

BMJ Open is committed to open peer review. As part of this commitment we make the peer review history of every article we publish publicly available.

When an article is published we post the peer reviewers' comments and the authors' responses online. We also post the versions of the paper that were used during peer review. These are the versions that the peer review comments apply to.

The versions of the paper that follow are the versions that were submitted during the peer review process. They are not the versions of record or the final published versions. They should not be cited or distributed as the published version of this manuscript.

BMJ Open is an open access journal and the full, final, typeset and author-corrected version of record of the manuscript is available on our site with no access controls, subscription charges or pay-per-view fees (<u>http://bmjopen.bmj.com</u>).

If you have any questions on BMJ Open's open peer review process please email <u>info.bmjopen@bmj.com</u>

BMJ Open

Development of the Transparent Reporting of Observational Studies Emulating a Target Trial (TARGET) Guideline

| Journal: | BMJ Open |
|----------------------------------|--|
| | |
| Manuscript ID | bmjopen-2023-074626 |
| Article Type: | Protocol |
| Date Submitted by the Author: | 12-Apr-2023 |
| Complete List of Authors: | Hansford, Harrison; University of New South Wales; Neuroscience Research Australia Cashin, Aidan; Neuroscience Research Australia, Centre for Pain IMPACT; University of New South Wales, School of Health Sciences, Faculty of Medicine and Health Jones, Matthew; University of New South Wales; Neuroscience Research Australia, Centre for Pain IMPACT Swanson, Sonja; University of Pittsburgh, Department of Epidemiology; Harvard T.H. Chan School of Public Health, CAUSALab, Department of Epidemiology Islam, Nazrul; University of Oxford, Big data institute; University of Southampton, Faculty of Medicine Dahabreh, Isa; , Beth Israel Deaconess Medical Center and Harvard Medical School, Richard A. and Susan F. Smith Center for Outcomes Research; Harvard T.H. Chan School of Public Health, CAUSALab, Department of Epidemiology, Department of Biostatistics Dickerman, Barbra; Harvard TH Chan School of Public Health, CAUSALab; Harvard TH Chan School of Public Health, CAUSALab; Deger, Matthias; University of Bern, Institute of Social & Preventive Medicine; University of Cape Town Faculty of Health Sciences, Centre for Infectious Disease Epidemiology and Research Garcia-De-Albeniz, Xavier ; Harvard University T H Chan School of Public Health, CAUSALab; RTI Health Solutions Barcelona Golub, Robert ; Northwestern University Feinberg School of Medicine Lodi, Sara; Harvard TH Chan School of Public Health, CAUSALab; Boston University School of Public Health, Department of Biostatistics Moreno-Betancur , Margarita ; Murdoch Children's Research Institute, Melbourne, Clinical Epidemiology & Biostatistics Unit; The University of Melbourne, Department of Paediatrics Pearson, Sallie-Anne; University of New South Wales, School of Population Health Schneeweiss , Sebastian ; Harvard Medical School, Boston, USA, Division of Pharmacoepidemiology, Department of Medicine, Brigham & Women's Hospital, Sterne, Jonathan; University of Bristol, Department of Population Health Sciences; NIHR Bristol Biomedical Research Centre Sharp, Melissa; RCSI Universi |

| 1 | | |
|-----------------------|--|--|
| 2 3 | | |
| 3 4 5 6 7 | | |
| 6 7 8 | | |
| 8 9 10 | | |
| 10 11 12 | | |
| 13 14 | | |
| 15 16 | | |
| 17 18 | | |
| 19 20 21 | | |
| 21 22 23 | | |
| 23 24 25 | | |
| 26 27 | | |
| 28 29 | | |
| 30 31 | | |
| 32 33 34 | | |
| 34 35 36 | | |
| 37 38 | | |
| 39 40 | | |
| 41 42 | | |
| 43 44 | | |
| 45 46 | | |
| 47 48 49 | | |
| 49 50 51 | | |
| 52 53 | | |
| 54 55 | | |
| 56 57 | | |

| | Hernan, M; Harvard School of Public Health, CAUSALab; Harvard T.H Chan School of Public Health, Department of Epidemiology, Department of Biostatistics Lee, Hopin; University of Exeter Medical School McAuley, James; University of New South Wales, School of Health Sciences, Faculty of Medicine and Health; Neuroscience Research Australia, Centre for Pain IMPACT |
|-----------|---|
| Keywords: | EPIDEMIOLOGY, Retrospective Studies, STATISTICS & RESEARCH METHODS |

SCHOLARONE[™] Manuscripts

| 2 3 4 | 1 | Development of the Transparent Reporting of Observational Studies Emulating a Target |
|----------------|----|---|
| 5 | | |
| 6 7 | 2 | Trial (TARGET) Guideline |
| 8 9 10 | 3 | |
| 11 12 | 4 | Harrison J. Hansford ^{1,2} , Aidan G. Cashin ^{1,2} , Matthew D. Jones ^{1,2} , Sonja A. Swanson ^{3,8,9} , |
| 13 | 5 | Nazrul Islam ^{5,6} , Issa J. Dahabreh ^{7,8, 9,10} , Barbra A. Dickerman ^{8,9} , Matthias Egger ^{11,12,13} , |
| 14 15 | 6 | Xabier Garcia-Albeniz ^{8, 14} , Robert M. Golub ¹⁵ , Sara Lodi ^{8,16} , Margarita Moreno- |
| 16 17 | 7 | Betancur ^{17,18} , Sallie-Anne Pearson ¹⁹ , Sebastian Schneeweiss ²⁰ , Jonathan A. C. |
| 18 | 8 | Sterne ^{21,22,23} , Melissa K. Sharp ²⁴ , Elizabeth A. Stuart ²⁵ , Miguel A. Hernán ^{8,9,10} , Hopin |
| 19 20 | 9 | Lee ²⁶ , James H. McAuley ^{1,2} |
| 21 22 | 10 | |
| 23 24 | 11 | 1. School of Health Sciences, Faculty of Medicine and Health, University of New South Wales, |
| 25 | 12 | Sydney, Australia |
| 26 27 | 13 | 2. Centre for Pain IMPACT, Neuroscience Research Australia, Sydney, Australia |
| 28 29 | 14 | 3. Department of Epidemiology, University of Pittsburgh, Pittsburgh, United States of America |
| 30 | 15 | 5. Oxford Population Health, Big Data Institute, University of Oxford, Oxford, UK |
| 31 32 | 16 | 6. Faculty of Medicine, University of Southampton, Southampton, UK |
| 33 34 | 17 | 7. Richard A. and Susan F. Smith Center for Outcomes Research, Beth Israel Deaconess |
| 35 | 18 | Medical Center and Harvard Medical School, Boston, MA, USA |
| 36 37 | 19 | 8. CAUSALab, Harvard T.H. Chan School of Public Health, Boston, MA, USA |
| 38 | 20 | 9. Department of Epidemiology, Harvard T.H. Chan School of Public Health, Boston, MA, USA |
| 39 40 | 21 | 10. Department of Biostatistics, Harvard T.H. Chan School of Public Health, Boston, MA, USA |
| 41 42 | 22 | 11. Institute of Social and Preventive Medicine, University of Bern, Bern, Switzerland |
| 43 | 23 | 12. Centre for Infectious Disease Epidemiology and Research, Faculty of Health Sciences, |
| 44 45 | 24 | University of Cape Town, Cape Town, South Africa |
| 46 47 | 25 | 13. Population Health Sciences, Bristol Medical School, University of Bristol, Bristol, UK |
| 48 | 26 | 14. RTI Health Solutions, Barcelona, Spain |
| 49 50 | 27 | 15. Northwestern University Feinberg School of Medicine, Chicago, IL, USA |
| 51 | 28 | 16. Department of Biostatistics, Boston University School of Public Health, Boston, MA, USA |
| 52 53 | 29 | 17. Clinical Epidemiology & Biostatistics Unit, Murdoch Children's Research Institute, Royal |
| 54 55 | 30 | Children's Hospital, 50 Flemington Rd, Parkville, Melbourne, VIC, Australia |
| 56 57 58 | 31 | 18. Department of Paediatrics, The University of Melbourne, Parkville, Australia |
| 59 60 | | For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml Page 1 of 25 |

| 1 2 | | |
|----------|----|---|
| 3 | 32 | 19. School of Population Health, Faculty of Medicine and Health, UNSW Sydney, Sydney, |
| 4 5 | 33 | Australia |
| 6 7 | 34 | 20. Division of Pharmacoepidemiology, Department of Medicine, Brigham & Women's Hospital, |
| 8 | 35 | Harvard Medical School, Boston, MA, USA |
| 9 10 | 36 | 21. Department of Population Health Sciences, Bristol Medical School, University of Bristol, UK |
| 11 12 | 37 | 22. NIHR Bristol Biomedical Research Centre, UK |
| 13 | 38 | 23. Health Data Research UK South-West, Bristol, UK |
| 14 15 | 39 | 24. Department of General Practice, RCSI University of Medicine and Health Sciences, Dublin, |
| 16 17 | 40 | Ireland |
| 18 | 41 | 25. Department of Mental Health, Johns Hopkins Bloomberg School of Public Health, Baltimore, |
| 19 20 | 42 | MD, USA |
| 21 | 43 | 26. University of Exeter Medical School, Exeter, UK |
| 22 23 | 44 | |
| 24 25 | 45 | |
| 26 | 46 | |
| 27 28 | | |
| 29 30 | 47 | Corresponding Author |
| 31 32 | 48 | Harrison J Hansford |
| 33 | 49 | E: h.hansford@unsw.edu.au |
| 34 35 | 50 | School of Health Sciences, UNSW Sydney, |
| 36 37 | 51 | 2052, Sydney, Australia |
| 38 39 | 52 | |
| 40 | | Words: 2809 |
| 41 42 | 53 | Words: 2809 |
| 43 44 | 54 | |
| 45 | 54 | |
| 46 47 | | |
| 48 49 | | |
| 50 | | |
| 51 52 | | |
| 53 54 | | |
| 55 | | |
| 56 57 | | |
| 58 | | |
| 59 60 | | For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml Page 2 of 25 |

55 Abstract

1 2 3

| 5 | | |
|----------------------------------|----|--|
| 6 7 | 56 | |
| 8 9 10 | 57 | Background |
| 11 12 | 58 | Observational studies are increasingly being used to inform health decision-making |
| 13 14 15 | 59 | when randomised trials are not feasible, ethical, or timely. The target trial approach |
| 16 17 18 | 60 | provides a framework to help minimise common biases in observational studies that |
| 19 20 | 61 | aim to estimate the causal effect of interventions. Incomplete reporting of studies using |
| 21 22 23 | 62 | the target trial framework limits the ability for clinicians, researchers, patients, and |
| 24 25 | 63 | other decision-makers to appraise, synthesise, and interpret findings to inform clinical |
| 26 27 28 | 64 | and public health practice and policy. This paper describes the methods that we will |
| 29 30 31 | 65 | use to develop the Transparent reporting of observational studies emulating a target |
| 32 33 | 66 | trial (TARGET) reporting guideline. |
| 34 35 36 | 67 | |
| 37 38 | 68 | Methods/design |
| 39 40 41 | 69 | The TARGET reporting guideline will be developed in five stages. The first stage will |
| 42 43 44 | 70 | identify current target trial reporting practices by systematically reviewing published |
| 44 45 46 | 71 | studies that explicitly emulated a target trial. The second stage will identify and refine |
| 47 48 49 | 72 | items to be considered for inclusion in the TARGET guideline by consulting content |
| 50 51 | 73 | experts using two online surveys. The third stage will prioritise and consolidate key |
| 52 53 54 | 74 | items to be included in the TARGET guideline at a consensus meeting of TARGET |
| 55 56 57 58 59 60 | 75 | investigators. The fourth stage will produce and pilot-test the TARGET guideline and |

| 2 | | |
|----------------|----|---|
| 3 4 5 | 76 | explanation and elaboration document. The fifth stage will disseminate the TARGET |
| 6 7 | 77 | guideline and resources via journals, conferences, and courses. |
| 8 9 10 | 78 | |
| 11 12 | 79 | Ethics and Dissemination |
| 13 14 15 | 80 | Ethical approval for the survey to be conducted has been attained (HC220536). The |
| 16 17 18 | 81 | TARGET guideline will be disseminated widely and should improve the transparency |
| 19 20 | 82 | and completeness of reporting in studies using the target trial framework. |
| 21 22 23 | 83 | |
| 24 25 26 | 84 | Key words: target trial emulation, causal inference, reporting guideline, observational |
| 27 28 | 85 | studies |
| 29 30 31 | 86 | |
| 32 33 34 | 87 | Strengths and Limitations |
| 35 36 | 88 | - The TARGET reporting guideline will be developed according to |
| 37 38 39 | 89 | recommendations for health research reporting guidelines |
| 40 41 | 90 | - The TARGET working group has been established to include stakeholders from |
| 42 43 44 | 91 | a variety of backgrounds |
| 45 46 47 | 92 | |
| 48 | | |
| 49 | | |
| 50 | | |
| 51 52 | | |
| 52 53 | | |
| 55 54 | | |
| 55 | | |
| 56 | | |
| 57 | | |
| 58 | | |
| 59 60 | | |
| | | |

Enseignement Superieur (ABES) . Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies

93 Introduction

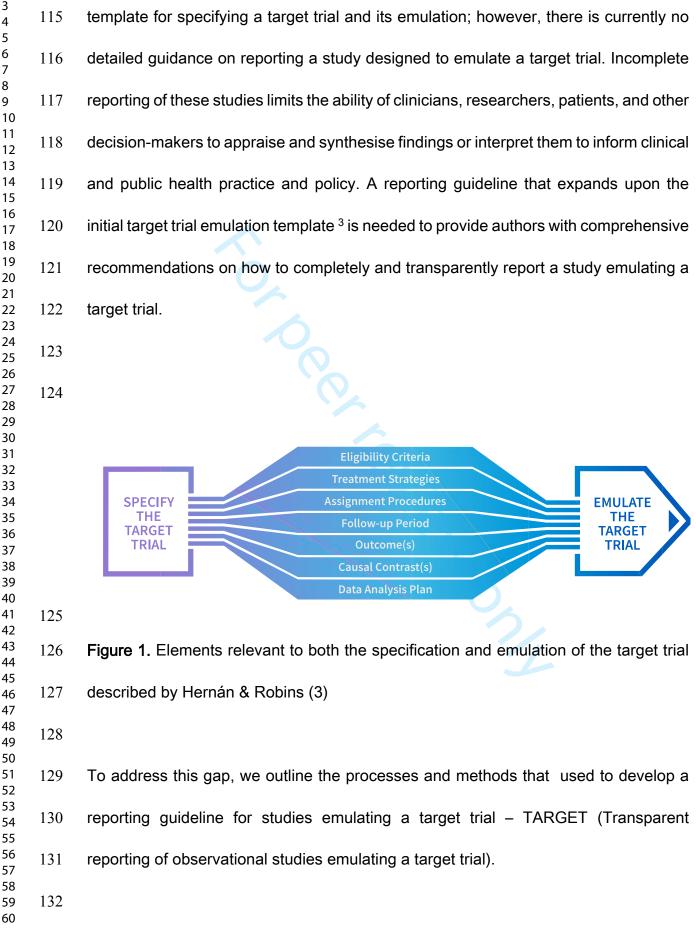
Observational studies can provide evidence on the causal effects of interventions when it is not feasible, ethical, or timely to conduct a relevant randomised trial. However, making causal inferences from observational data is challenging due to confounding and design-related biases such as selection bias and immortal time bias. ^{1 2} Design-related biases can be avoided using the target trial framework. ^{3 4} The framework involves the specification of the hypothetical randomised pragmatic trial — the target trial — that would ideally be conducted and how this trial might be emulated using observational data. ^{3 4} The two stages of the target trial framework are 1) specification of the target trial, and 2) emulation of the target trial. ^{3 4} Using observational data to mimic a randomised experiment was proposed in the mid 20th century, 5-8 and extended to time-varying treatments by Robins in 1986. 9

The value of using the target trial framework to design the analysis of observational studies has been recognised by international regulatory bodies in the field of medicine and health, ¹⁰⁻¹⁴ and the framework underpins the widely-used ROBINS-I tool for assessing risk of bias in non-randomised studies of interventions. ¹⁵ Studies that are explicit in using the target trial framework have been published with increasing frequency in leading general medical and specialty journals. ¹⁶⁻²¹

3 112

Application of the target trial framework requires the complete specification of the 113 Application of the target trial protocol and its emulation (Figure 1). ³ Hernán & Robins ³ provide a

BMJ Open



Enseignement Superieur (ABES) Protected by copyright, including for uses related to text and data mining, Al training, and similar technologies.

Enseignement Superieur (ABES) Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies.

The objective of the TARGET guideline is to provide guidance on the minimum set of

items that should be reported to provide a clear and transparent account of

observational studies that investigate the comparative effectiveness and safety of

We will develop the TARGET Guideline in five stages following recommendations for

health interventions explicitly using the target trial framework.

the development of health research reporting guidelines (Figure 2).²²

| 2 | |
|----------|------|
| 3 | 133 |
| 4 | 155 |
| 5 6 | 10.4 |
| 7 | 134 |
| 8 | |
| 9 | 135 |
| 10 | |
| 11 12 | 136 |
| 12 | |
| 14 | 137 |
| 15 | 107 |
| 16 | 138 |
| 17 | 130 |
| 18 19 | |
| 20 | 139 |
| 21 | |
| 22 | 140 |
| 23 | |
| 24 25 | 141 |
| 25 26 | |
| 27 | |
| 28 | |
| 29 | |
| 30 | |
| 31 | |
| 32 33 | |
| 33 34 | |
| 35 | |
| 36 | |
| 37 | |
| 38 | |
| 39 | |
| 40 41 | |
| 42 | |
| 43 | |
| 44 | |
| 45 | |
| 46 47 | |
| 47 48 | |
| 40 49 | |
| 50 | |
| 51 | |
| 52 | |
| 53 | |
| 54 55 | |
| 55 56 | |
| 57 | |
| 58 | |
| 59 | |

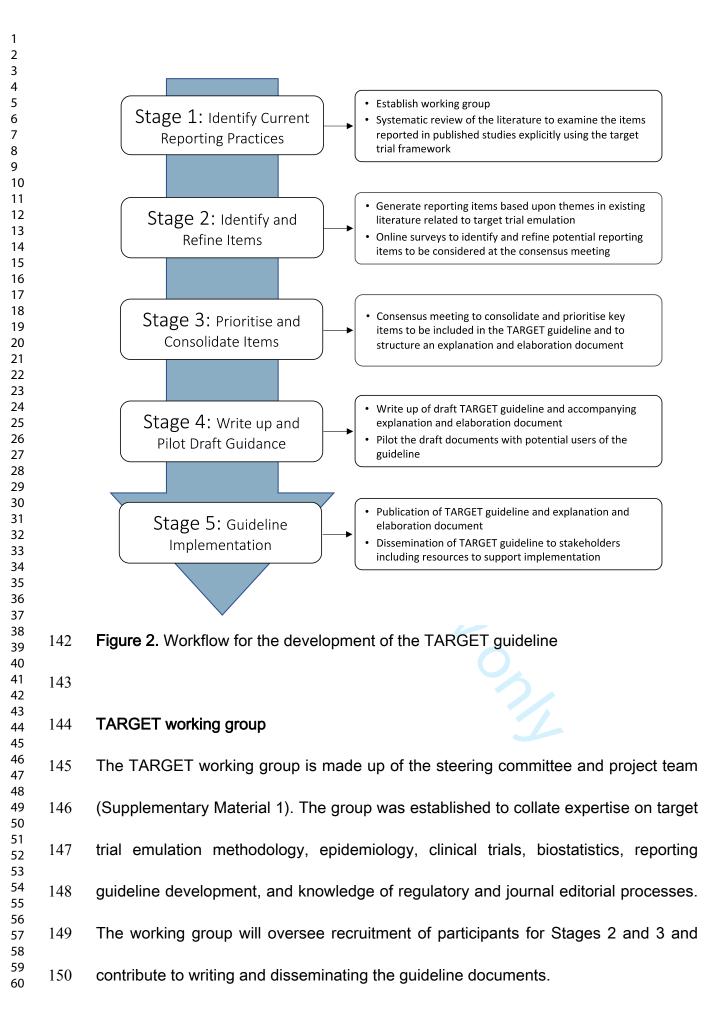
60

1

Objective

Methods/design

Jort.



