External controls in drug development

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Views presented are our own.

Many discussions with

• MCO and

• Roche biostatistics

colleagues are gratefully acknowledged.
Context
Make drug development more efficient

• Real-world data is **one option**. Other options are
  – Adjust estimates for baseline covariates.
  – Platform or adaptive designs.
  – Use of parametric models.
  – …

• Focus of today: **external controls**.
From RCT to single-arm trial with external control

- RCT
- "Hybrid" design
- Dynamic borrowing
- Single arm studies
- External control

More bias, less type I error control

More patients in randomized control group
Randomization and data quality

• Pivotal drug RCT has two key properties:
  – **Randomization**  ‡  avoid confounding, get unbiased effect estimate.
  – **Systematic collection of high quality data** ‡  avoid many other biases.

• External controls:
  – No randomization.
  – Data quality heterogeneous.

• **ICH E10** discusses choice of control arm.
<table>
<thead>
<tr>
<th>Bias</th>
<th>Description</th>
<th>Design limitation or potential adjustment method</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Selection</strong></td>
<td>• External control group: highly selected set of patients</td>
<td>• Covariate-adjustment</td>
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<tr>
<td></td>
<td>• Single-arm trial might enroll different patients compared to RCT</td>
<td>• Maybe propensity score</td>
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<tr>
<td><strong>Assessment</strong></td>
<td>• Lack of blinding</td>
<td>• Robust endpoints</td>
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<td></td>
<td>• Heterogeneous assessment of endpoints</td>
<td>• Flatiron data?</td>
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<tr>
<td><strong>Calendar time</strong></td>
<td>• External controls not concurrent</td>
<td>• Statistical modelling:</td>
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<td>• Time-dependent Cox,</td>
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<td></td>
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<td>• Time-effect via covariates,</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• …</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Flatiron data</td>
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<tr>
<td><strong>Immortal</strong></td>
<td>• Time origin difficult to determine</td>
<td>• Need clearly defined time origin</td>
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<td></td>
<td>• Patients in experimental group need to live «long enough» to be included</td>
<td></td>
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<tr>
<td><strong>Regional</strong></td>
<td>• Flatiron in US – implications for other regions?</td>
<td>• Statistical methods for extrapolation</td>
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<td></td>
<td>• TransCelerate’s Placebo and Standard of Care</td>
<td>• Build high-quality databases globally?</td>
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Type I error

• Relevance:
  – In many instances non-negotiable by Health Authorities.
  – Exceptions exist, e.g. rare diseases.

• Simulations in Tang et al (2010):
  – Reasonable assumptions on patient selection, outcome drift over time, variability in historical control success rate.
  – 2- to 4-fold increase of type I error for single-arm trials.

• Type I error can also decrease.

• Prospectively planned trial:
  – possibility to control type I error,
  – typically uniformly over all possible parameter choices.
# RCT and single-arm trial with external controls

<table>
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<tr>
<th></th>
<th><strong>RCT</strong></th>
<th><strong>External controls</strong></th>
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<tbody>
<tr>
<td><strong>Effect estimate</strong></td>
<td>Unbiased</td>
<td>potentially biased</td>
</tr>
<tr>
<td><strong>Data quality</strong></td>
<td>controlled trial setting, typically high</td>
<td>variable</td>
</tr>
<tr>
<td><strong>Type I error</strong></td>
<td>protected</td>
<td>potentially inflated, pre-specification unclear</td>
</tr>
<tr>
<td><strong>Number of patients assigned to control</strong></td>
<td>Relevant portion, even if non-1:1 randomization</td>
<td>potentially none</td>
</tr>
<tr>
<td><strong>Need to identify confounders</strong></td>
<td>None, equal distribution of any variable in both arms</td>
<td>Unbiased effect estimate if relevant confounders identified and collected.</td>
</tr>
<tr>
<td><strong>Applicability</strong></td>
<td></td>
<td>Scenarios where RCT is unfeasible. Broader?</td>
</tr>
<tr>
<td><strong>Totality of evidence</strong></td>
<td>2ry endpoints, QoL, PK, safety, ... straightforward inference</td>
<td>Adjustment for all these endpoints?</td>
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</table>
Focus on features of the data

- «RWD» terminology ambiguous.
- Focus on **features of data**, such as:
  - randomized or not,
  - concurrency,
  - systematically collected or not (e.g. tumor assessments),
  - robustness of endpoints,
  - relevant data available, e.g. to identify population of interest at baseline,
  - IPD vs. summary statistics only,
  - …
- Depending on your answer to these questions: find / develop **fit-for-purpose statistical method** to answer **scientific question**.
- Be transparent on **assumptions** of analysis.
Framework for regulatory approval
External control groups – fit-for-purpose for regulatory approval? Under what circumstances?

