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# BMJ Open

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

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# 1 Development of the Transparent Reporting of Observational Studies Emulating a Target 2 Trial (TARGET) Guideline

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4 55 **Abstract**  
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9 57 **Background**  
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11 58 Observational studies are increasingly being used to inform health decision-making  
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14 59 when randomised trials are not feasible, ethical, or timely. The target trial approach  
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16  
17 60 provides a framework to help minimise common biases in observational studies that  
18  
19 61 aim to estimate the causal effect of interventions. Incomplete reporting of studies using  
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21  
22 62 the target trial framework limits the ability for clinicians, researchers, patients, and  
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24  
25 63 other decision-makers to appraise, synthesise, and interpret findings to inform clinical  
26  
27 64 and public health practice and policy. This paper describes the methods that we will  
28  
29  
30 65 use to develop the Transparent reporting of observational studies emulating a target  
31  
32 66 trial (TARGET) reporting guideline.  
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37 68 **Methods/design**  
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40 69 The TARGET reporting guideline will be developed in five stages. The first stage will  
41  
42  
43 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  
52 73 experts using two online surveys. The third stage will prioritise and consolidate key  
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55 74 items to be included in the TARGET guideline at a consensus meeting of TARGET  
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58 75 investigators. The fourth stage will produce and pilot-test the TARGET guideline and  
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4 76 explanation and elaboration document. The fifth stage will disseminate the TARGET  
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6 77 guideline and resources via journals, conferences, and courses.  
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## 10 11 79 **Ethics and Dissemination**

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14 80 Ethical approval for the survey to be conducted has been attained (HC220536). The  
15  
16 81 TARGET guideline will be disseminated widely and should improve the transparency  
17  
18  
19 82 and completeness of reporting in studies using the target trial framework.  
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22 83

23  
24 84 **Key words:** target trial emulation, causal inference, reporting guideline, observational  
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27 85 studies  
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## 31 32 87 **Strengths and Limitations**

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35 88 - The TARGET reporting guideline will be developed according to  
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37 89 recommendations for health research reporting guidelines  
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40 90 - The TARGET working group has been established to include stakeholders from  
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43 91 a variety of backgrounds  
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## 93 Introduction

94 Observational studies can provide evidence on the causal effects of interventions  
95 when it is not feasible, ethical, or timely to conduct a relevant randomised trial.

96 However, making causal inferences from observational data is challenging due to  
97 confounding and design-related biases such as selection bias and immortal time bias.

98 <sup>1 2</sup> Design-related biases can be avoided using the target trial framework. <sup>3 4</sup> The  
99 framework involves the specification of the hypothetical randomised pragmatic trial —  
100 the target trial — that would ideally be conducted and how this trial might be emulated  
101 using observational data. <sup>3 4</sup> The two stages of the target trial framework are 1)  
102 specification of the target trial, and 2) emulation of the target trial. <sup>3 4</sup> Using  
103 observational data to mimic a randomised experiment was proposed in the mid 20<sup>th</sup>  
104 century, <sup>5-8</sup> and extended to time-varying treatments by Robins in 1986. <sup>9</sup>

105  
106 The value of using the target trial framework to design the analysis of observational  
107 studies has been recognised by international regulatory bodies in the field of medicine  
108 and health, <sup>10-14</sup> and the framework underpins the widely-used ROBINS-I tool for  
109 assessing risk of bias in non-randomised studies of interventions. <sup>15</sup> Studies that are  
110 explicit in using the target trial framework have been published with increasing  
111 frequency in leading general medical and specialty journals. <sup>16-21</sup>

112  
113 Application of the target trial framework requires the complete specification of the  
114 target trial protocol and its emulation (Figure 1). <sup>3</sup> Hernán & Robins <sup>3</sup> provide a



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4 115 template for specifying a target trial and its emulation; however, there is currently no  
5  
6 116 detailed guidance on reporting a study designed to emulate a target trial. Incomplete  
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9 117 reporting of these studies limits the ability of clinicians, researchers, patients, and other  
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11 118 decision-makers to appraise and synthesise findings or interpret them to inform clinical  
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14 119 and public health practice and policy. A reporting guideline that expands upon the  
15  
16 120 initial target trial emulation template<sup>3</sup> is needed to provide authors with comprehensive  
17  
18 121 recommendations on how to completely and transparently report a study emulating a  
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21  
22 122 target trial.

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126 **Figure 1.** Elements relevant to both the specification and emulation of the target trial  
127 described by Hernán & Robins (3)

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129 To address this gap, we outline the processes and methods that used to develop a  
130 reporting guideline for studies emulating a target trial – TARGET (Transparent  
131 reporting of observational studies emulating a target trial).

132

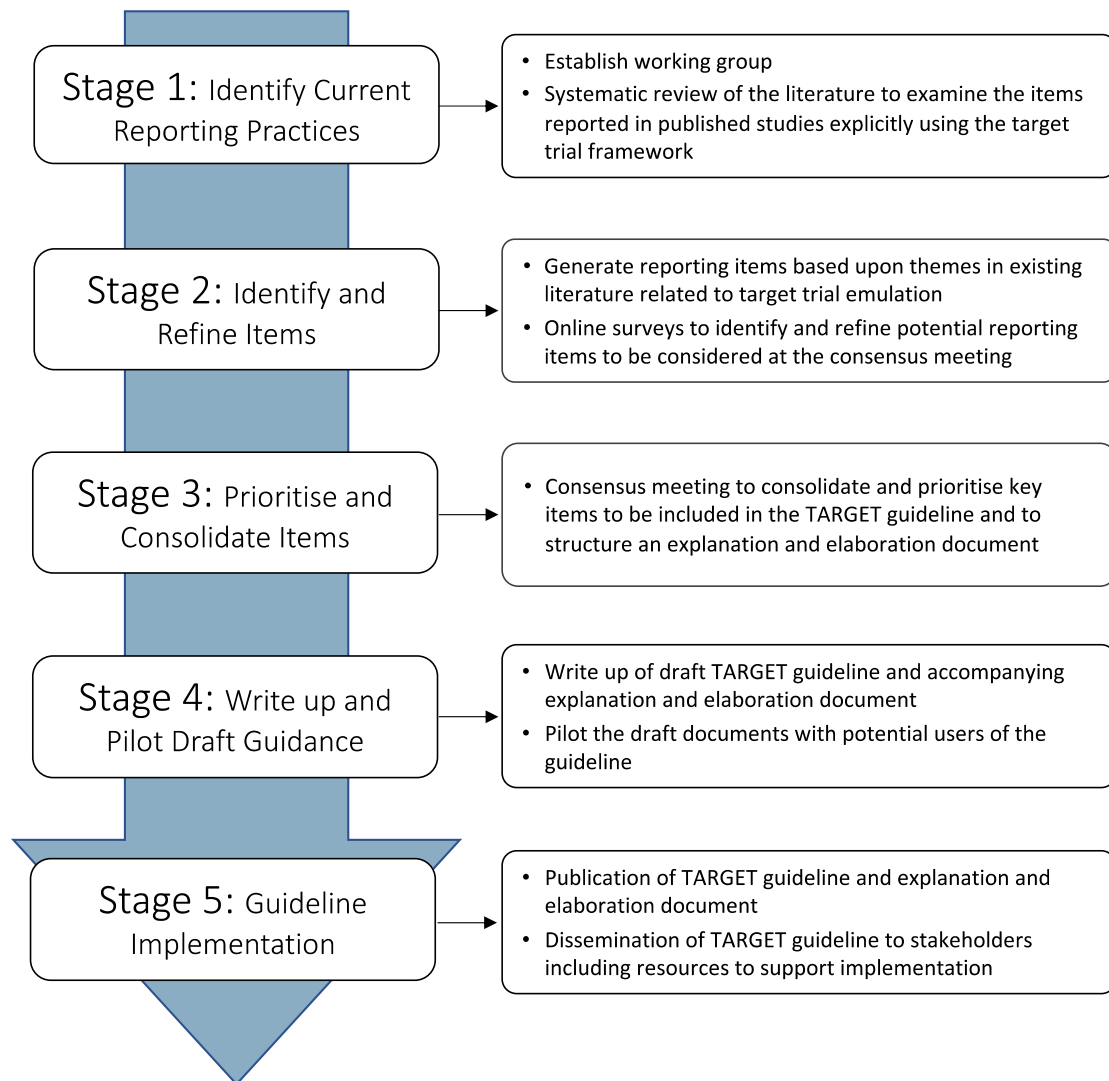
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4 133 **Objective**

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6 134 The objective of the TARGET guideline is to provide guidance on the minimum set of  
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9 135 items that should be reported to provide a clear and transparent account of  
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11 136 observational studies that investigate the comparative effectiveness and safety of  
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14 137 health interventions explicitly using the target trial framework.  
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19 139 **Methods/design**

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22 140 We will develop the TARGET Guideline in five stages following recommendations for  
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24 141 the development of health research reporting guidelines (Figure 2).<sup>22</sup>  
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142 **Figure 2.** Workflow for the development of the TARGET guideline

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#### 144 **TARGET working group**

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

151

**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<sup>23</sup>) was used. The protocol for this systematic review was registered on the Open Science Framework on 13 March 2022 (osf.io/uj56m).

157

*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.