Enseignement Superieur (ABES) . Protected by copyright, including for uses related to text and data mining, Al training, and similar technologies.

Stage 1: Identify current reporting practices

The systematic review aims to assess whether and how important items are reported by published studies explicitly emulating a target trial and whether reporting guidance (e.g., STROBE ²³) was used. The protocol for this systematic review was registered on the Open Science Framework on 13 March 2022 (osf.io/uj56m).

Databases, eligibility, and search terms

We will search Medline, EMBASE, PsycINFO and Science Citation Index for observational studies that stated in their methods that they explicitly emulated a target trial. We will exclude studies not written in English, not in the field of medicine and health, not conducted in humans, or not observational designs. Many observational studies may implicitly use the framework of a randomised trial. However, to be included in this review studies must be explicit in their attempt to emulate a target trial (e.g., stated 'target trial emulation' in the article). To identify eligible studies, we developed a literature search in collaboration with an expert librarian at the University of Oxford. Our approach used sensitive search terms including emulat*, target trial, observational data, real-world data, comparative effectiveness, and causal inference, to try to capture all papers explicitly emulating a target trial. The complete search strategy is in Supplementary Material 2. In duplicate, independent reviewers will conduct title, abstract, and full text screening. We will resolve disagreements between reviewers through discussion.

| 1 2 | | |
|----------------|-----|---|
| 3 4 | 173 | |
| 5 6 7 | 174 | Data Extraction |
| 8 9 10 | 175 | We will extract items regarded by the steering committee as potentially important for |
| 11 12 | 176 | the reporting of a target trial emulation, including those outlined by Hernán and Robins, |
| 13 14 15 | 177 | 2016. ³ Two independent reviewers will extract information on study authors, year of |
| 16 17 18 | 178 | publication, journal, sub-field of medicine, study design, sample size, intervention, |
| 19 20 | 179 | comparison group, outcomes assessed, and whether the study was prospectively |
| 21 22 23 | 180 | registered. We will extract items relevant to the methods and results of the target trial |
| 24 25 | 181 | emulation, including whether and how all components of the protocol of the proposed |
| 26 27 28 | 182 | target trial, and how they were emulated, were specified (i.e., eligibility criteria, |
| 29 30 31 | 183 | treatment strategies, assignment procedures, follow-up period, outcome(s), causal |
| 32 33 | 184 | contrast(s), and data analysis plan). We will enter data into a standardised data |
| 34 35 36 | 185 | extraction form which two authors will pilot with a selection of included studies. We will |
| 37 38 | 186 | resolve disagreements in data extraction between reviewers through discussion, or |
| 39 40 41 | 187 | where necessary, consultation with a third reviewer. |
| 42 43 44 | 188 | |
| 45 46 | 189 | Data analysis |
| 47 48 49 | 190 | We will use R ²⁴ for all data analyses. Categorical variables will be summarised using |
| 50 51 | 191 | frequencies and percentages. Continuous variables will be summarised using mean |
| 52 53 54 | 192 | and standard deviation, or median and interquartile range, as appropriate. |
| 55 56 57 | 193 | |
| 58 59 | 194 | Outcomes of the systematic review |
| 60 | | |

Enseignement Superieur (ABES) . Protected by copyright, including for uses related to text and data mining, Al training, and similar technologies.

BMJ Open

The systematic review will provide evidence on reporting in studies explicitly emulating a target trial. The findings will inform the online surveys (Stage 2) and the consensus meeting (Stage 3). We will submit the findings of this review for publication and all data and code made publicly available. Stage 2: Identify and refine items for the TARGET guideline We will conduct two online surveys to generate a list of candidate items that add detail to each of the protocol elements in Figure 1. Ethics Ethical approval has been obtained for the online surveys from the University of New South Wales Human Research Ethics Committee (HC220536). Selection of initial items The steering group will develop a list of key items, informed by the systematic review (Stage 1), and the target trial framework described by Hernán & Robins (3), thought important for the conduct and reporting target trial emulations (Figure 1). Other potential sources of items include: published guidance for observational studies and randomised controlled trials, the ROBINS-I tool, ¹⁵ and studies that describe items that may be important for the conduct or reporting of target trial emulations.

^o 216 *Participants*

BMJ Open

| 2 | | |
|----------------------------|-----|--|
| 3 4 5 | 217 | Members of the TARGET working group (Supplementary Material 1) will be invited to |
| 6 7 | 218 | participate in the surveys. |
| 8 9 10 | 219 | |
| 11 12 13 | 220 | Procedure |
| 14 15 | 221 | We will host two online surveys using REDCap. ^{25 26} We will send each online survey |
| 16 17 18 | 222 | via email to the participants. We will ask participants to rate the importance of each |
| 19 20 | 223 | potential reporting item on a 9-point Likert scale (1, "not important", to 9, "critically |
| 21 22 23 | 224 | important"). Participants will have the opportunity to provide suggestions or |
| 24 25 26 | 225 | modifications to the wording of items as well as suggest additional items or make other |
| 27 28 | 226 | comments. |
| 29 30 31 | 227 | |
| 32 33 34 | 228 | In the second survey, we will send participants a summary of the results for each |
| 35 36 | 229 | potential reporting item (mean scores and standard deviations, median scores and |
| 37 38 39 | 230 | interquartile ranges, and histograms), their own score for each item, and any |
| 40 41 | 231 | comments from participants on each item from the first survey. We will also present |
| 42 43 44 | 232 | any new items and suggested modifications to items. We will then invite participants |
| 45 46 47 | 233 | to re-score the importance of each item, and score any additional items, considering |
| 48 49 | 234 | the aggregated ratings. Participants will have the opportunity to provide additional |
| 50 51 52 | 235 | feedback on each item in the form of open ended responses. |
| 53 54 55 | 236 | |
| 56 57 58 59 60 | 237 | Analysis |

Enseignement Superieur (ABES) . Protected by copyright, including for uses related to text and data mining, Al training, and similar technologies.

Continuous variables will be summarised using mean and standard deviation, and median and interguartile range. We will analyse the free-text responses from the first and second surveys using an inductive approach, in which we will use reflexive thematic analysis to identify, organise and generate codes, and then identify themes found within the dataset. These data will contribute to the creation of new items and modification of existing items to be included in the subsequent survey. Outcome of the online surveys We will generate a preliminary list of items with corresponding ratings of importance to be considered in the TARGET guideline at the consensus meeting (Stage 3). We will also generate qualitative insights to guide item refinement and prioritisation in preparation for the consensus meeting. Stage 3 – Consolidate and prioritise key items to be included in the TARGET guideline A consensus meeting will finalise reporting items for the TARGET guideline. ²² The consensus meeting will follow suggested methods for developing reporting guidelines ²², including guidance for consensus-based methods currently being developed which we will use if they become available. ²⁷ Process We will invite stakeholders identified by the working group to participate in a two-day

259 consensus meeting. The TARGET working group will ensure that the expertise of

BMJ Open

consensus meeting participants includes target trial emulation methodology, epidemiology, clinical trials, biostatistics, reporting guideline development, and regulatory and journal editorial processes. Prior to the consensus meeting, the core team will provide attendees with evidence from the systematic review (Stage 1) and findings from the online surveys (Stage 2) including a draft of the items proposed for inclusion in the guideline. We will present the findings from Stage 1 and 2 at the consensus meeting. A member of the TARGET working group will facilitate a structured discussion on the rationale for including items from the online surveys. If there are disagreements, they will first be debated and, if disagreements remain, we will hold an anonymised vote to establish the importance of including the item in the guideline. For the anonymised vote, a simple majority will be sufficient to guide the inclusion/exclusion of an item. The meeting will conclude with discussion about the content and production of relevant documents (TARGET guideline, draft explanation and elaboration document) as well as strategies for dissemination and implementation. Following the conclusion of the consensus meeting, we will circulate a report on the outcome to the meeting participants for review and approval.

Stage 4 – Development and piloting of the draft TARGET guideline and explanation and elaboration document

Stage 4 involves drafting the TARGET guideline and accompanying explanation and
 elaboration document to ensure that the wording and content of the documents are
 clear, precise, and suitable for all identified stakeholders. The purpose of the

Enseignement Superieur (ABES) . Protected by copyright, including for uses related to text and data mining, Al training, and similar technologies.

Enseignement Superieur (ABES) . Protected by copyright, including for uses related to text and data mining, Al training, and similar technologies.

BMJ Open

explanation and elaboration document is to explain each item by providing background information, a rationale, and clear reporting examples from published target trial emulations. We will design the explanation and elaboration document to facilitate adherence to the TARGET guideline by clarifying the importance of each item, highlighting relevant reporting issues and providing examples to assist authors using the guideline. The consensus meeting participants may be asked to review and comment on the draft TARGET guideline and explanation and elaboration document.

We will evaluate the TARGET guideline by piloting the proposed guideline and the explanation and elaboration document with 20-30 expert methodologists and potential users of TARGET, identified from TARGET working group networks. We will ask participants to provide general feedback on accessibility and usability, and to identify possible reporting items that might have been overlooked. We will also ask for specific feedback about the utility and clarity of each TARGET item. We will collect data through online surveys, hosted by REDCap. ^{25 26} We will incorporate feedback from the piloting exercise into the final guideline and explanation and elaboration document, as required. If suggested revisions are extensive, we will conduct a further round of piloting.

, 300

301 Stage 5 – Guideline implementation

The goal of the final stage of guideline development is to maximise reach and use of the TARGET guideline. The TARGET working group will guide the dissemination

BMJ Open

strategy with advice from consensus meeting participants. We aim to publish the TARGET guideline and the explanation and elaboration document and disseminate the findings through traditional and social media. We will engage journal editors and funding agencies to encourage TARGET guideline endorsement alongside other published reporting guidance. We will publicly host the TARGET guideline and explanation and elaboration paper, and any other relevant material on a TARGET website. We will index the guideline on the Enhancing the QUAlity and Transparency Of health Research (EQUATOR) Network website. ²⁸ ²⁹ We will create online resources including infographics, blog posts and podcasts, which will be available on the TARGET website. We will share the TARGET guideline with authors in the field, and at relevant scientific conferences and methodological courses.

Discussion

Studies that explicitly aim to emulate a target trial are increasingly published in the medical literature and are used to inform practice and policy decisions. A reporting guideline for these studies will facilitate comprehensive and transparent reporting and support accurate appraisal and implementation of study findings by researchers, clinicians, patients, and other decision-makers.

The TARGET guideline and supporting guidance material aim to improve the completeness and transparency of reporting of observational studies that aim to explicitly emulate a target trial in medical and health research. Although the focus is

Enseignement Superieur (ABES) Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies

BMJ Open

on studies that explicitly use the target trial emulation framework much of the guidance will be applicable to studies using non-experimental comparison group designs to estimate causal effects. We will develop the TARGET guideline following accepted recommendations for the development of health research reporting guidelines to maximise the guidelines usefulness and usage. ²² We plan to use a structured .mis. d easily ac. dissemination approach to maximise uptake of the TARGET guideline and will ensure that the guideline is freely and easily accessible.

| 1 2 | | |
|----------------------|-----|--|
| 3 4 | 333 | Declarations |
| 5 6 7 | 334 | |
| 8 9 10 | 335 | Ethics approval and consent to participate |
| 11 12 | 336 | Not Applicable |
| 13 14 15 | 337 | |
| 16 17 | 338 | Consent for publication |
| 18 19 20 | 339 | All authors consent to publication of this manuscript |
| 21 22 | 340 | |
| 23 24 25 | 341 | Availability of data and materials |
| 26 27 | 342 | Not applicable |
| 28 29 30 | 343 | |
| 31 32 | 344 | Funding |
| 33 34 35 | 345 | There was no specific funding for this study. HJH was supported by an Australian |
| 36 37 | 545 | There was no specific funding for this study. Fish was supported by an Australian |
| 38 39 | 346 | National Health and Medical Research Council (NHMRC) Postgraduate Scholarship, |
| 40 41 | 347 | a PhD Top-Up Scholarship from Neuroscience Research Australia, and was a |
| 42 43 44 | 348 | Neuroscience Research Australia PhD Pearl sponsored by Paul Salteri AO. AGC |
| 45 46 | 349 | was supported by an Australian NHMRC Investigator Grant (ID 2010088). MM-B was |
| 47 48 49 | 350 | supported by an Australian NHMRC Investigator Grant (ID 2009572). JMH was |
| 50 51 | 351 | supported by an Australian NHMRC Investigator Grant (ID 2010128). BAD was |
| 52 53 54 | 352 | supported by a grant from the National Institutes of Health (R00 CA248335). ME was |
| 55 56 | 353 | supported by grants from the National Institutes of Health (R01 AI152772-01, 5U01- |
| 57 58 59 60 | 354 | AI069924-05) and the Swiss National Science Foundation (32FP30-174281). NI was |

| 2 | | |
|----------------------------|-----|--|
| 3 4 5 | 355 | supported by grants from the National Institute for Health and Care Research |
| 6 7 | 356 | (HDRUK2022.0313) and the UK Office for National Statistics (2002563). MAH was |
| 8 9 10 | 357 | supported by NIH grant R37 AI102634. |
| 11 12 13 | 358 | |
| 14 15 | 359 | Competing interests |
| 16 17 18 | 360 | All authors declare no competing interests. |
| 19 20 21 | 361 | |
| 22 23 | 362 | Author Contributions |
| 24 25 26 | 363 | HJH, AGC, MDJ, HL, JHM, conceived the idea for the project protocol. All authors |
| 27 28 29 | 364 | contributed to the design and methodology of the project protocol. HJH and AGC wrote |
| 30 31 | 365 | the first draft of the manuscript. All authors provided feedback, revised the manuscript |
| 32 33 34 | 366 | and have read and approved the final version. |
| 35 36 | 367 | |
| 37 38 39 | 368 | Acknowledgements |
| 40 41 42 | 369 | We acknowledge Nia Roberts, outreach librarian and information specialist at the |
| 43 44 | 370 | University of Oxford for assistance designing the literature search. |
| 45 46 47 | 371 | |
| 48 49 50 | 372 | Article Summary |
| 51 52 | 373 | Strengths and Limitations |
| 53 54 55 | 374 | |
| 56 57 58 59 60 | 375 | |
| | | |

| 2 3 | 276 | Abbrevietiene |
|----------------|-----|--|
| 4 5 | 376 | Abbreviations |
| 6 7 | 377 | |
| 8 9 10 | 378 | EQUATOR: Enhancing the QUAlity and Transparency Of health Research |
| 11 12 13 | 379 | REDCap: Research Electronic Data Capture |
| 14 15 | 380 | STROBE: Strengthening the Reporting of Observational Studies in Epidemiology |
| 16 17 18 | 381 | TARGET: TrAnsparent ReportinG of studies Emulating a Target trial |
| 19 20 21 | 382 | |
| 21 22 23 | 383 | |
| 24 25 | | |
| 26 27 | | |
| 28 29 | | |
| 30 31 | | |
| 32 33 | | |
| 34 35 | | |
| 36 37 | | |
| 38 | | |
| 39 40 | | |
| 41 42 | | |
| 43 44 | | |
| 45 | | |
| 46 47 | | |
| 48 | | |
| 49 50 | | |
| 51 | | |
| 52 53 | | |
| 54 | | |
| 55 56 | | |
| 57 | | |
| 58 59 | | |
| 59 60 | | |

