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

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SCHOLARONE[™] Manuscripts

2 3 4	1	Development of the Transparent Reporting of Observational Studies Emulating a Target
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6 7	2	Trial (TARGET) Guideline
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55 Abstract

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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

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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
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93 Introduction

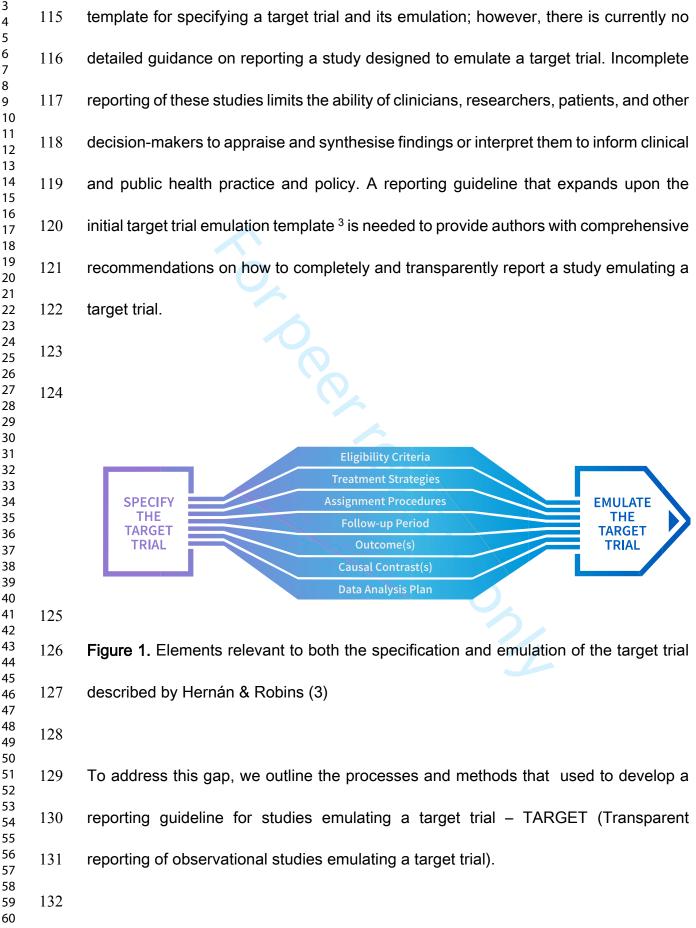
Observational studies can provide evidence on the causal effects of interventions when it is not feasible, ethical, or timely to conduct a relevant randomised trial. However, making causal inferences from observational data is challenging due to confounding and design-related biases such as selection 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

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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

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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

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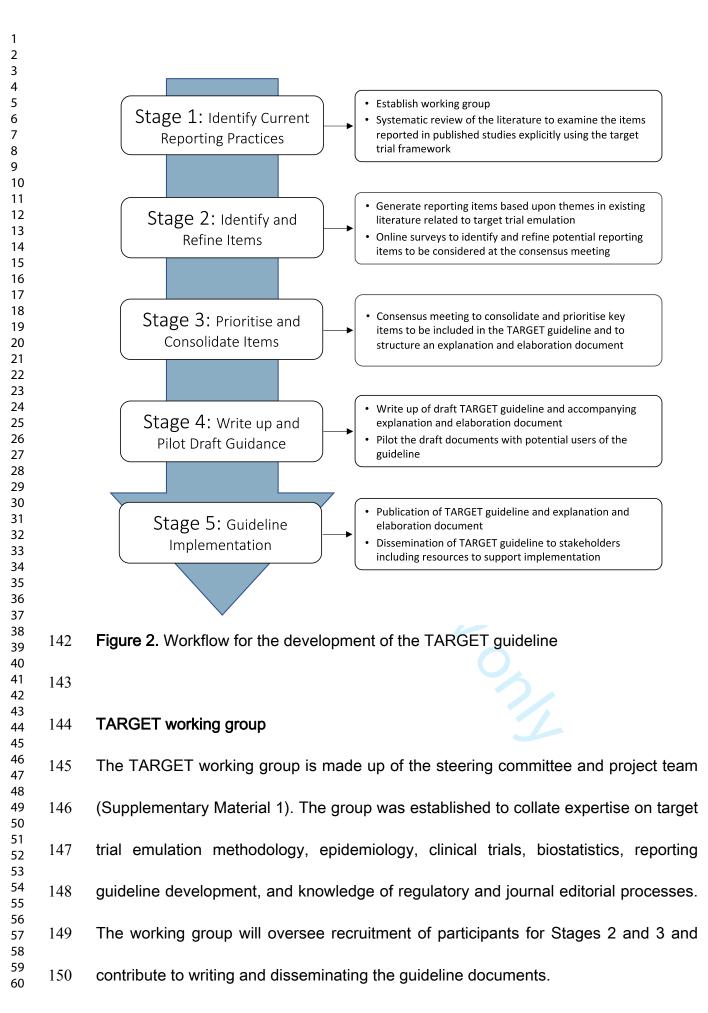
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Objective

Methods/design

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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.

