HARPER

HARmonized Protocol Template to Enhance Reproducibility (HARPER) of Hypothesis Evaluating Real-World Evidence Studies on Treatment Effects: An ISPOR-ISPE Joint Task Force of the Real-World Evidence Initiative

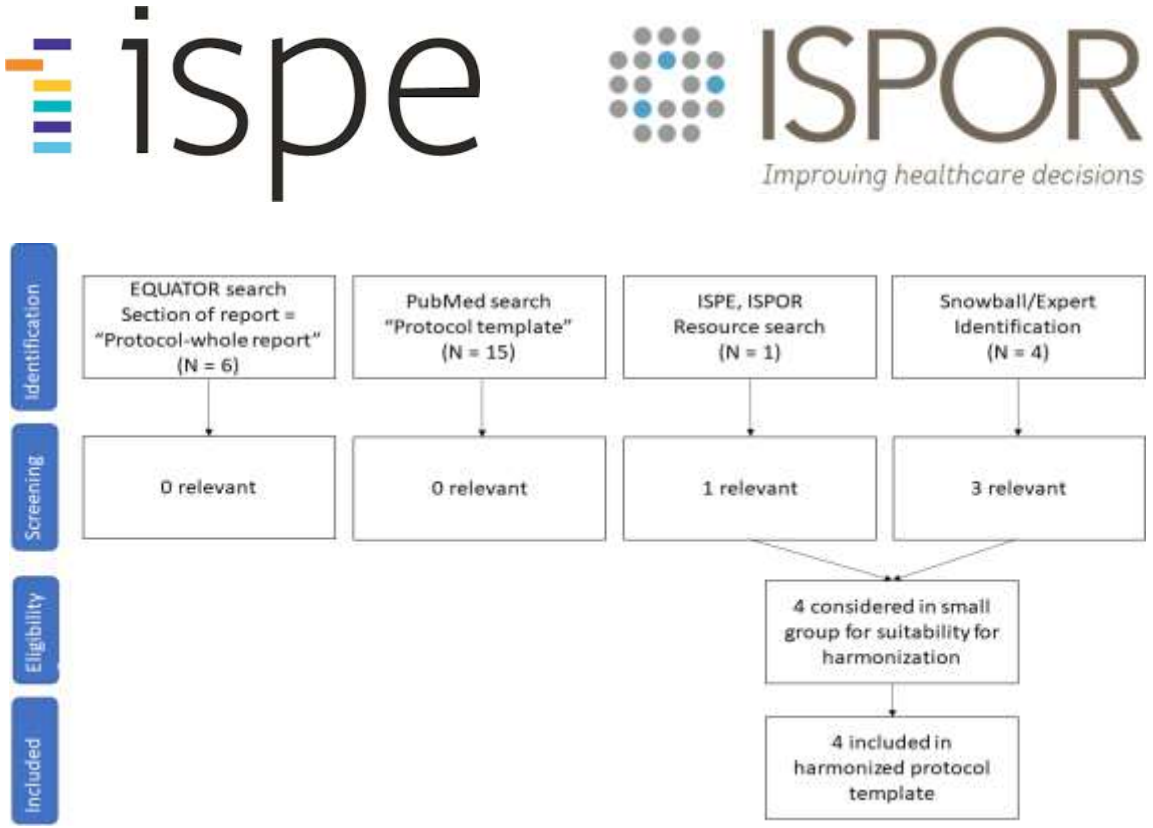


Figure 1. PRISMA Diagram

Joint Task Force

Co-led by Shirley Wang, Anton Pottegård, William Crown

HARPER (harmonized protocol template)

