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An agency of the European Union

20 December 2023
EMA/581874/2023

Overview of comments received

on ICH Reflection paper on proposed international harmonisation of real-world evidence terminology and convergence of general principles regarding planning and reporting of studies using real-world data, with a focus on effectiveness of medicines

EMA/CHMP/ICH/295401/2023

1. General comments – overview

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
C4C conect4children	N/A	N/A	General	Ensure that the terminology used is computer-readable, consistently applied across data, metadata and protocols, and based on existing terminologies and vocabularies	
C4C conect4children	N/A	N/A	General	Explicitly address schemas for metadata and for data	
C4C conect4children	N/A	N/A	General	Explicitly address the alignment with EHDS	
C4C conect4children	N/A	N/A	General	Explicitly address harmonization of terminology across domains (e.g., pediatric versus adults; healthare versus social domain; observational versus study data)	
AESGP	N/A	N/A		AESGP welcomes the opportunity to comment on this ICH Reflection paper on proposed international harmonisation of real-world evidence terminology and convergence of general principles regarding planning and reporting of studies using real-world data, with a focus on effectivness of medicines.	
AESGP	N/A	N/A		The inclusion of comments and review of topics such as this reflection Paper is needed and the practice should be continued to allow for insight generation prior to the working groups being formed	

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
ACRO	N/A	N/A		The Association of Clinical Research Organizations (ACRO) represents the world's leading clinical research and technology organizations. Our member companies provide a wide range of specialized services across the entire spectrum of development for new drugs, biologics and medical devices, from pre-clinical, proof of concept and first-in-human studies through post-approval, pharmacovigilance and health data research. ACRO member companies manage or otherwise support the majority of all biopharmaceutical sponsored clinical investigations worldwide and advance clinical outsourcing to improve the quality, efficiency and safety of biomedical research. ACRO recognize the challenges acknowledged by ICH in the reflection paper and is therefore supportive of the need for harmonization of terminology and general principles in order to enable the use of RWE in regulatory decision-making.	
European Hematology Association (EHA)	N/A	N/A		The European Hematology Association (EHA) welcomes the opportunity to comment on the ICH Reflection Paper on International Harmonisation of Real-World Evidence Terminology and Convergence of General Principles Regarding Planning and Reporting of Studies Using Real-World Data, with a Focus on Effectiveness of Medicines. The document is a valuable compilation of a variety of RWD/RWE initiatives and an important initiative for the design of future studies and world-wide harmonization of terms and definitions	
European Hematology Association (EHA)	N/A	N/A		As a general observation, and perhaps too late given the evolution of the literature on this topic, some of our leading experts have questioned whether the term 'real-world' is either appropriate or future proof. They consider that the use of this term may be inappropriate as it disrespects patients taking part in clinical trials, who are also "real" and come from the "world". Furthermore, the term 'real-world' may not be future proof in that it inherently draws centricity to the biggest/economically strongest healthcare market. Whilst economically logical today, it might be perceived aggressive/outdated in the future. A more nuanced approach such as 'Standard of Care + [healthcare system of reference/data source]', might future proof terminology and facilitate true application for its multiple purposes. Another option may be to return to the use of the terms 'Registry Data' and 'Registry Evidence'	

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
European Hematology Association (EHA)	N/A	N/A		In developing an internationally harmonized definition for real-world data (RWD), EHA finds that the definition should explicitly distinguish RWD from data collected as part of clinical studies. It should be made explicitly clear that the term RWD refers to data collected as part of routine healthcare operations or every-day activities, not specifically focusing on a research-oriented use case. In addition, EHA finds it important to include the data collected as part of telehealth/decentralized healthcare etc. in the proposed definition of RWD. As the adoption of digital health technologies and tools (such as wearables and direct-to-patient digital tools) expands, we expect these data to play a prominent role in the near future. EHA considers that the EU-led definition, as outlined in lines 54-57 of this reflection paper, is in keeping with these points and also has the added advantages of simplicity and brevity	
PFMD	N/A	N/A	General	PFMD welcomes the opportunity to respond to the ICH Reflection Paper on the International Harmonisation of Real-World Evidence Terminology and Convergence of General Principles Regarding Planning and Reporting of Studies Using Real-World Data, with a Focus on Effectiveness of Medicines. The patient community is uniquely placed to increase real world evidence relevance, accessibility, efficiency, and meaningful results for patients and health systems. Despite being such a critical party and stakeholder to involve in all aspects relating to real world evidence, the draft guidelines falls far short of systematically listing them, their role, and their input, everywhere that it should. A mindset shift is needed from viewing this stakeholder group democratically (important public/lay stakeholder), to understanding and enabling their full value potential as an embedded partner/key player in all aspects of the collection of RWD and the use of RWE, from governance, design, and execution, through to interpretation of data and policy-/clinical decision-making	

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PFMD	N/A	N/A	General	PFMD is a global not-for-profit collaborative initiative dedicated to ensuring that medicinal product development and healthcare systems are patient-centered. Composed of 47 member organizations – representing patient communities, healthcare institutions, academia, industry – we work with all stakeholders and actively engage in initiatives to enhance the patient role in and contribution to healthcare decision-making. PFMD's Patient Engagement and Patient Experience Data project aims to understand better what experiences are most significant and valuable to patients and their families/caregivers, when and how these experiences can be measured, and their impact on decision-making. We are working to transform the first-ever co-created Global Patient Experience Data Navigator into a Global PE & PED Roadmap by incorporating patient engagement in the design, generation, analysis, and use of PED. These efforts are essential to maximize the impact of PE initiatives and drive meaningful improvements in patient experiences and outcomes. Specifically, the Global PED Navigator calls for the use of Real Word Data as a means to gather patients' experience in real-world settings.	
TFDA, Chinese Taipei (Taiwan Food and Drug Administration)	N/A	N/A	Annex	Several guidances related to RWD/RWE: 1.Basic Considerations in Supporting Drug Research and Development with Real-World Evidence 2.Use of Electronic Medical Record Data in Clinical Studies 3.RWE Study Designs- Considerations and Key Points for Pragmatic Clinical Trial 4.Real World Data Quality Evaluation- Relevance and Reliability Considerations 5.Precautions for submitting technical documents using RWD/RWE for drug application 6.Guidelines for Using Electronic Healthcare Data to Conduct Pharmacoepidemiologic Safety Studies	TFDA RWD/RWE guildelines website link as below : http://www.fda.gov.tw/TC/siteList.aspx?sid=12735
GSCF	N/A	N/A		GSCF and its members welcome the opportunity to comment on this ICH Reflection paper on proposed international harmonisation of real-world evidence terminology and convergence of general principles regarding planning and reporting of studies using real-world data, with a focus on effectivness of medicines.	
GSCF	N/A	N/A		The inclusion of comments and review of topics such as this reflection Paper is needed and the practice should be continued to allow for insight generation prior to the working groups being formed	