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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
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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*

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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

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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

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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

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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.

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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

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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

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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.

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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
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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.
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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
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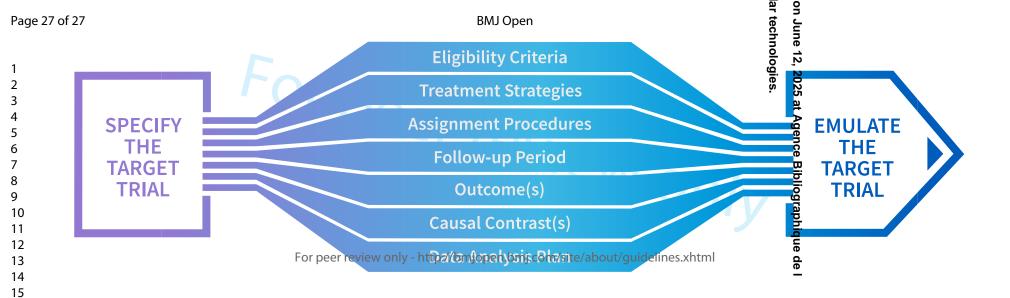
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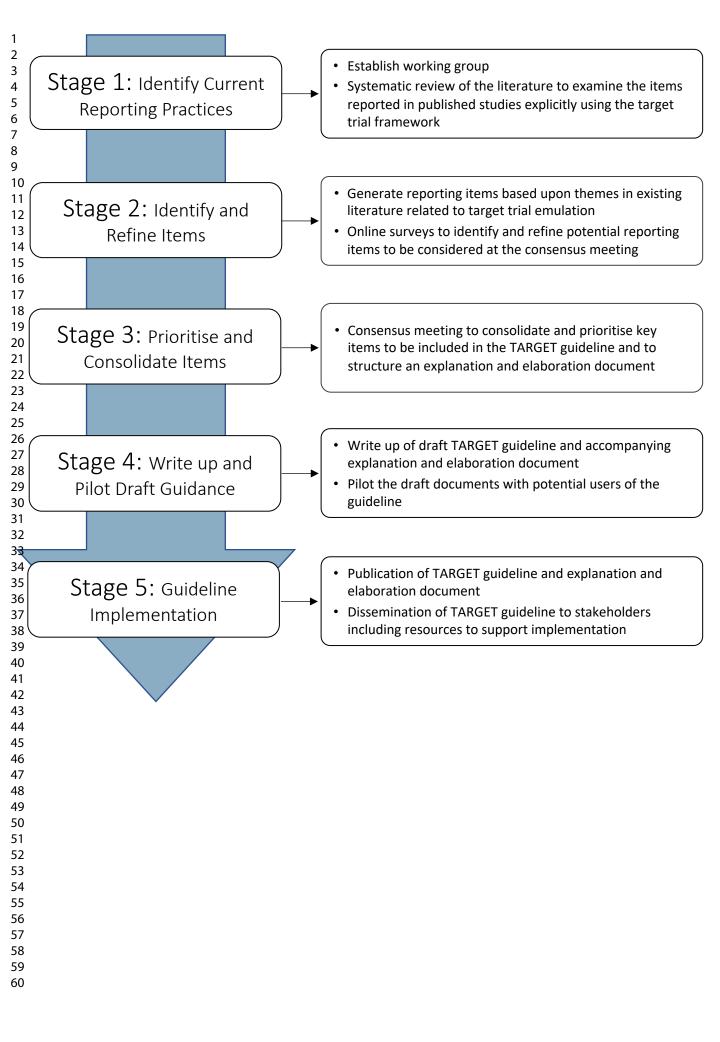
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2 3 4 5	463	Supplementary Material
6	464	
7 8 9 10	465	Supplementary Material 1: TARGET working group members (alphabetical)
11 12	466	
13 14	467	Steering committee
15	468	Dr Aidan G. Cashin
16 17	469	Mr Harrison J. Hansford
18 19	470	Prof Miguel A. 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	
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56 57		
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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)
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Development of the Transparent Reporting of Observational Studies Emulating a Target Trial (TARGET) Guideline

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Primary Subject Heading :	Epidemiology
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Keywords:	EPIDEMIOLOGY, Retrospective Studies, STATISTICS & RESEARCH METHODS

SCHOLARONE[™] Manuscripts

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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	
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59		For poor review only http://bmienen.hmi.com/site/about/guidelines.yhtml Page 1 of 20

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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

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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	
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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

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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.