173

### 174 *Data Extraction*

175 We will extract items regarded by the steering committee as potentially important for  
176 the reporting of a target trial emulation, including those outlined by Hernán and Robins,  
177 2016.<sup>3</sup> Two independent reviewers will extract information on study authors, year of  
178 publication, journal, sub-field of medicine, study design, sample size, intervention,  
179 comparison group, outcomes assessed, and whether the study was prospectively  
180 registered. We will extract items relevant to the methods and results of the target trial  
181 emulation, including whether and how all components of the protocol of the proposed  
182 target trial, and how they were emulated, were specified (i.e., eligibility criteria,  
183 treatment strategies, assignment procedures, follow-up period, outcome(s), causal  
184 contrast(s), and data analysis plan). We will enter data into a standardised data  
185 extraction form which two authors will pilot with a selection of included studies. We will  
186 resolve disagreements in data extraction between reviewers through discussion, or  
187 where necessary, consultation with a third reviewer.

188

### 189 *Data analysis*

190 We will use R<sup>24</sup> for all data analyses. Categorical variables will be summarised using  
191 frequencies and percentages. Continuous variables will be summarised using mean  
192 and standard deviation, or median and interquartile range, as appropriate.

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### 194 *Outcomes of the systematic review*

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4 195 The systematic review will provide evidence on reporting in studies explicitly emulating  
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6 196 a target trial. The findings will inform the online surveys (Stage 2) and the consensus  
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9 197 meeting (Stage 3). We will submit the findings of this review for publication and all data  
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11 198 and code made publicly available.  
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## 16 200 **Stage 2: Identify and refine items for the TARGET guideline**

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19 201 We will conduct two online surveys to generate a list of candidate items that add detail  
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22 202 to each of the protocol elements in Figure 1.  
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### 26 204 *Ethics*

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29 205 Ethical approval has been obtained for the online surveys from the University of New  
30  
31  
32 206 South Wales Human Research Ethics Committee (HC220536).  
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### 36 208 *Selection of initial items*

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39 209 The steering group will develop a list of key items, informed by the systematic review  
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41  
42 210 (Stage 1), and the target trial framework described by Hernán & Robins (3), thought  
43  
44  
45 211 important for the conduct and reporting target trial emulations (Figure 1). Other  
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48 212 potential sources of items include: published guidance for observational studies and  
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51 213 randomised controlled trials, the ROBINS-I tool, <sup>15</sup> and studies that describe items that  
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53 214 may be important for the conduct or reporting of target trial emulations.  
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### 56 216 *Participants*

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4 217 Members of the TARGET working group (Supplementary Material 1) will be invited to  
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6 218 participate in the surveys.  
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11 220 *Procedure*  
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14 221 We will host two online surveys using REDCap.<sup>25 26</sup> We will send each online survey  
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16 222 via email to the participants. We will ask participants to rate the importance of each  
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18 223 potential reporting item on a 9-point Likert scale (1, “not important”, to 9, “critically  
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20 224 important”). Participants will have the opportunity to provide suggestions or  
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22 225 modifications to the wording of items as well as suggest additional items or make other  
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24 226 comments.  
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32 228 In the second survey, we will send participants a summary of the results for each  
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34 229 potential reporting item (mean scores and standard deviations, median scores and  
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36 230 interquartile ranges, and histograms), their own score for each item, and any  
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38 231 comments from participants on each item from the first survey. We will also present  
39  
40 232 any new items and suggested modifications to items. We will then invite participants  
41  
42 233 to re-score the importance of each item, and score any additional items, considering  
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44 234 the aggregated ratings. Participants will have the opportunity to provide additional  
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46 235 feedback on each item in the form of open ended responses.  
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55 237 *Analysis*  
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4 238 Continuous variables will be summarised using mean and standard deviation, and  
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6 239 median and interquartile range. We will analyse the free-text responses from the first  
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9 240 and second surveys using an inductive approach, in which we will use reflexive  
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11 241 thematic analysis to identify, organise and generate codes, and then identify themes  
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14 242 found within the dataset. These data will contribute to the creation of new items and  
15  
16 243 modification of existing items to be included in the subsequent survey.  
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#### 22 245 *Outcome of the online surveys*

23  
24 246 We will generate a preliminary list of items with corresponding ratings of importance  
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26  
27 247 to be considered in the TARGET guideline at the consensus meeting (Stage 3). We  
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29  
30 248 will also generate qualitative insights to guide item refinement and prioritisation in  
31  
32 249 preparation for the consensus meeting.  
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#### 37 251 **Stage 3 – Consolidate and prioritise key items to be included in the TARGET guideline**

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40 252 A consensus meeting will finalise reporting items for the TARGET guideline.<sup>22</sup> The  
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43 253 consensus meeting will follow suggested methods for developing reporting guidelines  
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45 254 <sup>22</sup>, including guidance for consensus-based methods currently being developed which  
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47  
48 255 we will use if they become available.<sup>27</sup>  
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#### 53 257 *Process*

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56 258 We will invite stakeholders identified by the working group to participate in a two-day  
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58 259 consensus meeting. The TARGET working group will ensure that the expertise of  
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4 260 consensus meeting participants includes target trial emulation methodology,  
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6 261 epidemiology, clinical trials, biostatistics, reporting guideline development, and  
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9 262 regulatory and journal editorial processes. Prior to the consensus meeting, the core  
10  
11 263 team will provide attendees with evidence from the systematic review (Stage 1) and  
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14 264 findings from the online surveys (Stage 2) including a draft of the items proposed for  
15  
16 265 inclusion in the guideline. We will present the findings from Stage 1 and 2 at the  
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18  
19 266 consensus meeting. A member of the TARGET working group will facilitate a  
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22 267 structured discussion on the rationale for including items from the online surveys. If  
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25 268 there are disagreements, they will first be debated and, if disagreements remain, we  
26  
27 269 will hold an anonymised vote to establish the importance of including the item in the  
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30 270 guideline. For the anonymised vote, a simple majority will be sufficient to guide the  
31  
32 271 inclusion/exclusion of an item. The meeting will conclude with discussion about the  
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35 272 content and production of relevant documents (TARGET guideline, draft explanation  
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37 273 and elaboration document) as well as strategies for dissemination and implementation.  
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40 274 Following the conclusion of the consensus meeting, we will circulate a report on the  
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43 275 outcome to the meeting participants for review and approval.  
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48 277 **Stage 4 – Development and piloting of the draft TARGET guideline and explanation**  
49  
50 278 **and elaboration document**

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53 279 Stage 4 involves drafting the TARGET guideline and accompanying explanation and  
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56 280 elaboration document to ensure that the wording and content of the documents are  
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58 281 clear, precise, and suitable for all identified stakeholders. The purpose of the  
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4 282 explanation and elaboration document is to explain each item by providing background  
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6 283 information, a rationale, and clear reporting examples from published target trial  
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9 284 emulations. We will design the explanation and elaboration document to facilitate  
10  
11 285 adherence to the TARGET guideline by clarifying the importance of each item,  
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13  
14 286 highlighting relevant reporting issues and providing examples to assist authors using  
15  
16 287 the guideline. The consensus meeting participants may be asked to review and  
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18  
19 288 comment on the draft TARGET guideline and explanation and elaboration document.  
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24 290 We will evaluate the TARGET guideline by piloting the proposed guideline and the  
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27 291 explanation and elaboration document with 20-30 expert methodologists and potential  
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30 292 users of TARGET, identified from TARGET working group networks. We will ask  
31  
32 293 participants to provide general feedback on accessibility and usability, and to identify  
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35 294 possible reporting items that might have been overlooked. We will also ask for specific  
36  
37 295 feedback about the utility and clarity of each TARGET item. We will collect data  
38  
39  
40 296 through online surveys, hosted by REDCap. <sup>25</sup> <sup>26</sup> We will incorporate feedback from  
41  
42  
43 297 the piloting exercise into the final guideline and explanation and elaboration document,  
44  
45 298 as required. If suggested revisions are extensive, we will conduct a further round of  
46  
47  
48 299 piloting.

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### 51 52 53 301 **Stage 5 – Guideline implementation**

54  
55 302 The goal of the final stage of guideline development is to maximise reach and use of  
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58 303 the TARGET guideline. The TARGET working group will guide the dissemination  
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4 304 strategy with advice from consensus meeting participants. We aim to publish the  
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6 305 TARGET guideline and the explanation and elaboration document and disseminate  
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9 306 the findings through traditional and social media. We will engage journal editors and  
10  
11 307 funding agencies to encourage TARGET guideline endorsement alongside other  
12  
13  
14 308 published reporting guidance. We will publicly host the TARGET guideline and  
15  
16 309 explanation and elaboration paper, and any other relevant material on a TARGET  
17  
18  
19 310 website. We will index the guideline on the Enhancing the QUALity and Transparency  
20  
21  
22 311 Of health Research (EQUATOR) Network website.<sup>28 29</sup> We will create online  
23  
24 312 resources including infographics, blog posts and podcasts, which will be available on  
25  
26  
27 313 the TARGET website. We will share the TARGET guideline with authors in the field,  
28  
29  
30 314 and at relevant scientific conferences and methodological courses.

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## 316 Discussion

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37 317 Studies that explicitly aim to emulate a target trial are increasingly published in the  
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40 318 medical literature and are used to inform practice and policy decisions. A reporting  
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43 319 guideline for these studies will facilitate comprehensive and transparent reporting and  
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45 320 support accurate appraisal and implementation of study findings by researchers,  
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48 321 clinicians, patients, and other decision-makers.