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
IQVIA	N/A	N/A	(General comment)	IQVIA appreciates the opportunity to comment on this ICH reflection paper and believes that the envisioned harmonisation project will serve to advance the use of RWE in regulatory decision-making. IQVIA is a global provider of advanced analytics, technology solutions, and clinical research services to the life sciences industry. IQVIA creates connections across all aspects of healthcare, enabling customers to accelerate the clinical development and commercialization of innovative medical treatments to improve healthcare outcomes for patients. With over 90,000 employees, IQVIA conducts operations in more than one hundred countries. We offer these comments in the spirit of collaboration and hope that ICH finds them useful. Please do not hesitate to contact us with any questions you may have. Please reach out to Daniel Campion, principal, Global Regulatory Science & Strategy, (Daniel.Campion@IQVIA.com; 617-599-9409), who will be happy to connect you with any of our subject matter experts from around the world who work tirelessly to reimagine and develop novel approaches to clinical development, speed innovation, and accelerate improvements in patient outcomes.	N/A
IQVIA	N/A	N/A	(General comment)	Adding a concluding statement that summarizes the project's purpose and emphasizes ICH's call to action would strengthen this reflection paper.	IQVIA recommends adding a concluding paragraph that recaps the project's purpose, next steps, and any other take home messages.

2. Specific comments on text

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
IQVIA	3	5	Title	The title of the document states that this harmonisation project will have "...a Focus on Effectiveness in Medicines," yet establishing fundamental terminology, like the definitions of RWD and RWE, will have an impact on other aspects of clinical research, such as assessing safety, either pre- or post-authorisation. The current wording also leads to some confusion later in the document regarding the overall scope of the project under "Main Technical Issues to be Addressed" and under the discussion of the interface with existing and upcoming guidances.	IQVIA recommends clarifying the title by either deleting the phrase, "…with a Focus on Effectiveness of Medicines," or adding the term safety to read, "…with a Focus on Safety and Effectiveness of Medicines."
Purpose Life Sciences	8	9	Introduction	Should consider disease management (clinical care/treatment) including here since this is where the evidence generation starts. As demonstrated in the WHO guidelines for clinical trials promoting research be more integrated with clinical care	
IQVIA	9	9	Introduction	A dash is not needed between "lifecycle" and "is"	Please delete the dash between "lifecycle" and "is."

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
IQVIA	11	12	Introduction	The paper refers only in general to the ENCePP Guide on Methodological Standards in Pharmacoepidemiology but should direct the reader to use the latest version.	Refer to the latest version, (i.e., version 11, dated July 2023), or otherwise alert the reader to use the latest version.
European Hematology Association (EHA)	12	12		EHA suggests also adding a reference to the article "Real-World Evidence in EU Medicines Regulation: Enabling Use and Establishing Value" authored by Peter Arlett (Head of Pharmacovigilance and Epidemiology Department at the European Medicines Agency), which outlines the vision of using RWD in the context of the EMA processes (https://ascpt.onlinelibrary.wiley.com/doi/full/10.1002/cpt.2479)	Add the reference, as proposed in the comment.
Plasma Protein Therapeutics Association - PPTA	13	22		We welcome the initiative of international harmonisation of real-world evidence terminology and convergence of general principles regarding planning and reporting of studies using real-world data, with a focus on effectiveness of medicines. We welcome the proposal to convergence and harmonisation of terminology and convergence of guidance related to RWD/RWE to further enable the integration of RWE into regulatory submissions globally and timely regulatory decision-making across different regions. We propose that the terminology takes into account the heterogeneity of RWD sources and the different study designs used depending on disease type and rarity, experience in using effective and safe medicines, and the regulatory context, so as to maintain a broad and innovative spectrum of RWD/RWE applications.	
ISPE	15	17	Introduction	The purpose of this reflection paper is a great initiative and kudos to ICH for taking on a topic that certainly needs standardization within the field	
Purpose Life Sciences	17	17	Introduction	Understanding this is a quote from ICHRA, Suggest the guidanace must separate data quality from data sources ("data quality across RWD sources") since they are not uniquely related. To achieve improved outcomes in both Data Quality and Data sources, each needs to be viewed separately	
Purpose Life Sciences	17	18	Introduction	Need to write the guidance with consideration to future innovative study designs (those not yet known)	
CEPI	18	18	Introduction	It is not clear whether medicines include vaccines and diagnostics as well. This comment applies to the use of medicines throughout the document	Suggest changing to medicinal tools or include a footnote what is meant with medicines
GSCF	18	18		non-prescription medicines are often taken for self-treatable conditions. The term conditions also includes diseases. Hence, suggestion is to add this element.	depending on the types of conditions, medicines and regulatory context.

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
Evidera	20	22	Introduction	The sentence mentions that the goal is to further enable the integration of RWE into regulatory submissions and timely regulatory decision-making. However, the title of the guidance is referring to RWE in general.	Modify title to clarify the focus on RWE/RWD to support regulatory decision-making.
Purpose Life Sciences	21	21	Introduction	The ICH may wish to consider reimbursement or non-regulatory elements of RWD guidance. ISPE, Harper and others are typically geared more towards these audiences, and this would substantially increase the available guidance documents available to consult against.	
Plasma Protein Therapeutics Association - PPTA	22	23	Introduction and content in general	The document is not addressing the role of RWD/RWE in rare diseases: Natural History and Real-World Data in Rare Diseases: Applications, Limitations, and Future Perspectives Jing Liu PhD, Jeffrey S. Barrett PhD, FCP, Efthimia T. Leonardi PhD, Lucy Lee PharmD, FCP, Satrajit Roychoudhury PhD, Yong Chen PhD, Panayiota Trifillis PhD First published: 03 December 2022 https://doi.org/10.1002/jcph.2134	
GSCF	23	26		It seems to be unclear if the term "pre-authorisation" refers to the HA's assessment status prior to final HA decision-making or if it also includes for example conditional approvals. However, "other approaches" like RWE, and especially the RWD-types described in lines 27-28, potentially (and pending respective regulations) could also serve a "pre-authorization" purpose, rather than just generating suitable evidence for (final) regulatory decision making, unless the latter is always considered just complementary to RCT-derived conclusions.	Recognising that traditional randomised clinical trials (RCTs) are foundational for generating evidence on safety and effectiveness ~~pre-authorisation~~, under appropriate circumstances other approaches can generate evidence suitable for pre-authorisation and/or regulatory decision-making. For example, RWE can be generated by using RWD to ascertain endpoints in point-of-care RCTs or serve as a comparator arm in an externally 27 controlled trial…
AESGP	24	25		"RCT" means randomized controlled trial. It is important to not confuse RCT terminology in the advancement of RWD/E terminology.	