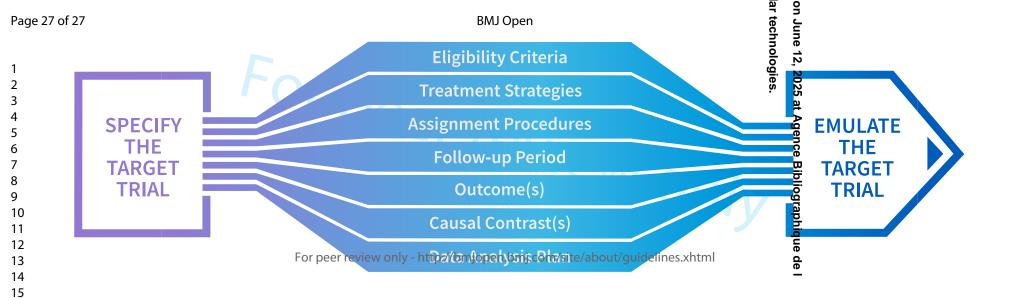
| 1 2 | | |
|----------|-----|--|
| 2 | | |
| 4 | 384 | References |
| 5 | 205 | 1 Hornán MA. Souar DC. Hornándoz Díaz C. et al. Specifizing a target trial provents immertal |
| 6 7 | 385 | 1. Hernán MA, Sauer BC, Hernández-Díaz S, et al. Specifying a target trial prevents immortal |
| 8 | 386 | time bias and other self-inflicted injuries in observational analyses. J Clin Epidemiol |
| 9 | 387 | 2016;79:70-75. doi: 10.1016/j.jclinepi.2016.04.014 [published Online First: |
| 10 | 388 | 2016/05/31] |
| 11 | 389 | 2. Dickerman BA, García-Albéniz X, Logan RW, et al. Avoidable flaws in observational |
| 12 13 | 390 | analyses: an application to statins and cancer. <i>Nature Medicine</i> 2019;25(10):1601- |
| 13 | 391 | 06. doi: 10.1038/s41591-019-0597-x |
| 15 | 392 | 3. Hernán MA, Robins JM. Using big data to emulate a target trial when a randomized trial is |
| 16 | 393 | not available. American journal of epidemiology 2016;183(8):758-64. |
| 17 | 394 | Hernán MA. Methods of public health research—strengthening causal inference from |
| 18 10 | 395 | observational data. New England Journal of Medicine 2021;385(15):1345-48. |
| 19 20 | 396 | 5. Cochran WG. Observational studies. Statistical papers in honor of George W Snedecor |
| 21 | 397 | 1972:77-90. |
| 22 | 398 | 6. Dorn HF. Philosophy of inferences from retrospective studies. American Journal of Public |
| 23 | 399 | Health and the Nations Health 1953;43(6_Pt_1):677-83. |
| 24 | 400 | 7. Rubin DB. Estimating causal effects of treatments in randomized and nonrandomized |
| 25 26 | 401 | studies. Journal of educational Psychology 1974;66(5):688. |
| 20 | 402 | 8. Wold H. Causality and econometrics. Econometrica: Journal of the Econometric Society |
| 28 | 403 | 1954:162-77. |
| 29 | 404 | 9. Robins J. A new approach to causal inference in mortality studies with a sustained |
| 30 | 405 | exposure period—application to control of the healthy worker survivor effect. |
| 31 32 | 406 | Mathematical modelling 1986;7(9-12):1393-512. |
| 33 | 407 | 10. Concato J, Stein P, Dal Pan GJ, et al. Randomized, observational, interventional, and |
| 34 | 408 | real-world—What's in a name? Pharmacoepidemiology and drug safety |
| 35 | 409 | 2020;29(11):1514-17. |
| 36 | 410 | 11. Agency EM. European medicines agencies network strategy to 2025. The Netherlands: |
| 37 38 | 411 | Health of Medicines Agencies, 2020. |
| 39 | 412 | 12. National Institute for Health and Care Excellence. The NICE strategy 2021 to 2026, 2021. |
| 40 | 413 | 13. Health Canada. Optimizing the Use of Real World Evidence to Inform Regulatory |
| 41 | 414 | Decision-Making: Government of Canada, 2019. |
| 42 | 415 | 14. Therapeutic Goods Administration. Real world evidence and patient reported outcomes |
| 43 44 | 416 | in the regulatory context. <u>https://www.tga.gov.au/review-real-world-evidence-and-</u> |
| 44 45 | 417 | patient-reported-outcomes: Australian Government, Department of Health, 2021. |
| 46 | 418 | 15. Sterne JA, Hernán MA, Reeves BC, et al. ROBINS-I: a tool for assessing risk of bias in non- |
| 47 | 419 | randomised studies of interventions. <i>BMJ</i> 2016;355:i4919. doi: 10.1136/bmj.i4919 |
| 48 | 420 | 16. Garcia-Albeniz XH, J.: Bretthauer, M.: Hernan, M. A. Effectiveness of screening |
| 49 50 | 421 | colonoscopy to prevent colorectal cancer among medicare beneficiaries aged 70 to |
| 50 51 | 422 | 79 years: A prospective observational study. <i>Annals of Internal Medicine</i> 2017 doi: |
| 52 | 423 | |
| 53 | | http://dx.doi.org/10.7326/M16-0758 |
| 54 | 424 | 17. Mahévas M, Tran V-T, Roumier M, et al. Clinical efficacy of hydroxychloroquine in |
| 55 56 | 425 | patients with covid-19 pneumonia who require oxygen: observational comparative |
| 56 57 | 426 | study using routine care data. <i>BMJ</i> 2020;369:m1844. doi: 10.1136/bmj.m1844 |
| 58 | 427 | 18. Kaura A, Sterne JAC, Trickey A, et al. Invasive versus non-invasive management of older |
| 59 | 428 | patients with non-ST elevation myocardial infarction (SENIOR-NSTEMI): a cohort |
| 60 | | |

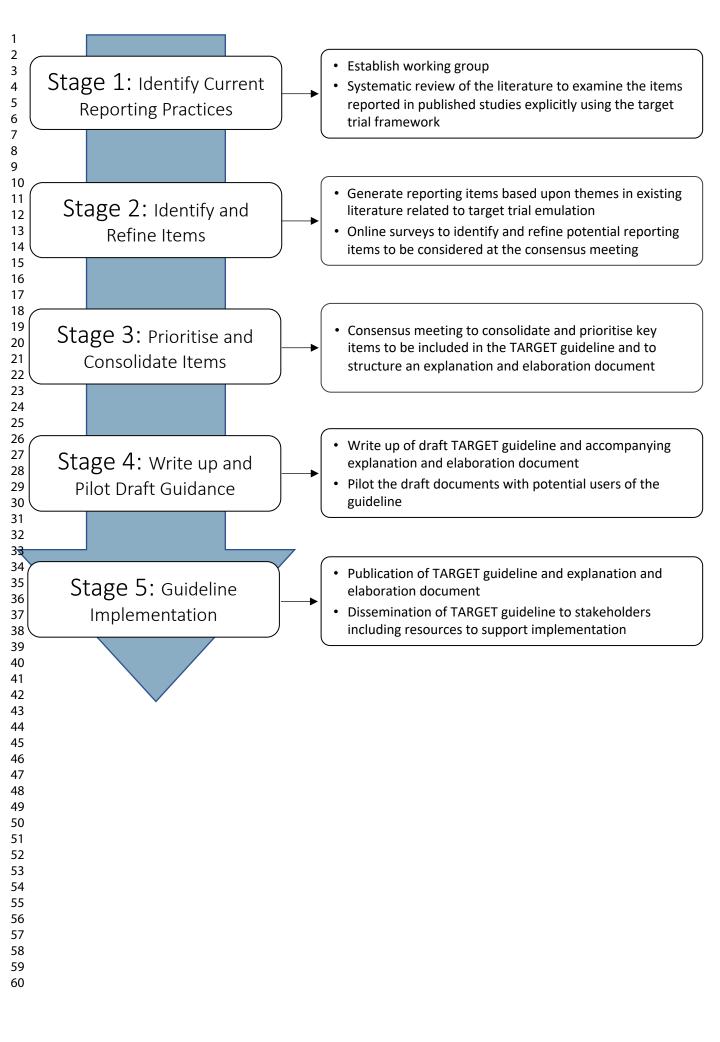
| 2 | | |
|----------|-----|--|
| 3 | 429 | study based on routine clinical data. <i>The Lancet</i> 2020;396(10251):623-34. doi: |
| 4 | 430 | 10.1016/S0140-6736(20)30930-2 |
| 5 6 | 431 | 19. Emilsson L, García-Albéniz X, Logan RW, et al. Examining Bias in Studies of Statin |
| 7 | 432 | Treatment and Survival in Patients With Cancer. JAMA Oncol 2018;4(1):63-70. doi: |
| 8 | 433 | 10.1001/jamaoncol.2017.2752 |
| 9 | 434 | 20. Chan You S, Krumholz HM, Suchard MA, et al. Comprehensive Comparative Effectiveness |
| 10 | 435 | and Safety of First-Line β -Blocker Monotherapy in Hypertensive Patients: A Large- |
| 11 12 | 436 | Scale Multicenter Observational Study. <i>Hypertension</i> 2021;77(5):1528-38. doi: |
| 13 | 437 | 10.1161/hypertensionaha.120.16402 [published Online First: 20210329] |
| 14 | 438 | 21. Caniglia EC, Robins JM, Cain LE, et al. Emulating a trial of joint dynamic strategies: An |
| 15 | 439 | application to monitoring and treatment of HIV-positive individuals. <i>Stat Med</i> |
| 16 17 | 440 | 2019;38(13):2428-46. doi: 10.1002/sim.8120 [published Online First: 20190318] |
| 17 | 441 | 22. Moher D, Schulz KF, Simera I, et al. Guidance for developers of health research reporting |
| 19 | 442 | guidelines. <i>PLoS medicine</i> 2010;7(2):e1000217. |
| 20 | 443 | 23. Von Elm E, Altman DG, Egger M, et al. The Strengthening the Reporting of Observational |
| 21 | 444 | Studies in Epidemiology (STROBE) statement: guidelines for reporting observational |
| 22 23 | 445 | studies. Bulletin of the World Health Organization 2007;85:867-72. |
| 24 | 446 | 24. R Core Team. R: A language and environment for statistical computing. 2013 |
| 25 | 447 | 25. Harris PA, Taylor R, Minor BL, et al. The REDCap consortium: Building an international |
| 26 | 448 | community of software platform partners. <i>Journal of Biomedical Informatics</i> |
| 27 | 449 | 2019;95:103208. doi: <u>https://doi.org/10.1016/j.jbi.2019.103208</u> |
| 28 29 | 450 | 26. Harris PA, Taylor R, Thielke R, et al. Research electronic data capture (REDCap)—A |
| 30 | 451 | metadata-driven methodology and workflow process for providing translational |
| 31 | 452 | research informatics support. Journal of Biomedical Informatics 2009;42(2):377-81. |
| 32 | 453 | doi: https://doi.org/10.1016/j.jbi.2008.08.010 |
| 33 34 | 454 | 27. Gattrell WT, Hungin AP, Price A, et al. ACCORD guideline for reporting consensus-based |
| 35 | 455 | methods in biomedical research and clinical practice: a study protocol. <i>Research</i> |
| 36 | 456 | Integrity and Peer Review 2022;7(1):3. doi: 10.1186/s41073-022-00122-0 |
| 37 | 457 | 28. The EQUATOR Network. EQUATOR Network - Enhancing the QUAlity and Transparency |
| 38 | 458 | Of health Research 2022 [Available from: <u>https://www.equator-network.org/2022</u> . |
| 39 40 | 459 | 29. Simera I, Moher D, Hoey J, et al. A catalogue of reporting guidelines for health research. |
| 41 | 460 | European journal of clinical investigation 2010;40(1):35-53. |
| 42 | | |
| 43 | 461 | |
| 44 45 | | |
| 46 | 462 | |
| 47 | | |
| 48 | | |
| 49 50 | | |
| 50 51 | | |
| 52 | | |
| 53 | | |
| 54 | | |
| 55 56 | | |
| 57 | | |
| 58 | | |
| 59 60 | | |
| 60 | | |
| | | |

| 2 3 4 5 | 463 | Supplementary Material |
|-------------------|-----|---|
| 6 | 464 | |
| 7 8 9 10 | 465 | Supplementary Material 1: TARGET working group members (alphabetical) |
| 11 12 | 466 | |
| 13 14 | 467 | Steering committee |
| 15 | 468 | Dr Aidan G. Cashin |
| 16 17 | 469 | Mr Harrison J. Hansford |
| 18 19 | 470 | Prof Miguel A. Hernán |
| 20 | 471 | Dr Hopin Lee |
| 21 22 | 472 | Dr Matthew D. Jones |
| 23 24 | 473 | Prof James H. McAuley 🦯 |
| 25 26 | 474 | A/Prof Sonja A. Swanson |
| 27 | 475 | |
| 28 29 | 476 | Project team |
| 30 31 | 477 | A/Prof Issa J. Dahabreh |
| 32 33 | 478 | A/Prof Barbra A. Dickerman |
| 34 | 479 | Prof Matthias Egger |
| 35 36 | 480 | Dr Xabier Garcia-Albeniz |
| 37 38 | 481 | Prof Robert M. Golub |
| 39 40 | 482 | A/Prof Nazrul Islam |
| 41 | 483 | A/Prof Sara Lodi |
| 42 43 | 484 | A/Prof Margarita Moreno-Betancur |
| 44 45 | 485 | Prof Sallie A. Pearson |
| 46 | 486 | Prof Sebastian Schneeweiss |
| 47 48 | 487 | Prof Jonathan A. C. Sterne |
| 49 50 | 488 | Dr Melissa K. Sharp |
| 51 52 | 489 | Prof Elizabeth A. Stuart |
| 53 | 490 | |
| 54 55 | 491 | |
| 56 57 | | |
| 58 59 | | |
| 60 | | |
| | | |

| 2 3 4 5 | 492 | Supplementary Material 2: Complete search strategies for all databases |
|--|-----|---|
| 5 6 7 | 493 | |
| 8 9 | 494 | Medline |
| 10 11 | 495 | 1 (emulat* adj5 trial?).mp. |
| 12 13 | 496 | 2 (target adj (trial? or experiment?)).mp. |
| 14 15 | 497 | 3. (observational adj (stud* or research or data)).mp. |
| 16 17 | 498 | 4. ((real world or rwd) adj2 (stud* or research or data)).mp. |
| 18 19 | 499 | 5. (routine* adj2 data).mp. |
| 20 21 | 500 | 6. (comparative effectiveness adj2 (stud* or research or data)).mp. |
| 22 23 | 501 | 7. (emulat* or propensity score? or (causal adj2 (inference? or analys?s or |
| 24 25 | 502 | effect*))).mp. |
| 26 27 | 503 | 8. 3 or 4 or 5 or 6 or 7 |
| 28 29 30 31 32 33 34 35 | 504 | 9. 2 and 8 |
| | 505 | 10. (target adj (trial? or experiment?)).ti. |
| | 506 | 11. 1 or 9 or 10 |
| | 507 | Filtered for time (2012-2022) manually after search |
| 36 37 | 508 | |
| 38 39 | 509 | Embase |
| 40 41 | 510 | 1. (emulat* adj5 trial?).mp. |
| 42 43 | 511 | 2. (target adj (trial? or experiment?)).mp. |
| 44 45 | 512 | 3. (observational adj (stud* or research or data)).mp. |
| 46 47 | 513 | 4. ((real world or rwd) adj2 (stud* or research or data)).mp. |
| 48 49 | 514 | 5. (routine* adj2 data).mp. |
| 50 51 | 515 | 6. (comparative effectiveness adj2 (stud* or research or data)).mp. |
| 52 53 | 516 | 7. (emulat* or propensity score? or (causal adj2 (inference? or analys?s or |
| 54 55 | 517 | effect*))).mp. |
| 56 57 | 518 | 8. 3 or 4 or 5 or 6 or 7 |
| 58 59 60 | 519 | 9. 2 and 8 |

| 2 | | |
|----------|-----|---|
| 3 4 | 520 | 10. (target adj (trial? or experiment?)).ti. |
| 5 6 | 521 | 11. 1 or 9 or 10 |
| 7 8 | 522 | |
| 9 10 | 523 | psycINFO |
| 11 12 | 524 | noft(target trial emulat*) OR ((noft(real world data) OR (noft(emulat* trial)) OR |
| 13 14 | 525 | noft(observational) OR noft(routine* data)) AND noft(comparative effective*) |
| 15 16 | 526 | AND noft(causal infer*)) |
| 17 18 | 527 | |
| 19 20 | 528 | Web of Science |
| 21 22 | 529 | (TI=(emulat* trial)) OR (TI=(real world data) OR TI=(routine* data) OR |
| 23 24 | 530 | TI=(comparative effectiveness study comparative effectiveness research or |
| 25 26 | 531 | comparative effectiveness data) OR (TI=(emulat* or propensity score?) AND |
| 27 28 | 532 | TI=(causal inference or causal analysis or causal effect*))) AND ALL=(target |
| 29 30 | 533 | trial or emulat* or target trial emulation) |
| 31 32 | | |
| 33 34 | | |
| 35 36 | | |
| 37 38 | | |
| 39 40 | | |
| 41 42 | | |
| 43 44 | | |
| 45 46 | | |
| 47 48 | | |
| 49 50 | | |
| 51 52 | | |
| 53 54 | | |
| 55 56 | | |
| 57 58 | | |
| 59 60 | | |
| | | |





BMJ Open

Development of the Transparent Reporting of Observational Studies Emulating a Target Trial (TARGET) Guideline

| Journal: | BMJ Open |
|----------------------------------|---|
| Manuscript ID | bmjopen-2023-074626.R1 |
| Article Type: | Protocol |
| Date Submitted by the Author: | 26-Jul-2023 |
| Complete List of Authors: | Hansford, Harrison; University of New South Wales; Neuroscience Research Australia Cashin, Aidan; Neuroscience Research Australia, Centre for Pain IMPACT; University of New South Wales, School of Health Sciences, Faculty of Medicine and Health Jones, Matthew; University of New South Wales; Neuroscience Research Australia, Centre for Pain IMPACT Swanson, Sonja; University of Pittsburgh, Department of Epidemiology; Harvard T.H. Chan School of Public Health, CAUSALab, Department of Epidemiology Islam, Nazrul; University of Oxford, Big data institute; University of Southampton, Faculty of Medicine Dahabreh, Isa; , Beth Israel Deaconess Medical Center and Harvard Medical School, Richard A. and Susan F. Smith Center for Outcomes Research; Harvard T.H. Chan School of Public Health, CAUSALab, Department of Epidemiology, Department of Biostatistics Dickerman, Barbra; Harvard TH Chan School of Public Health, CAUSALab; Harvard T H Chan School of Public Health, CAUSALab; Deger, Matthias; University of Bern, Institute of Social & Preventive Medicine; University of Cape Town Faculty of Health Sciences, Centre for Infectious Disease Epidemiology and Research Garcia-De-Albeniz, Xavier ; Harvard University T H Chan School of Public Health, CAUSALab; RTI Health Solutions Barcelona Golub, Robert ; Northwestern University Feinberg School of Medicine Lodi, Sara; Harvard TH Chan School of Public Health, CAUSALab; Boston University School of Public Health, Department of Biostatistics Moreno-Betancur , Margarita ; Murdoch Children's Research Institute, Melbourne, Clinical Epidemiology & Biostatistics Unit; The University of Melbourne, Sebastian ; Harvard Medical School, Boston, USA, Division of Pharmacoepidemiology, Department of Medicine, Brigham & Women's Hospital, Sterne, Jonathan; University of Bristol, Department of Population Health Sciences; NIHR Bristol Biomedical Research Centre Sharp, Melissa; RCSI University of Medicine and Health Sciences, Department of General Practice Stuart, Elizabeth A; Johns Hopkins Bloomberg School o |

| | Hernan, M; Harvard School of Public Health, CAUSALab; Harvard T.H Chan School of Public Health, Department of Epidemiology, Departme of Biostatistics Lee, Hopin; University of Exeter Medical School McAuley, James; University of New South Wales, School of Health Sciences, Faculty of Medicine and Health; Neuroscience Research Australia, Centre for Pain IMPACT |
|--------------------------------------|---|
| Primary Subject Heading : | Epidemiology |
| Secondary Subject Heading: | Research methods |
| Keywords: | EPIDEMIOLOGY, Retrospective Studies, STATISTICS & RESEARCH METHODS |