	EMA GVP Mod VIII PASS (Rev 3, Oct 2017)	ISPE GPP (June 2015)	NESTcc (Feb 2020)	STaRT-RWE (2021)	Harmonized Template
High level summary	Largely free text, with guidance on what to include under section headers - details in the *Guidance for the format and content of the protocol of non-interventional post-authorisation safety studies (www.ema.europa.eu)*	Largely free text, with guidance on what to include under section headers - details in report https://www.pharmacoepi.org/resources/policies/guidelines-08027/	Largely free text, with guidance on what to include under section headers - details in NESTcc report	Structured tables that lay out operational parameters to be specified - details in Wang et al, BMJ	Combination of free text with structured tables under section headers
Section Header					
Title page with administrative information (e.g. title, registry ID, drug/device ID, sponsor)	1	A, C, M	2, 10	Table 1	1, table
Table of contents	2			Table of Contents	2, table
Abbreviations	3			Table 9	
Glossary of terminology				Table 8	
Responsible parties	4	B		Table 1	1, table
Abstract	5	D			2, free text
Amendments and updates	6	L		Table 2	3, table
Milestones/timeline	7	E			4, table
Rationale and background	8	G	1		5, structured free text
Research question and objectives	9	F	3	Table 1	6, table
Study design	9.1	H1	7	Figure 1, Table 3	7.1, 7.2, free text, table
Setting	9.2	H2	4	Table 3A, 3B, 3C, 3D, Table 6	7.3, free text, table
Variables	9.3	H4	5, 6	Table 3B, 3E & 3F, 3G, 3H	7.4, free text, table
Device description			2		
Data sources	9.4	H3		Table 3A, Appendices	7.5, free text, table
Study size	9.5	H5	9	Table 7	7.6, free text, table
Data management	9.6	H6, H7		Table 3A, Appendices	7.7, free text, table
Data analysis	9.7	H8	12	Table 4, Table 5	7.8, free text, table
Quality control	9.8	H9	11		
Limitations of the methods	9.9	H10			
Other aspects	9.1				
Protection of human subjects	10	I	8	Table 1	9, free text
Management and reporting of adverse events	11				10, free text
Plans for disseminating and communicating study results	12	J			
References	13	K			References
Appendices	Annex			Appendices	Appendices
ENCePP Checklist for study protocols	Annex				Appendix

Shaded gray area within bold black lines reflects core protocol components

HARPER (harmonized protocol template)

Pilot testing with use cases varying design and data:

1. Active comparator new user design effectiveness study
2. Nested case control
3. Oncology drug versus standard of care
4. Pregnancy safety study
5. Self-controlled case series

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Section Header					
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Version date	Version number	Section of protocol	Amendment or update	Reason
Date	Number	Text	Text	Text



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1. Rationale and background

   What is known about the condition: <Text>

   What is known about the exposure of interest: <Text>

   Gaps in knowledge: <Text>

   What is the expected contribution of this study? <Text>

2. Research question and objectives

Objective:	<Text>
Hypothesis:	<Text>
Population (mention key inclusion-exclusion criteria):	<Text>
Exposure:	<Text>
Comparator:	<Text>
Outcome:	<Text>
Time:	<Text>
Setting:	<Text>
Main measure of effect:	<Text>

PICOT!

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Free-text

Tables and figure

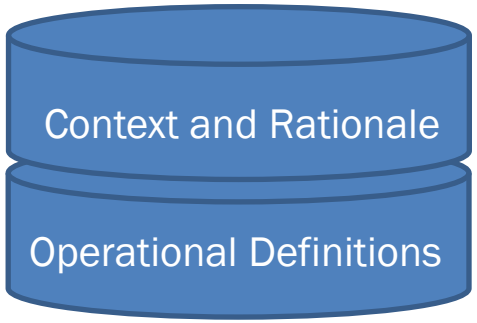


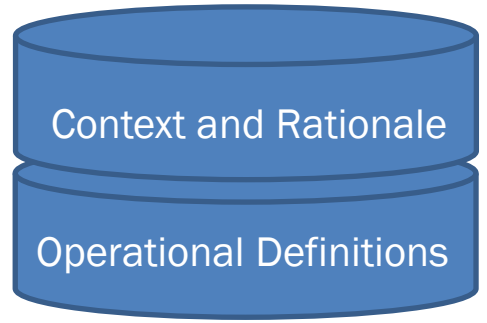
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7.1 Study Design
7.2 Study Design Diagram

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Figure



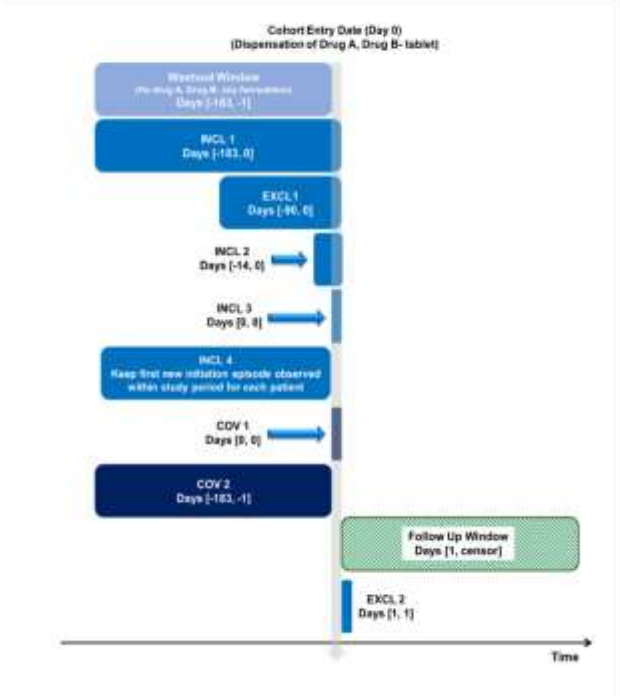
7.1 Study design

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

Rationale for study design choice: <Text>

7.2 Study design diagram

New initiator, active comparator cohort design evaluating risk of outcome Y for Drug A vs Drug B