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
Evidera	24	25	Main technical issues to be addressed	There is not consensus among regulatory bodies on the use of the terms 'efficacy' and 'effectiveness'. According to the FDA Integrated Summary of Effectiveness, Guidance for Industry, October 2015, glossary, "Efficacy and Effectiveness — These terms are used variably and often interchangeably by the scientific and regulatory communities." and according to the EMA glossary of regulatory terms efficacy is "The measurement of a medicine's desired effect under ideal conditions, such as in a clinical trial." Commonly used references provide a clearer distinction: According to the Dictionary of Epidemiology 6th Ed. 'Effectiveness' is "The extent to which a specific intervention, procedure, regimen, or service, when deployed in the usual circumstances of living and practice, does what it is intended to do for a specified population... A measure of the extent to which an intervention or policy fulfills its objectives in practice... If possible, the determination of effectiveness should be based on pragmatic randomized controlled trials." in contrast to 'Efficacy' that is "the extent to which a specific intervention, procedure, regimen, or service produces a beneficial result under ideal conditions ... If possible, the determination of efficacy should be based on the results of randomized controlled trials."	Refer to 'efficacy' instead of 'effectiveness': "Recognising that traditional randomised clinical trials (RCTs) are foundational for generating evidence on safety and efficacy pre-authorisation, under appropriate circumstances other approaches can generate evidence suitable for regulatory decision-making."
Evidera	24	25	Main technical issues to be addressed	According to Pharmacoepidemiology / edited by Brian L. Strom, Stephen E. Kimmel, Sean Hennessy. Sixth edition, "Much attention is now being paid to assessment of the outcomes of medication use in typical real-world populations. This perspective is based on the difference between efficacy, the effect of a medication in the rigorous but idealized setting of a clinical trial, and its effectiveness, a measure of its outcomes in typical practice settings". According to the Glossary IMI ADAPT SMART version 1, efficacy " refers to the benefits (e.g. to health outcomes) a health intervention produces under controlled conditions." and effectiveness "refers to the benefits (e.g. to health outcomes) a health intervention produces in routine clinical practice." According to the 'The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) Guide on Methodological Standards in Pharmacoepidemiology (Revision 11)', "randomised clinical trials (RCTs), and are typically conducted to test the efficacy of treatments such as new medications." and "While RCTs are the gold standard for demonstrating the efficacy of medicinal products, they rarely measure the benefits and risks of an intervention when used in contemporary clinical practice".	Refer to 'efficacy' instead of 'effectiveness': "Recognising that traditional randomised clinical trials (RCTs) are foundational for generating evidence on safety and efficacy pre-authorisation, under appropriate circumstances other approaches can generate evidence suitable for regulatory decision-making."
GSCF	24	25		"RCT" means randomized controlled trial. It is important to not confuse RCT terminology in the advancement of RWD/E terminology. Case in point, both latest FDA guidance and MHRA guidance on RWD/E allow for randomized evidence within a real-world setting. These would satisfy RCT criteria while not being clinic-based studies.	Randomized controlled trial.

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
PFMD	25	26		"under appropriate circumstances other approaches can generate evidence suitable for regulatory decision-making". What are the appropriate circumstances?	This should be further emphasised in the final guidelines.
CEPI	25	25	Main techncial issues to be addressed	Efficacy can be defined as the performance of an intervention under ideal and controlled circumstances, such as part of a RCT, whereas effectiveness refers to its performance under 'real-world' conditions.	Suggest changing to efficacy
CEPI	25	25	Main techncial issues to be addressed	Unclear what is meant under appropriate circumstances	Suggest including an example of what is meant here
GSCF	25	25		It should be "efficacy" in the context of pre-authorisation	
ISPE	25	25	Main technical issues to be addressed	Effectiveness of medical products is done only during pos-authorization. I can't think an instances where it's determined per-authorization; or perhaps the authors' mean 'efficacy'?	Suggest changing to 'efficacy'
GSCF	27	27		Include self-treatment settings. Most non-prescription medicines are consumed in the absence of a healthcare practitioner	point-of-care or self-treatment settings
CEPI	29	29	Main techncial issues to be addressed	It can be argued that RWD is more commonly used in non-interventional studies compared to interventional studies.	Suggest including frequently instead of also
GSCF	31	32		Include self-treatable conditions	analyse the utilisation of an authorised medicine in routine medical practice or self-treatable conditions
Purpose Life Sciences	32	33	Main Technical Issue	Integrating clinical practice data is broader than just post-marketing safety data. Guidance should include all aspects of clinical care data	
PFMD	34	35		RWD and RWE can also be used to understand the patient-relevant context of care, for example the pathways that patients follow, the experience of care, the compliance with current medications, as well as the real-world outcomes achieved. This is important context for regulatory decisions.	The guidelines should reflect various use of RWD & RWE.
Health Action International	35	35	Main technical issues to be addressed	This reference is missing in the bibliography. If it is this paper, which we suspect: https://ascpt.onlinelibrary.wiley.com/doi/full/10.1002/cpt.2480 --> the authors are from Pfizer. ICH/EMA should reference a more objective source.	Replace reference with a more objective source.

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
Health Action International	36	42	Main technical issues to be addressed	Other challenges of RWD stem from ethical concerns around data collection practices and privacy. In addition to data validity, data representativeness is an issue for RWD.	Add 'and data collection practices and privacy' after data source characteristics in this sum up. Add 'data representativeness' after data validity in this sum up.
Purpose Life Sciences	36	42	Main Technical Issue	Important to clearly delinate the factors from each other (quality vs source) as mentioned above	
Purpose Life Sciences	36	44	Main Technical Issue	The predominant theme covered in this section is focused on retrospective data and analysis. Several groups, such as EORTC, are proposing a more blended approach towards randomized real-world evidence through designs such as trial-within-cohort approaches. This should be highlighted, as many of the challenges identified in existing guidance pertain to retrospective data alone.	
ISPE	36	40	Main technical issues to be addressed	There are many different RWD types than what listed in (e.g., …), many healthcare settings and different data source categories, thus suggest adding etc. after providing examples	RWD types (e.g., electronic health, …..patient-generated data etc.), healthcare settings (e.g., primary….conditions etc.), data source characteristics (e.g., purpose, …. Terminology etc.).
AESGP	38	40		To include sales data as a source for OTC medicines	
PFMD	38	38		In the RWD types, the paper calls in "Patient generated data". In the future ICH guidelines on RWD/RWE, we recommend to emphasize the importance of Patient Experience Data (PED) which provide information about aspects of patients' experiences that are most important to them. Real-World Data may provide information about patients' experiences with a disease or condition, but that does not mean the information collected is important and meaningful to patients. PED should be seen as part of the shifting paradigm in generating the totality of evidence to support the regulatory assessment of the Benefit/Risk balance of medicines. Ultimately using RWE benefits patients by expediting the drug development process and bringing medicines to patients faster while lowering their exposure to the potential risks associated with clinical investigations.	https://patientengagement.synapseconnect.org/initiatives/patient-engagement-patient-experience-data-fusion-project https://pemsuite.org/ped-navigator/
GSCF	38	40		To include data on source for OTC medicines	non-prescription medicines usage
ACRO	40	40	Main technical issues to be addressed	ACRO recommends adding in further detail on the challenges relating to levels of data quality and validity. This should include data completeness to allow comparability and data integrity to a level that is acceptable for use.	Add "(data completeness to allow comparability and data integrity to a level that is acceptable for use)" so text reads "levels of data quality (data completeness to allow comparability and data integrity to a level that is acceptable for use) and data validity"

