

DPWG: Dutch Pharmacogenetics Working Group. PharmGKB. https://www.pharmgkb.org/page/dpwg

Drug Discovery: A Historical Perspective | Science. https://www.science.org/doi/10.1126/science.287.5460.1960

Dunnenberger, H. M., Biszewski, M., Bell, G. C., Sereika, A., May, H., Johnson, S. G., Hulick, P. J., & Khandekar, J. (2016). Implementation of a multidisciplinary pharmacogenomics clinic in a community health system. American Journal of Health-System Pharmacy, 73(23), 1956–1966. https://doi.org/10.2146/ajhp160072

Ehmann, F., Caneva, L., Prasad, K., Paulmichl, M., Maliepaard, M., Llerena, A., Ingelman-Sundberg, M., & Papaluca-Amati, M. (2015). Pharmacogenomic information in drug labels: European Medicines Agency perspective. The Pharmacogenomics Journal, 15(3), Art. 3. https://doi.org/10.1038/tpj.2014.86

CHMP: Working parties and other groups [Text]. European Medicines Agency. https://www.ema.europa.eu/en/committees/working-parties-other-groups/chmp-working-parties-other-groups

EMA recommendations on DPD testing prior to treatment with fluorouracil, capecitabine, tegafur and flucytosine | European Medicines Agency. https://www.ema.europa.eu/en/news/ema-recommendations-dpd-testing-prior-treatment-fluorouracil-capecitabine-tegafur-flucytosine

Evans, D. M., & Davey Smith, G. (2015). Mendelian Randomization: New Applications in the Coming Age of Hypothesis-Free Causality. Annual Review of Genomics and Human Genetics, 16(1), 327–350. https://doi.org/10.1146/annurev-genom-090314-050016

Evans, W. E., & Relling, M. V. (1999). Pharmacogenomics: Translating Functional Genomics into Rational Therapeutics. Science, 286(5439), 487–491. https://doi.org/10.1126/science.286.5439.487

The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
(ENCePP) Guide on Methodological Standards in Pharmacoepidemiology
EMA/228452/2023   Page 63/76

Evans, W. E., & Relling, M. V. (2004). Moving towards individualized medicine with pharmacogenomics. Nature, 429(6990), Art. 6990. https://doi.org/10.1038/nature02626

Fahed, A. C., Philippakis, A. A., & Khera, A. V. (2022). The potential of polygenic scores to improve cost and efficiency of clinical trials. Nature Communications, 13, 2922. https://doi.org/10.1038/s41467-022-30675-z

Gatto, N. M., Campbell, U. B., Rundle, A. G., & Ahsan, H. (2004). Further development of the case-only design for assessing gene–environment interaction: Evaluation of and adjustment for bias. International Journal of Epidemiology, 33(5), 1014–1024. https://doi.org/10.1093/ije/dyh306

Grady, B. J., & Ritchie, M. D. Statistical Optimization of Pharmacogenomics Association Studies: Key Considerations from Study Design to Analysis. Current Pharmacogenomics and Personalized Medicine, 9(1), 41–66. https://www.eurekaselect.com/article/40632

Hayney, M. S. (2002). Pharmacogenomics and infectious diseases: Impact on drug response and applications to disease management. American Journal of Health-System Pharmacy, 59(17), 1626–1631. https://doi.org/10.1093/ajhp/59.17.1626

Hellwege, J., Keaton, J., Giri, A., Gao, X., Velez Edwards, D. R., & Edwards, T. L. (2017). Population Stratification in Genetic Association Studies. Current Protocols in Human Genetics, 95, 1.22.1-1.22.23. https://doi.org/10.1002/cphg.48

Hingorani, A. D., Windt, D. A. van der, Riley, R. D., Abrams, K., Moons, K. G. M., Steyerberg, E. W., Schroter, S., Sauerbrei, W., Altman, D. G., & Hemingway, H. (2013). Prognosis research strategy (PROGRESS) 4: Stratified medicine research. BMJ, 346, e5793. https://doi.org/10.1136/bmj.e5793

HLA-B*5701 Screening for Hypersensitivity to Abacavir | NEJM. https://www.nejm.org/doi/full/10.1056/nejmoa0706135

Jorgensen, A. L., & Williamson, P. R. (2008). Methodological quality of pharmacogenetic studies: Issues of concern. Statistics in Medicine, 27(30), 6547–6569. https://doi.org/10.1002/sim.3420

Karlsen, T. H. (2022). Understanding COVID-19 through genome-wide association studies. Nature Genetics, 54(4), Art. 4. https://doi.org/10.1038/s41588-021-00985-x

Khera, A. V., Chaffin, M., Aragam, K. G., Haas, M. E., Roselli, C., Choi, S. H., Natarajan, P., Lander, E. S., Lubitz, S. A., Ellinor, P. T., & Kathiresan, S. (2018). Genome-wide polygenic scores for common diseases identify individuals with risk equivalent to monogenic mutations. Nature Genetics, 50(9), Art. 9. https://doi.org/10.1038/s41588-018-0183-z

Khoury, M. J., & Flanders, W. D. (1996). Nontraditional Epidemiologic Approaches in the Analysis of Gene Environment Interaction: Case-Control Studies with No Controls! American Journal of Epidemiology, 144(3), 207–213. https://doi.org/10.1093/oxfordjournals.aje.a008915

Lee, C. R., Luzum, J. A., Sangkuhl, K., Gammal, R. S., Sabatine, M. S., Stein, C. M., Kisor, D. F., Limdi, N. A., Lee, Y. M., Scott, S. A., Hulot, J.-S., Roden, D. M., Gaedigk, A., Caudle, K. E., Klein, T. E., Johnson, J. A., & Shuldiner, A. R. (2022). Clinical Pharmacogenetics Implementation Consortium Guideline for CYP2C19 Genotype and Clopidogrel Therapy: 2022 Update. Clinical Pharmacology & Therapeutics, 112(5), 959–967. https://doi.org/10.1002/cpt.2526

Leitsalu, L., Haller, T., Esko, T., Tammesoo, M.-L., Alavere, H., Snieder, H., Perola, M., Ng, P. C., Mägi, R., Milani, L., Fischer, K., & Metspalu, A. (2015). Cohort Profile: Estonian Biobank of the Estonian Genome Center, University of Tartu. International Journal of Epidemiology, 44(4), 1137–1147. https://doi.org/10.1093/ije/dyt268

The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
(ENCePP) Guide on Methodological Standards in Pharmacoepidemiology
EMA/228452/2023
Page 64/76

Liu, R., Rizzo, S., Waliany, S., Garmhausen, M. R., Pal, N., Huang, Z., Chaudhary, N., Wang, L., Harbron, C., Neal, J., Copping, R., & Zou, J. (2022). Systematic pan-cancer analysis of mutation–treatment interactions using large real-world clinicogenomics data. Nature Medicine, 28(8), Art. 8. https://doi.org/10.1038/s41591-022-01873-5