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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).

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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.

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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

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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

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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

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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.

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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

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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.

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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

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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.

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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

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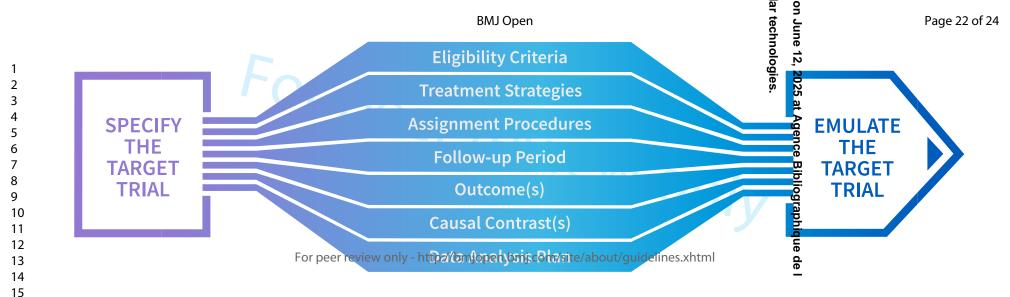
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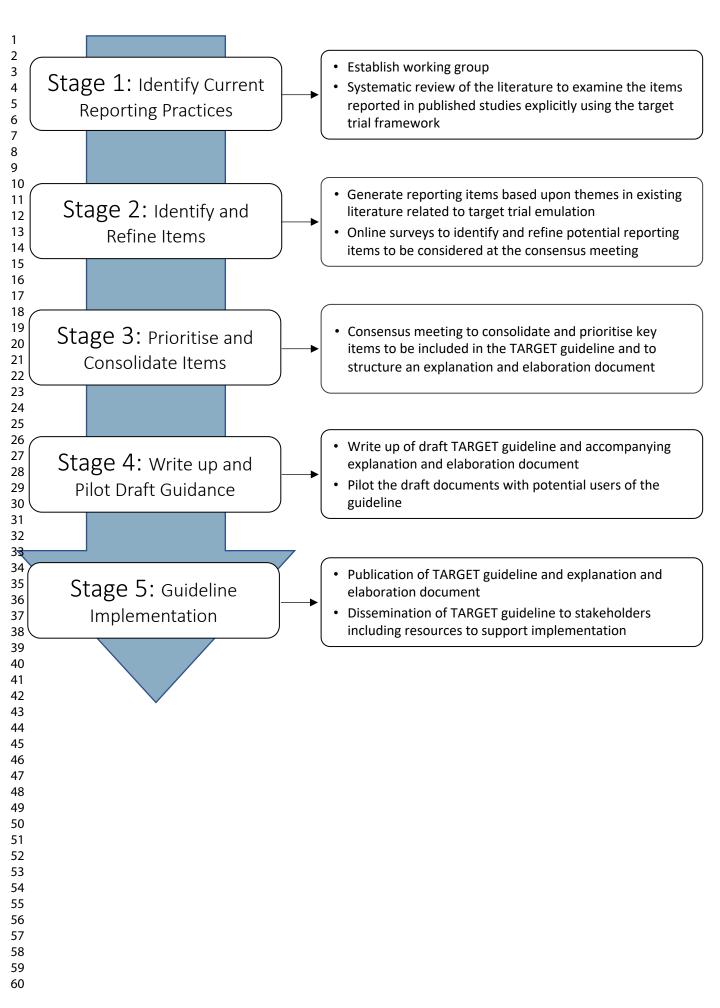
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8 9 10	356	supported by NIH grant R37 AI102634.
11 12	357	
13 14 15	358	Competing interests
16 17	359	All authors declare no competing interests.
18 19 20	360	
21 22 23	361	Author Contributions
24 25	362	HJH, AGC, MDJ, HL, JHM, conceived the idea for 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.
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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
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3	1	Supplementary Material
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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
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16	10	Dr Matthew D. Jones
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26	19	Prof Robert M. Golub
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28	20	A/Prof Nazrul Islam
29	21	A/Prof Sara Lodi
30 31	22	A/Prof Margarita Moreno-Betancur
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33	24	Prof Sebastian Schneeweiss
34	25	Prof Jonathan A. C. Sterne
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36	20	Prof Elizabeth A. Stuart
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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.
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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.
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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*))
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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)

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

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Manuscript ID	bmjopen-2023-074626.R2
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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

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Primary Subject Heading :	Epidemiology
Secondary Subject Heading:	Research methods
Keywords:	EPIDEMIOLOGY, Retrospective Studies, STATISTICS & RESEARCH METHODS

SCHOLARONE[™] Manuscripts

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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} ,
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16 17	7	Betancur ^{17,18} , Sallie-Anne Pearson ¹⁹ , Sebastian Schneeweiss ²⁰ , Jonathan A. C.
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59		For peer review only - http://bmionen.hmi.com/site/about/quidelines.yhtml Page 1 of 21

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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
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47 48	94	reporting guideline
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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

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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.