SCHOLARONE[™] Manuscripts

1

| 2 | | |
|----------------------|----|---|
| 3 4 5 | 1 | Development of the Transparent Reporting of Observational Studies Emulating a Target |
| 6 7 | 2 | Trial (TARGET) Guideline |
| 8 9 10 | 3 | |
| 11 12 | 4 | Harrison J. Hansford ^{1,2} , Aidan G. Cashin ^{1,2} , Matthew D. Jones ^{1,2} , Sonja A. Swanson ^{3,8,9} , |
| 13 | 5 | Nazrul Islam ^{5,6} , Issa J. Dahabreh ^{7,8, 9,10} , Barbra A. Dickerman ^{8,9} , Matthias Egger ^{11,12,13} , |
| 14 15 | 6 | Xabier Garcia-Albeniz ^{8, 14} , Robert M. Golub ¹⁵ , Sara Lodi ^{8,16} , Margarita Moreno- |
| 16 17 | 7 | Betancur ^{17,18} , Sallie-Anne Pearson ¹⁹ , Sebastian Schneeweiss ²⁰ , Jonathan A. C. |
| 18 | 8 | Sterne ^{21,22,23} , Melissa K. Sharp ²⁴ , Elizabeth A. Stuart ²⁵ , Miguel A. Hernán ^{8,9,10} , Hopin |
| 19 20 | 9 | Lee ²⁶ , James H. McAuley ^{1,2} |
| 21 22 | 10 | |
| 23 24 | 11 | 1. School of Health Sciences, Faculty of Medicine and Health, University of New South Wales, |
| 25 | 12 | Sydney, Australia |
| 26 27 | 13 | 2. Centre for Pain IMPACT, Neuroscience Research Australia, Sydney, Australia |
| 28 29 | 14 | 3. Department of Epidemiology, University of Pittsburgh, Pittsburgh, United States of America |
| 30 | 15 | 5. Oxford Population Health, Big Data Institute, University of Oxford, Oxford, UK |
| 31 32 | 16 | 6. Faculty of Medicine, University of Southampton, Southampton, UK |
| 33 34 | 17 | 7. Richard A. and Susan F. Smith Center for Outcomes Research, Beth Israel Deaconess |
| 34 35 | 18 | Medical Center and Harvard Medical School, Boston, MA, USA |
| 36 37 | 19 | 8. CAUSALab, Harvard T.H. Chan School of Public Health, Boston, MA, USA |
| 38 | 20 | 9. Department of Epidemiology, Harvard T.H. Chan School of Public Health, Boston, MA, USA |
| 39 40 | 21 | 10. Department of Biostatistics, Harvard T.H. Chan School of Public Health, Boston, MA, USA |
| 41 42 | 22 | 11. Institute of Social and Preventive Medicine, University of Bern, Bern, Switzerland |
| 43 | 23 | 12. Centre for Infectious Disease Epidemiology and Research, Faculty of Health Sciences, |
| 44 45 | 24 | University of Cape Town, Cape Town, South Africa |
| 46 | 25 | 13. Population Health Sciences, Bristol Medical School, University of Bristol, Bristol, UK |
| 47 48 | 26 | 14. RTI Health Solutions, Barcelona, Spain |
| 49 50 | 27 | 15. Northwestern University Feinberg School of Medicine, Chicago, IL, USA |
| 51 | 28 | 16. Department of Biostatistics, Boston University School of Public Health, Boston, MA, USA |
| 52 53 | 29 | 17. Clinical Epidemiology & Biostatistics Unit, Murdoch Children's Research Institute, Royal |
| 54 | 30 | Children's Hospital, 50 Flemington Rd, Parkville, Melbourne, VIC, Australia |
| 55 56 57 58 | 31 | 18. Department of Paediatrics, The University of Melbourne, Parkville, Australia |
| 59 | | For poor review only http://bmienen.hmi.com/site/about/guidelines.yhtml Page 1 of 20 |

| 32 | 19. School of Population Health, Faculty of Medicine and Health, UNSW Sydney, Sydney, |
|----|--|
| 33 | Australia |
| 34 | 20. Division of Pharmacoepidemiology, Department of Medicine, Brigham & Women's Hospital, |
| 35 | Harvard Medical School, Boston, MA, USA |
| 36 | 21. Department of Population Health Sciences, Bristol Medical School, University of Bristol, UK |
| 37 | 22. NIHR Bristol Biomedical Research Centre, UK |
| 38 | 23. Health Data Research UK South-West, Bristol, UK |
| 39 | 24. Department of General Practice, RCSI University of Medicine and Health Sciences, Dublin, |
| 40 | Ireland |
| 41 | 25. Department of Mental Health, Johns Hopkins Bloomberg School of Public Health, Baltimore, |
| 42 | MD, USA |
| 43 | 26. University of Exeter Medical School, Exeter, UK |
| 44 | |
| 45 | |
| | |
| 46 | |
| 47 | Corresponding Author |
| 48 | Harrison J Hansford |
| 49 | E: h.hansford@unsw.edu.au |
| 50 | School of Health Sciences, UNSW Sydney, |
| 51 | 2052, Sydney, Australia |
| 52 | Words: 2809 |
| | |
| 53 | Words: 2809 |
| 54 | |
| 01 | |
| | |
| | |
| | |
| | |
| | |
| | |
| | |
| | |
| | For non-view only http://httpi |
| | For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml |

Enseignement Superieur (ABES) Protected by copyright, including for uses related to text and data mining, Al training, and similar technologies.

55 Abstract

| | 56 | |
|-----------------------|----|--|
| n | 57 | Background |
| 1 2 3 | 58 | Observational studies are increasingly used to inform health decision-making when |
| | 59 | randomised trials are not feasible, ethical, or timely. The target trial approach provides |
| 4 5 5 7 8 | 60 | a framework to help minimise common biases in observational studies that aim to |
| 9 0 | 61 | estimate the causal effect of interventions. Incomplete reporting of studies using the |
| 1 2 3 | 62 | target trial framework limits the ability for clinicians, researchers, patients, and other |
| | 63 | decision-makers to appraise, synthesise, and interpret findings to inform clinical and |
| 4 5 5 7 8 | 64 | public health practice and policy. This paper describes the methods that we will use to |
| 9 0 1 | 65 | develop the transparent reporting of observational studies emulating a target trial |
| 2 3 | 66 | (TARGET) reporting guideline. |
| 4 5 5 | 67 | |
| 7 3 | 68 | Methods/design |
| 9 0 1 | 69 | The TARGET reporting guideline will be developed in five stages following |
| 2 3 4 | 70 | recommended guidance. The first stage will identify target trial reporting practices by |
| 5 | 71 | systematically reviewing published studies that explicitly emulated a target trial. The |
| / 3 9 | 72 | second stage will identify and refine items to be considered for inclusion in the |
|) 1 2 | 73 | TARGET guideline by consulting content experts using online surveys. The third stage |
| 3 4 | 74 | will prioritise and consolidate key items to be included in the TARGET guideline at a |
| 5 5 7 | 75 | consensus meeting of TARGET investigators. The fourth stage will produce and pilot- |
| 8 9 | 76 | test the TARGET guideline and explanation and elaboration document with relevant |
| | | |

BMJ Open

| 3 4 5 | 77 | stakeholders. The fifth stage will disseminate the TARGET guideline and resources |
|--|----|---|
| 6 7 | 78 | via journals, conferences, and courses. |
| 8 9 10 | 79 | |
| 11 12 | 80 | Ethics and Dissemination |
| 13 14 15 | 81 | Ethical approval for the survey to be conducted has been attained (HC220536). The |
| 16 17 18 | 82 | TARGET guideline will be disseminated widely in partnership with stakeholders to |
| 19 20 | 83 | maximise adoption and improve reporting of these studies. |
| 21 22 23 | 84 | |
| 24 25 26 | 85 | Key words: target trial emulation, causal inference, reporting guideline, observational |
| 27 28 | 86 | studies |
| 29 30 31 | 87 | |
| 32 33 34 | 88 | Strengths and Limitations |
| 35 36 | 89 | - The TARGET reporting guideline will be developed according to |
| 37 38 39 | 90 | recommendations for health research reporting guidelines |
| 40 41 42 | 91 | - The TARGET working group has been established to include stakeholders |
| 43 44 | 92 | from a variety of backgrounds |
| 45 46 47 | 93 | - A comprehensive piloting phase may increase the usability and uptake of the |
| 48 49 | 94 | reporting guideline |
| 50 51 52 53 54 55 56 57 58 59 60 | 95 | |
| 60 | | |

Enseignement Superieur (ABES) . Protected by copyright, including for uses related to text and data mining, Al training, and similar technologies.

96 Introduction

> Observational studies can provide evidence on the causal effects of interventions when it is not feasible, ethical, or timely to conduct a relevant randomised trial. However, making causal inferences from observational data is challenging due to confounding and design-related biases such as selection bias and immortal time bias.¹ ² Design-related biases can be avoided using the target trial framework. ^{3 4} The framework involves the specification of the hypothetical randomised pragmatic trial — the target trial — that would ideally be conducted and how this trial might be emulated using observational data.^{3 4} The two stages of the target trial framework are 1) specification of the target trial, and 2) emulation of the target trial.³ ⁴ Using observational data to mimic a randomised experiment was proposed in the mid 20th century,⁵⁻⁸ and extended to time-varying treatments by Robins in 1986.⁹

The value of using the target trial framework to design the analysis of observational studies has been recognised by international regulatory bodies in the field of medicine and health,¹⁰⁻¹⁴ and the framework underpins the widely-used ROBINS-I tool for assessing risk of bias in non-randomised studies of interventions.¹⁵ Studies that are explicit in using the target trial framework have been published with increasing frequency in leading general medical and specialty journals.¹⁶⁻²¹

³ 115

⁶ 116 Application of the target trial framework requires the complete specification of the ⁷ 117 target trial protocol and its emulation (Figure 1).³ Hernán & Robins³ provide a template

BMJ Open

for specifying a target trial and its emulation; however, there is currently no detailed guidance on reporting a study designed to emulate a target trial. Incomplete reporting of these studies limits the ability of clinicians, researchers, patients, and other decision-makers to appraise and synthesise findings or interpret them to inform clinical and public health practice and policy. A reporting guideline that expands upon the initial target trial emulation template³ is needed to provide authors with comprehensive recommendations on how to completely and transparently report a study emulating a target trial. Sector [INSERT FIGURE 1] To address this gap, we outline the processes and methods that used to develop a reporting guideline for studies emulating a target trial - TARGET (Transparent reporting of observational studies emulating a target trial). Objective The objective of the TARGET guideline is to provide guidance on the minimum set of items that should be reported to provide a clear and transparent account of observational studies that investigate the comparative effectiveness and safety of health interventions explicitly using the target trial framework.

Enseignement Superieur (ABES) Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies.

Enseignement Superieur (ABES) . Protected by copyright, including for uses related to text and data mining, Al training, and similar technologies.

BMJ Open

Methods

We will develop the TARGET Guideline in five stages following recommendations for the development of health research reporting guidelines (Figure 2).²² The start date for the study was late 2022, with the planned end date early 2025.

- [INSERT FIGURE 2]
- TARGET working group

The TARGET working group is made up of the steering committee and project team (Supplementary Material 1). The group was established to collate expertise on target trial emulation methodology, epidemiology, clinical trials, biostatistics, reporting guideline development, and knowledge of regulatory and journal editorial processes. The working group will oversee recruitment of participants for Stages 2 and 3 and contribute to writing and disseminating the guideline documents.

Stage 1: Identify current reporting practices

The systematic review aims to assess whether and how important items are reported by published studies explicitly emulating a target trial and whether reporting guidance (e.g., STROBE²³) was used. The protocol for this systematic review was registered on the Open Science Framework on 13 March 2022 (osf.io/uj56m).

Page 9 of 24

BMJ Open

We will search Medline, EMBASE, PsycINFO and Science Citation Index for observational studies that stated in their methods that they explicitly emulated a target trial. We will exclude studies not written in English, not in the field of medicine and health, not conducted in humans, or not observational designs. Many observational studies may implicitly use the framework of a randomised trial. However, to be included in this review studies must be explicit in their attempt to emulate a target trial (e.g., stated 'target trial emulation' in the article). To identify eligible studies, we developed a literature search in collaboration with an expert librarian at the University of Oxford. Our approach used sensitive search terms including emulat*, target trial, observational data, real-world data, comparative effectiveness, and causal inference, to try to capture all papers explicitly emulating a target trial. The complete search strategy is in Supplementary Material 2. We will conduct forward citation tracking of selected seminal articles to maximise the chance of retrieving all relevant articles.^{3 9} 24-26 We will also include papers known to the authorship team. In duplicate, independent reviewers will conduct title, abstract, and full text screening. We will resolve disagreements between reviewers through discussion.

179 Data Extraction

We will extract items regarded by the steering committee as potentially important for the reporting of a target trial emulation, including those outlined by Hernán and Robins, 2016.³ Two independent reviewers will extract information on study authors, year of publication, journal, sub-field of medicine, study design, sample size, intervention, Enseignement Superieur (ABES) . Protected by copyright, including for uses related to text and data mining, Al training, and similar technologies.

Enseignement Superieur (ABES) Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies.

BMJ Open

comparison group, outcomes assessed, and whether the study was prospectively registered. We will extract items relevant to the methods and results of the target trial emulation, including whether and how all components of the protocol of the proposed target trial, and how they were emulated, were specified (i.e., eligibility criteria, treatment strategies, assignment procedures, follow-up period, outcome(s), causal contrast(s), and data analysis plan). We will enter data into a standardised data extraction form which two authors will pilot with a selection of included studies. We will resolve disagreements in data extraction between reviewers through discussion, or where necessary, consultation with a third reviewer. Data analysis We will use R²⁷ for all data analyses. Categorical variables will be summarised using frequencies and percentages. Continuous variables will be summarised using mean and standard deviation, or median and interguartile range, as appropriate. Outcomes of the systematic review The systematic review will provide evidence on reporting in studies explicitly emulating a target trial. We acknowledge that excluding studies not written in English and unpublished studies may cause potentially relevant articles to be excluded. The findings will inform the online surveys (Stage 2) and the consensus meeting (Stage 3). We will submit the findings of this review for publication and all data and code made publicly available.

| 1 2 | | |
|--|-----|---|
| 3 4 5 | 206 | |
| 6 7 | 207 | Stage 2: Identify and refine items for the TARGET guideline |
| 8 9 10 | 208 | We will conduct two online surveys to generate a list of candidate items that add detail |
| 11 12 | 209 | to each of the protocol elements in Figure 1. |
| 13 14 15 16 17 18 19 20 | 210 | |
| | 211 | Ethics |
| | 212 | Ethical approval has been obtained for the online surveys from the University of New |
| 21 22 22 | 213 | South Wales Human Research Ethics Committee (HC220536). |
| 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 | 214 | |
| | 215 | Selection of initial items |
| | 216 | The steering group will develop a list of key items, informed by the systematic review |
| | 217 | (Stage 1), and the target trial framework described by Hernán & Robins, ³ thought |
| | 218 | important for the conduct and reporting target trial emulations (Figure 1). Other |
| | 219 | potential sources of items include: published guidance for observational studies and |
| | 220 | randomised controlled trials, the ROBINS-I tool, ¹⁵ and studies that describe items that |
| 42 43 | 221 | may be important for the conduct or reporting of target trial emulations. |
| 44 45 46 | 222 | |
| 47 48 49 | 223 | Participants |
| 50 51 | 224 | Members of the TARGET working group (Supplementary Material 1) will be invited to |
| 52 53 54 | 225 | participate in the surveys. |
| 55 56 | 226 | |
| 57 58 59 60 | 227 | Procedure |
| | | |

Enseignement Superieur (ABES) Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies.

We will host two online surveys using REDCap.^{28 29} We will send each online survey via email to the participants. We will ask participants to rate the importance of each potential reporting item on a 9-point Likert scale (1, "not important", to 9, "critically important"). Participants will have the opportunity to provide suggestions or modifications to the wording of items as well as suggest additional items or make other comments.

In the second survey, we will send participants a summary of the results for each potential reporting item (mean scores and standard deviations, median scores and interquartile ranges, and histograms), their own score for each item, and any comments from participants on each item from the first survey. We will also present any new items and suggested modifications to items. We will then invite participants to re-score the importance of each item, and score any additional items, considering the aggregated ratings. Participants will have the opportunity to provide additional feedback on each item in the form of open ended responses.

3 243

244 Analysis

Continuous variables will be summarised using mean and standard deviation, or median and interquartile range, as appropriate. We will analyse the free-text responses from the first and second surveys using an inductive approach,³⁰ in which we will use reflexive thematic³⁰ analysis to identify, organise and generate codes, and then identify themes found within the dataset. Briefly, inductive coding is a process

BMJ Open

| 2 | | |
|----------------|-----|---|
| 3 4 5 | 250 | pooling common ideas without trying to fit ideas/codes into a pre-existing framework. |
| 6 7 | 251 | These data will contribute to the creation of new items and modification of existing |
| 8 9 10 | 252 | items to be included in the subsequent survey. |
| 11 12 13 | 253 | |
| 14 15 | 254 | Outcome of the online surveys |
| 16 17 18 | 255 | We will generate a preliminary list of items with corresponding ratings of importance |
| 19 20 | 256 | to be considered in the TARGET guideline at the consensus meeting (Stage 3). We |
| 21 22 23 | 257 | will also generate qualitative insights to guide item refinement and prioritisation in |
| 24 25 26 | 258 | preparation for the consensus meeting. |
| 27 28 | 259 | |
| 29 30 31 | 260 | Stage 3 – Consolidate and prioritise key items to be included in the TARGET guideline |
| 32 33 | 261 | A consensus meeting will finalise reporting items for the TARGET guideline. ²² The |
| 34 35 36 | 262 | consensus meeting will follow suggested methods for developing reporting |
| 37 38 39 | 263 | guidelines, ²² including guidance for consensus-based methods currently being |
| 40 41 | 264 | developed which we will use if they become available.31 |
| 42 43 44 | 265 | |
| 45 46 47 | 266 | Process |
| 47 48 49 | 267 | We will invite stakeholders identified by the working group to participate in a two-day |
| 50 51 52 | 268 | consensus meeting. The TARGET working group will ensure that the expertise of |
| 53 54 | 269 | consensus meeting participants includes target trial emulation methodology, |
| 55 56 57 | 270 | epidemiology, clinical trials, biostatistics, reporting guideline development, and |
| 58 59 60 | 271 | regulatory and journal editorial processes. Prior to the consensus meeting, the core |

Enseignement Superieur (ABES) . Protected by copyright, including for uses related to text and data mining, Al training, and similar technologies.

BMJ Open

team will provide attendees with evidence from the systematic review (Stage 1) and findings from the online surveys (Stage 2) including a draft of the items proposed for inclusion in the guideline. We will present the findings from Stage 1 and 2 at the consensus meeting. A member of the TARGET working group will facilitate a structured discussion on the rationale for including items from the online surveys. If there are disagreements, they will first be debated and, if disagreements remain, we will hold an anonymised vote to establish the importance of including the item in the guideline. For the anonymised vote, a simple majority will be sufficient to guide the inclusion/exclusion of an item. The meeting will conclude with discussion about the content and production of relevant documents (TARGET guideline, draft explanation and elaboration document) as well as strategies for dissemination and implementation. Following the conclusion of the consensus meeting, we will circulate a report on the outcome to the meeting participants for review and approval.

285 g

Stage 4 – Development and piloting of the draft TARGET guideline and explanation
 and elaboration document

Stage 4 involves drafting the TARGET guideline and accompanying explanation and elaboration document to ensure that the wording and content of the documents are clear, precise, and suitable for all identified stakeholders. The purpose of the explanation and elaboration document is to explain each item by providing background information, a rationale, and clear reporting examples from published target trial emulations. We will design the explanation and elaboration document to facilitate

BMJ Open

adherence to the TARGET guideline by clarifying the importance of each item, highlighting relevant reporting issues and providing examples to assist authors using the guideline. The consensus meeting participants may be asked to review and comment on the draft TARGET guideline and explanation and elaboration document.

We will evaluate the TARGET guideline by piloting the proposed guideline and the explanation and elaboration document with 20-30 expert methodologists and potential users of TARGET, identified from TARGET working group networks. We will ask participants to provide general feedback on accessibility and usability, and to identify possible reporting items that might have been overlooked. We will also ask for specific feedback about the utility and clarity of each TARGET item. We will collect data through online surveys, hosted by REDCap.^{28 29} We will incorporate feedback from the piloting exercise into the final guideline and explanation and elaboration document, as required. If suggested revisions are extensive, we will conduct a further round of piloting.