Liu, Y., Nyunoya, T., Leng, S., Belinsky, S. A., Tesfaigzi, Y., & Bruse, S. (2013). Softwares and methods for estimating genetic ancestry in human populations. Human Genomics, 7(1), 1. https://doi.org/10.1186/1479-7364-7-1

McInnes, G., & Altman, R. B. (2020). Drug Response Pharmacogenetics for 200,000 UK Biobank Participants. In Biocomputing 2021 (pp. 184–195). WORLD SCIENTIFIC. https://doi.org/10.1142/9789811232701_0018

McInnes, G., Lavertu, A., Sangkuhl, K., Klein, T. E., Whirl-Carrillo, M., & Altman, R. B. (2021). Pharmacogenetics at Scale: An Analysis of the UK Biobank. Clinical Pharmacology & Therapeutics, 109(6), 1528–1537. https://doi.org/10.1002/cpt.2122

MHRA and Genomics England to launch pioneering resource to better understand how genetic makeup influences the safety of medicines. GOV.UK. https://www.gov.uk/government/news/mhra-and-genomics-england-to-launch-pioneering-resource-to-better-understand-how-genetic-makeup-influences-the-safety-of-medicines

Molokhia, M., & McKeigue, P. (2006). EUDRAGENE: European collaboration to establish a case–control DNA collection for studying the genetic basis of adverse drug reactions. Pharmacogenomics, 7(4), 633–638. https://doi.org/10.2217/14622416.7.4.633

Niemi, M. E. K., Karjalainen, J., Liao, R. G., Neale, B. M., Daly, M., Ganna, A., Pathak, G. A., Andrews, S. J., Kanai, M., Veerapen, K., Fernandez-Cadenas, I., Schulte, E. C., Striano, P., Marttila, M., Minica, C., Marouli, E., Karim, M. A., Wendt, F. R., Savage, J., … Admin team leader. (2021). Mapping the human genetic architecture of COVID-19. Nature, 600(7889), Art. 7889. https://doi.org/10.1038/s41586-021-03767-x

Nøhr, A. K., Forsingdal, A., Moltke, I., Howes, O. D., Vitezic, M., Albrechtsen, A., & Dalby, M. (2022). Polygenic heterogeneity in antidepressant treatment and placebo response. Translational Psychiatry, 12(1), Art. 1. https://doi.org/10.1038/s41398-022-02221-4

Papez, V., Moinat, M., Voss, E. A., Bazakou, S., Van Winzum, A., Peviani, A., Payralbe, S., Lara, E. G., Kallfelz, M., Asselbergs, F. W., Prieto-Alhambra, D., Dobson, R. J. B., & Denaxas, S. (2023). Transforming and evaluating the UK Biobank to the OMOP Common Data Model for COVID-19 research and beyond. Journal of the American Medical Informatics Association, 30(1), 103–111. https://doi.org/10.1093/jamia/ocac203

Pereira, N. L., Farkouh, M. E., So, D., Lennon, R., Geller, N., Mathew, V., Bell, M., Bae, J.-H., Jeong, M. H., Chavez, I., Gordon, P., Abbott, J. D., Cagin, C., Baudhuin, L., Fu, Y.-P., Goodman, S. G., Hasan, A., Iturriaga, E., Lerman, A., … Rihal, C. (2020). Effect of Genotype-Guided Oral P2Y12 Inhibitor Selection vs Conventional Clopidogrel Therapy on Ischemic Outcomes After Percutaneous Coronary Intervention: The TAILOR-PCI Randomized Clinical Trial. JAMA, 324(8), 761–771. https://doi.org/10.1001/jama.2020.12443

Peters, B. J. M., Rodin, A. S., De Boer, A., & Maitland-van der Zee, A.-H. (2010). Methodological and statistical issues in pharmacogenomics. Journal of Pharmacy and Pharmacology, 62(2), 161–166. https://doi.org/10.1211/jpp.62.02.0002

Peterson, J. F., Field, J. R., Shi, Y., Schildcrout, J. S., Denny, J. C., McGregor, T. L., Van Driest, S. L., Pulley, J. M., Lubin, I. M., Laposata, M., Roden, D. M., & Clayton, E. W. (2016). Attitudes of clinicians

following large-scale pharmacogenomics implementation. The Pharmacogenomics Journal, 16(4), Art. 4. https://doi.org/10.1038/tpj.2015.57

Pharmacogenomics Implementation at the National Institutes of Health Clinical Center—Sissung—2017—The Journal of Clinical Pharmacology—Wiley Online Library. https://accp1.onlinelibrary.wiley.com/doi/10.1002/jcph.993

PharmGKB. PharmGKB. https://www.pharmgkb.org/

Preventing the exacerbation of health disparities by iatrogenic pharmacogenomic applications: Lessons from warfarin | Pharmacogenomics. https://www.futuremedicine.com/doi/full/10.2217/pgs-2018-0055

Pritchard, J. K., Stephens, M., Rosenberg, N. A., & Donnelly, P. (2000). Association Mapping in Structured Populations. The American Journal of Human Genetics, 67(1), 170–181. https://doi.org/10.1086/302959

Promises and challenges of pharmacogenetics: An overview of study design, methodological and statistical issues—Stephanie Ross, Sonia S Anand, Philip Joseph, Guillaume Paré, 2012. https://journals.sagepub.com/doi/10.1258/cvd.2012.012001

Psaty, B. M., & Sitlani, C. (2013). The Cohorts for Heart and Aging Research in Genomic Epidemiology (CHARGE) Consortium as a Model of Collaborative Science. Epidemiology, 24(3), 346. https://doi.org/10.1097/EDE.0b013e31828b2cbb

Psaty, B. M., Smith, N. L., Heckbert, S. R., Vos, H. L., Lemaitre, R. N., Reiner, A. P., Siscovick, D. S., Bis, J., Lumley, T., Longstreth, J., W. T., & Rosendaal, F. R. (2002). Diuretic Therapy, the α-Adducin Gene Variant, and the Risk of Myocardial Infarction or Stroke in Persons With Treated Hypertension. JAMA, 287(13), 1680–1689. https://doi.org/10.1001/jama.287.13.1680

Rafi, I., Crinson, I., Dawes, M., Rafi, D., Pirmohamed, M., & Walter, F. M. (2020). The implementation of pharmacogenomics into UK general practice: A qualitative study exploring barriers, challenges and opportunities. Journal of Community Genetics, 11(3), 269–277. https://doi.org/10.1007/s12687-020-00468-2

Reisberg, S., Krebs, K., Lepamets, M., Kals, M., Mägi, R., Metsalu, K., Lauschke, V. M., Vilo, J., & Milani, L. (2019). Translating genotype data of 44,000 biobank participants into clinical pharmacogenetic recommendations: Challenges and solutions. Genetics in Medicine, 21(6), 1345–1354. https://doi.org/10.1038/s41436-018-0337-5

Robarge, J. D., Li, L., Desta, Z., Nguyen, A., & Flockhart, D. A. (2007). The Star-Allele Nomenclature: Retooling for Translational Genomics. Clinical Pharmacology & Therapeutics, 82(3), 244–248. https://doi.org/10.1038/sj.clpt.6100284