INCL/EXCL = Inclusion/Exclusion
Assessment Window
INCL1
Medical and Drug coverage (45 day gaps allowed)
INCL2
Community acquired pneumonia diagnosis and chest radiography
INCL3
Age between 18-65
INCL4
Keep first new initiator episode
EXCL1
Inpatient hospitalization
EXCL2
Censored on day follow up starts

Censoring
183 days
30-Sep-15
Discharged dead
Disenroll medical or drug coverage (45 day gaps allowed)

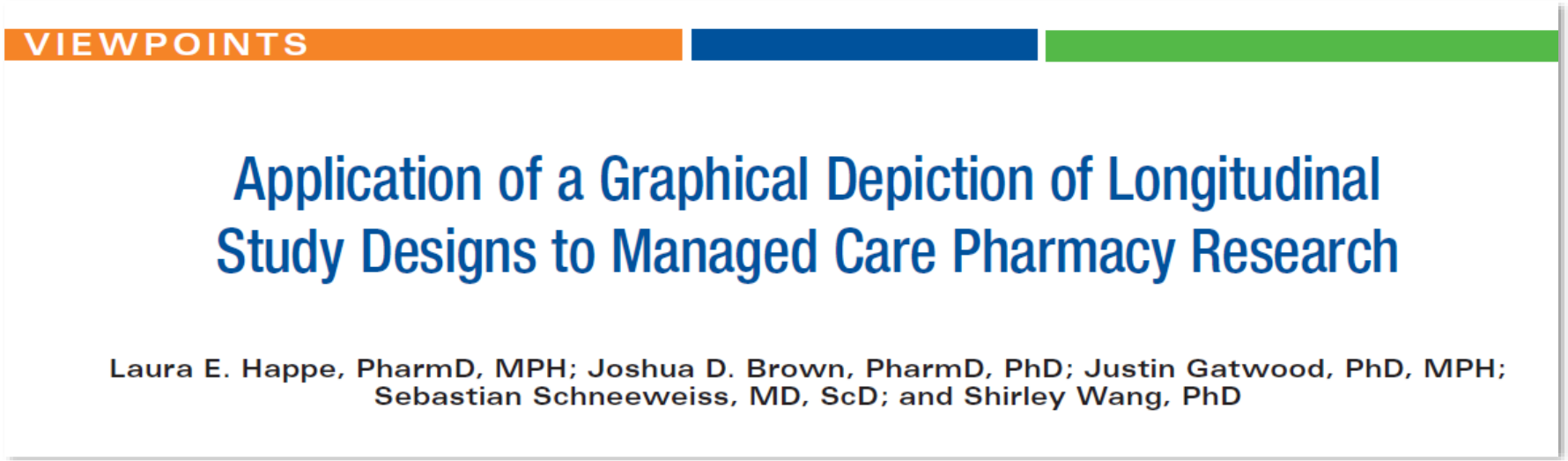
COV = Covariate Assessment Window
COV1
Age (continuous)
Gender

COV2
Metastatic cancer
Tumor
Arrhythmia
Congestive heart failure
Dementia
Renal failure
Weight loss
Hemiplegia
Alcohol abuse
Number of inpatient hospitalizations
Number of outpatient visits
Number of emergency department visit
Number of unique generics
Prior prescription of penicillins
Prior prescription of cephalosporins
Prior prescription of sulfonamides
Prior prescription of tetracyclines
Prior prescription of aminoglycosides
Pregnancy at time of initiation

“A picture is worth a thousand words…” Fred Barnard

- 42% of RWD studies in JMCP included design diagram
- Tried diagramming 2 published studies and noticed ambiguity and inconsistency in text

J Manag Care Spec Pharm 2020 Mar;26(3):268-274. doi: 10.18553/jmcp.2020.26.3.268.


