Medicines & Healthcare products
Regulatory Agency

MHRA draft guideline on the use of external control arms based on real-world data to support regulatory decisions

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Contents

Overview

1. This guideline is for sponsors planning a clinical trial which will include a real-world data (RWD) external control arm (ECA), with the intention of using the trial to support a regulatory decision.

2. This is one of a series of guidelines on the use of RWD for supporting regulatory decisions and sits alongside the MHRA guideline on randomised controlled trials using real-world data to support regulatory decisions[1]. For a general introduction to the series, see 'MHRA Guidance on the use of Real-World Data in Clinical Studies to Support Regulatory Decisions'.[2]

3. Sponsors interested in the use of RWD in their development programmes are encouraged to engage with the MHRA for further advice on specific proposals.[3]

[1] https://www.gov.uk/government/publications/mhra-guidance-on-the-use-of-real-world-data-in-clinical-studies-to-support-regulatory-decisions/mhra-guideline-on-randomised-controlled-trials-using-real-world-data-to-support-regulatory-decisions
[2] https://www.gov.uk/government/publications/mhra-guidance-on-the-use-of-real-world-data-in-clinical-studies-to-support-regulatory-decisions/mhra-guidance-on-the-use-of-real-world-data-in-clinical-studies-to-support-regulatory-decisions
[3] https://www.gov.uk/guidance/medicines-get-scientific-advice-from-mhra

Scope

4. This guideline provides points to consider when planning a clinical trial which will include a RWD ECA, with the intention of using the trial to support a regulatory decision.

5. The guideline does not aim to cover every possible scenario but rather highlights key principles that should be taken into account when considering the use of RWD ECAs.

6. Points covered include the circumstances under which the use of RWD ECAs might be most appropriate, and clinical trial design and analysis considerations with an emphasis on minimising bias. The guideline addresses the use of a RWD ECA as the sole control for a non-randomised/single-arm trial, and the use of a RWD ECA to augment a randomised internal control arm.

7. Specific methods for incorporating RWD ECAs into a trial will not be discussed, nor will specific approaches to statistical analysis. Further advice can be sought from MHRA experts by requesting a scientific advice meeting as outlined in the Advice section of this guideline.

8. While the guideline is specifically aimed at sponsors planning to use RWD ECAs, many of the general principles would be relevant for external controls drawn from other sources, such as previously completed clinical trials. MHRA is also interested in engaging with sponsors who have proposals for using such data sources.

9. For requirements relating to RWD database quality and suitability for use and to inspection please see 'MHRA Guidance on the use of Real-World Data in Clinical Studies to Support Regulatory Decisions'[4].

10. The guideline does not cover: 1) other types of studies that could be run using RWD such as randomised controlled trials mainly using RWD sources for selecting, randomising or following up participants, or observational studies; 2) natural history studies used to give context to clinical trial results; 3) wider issues such as disease and product specific requirements; 4) the use of synthetic or virtual control arms comprising simulated patient data, nor does it cover in silico trials (e.g. virtual clinical trials where computer modelling and simulation is used instead of patients).

[4] https://www.gov.uk/government/publications/mhra-guidance-on-the-use-of-real-world-data-in-clinical-studies-to-support-regulatory-decisions/mhra-guidance-on-the-use-of-real-world-data-in-clinical-studies-to-support-regulatory-decisions

General principles and regulatory acceptability of designs depending on external RWD controls

11. A trial with an ECA is not the preferred clinical trial design as a fully powered randomised controlled trial (RCT) should be used if possible. However, any regulatory decision is based upon the data presented in the submission, and if those data are sufficiently convincing then a positive decision can be reached, even if alternative approaches may have ideally been preferred. Therefore, there is no general scenario where the use of RWD external controls is explicitly ruled out.

12. Given the inherent limitations of drawing inferences from a trial with an ECA due to potential bias, this approach is more likely to be accepted in situations where conducting an adequately powered randomised trial is not ethical or feasible, would result in a significant delay, or where the effect of the intervention is expected to be large enough to allow interpretation of the study results despite potential bias.

13. A randomised trial with an internal control arm which is augmented with external controls is preferred to a single arm trial with only an external control, as such a design allows for better control of potential biases.

Types of studies and points to consider

14. For the purposes of this guideline, RWD is defined as data relating to patient health status or delivery of health care collected outside of a clinical study. Sources of RWD include electronic healthcare records (EHR) defined as structured, digital collections of patient level medical data, primary and secondary care records, disease registries, and administrative data on births and deaths. Other sources of RWD include patient reported outcomes (PRO) data and data which are collected outside of a clinical study setting such as through wearable devices, specialised/secure websites, or tablets.