Smit, R. a. j., Noordam, R., le Cessie, S., Trompet, S., & Jukema, J. w. (2018). A critical appraisal of pharmacogenetic inference. Clinical Genetics, 93(3), 498–507. https://doi.org/10.1111/cge.13178

Stockdale, J. E., Liu, P., & Colijn, C. (2022). The potential of genomics for infectious disease forecasting. Nature Microbiology, 7(11), Art. 11. https://doi.org/10.1038/s41564-022-01233-6

Storey, J. D., & Tibshirani, R. (2003). Statistical significance for genomewide studies. Proceedings of the National Academy of Sciences, 100(16), 9440–9445. https://doi.org/10.1073/pnas.1530509100

Sudlow, C., Gallacher, J., Allen, N., Beral, V., Burton, P., Danesh, J., Downey, P., Elliott, P., Green, J., Landray, M., Liu, B., Matthews, P., Ong, G., Pell, J., Silman, A., Young, A., Sprosen, T., Peakman, T., & Collins, R. (2015). UK Biobank: An Open Access Resource for Identifying the Causes of a Wide Range

The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) Guide on Methodological Standards in Pharmacoepidemiology
EMA/228452/2023

Page 66/76

of Complex Diseases of Middle and Old Age. PLOS Medicine, 12(3), e1001779. https://doi.org/10.1371/journal.pmed.1001779

Swen, J. J., van der Wouden, C. H., Manson, L. E., Abdullah-Koolmees, H., Blagec, K., Blagus, T., Böhringer, S., Cambon-Thomsen, A., Cecchin, E., Cheung, K.-C., Deneer, V. H., Dupui, M., Ingelman-Sundberg, M., Jonsson, S., Joefield-Roka, C., Just, K. S., Karlsson, M. O., Konta, L., Koopmann, R., … Rajasingam, A. (2023). A 12-gene pharmacogenetic panel to prevent adverse drug reactions: An open-label, multicentre, controlled, cluster-randomised crossover implementation study. The Lancet, 401(10374), 347–356. https://doi.org/10.1016/S0140-6736(22)01841-4

Swen, J., Nijenhuis, M., de Boer, A., Grandia, L., Maitland-van der Zee, A., Mulder, H., Rongen, G., van Schaik, R., Schalekamp, T., Touw, D., van der Weide, J., Wilffert, B., Deneer, V., & Guchelaar, H.-J. (2011). Pharmacogenetics: From Bench to Byte— An Update of Guidelines. Clinical Pharmacology & Therapeutics, 89(5), 662–673. https://doi.org/10.1038/clpt.2011.34

Taylor, C., Crosby, I., Yip, V., Maguire, P., Pirmohamed, M., & Turner, R. M. (2020). A Review of the Important Role of CYP2D6 in Pharmacogenomics. Genes, 11(11), 1295. https://doi.org/10.3390/genes11111295

The COVID-19 Host Genetics Initiative, a global initiative to elucidate the role of host genetic factors in susceptibility and severity of the SARS-CoV-2 virus pandemic. - Abstract—Europe PMC. https://europepmc.org/article/PMC/7220587#free-full-text

Thorn, C. F., Whirl-Carrillo, M., Hachad, H., Johnson, J. A., McDonagh, E. M., Ratain, M. J., Relling, M. V., Scott, S. A., Altman, R. B., & Klein, T. E. (2019). Essential Characteristics of Pharmacogenomics Study Publications. Clinical Pharmacology & Therapeutics, 105(1), 86–91. https://doi.org/10.1002/cpt.1279

van der Baan, F. H., Klungel, O. H., Egberts, A. C., Leufkens, H. G., Grobbee, D. E., Roes, K. C., & Knol, M. J. (2011). Pharmacogenetics in randomized controlled trials: Considerations for trial design. Pharmacogenomics, 12(10), 1485–1492. https://doi.org/10.2217/pgs.11.95

van der Baan, F. H., Knol, M. J., Klungel, O. H., Egberts, A. C., Grobbee, D. E., & Roes, K. C. (2012). Potential of adaptive clinical trial designs in pharmacogenetic research. Pharmacogenomics, 13(5), 571–578. https://doi.org/10.2217/pgs.12.10

van der Wouden, C., Cambon-Thomsen, A., Cecchin, E., Cheung, K., Dávila-Fajardo, C., Deneer, V., Dolžan, V., Ingelman-Sundberg, M., Jönsson, S., Karlsson, M., Kriek, M., Mitropoulou, C., Patrinos, G., Pirmohamed, M., Samwald, M., Schaeffeler, E., Schwab, M., Steinberger, D., Stingl, J., … Consortium, on behalf of the U. P. (2017). Implementing Pharmacogenomics in Europe: Design and Implementation Strategy of the Ubiquitous Pharmacogenomics Consortium. Clinical Pharmacology & Therapeutics, 101(3), 341–358. https://doi.org/10.1002/cpt.602

van Wieren-de Wijer, D. B., Maitland-van der Zee, A.-H., de Boer, A., Kroon, A. A., de Leeuw, P. W., Schiffers, P., Janssen, R. G., Psaty, B. M., van Duijn, C. M., Ch. Stricker, B. H., & Klungel, O. H. (2009). Interaction between the Gly460Trp α-adducin gene variant and diuretics on the risk of myocardial infarction. Journal of Hypertension, 27(1), 61. https://doi.org/10.1097/HJH.0b013e328317a74d

Wang, R., Chen, J., Gao, K., & Wei, G.-W. (2021). Vaccine-escape and fast-growing mutations in the United Kingdom, the United States, Singapore, Spain, India, and other COVID-19-devastated countries. Genomics, 113(4), 2158–2170. https://doi.org/10.1016/j.ygeno.2021.05.006

Xie, J., Prats-Uribe, A., Gordillo-Marañón, M., Strauss, V. Y., Gill, D., & Prieto-Alhambra, D. (2022). Genetic risk and incident venous thromboembolism in middle-aged and older adults following COVID-19

vaccination. Journal of Thrombosis and Haemostasis, 20(12), 2887–2895. https://doi.org/10.1111/jth.15879

Yellow Card biobank | Making medicines and medical devices safer. https://yellowcard.mhra.gov.uk/biobank

Zhang, H., Liu, L., Wang, X., & Gruen, J. R. (2007). Guideline for data analysis of genomewide association studies. Cancer Genomics & Proteomics, 4(1), 27–34.

