Response document for consultation on MHRA draft guidance on randomised controlled trials generating real-world evidence to support regulatory decisions

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Please indicate if you are responding to this consultation as an individual or on behalf of an organisation Individual ☐ Organisation ☒

1. General comments

Stakeholder number (To be completed by MHRA)	General comment (if any)	Outcome (if applicable) (To be completed by MHRA)
	Could MHRA clarify whether data sources (e.g. administrative claims) or evidence from non-UK countries/regions or populations are within scope of this guidance?	
	EHR and registries were referred to in the beginning of the guidance as sources of RWD. Can the MHRA confirm whether RWD is limited to these sources or can others be considered?	
	The MHRA should be commended for developing this guidance and for encouraging sponsors to explore opportunities for utilizing RWD in support of regulatory decision-making.	
	We recommend referencing the following in the guidance: International Society for Pharmacoepidemiology. Guidelines for Good Pharmacoepidemiology Practices (GPP). Pharmacoepidemiol Drug Saf. 2016;25:2-10. Wang SV, Schneeweiss S, Berger ML, et al. Reporting to Improve Reproducibility and Facilitate Validity Assessment for Healthcare Database Studies V1.0 [published correction appears in Pharmacoepidemiol Drug Saf. 2017 Dec;26(12):1570] Pharmacoepidemiol Drug Saf. 2017;26(9):1018-1032.	

2. Specific comments on text

Title and section number of the relevant text	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	Outcome (To be completed by MHRA)
Intro - 3	Comment: The definition of RWE needs to be brought forward into this section. Also the definition does not mention safety, while efficacy is not very relevant in the real-world setting. Proposed change (if any): "When such data ~~is~~ are analysed to make inferences about the effects of different treatments, the information produced is similarly called real-world evidence (RWE). While extensively used for monitoring the safety and performance of drugs and devices after approval, RWE is utilised much less frequently when it comes to demonstrating the ~~efficacy~~safety or effectiveness of an intervention to gain an initial approval or an extension of an indication for an existing product."	
Intro - 4	Comment: Reasons for using pre-existing data sources are more than just increasing speed and reducing cost of development programmes. Proposed change (if any): "Use of such pre-existing data sources has the potential for increasing the speed and reducing the cost of development programmes, which ~~would see~~could result in effective medications being approved more quickly, or even programmes which were previously thought to be unfeasible becoming feasible (e.g., studies of rare diseases, rarely occurring outcomes or drug-drug interactions), with the consequent benefit to public health. In addition, RWE can have utility in certain scenarios such as collecting data on patients receiving innovative transformative treatments to inform benefit-risk assessments."	
Intro - 5	Comment: Why are no other databases mentioned specifically, other than CPRD?	

	Proposed change (if any) Suggest mentioning other examples or remove reference to CPRD specifically. If reference remains, also add “CPRD (Clinical Practice Research Datalink)”	
Intro - 6	Comment: It would be helpful to understand what background is needed in order to discuss use of RWD in prospective RCTs with MHRA - is a full protocol necessary? Or a briefing document? Proposed change (if any): State what specific information is needed to discuss use of RWD for specific regulatory decisions with MHRA. For example, when bringing innovative medicines to patients, there is a need for designing RCTs that can better capture the totality of clinical evidence.	
Intro - 9	Comment: More clarity around what is meant by ‘robust data quality’ is needed. In addition, the decision is based on benefit-risk, which should be referenced. Proposed change (if any): Clarify what specific documentation on what specific data attributes are needed to justify robust data quality. Is CPRD data, for example, acceptable without such justification because it is curated? In addition, we propose the following text change: “Running a randomised trial using a RWD source can generate RWE to support a regulatory benefit-risk decision.”	
Scope – 14, 15	Comment: “non-interventional trial” seems incorrect word choice in the context of a study that is purely observational, based on the definitions provided immediately following. Trial implies some kind of intervention on the part of the investigator or protocol. Proposed change (if any): “non-interventional ~~trial~~study”	
Scope - 16	Comment: Type A can still apply under certain other conditions that may initially be regarded as other types	