15. A RWD ECA comprises patient level data collected outside of a clinical study which will be used as a control or part of a control arm to estimate the comparative efficacy and safety of an intervention being studied in a clinical trial.

16. One of the key factors in determining the strength of evidence provided by the comparison to the RWD ECA is the quality and fitness for purpose of the external data source. Therefore, the choice of external data source should be robustly justified (see 'MHRA Guidance on the use of Real-World Data in Clinical Studies to Support Regulatory Decisions'[5]).

17. Given that there is no randomisation or blinding, it will be necessary to address issues relating to bias when using an ECA.

Types of studies

Single arm clinical trial with an external RWD control arm

18. For trials where an internal randomised control arm would be considered infeasible or unethical (e.g., in severe diseases where there is no effective standard of care, or in a rare disease with limited numbers of patients), a RWD ECA offers the possibility of providing comparative evidence not available from a single-arm trial.

19. No specific therapeutic area is intrinsically more suited to the use of an ECA than another, but certain fields such as rare or severe diseases with unmet clinical need may rely more on evidence from single-arm trials and therefore may benefit from the inclusion of an external RWD control arm.

Randomised controlled clinical trial augmented with RWD external control arm

20. An underpowered RCT may be able to borrow strength from an external control arm to improve its power.

21. An RCT augmented by an ECA may provide sufficient power for additional secondary endpoints.

22. An ECA may be used to assess the extent to which participants or practitioners modify their behaviour due to an awareness of being observed (e.g., the Hawthorne effect) which can affect the generalisability of clinical research. Analysing the ECA may help to quantify the

magnitude of this issue by examining how patients and practitioners act when not under observation.

Points to Consider

Expectations for protocol and pre-specification

23. The protocol for the trial should be of the same standard, style and level of detail as would be expected for a traditional RCT intended to support a regulatory submission, including pre-specification of the objectives, data to be collected, primary and secondary endpoints and analysis methods.

24. The protocol must provide robust justification for selection of the data sources included and methods for constructing the external control arm, including the ability to match the populations based on the inclusion/exclusion criteria of the trial. The justification should consider both the data quality and the suitability of the data for the intended comparison.

25. Appropriate study design and analysis methods must be pre-specified in the protocol (see next section). Potential sources of bias should be identified and discussed in the protocol, along with details of how these will be explored and addressed.

26. It is important that the protocol is finalised before enrolment begins e.g. the design and analysis methods should be sufficiently specified in the protocol and there should be no amendments planned to fill in important missing details. Ideally the protocol should encompass all plans for the trial including the use of a pre-specified RWD ECA.

27. Without sufficient pre-specification there could be issues related to multiplicity. For example, if a trial is analysed without an external control, and after the analysis an external control is added, this may inflate type I error if it is not clear which was the primary analysis. Therefore, it must be clear what the pre-specified primary analysis for the trial is.

28. There may be circumstances where a RWD ECA is added to a trial after it has begun. If there is a legitimate reason for the addition of an ECA to a trial and this was not pre-specified (e.g., an appropriate dataset for an ECA was not available at the time of commencing a single arm trial) appropriate amendments to the protocol should be made along with justification for why it has been added. This should also be reflected in the clinical study report and any regulatory applications. Scientific advice may be considered before important changes are made to an ongoing protocol.

29. The ECA can be either prospective, based on data collected contemporaneously to the clinical trial, or a historical control based on existing data. The timing of the collection of the ECA should be specified in the protocol. This guideline is not prescriptive as to the timing of the data collection, however concurrent data collection is considered the ideal. If historical controls are used, more recent data are preferable, all other things being equal.

Addressing bias – trial design considerations

30. When including a RWD ECA there are a number of potential biases that need to be mitigated so far as is possible.

31. In order to minimise bias in comparisons between groups the ECA should be as similar as possible to the single-arm trial in all important factors. These include, but may not be limited to, the patient population (inclusion/exclusion criteria), important baseline characteristics, variables and outcomes collected, and the timing of key efficacy assessments. It is important that these details are available in sufficient granularity in the data chosen for the ECA.

32. Ideally, the source of RWD should be identified before the clinical trial starts, as it may then be possible to design the trial to align with certain aspects of the external dataset.