16.4. Methods for pharmacovigilance impact research

Note: Chapter 16.4 has not been updated for the 11th revision of the Guide

Banerjee, A. K., Zomerdijk, I. M., Wooder, S., Ingate, S., & Mayall, S. J. (2014a). Post-Approval Evaluation of Effectiveness of Risk Minimisation: Methods, Challenges and Interpretation. Drug Safety, 37(1), 33–42. https://doi.org/10.1007/s40264-013-0126-7

Bernal, J. L., Cummins, S., & Gasparrini, A. (2017). Interrupted time series regression for the evaluation of public health interventions: A tutorial. International Journal of Epidemiology, 46(1), 348–355. https://doi.org/10.1093/ije/dyw098

Bradley, C. J., Penberthy, L., Devers, K. J., & Holden, D. J. (2010). Health Services Research and Data Linkages: Issues, Methods, and Directions for the Future. Health Services Research, 45(5p2), 1468–1488. https://doi.org/10.1111/j.1475-6773.2010.01142.x

Charlton, R. A., Bettoli, V., Bos, H. J., Engeland, A., Garne, E., Gini, R., Hansen, A. V., de Jong-van den berg, L. T. W., Jordan, S., Klungsøyr, K., Neville, A. J., Pierini, A., Puccini, A., Sinclair, M., Thayer, D., & Dolk, H. (2018). The limitations of some European healthcare databases for monitoring the effectiveness of pregnancy prevention programmes as risk minimisation measures. European Journal of Clinical Pharmacology, 74(4), 513–520. https://doi.org/10.1007/s00228-017-2398-9

Cohen, A., Rabbani, A., Shah, N., & Alexander, G. C. (2010). Changes in Glitazone Use Among Office-Based Physicians in the U.S., 2003–2009. Diabetes Care, 33(4), 823–825. https://doi.org/10.2337/dc09-1834

Crijns, H. J. M. J., van Rein, N., Gispen-de Wied, C. C., Straus, S. M., & de Jong-van den Berg, L. T. W. (2012). Prescriptive contraceptive use among isotretinoin users in the Netherlands in comparison with non-users: A drug utilisation study. Pharmacoepidemiology and Drug Safety, 21(10), 1060–1066. https://doi.org/10.1002/pds.3200

Crijns, I., Mantel-Teeuwisse, A., Bloemberg, R., Pinas, E., Straus, S., & de Jong-van den Berg, L. (2013). Healthcare professional surveys to investigate the implementation of the isotretinoin Pregnancy Prevention Programme: A descriptive study. Expert Opinion on Drug Safety, 12(1), 29–38. https://doi.org/10.1517/14740338.2013.745850

Durbin, J., & Watson, G. S. (1950). Testing for serial correlation in least squares regression. I. Biometrika, 37(3–4), 409–428.

Durbin, J., & Watson, G. S. (1951). Testing for serial correlation in least squares regression. II. Biometrika, 38(1–2), 159–178.

Eccles, M., Grimshaw, J., Campbell, M., & Ramsay, C. (2003). Research designs for studies evaluating the effectiveness of change and improvement strategies. BMJ Quality & Safety, 12(1), 47–52. https://doi.org/10.1136/qhc.12.1.47

Eworuke, E., Lee, J.-Y., Soule, L., Popat, V., & Moeny, D. G. (2017). The impact of the boxed warning on the duration of use for depot medroxprogesterone acetate. Pharmacoepidemiology and Drug Safety, 26(7), 827–836. https://doi.org/10.1002/pds.4227

Feldstein, A. C., Smith, D. H., Perrin, N., Yang, X., Rix, M., Raebel, M. A., Magid, D. J., Simon, S. R., & Soumerai, S. B. (2006). Improved Therapeutic Monitoring With Several Interventions: A Randomized Trial. Archives of Internal Medicine, 166(17), 1848–1854. https://doi.org/10.1001/archinte.166.17.1848

Goedecke, T., Morales, D. R., Pacurariu, A., & Kurz, X. (2018). Measuring the impact of medicines regulatory interventions – Systematic review and methodological considerations. British Journal of Clinical Pharmacology, 84(3), 419–433. https://doi.org/10.1111/bcp.13469

Good pharmacovigilance practices. European Medicines Agency. https://www.ema.europa.eu/en/human-regulatory/post-authorisation/pharmacovigilance/good-pharmacovigilance-practices

Haneuse, S., & Daniels, M. (2016). A General Framework for Considering Selection Bias in EHR-Based Studies: What Data are Observed and Why? EGEMs (Generating Evidence & Methods to Improve Patient Outcomes), 4(1), 16. https://doi.org/10.13063/2327-9214.1203

Hawton, K., Bergen, H., Simkin, S., Dodd, S., Pocock, P., Bernal, W., Gunnell, D., & Kapur, N. (2013). Long term effect of reduced pack sizes of paracetamol on poisoning deaths and liver transplant activity in England and Wales: Interrupted time series analyses. BMJ, 346, f403. https://doi.org/10.1136/bmj.f403

Hedenmalm, K., Kurz, X., & Morales, D. (2019). Effect of withdrawal of fusafungine from the market on prescribing of antibiotics and other alternative treatments in Germany: A pharmacovigilance impact study. European Journal of Clinical Pharmacology, 75(7), 979–984. https://doi.org/10.1007/s00228-019-02650-z

Heller, R. F., Buchan, I., Edwards, R., Lyratzopoulos, G., McElduff, P., & Leger, S. S. (2003). Communicating risks at the population level: Application of population impact numbers. BMJ, 327(7424), 1162–1165. https://doi.org/10.1136/bmj.327.7424.1162

Horton, D. B., Gerhard, T., Davidow, A., & Strom, B. L. (2017). Impact of the black triangle label on prescribing of new drugs in the United Kingdom: Lessons for the United States at a time of deregulation. Pharmacoepidemiology and Drug Safety, 26(11), 1307–1313. https://doi.org/10.1002/pds.4304

Jordan, S., Gabe-Walters, M. E., Watkins, A., Humphreys, I., Newson, L., Snelgrove, S., & Dennis, M. S. (2015). Nurse-Led Medicines' Monitoring for Patients with Dementia in Care Homes: A Pragmatic Cohort Stepped Wedge Cluster Randomised Trial. PLOS ONE, 10(10), e0140203. https://doi.org/10.1371/journal.pone.0140203

Jordan, S., Morris, J. K., Davies, G. I., Tucker, D., Thayer, D. S., Luteijn, J. M., Morgan, M., Garne, E., Hansen, A. V., Klungsøyr, K., Engeland, A., Boyle, B., & Dolk, H. (2016). Selective Serotonin Reuptake Inhibitor (SSRI) Antidepressants in Pregnancy and Congenital Anomalies: Analysis of Linked Databases in Wales, Norway and Funen, Denmark. PLOS ONE, 11(12), e0165122. https://doi.org/10.1371/journal.pone.0165122

Juhaeri, J., Juhaeri, J., Mt-Isa, S., Chan, E., Genov, G., Genov, G., & Hirsch, I. IMI Work Package 5: Benefit –Risk Integration and Visual Representation. PROTECT. https://protectbenefitrisk.eu/documents/JuhaerietalBenefitRiskWave1CasestudyreportRimonabantOct2011.pdf

The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
(ENCePP) Guide on Methodological Standards in Pharmacoepidemiology
EMA/228452/2023   Page 69/76

Kendrick, T., Stuart, B., Newell, C., Geraghty, A. W. A., & Moore, M. (2015). Changes in rates of recorded depression in English primary care 2003–2013: Time trend analyses of effects of the economic recession, and the GP contract quality outcomes framework (QOF). Journal of Affective Disorders, 180, 68–78. https://doi.org/10.1016/j.jad.2015.03.040

