## Response document for consultation on MHRA draft guidance on randomised controlled trials generating real-world evidence to support regulatory decisions

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| About You Name: |
| Position: |
| Organisation: Faculty of Pharmaceutical Medicine |
| Email: |
| Please indicate if you are responding to this consultation as an individual or on behalf of an organisation Individual  Organisation X |
| General comments  | Stakeholder number  (To be completed by MHRA) | General comment (if any) | Outcome (if applicable)  (To be completed by MHRA) | | --- | --- | --- | |  | There may be slightly different interpretations / definitions for RWD and RWE. Consider adding definitions for these.  Decentralized approaches may be very attractive for patients (eg oncology, or general RCT participants, visiting a local lab for routine blood safety monitoring and telemedicine (where possible) with the tertiary oncology/trial centre. This may increase the enrolment and diversity of patient populations. A caveat is the differing data standards in the peripheral sites. |  | |
| 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) | | --- | --- | --- | | 1. Introduction, section 6 | Comment: 1. We welcome this for early dialogue if it can be flexible and agreed upon as an evidence-based path forward for efficacy and [cost] effectiveness in discussion with NICE also, even if not fully binding  2. MHRA may want to consider creating a route to do this at least in tandem with other major ICH region(s), especially Europe. |  | | 1. Introduction, section 9 | Comment: (On “data quality is robust and the trial well designed.”). Encouraging to see and should be welcomed. Agree with and note importance of this being part of a robust data set in a well-designed study. Also note the importance of large simple randomised population studies with wide inclusion criteria such as RECOVERY, that would not have been designed by a pharma sponsor, but by virtue of its scale is valid. |  | | 1. Introduction, section 10 | Comment: (On “…..nothing is completely ruled out on principle, including the investigation of new products.”). This is supported |  | | 2. Scope and definitions, section 13 | Comment: (On “….interventional clinical trials of investigational medicinal products (“CTIMPs”)……”). Could MHRA consider widening the scope and include also devices and surgical procedures into the scope? This current scope and ensuing text seems to rule out any trial comparing drug treatment with alternative treatments like medical devices or operative procedures, which for many classes of drugs may be relevant information.  Eg new/recently introduced anti-Parkinson drug (class) vs deep brain stimulation, just to name one of many thinkable possibilities that would greatly benefit from RWE design. |  | | 2. Scope and definitions, section 15 bullet 4 | Comment: (On ” No diagnostic or monitoring procedures are applied to the patients included in the study, other than those which are ordinarily applied….”). This strict wording is risky, as for trials it may be relevant to add a small portion of non-routine and riskless minimal-burden data collections like periodic questionnaire data during the trial (eg SF-36/EQ-5D). That then the trial immediately reverts to the "interventional trial" group is a missed opportunity. |  | | 2. Scope and definitions, section 17 | Comment: (On “RWD is defined as routinely collected data relating to patient health status or delivery of health care. Sources of RWD include electronic healthcare records (EHR) defined as structured, digital collections of clinician-recorded patient level medical data. These include, but are not limited to, primary and secondary care records, disease registries, and administrative data on births and deaths. Other sources of RWD include patient reported data via wearable devices.”). Wording here is slightly contradictory in stating that there is nothing non routine in the data collection, but there would be an acceptance of RWD provided by wearables which may not be normal clinical care. Although we support this, there may have to be an acknowledgment that the first part of the statement is the purest definition, but that they would accept minimal additional non-invasive / intrusive data collection that COULD have an effect on patient behaviour because they knew they were being monitored by a wearable. (eg maybe they would increase their activity if they knew their step counts were being recorded?) |  | | 2. Scope and definitions, section 19 | Comment: (On “A conventional trial would also generally involve study specific visits which require attendance at a centre.”). Agree, but in this case, there could be study and regular clinic visits, plus RWD in between? Should be clarified. |  | | 2. Scope and definitions, section 20 | Comment: (On “……while a trial using a RWD source could choose to specify a narrow study population.”). This is unhelpful - although it is a definition, the implication is that this is their guidance, whereas the reverse could equally be true and the data would still be valid if well managed and design controlled for. |  | | 2. Scope and definitions, section 21 | Comment: (On “Such a trial produces RWE and is in the scope of this guidance.”). Agree and seems to reinforce the comment on Para 19. |  | | 3.1 Simple trials, section 25 | Comment: (On “…..experience would not be altered by being in the trial….”). Agree, but see and note point about wearables above. |  | | 3.1 Simple trials, section 27 | Comment: There are many more ways bias from the open-label setting could ensue than via "subjective" endpoints, e.g. cross-overs between trial treatments and to non-trial treatments (some potentially unknown to the triallist e.g. OTC meds), behavioural changes (in)directly confounding the "hard" outcomes of interest etc.  It would be interesting to see MHRA advice how research would need to be designed to be acceptable by regulators, which in the vast majority of indications only accept as valid data from blinded trials. Especially if these confounders would not normally be systematically be recorded in the RWE setting and thus remain unmeasured. |  | | 3.2 Hybrid trials, section 29 | Comment: (On “This could be done remotely via  electronic data capture but may require specific study visits.”). Agree and expect this should be explicitly stated as in scope. |  | | 3.3 Safety monitoring section 32 | Comment: (On “The extent of safety monitoring needed would be considered on a case by case basis, but a minimum standard would still be required.”). Agree and expect this should be seen as being in scope and RCT formal evaluation being augmented by RWD data collection. The definition of “standard”is unclear: is it the standard for the site, or standard of care or the standard for regulatory trials? It would be very helpful if MHRA could state what it considers to be the “minimum standard”. |  | | 3.4 Regulatory acceptability