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Current and future challenges of innovative oncology drug development

RWE/RWD – hot topic!

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The views expressed in this presentation are my personal views and should not be understood or quoted as being made on behalf of or reflecting the position of the regulatory agency/agencies or organisations with which I am employed/affiliated.

Contents

1. The ICH-E10 view on external controls

- For several decades, the Randomised Controlled Trial (RCT) has been considered the gold standard for the generation of reliable data on the efficacy and safety of medicinal products and the ICH-E10 reflects this position.
- ICH-E10 states that "**inability to control bias is the major and well-recognized limitation of externally controlled trials and is sufficient in many cases to make the design unsuitable".**
- Given an **increasing interest** among drug developers to **replace** the control arm in RCTs with external controls based on RWE , the **question arises** whether and to what extent the considerations of ICH-E10 document might be overly cautious?
- Another issue is how **unmeasured confounding** in such scenarios could be better understood, minimised and quantified?

2. The problem of matching controls

- In a randomized clinical trial the treatment and control are **well balanced for both known and unknown characteristics** and are treated under the same conditions.
- With regards to the reliability of an external control group as a substitute for a control arm of an RCT, focus is often placed on the matching of patients and controls, to adjust for measured confounders.
- Numerous different procedures have been suggested, frequently requiring knowledge of the actual patients included in the test arm of the trial.
- This issue is raised in ICH-E10: “Any matching on selection criteria or adjustments made to account for population differences **should be specified prior to selection of the control** and performance of the study.”
- For an external control group to be acceptable for regulatory decisions, it should to be clear that outcomes in the test arm as well as the controls, were unknown when the external controls were selected.
- Furthermore, the decision to use an external control arm and match subjects to those in the experimental arm **should always be specified prospectively** to avoid any convenient selection of criteria retrospectively.

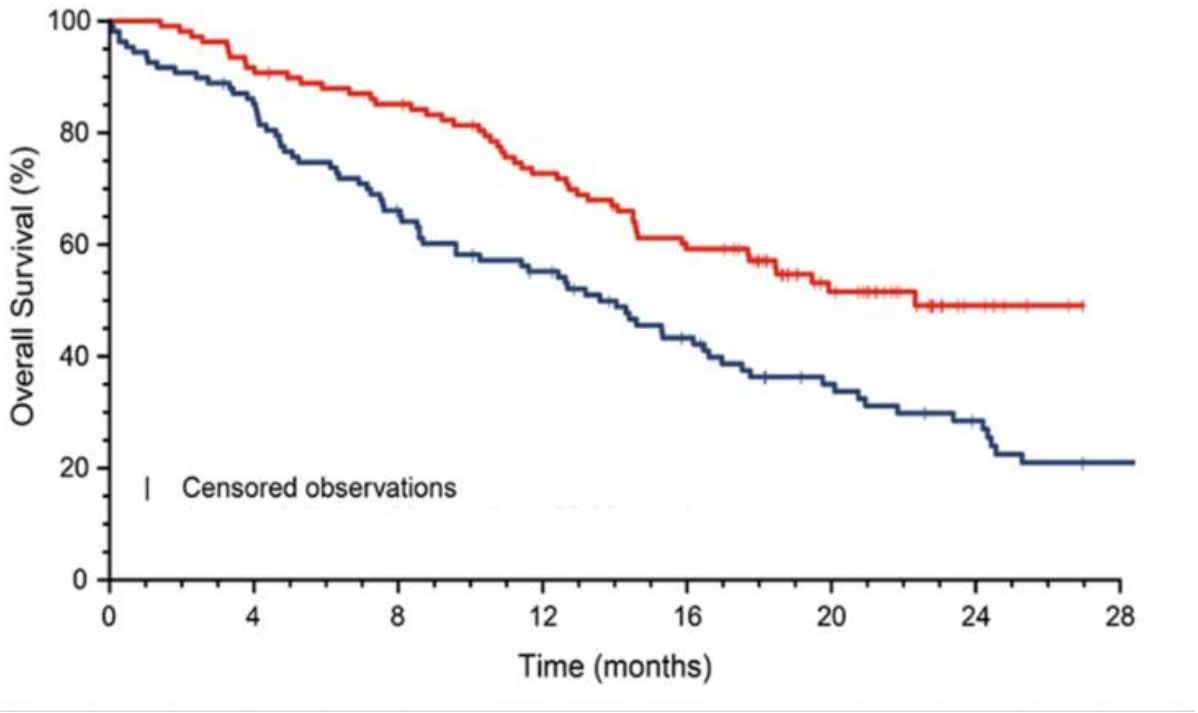
3. The broader issue of patient selection

- In addition to the concerns raised in **assessing measured confounders**, a further challenge is posed by the fact that patients by necessity enter the study and the external control group through **different mechanisms**.
- Clinical trials in oncology often have inclusion- and exclusion criteria such as "**likely to survive 3 months", "ECOG performance status 0-1", "no serious comorbidities" or "adequate organ functions".**
- On several occasions, it has been noted **that patients in the external control cohorts have started dying immediately** after the supposedly common baseline, while there is a lag period in the Kaplan-Meyer curve of the study arm; a hint of such unmeasured confounding.
- We have encountered examples, where **key data in the external control arm are missing** and would be have been an inclusion/exclusion criterion; a criterion for selection that may not be independent of prognosis.
- It is generally **not possible to obtain this key data retrospectively** from an external control arm, thus emphasizing the importance of prospective collection of high-quality data in carefully designed registries fit for the purpose.