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PFMD	41	41		"emphasised by distinct national/regional laws and regulations."	Add "or lack of …"
Health Action International	42	44	Main technical issues to be addressed	The diverse nature of RWD as characterised above, makes this case-by-case analysis crucial. RWD will also often not be the best source of data to answer certain questions.	Clarify that a case-by-case analysis of suitability of RWD is crucial given the diverse nature of RWD and its quality.
Purpose Life Sciences	42	44	Main Technical Issue	This is a key result - to neutralize RWD / RWE factors as a component of the review. Although all compound reviews are "case-by-case", ultimately the result of this guidance will have RWD / RWE characteristics neutral or equivalent for review to "traditional" data in its integrity and quality.	
IQVIA	42	44	Main technical issues to be addressed	The draft reflection paper accurately states, "The suitability of RWD to generate adequate evidence to support regulatory applications currently requires a case-by-case analysis, which may be driven by different criteria related to the aforementioned factors and depending on the research question(s)." However, it does not clearly tie these assessments as an increasingly important step in assessing study feasibility, as indicated in FDA's guidance document, "Considerations for the Use of Real-World Data and Real-World Evidence to Support Regulatory Decision-Making for Drug and Biological Products," which is available online at https://www.fda.gov/media/171667/download	IQVIA recommends inserting the following new sentence: "The evaluation of relevant real-world data sources or databases is an important step in the design of a study and in evaluating a study's feasibility," prior to the sentence starting in Line 42, "The suitability of RWD...."
ACRO	46	61	Main technical issues to be addressed	ACRO notes that there is also lack of clarity regarding RWD in a clinical trial setting. RWD can come from both patient reported outcomes and wearables where data is collected in a trial setting in the Real World. The FDA documentation is not clear. In Guidance "Submitting Documents Using Real-World Data and Real-World Evidence to FDA for Drug and Biological Products", section IV B discusses study designs using RWD to collect trial endpoints, but section IV C describes RWD (inter alia) as "data collected from digital health technologies in non-research settings". We recommend that clarification is added to this document to confirm that RWD can be collected in a research setting providing it is in the Real World.	Addition of the need for consistency in approach with respect to RWD in a clinical trial setting.
PFMD	46	46		We are calling for the definition of CIOMS draft report on the Real-World Data and Real-World Evidence in regulatory decision making:"RWD as health-related data collected from patients or caregivers in routine clinical practice without a study-determined intervention. RWD can come from a wide variety of sources such as healthcare claims and health records, registries, patient reported outcomes, digital tools/wearables/mobile devices. Data collected can include clinical and economic outcomes, patient-reported outcomes (PROs), such as disease activity and quality of life (QoL), and resource utilisation".	we believe the definition should reflect PED considerations when discussing RWD and RWE.

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CEPI	47	53	Main techncial issues to be addressed	The reference to the FDA framework is missing	Include reference
ISPE	47	53	Main technical issues to be addressed	Missing reference after the Framework for FDA	Add reference
GSCF	48	49		To our knowledge, the first mention of this within public FDA documents was in "final guidance on submitting documents utilising RWD/RWE in 2022". Please check before attributing to the 2018 framework.	
AESGP	50	53		To our knowledge, the first mention of this within public FDA documents was in "final guidance on submitting documents utilising RWD/RWE in 2022". Please check before attributing to the 2018 framework.	
GSCF	50	56		The definitions of RWE by FDA and EU are not just inconsistent and fairly generic but also lacking clarity on which approaches could be considered acceptable by competent authorities for regulatory decision-making. Therefore, the call in Line 87 to "inform the assessment of RWD and RWE for regulatory purposes" is especially important. In Europe, different organisations including the EMA and the Big Data Steering Group aim to establish a sustainable RWE framework. In that context, the differences or overlaps of 'big data' and 'real world data' are not fully clear. Therefore, the aim for converging terminology for RWE should also clarify if and how different but analogous terms (like big data) are in or out of scope of the agreed nomenclature.	
GSCF	50	53		To our knowledge, the first mention of this within public FDA documents was in "final guidance on submitting documents utilising RWD/RWE in 2022". Please check before attributing to the 2018 framework.	

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Kaat Van Delm, KU Leuven	54	57		It may be interesting to also refer to the following authoritative (from a legal point of view) source, which states a similar definition: European Commission, §2(5) Proposal for a Council Regulation on a Framework of Measures for Ensuring the Supply of Crisis-Relevant Medical Countermeasures in the Event of a Public Health Emergency at Union Level," Pub. L. No. COM(2021) 577 final (2021)(*): "'real-world data' means data relating to patient health status or the delivery of healthcare from sources other than clinical trials.'" (*)the European Commission issued many other definitions in other documents. I took the liberty of suggesting the one which - on the basis of my current, ongoing research - is the most coherent definition from a legal point of view (i.e. in light of the applicable EU legal framework and pre-existing other definitions embedded therein), which to my pleasant surprise is also most aligned with the definition already included by you in this ICH Reflection Paper.	
ISPE	58	59	Main technical issues to be addressed	Fully agree with the authors' claim that RWD and RWE are often used inconsistently and interchangeably	
Kaat Van Delm, KU Leuven	58	59		The language used for defining RWD and RWE has far-reaching consequences regarding the scope of the concepts. Therefore, at least regarding their scope, the definitions are not similar (even though the wording may appear similar). Hence the suggestion to alter this sentence.	"Although the wording used in these definitions (and others such as from learned societies, other regulators, etc.) may appear similar, the resulting scope of the definitions varies significantly depending on the terminology used. In addition, in practice, the terms RWD and RWE are still used inconsistently and interchangeably [...]"
Purpose Life Sciences	61	61	Main Technical Issue	and researchers	
GSCF	63	63		also include reclassification (Rx to OTC switches)	in medicines approval and reclassification
Purpose Life Sciences	64	65	Main Technical Issue	There is no mention of prospective vs retrospecitve sources. This may be an element separate from the source as a characteristic	
GSCF	64	64		Include the following publication: How can real-world evidence aid decision making during the life cycle of nonprescription medicines? Emese Csoke, Sabine Landes, Matthew J Francis, Larry Ma, Denise Teotico Pohlhaus, Christelle Anquez-Traxler Clin Transl Sci . 2022 Jan;15(1):43-54. doi: 10.1111/cts.13129. Epub 2021 Nov 15.	Csoke et al., 2022

