Combining real-world and clinical trial data to estimate COVID-19 treatment effects

Ravinder Claire[1], Christina Read[1,2], Jamie Elvidge[1], Thomas Debray[2], Dalia Dawoud[1]
[1] National Institute for Health and Care Excellence (NICE), Manchester, UK
[2] University Medical Center Utrecht, Utrecht, The Netherlands

Background

As part of the European Health Data and Evidence Network (EHDEN), we are seeking to understand the potential usefulness of the Observational Medical Outcomes Partnership (OMOP) Common Data Model (CDM) and the Observational Health Data Science and Informatics (OHDSI) tools for health technology assessment (HTA). HTA is concerned with the systematic evaluation of the properties, effects, and impacts of health technologies (1,2). HTA should usually reflect all differences in outcomes (such as health benefits and costs) that are a result of using a healthcare technology of interest.

The COVID-19 pandemic posed—and continues to pose—unprecedented challenges for healthcare systems and the HTA agencies that operate within them (3,4). Among these challenges is the sheer volume of rapidly disseminated, disparate evidence about tests and treatments. During the first year of the COVID-19 pandemic, over 2,800 trials assessing the clinical efficacy of treatments for COVID-19 were in place (5). These trials have provided evidence about the efficacy of many treatments, such as hydroxychloroquine, tocilizumab, baricitinib and aspirin. Evidence from randomised trials continues to be synthesised in "living" network meta-analyses (NMAs) (5), which have informed clinical guidelines such as the National Institute for Health and Care Excellence (NICE) rapid guideline for managing COVID-19 (6). However, in a fast-moving context like the COVID-19 pandemic, HTA agencies may be particularly interested in using real-world evidence to support their reimbursement decisions about health technologies (7). For example, when timely decision-making is imperative, real-world data may be well-placed provide relevant information more quickly than clinical trials, which may be subject to predefined reporting timepoints, or might not exist in the first place. While some large trials, such as RECOVERY (8) and Solidarity (9), have used adaptive trial designs that reflect some elements of real-world practice, HTA agencies may want to explore what insights real-world data can provide to support their decisions about the large number of COVID-related technologies in the pipeline.

In this report, we describe a proposed EHDEN use case that is in development to demonstrate how real-world data could help to address this priority issue for HTA.

Methods

Collaborating partners within the EHDEN 'outcomes-driven health care' work package—from HTA, industry, and academic groups—deliberated and agreed on potential uses of real-world data to support evidence-based healthcare reimbursement decisions and prioritised them for the purpose of planning research. The identified uses include the extrapolation of cancer survival outcomes; characterisation of patients, treatment pathways, and outcomes; estimating comparative effectiveness using external control data; modelling healthcare costs, and health-related quality of life. Another priority that emerged was exploring whether data from real-world evidence and randomised clinical trials can be synthesized in mixed treatment comparisons.

Following this engagement, we sought to develop specific EHDEN use cases that illustrate the value (and limitations) of using real-world evidence to support HTA decisions. Since combining real-world and randomised clinical trial data in NMA was identified as a priority topic, one use case intends to

explore the possibility of using data from EHDEN partners—mapped to the OMOP-CDM—to do so. We will perform a multinational, multi-database network comparative cohort study, focusing on the topical issue of medicines for the treatment of COVID-19. We will use new user comparative study cohorts to identify health outcomes for 2 treatment comparisons of interest, using data from the EHDEN network, as follows:

1. Primary objective: to assess the comparative effectiveness and safety of tocilizumab and baricitinib in hospitalised patients
2. Secondary objective: to assess comparative effectiveness and safety among aspirin and heparin in hospitalised patients

Comparison 1, tocilizumab vs. baricitinib, was identified as of interest to NICE, who are planning their assessments of COVID-related medicines, as they are direct comparators at the same position in the treatment pathway (10). Comparison 2, aspirin vs. heparin, will provide an update to previous work conducted as part of the OHDSI SCYLLA study (11). Results will be compared with the results of published NMAs that include only randomised control trials. Relative treatment effect estimates from the randomised and observational sources will be combined in random effects meta-analyses with Sidik-Jonkman Hartung-Knapp adjustment and restricted maximum likelihood estimation (12). Furthermore, we will explore bias modelling and weighting approaches, to account for potential issues in the non-randomised data (13).

Participants from organisations in the EHDEN network will be included. Electronic health records and administrative claims from primary care and secondary care will be utilised. Data will be linked to additional data sources including biobanks (e.g. UK Biobank), laboratory test data (e.g. Catalan central registry of COVID-19 PCR tests), national audits (e.g. UK National Audit of Intensive Care Units), and other relevant data sources where relevant and possible. The study will be conducted using data from multiple real world data sources previously mapped to the OMOP-CDM. Differences between the results of the original NMAs and the 'new' NMAs including real-world evidence will be evaluated.

