EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

HARmonized Protocol to Enhance Reproducibility (HARPER): An ISPE-ISPOR Joint Task Force of the RWE Initiative

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Reproducibility is closely related to clear reporting

- Credibility of RWE from RWD has suffered from apparent divergence between database studies and between database studies and trials
- Unambiguous scientific process increases understanding of
    - How evidence is generated
    - Validity of methods
    - Reasons for divergence in results
- Developing a protocol template

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	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

Template for PASS protocols

1. Table of content, 2. List of abbreviations, 3. Responsible parties
4. Abstract
5. Amendments and updates
6. Milestones
7. Rationale and background
8. Research questions and objectives
9. Research methods
    - 9.1. Study design
    - 9.2. Setting
    - 9.3. Variables
    - 9.4. Data sources
    - 9.5. Study size
    - 9.6. Data management
    - 9.7. Data analysis
    - 9.8. Quality control
    - 9.9. Limitations of the research methods
10. Protection of human subjects
11. Management and reporting of adverse events/ adverse reactions
12. Plans for disseminating and communicating study results
13. References

Annex 1. List of stand-alone documents
Annex 2. ENCePP checklist for study protocol
Annex 3. Additional information

HARPER

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5. Rationale and background
6. Research questions and objectives
7. Research methods
    - 7.1. Study design
    - 7.2. Study design diagram
    - 7.3. Setting
    - 7.4. Variables
    - 7.5. Data analysis
    - 7.6. Data sources
    - 7.7. Data management
    - 7.8. Quality control
    - 7.9. Study size
8. Limitations of the methods
9. Protection of human subjects
10. Reporting of adverse events
11. References
12. Appendices