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Health Action International	69	71	Main technical issues to be addressed	Effectiveness testing happens before market-authorisation. Using RWE (essentially observational data) for effectiveness studies poses serious risks and should not replace RCT study designs.	Acknowledge the limitations of RWE in effectiveness testing.
Purpose Life Sciences	71	73	Main Technical Issue	"in-depth analysis of the actual contribution of RWE to regulatory decision-making" - Is this an analysis of the diversity of RWE or the processes of requlators? i.e. to consider the scope of this guidance - what the guidance cannot change at the regulators. Acceptance of new study designs with imbedded principles for data quality and integrity	
ISPE	71	71	Main technical issues to be addressed	“effectiveness is more nascent”	Effectiveness data based on RWD is generated more frequently and its adoption into product label needs to be more common. Some of the pushback from regulators (from my perspective) has been due to RWD data quality and validity as described within this paper
Purpose Life Sciences	72	73	Main Technical Issue	There have been several peer-reviewed publications, recently, (e.g. DOI 10.1002/cpt.2272 by Duke) which attempt to synthesize the filing types and perceived reaction to evidence types which should be considered.	
CEPI	78	81	Main techncial issues to be addressed	Considering the G7 100 days mission to reducing the impact of future pandemics by making diagnostics, therapeutics and vaccines available within 100 days of a public health emergency being declared, harmonization of terminology and convergence of guidance related to RWE/RWD is critical to prepare and address future pandemics	Suggest including a statement to 100DM and global preparedness
Health Action International	79	81	Main technical issues to be addressed	This sentence seems incomplete. How will common understanding of terminology on RWD/RWE drive access to innovative medicines? For other harmonisation efforts of ICH, it is not proven that they drive access to innovative medicines, but, due to the industry-driven nature of ICH, that there's actually a risk of watering down standards (see: https://www.sciencedirect.com/science/article/abs/pii/S0277953602003398?via%3Dihub).	Critically revise this sentence, as the link between better terminology and access to innovative medicines is unclear, also back this statement with (objective) evidence.
PFMD	79	81		"However, reaching common understanding at international level on terminology and how RWD/RWE can reduce gaps in knowledge for new and existing medicines, and would help drive forward access to innovative medicines"	The wording does not read correctly. Need for re-write

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
IQVIA	79	81	Main technical issues to be addressed	The paragraph begins by stating that national/regional laws and regulations can present challenges to convergence and harmonisation efforts, however, the second sentence does not discuss this challenge, rather, it make a vague, general statement about reducing gaps in knowledge.	IQVIA suggests either rewriting the second sentence to explain how national laws/regulations can present challenges to hamonisation efforts, or omitting the paragraph.
AESGP	84	87		General comments- Good quality data is a "must need" for quality output related to RWD/RWE. It would be important if attention could be brought to also structure of exiting sources of data eg including pain scores at stipulated visits for biobank data or data completeness.	
Purpose Life Sciences	84	85	Objectives	Format of protocols cannot be so prescriptive that it limits study design. Flexibility is required to include new research methods / study design. Suggest leaning on research methodologies and principles to inform options.	
GSCF	84	87		General comments- Good quality data is a "must need" for quality output related to RWD/RWE. It would be important if attention could be brought to also structure of exiting sources of data eg including pain scores at stipulated visits for biobank data or data completeness.	
ISPE	84	85	Objectives and potential benefits	Fully support the need to have a standardized protocol/report templates for submission to regulatory agencies	Suggest that depending on the data source, more than one template may be needed
Purpose Life Sciences	85	86	Objectives	Format of study results throughout the lifecycle? Suggest RWE be reported outside a CSR?	
Purpose Life Sciences	86	87	Objectives	Registration - a process different than the current? Suggest making updates to current registration process to incorporate new requirements.	
Purpose Life Sciences	86	87	Objectives	With respect to registration, guidance would be appreciated on the level and detail of up-front work with data assets prior to formalization of registration and protocol development. Activation early is important for transparency, but necessitates making some unverifiable assumptions on the data of eventual choice. For example, FDA guidance suggests early discussion with the agency prior to acquisition of data, but this can create a catch-22, wherein data cannot be decided until it has been explored, which in turn means the data has been a-priori assessed which can bias data choice	

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
Purpose Life Sciences	86	87	Objectives	While registration is an important part of the protocol process, it is important to consider the challenge from a sponsor perspective with regards to anticipating the availability of data elements a-priori. For example, when considering analytical methods for missing data, approaches may vary with respect to the proportion of missingness. Could it transpire that sponsors leave insufficiently specific protocols to account of unanticipated data challenges which cannot be known a-priori?	
European Hematology Association (EHA)	87	87		While EHA recognizes that this reflection paper is a start to show how much we need to systematize and harmonize on this topic, we do not consider that the paper by itself, gives specific enough direction to be able to "Inform the assessment of RWD and RWE for regulatory purposes".	
PFMD	87	87		The objectives of this reflection Paper could also be to outline the rationale for RWE/RWD to inform the various steps in the regulatory process, setting the benchmark for the potential uses of RWE/RWD across the regulatory lifecycle.	
Purpose Life Sciences	87	87	Objectives	This should be the priority objective	
Health Action International	88	89	Objectives and potential benefits	But RWE won't always be suited to do this. Add as aim: with strong safeguards to protect standards of evidence in regulatory decision-making.	Add to this sentence: 'with strong safeguards to protect standards of evidence in regulatory decision-making.'
PFMD	90	92	Table	We welcome the report's emphasis on the importance of transparency in research processes to improve trust, credibility, and reliability in the evidence generated. At PFMD, we firmly believe in the importance of the patient community receiving feedback on how their data are generated, analyzed, and utilized in decision-making. Patients should have access to the data following decisions, and PED/RWD should be made publicly available to improve the understanding of diseases and their impact, inform treatment decisions, and/or reduce duplication of effort.	This should be further emaphasised in the final guidelines
AESGP	91	91		We would suggest to add in the different types of medicines(Rx, non-Rx, herbals classified as medicines) to the first bullet of Deliverables, due to the importance of the differences in data sources of medicines and increase the granularity of the definition of RWD/RWE	
AESGP	91	91		As mentionned in the litterature, routinely collected data typically excludes non-Rx medicines as they are generally not prescribed nor reimbursed and therefore terminology related to RWD sources must include collected and generated data in real world settings. (https://ascpt.onlinelibrary.wiley.com/doi/full/10.1111/cts.13129)	