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53 323 The TARGET guideline and supporting guidance material aim to improve the  
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56 324 completeness and transparency of reporting of observational studies that aim to  
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59 325 explicitly emulate a target trial in medical and health research. Although the focus is  
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4 326 on studies that explicitly use the target trial emulation framework much of the guidance  
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6 327 will be applicable to studies using non-experimental comparison group designs to  
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9 328 estimate causal effects. We will develop the TARGET guideline following accepted  
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11 329 recommendations for the development of health research reporting guidelines to  
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14 330 maximise the guidelines usefulness and usage. <sup>22</sup> We plan to use a structured  
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16 331 dissemination approach to maximise uptake of the TARGET guideline and will ensure  
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19 332 that the guideline is freely and easily accessible.  
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4 333 **Declarations**

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9 335 **Ethics approval and consent to participate**

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11 336 Not Applicable

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16 338 **Consent for publication**

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19 339 All authors consent to publication of this manuscript

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24 341 **Availability of data and materials**

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11 358

### 14 359 **Competing interests**

16 360 All authors declare no competing interests.

19 361

### 22 362 **Author Contributions**

24 363 HJH, AGC, MDJ, HL, JHM, conceived the idea for the project protocol. All authors  
25  
26  
27 364 contributed to the design and methodology of the project protocol. HJH and AGC wrote  
28  
29  
30 365 the first draft of the manuscript. All authors provided feedback, revised the manuscript  
31  
32 366 and have read and approved the final version.  
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### 48 372 **Article Summary**

### 50 373 **Strengths and Limitations**

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376 **Abbreviations**

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378 **EQUATOR:** Enhancing the QUALity and Transparency Of health Research

379 **REDCap:** Research Electronic Data Capture

380 **STROBE:** Strengthening the Reporting of Observational Studies in Epidemiology

381 **TARGET:** TrAnsparent ReportinG of studies Emulating a Target trial

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For peer review only

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4 463 **Supplementary Material**  
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4 492 **Supplementary Material 2: Complete search strategies for all databases**

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8 494 **Medline**

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12 496 2 (target adj (trial? or experiment?)).mp.

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14 497 3. (observational adj (stud\* or research or data)).mp.

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16 498 4. ((real world or rwd) adj2 (stud\* or research or data)).mp.

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18 499 5. (routine\* adj2 data).mp.

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20 500 6. (comparative effectiveness adj2 (stud\* or research or data)).mp.

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22 501 7. (emulat\* or propensity score? or (causal adj2 (inference? or analys?s or  
23 effect\*))).mp.

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25 502 8. 3 or 4 or 5 or 6 or 7

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53 effect\*))).mp.

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13 525 noft(observational) OR noft(routine\* data)) AND noft(comparative effective\*)

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15 526 AND noft(causal infer\*))

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21 529 (TI=(emulat\* trial)) OR (TI=(real world data) OR TI=(routine\* data) OR

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23 530 TI=(comparative effectiveness study comparative effectiveness research or

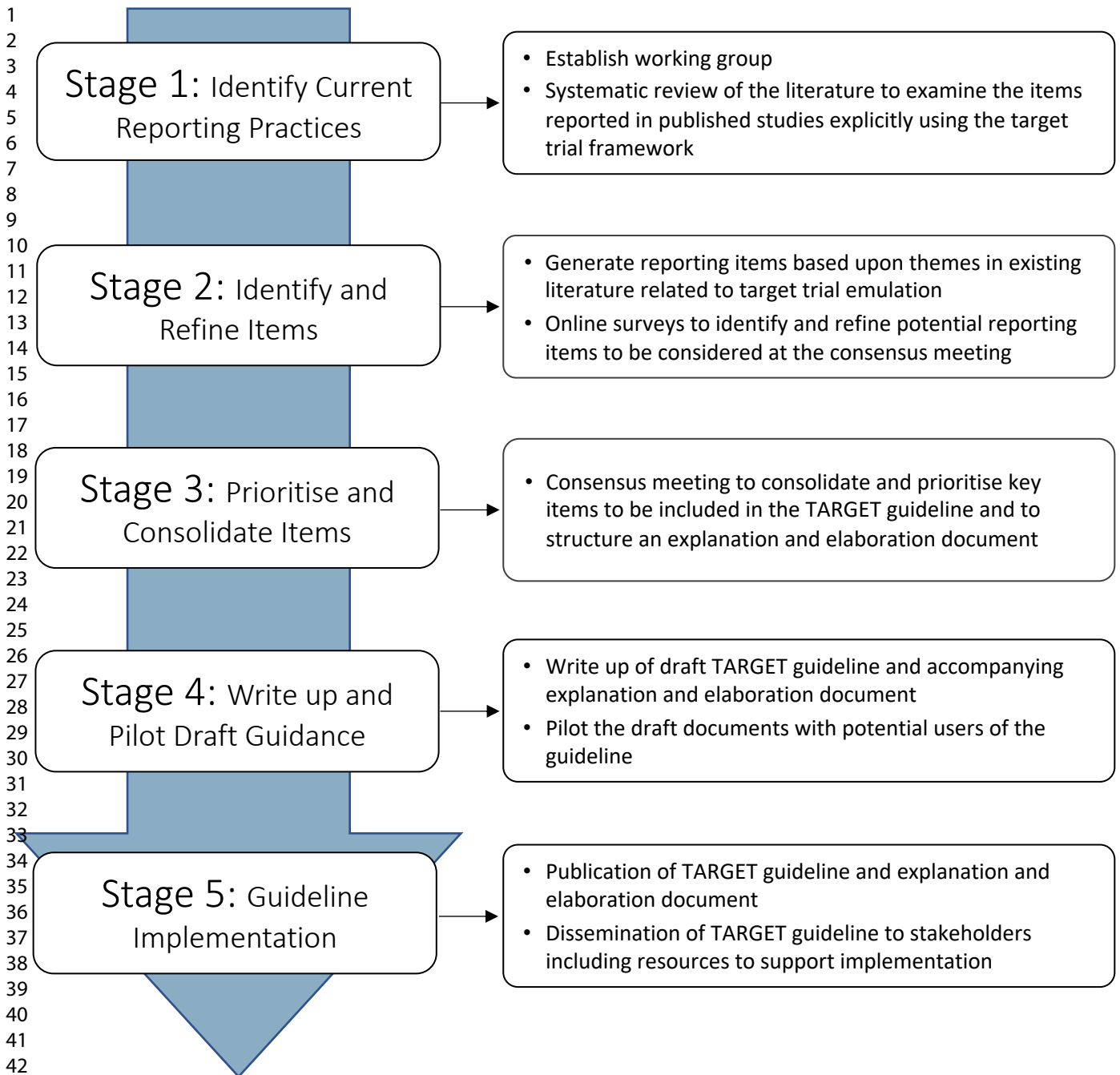
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25 531 comparative effectiveness data) OR (TI=(emulat\* or propensity score?) AND

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27 532 TI=(causal inference or causal analysis or causal effect\*)) AND ALL=(target

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29 533 trial or emulat\* or target trial emulation)

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# BMJ Open

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

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

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Manuscripts



# 1 Development of the Transparent Reporting of Observational Studies Emulating a Target 2 Trial (TARGET) Guideline

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4 55 **Abstract**  
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9 57 **Background**

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11 58 Observational studies are increasingly used to inform health decision-making when  
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14 59 randomised trials are not feasible, ethical, or timely. The target trial approach provides  
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17 60 a framework to help minimise common biases in observational studies that aim to  
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19 61 estimate the causal effect of interventions. Incomplete reporting of studies using the  
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22 62 target trial framework limits the ability for clinicians, researchers, patients, and other  
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25 63 decision-makers to appraise, synthesise, and interpret findings to inform clinical and  
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27 64 public health practice and policy. This paper describes the methods that we will use to  
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30 65 develop the transparent reporting of observational studies emulating a target trial  
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32 66 (TARGET) reporting guideline.  
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37 68 **Methods/design**

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40 69 The TARGET reporting guideline will be developed in five stages following  
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43 70 recommended guidance. The first stage will identify target trial reporting practices by  
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46 71 systematically reviewing published studies that explicitly emulated a target trial. The  
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49 72 second stage will identify and refine items to be considered for inclusion in the  
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52 73 TARGET guideline by consulting content experts using online surveys. The third stage  
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55 74 will prioritise and consolidate key items to be included in the TARGET guideline at a  
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58 75 consensus meeting of TARGET investigators. The fourth stage will produce and pilot-  
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60 76 test the TARGET guideline and explanation and elaboration document with relevant

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4 77 stakeholders. The fifth stage will disseminate the TARGET guideline and resources  
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6 78 via journals, conferences, and courses.  
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## 10 11 80 **Ethics and Dissemination**

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14 81 Ethical approval for the survey to be conducted has been attained (HC220536). The  
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16 82 TARGET guideline will be disseminated widely in partnership with stakeholders to  
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19 83 maximise adoption and improve reporting of these studies.  
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24 85 **Key words:** target trial emulation, causal inference, reporting guideline, observational  
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## 31 32 88 **Strengths and Limitations**

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34  
35 89 - The TARGET reporting guideline will be developed according to  
36  
37 90 recommendations for health research reporting guidelines  
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40 91 - The TARGET working group has been established to include stakeholders  
41  
42 92 from a variety of backgrounds  
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44  
45 93 - A comprehensive piloting phase may increase the usability and uptake of the  
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47 94 reporting guideline  
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## 96 Introduction

97 Observational studies can provide evidence on the causal effects of interventions  
98 when it is not feasible, ethical, or timely to conduct a relevant randomised trial.