	Proposed change (if any): A sentence should be added to clarify this	
Scope - 16	Comment : "....if this off-label use is established practice and supported by sufficient published evidence and/or guidelines." Some off-label use may be widespread even if not supported published evidence or guidelines; the current statement implies off-label use that is not documented or published in "insufficient" sources would not be acceptable. Suggest that the availability and rigor of the data be evaluated on its own merits, or that more flexibility be connoted given most pediatric, oncology, and other rare diseases may never be able to achieve this threshold. Proposed change (if any): "...if this off-label use is established practice and preferably supported by sufficient published evidence and/or guidelines, however each situation may need to be evaluated in light of data availability and clinical circumstances."	
Scope - 17	Comment: Are all clinical outcome assessments (COAs) and PROs acceptable or only those via wearable devices? The definitions of RWE and RWD may not be complete enough as this is unclear. Proposed change (if any): "Other sources of RWD include patient reported data through through Clinical Outcome Assessments (COAs), PROs or data collected via wearable devices."	
Scope - 17	Comment: The document defines EHRs as "structured, digital collections of clinician-recorded patient level medical data." This implies that information derived from unstructured data (e.g., natural language processing of free text clinical notes) is not considered RWD. Proposed change (if any): Clarify whether information derived from unstructured portions of the EHR (e.g., natural	

	language processing of free text clinical notes) is considered RWD, as part of the EHR, for the purposes of this document. "Sources of RWD include electronic healthcare records (EHR) defined as ~~structured,~~ digital collections of clinician-recorded patient level medical data, encompassing structured and unstructured (e.g., free-text notes) fields."	
Scope - 19	Comment: "Conventional trial" may not be the best terminology. Since the guidance refers to aspects from PRECIS-2, "explanatory" may be a better term. Proposed change (if any): Suggest changing to "explanatory" throughout	
Scope - 20	Comment: The inference here is that the main difference is about selection. This may be true but the last sentence describing that a conventional (explanatory) clinical trial can be run using a broad study population whilst a RWD trial uses a narrow study population isn't clear. RCTs typically define a specific population, often with limited pre-existing disease or other concomitant medications, to test their intervention in the most likely population they would see an effect to evaluate whether the drug can work, while at the same time minimising potential risk to patients. The cost of scaling a proper RCT to broad populations may not be feasible. Whereas the additional costs for fluctuating the size of RWE might be negligible. Proposed change (if any): The key message should be clarified.	
Scope - 22	Comment: A better definition is available for pragmatic trials; the definition of explanatory trial given is not adequate to distinguish the two types. Proposed change (if any): The distinction between pragmatic and explanatory trials should be clarified: Pragmatic clinical trials (PCTs), which leverage existing clinical infrastructure, are designed to test interventions in everyday clinical real world settings to maximize therapeutic applicability	

	and generalizability. Explanatory trials study patients in highly controlled experimental settings and typically measure efficacy in phase II-III. Both types of trials randomize patients to treatments where feasible. Pragmatic trials examine effectiveness.	
Simple trials - 23	Comment: What is described is what most consider a pragmatic trial. Simple trials typically have limited visits and data collection but still lean toward explanatory RCTs. Pragmatic randomized trials are typically conducted in routine medical practices, and not necessarily in clinical trial sites. Proposed change (if any): Terminology should be clarified. Pragmatic trials should be referred to instead of simple trials for this section heading or a description of large simple trials should be added instead.	
Simple trials - 25	Comment: While it is true that patients are not blinded, HCPs may be. Such studies may still be subject to information bias (and other biases). Proposed change (if any): Blinding to minimise information bias is only one way to minimise bias. The degree of bias can greatly depend on the setting and outcomes being assessed. The potential for other biases should be clarified. Reference: Christian JB, Brouwer ES, Girman CJ, Bennett D, Davis KJ, Dreyer NA. Masking in Pragmatic Trials: Who, What and When to Blind. Ther Innov & Reg Sci 2020; doi.org/10.1177/2168479019843129	
Simple trials - 26	Comment: This is the first explicit mention of safety. Proposed change (if any): The MHRA guidance should discuss safety throughout, not just efficacy and effectiveness.	
Simple trials - 27	Comment: A reference is made to key endpoints, but it is also about key variables. Proposed change (if any): “Running a trial that would be acceptable for regulatory purposes in this way would be	

