Study protocol

Based on the HARPER template

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Title page

This protocol is based on the *HARmonized Protocol Template to Enhance Reproducibility (HARPER) of Hypothesis Evaluating Real-World Evidence Studies on Treatment Effects: A Good Practices Report of a Joint ISPE/ISPOR Task Force* (**HARPER**) protocol by (Wang et al. 2022).

Title

Research question and objectives

Protocol version

Contributors

Primary investigator contact information:

Contributor names:

Study registration

Site:

Identifier:

Sponsor

Organization:

Contact:

Conflict of interest

Abstract

Amendments and updates

Version date	Version number	Section of protocol
<Date of the protocol version change>	<Number or other identifier for the protocol version>	<Brief text description of which sections of

Milestones

Table 2: Milestones

Milestone	Date
<Milestone description>	<Date>
<Milestone description>	<Date>
<Milestone description>	<Date>

Rationale and background

What is known about the condition:

What is known about the exposure of interest:

Gaps in knowledge:

What is the expected contribution of this study?

The purpose of this protocol is to describe the emulation of trial INSERT TRIAL NAME. The primary trial estimate targeted for emulation is INSERT. Market availability of EXPOSURE began DATE.

Research question and objectives

Research methods

Study design

Research design (e.g. cohort, case-control, etc.):

Rationale for study design choice:

Study design diagram

Setting

Context and rationale for definition of time 0 (and other primary time anchors) for entry to the study population

Table 6: Operational Definition of Time 0 (index date)

Study population name(s)	Time Anchor Description (e.g. time 0)	Number of entries	Type of entry	Washout window	Care setting	C

Context and rationale for study inclusion criteria

Table 7: Operational Definitions of Inclusion Criteria

Criterion	Details	Order of application	Assessment window	Care settings	Code Type	Diagnosis position	Applied to study populati

Context and rationale for study exclusion criteria

Table 3: Research questions and objectives

(a) Primary research question and objective

Study element	Specification
Objective:	<Text>
Hypothesis:	<Text>
Population (mention key inclusion-exclusion criteria):	<Text>
Exposure:	<Text>
Comparator:	<Text>
Outcome:	<Text>
Time (when follow up begins and ends):	<Text>
Setting:	<Text>
Main measure of effect:	<Text>

(a) Secondary research question and objective

Study element	Specification
Objective:	<Text>
Hypothesis:	<Text>
Population (mention key inclusion-exclusion criteria):	<Text>
Exposure:	<Text>
Comparator:	<Text>
Outcome:	<Text>
Time (when follow up begins and ends):	<Text>
Setting:	<Text>
Main measure of effect:	<Text>

Table 8: Operational Definitions of Exclusion Criteria

Criterion	Details	Order of application	Assessment window	Care settings	Code Type	Diagnosis position	Applied to study populati

Variables

Context and rationale for exposure(s) of interest

Algorithm to define duration of exposure effect:

Table 9: Operational Definitions of Exp

Exposure group name(s)	Details	Washout window	Assessment window	Care settings	Code Type	Diagnosis position	Applied to stu

Context and rationale for outcome(s) of interest

Table 10: Operational Definitions of Outcome

Outcome name	Details	Primary outcome?	Type of outcome	Washout window	Care settings	Code Type	Diagnosis position	Appl

Context and rationale for follow up

Table 11: Operational Definitions of Follow up

Time point	Select all that apply	Specify
Follow up start	NA	NA
Follow up end	NA	NA
Date of outcome	NA	NA
Date of death	NA	NA

End of observation in data	NA	NA
Day X following index date	NA	NA
End of study period	NA	NA
End of exposure	NA	NA
Date of add to/switch from exposure	NA	NA
Other date	NA	NA

Context and rationale for covariates (confounding variables and effect modifiers, e.g. risk factors, comorbidities, comedications)

Table 12: Operational Definitions of Covariates

Characteristic	Details	Type of variable	Assessment window	Care settings	Code Type	Diagnosis position	Applied to study populat

Data analysis

Context and rationale for analysis plan

A. Primary analysis

Table 16: Sensitivity analyses – rationale, strengths and limitations

Analysis	What is being varied?	Why (expected learning)?	Strengths of the sensitivity analysis compared to primary	Limitations of the
<Text>	<Text>	<Text>	<Text>	<Text>

Data sources

Context and rationale for data sources

Reason for selection:

Table 13: Primary, secondary, and subgroup analysis specification

(a) Primary analysis

Analysis element	Specification
Hypothesis:	<Text>
Exposure contrast:	<Text>
Outcome:	<Text>
Analytical software	<Text>
Model(s):	<Text>
Conofunding adjustment method	Name method and provide relevant details, e.g. bivariate, multivariable, propensity score matching (specif
Missing data methods	Name method and provide relevant details, e.g. missing indicators, complete case, last value carried forwa
Subgroup Analyses	List all subgroups

(a) Secondary analysis

Analysis element	Specification
Hypothesis:	<Text>
Exposure contrast:	<Text>
Outcome:	<Text>
Analytical software	<Text>
Model(s):	<Text>
Conofunding adjustment method	Name method and provide relevant details, e.g. bivariate, multivariable, propensity score matching (specif
Missing data methods	Name method and provide relevant details, e.g. missing indicators, complete case, last value carried forwa
Subgroup Analyses	List all subgroups

Strengths of data source(s):

Limitations of data source(s):

Data source provenance/curation:

Table 17: Metadata about data sources and software

Data element	Data 1	Data 2	Data 3
Data Sources:	<Text>	<Text>	<Text>
Study Period:	<Text>	<Text>	<Text>
Eligibile Cohort Entry Period:	<Text>	<Text>	<Text>
Data version (or date of last update):	<Text>	<Text>	<Text>
Data sampling/extraction criteria:	<Text>	<Text>	<Text>
Type(s) of data:	<Text>	<Text>	<Text>
Data linkage	<Text>	<Text>	<Text>
Conversion to CDM:	<Text>	<Text>	<Text>
Software for data management:	<Text>	<Text>	<Text>

Data management

Quality control

Study size and feasibility

Limitation of the methods

Protection of human subjects

Reporting of adverse events

References

Appendices

Change log

Detailed change log based on previous commits.

```
Mon, 17 Apr 2023 16:14:43 -0400
Changes made by: jweberpals@bwh.harvard.edu
Commit hash:  c0f1b13
Changes made: with format gt

Mon, 17 Apr 2023 15:24:42 -0400
Changes made by: jweberpals@bwh.harvard.edu
Commit hash:  106faf2
Changes made: attempt  to balance html and pdf output using gt
```

```
Sun, 16 Apr 2023 19:20:26 -0400
Changes made by: jweberpals@bwh.harvard.edu
Commit hash:  f0bde2b
Changes made: first HARPER draft; TODO: Tables in pdf

Sun, 16 Apr 2023 19:12:50 -0400
Changes made by: jweberpals@bwh.harvard.edu
Commit hash:  34b0c71
Changes made: initial commit
```

Wang, Shirley V., Anton Pottegård, William Crown, Peter Arlett, Darren M. Ashcroft, Eric I. Benchimol, Marc L. Berger, et al. 2022. "HARmonized Protocol Template to Enhance Reproducibility of Hypothesis Evaluating Real-World Evidence Studies on Treatment Effects: A Good Practices Report of a Joint ISPE/ISPOR Task Force." *Pharmacoepidemiology and Drug Safety* 32 (1): 44–55. https://doi.org/10.1002/pds.5507.