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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).

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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.

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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.

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	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
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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

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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

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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.

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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

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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.

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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
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31 32		
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33 34 35 36 37 38 39 40	344	There was no specific funding for this study. HJH was supported by an Australian
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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

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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.
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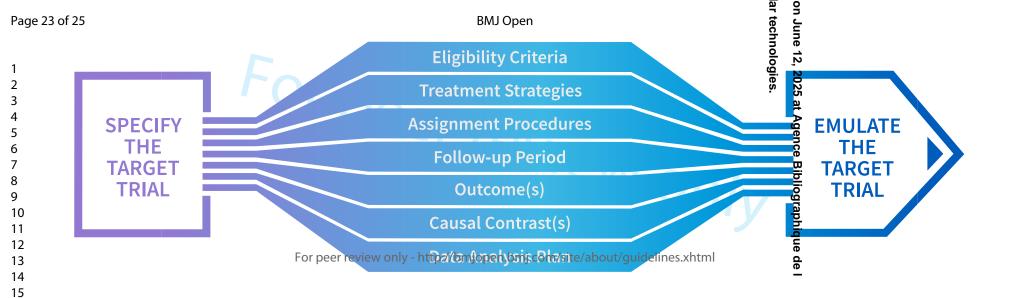
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3 4	372	Abbreviations
5	373	
6	575	
7 8 9	374	EQUATOR: Enhancing the QUAlity and Transparency Of health Research
10 11 12	375	REDCap: Research Electronic Data Capture
13 14	376	STROBE: Strengthening the Reporting of Observational Studies in Epidemiology
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
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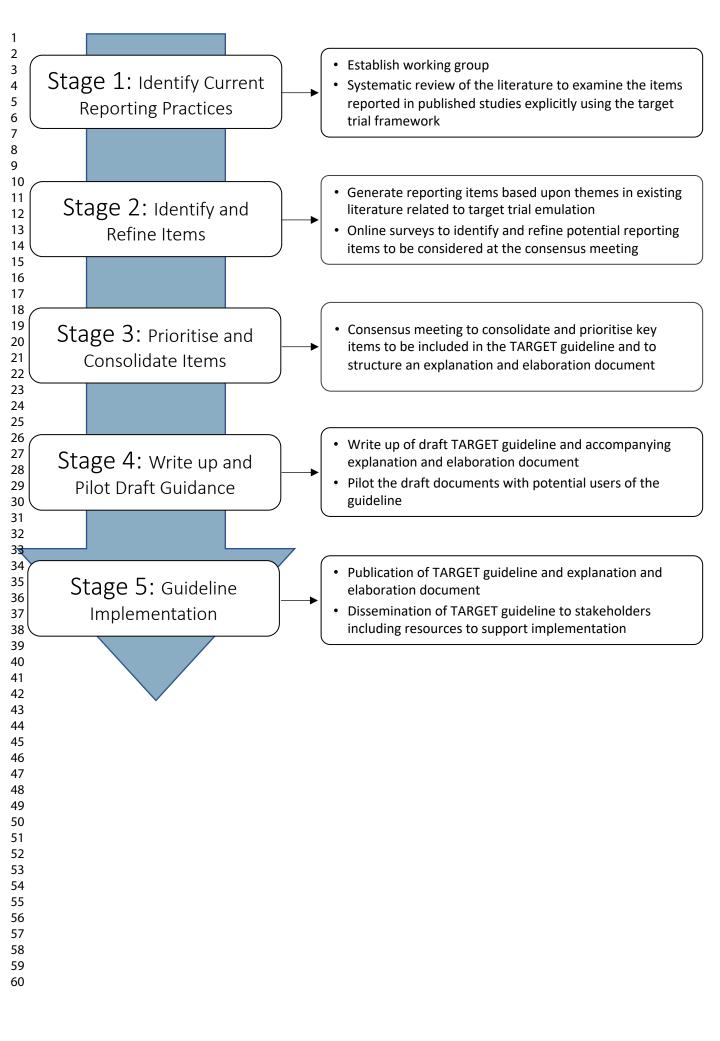
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3	1	Supplementary Material
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7	3	Supplementary Material 1: TARGET working group members (alphabetical)
8	4	
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10	5	Steering committee
11 12	6	Dr Aidan G. Cashin
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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
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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
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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
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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
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41 42	58	10. (target adj (trial? or experiment?)).ti.
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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*))
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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)