99 However, making causal inferences from observational data is challenging due to  
100 confounding and design-related biases such as selection bias and immortal time bias.<sup>1</sup>

101 <sup>2</sup> Design-related biases can be avoided using the target trial framework. <sup>3 4</sup> The  
102 framework involves the specification of the hypothetical randomised pragmatic trial —  
103 the target trial — that would ideally be conducted and how this trial might be emulated  
104 using observational data.<sup>3 4</sup> The two stages of the target trial framework are 1)  
105 specification of the target trial, and 2) emulation of the target trial.<sup>3 4</sup> Using  
106 observational data to mimic a randomised experiment was proposed in the mid 20<sup>th</sup>  
107 century,<sup>5-8</sup> and extended to time-varying treatments by Robins in 1986.<sup>9</sup>

108  
109 The value of using the target trial framework to design the analysis of observational  
110 studies has been recognised by international regulatory bodies in the field of medicine  
111 and health,<sup>10-14</sup> and the framework underpins the widely-used ROBINS-I tool for  
112 assessing risk of bias in non-randomised studies of interventions.<sup>15</sup> Studies that are  
113 explicit in using the target trial framework have been published with increasing  
114 frequency in leading general medical and specialty journals.<sup>16-21</sup>

115  
116 Application of the target trial framework requires the complete specification of the  
117 target trial protocol and its emulation (Figure 1).<sup>3</sup> Hernán & Robins<sup>3</sup> provide a template

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3  
4 118 for specifying a target trial and its emulation; however, there is currently no detailed  
5  
6 119 guidance on reporting a study designed to emulate a target trial. Incomplete reporting  
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8  
9 120 of these studies limits the ability of clinicians, researchers, patients, and other  
10  
11 121 decision-makers to appraise and synthesise findings or interpret them to inform clinical  
12  
13  
14 122 and public health practice and policy. A reporting guideline that expands upon the  
15  
16 123 initial target trial emulation template<sup>3</sup> is needed to provide authors with comprehensive  
17  
18  
19 124 recommendations on how to completely and transparently report a study emulating a  
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21  
22 125 target trial.  
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27 127  
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30 128 **[INSERT FIGURE 1]**  
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35 130 To address this gap, we outline the processes and methods that used to develop a  
36  
37 131 reporting guideline for studies emulating a target trial – TARGET (Transparent  
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39  
40 132 reporting of observational studies emulating a target trial).  
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#### 45 134 **Objective**

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48 135 The objective of the TARGET guideline is to provide guidance on the minimum set of  
49  
50 136 items that should be reported to provide a clear and transparent account of  
51  
52  
53 137 observational studies that investigate the comparative effectiveness and safety of  
54  
55  
56 138 health interventions explicitly using the target trial framework.  
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## 140 **Methods**

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

144  
145 **[INSERT FIGURE 2]**

### 147 **TARGET working group**

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

### 155 **Stage 1: Identify current reporting practices**

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

160  
161 *Databases, eligibility, and search terms*

1  
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4 162 We will search Medline, EMBASE, PsycINFO and Science Citation Index for  
5  
6 163 observational studies that stated in their methods that they explicitly emulated a target  
7  
8 164 trial. We will exclude studies not written in English, not in the field of medicine and  
9  
10  
11 165 health, not conducted in humans, or not observational designs. Many observational  
12  
13  
14 166 studies may implicitly use the framework of a randomised trial. However, to be  
15  
16 167 included in this review studies must be explicit in their attempt to emulate a target trial  
17  
18  
19 168 (e.g., stated 'target trial emulation' in the article). To identify eligible studies, we  
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21  
22 169 developed a literature search in collaboration with an expert librarian at the University  
23  
24  
25 170 of Oxford. Our approach used sensitive search terms including emulat\*, target trial,  
26  
27 171 observational data, real-world data, comparative effectiveness, and causal inference,  
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29  
30 172 to try to capture all papers explicitly emulating a target trial. The complete search  
31  
32  
33 173 strategy is in Supplementary Material 2. We will conduct forward citation tracking of  
34  
35 174 selected seminal articles to maximise the chance of retrieving all relevant articles.<sup>3 9</sup>  
36  
37 175 <sup>24-26</sup> We will also include papers known to the authorship team. In duplicate,  
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39  
40 176 independent reviewers will conduct title, abstract, and full text screening. We will  
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42  
43 177 resolve disagreements between reviewers through discussion.  
44

178

### 179 *Data Extraction*

180 We will extract items regarded by the steering committee as potentially important for  
181 the reporting of a target trial emulation, including those outlined by Hernán and Robins,  
182 2016.<sup>3</sup> Two independent reviewers will extract information on study authors, year of  
183 publication, journal, sub-field of medicine, study design, sample size, intervention,



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4 184 comparison group, outcomes assessed, and whether the study was prospectively  
5  
6 185 registered. We will extract items relevant to the methods and results of the target trial  
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8  
9 186 emulation, including whether and how all components of the protocol of the proposed  
10  
11 187 target trial, and how they were emulated, were specified (i.e., eligibility criteria,  
12  
13  
14 188 treatment strategies, assignment procedures, follow-up period, outcome(s), causal  
15  
16 189 contrast(s), and data analysis plan). We will enter data into a standardised data  
17  
18  
19 190 extraction form which two authors will pilot with a selection of included studies. We will  
20  
21  
22 191 resolve disagreements in data extraction between reviewers through discussion, or  
23  
24 192 where necessary, consultation with a third reviewer.  
25  
26  
27 193

#### 28 29 194 *Data analysis*

30  
31  
32 195 We will use R<sup>27</sup> for all data analyses. Categorical variables will be summarised using  
33  
34  
35 196 frequencies and percentages. Continuous variables will be summarised using mean  
36  
37 197 and standard deviation, or median and interquartile range, as appropriate.  
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#### 41 42 43 199 *Outcomes of the systematic review*

44  
45 200 The systematic review will provide evidence on reporting in studies explicitly emulating  
46  
47  
48 201 a target trial. We acknowledge that excluding studies not written in English and  
49  
50  
51 202 unpublished studies may cause potentially relevant articles to be excluded. The  
52  
53 203 findings will inform the online surveys (Stage 2) and the consensus meeting (Stage 3).  
54  
55  
56 204 We will submit the findings of this review for publication and all data and code made  
57  
58 205 publicly available.  
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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  
213 South Wales Human Research Ethics Committee (HC220536).

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,<sup>3</sup> 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,<sup>15</sup> and studies that describe items that  
221 may be important for the conduct or reporting of target trial emulations.

222

*223 Participants*

224 Members of the TARGET working group (Supplementary Material 1) will be invited to  
225 participate in the surveys.

226

*227 Procedure*

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4 228 We will host two online surveys using REDCap.<sup>28 29</sup> We will send each online survey  
5  
6 229 via email to the participants. We will ask participants to rate the importance of each  
7  
8 230 potential reporting item on a 9-point Likert scale (1, “not important”, to 9, “critically  
9  
10 231 important”). Participants will have the opportunity to provide suggestions or  
11  
12 232 modifications to the wording of items as well as suggest additional items or make other  
13  
14 233 comments.  
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19 234  
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21 235 In the second survey, we will send participants a summary of the results for each  
22  
23 236 potential reporting item (mean scores and standard deviations, median scores and  
24  
25 237 interquartile ranges, and histograms), their own score for each item, and any  
26  
27 238 comments from participants on each item from the first survey. We will also present  
28  
29 239 any new items and suggested modifications to items. We will then invite participants  
30  
31 240 to re-score the importance of each item, and score any additional items, considering  
32  
33 241 the aggregated ratings. Participants will have the opportunity to provide additional  
34  
35 242 feedback on each item in the form of open ended responses.  
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#### 45 244 *Analysis*