VIEWPOINTS

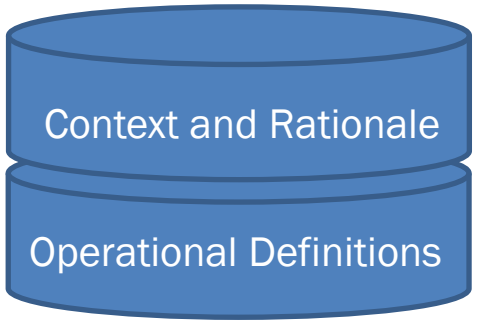
Application of a Graphical Depiction of Longitudinal Study Designs to Managed Care Pharmacy Research

Laura E. Happe, PharmD, MPH; Joshua D. Brown, PharmD, PhD; Justin Gatwood, PhD, MPH; Sebastian Schneeweiss, MD, ScD; and Shirley Wang, PhD

7.3.1 Time 0

Free-text

Table



7.3.1 Context and rationale for definition of time 0 for entry to the study population

<Text>

Table 1 Operational Definition of Time 0 (index date)

Study population name(s)	Day 0 Description	Number of entries	Type of entry	Washout window	Care Setting[1]	Code Type[2]	Diagnosis position	Incident with respect to…	Measurement characteristics /validation	Source of algorithm
<Text>	<Text>	<drop down>	<drop down>	Number range	<Text>	<Text>	<drop down>	<Text>	<Text>	<Text>
Exposure	*Date of incident dispensation for Drug A (tablets only)*	*Single*	*Incident*	*[-183, 0]*	*n/a*	*NDC*	*n/a*	*Drug A or B (any formulation)*	*Unknown*	*Investigator review of generic names*
Comparator	*Date of incident dispensation for Drug B (tablets only)*	*Single*	*Incident*	*[-183, 0]*	*n/a*	*NDC*	*n/a*	*Drug A or B (any formulation)*	*Unknown*	*Investigator review of generic names*

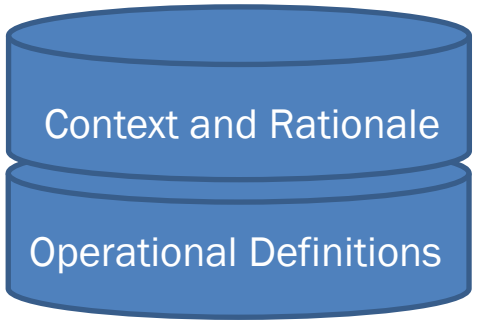
IP = inpatient, OP = outpatient, ED = emergency department, OT = other, n/a = not applicable

[2]See appendix for listing of clinical codes for each study parameter

7.4.3 Follow up

Free-text

Table



7.4.3 Context and rationale for follow up

<Text>

Table 6. Operational Definitions of Follow Up

Follow Up Start	Day 1	
Follow Up End[1]	**Select all that apply**	**Specify**
Date of Outcome	Yes	See Table 5
Date of Death	Yes	Discharged dead or Social Security Death Index, whichever came 1st
Date of Disenrollment	Yes	Allow 30 day gaps in enrolment
Day X following index date *(specify day)*	Yes	Day 183
End of study period (specify date)	Yes	30-Sep-15
End of exposure *(specify operational details, e.g. stockpiling algorithm, grace period)*	No	**Stockpiling algorithm:** If refill occurs before end of days supply, count overlapping days at the end of the subsequent dispensing's day supply. **Grace period:** Bridge gaps of ≤30 days between dispensation + days supply and refill. Add 30 days to last dispensation + days supply in a treatment episode.
Date of add to/switch from exposure *(specify algorithm)*	Yes	Date that patient in exposed group is dispensed comparator drug or vice versa
Other date *(specify)*	No	

7.5 Data Analysis

7.5.1 Context and rationale for analysis plan

<Text>

Table 10. Primary, secondary, and subgroup analysis specification

Hypothesis:	<Text>
Exposure contrast:	<Text>
Outcome:	<Text>
Analytic software:	<Text>
Model(s): *(provide details or code)*	<Text>
Confounding adjustment method	*Name method and provide relevant details, e.g. bivariate, multivariable, propensity score matching (specify matching algorithm ratio and caliper), propensity score weighting (specify weight formula, trimming, truncation), propensity score stratification (specify strata definition), other.*
	<Text>
Missing data methods	*Name method and provide relevant details, e.g. missing indicators, complete case, last value carried forward, multiple imputation (specify model/variables), other.*
	<Text>
Subgroup Analyses	*List all subgroups*
	<Text>