Enseignement Superieur (ABES) Protected by copyright, including for uses related to text and data mining, Al training, and similar technologies.

3 309

310 Patient and public involvement

Potential users of this research include health researchers conducting observational
analyses, regulatory bodies, public health and other health decision-makers. We aim
to include relevant decision-makers in the piloting phase of the guideline development
process to maximise the usefulness and uptake of the TARGET guideline. Participants

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Page 15 of 20

The goal of the final stage of guideline development is to maximise reach and use of the TARGET guideline. The TARGET working group will guide the dissemination strategy with advice from consensus meeting participants. We aim to publish the TARGET guideline and the explanation and elaboration document and disseminate the findings through traditional and social media. We will engage journal editors and funding agencies to encourage TARGET guideline endorsement alongside other published reporting guidance. We will publicly host the TARGET guideline and explanation and elaboration paper, and any other relevant material on a TARGET website. We will index the guideline on the Enhancing the QUAlity and Transparency Of health Research (EQUATOR) Network website.^{32,33} We will create online resources including infographics, blog posts and podcasts, which will be available on the TARGET website. We will share the TARGET guideline with authors in the field, and at relevant scientific conferences and methodological courses.

Stage 5 – Guideline implementation

in any stage of the guideline development will be informed of the results and final guidance.

BMJ Open

| 2 | | |
|--|--|---|
| 3 4 5 | 332 | Declarations |
| 6 7 | 333 | |
| 8 9 10 | 334 | Ethics approval and consent to participate |
| 11 12 | 335 | Not Applicable |
| 13 14 15 | 336 | |
| 16 17 18 | 337 | Consent for publication |
| 19 20 | 338 | All authors consent to publication of this manuscript |
| 21 22 23 | 339 | |
| 24 25 | 340 | Availability of data and materials |
| 26 27 28 | 341 | Not applicable |
| 29 30 | 342 | |
| 31 | | |
| 32 33 | 343 | Funding |
| 33 34 35 | 343 344 | Funding There was no specific funding for this study. HJH was supported by an Australian |
| 33 34 35 36 37 38 | | |
| 33 34 35 36 37 | 344 | There was no specific funding for this study. HJH was supported by an Australian |
| 33 34 35 36 37 38 39 40 41 42 43 | 344 345 | There was no specific funding for this study. HJH was supported by an Australian National Health and Medical Research Council (NHMRC) Postgraduate Scholarship, |
| 33 34 35 36 37 38 39 40 41 42 | 344 345 346 | There was no specific funding for this study. HJH was supported by an Australian National Health and Medical Research Council (NHMRC) Postgraduate Scholarship, a PhD Top-Up Scholarship from Neuroscience Research Australia, and was a |
| 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 | 344345346347 | There was no specific funding for this study. HJH was supported by an Australian National Health and Medical Research Council (NHMRC) Postgraduate Scholarship, a PhD Top-Up Scholarship from Neuroscience Research Australia, and was a Neuroscience Research Australia PhD Pearl sponsored by Paul Salteri AO. AGC |
| 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 | 344 345 346 347 348 | There was no specific funding for this study. HJH was supported by an Australian National Health and Medical Research Council (NHMRC) Postgraduate Scholarship, a PhD Top-Up Scholarship from Neuroscience Research Australia, and was a Neuroscience Research Australia PhD Pearl sponsored by Paul Salteri AO. AGC was supported by an Australian NHMRC Investigator Grant (ID 2010088). MM-B was |
| 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50 | 344 345 346 347 348 349 | There was no specific funding for this study. HJH was supported by an Australian National Health and Medical Research Council (NHMRC) Postgraduate Scholarship, a PhD Top-Up Scholarship from Neuroscience Research Australia, and was a Neuroscience Research Australia PhD Pearl sponsored by Paul Salteri AO. AGC was supported by an Australian NHMRC Investigator Grant (ID 2010088). MM-B was supported by an Australian NHMRC Investigator Grant (ID 2009572). JMH was |
| 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 56 | 344 345 346 347 348 349 350 | There was no specific funding for this study. HJH was supported by an Australian National Health and Medical Research Council (NHMRC) Postgraduate Scholarship, a PhD Top-Up Scholarship from Neuroscience Research Australia, and was a Neuroscience Research Australia PhD Pearl sponsored by Paul Salteri AO. AGC was supported by an Australian NHMRC Investigator Grant (ID 2010088). MM-B was supported by an Australian NHMRC Investigator Grant (ID 2009572). JMH was supported by an Australian NHMRC Investigator Grant (ID 2010128). BAD was |
| 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 53 54 55 | 344 345 346 347 348 349 350 351 | There was no specific funding for this study. HJH was supported by an Australian National Health and Medical Research Council (NHMRC) Postgraduate Scholarship, a PhD Top-Up Scholarship from Neuroscience Research Australia, and was a Neuroscience Research Australia PhD Pearl sponsored by Paul Salteri AO. AGC was supported by an Australian NHMRC Investigator Grant (ID 2010088). MM-B was supported by an Australian NHMRC Investigator Grant (ID 2009572). JMH was supported by an Australian NHMRC Investigator Grant (ID 2010128). BAD was supported by a grant from the National Institutes of Health (R00 CA248335). ME was |

BMJ Open

1

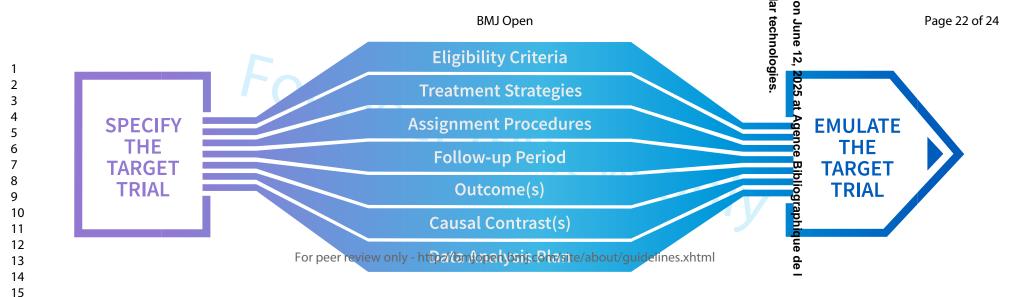
Enseignement Superieur (ABES) Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies.

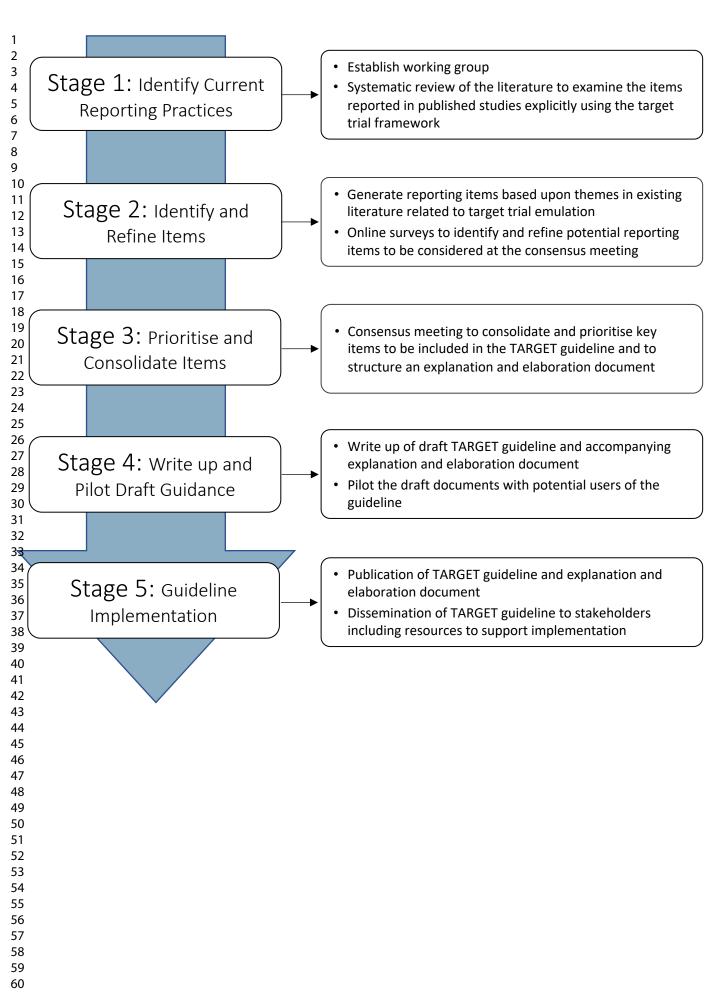
| 2 | | |
|----------------------------------|-----|--|
| 3 4 5 | 354 | supported by grants from the National Institute for Health and Care Research |
| 6 7 | 355 | (HDRUK2022.0313) and the UK Office for National Statistics (2002563). MAH was |
| 8 9 10 | 356 | supported by NIH grant R37 AI102634. |
| 11 12 | 357 | |
| 13 14 15 | 358 | Competing interests |
| 16 17 | 359 | All authors declare no competing interests. |
| 18 19 20 | 360 | |
| 21 22 23 | 361 | Author Contributions |
| 24 25 | 362 | HJH, AGC, MDJ, HL, JHM, conceived the idea for the project protocol. All authors |
| 26 27 28 | 363 | contributed to the design and methodology of the project protocol. HJH and AGC wrote |
| 29 30 31 | 364 | the first draft of the manuscript. MAH, SAS, IJD, BAD, XG-A, ME, RMG, NI, SL, MM- |
| 32 33 | 365 | B, SAP, SS, JACS, MKS, EAS provided feedback, revised the manuscript and have |
| 34 35 36 | 366 | read and approved the final version. |
| 37 38 | 367 | |
| 39 40 41 | 368 | Acknowledgements |
| 42 43 44 | 369 | We acknowledge Nia Roberts, outreach librarian and information specialist at the |
| 45 46 47 48 49 50 | 370 | University of Oxford for assistance designing the literature search. |
| 51 52 53 54 | | |
| 55 56 57 | | |
| 58 59 60 | | |

| 2 3 4 5 6 | 372 373 | Abbreviations |
|--|------------|---|
| 7 8 9 | 374 | EQUATOR: Enhancing the QUAlity and Transparency Of health Research |
| 10 11 | 375 | REDCap: Research Electronic Data Capture |
| 12 13 14 | 376 | STROBE: Strengthening the Reporting of Observational Studies in Epidemiology |
| 15 16 17 | 377 | TARGET: TrAnsparent ReportinG of studies Emulating a Target trial |
| 18 19 | 378 | |
| 20 21 22 | 379 | Figure Captions |
| 23 24 25 | 380 | |
| 25 26 27 | 381 | Figure 1: Elements relevant to both the specification and emulation of the target trial |
| 28 29 30 | 382 | described by Hernán & Robins ³ |
| 31 32 | 383 | Figure 2: Workflow for the development of the TARGET guideline |
| 33 34 35 | 384 | |
| 36 37 38 | 385 | |
| 38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 53 54 55 56 57 58 59 60 | 386 | |

| 1 2 | | |
|-------------|-----|---|
| 2 3 4 | 387 | References |
| 5 | | |
| 6 | 388 | 1. Hernán MA, Sauer BC, Hernández-Díaz S, et al. Specifying a target trial prevents immortal |
| 7 | 389 | time bias and other self-inflicted injuries in observational analyses. J Clin Epidemiol |
| 8 9 | 390 | 2016;79:70-75. doi: 10.1016/j.jclinepi.2016.04.014 [published Online First: |
| 10 | 391 | 2016/05/31] |
| 11 | 392 | Dickerman BA, García-Albéniz X, Logan RW, et al. Avoidable flaws in observational |
| 12 | 393 | analyses: an application to statins and cancer. Nature Medicine 2019;25(10):1601- |
| 13 14 | 394 | 06. doi: 10.1038/s41591-019-0597-x |
| 14 | 395 | 3. Hernán MA, Robins JM. Using big data to emulate a target trial when a randomized trial is |
| 16 | 396 | not available. American journal of epidemiology 2016;183(8):758-64. |
| 17 | 397 | Hernán MA. Methods of public health research—strengthening causal inference from |
| 18 | 398 | observational data. New England Journal of Medicine 2021;385(15):1345-48. |
| 19 20 | 399 | 5. Cochran WG. Observational studies. Statistical papers in honor of George W Snedecor |
| 20 | 400 | 1972:77-90. |
| 22 | 401 | 6. Dorn HF. Philosophy of inferences from retrospective studies. American Journal of Public |
| 23 | 402 | Health and the Nations Health 1953;43(6_Pt_1):677-83. |
| 24 | 403 | 7. Rubin DB. Estimating causal effects of treatments in randomized and nonrandomized |
| 25 26 | 404 | studies. Journal of Educational Psychology 1974;66(5):688. |
| 20 | 405 | 8. Wold H. Causality and econometrics. Econometrica: Journal of the Econometric Society |
| 28 | 406 | 1954:162-77. |
| 29 | 407 | 9. Robins J. A new approach to causal inference in mortality studies with a sustained |
| 30 | 408 | exposure period—application to control of the healthy worker survivor effect. |
| 31 32 | 409 | Mathematical Modelling 1986;7(9-12):1393-512. |
| 33 | 410 | 10. Concato J, Stein P, Dal Pan GJ, et al. Randomized, observational, interventional, and |
| 34 | 411 | real-world—What's in a name? <i>Pharmacoepidemiology and Drug Safety</i> |
| 35 | 412 | 2020;29(11):1514-17. |
| 36 37 | 413 | 11. Agency EM. European medicines agencies network strategy to 2025. The Netherlands: |
| 38 | 414 | Health of Medicines Agencies, 2020. |
| 39 | 415 | 12. Excellence NIfHaC. The NICE strategy 2021 to 2026, 2021. |
| 40 | 416 | 13. Health Canada. Optimizing the Use of Real World Evidence to Inform Regulatory |
| 41 | 417 | Decision-Making: Government of Canada, 2019. |
| 42 43 | 418 | 14. Therapeutic Goods Administration. Real world evidence and patient reported outcomes |
| 44 | 419 | in the regulatory context. <u>https://www.tga.gov.au/review-real-world-evidence-and-</u> |
| 45 | 420 | patient-reported-outcomes: Australian Government, Department of Health, 2021. |
| 46 | 421 | 15. Sterne JA, Hernán MA, Reeves BC, et al. ROBINS-I: a tool for assessing risk of bias in non- |
| 47 49 | 422 | randomised studies of interventions. BMJ 2016;355:i4919. doi: 10.1136/bmj.i4919 |
| 48 49 | 423 | 16. Garcia-Albeniz XH, J.: Bretthauer, M.: Hernan, M. A. Effectiveness of screening |
| 50 | 424 | colonoscopy to prevent colorectal cancer among medicare beneficiaries aged 70 to |
| 51 | 425 | 79 years: A prospective observational study. Annals of Internal Medicine 2017 doi: |
| 52 | 426 | http://dx.doi.org/10.7326/M16-0758 |
| 53 54 | 427 | 17. Mahévas M, Tran V-T, Roumier M, et al. Clinical efficacy of hydroxychloroquine in |
| 54 55 | 428 | patients with covid-19 pneumonia who require oxygen: observational comparative |
| 56 | 429 | study using routine care data. BMJ 2020;369:m1844. doi: 10.1136/bmj.m1844 |
| 57 | 430 | 18. Kaura A, Sterne JAC, Trickey A, et al. Invasive versus non-invasive management of older |
| 58 | 431 | patients with non-ST elevation myocardial infarction (SENIOR-NSTEMI): a cohort |
| 59 60 | | |
| 00 | | |

| 1 2 | | |
|----------|------------|---|
| 3 | 432 | study based on routing clinical data. The Lancet 2020;206(102E1);622.24 dai: |
| 4 | 432 | study based on routine clinical data. <i>The Lancet</i> 2020;396(10251):623-34. doi: 10.1016/S0140-6736(20)30930-2 |
| 5 | 433 | 19. Emilsson L, García-Albéniz X, Logan RW, et al. Examining Bias in Studies of Statin |
| 6 7 | 434 435 | Treatment and Survival in Patients With Cancer. JAMA Oncol 2018;4(1):63-70. doi: |
| 8 | 435 436 | |
| 9 | 430 437 | 10.1001/jamaoncol.2017.2752 |
| 10 | 437 438 | 20. Chan You S, Krumholz HM, Suchard MA, et al. Comprehensive Comparative Effectiveness |
| 11 | 438 439 | and Safety of First-Line β -Blocker Monotherapy in Hypertensive Patients: A Large- |
| 12 13 | 439 440 | Scale Multicenter Observational Study. <i>Hypertension</i> 2021;77(5):1528-38. doi: 10.1161/hypertensionaba. 120.16402 [published Opling First: 20210220] |
| 14 | 440 441 | 10.1161/hypertensionaha.120.16402 [published Online First: 20210329] 21. Caniglia EC, Robins JM, Cain LE, et al. Emulating a trial of joint dynamic strategies: An |
| 15 | 441 | application to monitoring and treatment of HIV-positive individuals. <i>Stat Med</i> |
| 16 | 442 443 | 2019;38(13):2428-46. doi: 10.1002/sim.8120 [published Online First: 20190318] |
| 17 18 | 444 | 2019,58(13).2428-40. doi: 10.1002/sini.8120 [published Online First: 20190518] 22. Moher D, Schulz KF, Simera I, et al. Guidance for developers of health research reporting |
| 10 | 444 445 | guidelines. <i>PLoS medicine</i> 2010;7(2):e1000217. |
| 20 | | |
| 21 | 446 | 23. Von Elm E, Altman DG, Egger M, et al. The Strengthening the Reporting of Observational |
| 22 | 447 448 | Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. Bullatin of the World Legith Organization 2007;85:867,72 |
| 23 24 | 448 449 | studies. Bulletin of the World Health Organization 2007;85:867-72. |
| 25 | 449 450 | 24. Hernán MA, Sauer BC, Hernández-Díaz S, et al. Specifying a target trial prevents |
| 26 | | immortal time bias and other self-inflicted injuries in observational analyses. <i>Journal</i> |
| 27 | 451 452 | of Clinical Epidemiology 2016;79:70-75. doi: 10.1016/j.jclinepi.2016.04.014 |
| 28 | 452 | [published Online First: 2016/05/31] |
| 29 30 | 453 454 | 25. Hernán MA. How to estimate the effect of treatment duration on survival outcomes |
| 31 | | using observational data. <i>Bmj</i> 2018;360:k182. doi: 10.1136/bmj.k182 [published |
| 32 | 455 | Online First: 2018/02/09] |
| 33 | 456 | 26. Robins JM, Hernan, M. J. Estimation of the causal effects of time-varying exposures. In: |
| 34 35 | 457 | Fitzmaurice G, Davidian M, Verbeke G, et al., eds. Longitudinal Data Analysis: CRC |
| 36 | 458 | press 2008. |
| 37 | 459 460 | 27. R Core Team. R: A language and environment for statistical computing. 2013 |
| 38 | 460 461 | 28. Harris PA, Taylor R, Minor BL, et al. The REDCap consortium: Building an international |
| 39 | 461 | community of software platform partners. <i>Journal of Biomedical Informatics</i> 2019;95:103208. doi: https://doi.org/10.1016/j.jbi.2019.103208 |
| 40 41 | 462 463 | 29. Harris PA, Taylor R, Thielke R, et al. Research electronic data capture (REDCap)—A |
| 42 | 463 464 | metadata-driven methodology and workflow process for providing translational |
| 43 | 464 465 | research informatics support. <i>Journal of Biomedical Informatics</i> 2009;42(2):377-81. |
| 44 | 465 466 | doi: https://doi.org/10.1016/j.jbi.2008.08.010 |
| 45 46 | 400 467 | 30. Braun V, Clarke V. Using thematic analysis in psychology. <i>Qualitative Research in</i> |
| 47 | 467 | Psychology 2006;3(2):77-101. doi: 10.1191/1478088706qp0630a |
| 48 | 408 469 | |
| 49 | | 31. Gattrell WT, Hungin AP, Price A, et al. ACCORD guideline for reporting consensus-based |
| 50 | 470 471 | methods in biomedical research and clinical practice: a study protocol. <i>Research</i> |
| 51 52 | | Integrity and Peer Review 2022;7(1):3. doi: 10.1186/s41073-022-00122-0 |
| 53 | 472 473 | 32. The EQUATOR Network. EQUATOR Network - Enhancing the QUAlity and Transparency |
| 54 | | Of health Research 2022 [Available from: <u>https://www.equator-network.org/2022</u> . |
| 55 | 474 475 | 33. Simera I, Moher D, Hoey J, et al. A catalogue of reporting guidelines for health research. |
| 56 57 | 475 | European journal of clinical investigation 2010;40(1):35-53. |
| 57 58 | 476 | |
| 59 | 177 | |
| 60 | 477 | |
| | | |