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47  
48 245 Continuous variables will be summarised using mean and standard deviation, or  
49  
50 246 median and interquartile range, as appropriate. We will analyse the free-text  
51  
52 247 responses from the first and second surveys using an inductive approach,<sup>30</sup> in which  
53  
54 248 we will use reflexive thematic<sup>30</sup> analysis to identify, organise and generate codes, and  
55  
56 249 then identify themes found within the dataset. Briefly, inductive coding is a process  
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4 250 pooling common ideas without trying to fit ideas/codes into a pre-existing framework.  
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6 251 These data will contribute to the creation of new items and modification of existing  
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9 252 items to be included in the subsequent survey.  
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11 253  
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14 254 *Outcome of the online surveys*  
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16 255 We will generate a preliminary list of items with corresponding ratings of importance  
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18  
19 256 to be considered in the TARGET guideline at the consensus meeting (Stage 3). We  
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21  
22 257 will also generate qualitative insights to guide item refinement and prioritisation in  
23  
24  
25 258 preparation for the consensus meeting.  
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30 260 **Stage 3 – Consolidate and prioritise key items to be included in the TARGET guideline**  
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32 261 A consensus meeting will finalise reporting items for the TARGET guideline.<sup>22</sup> The  
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35 262 consensus meeting will follow suggested methods for developing reporting  
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38 263 guidelines,<sup>22</sup> including guidance for consensus-based methods currently being  
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40 264 developed which we will use if they become available.<sup>31</sup>  
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45 266 *Process*  
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48 267 We will invite stakeholders identified by the working group to participate in a two-day  
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51 268 consensus meeting. The TARGET working group will ensure that the expertise of  
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54 269 consensus meeting participants includes target trial emulation methodology,  
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56 270 epidemiology, clinical trials, biostatistics, reporting guideline development, and  
57  
58 271 regulatory and journal editorial processes. Prior to the consensus meeting, the core  
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4 272 team will provide attendees with evidence from the systematic review (Stage 1) and  
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6 273 findings from the online surveys (Stage 2) including a draft of the items proposed for  
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9 274 inclusion in the guideline. We will present the findings from Stage 1 and 2 at the  
10  
11 275 consensus meeting. A member of the TARGET working group will facilitate a  
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13  
14 276 structured discussion on the rationale for including items from the online surveys. If  
15  
16  
17 277 there are disagreements, they will first be debated and, if disagreements remain, we  
18  
19 278 will hold an anonymised vote to establish the importance of including the item in the  
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22 279 guideline. For the anonymised vote, a simple majority will be sufficient to guide the  
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24  
25 280 inclusion/exclusion of an item. The meeting will conclude with discussion about the  
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27 281 content and production of relevant documents (TARGET guideline, draft explanation  
28  
29 282 and elaboration document) as well as strategies for dissemination and implementation.  
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32 283 Following the conclusion of the consensus meeting, we will circulate a report on the  
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35 284 outcome to the meeting participants for review and approval.  
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40 286 **Stage 4 – Development and piloting of the draft TARGET guideline and explanation**  
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42 287 **and elaboration document**  
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45 288 Stage 4 involves drafting the TARGET guideline and accompanying explanation and  
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48 289 elaboration document to ensure that the wording and content of the documents are  
49  
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51 290 clear, precise, and suitable for all identified stakeholders. The purpose of the  
52  
53 291 explanation and elaboration document is to explain each item by providing background  
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56 292 information, a rationale, and clear reporting examples from published target trial  
57  
58 293 emulations. We will design the explanation and elaboration document to facilitate  
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4 294 adherence to the TARGET guideline by clarifying the importance of each item,  
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6 295 highlighting relevant reporting issues and providing examples to assist authors using  
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9 296 the guideline. The consensus meeting participants may be asked to review and  
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11 297 comment on the draft TARGET guideline and explanation and elaboration document.  
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16 299 We will evaluate the TARGET guideline by piloting the proposed guideline and the  
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19 300 explanation and elaboration document with 20-30 expert methodologists and potential  
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22 301 users of TARGET, identified from TARGET working group networks. We will ask  
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24  
25 302 participants to provide general feedback on accessibility and usability, and to identify  
26  
27 303 possible reporting items that might have been overlooked. We will also ask for specific  
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30 304 feedback about the utility and clarity of each TARGET item. We will collect data  
31  
32 305 through online surveys, hosted by REDCap.<sup>28 29</sup> We will incorporate feedback from the  
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35 306 piloting exercise into the final guideline and explanation and elaboration document, as  
36  
37 307 required. If suggested revisions are extensive, we will conduct a further round of  
38  
39  
40 308 piloting.  
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#### 44 45 310 *Patient and public involvement*

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48 311 Potential users of this research include health researchers conducting observational  
49  
50 312 analyses, regulatory bodies, public health and other health decision-makers. We aim  
51  
52  
53 313 to include relevant decision-makers in the piloting phase of the guideline development  
54  
55  
56 314 process to maximise the usefulness and uptake of the TARGET guideline. Participants  
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4 315 in any stage of the guideline development will be informed of the results and final  
5  
6 316 guidance.  
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## 10 11 318 **Stage 5 – Guideline implementation**

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14 319 The goal of the final stage of guideline development is to maximise reach and use of  
15  
16 320 the TARGET guideline. The TARGET working group will guide the dissemination  
17  
18 321 strategy with advice from consensus meeting participants. We aim to publish the  
19  
20 322 TARGET guideline and the explanation and elaboration document and disseminate  
21  
22 323 the findings through traditional and social media. We will engage journal editors and  
23  
24 324 funding agencies to encourage TARGET guideline endorsement alongside other  
25  
26 325 published reporting guidance. We will publicly host the TARGET guideline and  
27  
28 326 explanation and elaboration paper, and any other relevant material on a TARGET  
29  
30 327 website. We will index the guideline on the Enhancing the QUALity and Transparency  
31  
32 328 Of health Research (EQUATOR) Network website.<sup>32 33</sup> We will create online resources  
33  
34 329 including infographics, blog posts and podcasts, which will be available on the  
35  
36 330 TARGET website. We will share the TARGET guideline with authors in the field, and  
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38 331 at relevant scientific conferences and methodological courses.  
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4 332 **Declarations**

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7  
8  
9 334 **Ethics approval and consent to participate**

10  
11 335 Not Applicable

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14 336

15  
16 337 **Consent for publication**

17  
18  
19 338 All authors consent to publication of this manuscript

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23  
24 340 **Availability of data and materials**

25  
26  
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30 342

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11 357

### 14 358 **Competing interests**

16 359 All authors declare no competing interests.  
17  
18

19 360

### 22 361 **Author Contributions**

24 362 HJH, AGC, MDJ, HL, JHM, conceived the idea for the project protocol. All authors  
25  
26  
27 363 contributed to the design and methodology of the project protocol. HJH and AGC wrote  
28  
29  
30 364 the first draft of the manuscript. MAH, SAS, IJD, BAD, XG-A, ME, RMG, NI, SL, MM-  
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33  
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35 366 read and approved the final version.  
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4 372 **Abbreviations**

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8 374 **EQUATOR:** Enhancing the QUALity and Transparency Of health Research

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10 375 **REDCap:** Research Electronic Data Capture

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13 376 **STROBE:** Strengthening the Reporting of Observational Studies in Epidemiology

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16 377 **TARGET:** TrAnSPARENT ReportinG of studies Emulating a Target trial

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21 379 **Figure Captions**

22  
23 380

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25  
26 381 Figure 1: Elements relevant to both the specification and emulation of the target trial  
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28 described by Hernán & Robins<sup>3</sup>

29 382  
30  
31 383 Figure 2: Workflow for the development of the TARGET guideline

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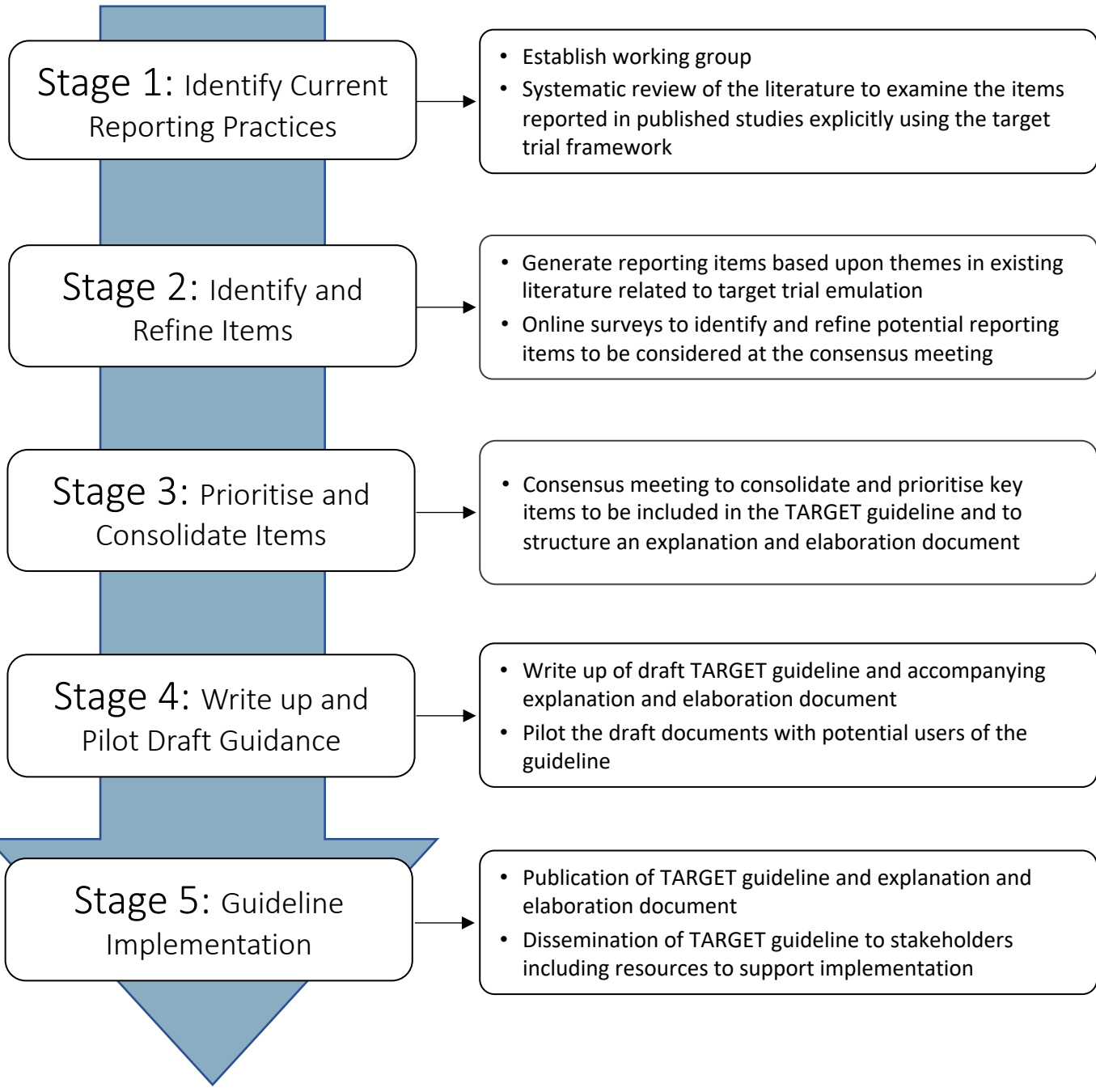
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3 1 **Supplementary Material**  
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7 3 **Supplementary Material 1: TARGET working group members (alphabetical)**  
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3 **30 Supplementary Material 2: Complete search strategies for all databases**  
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6 32 **Medline**