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
AESGP	91	91		Principles should include the various types of medicines (Rx, non-Rx, herbals classified as medicines, etc.) to ensure fit for purpose of content of protocols and reports	
Health Action International	91	91	Objectives and potential benefits.	Location: Table after line 91, second row, objective. Bullet 1 "agree on common principles…". Comment: Because ICH is largely industry driven, the EMA should ensure the possibility to come up with additional criteria and requirements to ensure use of RWE will never water down standards of evidence.	
Health Action International	91	91	Objectives and potential benefits	Location: Table after line 91, second row, objective. Bullet 1 "agree on common principles…". Comment: The use of RWD/RWE cannot be seen independently from how it has been analysed and processed. Especially if advanced data analytics are used, there are some risks. Therefore, emphasise its protocols for RWD/RWE as well as the methods of analysis for evidence generation.	Include 'reporting of data analysis, including analyses using machine learning, in protocols.'
Health Action International	91	91	Objectives and potential benefits	Location: Table after line 91, second row, objective. Bullet 2 "promote transparency by…". Comment: Now transparency seems voluntary. Transparency efforts are usually only effective when they are compulsory. Public transparency on use of RWD should be an obligation, through registration in publicly available and accessible registries.	Rephrase objective to make obligatory transparency the aim.
European Hematology Association (EHA)	91	91		Table under line 91, point 2.: "RWD/RWE protocol and report format, and study of transparency", 3rd column: "Objective": EHA considers that what the field really needs is an OMOP type format for RWD, to allow interoperability. We note that this would have to be specific to different disease types but could be a distillation of RCT data points for the same indication. Ideally data heterogeneity would also have to be modelled to allow for heterogeneity and missing datapoints to be accounted for.	
Evidera	91	92	Table page 3, row 1	Deliverables is unclear as regards granularity: is ICH planning to recommend a minimal level of granularity for RWD? Needs might depend on the research question and RWE application.	We recommend to include consultation of RWE professionals and data source representatives in this workstream.
Evidera	91	92	Table page 3, row 2	Where it reads "Initiate work after the first guideline reaches Step 4 of the ICH Procedure". This is the first time 'guideline' is mentioned, it is unclear which guideline is the reflection paper referring to when ir reads 'after the first guideline reaches ...'.	Please clarify which guideline is the 'first guideline' referring to. Apparently, the header of the first column should be "Guideline".
PFMD	91	92	Table	Row 1: "RWD/RWE terminology, metadata and assessment principles": The objective is missing the rationale for considering RWE/RWD across the regulatory lifecycle – such as providing context to other forms of data such as RCT data	To be added

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
IFCT	91	91		Time to next treatment or death as a candidate surrogate endpoint for overall survival	To challenge rwPFS
Purpose Life Sciences	91	91	Objectives	Highly support a Dec 2023 submission date (not 2024)	
GSCF	91	91		We would suggest to add in the different types of medicines(Rx, non-Rx, herbals classified as medicines) to the first bullet of Deliverables, due to the importance of the differences in data sources of medicines and increase the granularity of the definition of RWD/RWE	
GSCF	91	91		As mentionned in the litterature, routinely collected data typically excludes non-Rx medicines as they are generally not prescribed nor reimbursed and therefore terminology related to RWD sources must include collected and generated data in real world settings. Emese Csoke, Sabine Landes, Matthew J Francis, Larry Ma, Denise Teotico Pohlhaus, Christelle Anquez-Traxler Clin Transl Sci . 2022 Jan;15(1):43-54. doi: 10.1111/cts.13129. Epub 2021 Nov 15.	
GSCF	91	91		Principles should include the various types of medicines (Rx, non-prescription medicines, etc.) to ensure fit for purpose of content of protocols and reports	
GSCF	91	92		(table point 2): Given the presence of radically different design types (e.g. prospective vs retrospective, interventional vs non-interventional, randomized vs observational, secondary data vs. primary data), consider allowing for different protocol formats for different RWE design types.	
IQVIA	91	96	Main technical issues to be addressed	The use of widely accepted health care data standards (e.g., HL7, FHIR) is considered a best practice when constructing RWD data sets that will be used to generate RWE. However, the draft reflection paper does not discuss issues related to data standardization or ontology harmonization in any detail. The proposed content under Topic 1 will help to address some related issues, through building a common understanding of types of RWD and metadata. Line 96 lists "data standards for RWD" as a possible topic for subsequent ICH guidelines. IQVIA believes that further elaboration would be helpful to clarify what kinds of standardized approaches will be considered under Topic 1 and what will be left for a potential future project. Similarly, data quality is not discussed in any significant detail under either Topic 1 or 2 but is listed as a priority topic for a potential future project on Line 95.	IQVIA suggests describing in greater detail what ICH means by "Data standards for RWD" and "data quality," in order to clarify what aspects of these priority topics would be inbounds for the current project vs. potential future projects. In the context of data quality, it would be important to discuss the differences between managing primary collection vs. secondary of RWD.

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
ISPE	91	97	Table (2)	(1) Consider harmonization of code/platform/data sharing expectations in regulatory submissions; (2) There is ongoing debate about the level of detail a protocol needs to be at for the study to be considered pre-registered, and whether feasibility and early validity checks can happen before or after registration of a protocol. (3) It is not clear that principles for assessing fitness of data for purpose when planning a regulatory submission will be part of the discussion of the format and structure of protocols. Many assessments of fitness of data involve feasibility checks, prior to being able to create and register a protocol	When working on topic 2, consider discussion of the timing of study registration relative to the stage of protocol development
PFMD	94	94		Subsequent ICH guidelines: to also consider Data Exchange across juridictions or data sources	
Health Action International	95	97	Objectives and potential benefits	Something that should not be overlooked is best practices for data collection. During data collection one has a lot of influence on data quality. By adding a focus on high-quality data collection, many challenges later on can be avoided, and the utility of RWD will be increased. This approach, although not easy, better addresses the root cause of poor-quality data and is therefore potent in reaching high standards of RWE. Also, there are many exploitative data collection practices, which should be actively combatted and avoided for RWE in medicines regulation.	Include: "best practices for data collection" as priority.
Evidera	95	97	Objectives and potential benefits	Are these priorities in the context of RWE/RWD for regulatory decision-making?	
European Hematology Association (EHA)	96	96		EHA notes that defining quality levels of evidence (as in the levels 1-5 defined for “evidence based medicine”) would help with interoperability.	Revise line 96 to read: Data standards for RWD, including defining quality levels of evidence
CEPI	96	96	Main techncial issues to be addressed	Data standards for RWD. This statement is too broad, and it would be good to define what the minimal data quality standards for regulators to accept RWE results for labeling/licensing etc. would be	Define minimum data standards acceptable to regulators