33. The estimand(s) – i.e., what is to be estimated – in the ECA should be aligned with the estimand(s) of the single-arm trial, or at least, data collected in the ECA should allow estimation of the effect of interest in the trial. In particular, the five estimand attributes as described in ICH E9(R1)[6] should be considered when choosing an ECA: population, intervention, variable, other intercurrent events and population-level summary.

34. Potential differences between populations included in the RWD source and the intended population for the target scientific question of interest of the clinical trial should be considered and minimised wherever possible. The population attribute introduced in the estimand framework, as described in ICH E9(R1)[7], can be used in such discussions.

35. Since the comparisons are not randomised it will be important to consider all the factors that could differ between the single-arm trial and the ECA. These include the time period when the data were collected and whether the methods of diagnosis, staging, treatment, etc. have changed over time. To minimise these issues, as noted previously, use of concurrent external controls, rather than historical external controls, is generally preferable, and if historical controls are used more recent data are preferable, all other things being equal.

36. Intercurrent events with the potential to bias the estimated effect of the intervention, and the strategies that will be used to address them, should be considered at the design stage. Intercurrent events should be defined and handled in the same way for the trial and ECAs. A RWD source in which the data needed to ascertain and/or address intercurrent events are unavailable or of low quality is therefore unlikely to be a suitable dataset for an ECA.

37. When considering the possible ECA or RWD source, it is important to fully characterise the treatments given, including the main intervention under investigation, rescue medication and other treatments used. The treatment attribute of the estimand framework can be helpful in this exercise.

38. If the ECA is identified after the clinical trial has finished, it will be important to adequately justify the choice of external control and how it was chosen from amongst all possible other data sources. In particular, as the results of the clinical trial are already known, it will be important to demonstrate that the decision was not result driven, i.e., a dataset with particularly poor results was chosen for comparison when another dataset exists for the same population with better results. NICE's RWE framework[8] provides guidance on how to systematically/transparently select data sources.

[6] https://www.ema.europa.eu/en/documents/scientific-guideline/ich-e9-r1-addendum-estimands-and-sensitivity-analysis-clinical-trials-guideline-statistical-principles-clinical-trials-step-5_en.pdf
[7] https://www.ema.europa.eu/en/documents/scientific-guideline/ich-e9-r1-addendum-estimands-and-sensitivity-analysis-clinical-trials-guideline-statistical-principles-clinical-trials-step-5_en.pdf
[8] https://www.nice.org.uk/corporate/ecd9/resources/nice-realworld-evidence-framework-pdf-1124020816837

39. Ideally, objective endpoints should be chosen for trials that will then be compared to external controls, as knowledge of the intervention received could have an effect on the assessment of subjective endpoints.

40. The index date or time zero (start of the observation period for assessing endpoints) as well as the definition of the follow-up period of the non-randomised ECA should be carefully chosen to align with the clinical trial as temporal differences in key dates between trial arms may lead to biased effect estimates. In a RWD ECA the index date may be determined in multiple ways. This is particularly relevant for interventions with multiple lines of therapy, where the patients in the ECA may meet the index date criteria at multiple different points in time. Defining key dates is even more complex for non-discrete or less readily identifiable events, or when no treatment is used in the ECA. Therefore, when defining key dates, the clinical context, eligibility criteria and data availability for both trial arms must be carefully considered to minimise bias.

41. The choice of the index date should exclude any period in which the outcome could not have occurred, known as “immortal time”. This period artificially extends survival time in the affected arm, leading to bias. The index date for the ECA should correspond to when patients could feasibly have started the intervention under investigation, and the consideration of which events prompt the choice of treatment is critical. Importantly, immortal time bias is just one type of time-related bias; selecting appropriate dates alone may not eliminate all sources of bias. Statistical techniques may be necessary at the analysis stage to account for residual bias.

Using RWD to augment a randomised internal control arm

42. An alternative to a fully external control arm would be a randomised trial with a small internal randomised control arm which is augmented with RWD to achieve a fully powered comparison.

43. The points from the previous section are relevant here too. In addition, it will be possible to see whether the results in the external dataset are similar to those of the randomised internal control. It will be difficult to justify the augmentation if the results are very different.

44. Consistency with the randomised internal control arm in terms of results provides some reassurance that the external dataset has been chosen appropriately. Because of this, a randomised trial with a small control arm which is augmented with external controls is preferred over a single arm trial with only an external control.

45. If this approach is being considered it will be important to pre-specify and justify how the external dataset will be incorporated into the analysis.

