



The use of external controls: To what extent can it currently be recommended?



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The use of external controls: To what extent can it currently be recommended?

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Why this paper?

- // Real world data becomes more and more easily available
 - // Mounting interest to use this data in drug development
 - // Some examples of successful NDAs with external controls
- // Hype to use external controls in drug development
 - // „do phase III with half the patients in half the time thanks to external/synthetic/historic controls“
 - // Little discussion on key methodological issues
 - // Randomization
 - // Blinding
 - // Other assumptions needed
- // Joint statement of industry, academic, and regulatory statisticians
 - // Should serve as reference for discussions with non-statisticians in industry, agencies, etc.



Outline of the paper

1. Introduction: Short overview on what is going on from regulatory perspective
2. Why is it important for statisticians to get engaged?
3. Sources of bias when using external controls
4. Adjustment for additional variability and bias
5. Benefits and risks of external controls
6. The importance of quality
7. Examples and applications
8. Conclusions



Introduction:

Short overview on what is going on from regulatory perspective

- // RCT is the established gold standard for medical research
- // increasing number of single arm studies, particularly in oncology
- // Not a new topic, see ICH E10 guideline on the choice of control group from 2000
- // View of health authorities on external controls is still evolving and they are open to a dialogue. BUT, health authorities
 - // will maintain their current high standard of evidence for approval
 - // will need to be convinced that this is not being eroded as a result of the use of external controls



2. Why is it important for statisticians to get engaged?

- // External controls are promoted as benefit to
 - // patients by speeding up access to new therapies and exposing less patients to a potentially suboptimal treatment
 - // the company by potentially speeding up drug development.
- // On the other hand, external control studies
 - // open up the risk for biased estimation of treatment effects
 - // may increase the risk of false positive or false negative results.
- // Statisticians have a unique set of skills and understanding of adequate methodology
 - // ensuring external control data has a sufficiently high level of quality.
 - // fully engaged in the use of external controls and supporting clinical teams to find the right applications of external data for the benefit of patients.



3. Sources of bias when using external controls

- // The paper discussed several types of biases and possible mitigation strategies
 - // Selection bias
 - // Calendar time bias
 - // Regional bias
 - // Assessment bias
 - // Different endpoint bias
 - // Immortal bias
 - // Retrospective selection bias
 - // Study bias
 - // Intercurrent event bias after study entry



4. Adjustment for additional variability and bias

- // External controls generate additional variability and bias leading to alpha inflation of unknown size.
- // Researchers have started to look into completed RCTs in a meta-analytic fashion, replacing the randomized control arm by an external control arm to see how well the arms match.
 - // E.g. MSc thesis of Marius Sieverding (<https://easychair.org/smart-program/ISCB2021/2021-07-19.html#talk:172983>)
- // Methods need to be developed to take the additional variability and bias identified from sets of historical studies into account and incorporate these insights into new studies and into decision making.
- // As with surrogate endpoint validation there are some limitations: validation is likely only to be valid for one specific treatment or class of treatments and extrapolation beyond this may be challenging and such a framework for external control may be bound to a specific indication, endpoint and source of external control.
- // More consideration needs to be given to understanding when meta-analysis approaches of existing studies can be extrapolated to a new study with external controls, how many studies are required to robustly generate such a relationship and how well relationships in a particular indication or class of drugs can be extrapolated to other scenarios.



5. Benefits and risks of external controls

- // Reduction in time and cost, for the benefit of patients as well as for the company
 - // However, 50% of patients is not equal to 50% cost or time

- // Patient's perspective and its potential ethical implications
 - // Patients are seldom at equipoise with respect to randomization to placebo

- // Risk for industry which is often underestimated when embarking on single-arm clinical trials
 - // Lack of fit of external control in the current treatment context
 - // Bias could lead to wrong conclusions at the end, to false investment or a delay of a whole development program
 - // This risk is not fully covered by a dynamic borrowing design as the consequence of a population mismatch would be an underpowered trial



6. The importance of quality

// Quality of data

// The outcome of any study can only be as good as the quality of its underlying data.

// Even more true for external controls, as the quality of data is beyond the control of the investigator.

// Quality of how we deal with sources of bias

// Additional efforts are needed in the interpretation of a study with an external control, including a thorough consideration of underlying sources of bias and their likely impact on conclusions.

// Transparency

// There is a critical need for transparency on the processes, assumptions, ...

// Patient level data of most clinical trials can be freely accessed by independent researchers as all major pharmaceutical companies have pledged to share data.

// However, RWD are typically not freely available and independent researchers might find it difficult if not impossible to reanalyze the data of a trial with external control.



7. Examples and applications

- // The paper list some examples under these headings
 - // Traditional: Designs using threshold crossing (e.g., oncology, contraceptives)
 - // Situations where randomized control is not feasible
 - // Designs with both randomized and external control
 - // External control studies in early development
 - // The role of frequentist hypothesis testing in studies with external controls
 - // More general considerations: What do we need?
 - // To achieve the goal of making drug development more efficient we should never forget that there are a broad range of options, tools and study designs available.
 - // Using external control studies is just one option, but in any particular situation it may not be the most effective choice to improve drug development.



8. Conclusions

- // RCTs are likely to remain the gold standard for generating clinical evidence
- // External control trials used in situations where RCTs are not feasible or not ethical.
- // Statisticians in industry, health authorities, health technology agencies, and academia should support the adoption and use of all new data sources, including RWD, which can assist in either improving decisions made within drug development or allowing drug development to proceed either more rapidly or in a way that better meets patients' needs
- // When designing trials with external controls we need to focus on data quality, data identification and qualification, and on a rigorous discussion of underlying types of bias.



Summary

- // External controls: à consommer avec modération
- // Paper might serve as a good reference for internal and external discussions
- // Link to paper: <https://doi.org/10.1002/pst.2120>