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
AESGP	97	97		We do understand that this Reflection Paper will focus on RWD terminology and protocol/report format, we are of the opinion that the following topics are still missing and have not been addressed yet are: (i) Harmonisation of raw data submitted to Agencies/Health Authorities, especially to EMA (harmonised requirements would be of high value, such as FDA requirements regarding CDISC, SDTM submission); (ii) Harmonisation of electronic records (such as the 21 CFR Part 11 by FDA).	We would recommend to add these 2 points among the priorities for subsequent ICH Reflection Paper so that these topics should be addressed. Please find hereafter the proposed changes: This Reflection Paper represents the initial step of an incremental approach towards harmonisation of regulatory RWE guidance. The following topics could be considered priorities for subsequent ICH guidelines, based on stakeholders' feedback: . Best practices for data quality (including recommendation for harmonised electronic records for RWE collection); . Data standards for RWD (including recommendation for harmonised raw data submission); . Appropriate application of study designs and data analyses.
GSCF	97	97	3	We do understand that this Reflection Paper will focus on RWD terminology and protocol/report format, we are of the opinion that the following topics are still missing and have not been addressed yet are: (i) Harmonisation of raw data submitted to Agencies/Health Authorities, especially to EMA (harmonised requirements would be of high value, such as FDA requirements regarding CDISC, SDTM submission); (ii) Harmonisation of electronic records (such as the 21 CFR Part 11 by FDA).	We would recommend to add these 2 points among the priorities for subsequent ICH Reflection Paper so that these topics should be addressed. Please find hereafter the proposed changes: This Reflection Paper represents the initial step of an incremental approach towards harmonisation of regulatory RWE guidance. The following topics could be considered priorities for subsequent ICH guidelines, based on stakeholders' feedback: . Best practices for data quality (including recommendation for harmonised electronic records for RWE collection); . Data standards for RWD (including recommendation for harmonised raw data submission); . Appropriate application of study designs and data analyses.
Evidera	98	154	Important considerations	"Whether there is consistency or not in the estimates of the effect of the drug from different sources can help decide whether an effect is real or not." from "Pharmacoepidemiology / edited by Brian L. Strom, Stephen E. Kimmel, Sean Hennessy. Sixth edition." and also mentioned in 'The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) Guide on Methodological Standards in Pharmacoepidemiology (Revision 11)'	Consider adding a paragraph or a subsection on the importance of accruing consistent RWE from diverse sources of RWD to support regulatory decision making.
European Hematology Association (EHA)	99	108		Participation of stakeholders should also be looking for articulating the different RWD/RWE requirements depending on the intent of use e.g. Regulatory, HTA, Payers, Public Health, etc.	

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
CEPI	107	108	Important considerations	It is unclear which Concept paper and Business plan is being referred to.	Suggest explaining both documents
ISPE	107	107	Stakeholders and consultation	It's not immediately clear what the "Concept Paper" and "Business Plan" refer to	Suggest explaining
GSCF	110	110		Page 6/FDA (Use of Real-World Evidence to Support Regulatory Decision-Making for Medical Devices): As use of RWE is also increasing in development and registration of medical devices and considering development of drug/device combination products, there should also be measures to try achieving convergence of terminology for RWD and RWE beyond medicinal products, especially when it comes to data created by AI-powered software (SaMD) which might also be used in RCTs.	This proposal will aim to benefit all types of medicinal and medical device or relevant combination products at any stage of their lifecycle, i.e., …
PFMD	111	115		The reflection paper is missing the important link with HTA bodies who would also use RWE/RWD presented to regulators as part of their assessment into a health technology. It is important that there is an effort to reduce duplication and provide guidance that allows for the generation and use of RWD/RWE across multiple assessment points beyond regulators.	This should be elaborated in the final guideline
Purpose Life Sciences	111	111	Important Considerations	The reference to post-authorization efficacy studies (PAES) is critical. Present guidance is largely focused on procedural elements of submission, but does not speak to topics of quality and data type. For example, existing guidance by EMA (EMEA-H-19984/03) makes no reference of "real-world data/evidence" or any variations thereof. Understandably, developing PAES amongst a prospective cohort may very well be reviewed entirely differently to those collected from routinely monitored medical record systems	
ACRO	112	115	Important considerations	ACRO notes that Health Technology Assessment (HTA) bodies are not explicitly mentioned as a stakeholder benefiting from ICH harmonization. In order to represent the medicinal product lifecycle, ACRO recommends explicitly including HTA bodies as a stakeholder.	Add HTA bodies as important stakeholders.
PFMD	113	113		Welcome the call for patient Advocacy Groups : Incorporating the patient's voice, priorities, and experiences in developing PED, and RWD/E is critical to ensure representative data and well-informed decisions. Patients should also be involved in all aspects of selection, study design, generation, and analysis of RWD when PED is considered to ensure the best patient representation throughout any process where PED is utilized for decisions. Patient Engagement Data (PED) is not separate from patient engagement (PE); the two enable effective decision-making for better patient outcomes.	This should be further emaphasised in the final guidelines

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
CEPI	113	114	Benefits of ICH harmonisation	International organizations such as WHO that use RWD/RWE for PQ purposes are critical stakeholders	Suggest Including international organizations (e.g., WHO, PAHO etc.)
GSCF	113	113		Medicines manufacturers (such as the ones manufacturing non-prescription medicines) are a part of the medicines industry along with medicines developers	medicines manufacturers / pharmaceuticals and consumer health industry
GSCF	116	117		The aim to support integration of RWE, rather than just RWD, into submissions for medicines approval and decision-making will depend on the competent authorities' willingness to agree on clear definitions and formats how applicants may generate RWE that could be considered acceptable by competent authorities. However, as this may remain a tentative outcome, the aim should also be to support integration of RWD into respective submissions.	By supporting the delivery of a regulatory system able to integrate RWD and RWE in a more harmonised way 116 into submissions for medicines approval and decision-making.
Health Action International	117	119	Important considerations	All efforts should be centred around protecting standards of evidence. By extensively analysing risks of use of low-quality or biased data and installing comprehensive safeguards to prevent deterioration of evidence standards. Again, the link between harmonisation of RWE terminology and access to innovative treatments is again not clear.	Emphasise importance of protecting standards of evidence.
GSCF	119	119		RWE has great potential to support Rx-to-OTC switches too	, help support innovative or new Rx-to OTC-Switches and Non-prescription medicines life cycle management.
ACRO	120	148	Important considerations	ACRO supports the integration of existing and upcoming guidances in the development process in order to minimize duplication. As noted in the paper, the evolution of trial methodology and data collection is enabling an interoperability and integration of clinical research and clinical care. ACRO and ACRO members are providing thought leadership in decentralized clinical trials through the ACRO DCT Toolkit. Digital endpoints and EMR/EHRs have been identified as one of the key elements defining decentralized trials. As such, ACRO would recommend that the interface considers initiatives relating to DCTs and modern clinical trial design in addition to those listed. This would also include ICH E6(R3) annex 2 contents relating to decentralized elements	Addition of Guidance relating to Decentralized Clinical Trials.
CEPI	124	133	Interface with existing and upcoming guidances	Reference to the different initiatives is missing.	Include references.