Kim, H.-J., Fay, M. P., Feuer, E. J., & Midthune, D. N. (2000). Permutation tests for joinpoint regression with applications to cancer rates. Statistics in Medicine, 19(3), 335–351. https://doi.org/10.1002/(SICI)1097-0258(20000215)19:3<335::AID-SIM336>3.0.CO;2-Z

Lopez Bernal, J., Cummins, S., & Gasparrini, A. (2018). The use of controls in interrupted time series studies of public health interventions. International Journal of Epidemiology, 47(6), 2082–2093. https://doi.org/10.1093/ije/dyy135

Madison, T., Donner, B., Mutter, R., Mingrino, R., & Alvaro, G. (2019). Effectiveness of Risk Minimization Measures to Prevent Pregnancy Exposure to Mycophenolate-Containing Medicines in Europe. Pharmaceutical Medicine, 33(5), 395–406. https://doi.org/10.1007/s40290-019-00304-0

Marston, L., Nazareth, I., Petersen, I., Walters, K., & Osborn, D. P. J. (2014). Prescribing of antipsychotics in UK primary care: A cohort study. BMJ Open, 4(12), e006135. https://doi.org/10.1136/bmjopen-2014-006135

Martin, R. M., Wheeler, B. W., Metcalfe, C., & Gunnell, D. (2010). What was the immediate impact on population health of the recent fall in hormone replacement therapy prescribing in England? Ecological study. Journal of Public Health, 32(4), 555–564. https://doi.org/10.1093/pubmed/fdq021

Mohammad, I., Korkis, B., & Garwood, C. L. (2017). Incorporating Comprehensive Management of Direct Oral Anticoagulants into Anticoagulation Clinics. Pharmacotherapy: The Journal of Human Pharmacology and Drug Therapy, 37(10), 1284–1297. https://doi.org/10.1002/phar.1991

Morales, D. R., Morant, S. V., MacDonald, T. M., Mackenzie, I. S., Doney, A. S. F., Mitchell, L., Bennie, M., Robertson, C., Hallas, J., Pottegard, A., Ernst, M. T., Wei, L., Nicholson, L., Morris, C., Herings, R. M. C., Overbeek, J. A., Smits, E., & Flynn, R. W. V. (2020). Impact of EMA regulatory label changes on systemic diclofenac initiation, discontinuation, and switching to other pain medicines in Scotland, England, Denmark, and The Netherlands. Pharmacoepidemiology and Drug Safety, 29(3), 296–305. https://doi.org/10.1002/pds.4955

Morrato, E. H., Nicol, G. E., Maahs, D., Druss, B. G., Hartung, D. M., Valuck, R. J., Campagna, E., & Newcomer, J. W. (2010). Metabolic Screening in Children Receiving Antipsychotic Drug Treatment. Archives of Pediatrics & Adolescent Medicine, 164(4), 344–351. https://doi.org/10.1001/archpediatrics.2010.48

Nkeng, L., Cloutier, A.-M., Craig, C., Lelorier, J., & Moride, Y. (2012). Impact of Regulatory Guidances and Drug Regulation on Risk Minimization Interventions in Drug Safety. Drug Safety, 35(7), 535–546. https://doi.org/10.2165/11599720-000000000-00000

Nyeland, M. E., Laursen, M. V., & Callréus, T. (2017). Evaluating the effectiveness of risk minimisation measures: The application of a conceptual framework to Danish real-world dabigatran data. Pharmacoepidemiology and Drug Safety, 26(6), 607–614. https://doi.org/10.1002/pds.4203

Practical Approaches to Risk Minimisation for Medicinal Products: Report of CIOMS Working Group IX • COUNCIL FOR INTERNATIONAL ORGANIZATIONS OF MEDICAL SCIENCES. (2014). CIOMS. https://cioms.ch/publications/product/practical-approaches-to-risk-minimisation-for-medicinal-products-report-of-cioms-working-group-ix/

The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
(ENCePP) Guide on Methodological Standards in Pharmacoepidemiology
EMA/228452/2023   Page 70/76

Rubino, A., & Artime, E. (2017). A descriptive review of additional risk minimisation measures applied to EU centrally authorised medicines 2006-2015. Expert Opinion on Drug Safety, 16(8), 877–884. https://doi.org/10.1080/14740338.2017.1335303

Shi, L., Zhao, Y., Szymanski, K., Yau, L., & Fonseca, V. (2011). Impact of thiazolidinedione safety warnings on medication use patterns and glycemic control among veterans with diabetes mellitus. Journal of Diabetes and Its Complications, 25(3), 143–150. https://doi.org/10.1016/j.jdiacomp.2010.06.003

Singh, R. R., & Nayak, R. (2016). Impact of FDA Black Box Warning on Psychotropic Drug Use in Noninstitutionalized Elderly Patients Diagnosed With Dementia: A Retrospective Study. Journal of Pharmacy Practice, 29(5), 495–502. https://doi.org/10.1177/0897190015579451

Sobel, R. E., Blackwell, W., Fram, D. M., & Bate, A. (2019). A Novel Approach to Visualize Risk Minimization Effectiveness: Peeping at the 2012 UK Proton Pump Inhibitor Label Change Using a Rapid Cycle Analysis Tool. Drug Safety, 42(11), 1365–1376. https://doi.org/10.1007/s40264-019-00853-y

Sultana, J., Fontana, A., Giorgianni, F., Pasqua, A., Cricelli, C., Spina, E., Gambassi, G., Ivanovic, J., Ferrajolo, C., Molokhia, M., Ballard, C., Sharp, S., Sturkenboom, M., & Trifirò, G. (2016). The Effect of Safety Warnings on Antipsychotic Drug Prescribing in Elderly Persons with Dementia in the United Kingdom and Italy: A Population-Based Study. CNS Drugs, 30(11), 1097–1109. https://doi.org/10.1007/s40263-016-0366-z

Sultana, J., Fontana, A., Giorgianni, F., Tillati, S., Cricelli, C., Pasqua, A., Patorno, E., Ballard, C., Sturkenboom, M., & Trifirò, G. (2019). Measuring the Effectiveness of Safety Warnings on the Risk of Stroke in Older Antipsychotic Users: A Nationwide Cohort Study in Two Large Electronic Medical Records Databases in the United Kingdom and Italy. Drug Safety, 42(12), 1471–1485. https://doi.org/10.1007/s40264-019-00860-z

THE INTERNATIONAL MARCÉ SOCIETY FOR PERINATAL MENTAL HEALTH BIENNIAL SCIENTIFIC CONFERENCE. (2015). Archives of Women's Mental Health, 18(2), 269–408. https://doi.org/10.1007/s00737-014-0488-6

Thompson, C. A., Kurian, A. W., & Luft, H. S. (2015). Linking Electronic Health Records to Better Understand Breast Cancer Patient Pathways Within and Between Two Health Systems. EGEMs (Generating Evidence & Methods to Improve Patient Outcomes), 3(1), 5. https://doi.org/10.13063/2327-9214.1127