| 2 | | |
|----------|----|---|
| 3 | 1 | Supplementary Material |
| 4 | | |
| 5 | 2 | |
| 6 | 2 | Cumplementers Meterial 4. TADOET werking averus merekers (alabab atias) |
| 7 | 3 | Supplementary Material 1: TARGET working group members (alphabetical) |
| 8 | 4 | |
| 9 10 | | Staaring committee |
| 10 11 | 5 | Steering committee |
| 12 | 6 | Dr Aidan G. Cashin |
| 13 | 7 | Mr Harrison J. Hansford |
| 14 | 8 | Prof Miguel A. Hernán |
| 15 | 9 | Dr Hopin Lee |
| 16 | 10 | Dr Matthew D. Jones |
| 17 | 11 | Prof James H. McAuley |
| 18 | 12 | |
| 19 | | A/Prof Sonja A. Swanson |
| 20 | 13 | |
| 21 | 14 | Project team |
| 22 | 15 | A/Prof Issa J. Dahabreh |
| 23 | 16 | A/Prof Barbra A. Dickerman |
| 24 | 17 | Prof Matthias Egger |
| 25 | 18 | Dr Xabier Garcia-Albeniz |
| 26 | 19 | Prof Robert M. Golub |
| 27 | | |
| 28 | 20 | A/Prof Nazrul Islam |
| 29 | 21 | A/Prof Sara Lodi |
| 30 31 | 22 | A/Prof Margarita Moreno-Betancur |
| 32 | 23 | Prof Sallie A. Pearson |
| 33 | 24 | Prof Sebastian Schneeweiss |
| 34 | 25 | Prof Jonathan A. C. Sterne |
| 35 | 26 | Dr Melissa K. Sharp |
| 36 | 20 | Prof Elizabeth A. Stuart |
| 37 | | FIOI LIIZADELITA. SIUAT |
| 38 | 28 | |
| 39 | 29 | |
| 40 | | |
| 41 | | |
| 42 | | |
| 43 | | |
| 44 | | |
| 45 46 | | |
| 46 47 | | |
| 47 48 | | |
| 49 | | |
| 50 | | |
| 51 | | |
| 52 | | |
| 53 | | |
| 54 | | |
| 55 | | |
| 56 | | |
| 57 | | |
| 58 | | |
| 59 | | |
| 60 | | |

| 2 | | |
|----------|----------|---|
| 3 4 | 30 | Supplementary Material 2: Complete search strategies for all databases |
| 5 | 31 | |
| 6 7 | 32 | Medline |
| / 8 | 33 | 1 (emulat* adj5 trial?).mp. |
| 9 | 34 | 2 (target adj (trial? or experiment?)).mp. |
| 10 | 35 | 3. (observational adj (stud* or research or data)).mp. |
| 11 12 | | |
| 12 | 36 | 4. ((real world or rwd) adj2 (stud* or research or data)).mp. |
| 14 | 37 | 5. (routine* adj2 data).mp. |
| 15 | 38 | 6. (comparative effectiveness adj2 (stud* or research or data)).mp. |
| 16 17 | 39 | 7. (emulat* or propensity score? or (causal adj2 (inference? or analys?s or |
| 18 | 40 | effect*))).mp. |
| 19 | 41 | 8. 3 or 4 or 5 or 6 or 7 |
| 20 21 | 42 | 9. 2 and 8 |
| 22 | 43 | 10. (target adj (trial? or experiment?)).ti. |
| 23 | 44 | 11. 1 or 9 or 10 |
| 24 25 | 45 | Filtered for time (2012-2022) manually after search |
| 25 26 | 46 | |
| 27 | 47 | Embase |
| 28 | 48 | 1. (emulat* adj5 trial?).mp. |
| 29 30 | 49 | 2. (target adj (trial? or experiment?)).mp. |
| 31 | 50 | 3. (observational adj (stud* or research or data)).mp. |
| 32 | 51 | 4. ((real world or rwd) adj2 (stud* or research or data)).mp. |
| 33 34 | 52 | 5. (routine* adj2 data).mp. |
| 35 | 53 | 6. (comparative effectiveness adj2 (stud* or research or data)).mp. |
| 36 37 | 54 | 7. (emulat* or propensity score? or (causal adj2 (inference? or analys?s or |
| 37 38 | 55 | effect*))).mp. |
| 39 | 56 | 8. 3 or 4 or 5 or 6 or 7 |
| 40 41 | 50 57 | 9. 2 and 8 |
| 42 | 58 | 10. (target adj (trial? or experiment?)).ti. |
| 43 | 59 | 11. 1 or 9 or 10 |
| 44 45 | 60 | |
| 45 46 | 60 61 | psycINFO |
| 47 | | |
| 48 40 | 62 | noft(target trial emulat*) OR ((noft(real world data) OR (noft(emulat* trial)) OR |
| 49 50 | 63 | noft(observational) OR noft(routine* data)) AND noft(comparative effective*) |
| 51 | 64 | AND noft(causal infer*)) |
| 52 | 65 | |
| 53 54 | 66 | Web of Science |
| 55 | 67 | (TI=(emulat* trial)) OR (TI=(real world data) OR TI=(routine* data) OR |
| 56 | 68 | TI=(comparative effectiveness study comparative effectiveness research or |
| 57 58 | 69 | comparative effectiveness data) OR (TI=(emulat* or propensity score?) AND |
| 59 | 70 | TI=(causal inference or causal analysis or causal effect*))) AND ALL=(target |
| 60 | 71 | trial or emulat* or target trial emulation) |
| | | |

BMJ Open

BMJ Open

Development of the Transparent Reporting of Observational Studies Emulating a Target Trial (TARGET) Guideline

| Journal: | BMJ Open |
|----------------------------------|---|
| Manuscript ID | bmjopen-2023-074626.R2 |
| Article Type: | Protocol |
| Date Submitted by the Author: | 24-Aug-2023 |
| Complete List of Authors: | Hansford, Harrison; University of New South Wales; Neuroscience Research Australia Cashin, Aidan; Neuroscience Research Australia, Centre for Pain IMPACT; University of New South Wales, School of Health Sciences, Faculty of Medicine and Health Jones, Matthew; University of New South Wales; Neuroscience Research Australia, Centre for Pain IMPACT Swanson, Sonja; University of Pittsburgh, Department of Epidemiology; Harvard T.H. Chan School of Public Health, CAUSALab, Department of Epidemiology Islam, Nazrul; University of Oxford, Big data institute; University of Southampton, Faculty of Medicine Dahabreh, Isa; , Beth Israel Deaconess Medical Center and Harvard Medical School, Richard A. and Susan F. Smith Center for Outcomes Research; Harvard T.H. Chan School of Public Health, CAUSALab, Department of Epidemiology, Department of Biostatistics Dickerman, Barbra; Harvard TH Chan School of Public Health, CAUSALab, CAUSALab; Harvard TH Chan School of Public Health, Department of Epidemiology Egger, Matthias; University of Bern, Institute of Social & Preventive Medicine; University of Cape Town Faculty of Health Sciences, Centre for Infectious Disease Epidemiology and Research Garcia-De-Albeniz, Xavier ; Harvard University T H Chan School of Public Health, CAUSALab; RTI Health Solutions Barcelona Golub, Robert ; Northwestern University Feinberg School of Medicine Lodi, Sara; Harvard TH Chan School of Public Health, CAUSALab; Boston University School of Public Health, Department of Biostatistics Moreno-Betancur , Margarita ; Murdoch Children's Research Institute, Melbourne, Clinical Epidemiology & Biostatistics Unit; The University of Melbourne, Department of Paediatrics Pearson, Sallie-Anne; University of New South Wales, School of Population Health Schneeweiss , Sebastian ; Harvard Medical School, Boston, USA, Division of Pharmacoepidemiology, Department of Medicine, Brigham & Women's Hospital, Sterne, Jonathan; University of Bristol, Department of Population Health Sciences; NIHR Bristol Biomedical Research Centre Sh |

| | Hernan, M; Harvard School of Public Health, CAUSALab; Harvard T.H Chan School of Public Health, Department of Epidemiology, Departme of Biostatistics Lee, Hopin; University of Exeter Medical School McAuley, James; University of New South Wales, School of Health Sciences, Faculty of Medicine and Health; Neuroscience Research Australia, Centre for Pain IMPACT |
|--------------------------------------|---|
| Primary Subject Heading : | Epidemiology |
| Secondary Subject Heading: | Research methods |
| Keywords: | EPIDEMIOLOGY, Retrospective Studies, STATISTICS & RESEARCH METHODS |

SCHOLARONE[™] Manuscripts

BMJ Open

1

| 2 3 4 5 | 1 | Development of the Transparent Reporting of Observational Studies Emulating a Target |
|----------------------|----|---|
| 6 7 | 2 | Trial (TARGET) Guideline |
| 8 9 10 | 3 | |
| 11 | 4 | Harrison J. Hansford ^{1,2} , Aidan G. Cashin ^{1,2} , Matthew D. Jones ^{1,2} , Sonja A. Swanson ^{3,8,9} , |
| 12 13 | 5 | Nazrul Islam ^{5,6} , Issa J. Dahabreh ^{7,8, 9,10} , Barbra A. Dickerman ^{8,9} , Matthias Egger ^{11,12,13} , |
| 14 15 | 6 | Xabier Garcia-Albeniz ^{8, 14} , Robert M. Golub ¹⁵ , Sara Lodi ^{8,16} , Margarita Moreno- |
| 16 17 | 7 | Betancur ^{17,18} , Sallie-Anne Pearson ¹⁹ , Sebastian Schneeweiss ²⁰ , Jonathan A. C. |
| 18 | 8 | Sterne ^{21,22,23} , Melissa K. Sharp ²⁴ , Elizabeth A. Stuart ²⁵ , Miguel A. Hernán ^{8,9,10} , Hopin |
| 19 20 | 9 | Lee ²⁶ , James H. McAuley ^{1,2} |
| 21 22 | 10 | |
| 23 24 | 11 | 1. School of Health Sciences, Faculty of Medicine and Health, University of New South Wales, |
| 24 25 | 12 | Sydney, Australia |
| 26 27 | 13 | 2. Centre for Pain IMPACT, Neuroscience Research Australia, Sydney, Australia |
| 28 29 | 14 | 3. Department of Epidemiology, University of Pittsburgh, Pittsburgh, United States of America |
| 29 30 | 15 | 5. Oxford Population Health, Big Data Institute, University of Oxford, Oxford, UK |
| 31 32 | 16 | 6. Faculty of Medicine, University of Southampton, Southampton, UK |
| 33 | 17 | 7. Richard A. and Susan F. Smith Center for Outcomes Research, Beth Israel Deaconess |
| 34 35 | 18 | Medical Center and Harvard Medical School, Boston, MA, USA |
| 36 37 | 19 | 8. CAUSALab, Harvard T.H. Chan School of Public Health, Boston, MA, USA |
| 38 | 20 | 9. Department of Epidemiology, Harvard T.H. Chan School of Public Health, Boston, MA, USA |
| 39 40 | 21 | 10. Department of Biostatistics, Harvard T.H. Chan School of Public Health, Boston, MA, USA |
| 41 42 | 22 | 11. Institute of Social and Preventive Medicine, University of Bern, Bern, Switzerland |
| 43 | 23 | 12. Centre for Infectious Disease Epidemiology and Research, Faculty of Health Sciences, |
| 44 45 | 24 | University of Cape Town, Cape Town, South Africa |
| 46 | 25 | 13. Population Health Sciences, Bristol Medical School, University of Bristol, Bristol, UK |
| 47 48 | 26 | 14. RTI Health Solutions, Barcelona, Spain |
| 49 50 | 27 | 15. Northwestern University Feinberg School of Medicine, Chicago, IL, USA |
| 51 | 28 | 16. Department of Biostatistics, Boston University School of Public Health, Boston, MA, USA |
| 52 53 | 29 | 17. Clinical Epidemiology & Biostatistics Unit, Murdoch Children's Research Institute, Royal |
| 54 | 30 | Children's Hospital, 50 Flemington Rd, Parkville, Melbourne, VIC, Australia |
| 55 56 57 58 | 31 | 18. Department of Paediatrics, The University of Melbourne, Parkville, Australia |
| 59 | | For peer review only - http://bmionen.hmi.com/site/about/quidelines.yhtml Page 1 of 21 |

BMJ Open

| 1 2 | | |
|----------------|----|---|
| 3 | 32 | 19. School of Population Health, Faculty of Medicine and Health, UNSW Sydney, Sydney, |
| 1 5 | 33 | Australia |
| 5 7 | 34 | 20. Division of Pharmacoepidemiology, Department of Medicine, Brigham & Women's Hospital, |
| 3 | 35 | Harvard Medical School, Boston, MA, USA |
| ə 10 | 36 | 21. Department of Population Health Sciences, Bristol Medical School, University of Bristol, UK |
| 11 12 | 37 | 22. NIHR Bristol Biomedical Research Centre, UK |
| 13 | 38 | 23. Health Data Research UK South-West, Bristol, UK |
| 14 15 | 39 | 24. Department of Public Health and Epidemiology, RCSI University of Medicine and Health |
| 16 | 40 | Sciences, Dublin, Ireland |
| 17 18 | 41 | 25. Department of Mental Health, Johns Hopkins Bloomberg School of Public Health, Baltimore, |
| 19 20 | 42 | MD, USA |
| 21 | 43 | 26. University of Exeter Medical School, Exeter, UK |
| 22 23 | 44 | |
| 24 25 | 45 | |
| 26 | | |
| 27 28 | 46 | |
| 29 | 47 | Corresponding Author |
| 30 31 | 48 | Harrison J Hansford |
| 32 33 | 49 | Corresponding Author Harrison J Hansford E: <u>h.hansford@unsw.edu.au</u> School of Health Sciences, UNSW Sydney, 2052. Sydney, Australia |
| 34 35 | 50 | School of Health Sciences, UNSW Sydney, |
| 36 37 | 51 | |
| 38 39 | 52 | Words: 2247 |
| 40 41 | | |
| 12 | 53 | Words: 2247 |
| 43 44 | 54 | |
| 45 | 01 | |
| 46 47 | | |
| 48 | | |
| 49 50 | | |
| 51 | | |
| 52 53 | | |
| 55 54 | | |
| 55 | | |
| 56 57 | | |
| 58 | | |
| | | For peer review only - http://bmiopen.bmi.com/site/about/quidelines.xbtml Page 2 of 21 |
| 50 59 60 | | For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml Page 2 of 21 |

Enseignement Superieur (ABES) Protected by copyright, including for uses related to text and data mining, Al training, and similar technologies.

55 Abstract

| | 56 | |
|-----------------------|----|--|
| 0 | 57 | Background |
| 1 2 3 | 58 | Observational studies are increasingly used to inform health decision-making when |
| 5 4 5 6 7 | 59 | randomised trials are not feasible, ethical, or timely. The target trial approach provides |
| 6 7 8 | 60 | a framework to help minimise common biases in observational studies that aim to |
| 9 0 | 61 | estimate the causal effect of interventions. Incomplete reporting of studies using the |
| 1 2 3 | 62 | target trial framework limits the ability for clinicians, researchers, patients, and other |
| 4 5 | 63 | decision-makers to appraise, synthesise, and interpret findings to inform clinical and |
| 6 7 8 | 64 | public health practice and policy. This paper describes the methods that we will use to |
| 9 0 1 | 65 | develop the transparent reporting of observational studies emulating a target trial |
| 2 3 | 66 | (TARGET) reporting guideline. |
| 4 5 6 | 67 | |
| 7 8 | 68 | Methods/design |
| 9 0 1 | 69 | The TARGET reporting guideline will be developed in five stages following |
| 2 3 4 | 70 | recommended guidance. The first stage will identify target trial reporting practices by |
| 5 6 | 71 | systematically reviewing published studies that explicitly emulated a target trial. The |
| 7 8 9 | 72 | second stage will identify and refine items to be considered for inclusion in the |
| 0 1 | 73 | TARGET guideline by consulting content experts using sequential online surveys. The |
| 2 3 4 | 74 | third stage will prioritise and consolidate key items to be included in the TARGET |
| 5 6 7 | 75 | guideline at an in-person consensus meeting of TARGET investigators. The fourth |
| 7 8 9 0 | 76 | stage will produce and pilot-test both the TARGET guideline and explanation and |

| 2 | | |
|-------------|------------|---|
| 3 | 77 | elaboration document with relevant stakeholders. The fifth stage will disseminate the |
| 4 | // | elaboration document with relevant stakeholders. The intri stage will disseminate the |
| 5 6 7 | 78 | TARGET guideline and resources via journals, conferences, and courses. |
| 7 8 9 | 79 | |
| 10 | 17 | |
| 11 12 | 80 | Ethics and Dissemination |
| 13 | | |
| 14 | 81 | Ethical approval for the survey has been attained (HC220536). The TARGET guideline |
| 15 16 | | |
| 17 | 82 | will be disseminated widely in partnership with stakeholders to maximise adoption and |
| 18 | | |
| 19 | 83 | improve reporting of these studies. |
| 20 | 05 | |
| 21 | 01 | |
| 22 23 | 84 | |
| 24 | | |
| 25 | 85 | Key words: target trial emulation, causal inference, reporting guideline, observational |
| 26 | | |
| 27 | 86 | studies |
| 28 29 | | |
| 29 30 | 87 | |
| 31 | | |
| 32 | 88 | Strengths and Limitations |
| 33 | 00 | |
| 34 35 | 89 | The TARGET reporting guideline will be developed according to |
| 36 | 09 | The TARGET reporting guideline will be developed according to |
| 37 | 0.0 | |
| 38 | 90 | recommendations for health research reporting guidelines |
| 39 | | |
| 40 | 91 | The TARGET working group has been established to include stakeholders |
| 41 42 | | |
| 43 | 92 | from a variety of backgrounds |
| 44 | | |
| 45 | 93 | - A comprehensive piloting phase may increase the usability and uptake of the |
| 46 | ,, | |
| 47 48 | 94 | reporting guideline |
| 49 | 94 | |
| 50 | ~ - | |
| 51 | 95 | |
| 52 | | |
| 53 54 | | |
| 54 55 | | |
| 56 | | |
| 57 | | |
| 58 | | |
| 59 | | |
| 60 | | |
| | | |

Enseignement Superieur (ABES) . Protected by copyright, including for uses related to text and data mining, Al training, and similar technologies.