Addressing bias - analysis considerations

46. To avoid decisions driven by the knowledge of the accumulating data, it is important that the factors to be included in the analysis model are clearly pre-specified in the protocol and/or the statistical analysis plan before the data collection begins. This is particularly important in this setting where there is no blinding.

47. The precise method to be used for the analysis and the covariates to be included should be pre-specified and justified in the protocol.

48. It is however impossible to know whether all important factors that affect intervention assignment or outcome have been accounted for in the study design and analysis. Whilst

randomisation balances measured and unmeasured confounders, the same cannot be said for matching on a limited number of factors. Therefore, it remains possible that the unmeasured confounders will introduce some bias in the estimate of the effect of the intervention. Bearing this in mind, the results will need to be very convincing; especially in indications where conducting an RCT would be possible.

49. One potential approach for strengthening confidence in trials using a RWD external control is to replicate results using two or more separate control arms. Similarly, if a control arm is pooled from multiple datasets the results could also be presented separately for each data source. Concordance of estimates of the effects of an intervention when using ECA derived from different data sources (which include different underlying populations) may help address concerns around unmeasured confounding. Where analyses are carried out using multiple ECAs, these should be pre-specified, standardized, and should control for type I error.

50. The frequency and distribution of missing data in the ECA should be considered as extensive missingness can render an ECA unusable. Missing data imputation should be performed in alignment with the chosen estimand(s). Exclusion of participants with missing data from the ECA is likely to introduce bias and can change the interpretation or generalisability of results.

51. The results of hypothesis tests, p-values and other inferential statistics such as confidence intervals computed with the input of the ECA should be interpreted very carefully due to possible bias. It may not be possible to use them for regulatory decision making in the same way as would be done when using an RCT, e.g. simply observing a statistically significant result may not in itself provide confidence that there is truly an effect of the intervention.

52. Sensitivity and supplementary analyses may be useful in exploring possible sources of bias and robustness of assumptions made in comparisons using the ECA.

Example of scenarios, endpoints and designs

53. Noting the points above, an example (this is not the only possibility or source of RWD) of a suitable scenario for a trial using a RWD ECA based on a RWD registry would be:
    - A rare disease where it is not considered appropriate or possible to randomise patients to standard-of-care treatment, or when patient communities are averse to randomisation.
    - A registry is available currently following up patients with the disease receiving current standard of care relevant to the UK from which it is possible to access individual patient data.
    - An objective endpoint routinely and consistently collected in the registry is identified as being a suitable primary efficacy endpoint.
    - The overall body of data captured in the registry are of good quality and sufficiently describe the overall condition of patients as well as important prognostic characteristics.
    - The interventional trial is designed based on knowledge of the methodology used to collect data in the registry allowing the minimisation of systematic differences between the data sources.
    - It is anticipated that the effect of the trial intervention on the primary (and other) endpoints will be large enough that differences between patients receiving the intervention and control could not plausibly be attributed entirely to bias from known or unknown differences between the RWD controls and the internal trial population.

54. The design and analysis of the trial should result in a presentation of a treatment effect accounting for factors that may influence the patient outcomes. If the data-source for the RWD control is identified subsequent to the initiation of the single arm trial the difficulties in optimising the design to minimise differences between the data sources will be increased.

55. If a registry with sufficient concurrent controls is not available, historical controls could be used as an alternative, but this increases the issues relating to comparability.

56. If the difference in efficacy outcomes between the treatment and control groups is small and in the range of general variability of the outcome it could be difficult to be confident in a comparison to a RWD ECA even if a statistically significant result is presented.

57. Inclusion of even a small internal randomised comparator arm can alleviate some of the difficulties around interpretation as the comparison between data from the internal and external control groups provides additional information on the comparability of the data sources.

58. If there are sufficient patients and it is possible to randomise then the decision to use a RWD ECA would be more difficult to justify and uncertainties resulting from the non-randomised design would be more difficult to overlook in this scenario. In such circumstances an RCT is preferred.

Advice

59. This guideline lays out general principles and points to consider for sponsors considering using a RWD ECA but cannot be comprehensive. If advice beyond what is contained in this guideline would be of interest, please request a scientific advice meeting. A scientific advice meeting to

discuss your plans can include representatives with expertise in licensing, clinical trial approval, post-licensing studies, paediatric studies, medical devices, inspection and Electronic Healthcare Records as applicable.[9]

[9] https://www.gov.uk/guidance/medicines-get-scientific-advice-from-mhra