Results (planned)

As this study is in development, there are currently no interim or final results to describe. The intention is to assess the feasibility of using the EHDEN network to identify relevant evidence about COVID-19 medicines and to conduct a combined randomised—non-randomised NMA, and evaluate how the results compare with NMAs informed by randomised evidence only. Outputs from this work are expected to be available by autumn 2022.

Discussion

Observational studies conducted in the real-world setting using secondary data can be used to complement clinical trials. The study population is generally more representative of the patients in clinical practice, without the restrictive inclusion criteria of trials. However, the lack of an active comparator in most observational studies could lead to confounding by indication. Our study aims to address this by combining results from real-world data with those from randomised controlled trials.

The use of real-world data to estimate relative clinical effectiveness of treatments was identified as a key area of interest for regulators and HTA agencies. The case of medicines for COVID-19 appears to be a highly appropriate case study for exploring this, due to the wealth of real-world evidence and prominence of multinational randomised trials, which might not be generalisable to HTA decision-

making in a particular jurisdiction. Focusing on treatments that show a clear signal of effectiveness in real-world settings may be a prudent first step to help HTA agencies recommend an effective and efficient use of scarce healthcare resources. These signals could also be used to inform potential candidates for further investment and testing in randomised controlled trials. Furthermore, by using databases from a variety of countries, our study can provide useful data on the effectiveness and safety of current standard of care in a particular jurisdiction of interest. The results will be directly applicable to HTA agencies when they start assessing the value of any newly developed treatment options for COVID-19, to inform decisions about which of those treatments should be reimbursed.

Other identified priority areas for HTA will be considered in future EHDEN HTA use cases in other disease areas.

References

1. Analysis of HTA and reimbursement procedures in EUnetHTA partner countries - EUnetHTA [Internet]. 2018 [cited 2022 Apr 18]. Available from: https://www.eunethta.eu/national-implementation/analysis-hta-reimbursement-procedures-eunethta-partner-countries/

2. Guyot P, Welton NJ, Ouwens MJNM, Ades AE. Survival Time Outcomes in Randomized, Controlled Trials and Meta-Analyses: The Parallel Universes of Efficacy and Cost-Effectiveness. Value Health. 2011 Jul 1;14(5):640–6.

3. Elvidge J, Dawoud D. Assessing Technologies for COVID-19: What are the Challenges for Health Technology Assessment Agencies? Findings From a Survey and Roundtable Workshop. PharmacoEconomics. 2021 Dec;39(12):1455–63.

4. COVID-19: Challenges and Opportunities for the Global Health Technology Assessment Community [Internet]. ISPOR | International Society For Pharmacoeconomics and Outcomes Research. [cited 2022 May 5]. Available from: https://www.ispor.org/publications/journals/value-outcomes-spotlight/vos-archives/issue/view/expanding-the-value-conversation/covid-19-challenges-and-opportunities-for-the-global-health-technology-assessment-community

5. Siemieniuk RA, Bartoszko JJ, Ge L, Zeraatkar D, Izcovich A, Kum E, et al. Drug treatments for covid-19: living systematic review and network meta-analysis. BMJ. 2020 Jul 30;370:m2980.

6. Overview | COVID-19 rapid guideline: managing COVID-19 | Guidance | NICE [Internet]. NICE; [cited 2022 May 5]. Available from: https://www.nice.org.uk/guidance/ng191

7. Elvidge J, Summerfield A, Knies S, Németh B, Kaló Z, Goettsch W, et al. Best-practice guidance for the health technology assessment of diagnostics and treatments for COVID-19 [Internet]. Zenodo; 2021 Sep [cited 2022 May 5]. Available from: https://zenodo.org/record/5530468

8. RECOVERY Collaborative Group, Horby P, Lim WS, Emberson JR, Mafham M, Bell JL, et al. Dexamethasone in Hospitalized Patients with Covid-19. N Engl J Med. 2021 Feb 25;384(8):693–704.

9. Repurposed Antiviral Drugs for Covid-19 — Interim WHO Solidarity Trial Results | NEJM [Internet]. [cited 2022 May 5]. Available from: https://www.nejm.org/doi/full/10.1056/nejmoa2023184

10. Project documents | Therapeutics for people with COVID-19 [ID4038] | Guidance | NICE [Internet]. NICE; [cited 2022 May 5]. Available from: https://www.nice.org.uk/guidance/indevelopment/gid-ta10936/documents

11. Ryan P, Prieto-Alhambra D. SARS-Cov-2 Large-scale Longitudinal Analyses on the comparative safety and effectiveness of treatments under evaluation for COVID-19 across an international observational data network. 2020.

12. Sidik K, Jonkman JN. A simple confidence interval for meta-analysis. Stat Med. 2002;21(21):3153–9.

13. Sarri G, Patorno E, Yuan H, Guo JJ, Bennett D, Wen X, et al. 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 Evid-Based Med. 2022 Apr;27(2):109–19.