Observational studies can provide evidence on the causal effects of interventions when it is not feasible, ethical, or timely to conduct a relevant randomised trial. However, making causal inferences from observational data is challenging due to confounding and design-related biases such as selection bias and immortal time bias. (1,2) Design-related biases can be avoided using the target trial framework. (3,4) The framework involves the specification of the hypothetical randomised pragmatic trial — the target trial — that would ideally be conducted and how this trial might be emulated using observational data. (3,4) The two stages of the target trial framework are 1) specification of the target trial, and 2) emulation of the target trial. (3,4) Using observational data to mimic a randomised experiment was proposed in the mid 20th century, (5-8) and extended to time-varying treatments by Robins in 1986. (9) The value of using the target trial framework to design the analysis of observational studies has been recognised by international regulatory bodies in the field of medicine

and health, (10-14) and the framework underpins the widely-used ROBINS-I tool for
assessing risk of bias in non-randomised studies of interventions. (15) Studies that are
explicit in using the target trial framework have been published with increasing
frequency in leading general medical and specialty journals. (16-23)

³ 115

 Application of the target trial framework requires the complete specification of the 117 target trial protocol and its emulation (Figure 1). (3) Hernán & Robins (3) provide a

BMJ Open

template for specifying a target trial and its emulation; however, there is currently no detailed guidance on reporting a study designed to emulate a target trial. Incomplete reporting of these studies limits the ability of clinicians, researchers, patients, and other decision-makers to appraise and synthesise findings or interpret them to inform clinical and public health practice and policy. A reporting guideline that expands upon the initial target trial emulation template(3) is needed to provide authors with comprehensive recommendations on how to completely and transparently report a study emulating a target trial. [INSERT FIGURE 1] To address this gap, we outline the processes and methods that used to develop a reporting guideline for studies emulating a target trial - TARGET (Transparent reporting of observational studies emulating a target trial). Objective The objective of the TARGET guideline is to provide guidance on the minimum set of items that should be reported to provide a clear and transparent account of observational studies that investigate the comparative effectiveness and safety of health interventions explicitly using the target trial framework.

Enseignement Superieur (ABES) Protected by copyright, including for uses related to text and data mining, Al training, and similar technologies.

Enseignement Superieur (ABES) . Protected by copyright, including for uses related to text and data mining, Al training, and similar technologies.

BMJ Open

Methods

> We will develop the TARGET Guideline in five stages following recommendations for the development of health research reporting guidelines (Figure 2). (24) The start date for the study was late 2022, with the planned end date early 2025.

- [INSERT FIGURE 2]
- TARGET working group

The TARGET working group is made up of the steering committee and project team (Supplementary Material 1). The group was established to collate expertise on target trial emulation methodology, epidemiology, clinical trials, biostatistics, reporting guideline development, and knowledge of regulatory and journal editorial processes. The working group will oversee recruitment of participants for Stages 2 and 3 and contribute to writing and disseminating the guideline documents.

Stage 1: Identify current reporting practices

The systematic review aims to assess whether and how important items are reported by published studies explicitly emulating a target trial and whether reporting guidance (e.g., STROBE(25)) was used. The protocol for this systematic review was registered on the Open Science Framework on 13 March 2022 (osf.io/uj56m).

Page 9 of 25

BMJ Open

We will search Medline, EMBASE, PsycINFO and Science Citation Index for observational studies that stated in their methods that they explicitly emulated a target trial. We will exclude studies not written in English, not in the field of medicine and health, not conducted in humans, or not observational designs. Many observational studies may implicitly use the framework of a randomised trial. However, to be included in this review studies must be explicit in their attempt to emulate a target trial (e.g., stated 'target trial emulation' in the article). To identify eligible studies, we developed a literature search in collaboration with an expert librarian at the University of Oxford. Our approach used sensitive search terms including emulat*, target trial, observational data, real-world data, comparative effectiveness, and causal inference, to try to capture all papers explicitly emulating a target trial. The complete search strategy is in Supplementary Material 2. We will conduct forward citation tracking of selected seminal articles to maximise the chance of retrieving all relevant articles. (3,9,26-28) We will also include papers known to the authorship team. In duplicate, independent reviewers will conduct title, abstract, and full text screening. We will resolve disagreements between reviewers through discussion.

179 Data Extraction

We will extract items regarded by the steering committee as potentially important for the reporting of a target trial emulation, including those outlined by Hernán and Robins, 2016. (3) Two independent reviewers will extract information on study authors, year of publication, journal, sub-field of medicine, study design, sample size, intervention, Enseignement Superieur (ABES) . Protected by copyright, including for uses related to text and data mining, Al training, and similar technologies.

Enseignement Superieur (ABES) Protected by copyright, including for uses related to text and data mining, Al training, and similar technologies.

BMJ Open

comparison group, outcomes assessed, and whether the study was prospectively registered. We will extract items relevant to the methods and results of the target trial emulation, including whether and how all components of the protocol of the proposed target trial, and how they were emulated, were specified (i.e., eligibility criteria, treatment strategies, assignment procedures, follow-up period, outcome(s), causal contrast(s), and data analysis plan). We will enter data into a standardised data extraction form which two authors will pilot with a selection of included studies. We will resolve disagreements in data extraction between reviewers through discussion, or where necessary, consultation with a third reviewer. Data analysis We will use R (29) for all data analyses. Categorical variables will be summarised using frequencies and percentages. Continuous variables will be summarised using mean and standard deviation, or median and interguartile range, as appropriate. Outcomes of the systematic review The systematic review will provide evidence on reporting in studies explicitly emulating a target trial. We acknowledge that excluding studies not written in English and unpublished studies may cause potentially relevant articles to be excluded. The findings will inform the online surveys (Stage 2) and the consensus meeting (Stage 3). We will submit the findings of this review for publication and all data and code made publicly available.

| 1 2 | | |
|--|-----|--|
| 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 | 206 | |
| | 207 | Stage 2: Identify and refine items for the TARGET guideline |
| | 208 | We will conduct two online surveys to generate a list of candidate items that add detail |
| | 209 | to each of the protocol elements in Figure 1. |
| | 210 | |
| | 211 | Ethics |
| | 212 | Ethical approval has been obtained for the online surveys from the University of New |
| 21 22 23 | 213 | South Wales Human Research Ethics Committee (HC220536). |
| 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 | 214 | |
| | 215 | Selection of initial items |
| | 216 | The steering group will develop a list of key items, informed by the systematic review |
| | 217 | (Stage 1), and the target trial framework described by Hernán & Robins, (3) thought |
| | 218 | important for the conduct and reporting target trial emulations (Figure 1). Other |
| | 219 | potential sources of items include: published guidance for observational studies and |
| | 220 | randomised controlled trials, the ROBINS-I tool, (15) and studies that describe items |
| 42 43 | 221 | that may be important for the conduct or reporting of target trial emulations. |
| 44 45 46 | 222 | |
| 47 48 49 | 223 | Participants |
| 50 51 | 224 | Members of the TARGET working group (Supplementary Material 1) will be invited to |
| 52 53 54 | 225 | participate in the surveys. |
| 55 56 | 226 | |
| 57 58 59 | 227 | Procedure |
| 60 | | |

Enseignement Superieur (ABES) Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies.

BMJ Open

We will host two online surveys using REDCap. (30,31) We will send each online survey via email to the participants. We will ask participants to rate the importance of each potential reporting item on a 9-point Likert scale (1, "not important", to 9, "critically important"). Participants will have the opportunity to provide suggestions or modifications to the wording of items as well as suggest additional items or make other comments.

In the second survey, we will send participants a summary of the results for each potential reporting item (mean scores and standard deviations, median scores and interquartile ranges, and histograms), their own score for each item, and any comments from participants on each item from the first survey. We will also present any new items and suggested modifications to items. We will then invite participants to re-score the importance of each item, and score any additional items, considering the aggregated ratings. Participants will have the opportunity to provide additional feedback on each item in the form of open ended responses.

244 Analysis

Continuous variables will be summarised using mean and standard deviation, or median and interquartile range, as appropriate. We will analyse the free-text responses from the first and second surveys using an inductive approach, (32) in which we will use reflexive thematic (32) analysis to identify, organise and generate codes, and then identify themes found within the dataset. Briefly, inductive coding is a

BMJ Open

| 2 | | |
|----------------|-----|---|
| 3 4 5 | 250 | process pooling common ideas without trying to fit ideas/codes into a pre-existing |
| 6 7 | 251 | framework. These data will contribute to the creation of new items and modification of |
| 8 9 10 | 252 | existing items to be included in the subsequent survey. |
| 11 12 | 253 | |
| 13 14 15 | 254 | Outcome of the online surveys |
| 16 17 18 | 255 | We will generate a preliminary list of items with corresponding ratings of importance |
| 19 20 | 256 | to be considered in the TARGET guideline at the consensus meeting (Stage 3). We |
| 21 22 23 | 257 | will also generate qualitative insights to guide item refinement and prioritisation in |
| 24 25 | 258 | preparation for the consensus meeting. |
| 26 27 28 | 259 | |
| 29 30 31 | 260 | Stage 3 – Consolidate and prioritise key items to be included in the TARGET guideline |
| 32 33 | 261 | A consensus meeting will finalise reporting items for the TARGET guideline. (24) The |
| 34 35 36 | 262 | consensus meeting will follow suggested methods for developing reporting guidelines, |
| 37 38 30 | 263 | (24) including guidance for consensus-based methods currently being developed |
| 39 40 41 | 264 | which we will use if they become available. (33) |
| 42 43 44 | 265 | |
| 45 46 | 266 | Process |
| 47 48 49 | 267 | We will invite stakeholders identified by the working group to participate in a two-day |
| 50 51 52 | 268 | consensus meeting. The TARGET working group will ensure that the expertise of |
| 53 54 | 269 | consensus meeting participants includes target trial emulation methodology, |
| 55 56 57 | 270 | epidemiology, clinical trials, biostatistics, reporting guideline development, and |
| 58 59 60 | 271 | regulatory and journal editorial processes. Prior to the consensus meeting, the core |
| | | |

Enseignement Superieur (ABES) . Protected by copyright, including for uses related to text and data mining, Al training, and similar technologies.

BMJ Open

team will provide attendees with evidence from the systematic review (Stage 1) and findings from the online surveys (Stage 2) including a draft of the items proposed for inclusion in the guideline. We will present the findings from Stage 1 and 2 at the consensus meeting. A member of the TARGET working group will facilitate a structured discussion on the rationale for including items from the online surveys. If there are disagreements, they will first be debated and, if disagreements remain, we will hold an anonymised vote to establish the importance of including the item in the guideline. For the anonymised vote, a simple majority will be sufficient to guide the inclusion/exclusion of an item. The meeting will conclude with discussion about the content and production of relevant documents (TARGET guideline, draft explanation and elaboration document) as well as strategies for dissemination and implementation. Following the conclusion of the consensus meeting, we will circulate a report on the outcome to the meeting participants for review and approval.

285 g

Stage 4 – Development and piloting of the draft TARGET guideline and explanation
 and elaboration document

Stage 4 involves drafting the TARGET guideline and accompanying explanation and elaboration document to ensure that the wording and content of the documents are clear, precise, and suitable for all identified stakeholders. The purpose of the explanation and elaboration document is to explain each item by providing background information, a rationale, and clear reporting examples from published target trial emulations. We will design the explanation and elaboration document to facilitate

BMJ Open

adherence to the TARGET guideline by clarifying the importance of each item, highlighting relevant reporting issues and providing examples to assist authors using the guideline. The consensus meeting participants may be asked to review and comment on the draft TARGET guideline and explanation and elaboration document.

We will evaluate the TARGET guideline by piloting the proposed guideline and the explanation and elaboration document with 20-30 expert methodologists and potential users of TARGET, identified from TARGET working group networks. We will ask participants to provide general feedback on accessibility and usability, and to identify possible reporting items that might have been overlooked. We will also ask for specific feedback about the utility and clarity of each TARGET item. We will collect data through online surveys, hosted by REDCap. (30,31) We will incorporate feedback from the piloting exercise into the final guideline and explanation and elaboration document, as required. If suggested revisions are extensive, we will conduct a further round of piloting.

3 309

310 Patient and public involvement

Potential users of this research include health researchers conducting observational analyses, regulatory bodies, public health and other health decision-makers. We aim to include relevant decision-makers in the piloting phase of the guideline development process to maximise the usefulness and uptake of the TARGET guideline. Participants Enseignement Superieur (ABES) Protected by copyright, including for uses related to text and data mining, Al training, and similar technologies.

BMJ Open

Page 16 of 25

Enseignement Superieur (ABES) . Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies

in any stage of the guideline development will be informed of the results and finalguidance.

318 Stage 5 – Guideline implementation

The goal of the final stage of guideline development is to maximise reach and use of the TARGET guideline. The TARGET working group will guide the dissemination strategy with advice from consensus meeting participants. We aim to publish the TARGET guideline and the explanation and elaboration document and disseminate the findings through traditional and social media. We will engage journal editors and funding agencies to encourage TARGET guideline endorsement alongside other published reporting guidance. We will publicly host the TARGET guideline and explanation and elaboration paper, and any other relevant material on a TARGET website. We will index the guideline on the Enhancing the QUAlity and Transparency Of health Research (EQUATOR) Network website. (34,35) We will create online resources including infographics, blog posts and podcasts, which will be available on the TARGET website. We will share the TARGET guideline with authors in the field, and at relevant scientific conferences and methodological courses.

| 2 | | |
|--|--|---|
| 3 4 5 | 332 | Declarations |
| 6 7 | 333 | |
| 8 9 10 | 334 | Ethics approval and consent to participate |
| 11 12 | 335 | Not Applicable |
| 13 14 15 | 336 | |
| 16 17 | 337 | Consent for publication |
| 18 19 20 | 338 | All authors consent to publication of this manuscript |
| 21 22 23 | 339 | |
| 24 25 | 340 | Availability of data and materials |
| 26 27 28 | 341 | Not applicable |
| 29 30 | 342 | |
| 31 32 | | |
| 33 | 343 | Funding |
| 33 34 35 | 343 344 | Funding There was no specific funding for this study. HJH was supported by an Australian |
| 33 34 35 36 37 38 | | |
| 33 34 35 36 37 38 39 40 | 344 | There was no specific funding for this study. HJH was supported by an Australian |
| 33 34 35 36 37 38 39 40 41 42 43 | 344 345 | There was no specific funding for this study. HJH was supported by an Australian National Health and Medical Research Council (NHMRC) Postgraduate Scholarship, |
| 33 34 35 36 37 38 39 40 41 42 | 344345346 | There was no specific funding for this study. HJH was supported by an Australian National Health and Medical Research Council (NHMRC) Postgraduate Scholarship, a PhD Top-Up Scholarship from Neuroscience Research Australia, and was a |
| 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 | 344345346347 | There was no specific funding for this study. HJH was supported by an Australian National Health and Medical Research Council (NHMRC) Postgraduate Scholarship, a PhD Top-Up Scholarship from Neuroscience Research Australia, and was a Neuroscience Research Australia PhD Pearl sponsored by Paul Salteri AO. AGC |
| 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 | 344 345 346 347 348 | There was no specific funding for this study. HJH was supported by an Australian National Health and Medical Research Council (NHMRC) Postgraduate Scholarship, a PhD Top-Up Scholarship from Neuroscience Research Australia, and was a Neuroscience Research Australia PhD Pearl sponsored by Paul Salteri AO. AGC was supported by an Australian NHMRC Investigator Grant (ID 2010088). MM-B was |
| 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 53 | 344 345 346 347 348 349 | There was no specific funding for this study. HJH was supported by an Australian National Health and Medical Research Council (NHMRC) Postgraduate Scholarship, a PhD Top-Up Scholarship from Neuroscience Research Australia, and was a Neuroscience Research Australia PhD Pearl sponsored by Paul Salteri AO. AGC was supported by an Australian NHMRC Investigator Grant (ID 2010088). MM-B was supported by an Australian NHMRC Investigator Grant (ID 2009572). JMH was |
| 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 53 54 55 56 | 344 345 346 347 348 349 350 | There was no specific funding for this study. HJH was supported by an Australian National Health and Medical Research Council (NHMRC) Postgraduate Scholarship, a PhD Top-Up Scholarship from Neuroscience Research Australia, and was a Neuroscience Research Australia PhD Pearl sponsored by Paul Salteri AO. AGC was supported by an Australian NHMRC Investigator Grant (ID 2010088). MM-B was supported by an Australian NHMRC Investigator Grant (ID 2009572). JMH was supported by an Australian NHMRC Investigator Grant (ID 2010128). BAD was |
| 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 53 54 55 | 344 345 346 347 348 349 350 351 | There was no specific funding for this study. HJH was supported by an Australian National Health and Medical Research Council (NHMRC) Postgraduate Scholarship, a PhD Top-Up Scholarship from Neuroscience Research Australia, and was a Neuroscience Research Australia PhD Pearl sponsored by Paul Salteri AO. AGC was supported by an Australian NHMRC Investigator Grant (ID 2010088). MM-B was supported by an Australian NHMRC Investigator Grant (ID 2009572). JMH was supported by an Australian NHMRC Investigator Grant (ID 2010128). BAD was supported by a grant from the National Institutes of Health (R00 CA248335). ME was |

BMJ Open

1

Enseignement Superieur (ABES) Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies.

| 2 | | |
|----------------------------------|-----|--|
| 3 4 5 | 354 | supported by grants from the National Institute for Health and Care Research |
| 6 7 | 355 | (HDRUK2022.0313) and the UK Office for National Statistics (2002563). MAH was |
| 8 9 10 | 356 | supported by NIH grant R37 AI102634. |
| 11 12 | 357 | |
| 13 14 15 | 358 | Competing interests |
| 16 17 | 359 | All authors declare no competing interests. |
| 18 19 20 | 360 | |
| 21 22 23 | 361 | Author Contributions |
| 24 25 | 362 | HJH, AGC, MDJ, HL, JHM, conceived the idea for the project protocol. All authors |
| 26 27 28 | 363 | contributed to the design and methodology of the project protocol. HJH and AGC wrote |
| 29 30 31 | 364 | the first draft of the manuscript. MAH, SAS, IJD, BAD, XG-A, ME, RMG, NI, SL, MM- |
| 32 33 | 365 | B, SAP, SS, JACS, MKS, EAS provided feedback, revised the manuscript and have |
| 34 35 36 | 366 | read and approved the final version. |
| 37 38 | 367 | |
| 39 40 41 | 368 | Acknowledgements |
| 42 43 44 | 369 | We acknowledge Nia Roberts, outreach librarian and information specialist at the |
| 45 46 47 48 49 50 | 370 | University of Oxford for assistance designing the literature search. |
| 51 52 53 54 | | |
| 55 56 57 | | |
| 58 59 60 | | |