	possible if the key endpoints and key variables (e.g. confounding variables) necessary to make the regulatory decision are routinely collected in the database…"	
Simple trials - 28	Comment: Blinding using RWD does not seem feasible in most scenarios, and may simply create an additional burden. Blinding may also be undertaken for outcome assessment without blinding all involved in the trial. Blinding of outcome assessment in the case of subjective outcomes that may be influenced by knowledge of treatment assignment can minimize bias. Reference: Christian JB, Brouwer ES, Girman CJ, Bennett D, Davis KJ, Dreyer NA. Masking in Pragmatic Trials: Who, What and When to Blind. Ther Innov & Reg Sci 2020; doi.org/10.1177/2168479019843129 Proposed change (if any): "This would represent an additional burden to patients above their routine care and may not be feasible, as specific trial medication would need to be received rather than an open prescription, but if feasible it can be done while avoiding the need for any additional deviations from routine."	
Safety monitoring - 31	Comment: IMP is not defined. Proposed change (if any): Suggest defining IMP in full at first use.	
Safety monitoring	Comment: AE reporting, even if just limited to SUSARS tend to defeat the advantages of real world studies. Proposed change (if any): Clarify exactly when SUSARs need to be reported for marketed products in real world studies, especially if already in labelling.	
Safety monitoring	Comment: If the RWD source is based in one setting, such as primary care, there may be a delay in knowledge of adverse events reported in other settings such as secondary care. How would that be accounted for in reporting timelines? From time first entered into the data source?	

	Proposed change (if any): Clarification of time zero in reporting timelines for RWD is required.	
Quality of data	Comment: The areas of consideration are broader than just quality focused and should be refined. Proposed change (if any): The following elements focus on data quality: · extractability of relevant fields in various RWD sources databases · defining, reporting and presenting of quality measures (e.g., data completeness, variable reliability, variable validity, sources of variables, data provenance) details to be captured with respect to cohort selection when generating RWE · additional analyses that need to be done to generate RWE (i.e., sensitivity analyses)?	
Examples - 49	Comment: Can more guidance be given as to what would need to be shown by a feasibility study prior to undertaking a RWD trial? Proposed change (if any): State more specifically what a feasibility study might need to demonstrate - e.g., capture of endpoint, exposure and key confounding variables, and define 'adequate' capture.	
Examples - 50	Comment: Please provide more clarification regarding what constitutes acceptable size, coverage and representativeness of samples drawn from RWD sources. Since RWD is collected in routine practice and not following a schedule of measurements, explain what is meant by 'using the value closest to <6 months> or another imputation technique is not an adequate replacement if a value is not generally recorded at 6 months'. This section also seems disproportionately heavy given the issue. Proposed change (if any): Following an ITT approach it seems reasonable to analyze closest values or use imputation, rather than excluding patients due to missing data. Sensitivity analyses can be used to understand the robustness of the results to varying time windows. Would also suggest summarising this section further.	

Examples - 50-51	Comment: Endpoints or technology validation is not defined and it is unclear what MHRA would expect. Proposed change (if any): Clarify whether validation would involve comparison of captured endpoints to charts or electronic health records, or assessing measurement properties of a PRO. Clarify when regulatory approval would need to be sought for such validation.	
Examples - 52	Comment: Additional safety monitoring should be considered even if there is more than “minimal confidence the existing knowledge of the safety profile could be carried across.” Proposed change (if any): Clarify what that additional monitoring and reporting might entail given the real world setting. Change “minimal” to “uncertain” or “reduced. “Returning to the example at the start of this section, if the new population is significantly removed from the existing licensed population such that there is ~~minimal~~ uncertain confidence the existing knowledge of the safety profile could be carried across, additional safety monitoring and reporting outside of routine practice could be required.”	

Please add more rows if needed

3. Would you be happy for the MHRA to contact you in order to discuss your responses in further detail?

Yes ☒ No ☐

4. The MHRA may publish consultation responses. Do you want your response to remain confidential?

Yes ☐ Partially* ☐ No ☒

*If partially, please indicate which parts you wish to remain confidential. In line with the Freedom of Information Act 2000, if we receive a request for disclosure of the information we will take full account of your explanation, but we cannot give an assurance that confidentiality can be maintained in all circumstances. Responses to consultation will not normally be released under FOI until the regulatory process is complete.

Responses can be continued onto a separate page if required. This form should be returned by email rwe@mhra.gov.uk to arrive by **11 December 2020.** Contributions received after that date cannot be included in the exercise.