7.5 Sensitivity Analyses

7.5.1 Context and rationale for analysis plan

<Text>

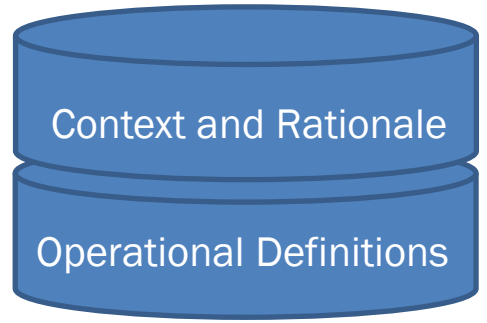
Table 11. Sensitivity analyses – rationale, strengths and weaknesses

	What/how is the parameter being varied?	Why? (What do you expect to learn?)	Strengths of the sensitivity analysis compared to the primary	Weaknesses of the sensitivity analysis compared to the primary
Sensitivity Analysis 1	We change the prior enrolment, covariate and inclusion/exclusion windows from 180 days to 365 days	We learn whether a longer assessment window to more fully capture baseline conditions results in similar estimated effect	Potentially more complete capture of baseline conditions used for inclusion-exclusion or covariate adjustment	Loss of sample size due to turnover in enrollment with health plan
Sensitivity Analysis 2	We analyse a negative control outcome (hospitalization for X) instead of the outcome of interest, myocardial infarction	We learn the magnitude of association for an outcome that is not expected to be differentially affected by Drug A and Drug B, except through confounding	The presumed true null relationship between Drug A, Drug B and hospitalization for X means that observed effects are due to bias or random chance. If results are null, this could strengthen the argument for the causal effect of Drug A vs. Drug B and myocardial infarction. If results are not null, the magnitude of observed effect could be used to calibrate the effect of Drug A vs. Drug B and myocardial infarction.	The confounding structure may not be the same for hospitalization for X as for myocardial infarction. If that is the case, a null effect from the analyzing the negative control, provides less reassurance of the casual effect for Drug A vs. Drug B on myocardial infarction and could increase bias is used to calibrate the effect size.

What is varied?

Why?

7.6 Data Sources



7.6.1 Context and rationale for data sources

Reason for selection: <Text>

Strengths of data source(s): <Text>

Limitations of data source(s): <Text>

Data source provenance/curation: <Text>

Table 12. Metadata about data sources and software

	Data 1	Data 2	Data 3	Data 4
Data Source(s):	XYZ database version 5.1.2	XYZ database version 5.1.2	n/a	n/a
Study Period:	January 1, 2003 - September 30, 2015	January 1, 2012 – December 31, 2020		
Eligible Cohort Entry Period:	January 1, 2003 - September 30, 2015	January 1, 2012 - September 30, 2015		
Data Extraction Date/Version:	January 1, 2018	January 1, 2021		
Data sampling/extraction criteria:	All enrollees in data source between January, 2003 - September 30, 2015	All enrollees with <1 month Part A, B, D coverage between Jan 2012 and Dec 2020 and <1 diabetes diagnosis		
Type(s) of data:	Commercial claims	Commercial claims		
Data linkage:	None	Linkage to National Death Index. See appendix for details		
Data conversion:	ABC Common Data Model version 7.0	ABC Common Data Model version 7.0		
Software for data management:	Statistical software version 9.4	Statistical software version 9.4		

Sections on data management plans and quality control procedures not shown.

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Machine readable code algorithms

A. Cohort entry date defining criterion
B. Inclusion criteria
C. Exclusion criteria
D. Covariates
E. Outcome
F. Data conversion to a Common Data Model
G. Data linkage
H. …

Exclusion criteria	Code	Code Category	Code Type	Description	Route	Strength
Drug A	00003016050	NDC	11	Awesome Drug	tablet	250mg
Drug B	00003016050	NDC	11	Really Cool Drug	tablet	250mg
Drug A	01003016050	NDC	11	Awesome Drug oral	oral suspension	5 ml
Drug B	00803016050	NDC	11	Really Cool Drug injectable	injectable	5 y injectable
Chest radiography	87.44	PX	09	Routine chest x-ray, so described		
Chest radiography	87.49	PX	09	Other chest x-ray		
Chest radiography	71010	PX	C4	Radiologic examination, chest; single view, frontal		
Chest radiography	71015	PX	C4	Radiologic examination, chest; stereo, frontal		

HARPER (harmonized protocol template)

Why?

- Be clear about your intended scientific or operational decisions
- Make your work independently reproducible

How?

- Common structured, tabular and visual framework
- Know what to look for and where to find it

What?

- A template tool for unambiguous communication about study implementation