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
IQVIA	126	127	Interface	For external comparator studies, FDA uses the words "externally controlled trial" while the EMA uses "external comparator studies." These are important concepts in need of clarification.	IQVIA suggests including terms for external comparator study designs in the listing of terms for harmonization under Topic #1.
European Hematology Association (EHA)	134	140		The wording of this section indicates that 'RWD' can be 'used to plan and design safety studies' for marketing authorisation purposes and associated legal frameworks, whereas the potential of 'RWE can be broadened to include assessing the effectiveness of medicines and analysing utilisation of 140 marketed medicines administered in routine medical practice'. EHA believes that this section requires further explanation as it is not clear with the existing wording. For patients in nearly all developed public healthcare systems globally (EU, Canda, UK, Australia, New Zealand), access to medicines and medical devices will be depending on both marketing authorisation and health technology assessment. Standard of care data will likely be required for both purposes, but, as stated in our second comment above (Row 17), it might be more future-proof to base terminology of such data on its intended purpose with the MA (safety) and/or HTA (efficacy, value) framework. There might be a further application framework, e.g. for private healthcare providers, but their incentives might not be aligned with that of public healthcare systems (e.g. efficiency mechanisms/cost savings) and thus might require yet another set of data definitions.	Consider re-wording this section to account for the comment made.
GSCF	140	140		reflect non-prescription medicines when patients take them in absence of HCPs	administered in routine medical practice and in self-treatment settings.
IQVIA	145	146	Important considerations	The paper mentions "…proposed guideline 2…" but it's not clear what that term is referring to.	Please clarify what is meant by "guideline 2"
IQVIA	147	148	Important considerations	The subsection on Interfaces with existing and upcoming guidelines states, "Efforts will be needed to ensure that duplications are minimized...," however, this work of integrating the new terminologies and reporting formats into existing and upcoming guidelines is imperative and should be identified as a distinct objective under Topic #1. Planning this work in from the start will help clarify the scope of the harmonization project itself and provide direction to work streams still underway, such as ICH M14 (Guideline on "General principles on plan, design, and analysis of pharmacoepidemiological studies that utilize real-world data for safety assessment of medicines"). The ICH M14 guideline is intended to include its own glossary of terms, which should be consistent with those generated through the harmonization project.	IQVIA recommends emphasizing the importance of integrating the work products of this harmonization project with those of any existing or upcoming ICH guidelines by elevating it as a distinct objective under Topic #1.
ISPE	147	148	Interface with existing and upcoming guidance	Commend the authors for surveying all ongoing projects, would suggest to continually revisit as new guidelines are often published	

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
ACRO	149	150	Important considerations	ACRO notes the list of suggested expertise required in development of the initiative. ACRO would recommend inclusion of relevant technology, real world evidence and data source expertise. This is because techniques for data collection and evaluation are evolving rapidly and it would be important to ensure outputs from this initiative are "future-proof". In conclusion, thank you for this opportunity to provide feedback, and please do not hesitate to contact ACRO (knoonan@acrohealth.org) if we can provide additional information or answer any questions.	Add "technology" and "RWE professionals" and "data source experts" so text reads "(e.g., pharmacoepidemiology, biostatistics, regulatory science, technology, RWE professionals, data source experts)"
IQVIA	149	150	Important considerations	In addition to involving various subject matter experts from regulatory authorities and medicines developers, it would be valuable to include informaticists and data analysts from organizations that specialize in collecting, transforming, managing, and analyzing real-world data on behalf of study sponsors, such as those belonging to the Real-World Evidence Alliance.	IQVIA recommends involving real-world informaticists, data analysts, and AI experts who work directly with biopharmaceutical sponsors and health authorities in the harmonisation project.
Purpose Life Sciences	155	161	Annex	While we appreciate the global reach of the documentation and suggested reference materials, there are under-represented regions which should be considered. For example, there are no references to Southern American countries. The Brazilian regulatory group (Anvisa) are formulating formalized guidance and working with federal programs to enable RWD-RWE learnings. International consortia covering regions such as sub-Saharan Africa such as International Epidemiology Databases to Evaluate AIDS (IeDEA) and existing multi-country surveillance studies such as the AU-3S programme are of significance to the development of ICH guidance which can be utilized appropriately in local contexts.	
IQVIA	155	161	Annex	Including DKMA (Denmark) is appropriate, however, other Nordic countries have similar approaches regarding the use of RWD/RWE.	IQVIA recommends examining regulatory initiatives and guidance from all of the Nordic countries, including not only Denmark, but also Finland, Sweden, and Norway.
Purpose Life Sciences	161	161	Annex	Some of the cited documentation refers more to the data acquisition process and governance regarding data acquisition, rather than interpretation of findings from such data. As such, this may increase the scope of the document beyond the original intent.	
IQVIA	161	161	Annex	The Annex appropriate lists two EC initiatives related to metadata: the Metadata List and the Metadata Catalogue of RWD Sources. Please note that these ambitious projects are ongoing and will evolve even as the ICH harmonization project gets underway.	IQVIA recommends that ICH reach out to the project team responsible for these metadata projects for the latest updates. For more information, contact Ontologies@IQVIA.com.
ISPE	161	162	Annex Table	Move CIOMS to a separate bullet, which currently is under ISPE/ISPOR	Move a bullet point

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
Kaat Van Delm, KU Leuven	161	161		Although it is clear that the table does not aim to be exhaustive, it could be considered to also mention the EHDS when referring to Darwin EU, as Darwin EU 'will act as a pathfinder for the proposed European Health Data Space (EHDS), and will ultimately connect to the EHDS services" (EMA, https://www.ema.europa.eu/en/news/darwin-eur-welcomes-first-data-partners). As many readers may be more familiar with the EHDS initiative than with the Darwin EU initiative, this reference may give them a better understanding on the importance of the topic.	
IQVIA	162	209	Bibliography	Given the long list of documents cited or otherwise used in preparation of the reflection paper, it would be helpful if the bibliography is numbered.	Please number the works listed in the bibliography.
ISPE	161		Table (worldwide)	Consider the REPEAT Initiative paper about what is needed for reproducible and robust evidence	Wang SV, Sreedhara SK, Schneeweiss S; REPEAT Initiative. Reproducibility of real-world evidence studies using clinical practice data to inform regulatory and coverage decisions. Nat Commun. 2022 Aug 31;13(1):5126.