Torun, P., Heller, R. F., & Verma, A. (2009). Potential population impact of changes in heroin treatment and smoking prevalence rates: Using Population Impact Measures. European Journal of Public Health, 19(1), 28–31. https://doi.org/10.1093/eurpub/ckn103

Valuck, R. J., Libby, A. M., Orton, H. D., Morrato, E. H., Allen, R., & Baldessarini, R. J. (2007). Spillover Effects on Treatment of Adult Depression in Primary Care After FDA Advisory on Risk of Pediatric Suicidality With SSRIs. American Journal of Psychiatry, 164(8), 1198–1205. https://doi.org/10.1176/appi.ajp.2007.07010007

Van Ganse, E., Belhassen, M., Ginoux, M., Chrétien, E., Cornu, C., Ecoffey, C., & Aubrun, F. (2018). Use of analgesics in France, following dextropropoxyphene withdrawal. BMC Health Services Research, 18(1), 231. https://doi.org/10.1186/s12913-018-3058-1

van Hunsel, F., Gardarsdottir, H., de Boer, A., & Kant, A. (2019). Measuring the impact of pharmacovigilance activities, challenging but important. British Journal of Clinical Pharmacology, 85(10), 2235–2237. https://doi.org/10.1111/bcp.14042

The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
(ENCePP) Guide on Methodological Standards in Pharmacoepidemiology
EMA/228452/2023   Page 71/76

Verma, A., Torun, P., Harris, E., Edwards, R., Gemmell, I., Harrison, R. A., Buchan, I. E., Davies, L., Patterson, L., & Heller, R. F. (2012). Population Impact Analysis: A framework for assessing the population impact of a risk or intervention. Journal of Public Health, 34(1), 83–89. https://doi.org/10.1093/pubmed/fdr026

Weatherburn, C. J., Guthrie, B., Dreischulte, T., & Morales, D. R. (2020). Impact of medicines regulatory risk communications in the UK on prescribing and clinical outcomes: Systematic review, time series analysis and meta-analysis. British Journal of Clinical Pharmacology, 86(4), 698–710. https://doi.org/10.1111/bcp.14104

Zhou, H., Taber, C., Arcona, S., & Li, Y. (2016). Difference-in-Differences Method in Comparative Effectiveness Research: Utility with Unbalanced Groups. Applied Health Economics and Health Policy, 14, 419–429. https://doi.org/10.1007/s40258-016-0249-y

Zipitis, C. S., Mughal, Z. M., & Clayton, P. E. (2016). Assessing the population impact of low rates of vitamin D supplementation on type 1 diabetes using a new statistical method. JRSM Open, 7(11), 2054270416653522. https://doi.org/10.1177/2054270416653522

Zomerdijk, I. M., Ruiter, R., Houweling, L. M. A., Herings, R. M. C., Sturkenboom, M. C. J. M., Straus, S. M. J. M., & Stricker, B. H. (2014). Isotretinoin exposure during pregnancy: A population-based study in The Netherlands. BMJ Open, 4(11), e005602. https://doi.org/10.1136/bmjopen-2014-005602

16.5. Artificial intelligence in pharmacoepidemiology

Al-Zaiti, S. S., Alghwiri, A. A., Hu, X., Clermont, G., Peace, A., Macfarlane, P., & Bond, R. (2022). A clinician's guide to understanding and critically appraising machine learning studies: A checklist for Ruling Out Bias Using Standard Tools in Machine Learning (ROBUST-ML). European Heart Journal - Digital Health, 3(2), 125–140. https://doi.org/10.1093/ehjdh/ztac016

Bayer, S., Clark, C., Dang, O., Aberdeen, J., Brajovic, S., Swank, K., Hirschman, L., & Ball, R. (2021). ADE Eval: An Evaluation of Text Processing Systems for Adverse Event Extraction from Drug Labels for Pharmacovigilance. Drug Safety, 44(1), 83–94. https://doi.org/10.1007/s40264-020-00996-3

Cannas, M., & Arpino, B. (2019). A comparison of machine learning algorithms and covariate balance measures for propensity score matching and weighting. Biometrical Journal, 61(4), 1049–1072. https://doi.org/10.1002/bimj.201800132

Chapman, A. B., Peterson, K. S., Alba, P. R., DuVall, S. L., & Patterson, O. V. (2019). Detecting Adverse Drug Events with Rapidly Trained Classification Models. Drug Safety, 42(1), 147–156. https://doi.org/10.1007/s40264-018-0763-y

Clinical prediction models for mortality in patients with covid-19: External validation and individual participant data meta-analysis | The BMJ. https://www.bmj.com/content/378/bmj-2021-069881

Collins, G. S., Reitsma, J. B., Altman, D. G., & Moons, K. G. (2015). Transparent reporting of a multivariable prediction model for individual prognosis or diagnosis (TRIPOD): The TRIPOD Statement. BMC Medicine, 13(1), 1. https://doi.org/10.1186/s12916-014-0241-z

Collins, G. S., Dhiman, P., Navarro, C. L. A., Ma, J., Hooft, L., Reitsma, J. B., Logullo, P., Beam, A. L., Peng, L., Calster, B. V., Smeden, M. van, Riley, R. D., & Moons, K. G. (2021). Protocol for development of a reporting guideline (TRIPOD-AI) and risk of bias tool (PROBAST-AI) for diagnostic and prognostic prediction model studies based on artificial intelligence. *BMJ Open*, *11*(7), e048008. https://doi.org/10.1136/bmjopen-2020-048008

Combining deep learning with token selection for patient phenotyping from electronic health records | Scientific Reports. https://www.nature.com/articles/s41598-020-58178-1

Correia Pinheiro, L., Durand, J., & Dogné, J. (2020). An Application of Machine Learning in Pharmacovigilance: Estimating Likely Patient Genotype From Phenotypical Manifestations of Fluoropyrimidine Toxicity. Clinical Pharmacology and Therapeutics, 107(4), 944–947. https://doi.org/10.1002/cpt.1789

Evaluating large-scale propensity score performance through real-world and synthetic data experiments | International Journal of Epidemiology | Oxford Academic. https://academic.oup.com/ije/article/47/6/2005/5043131

Gates, A., Johnson, C., & Hartling, L. (2018). Technology-assisted title and abstract screening for systematic reviews: A retrospective evaluation of the Abstrackr machine learning tool. Systematic Reviews, 7(1), 45. https://doi.org/10.1186/s13643-018-0707-8

Ghassemi, M., Oakden-Rayner, L., & Beam, A. L. (2021). The false hope of current approaches to explainable artificial intelligence in health care. The Lancet Digital Health, 3(11), e745–e750. https://doi.org/10.1016/S2589-7500(21)00208-9