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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 36 4. ((real world or rwd) adj2 (stud\* or research or data)).mp.  
12 37 5. (routine\* adj2 data).mp.  
13 38 6. (comparative effectiveness adj2 (stud\* or research or data)).mp.  
14 39 7. (emulat\* or propensity score? or (causal adj2 (inference? or analys?s or  
15 40 effect\*))).mp.  
16 41 8. 3 or 4 or 5 or 6 or 7  
17 42 9. 2 and 8  
18 43 10. (target adj (trial? or experiment?)).ti.  
19 44 11. 1 or 9 or 10  
20 45 Filtered for time (2012-2022) manually after search  
21 46

22 47 **Embase**

- 23 48 1. (emulat\* adj5 trial?).mp.  
24 49 2. (target adj (trial? or experiment?)).mp.  
25 50 3. (observational adj (stud\* or research or data)).mp.  
26 51 4. ((real world or rwd) adj2 (stud\* or research or data)).mp.  
27 52 5. (routine\* adj2 data).mp.  
28 53 6. (comparative effectiveness adj2 (stud\* or research or data)).mp.  
29 54 7. (emulat\* or propensity score? or (causal adj2 (inference? or analys?s or  
30 55 effect\*))).mp.  
31 56 8. 3 or 4 or 5 or 6 or 7  
32 57 9. 2 and 8  
33 58 10. (target adj (trial? or experiment?)).ti.  
34 59 11. 1 or 9 or 10  
35 60

36 61 **psycINFO**

- 37 62 noft(target trial emulat\*) OR ((noft(real world data) OR (noft(emulat\* trial)) OR  
38 63 noft(observational) OR noft(routine\* data)) AND noft(comparative effective\*)  
39 64 AND noft(causal infer\*))  
40 65

41 66 **Web of Science**

- 42 67 (TI=(emulat\* trial)) OR (TI=(real world data) OR TI=(routine\* data) OR  
43 68 TI=(comparative effectiveness study comparative effectiveness research or  
44 69 comparative effectiveness data) OR (TI=(emulat\* or propensity score?) AND  
45 70 TI=(causal inference or causal analysis or causal effect\*)) AND ALL=(target  
46 71 trial or emulat\* or target trial emulation)



# BMJ Open

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

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Manuscripts

# 1 Development of the Transparent Reporting of Observational Studies Emulating a Target 2 Trial (TARGET) Guideline

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Observational studies are increasingly used to inform health decision-making when randomised trials are not feasible, ethical, or timely. The target trial approach provides a framework to help minimise common biases in observational studies that aim to estimate the causal effect of interventions. Incomplete reporting of studies using the target trial framework limits the ability for clinicians, researchers, patients, and other decision-makers to appraise, synthesise, and interpret findings to inform clinical and public health practice and policy. This paper describes the methods that we will use to develop the transparent reporting of observational studies emulating a target trial (TARGET) reporting guideline.

68 **Methods/design**

69 The TARGET reporting guideline will be developed in five stages following  
70 recommended guidance. The first stage will identify target trial reporting practices by  
71 systematically reviewing published studies that explicitly emulated a target trial. The  
72 second stage will identify and refine items to be considered for inclusion in the  
73 TARGET guideline by consulting content experts using sequential online surveys. The  
74 third stage will prioritise and consolidate key items to be included in the TARGET  
75 guideline at an in-person consensus meeting of TARGET investigators. The fourth  
76 stage will produce and pilot-test both the TARGET guideline and explanation and

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4 77 elaboration document with relevant stakeholders. The fifth stage will disseminate the  
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6 78 TARGET guideline and resources via journals, conferences, and courses.  
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## 10 11 80 **Ethics and Dissemination**

12  
13  
14 81 Ethical approval for the survey has been attained (HC220536). The TARGET guideline  
15  
16 82 will be disseminated widely in partnership with stakeholders to maximise adoption and  
17  
18  
19 83 improve reporting of these studies.  
20

21  
22 84

23  
24 85 **Key words:** target trial emulation, causal inference, reporting guideline, observational  
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26  
27 86 studies  
28

29  
30 87

## 31 32 88 **Strengths and Limitations**

- 33  
34  
35 89 - The TARGET reporting guideline will be developed according to  
36  
37 90 recommendations for health research reporting guidelines  
38  
39  
40 91 - The TARGET working group has been established to include stakeholders  
41  
42 92 from a variety of backgrounds  
43  
44  
45 93 - A comprehensive piloting phase may increase the usability and uptake of the  
46  
47 94 reporting guideline  
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## 96 Introduction

97 Observational studies can provide evidence on the causal effects of interventions  
98 when it is not feasible, ethical, or timely to conduct a relevant randomised trial.

99 However, making causal inferences from observational data is challenging due to  
100 confounding and design-related biases such as selection bias and immortal time bias.

101 (1,2) Design-related biases can be avoided using the target trial framework. (3,4) The  
102 framework involves the specification of the hypothetical randomised pragmatic trial —  
103 the target trial — that would ideally be conducted and how this trial might be emulated  
104 using observational data. (3,4) The two stages of the target trial framework are 1)  
105 specification of the target trial, and 2) emulation of the target trial. (3,4) Using  
106 observational data to mimic a randomised experiment was proposed in the mid 20<sup>th</sup>  
107 century, (5-8) and extended to time-varying treatments by Robins in 1986. (9)

108  
109 The value of using the target trial framework to design the analysis of observational  
110 studies has been recognised by international regulatory bodies in the field of medicine  
111 and health, (10-14) and the framework underpins the widely-used ROBINS-I tool for  
112 assessing risk of bias in non-randomised studies of interventions. (15) Studies that are  
113 explicit in using the target trial framework have been published with increasing  
114 frequency in leading general medical and specialty journals. (16-23)

115  
116 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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4 118 template for specifying a target trial and its emulation; however, there is currently no  
5  
6 119 detailed guidance on reporting a study designed to emulate a target trial. Incomplete  
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8  
9 120 reporting of these studies limits the ability of clinicians, researchers, patients, and other  
10  
11 121 decision-makers to appraise and synthesise findings or interpret them to inform clinical  
12  
13  
14 122 and public health practice and policy. A reporting guideline that expands upon the  
15  
16 123 initial target trial emulation template(3) is needed to provide authors with  
17  
18  
19 124 comprehensive recommendations on how to completely and transparently report a  
20  
21  
22 125 study emulating a target trial.  
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25 126  
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27 127  
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29  
30 128 **[INSERT FIGURE 1]**  
31  
32 129  
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34

35 130 To address this gap, we outline the processes and methods that used to develop a  
36  
37 131 reporting guideline for studies emulating a target trial – TARGET (Transparent  
38  
39  
40 132 reporting of observational studies emulating a target trial).  
41  
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#### 45 134 **Objective**

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47  
48 135 The objective of the TARGET guideline is to provide guidance on the minimum set of  
49  
50 136 items that should be reported to provide a clear and transparent account of  
51  
52  
53 137 observational studies that investigate the comparative effectiveness and safety of  
54  
55  
56 138 health interventions explicitly using the target trial framework.  
57  
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## 140 **Methods**

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

144  
145 **[INSERT FIGURE 2]**

### 147 **TARGET working group**

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

### 155 **Stage 1: Identify current reporting practices**

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

160  
161 *Databases, eligibility, and search terms*

1  
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3  
4 162 We will search Medline, EMBASE, PsycINFO and Science Citation Index for  
5  
6 163 observational studies that stated in their methods that they explicitly emulated a target  
7  
8 164 trial. We will exclude studies not written in English, not in the field of medicine and  
9  
10  
11 165 health, not conducted in humans, or not observational designs. Many observational  
12  
13  
14 166 studies may implicitly use the framework of a randomised trial. However, to be  
15  
16 167 included in this review studies must be explicit in their attempt to emulate a target trial  
17  
18  
19 168 (e.g., stated 'target trial emulation' in the article). To identify eligible studies, we  
20  
21  
22 169 developed a literature search in collaboration with an expert librarian at the University  
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24  
25 170 of Oxford. Our approach used sensitive search terms including emulat\*, target trial,  
26  
27 171 observational data, real-world data, comparative effectiveness, and causal inference,  
28  
29  
30 172 to try to capture all papers explicitly emulating a target trial. The complete search  
31  
32  
33 173 strategy is in Supplementary Material 2. We will conduct forward citation tracking of  
34  
35 174 selected seminal articles to maximise the chance of retrieving all relevant articles.  
36  
37 175 (3,9,26-28) We will also include papers known to the authorship team. In duplicate,  
38  
39  
40 176 independent reviewers will conduct title, abstract, and full text screening. We will  
41  
42  
43 177 resolve disagreements between reviewers through discussion.  
44