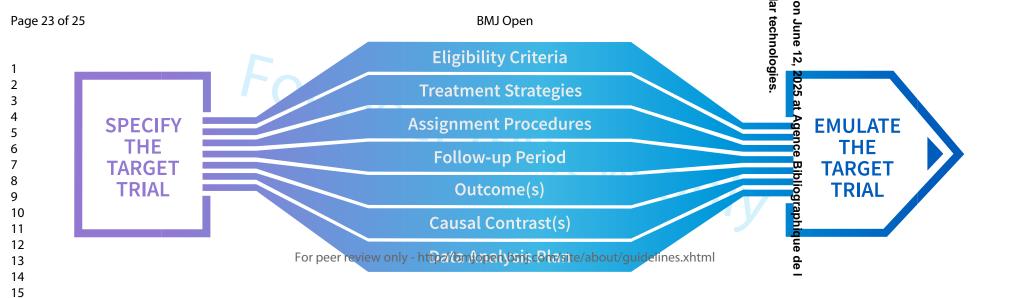
| 2 | | |
|----------------|-----|---|
| 3 4 | 372 | Abbreviations |
| 5 | 373 | |
| 6 | 575 | |
| 7 8 9 | 374 | EQUATOR: Enhancing the QUAlity and Transparency Of health Research |
| 10 11 12 | 375 | REDCap: Research Electronic Data Capture |
| 13 14 | 376 | STROBE: Strengthening the Reporting of Observational Studies in Epidemiology |
| 15 16 17 | 377 | TARGET: TrAnsparent ReportinG of studies Emulating a Target trial |
| 18 19 20 | 378 | |
| 21 22 | 379 | Figure Captions |
| 23 24 25 | 380 | |
| 26 27 28 | 381 | Figure 1: Elements relevant to both the specification and emulation of the target trial |
| 29 30 | 382 | described by Hernán & Robins (3) |
| 31 32 33 | 383 | Figure 2: Workflow for the development of the TARGET guideline |
| 34 35 36 | 384 | |
| 37 38 | 385 | |
| 39 40 41 | 386 | |
| 42 | | |
| 43 44 | | |
| 45 | | |
| 46 | | |
| 47 48 | | |
| 49 | | |
| 50 | | |
| 51 52 | | |
| 53 | | |
| 54 55 | | |
| 55 56 | | |
| 57 | | |
| 58 59 | | |
| 60 | | |

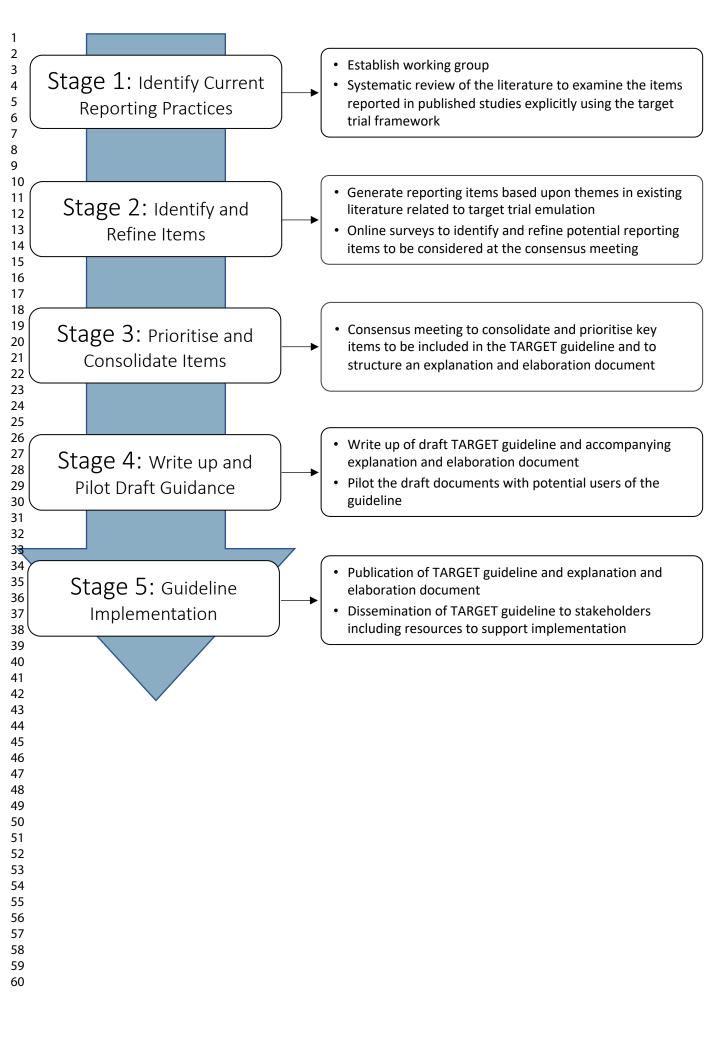
| BMJ | Open |
|-----|------|
|-----|------|

References 1. Hernán MA, Sauer BC, Hernández-Díaz S, et al. Specifying a target trial prevents immortal time bias and other self-inflicted injuries in observational analyses. J Clin Epidemiol 2016;79:70-75. doi: 10.1016/j.jclinepi.2016.04.014 [published Online First: 2016/05/31] 2. Dickerman BA, García-Albéniz X, Logan RW, et al. Avoidable flaws in observational analyses: an application to statins and cancer. Nature Medicine 2019;25(10):1601-06. doi: 10.1038/s41591-019-0597-x 3. Hernán MA, Robins JM. Using big data to emulate a target trial when a randomized trial is not available. American journal of epidemiology 2016;183(8):758-64. 4. Hernán MA. Methods of public health research—strengthening causal inference from observational data. New England Journal of Medicine 2021;385(15):1345-48. 5. Cochran WG. Observational studies. Statistical papers in honor of George W Snedecor 1972:77-90. 6. Dorn HF. Philosophy of inferences from retrospective studies. American Journal of Public Health and the Nations Health 1953;43(6 Pt 1):677-83. 7. Rubin DB. Estimating causal effects of treatments in randomized and nonrandomized studies. Journal of Educational Psychology 1974;66(5):688. 8. Wold H. Causality and econometrics. *Econometrica: Journal of the Econometric Society* 1954:162-77. 9. Robins J. A new approach to causal inference in mortality studies with a sustained exposure period—application to control of the healthy worker survivor effect. Mathematical Modelling 1986;7(9-12):1393-512. 10. Concato J, Stein P, Dal Pan GJ, et al. Randomized, observational, interventional, and real-world—What's in a name? *Pharmacoepidemiology and Drug Safety* 2020;29(11):1514-17. 11. Agency EM. European medicines agencies network strategy to 2025. The Netherlands: Health of Medicines Agencies, 2020. 12. Excellence NIfHaC. The NICE strategy 2021 to 2026, 2021. 13. Health Canada. Optimizing the Use of Real World Evidence to Inform Regulatory Decision-Making: Government of Canada, 2019. 14. Therapeutic Goods Administration. Real world evidence and patient reported outcomes in the regulatory context. https://www.tga.gov.au/review-real-world-evidence-and-patient-reported-outcomes: Australian Government, Department of Health, 2021. 15. Sterne JA, Hernán MA, Reeves BC, et al. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. BMJ 2016;355:i4919. doi: 10.1136/bmj.i4919 16. Garcia-Albeniz XH, J.: Bretthauer, M.: Hernan, M. A. Effectiveness of screening colonoscopy to prevent colorectal cancer among medicare beneficiaries aged 70 to 79 years: A prospective observational study. Annals of Internal Medicine 2017 doi: http://dx.doi.org/10.7326/M16-0758 17. Mahévas M, Tran V-T, Roumier M, et al. Clinical efficacy of hydroxychloroquine in patients with covid-19 pneumonia who require oxygen: observational comparative study using routine care data. BMJ 2020;369:m1844. doi: 10.1136/bmj.m1844 18. Kaura A, Sterne JAC, Trickey A, et al. Invasive versus non-invasive management of older patients with non-ST elevation myocardial infarction (SENIOR-NSTEMI): a cohort

| 1 2 | | |
|----------|------------|---|
| 3 | 432 | study based on routine clinical data. The Lancet 2020;396(10251):623-34. doi: |
| 4 | 433 | 10.1016/S0140-6736(20)30930-2 |
| 5 | 434 | 19. Emilsson L, García-Albéniz X, Logan RW, et al. Examining Bias in Studies of Statin |
| 6 7 | 435 | Treatment and Survival in Patients With Cancer. JAMA Oncol 2018;4(1):63-70. doi: |
| 8 | 436 | 10.1001/jamaoncol.2017.2752 |
| 9 | 437 | 20. Chan You S, Krumholz HM, Suchard MA, et al. Comprehensive Comparative Effectiveness |
| 10 | 438 | and Safety of First-Line β -Blocker Monotherapy in Hypertensive Patients: A Large- |
| 11 | 438 | Scale Multicenter Observational Study. <i>Hypertension</i> 2021;77(5):1528-38. doi: |
| 12 13 | 439 440 | 10.1161/hypertensionaha.120.16402 [published Online First: 20210329] |
| 14 | 440 441 | 21. Caniglia EC, Robins JM, Cain LE, et al. Emulating a trial of joint dynamic strategies: An |
| 15 | 441 | |
| 16 | 442 443 | application to monitoring and treatment of HIV-positive individuals. <i>Stat Med</i> |
| 17 | | 2019;38(13):2428-46. doi: 10.1002/sim.8120 [published Online First: 20190318] |
| 18 19 | 444 | 22. Zuo H, Yu L, Campbell SM, et al. The implementation of target trial emulation for causal |
| 20 | 445 | inference: a scoping review. <i>J Clin Epidemiol</i> 2023 doi: 10.1016/j.jclinepi.2023.08.003 |
| 21 | 446 | [published Online First: 20230808] |
| 22 | 447 | 23. Scola G, Chis Ster A, Bean D, et al. Implementation of the trial emulation approach in |
| 23 | 448 | medical research: a scoping review. BMC Medical Research Methodology |
| 24 25 | 449 | 2023;23(1):186. doi: 10.1186/s12874-023-02000-9 |
| 26 | 450 | 24. Moher D, Schulz KF, Simera I, et al. Guidance for developers of health research reporting |
| 27 | 451 | guidelines. PLoS medicine 2010;7(2):e1000217. |
| 28 | 452 | 25. Von Elm E, Altman DG, Egger M, et al. The Strengthening the Reporting of Observational |
| 29 | 453 | Studies in Epidemiology (STROBE) statement: guidelines for reporting observational |
| 30 31 | 454 | studies. Bulletin of the World Health Organization 2007;85:867-72. |
| 32 | 455 | 26. Hernán MA, Sauer BC, Hernández-Díaz S, et al. Specifying a target trial prevents |
| 33 | 456 | immortal time bias and other self-inflicted injuries in observational analyses. Journal |
| 34 | 457 | of Clinical Epidemiology 2016;79:70-75. doi: 10.1016/j.jclinepi.2016.04.014 |
| 35 | 458 | [published Online First: 2016/05/31] |
| 36 37 | 459 | 27. Hernán MA. How to estimate the effect of treatment duration on survival outcomes |
| 38 | 460 | using observational data. <i>Bmj</i> 2018;360:k182. doi: 10.1136/bmj.k182 [published |
| 39 | 461 | Online First: 2018/02/09] |
| 40 | 462 | 28. Robins JM, Hernan, M. J. Estimation of the causal effects of time-varying exposures. In: |
| 41 | 463 | Fitzmaurice G, Davidian M, Verbeke G, et al., eds. Longitudinal Data Analysis: CRC |
| 42 43 | 464 | press 2008. |
| 44 | 465 | 29. R Core Team. R: A language and environment for statistical computing. 2013 |
| 45 | 466 | 30. Harris PA, Taylor R, Minor BL, et al. The REDCap consortium: Building an international |
| 46 | 467 | community of software platform partners. Journal of Biomedical Informatics |
| 47 48 | 468 | 2019;95:103208. doi: <u>https://doi.org/10.1016/j.jbi.2019.103208</u> |
| 40 | 469 | 31. Harris PA, Taylor R, Thielke R, et al. Research electronic data capture (REDCap)—A |
| 50 | 470 | metadata-driven methodology and workflow process for providing translational |
| 51 | 471 | research informatics support. Journal of Biomedical Informatics 2009;42(2):377-81. |
| 52 | 472 | doi: <u>https://doi.org/10.1016/j.jbi.2008.08.010</u> |
| 53 54 | 473 | 32. Braun V, Clarke V. Using thematic analysis in psychology. Qualitative Research in |
| 54 55 | 474 | <i>Psychology</i> 2006;3(2):77-101. doi: 10.1191/1478088706qp063oa |
| 56 | 475 | 33. Gattrell WT, Hungin AP, Price A, et al. ACCORD guideline for reporting consensus-based |
| 57 | 476 | methods in biomedical research and clinical practice: a study protocol. Research |
| 58 | 477 | Integrity and Peer Review 2022;7(1):3. doi: 10.1186/s41073-022-00122-0 |
| 59 60 | | |
| 00 | | |
| | | |

| 1 2 3 4 5 6 7 8 9 | 478 479 480 481 482 | 34. The EQUATOR Network. EQUATOR Network - Enhancing the QUAlity and Transparency Of health Research 2022 [Available from: <u>https://www.equator-network.org/2022</u>. 35. Simera I, Moher D, Hoey J, et al. A catalogue of reporting guidelines for health research. <i>European journal of clinical investigation</i> 2010;40(1):35-53. |
|---|---------------------------------|---|
| 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 32 42 52 62 7 8 9 30 31 22 33 34 35 36 37 38 9 40 41 42 34 45 46 47 48 9 50 51 52 54 55 67 58 59 | | |
| 60 | | |





| 1 | | |
|----------|----------|---|
| 2 | | |
| 3 | 1 | Supplementary Material |
| 4 5 | 2 | |
| 6 | Z | |
| 7 | 3 | Supplementary Material 1: TARGET working group members (alphabetical) |
| 8 | 4 | |
| 9 | 4 | |
| 10 | 5 | Steering committee |
| 11 12 | 6 | Dr Aidan G. Cashin |
| 13 | 7 | Mr Harrison J. Hansford |
| 14 | 8 | Prof Miguel A. Hernán |
| 15 | 9 | Dr Hopin Lee |
| 16 | 10 | Dr Matthew D. Jones |
| 17 | 11 | Prof James H. McAuley |
| 18 | 12 | A/Prof Sonja A. Swanson |
| 19 | 13 | |
| 20 | 13 | Project team |
| 21 22 | 14 | A/Prof Issa J. Dahabreh |
| 22 | 15 16 | A/Prof Barbra A. Dickerman |
| 24 | | |
| 25 | 17 | Prof Matthias Egger |
| 26 | 18 | Dr Xabier Garcia-Albeniz |
| 27 | 19 | Prof Robert M. Golub |
| 28 | 20 | A/Prof Nazrul Islam |
| 29 30 | 21 | A/Prof Sara Lodi |
| 31 | 22 | A/Prof Margarita Moreno-Betancur |
| 32 | 23 | Prof Sallie A. Pearson |
| 33 | 24 | Prof Sebastian Schneeweiss |
| 34 | 25 | Prof Jonathan A. C. Sterne |
| 35 | 26 | Dr Melissa K. Sharp |
| 36 | 27 | Prof Elizabeth A. Stuart |
| 37 38 | 28 | |
| 39 | 29 | |
| 40 | | |
| 41 | | |
| 42 | | |
| 43 | | |
| 44 45 | | |
| 45 46 | | |
| 47 | | |
| 48 | | |
| 49 | | |
| 50 | | |
| 51 52 | | |
| 52 53 | | |
| 55 54 | | |
| 55 | | |
| 56 | | |
| 57 | | |
| 58 | | |
| 59 60 | | |
| 00 | | |

Enseignement Superieur (ABES) Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies.

BMJ Open

| 3 4 | 30 | Supplementary Material 2: Complete search strategies for all databases |
|-----------|----------|---|
| 5 6 | 31 | |
| b 7 | 32 | Medline |
| 8 | 33 | 1 (emulat* adj5 trial?).mp. |
| 9 | 34 | 2 (target adj (trial? or experiment?)).mp. |
| 10 11 | 35 | 3. (observational adj (stud* or research or data)).mp. |
| 12 | 36 | 4. ((real world or rwd) adj2 (stud* or research or data)).mp. |
| 13 | 37 | 5. (routine* adj2 data).mp. |
| 14 15 | 38 | 6. (comparative effectiveness adj2 (stud* or research or data)).mp. |
| 16 | 39 | 7. (emulat* or propensity score? or (causal adj2 (inference? or analys?s or |
| 17 | 40 | effect*))).mp. |
| 18 19 | 41 | 8. 3 or 4 or 5 or 6 or 7 |
| 20 | 42 | 9. 2 and 8 |
| 21 | 43 | 10. (target adj (trial? or experiment?)).ti. |
| 22 23 | 44 | 11. 1 or 9 or 10 |
| 24 | 45 | Filtered for time (2012-2022) manually after search |
| 25 26 | 46 | |
| 20 27 | 47 | Embase |
| 28 | 48 | 1. (emulat* adj5 trial?).mp. |
| 29 30 | 49 | 2. (target adj (trial? or experiment?)).mp. |
| 30 31 | 50 | 3. (observational adj (stud* or research or data)).mp. |
| 32 | 51 | 4. ((real world or rwd) adj2 (stud* or research or data)).mp. |
| 33 34 | 52 | 5. (routine* adj2 data).mp. |
| 35 | 52 | 6. (comparative effectiveness adj2 (stud* or research or data)).mp. |
| 36 | 55 54 | 7. (emulat* or propensity score? or (causal adj2 (inference? or analys?s or |
| 37 38 | 55 | effect*))).mp. |
| 39 | 55 56 | 8. 3 or 4 or 5 or 6 or 7 |
| 40 | 50 57 | 9. 2 and 8 |
| 41 42 | 58 | 10. (target adj (trial? or experiment?)).ti. |
| 43 | 58 59 | 11. 1 or 9 or 10 |
| 44 4 E | | |
| 45 46 | 60 | payelNEQ. |
| 47 | 61 | psycINFO |
| 48 49 | 62 | noft(target trial emulat*) OR ((noft(real world data) OR (noft(emulat* trial)) OR |
| 49 50 | 63 | noft(observational) OR noft(routine* data)) AND noft(comparative effective*) |
| 51 | 64 | AND noft(causal infer*)) |
| 52 | 65 | |
| 53 54 | 66 | Web of Science |
| 55 | 67 | (TI=(emulat* trial)) OR (TI=(real world data) OR TI=(routine* data) OR |
| 56 57 | 68 | TI=(comparative effectiveness study comparative effectiveness research or |
| 57 58 | 69 | comparative effectiveness data) OR (TI=(emulat* or propensity score?) AND |
| 59 | 70 | TI=(causal inference or causal analysis or causal effect*))) AND ALL=(target |
| 60 | 71 | trial or emulat* or target trial emulation) |