Hansen, P. W., Clemmensen, L., Sehested, T. S. G., Fosbøl, E. L., Torp-Pedersen, C., Køber, L., Gislason, G. H., & Andersson, C. (2016). Identifying Drug–Drug Interactions by Data Mining. *Circulation: Cardiovascular Quality and Outcomes*, *9*(6), 621–628. https://doi.org/10.1161/CIRCOUTCOMES.116.003055

Härkänen, M., Paananen, J., Murrells, T., Rafferty, A. M., & Franklin, B. D. (2019). Identifying risks areas related to medication administrations—Text mining analysis using free-text descriptions of incident reports. BMC Health Services Research, 19(1), 791. https://doi.org/10.1186/s12913-019-4597-9

Mayo clinical Text Analysis and Knowledge Extraction System (cTAKES): Architecture, component evaluation and applications | Journal of the American Medical Informatics Association | Oxford Academic. https://academic.oup.com/jamia/article/17/5/507/830823?login=true

Methods for Clinical Evaluation of Artificial Intelligence Algorithms for Medical Diagnosis | Radiology. https://pubs.rsna.org/doi/10.1148/radiol.220182

Nath, N., Lee, S.-H., & Lee, I. (2022). NEAR: Named entity and attribute recognition of clinical concepts. Journal of Biomedical Informatics, 130, 104092. https://doi.org/10.1016/j.jbi.2022.104092

Pfaff, E. R., Girvin, A. T., Bennett, T. D., Bhatia, A., Brooks, I. M., Deer, R. R., Dekermanjian, J. P., Jolley, S. E., Kahn, M. G., Kostka, K., McMurry, J. A., Moffitt, R., Walden, A., Chute, C. G., Haendel, M. A., Bramante, C., Dorr, D., Morris, M., Parker, A. M., … Niehaus, E. (2022). Identifying who has long COVID in the USA: A machine learning approach using N3C data. The Lancet Digital Health, 4(7), e532–e541. https://doi.org/10.1016/S2589-7500(22)00048-6

Pinheiro, L. C., & Kurz, X. (2022). Artificial intelligence in pharmacovigilance: A regulatory perspective on explainability. Pharmacoepidemiology and Drug Safety, 31(12), 1308–1310. https://doi.org/10.1002/pds.5524

Prediction models for diagnosis and prognosis of covid-19: Systematic review and critical appraisal | The BMJ. https://www.bmj.com/content/369/bmj.m1328

PROBAST: A Tool to Assess the Risk of Bias and Applicability of Prediction Model Studies | Annals of Internal Medicine. https://www.acpjournals.org/doi/10.7326/M18-1376

Reps, J. M., Garibaldi, J. M., Aickelin, U., Gibson, J. E., & Hubbard, R. B. (2015). A supervised adverse drug reaction signalling framework imitating Bradford Hill's causality considerations. Journal of Biomedical Informatics, 56, 356–368. https://doi.org/10.1016/j.jbi.2015.06.011

Seinen, T. M., Fridgeirsson, E. A., Ioannou, S., Jeannetot, D., John, L. H., Kors, J. A., Markus, A. F., Pera, V., Rekkas, A., Williams, R. D., Yang, C., van Mulligen, E. M., & Rijnbeek, P. R. (2022). Use of unstructured text in prognostic clinical prediction models: A systematic review. Journal of the American Medical Informatics Association, 29(7), 1292–1302. https://doi.org/10.1093/jamia/ocac058

Siontis, G. C. M., Tzoulaki, I., Castaldi, P. J., & Ioannidis, J. P. A. (2015). External validation of new risk prediction models is infrequent and reveals worse prognostic discrimination. Journal of Clinical Epidemiology, 68(1), 25–34. https://doi.org/10.1016/j.jclinepi.2014.09.007

Swerdel, J. N., Hripcsak, G., & Ryan, P. B. (2019). PheValuator: Development and evaluation of a phenotype algorithm evaluator. Journal of Biomedical Informatics, 97, 103258. https://doi.org/10.1016/j.jbi.2019.103258

Tiftikci, M., Özgür, A., He, Y., & Hur, J. (2019). Machine learning-based identification and rule-based normalization of adverse drug reactions in drug labels. BMC Bioinformatics, 20(21), 707. https://doi.org/10.1186/s12859-019-3195-5

Uzuner, Ö., South, B. R., Shen, S., & DuVall, S. L. (2011). 2010 i2b2/VA challenge on concepts, assertions, and relations in clinical text. Journal of the American Medical Informatics Association, 18(5), 552–556. https://doi.org/10.1136/amiajnl-2011-000203

Vasey, B., Nagendran, M., Campbell, B., Clifton, D. A., Collins, G. S., Denaxas, S., Denniston, A. K., Faes, L., Geerts, B., Ibrahim, M., Liu, X., Mateen, B. A., Mathur, P., McCradden, M. D., Morgan, L., Ordish, J., Rogers, C., Saria, S., Ting, D. S. W., … McCulloch, P. (2022). Reporting guideline for the early stage clinical evaluation of decision support systems driven by artificial intelligence: DECIDE-AI. BMJ, 377, e070904. https://doi.org/10.1136/bmj-2022-070904

Wang, G., Jung, K., Winnenburg, R., & Shah, N. H. (2015). A method for systematic discovery of adverse drug events from clinical notes. Journal of the American Medical Informatics Association, 22(6), 1196–1204. https://doi.org/10.1093/jamia/ocv102

Weinstein, E. J., Ritchey, M. E., & Lo Re III, V. (2023). Core concepts in pharmacoepidemiology: Validation of health outcomes of interest within real-world healthcare databases. Pharmacoepidemiology and Drug Safety, 32(1), 1–8. https://doi.org/10.1002/pds.5537

Yang, C., Kors, J. A., Ioannou, S., John, L. H., Markus, A. F., Rekkas, A., de Ridder, M. A. J., Seinen, T. M., Williams, R. D., & Rijnbeek, P. R. (2022). Trends in the conduct and reporting of clinical prediction model development and validation: A systematic review. Journal of the American Medical Informatics Association, 29(5), 983–989. https://doi.org/10.1093/jamia/ocac002

Yang, X., Bian, J., Gong, Y., Hogan, W. R., & Wu, Y. (2019). MADEx: A System for Detecting Medications, Adverse Drug Events, and Their Relations from Clinical Notes. Drug Safety, 42(1), 123–133. https://doi.org/10.1007/s40264-018-0761-0

Zrubka, Z., Gulácsi, L., & Péntek, M. (2022). Time to start using checklists for reporting artificial intelligence in health care and biomedical research: A rapid review of available tools. 2022 IEEE 26th International Conference on Intelligent Engineering Systems (INES), 000015–000020. https://doi.org/10.1109/INES56734.2022.9922639

16.6. Real-world evidence and pharmacoepidemiology

Bakker, E., Plueschke, K., Jonker, C. J., Kurz, X., Starokozhko, V., & Mol, P. G. M. (2023). Contribution of Real-World Evidence in European Medicines Agency's Regulatory Decision Making. Clinical Pharmacology & Therapeutics, 113(1), 135–151. https://doi.org/10.1002/cpt.2766