45 178

#### 48 179 *Data Extraction*

49  
50 180 We will extract items regarded by the steering committee as potentially important for  
51  
52  
53 181 the reporting of a target trial emulation, including those outlined by Hernán and Robins,  
54  
55  
56 182 2016. (3) Two independent reviewers will extract information on study authors, year of  
57  
58  
59 183 publication, journal, sub-field of medicine, study design, sample size, intervention,  
60

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4 184 comparison group, outcomes assessed, and whether the study was prospectively  
5  
6 185 registered. We will extract items relevant to the methods and results of the target trial  
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8  
9 186 emulation, including whether and how all components of the protocol of the proposed  
10  
11 187 target trial, and how they were emulated, were specified (i.e., eligibility criteria,  
12  
13  
14 188 treatment strategies, assignment procedures, follow-up period, outcome(s), causal  
15  
16 189 contrast(s), and data analysis plan). We will enter data into a standardised data  
17  
18  
19 190 extraction form which two authors will pilot with a selection of included studies. We will  
20  
21  
22 191 resolve disagreements in data extraction between reviewers through discussion, or  
23  
24 192 where necessary, consultation with a third reviewer.  
25  
26  
27 193

#### 28 29 194 *Data analysis*

30  
31  
32 195 We will use R (29) for all data analyses. Categorical variables will be summarised  
33  
34  
35 196 using frequencies and percentages. Continuous variables will be summarised using  
36  
37  
38 197 mean and standard deviation, or median and interquartile range, as appropriate.  
39

40 198

#### 41 42 43 199 *Outcomes of the systematic review*

44  
45 200 The systematic review will provide evidence on reporting in studies explicitly emulating  
46  
47  
48 201 a target trial. We acknowledge that excluding studies not written in English and  
49  
50  
51 202 unpublished studies may cause potentially relevant articles to be excluded. The  
52  
53 203 findings will inform the online surveys (Stage 2) and the consensus meeting (Stage 3).  
54  
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56 204 We will submit the findings of this review for publication and all data and code made  
57  
58 205 publicly available.  
59  
60

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  
213 South Wales Human Research Ethics Committee (HC220536).

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  
221 that may be important for the conduct or reporting of target trial emulations.

222

*223 Participants*

224 Members of the TARGET working group (Supplementary Material 1) will be invited to  
225 participate in the surveys.

226

*227 Procedure*

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4 228 We will host two online surveys using REDCap. (30,31) We will send each online  
5  
6 229 survey via email to the participants. We will ask participants to rate the importance of  
7  
8 230 each potential reporting item on a 9-point Likert scale (1, “not important”, to 9, “critically  
9  
10 231 important”). Participants will have the opportunity to provide suggestions or  
11  
12 232 modifications to the wording of items as well as suggest additional items or make other  
13  
14 233 comments.  
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19 234  
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21 235 In the second survey, we will send participants a summary of the results for each  
22  
23 236 potential reporting item (mean scores and standard deviations, median scores and  
24  
25 237 interquartile ranges, and histograms), their own score for each item, and any  
26  
27 238 comments from participants on each item from the first survey. We will also present  
28  
29 239 any new items and suggested modifications to items. We will then invite participants  
30  
31 240 to re-score the importance of each item, and score any additional items, considering  
32  
33 241 the aggregated ratings. Participants will have the opportunity to provide additional  
34  
35 242 feedback on each item in the form of open ended responses.  
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#### 44 244 *Analysis*

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46  
47 245 Continuous variables will be summarised using mean and standard deviation, or  
48  
49 246 median and interquartile range, as appropriate. We will analyse the free-text  
50  
51 247 responses from the first and second surveys using an inductive approach, (32) in  
52  
53 248 which we will use reflexive thematic (32) analysis to identify, organise and generate  
54  
55 249 codes, and then identify themes found within the dataset. Briefly, inductive coding is a  
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4 250 process pooling common ideas without trying to fit ideas/codes into a pre-existing  
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6 251 framework. These data will contribute to the creation of new items and modification of  
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9 252 existing items to be included in the subsequent survey.

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14 254 *Outcome of the online surveys*

15  
16 255 We will generate a preliminary list of items with corresponding ratings of importance  
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18  
19 256 to be considered in the TARGET guideline at the consensus meeting (Stage 3). We  
20  
21  
22 257 will also generate qualitative insights to guide item refinement and prioritisation in  
23  
24  
25 258 preparation for the consensus meeting.

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30 260 **Stage 3 – Consolidate and prioritise key items to be included in the TARGET guideline**

31  
32 261 A consensus meeting will finalise reporting items for the TARGET guideline. (24) The  
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35 262 consensus meeting will follow suggested methods for developing reporting guidelines,  
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38 263 (24) including guidance for consensus-based methods currently being developed  
39  
40 264 which we will use if they become available. (33)

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45 266 *Process*

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48 267 We will invite stakeholders identified by the working group to participate in a two-day  
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51 268 consensus meeting. The TARGET working group will ensure that the expertise of  
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53  
54 269 consensus meeting participants includes target trial emulation methodology,  
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56 270 epidemiology, clinical trials, biostatistics, reporting guideline development, and  
57  
58 271 regulatory and journal editorial processes. Prior to the consensus meeting, the core  
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4 272 team will provide attendees with evidence from the systematic review (Stage 1) and  
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6 273 findings from the online surveys (Stage 2) including a draft of the items proposed for  
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9 274 inclusion in the guideline. We will present the findings from Stage 1 and 2 at the  
10  
11 275 consensus meeting. A member of the TARGET working group will facilitate a  
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13  
14 276 structured discussion on the rationale for including items from the online surveys. If  
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16  
17 277 there are disagreements, they will first be debated and, if disagreements remain, we  
18  
19 278 will hold an anonymised vote to establish the importance of including the item in the  
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21  
22 279 guideline. For the anonymised vote, a simple majority will be sufficient to guide the  
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24  
25 280 inclusion/exclusion of an item. The meeting will conclude with discussion about the  
26  
27 281 content and production of relevant documents (TARGET guideline, draft explanation  
28  
29 282 and elaboration document) as well as strategies for dissemination and implementation.  
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31  
32 283 Following the conclusion of the consensus meeting, we will circulate a report on the  
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34  
35 284 outcome to the meeting participants for review and approval.  
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40 286 **Stage 4 – Development and piloting of the draft TARGET guideline and explanation**  
41  
42 287 **and elaboration document**  
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45 288 Stage 4 involves drafting the TARGET guideline and accompanying explanation and  
46  
47  
48 289 elaboration document to ensure that the wording and content of the documents are  
49  
50  
51 290 clear, precise, and suitable for all identified stakeholders. The purpose of the  
52  
53 291 explanation and elaboration document is to explain each item by providing background  
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55  
56 292 information, a rationale, and clear reporting examples from published target trial  
57  
58 293 emulations. We will design the explanation and elaboration document to facilitate  
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4 294 adherence to the TARGET guideline by clarifying the importance of each item,  
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6 295 highlighting relevant reporting issues and providing examples to assist authors using  
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9 296 the guideline. The consensus meeting participants may be asked to review and  
10  
11 297 comment on the draft TARGET guideline and explanation and elaboration document.  
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15  
16 299 We will evaluate the TARGET guideline by piloting the proposed guideline and the  
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19 300 explanation and elaboration document with 20-30 expert methodologists and potential  
20  
21  
22 301 users of TARGET, identified from TARGET working group networks. We will ask  
23  
24  
25 302 participants to provide general feedback on accessibility and usability, and to identify  
26  
27 303 possible reporting items that might have been overlooked. We will also ask for specific  
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29  
30 304 feedback about the utility and clarity of each TARGET item. We will collect data  
31  
32 305 through online surveys, hosted by REDCap. (30,31) We will incorporate feedback from  
33  
34  
35 306 the piloting exercise into the final guideline and explanation and elaboration document,  
36  
37 307 as required. If suggested revisions are extensive, we will conduct a further round of  
38  
39  
40 308 piloting.  
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#### 44 45 310 *Patient and public involvement*

46  
47  
48 311 Potential users of this research include health researchers conducting observational  
49  
50 312 analyses, regulatory bodies, public health and other health decision-makers. We aim  
51  
52  
53 313 to include relevant decision-makers in the piloting phase of the guideline development  
54  
55  
56 314 process to maximise the usefulness and uptake of the TARGET guideline. Participants  
57  
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4 315 in any stage of the guideline development will be informed of the results and final  
5  
6 316 guidance.  
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## 10 11 318 **Stage 5 – Guideline implementation**

12  
13  
14 319 The goal of the final stage of guideline development is to maximise reach and use of  
15  
16 320 the TARGET guideline. The TARGET working group will guide the dissemination  
17  
18 321 strategy with advice from consensus meeting participants. We aim to publish the  
19  
20 322 TARGET guideline and the explanation and elaboration document and disseminate  
21  
22 323 the findings through traditional and social media. We will engage journal editors and  
23  
24 324 funding agencies to encourage TARGET guideline endorsement alongside other  
25  
26 325 published reporting guidance. We will publicly host the TARGET guideline and  
27  
28 326 explanation and elaboration paper, and any other relevant material on a TARGET  
29  
30 327 website. We will index the guideline on the Enhancing the QUALity and Transparency  
31  
32 328 Of health Research (EQUATOR) Network website. (34,35) We will create online  
33  
34 329 resources including infographics, blog posts and podcasts, which will be available on  
35  
36 330 the TARGET website. We will share the TARGET guideline with authors in the field,  
37  
38 331 and at relevant scientific conferences and methodological courses.  
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4 332 **Declarations**

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7  
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9 334 **Ethics approval and consent to participate**

10  
11 335 Not Applicable

12  
13  
14 336

15  
16 337 **Consent for publication**

17  
18  
19 338 All authors consent to publication of this manuscript

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21  
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23  
24 340 **Availability of data and materials**

25  
26  
27 341 Not applicable

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29  
30 342

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11 357

### 14 358 **Competing interests**

16 359 All authors declare no competing interests.