3. The broader issue of patient selection (cont.)

- Further, experience-wise, prognostic data that are invariably strong regardless of study setting, and generally collected in interventional trials, such as **ECOG performance status or creatinine clearance,** may be missing in parts or the whole of the suggested external control dataset.
- Not only reasons for missingness may differ between test cohort and control; it may be unclear that **mechanisms for handling missing data**, including censoring rules, are similar in the external control and the test cohort.
- Transparency as to the comparability of the mechanism of inclusion, patient flow and data management are one of the key features of the RCT, which may be **difficult to achieve when the control is external**.
- Standardizing prospective data collection for outcome measures in patient registries is essential to expand its utility in generating valid RWE

3. The broader issue of patient selection (cont.)



4. The problem of determining a common baseline

- A **common baseline or "time zero" in both arms is crucial for time dependent endpoints** such as progression free- and overall survival.
- For instance, it has not always been clear if all patients in the study and in the external control dataset are **in progression at the time of initiation of therapy**.
- Notably the availability of a clinical trial may prompt initiation or switching of therapy. Information on the time from progression or another prognostic milestone in disease history, to the start of therapy, should be available for all patients in the test as well as control arm, if the latter is external.
- **Immortal time bias** refers to a period of cohort follow-up time during which, e.g. death or progression cannot occur due to the selection mechanism. In regulatory experience, this has proved an issue for Advanced Therapy Medicinal Products, e.g. where the time from an apheresis to medicinal product administration may be considerable.

5. The problem of measurement

- One of the major strengths of RCTs, is the use of **uniform methods for evaluation of treatment effect**.
- The fact that we sometimes see **considerable differences** between investigator and blinded independent review evaluation within the same trial, gives rise to concerns with respect to external controls.
- Issues may not only involve the use of similar criteria for evaluation (e.g., the RECIST criteria which are not systematically used in clinical practice), but also the time-schedules for evaluation.
- The use of any measurements that are liable to be impacted by center and setting is a **source of concern in the absence of randomization**. The directionality of bias due to such sources may vary and may not be clear.

6. The problem of post baseline treatment decisions, concomitant therapies and supportive care

- Another important aspect is the **background treatment and supportive care given in the test and control arm**, if not randomized.
- Different trends in disease management and outcome may be non-negligible. Further, we are aware that **geographical region may be a substantial effect modifier in RCT's**, and that this translates into an uncertainty with respect to external controls, as it indicates the dependence of outcomes on treatment setting.
- Specific issues include, e.g., the **frequency and timing of health-care visits**, **the use of supportive care such as antibiotics and haemato-poetic growth factors**, but also the principles of **post-baseline treatment decision-making** that are applied (e.g., when to perform a hematological stem cell transplantation). With regards to post-progression therapies, choice of treatment as well as available therapies may differ between settings.
- One might consider that the impact of such differences in standard of care may be reduced by the use of concurrent controls from the same centers as those of the test cohort; however, **that would raise concerns about the reasons why such patients were not included in the interventional trial running at the same center**, and consequently potential bias.

7. Achieving a better understanding of external controls and RWE

- Recognizing the above issues, the question arises as to what extent the impact of bias and confounding can be better understood and quantitated, as well as through what procedures it might be minimized.
- If external controls based on RWE/RWD are to be used more extensively in regulatory decision-making, their operational characteristics as research tools **need to be further validated.**
- One evident approach is the systematic comparison of control arms in RCT's with patients receiving the same anti-tumoral interventions in registries that might feed external control cohorts.
- Issues here include the generalizability of findings of such comparisons, both with respect to similar situations, as well as to different or over-lapping ones, where relevant confounders, such as when **treatment is initiated in relation to progression event**, or the key issues of post-baseline treatment decisions, may differ.

8. Conclusions

- It is <u>not</u>:
  - Easy
  - Black & white
- It <u>is</u>:
  - complicated
  - Linked with bias
  - Could have fatal consequences

“It should be noted that regulators are acting on behalf of a community including e.g. patients, clinicians, payers and HTAs. Therefore, the reliability of and trust in RWE/RWD data comparisons is not merely a matter between regulators and drug developers, but for the community at large.”

- Dr Sinan B Sarac & Dr Filip Josephson

Acknowledgement

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