Brown, J. P., Wing, K., Evans, S. J., Bhaskaran, K., Smeeth, L., & Douglas, I. J. (2019). Use of real-world evidence in postmarketing medicines regulation in the European Union: A systematic assessment of European Medicines Agency referrals 2013–2017. BMJ Open, 9(10), e028133. https://doi.org/10.1136/bmjopen-2018-028133

Canada, H. (2020, March 4). Elements of real world data/evidence quality throughout the prescription drug product life cycle [Guidance]. https://www.canada.ca/en/services/health/publications/drugs-health-products/real-world-data-evidence-drug-lifecycle-report.html

CADTH Methods and Guidelines | Guidance for Reporting Real-World Evidence. https://www.cadth.ca/sites/default/files/RWE/MG0020/MG0020-RWE-Guidance-Report.pdf

Cave, A., Kurz, X., & Arlett, P. (2019). Real-World Data for Regulatory Decision Making: Challenges and Possible Solutions for Europe. Clinical Pharmacology & Therapeutics, 106(1), 36–39. https://doi.org/10.1002/cpt.1426

Real-World Evidence. FDA. https://www.fda.gov/science-research/science-and-research-special-topics/real-world-evidence

Concato, J., & Corrigan-Curay, J. (2022). Real-World Evidence—Where Are We Now? New England Journal of Medicine, 386(18), 1680–1682. https://doi.org/10.1056/NEJMp2200089

Considerations for the Use of Real-World Data and Real-World Evidence to Support Regulatory Decision-Making for Drug and Biological Products. CDER, CBER. https://www.fda.gov/media/154714/download

Eichler, H., Pignatti, F., Schwarzer-Daum, B., Hidalgo-Simon, A., Eichler, I., Arlett, P., Humphreys, A., Vamvakas, S., Brun, N., & Rasi, G. (2021). Randomized Controlled Trials Versus Real World Evidence: Neither Magic Nor Myth. Clinical Pharmacology and Therapeutics, 109(5), 1212–1218. https://doi.org/10.1002/cpt.2083

Eskola, S. M., Leufkens, H. G. M., Bate, A., De Bruin, M. L., & Gardarsdottir, H. (2022). Use of Real-World Data and Evidence in Drug Development of Medicinal Products Centrally Authorized in Europe in 2018–2019. Clinical Pharmacology & Therapeutics, 111(1), 310–320. https://doi.org/10.1002/cpt.2462

Flynn, R., Plueschke, K., Quinten, C., Strassmann, V., Duijnhoven, R. G., Gordillo-Marañon, M., Rueckbeil, M., Cohet, C., & Kurz, X. (2022). Marketing Authorization Applications Made to the European Medicines Agency in 2018–2019: What was the Contribution of Real-World Evidence? Clinical Pharmacology & Therapeutics, 111(1), 90–97. https://doi.org/10.1002/cpt.2461

Franklin, J. M., Liaw, K.-L., Iyasu, S., Critchlow, C. W., & Dreyer, N. A. (2021). Real-world evidence to support regulatory decision making: New or expanded medical product indications. Pharmacoepidemiology and Drug Safety, 30(6), 685–693. https://doi.org/10.1002/pds.5222

Franklin, J. M., & Schneeweiss, S. (2017). When and How Can Real World Data Analyses Substitute for Randomized Controlled Trials? Clinical Pharmacology & Therapeutics, 102(6), 924–933. https://doi.org/10.1002/cpt.857

Guideline on registry-based studies. European Medicies Agency.
https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-registry-based-studies_en-0.pdf

Hennessy, S., & Berlin, J. A. (2023). Real-World Trends in the Evaluation of Medical Products. American Journal of Epidemiology, 192(1), 1–5. https://doi.org/10.1093/aje/kwac172

Levenson, M., He, W., Chen, J., Fang, Y., Faries, D., Goldstein, B. A., Ho, M., Lee, K., Mishra-Kalyani, P., Rockhold, F., Wang, H., & Zink, R. C. (2023). Biostatistical Considerations When Using RWD and RWE in Clinical Studies for Regulatory Purposes: A Landscape Assessment. Statistics in Biopharmaceutical Research, 15(1), 3–13. https://doi.org/10.1080/19466315.2021.1883473

MHRA guidance on the use of real-world data in clinical studies to support regulatory decisions. GOV.UK. https://www.gov.uk/government/publications/mhra-guidance-on-the-use-of-real-world-data-in-clinical-studies-to-support-regulatory-decisions/mhra-guidance-on-the-use-of-real-world-data-in-clinical-studies-to-support-regulatory-decisions

MHRA guideline on randomised controlled trials using real-world data to support regulatory decisions. GOV.UK. https://www.gov.uk/government/publications/mhra-guidance-on-the-use-of-real-world-data-in-clinical-studies-to-support-regulatory-decisions/mhra-guideline-on-randomised-controlled-trials-using-real-world-data-to-support-regulatory-decisions

Replacing RCTs with real world data for regulatory decision making: A self-fulfilling prophecy? | The BMJ. https://www.bmj.com/content/380/bmj-2022-073100

Research, C. for D. E. and. (2023, January 31). Considerations for the Design and Conduct of Externally Controlled Trials for Drug and Biological Products. U.S. Food and Drug Administration; FDA. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/considerations-design-and-conduct-externally-controlled-trials-drug-and-biological-products

Simon, G. E., Platt, R., Watanabe, J. H., Bindman, A. B., John London, A., Horberg, M., Hernandez, A., & Califf, R. M. (2022). When Can We Rely on Real-World Evidence to Evaluate New Medical Treatments? Clinical Pharmacology and Therapeutics, 111(1), 30–34. https://doi.org/10.1002/cpt.2253

Tang, M., Pearson, S.-A., Simes, R. J., & Chua, B. H. (2023). Harnessing Real-World Evidence to Advance Cancer Research. Current Oncology, 30(2), Art. 2. https://doi.org/10.3390/curroncol30020143

Wang, S. V., & Schneeweiss, S. (2022). Assessing and Interpreting Real-World Evidence Studies: Introductory Points for New Reviewers. Clinical Pharmacology & Therapeutics, 111(1), 145–149. https://doi.org/10.1002/cpt.2398

Wang, S. V., Schneeweiss, S., Berger, M. L., Brown, J., de Vries, F., Douglas, I., Gagne, J. J., Gini, R., Klungel, O., Mullins, C. D., Nguyen, M. D., Rassen, J. A., Smeeth, L., Sturkenboom, M., & Making, on behalf of the joint I.-I. S. T. F. on R. W. E. in H. C. D. (2017). Reporting to Improve Reproducibility and Facilitate Validity Assessment for Healthcare Database Studies V1.0. Pharmacoepidemiology and Drug Safety, 26(9), 1018–1032. https://doi.org/10.1002/pds.4295

Wang, S. V., Schneeweiss, S., & RCT-DUPLICATE Initiative. (2023). Emulation of Randomized Clinical Trials With Nonrandomized Database Analyses: Results of 32 Clinical Trials. JAMA, 329(16), 1376–1385. https://doi.org/10.1001/jama.2023.4221

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