- **RCT not an option**, see e.g. Simon et al. (2015):
  - Rare disease, biomarker subpopulations.
  - Unprecedented effect on surrogate endpoint (response) in high unmet need setting with no effective therapies.
  - Heterogeneity in current therapy, no «obvious» control arm.

- **Robust** endpoint: overall survival.

- **Large effect** anticipated ‡ overwhelms potential bias(es).

- Single-arm trials routinely performed ‡ external controls improve situation.
Considerations for regulatory approval framework

• Two-fully powered RCTs, both significant at $\alpha = 0.05 \implies$ high probability of approval.

• Can we develop similar framework for external controls?

• Qualify or even quantify how much «approval bar» is moved if using external controls compared to, e.g., RCT with established endpoint.

• Can we define «margin of error»?
  
  – Control arm in RCT (= controlled setting) often performs better than external control $\implies$ risk of underpowered study when using external control.
  
  – Target effect larger than in corresponding RCT:
    • Comparison to external control group gives hazard ratio of 0.65.
    • Can we provide quantitative statement – a probability! – that true HR is below, say, 0.75?
Considerations for regulatory approval framework

• Reduce bias ‡ **pre-specification** key!
  - Source of external control group.
  - Criteria how to select patients.
  - Endpoint definition and how assessed.
  - Clear definition of time origin.
  - Design and analytical methods to adjust for bias.
  - Sensitivity analyses to pressure test assumptions.
  - Handling of missing data:
    ▪ covariate adjustment or propensity score ‡ need covariate data at baseline,
    ▪ intercurrent events may be different between external control and experimental group.

• Use / develop statistical methods to reduce biases.
Considerations for regulatory approval framework

• Drug development routinely strikes bias – variance trade-off in other instances, e.g. independent vs. investigator response assessment.

• Pragmatic trials?
External controls – non-label-enabling context

• Potentially some **flexibility** on bias and type I error.

• Examples:
  
  – **Inform trial design** assumptions through external controls.
    
    ▪ Dose-finding.
    
    ▪ Phase 3 survival functions.
    
    ▪ …
  
  – Early development **decision-making**: use multistate model, potentially combined with propensity scoring (Beyer et al, 2019).
  
  – **Reimbursement**.
  
  – …

• How much can we expand beyond these «quick wins»?
Potential collaborations between industry, academia, and/or regulators

- Develop **framework** where single-arm / «RWD» trials with external control group can lead to regulatory approval.

- **Endpoints**: Overall survival – what else?

- Qualify or quantify how much «approval bar» is moved if using external controls compared to, e.g., RCT with established endpoint. **Transparency on assumptions**!

- Explore bias-variance tradeoff‡ statistical research.

- Refine statistical methods to **adjust for various biases**.

- Develop **sensitivity analyses**.
Potential collaborations between industry, academia, and/or regulators

- External control group may be very small portion of initially large database. Implication?
- **Regional** differences: Flatiron US – implication on other regions?
- Embed use of external controls (RWD in general) in **estimand** framework.
Summary
Summary

• External controls may be a valuable source of information:
  – Absence of randomization, heterogeneity in data quality.
  – Maximize use of external control data wherever it does not relevantly alter height of approval bar.
  – Use external controls to inform decision-making in non-label enabling situations.

• Scientific question and features of data guide choice of statistical method, not the term that is used.

• Need to understand bias-variance tradeoff.

• Work on analytical methods to address various biases. Sensitivity analyses.

• Pre-specification is key.

• Statisticians: proactively help shaping the way how external controls are used in drug development.
Examples
Examples

- **Alectinib** (Roche): reimbursement in >20 countries, Davies et al. (2018).

- **Kadcyla** (Roche): Safety evaluation:
  - Flatiron data helped fulfill regulatory requirement.
  - Helped avoid separate trial or access to registries.

- **Selinexor** (Karyopharm): [FDA ODAC](#) 26th February 2019:
  - Single-arm study of 122 patients in R/R multiple myeloma.
  - Approval based on Flatiron control arm not granted. Key concerns:
    - **Safety** cannot be sufficiently evaluated.
    - **Lack of pre-specification**.
    - **Populations not the same**, PS-matching not possible due to too low sample size.
    - **Immortal bias** in derivation of endpoints.
Examples

- **Blinatumomab** (Amgen): [FDA ODAC](https://www.fda.gov) 7th March 2018:
  - Single-arm study of 116 patients in ALL.
  - Approval based on single-arm trials, external controls used to expand indication.

- Cave et al (2019):
  - EMA authors discussing use of RWD for regulatory decision-making.
  - Five recent regulatory examples in which RWE has been utilised to
    - support regulatory decisions either at **authorization** or
    - to support **extension** of indication.
  - [Table with examples](#).


Doing now what patients need next