of RWD-based trials; section 33 | Comment: (On “….all the evidence generated by the trial would be classified as RWE.”). Agree but need to define the specific Q that RWE is looking to answer that may not be possible as part of a traditional trial visit. Hence the activity levels, biometric monitoring etc can all be included and v valuable RWE between visits if prospectively defined and ring fenced so as not to be unduly influenced by clinic visits or RCT procedures. |  | | 3.4 Regulatory acceptability of RWD-based trials; section 34 | Comment: See the earlier comment under 27. This section should be one of the most crucial elements of this entire guidance and the current text dos not provide relevant guidance and seems unhelpful. |  | | 4. Clinical trial authorisation considerations, section 37 | Comment: (on: “there is some flexibility around the requirements for safety reporting”). Agree this makes sense based upon the known profile and the risk of its use in a new or existing population, as such the IMP itself is not the only consideration and the AE reporting requirements and expectations should be agreed up front to avoid misaligned expectations.  Hence general agreement to Para 38 as well, but there should be a general understanding that AE follow up should not be seen as the exclusive remit of clinical trials, as it should also occur in clinical practice (even though it does not always occur). |  | | 5. Quality of the data, section 40 bullet 4 | Comment: Also note the lack of interoperability between different health systems in the UK (England / Wales / Scotland) and the likelihood that sponsors will try to run multicentric, multinational studies. As such there should be some discussion of the means to cross reference and manage the data between different health systems' standards of care and normal schedules of visits as well as a separate RWD database for other data collection if used. |  | | 5. Quality of the data, section 40 bullet 6 | Comment: (on: “……link the database to additional data sources…..”) Agree and as above - some GxP guidance or validation best practice should be included here rather than just asking the question. |  | | 5. Quality of the data, section 40 bullet 7 | Comment: Again, these should be statements of expectation that there should be privacy and security as well as QA rather than asking what the policy the sponsor will apply is. |  | | 5. Quality of the data, section 40 bullet 8 | Comment: Would be very helpful to have actual guidance here instead of a question. Will CRA/sponsor monitor inspection of source data be required? |  | | 5. Quality of the data, section 45 | Comment: Agree to have these and could simplify this guidance by taking out all the questions as above. |  | | 5. Quality of the data, section 45 bullet 2 | Comment: (on “….these must be appropriately validated to ensure that…..”) Validated is a multi-interpretable term (also in the precise context of the topic, RWD) where IT experts have an entirely different understanding of what this means than scientists. Suggest that MHRA explains in the guidance what validation it requires in the places where this word is used. |  | | 5. Quality of the data, section 45 bullet 3 | Comment: (on “Data quality assurance checks should be conducted with the ability to audit all data values……”.) Or does MHRA require this? See earlier comment, strongly advisable what degree of data monitoring /inspection by CRAs / data managers MHRA expects in order to consider data credible. |  | | 6. Examples, section 46 bullet 3 | Comment: This is actually not a simple straightforward example at all. This add-on treatment comparison vs standard of care is, in many TAs (oncology, epilepsy, to name a few), the principal design of the prelicensing registrational trials.  And once registered and proven superior, can no longer ethically be tested against "standard of care"- it WILL be the (new) standard of care.  Consider removing this example. |  | | 6. Examples, section 47 | Comment: (On “……and it would not be expected that significant additional knowledge would be gained on safety from the new trial…..”). This is very much against an important objective of RWD trials (also stated earlier): that in clinical practice with much larger exposures than in the pre-licensing trials (and less selected patients etc etc), the knowledge about the safety profile may certainly and importantly be improved. |  | | 6. Examples, section 47 | Comment: (On “As the endpoints are objective an open-label trial is acceptable.”). Agree - however if there was a risk to the intervention that was offset by the benefits of treating the more severe indication (by reducing inherent risk), the risk benefit would be positive. If the risk of the milder indication were lower, but the risks of the intervention the same, this is a different B:R equation. As such this is not so black and white and should be acknowledged as such here and not just in para 52 |  | | 6. Examples, section 49 | Comment: (On “The completeness and validity of the recording of potential endpoints in EHR should not be assumed.”): Would be good if MHRA could give guidance on what evidence of data completeness it requires to assess the acceptability of the trial, ideally with a threshold specification for minimum levels |  | | 6. Examples, section 50 | Comment: (On: “it would be necessary to at least perform a hybrid trial by scheduling blood pressure measurements outside of the patient’s routine care at the particular time-points of interest.”). Disagree as the use of a digital BP could be done as RWD without additional scheduling, (as noted in next sentence and Para 51) even though its use may alter behaviour to some extent, it should still be seen as a valid use of RWD.  As such this seems somewhat contradictory.  Agree strongly with validation need. |  | | 6. Examples, section 50 | Comment: (On “….any technology used must be validated.”). It is unclear what “validated” here means. If this could imply authorized for marketing, consider replacing (or adding) by CE-marked, or approved for marketing by [name of UK device authority]. |  | | 6. Examples, section 53 | Comment: (On: “However, there is a large middle-ground before this becomes the case.”). This sentence, plus "many" in the previous sentence, is discrepant with earlier text that no additional data can be taken over and above ordinary data collection (see the earlier comment on 15 bullet 4). That wording allows no flexibility or middle ground in that wording.  This (apparent) discrepancy should be clarified. |  | | 6. Examples, section 49 | Comment: |  | | 7. Advice | Comment: Overall the Faculty is supportive of this approach and intent, but we think the construction may be improved by resolving contradictions. Also it reads a bit as a discussion document and may be more written as clear guidance. |  |   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 X 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.