19 360

### 22 361 **Author Contributions**

24 362 HJH, AGC, MDJ, HL, JHM, conceived the idea for the project protocol. All authors  
25  
26  
27 363 contributed to the design and methodology of the project protocol. HJH and AGC wrote  
28  
29  
30 364 the first draft of the manuscript. MAH, SAS, IJD, BAD, XG-A, ME, RMG, NI, SL, MM-  
31  
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33  
34  
35 366 read and approved the final version.  
36

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4 372 **Abbreviations**

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7  
8 374 **EQUATOR:** Enhancing the QUALity and Transparency Of health Research

9  
10 375 **REDCap:** Research Electronic Data Capture

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12  
13 376 **STROBE:** Strengthening the Reporting of Observational Studies in Epidemiology

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16 377 **TARGET:** TrAnSPARENT ReportinG of studies Emulating a Target trial

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21 379 **Figure Captions**

22  
23 380

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25  
26 381 Figure 1: Elements relevant to both the specification and emulation of the target trial  
27  
28 382 described by Hernán & Robins (3)

29  
30  
31 383 Figure 2: Workflow for the development of the TARGET guideline

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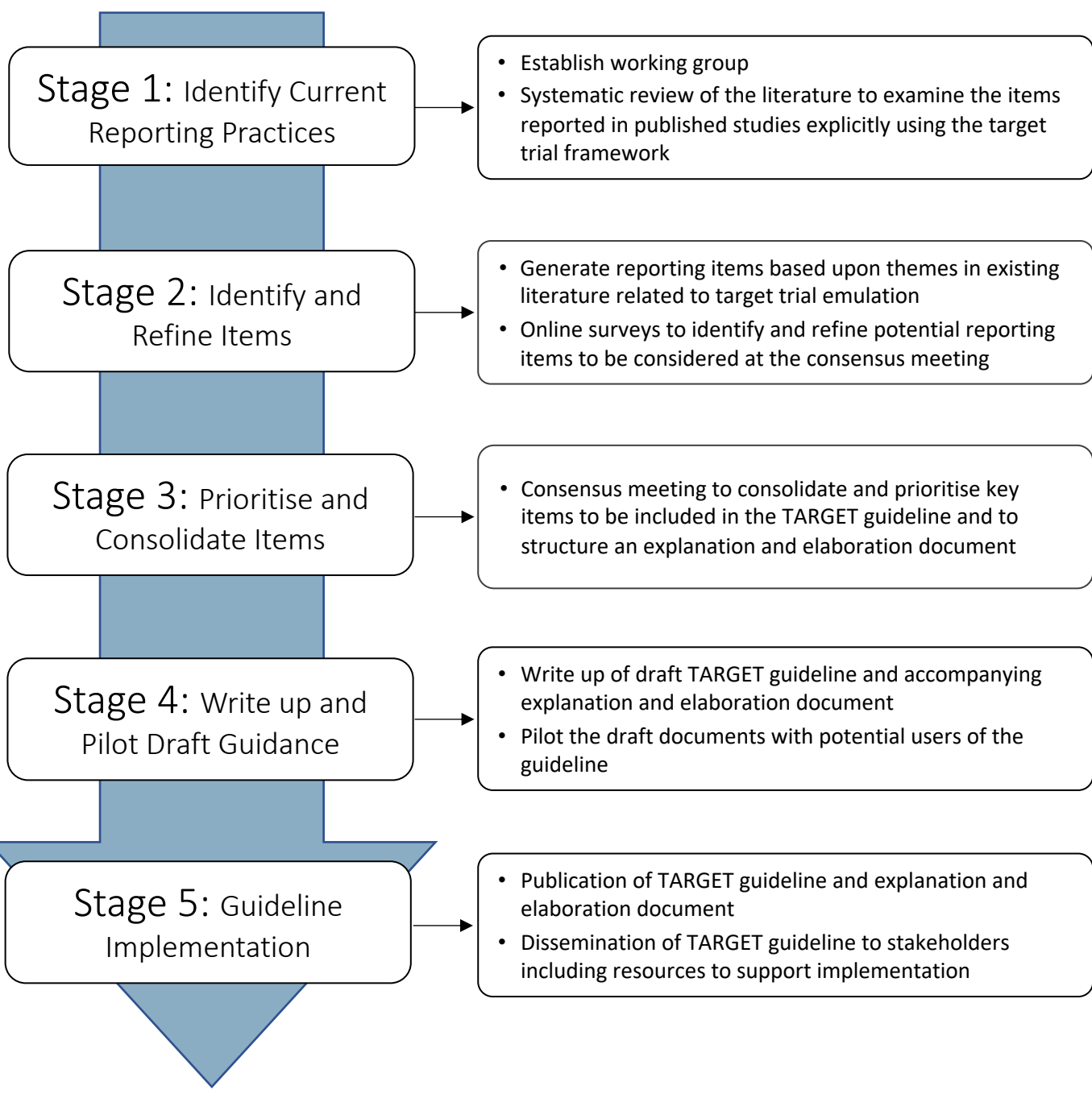
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3 1 **Supplementary Material**  
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7 3 **Supplementary Material 1: TARGET working group members (alphabetical)**  
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9 4  
10 5 *Steering committee*  
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26 19 Prof Robert M. Golub  
27 20 A/Prof Nazrul Islam  
28 21 A/Prof Sara Lodi  
29 22 A/Prof Margarita Moreno-Betancur  
30 23 Prof Sallie A. Pearson  
31 24 Prof Sebastian Schneeweiss  
32 25 Prof Jonathan A. C. Sterne  
33 26 Dr Melissa K. Sharp  
34 27 Prof Elizabeth A. Stuart  
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30 **Supplementary Material 2: Complete search strategies for all databases**

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32 **Medline**

- 33 1 (emulat\* adj5 trial?).mp.  
 34 2 (target adj (trial? or experiment?)).mp.  
 35 3. (observational adj (stud\* or research or data)).mp.  
 36 4. ((real world or rwd) adj2 (stud\* or research or data)).mp.  
 37 5. (routine\* adj2 data).mp.  
 38 6. (comparative effectiveness adj2 (stud\* or research or data)).mp.  
 39 7. (emulat\* or propensity score? or (causal adj2 (inference? or analys?s or  
 40 effect\*))).mp.  
 41 8. 3 or 4 or 5 or 6 or 7  
 42 9. 2 and 8  
 43 10. (target adj (trial? or experiment?)).ti.  
 44 11. 1 or 9 or 10  
 45 Filtered for time (2012-2022) manually after search

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47 **Embase**

- 48 1. (emulat\* adj5 trial?).mp.  
 49 2. (target adj (trial? or experiment?)).mp.  
 50 3. (observational adj (stud\* or research or data)).mp.  
 51 4. ((real world or rwd) adj2 (stud\* or research or data)).mp.  
 52 5. (routine\* adj2 data).mp.  
 53 6. (comparative effectiveness adj2 (stud\* or research or data)).mp.  
 54 7. (emulat\* or propensity score? or (causal adj2 (inference? or analys?s or  
 55 effect\*))).mp.  
 56 8. 3 or 4 or 5 or 6 or 7  
 57 9. 2 and 8  
 58 10. (target adj (trial? or experiment?)).ti.  
 59 11. 1 or 9 or 10

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61 **psycINFO**

- 62 noft(target trial emulat\*) OR ((noft(real world data) OR (noft(emulat\* trial)) OR  
 63 noft(observational) OR noft(routine\* data)) AND noft(comparative effective\*)  
 64 AND noft(causal infer\*))

65

66 **Web of Science**

- 67 (TI=(emulat\* trial)) OR (TI=(real world data) OR TI=(routine\* data) OR  
 68 TI=(comparative effectiveness study comparative effectiveness research or  
 69 comparative effectiveness data) OR (TI=(emulat\* or propensity score?) AND  
 70 TI=(causal inference or causal analysis or causal effect\*)) AND ALL=(target  
 71 trial or emulat\* or target trial emulation)