External controls in drug development

Kaspar Rufibach and Hans Ulrich Burger
Methods, Collaboration, and Outreach Group (MCO)
Department of Biostatistics, Roche Basel

BBS spring seminar, 10th May 2019

Acknowledgments

Views presented are our own.

Many discussions with

- **MCO and**
- **Roche biostatistics**

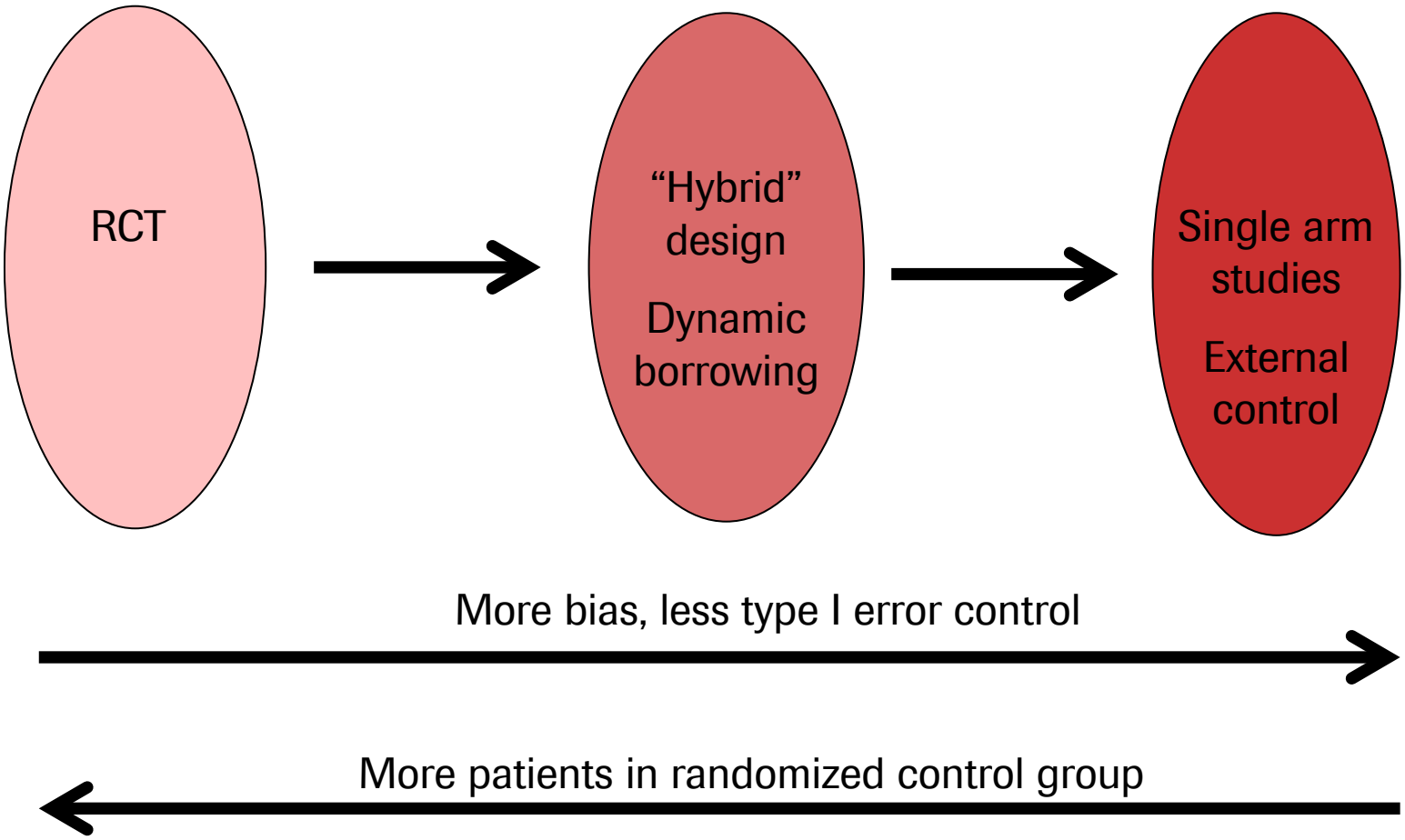
colleagues are gratefully acknowledged.

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



Randomization and data quality

- Pivotal drug RCT has two key properties:
  - **Randomization** à avoid confounding, get unbiased effect estimate.
  - **Systematic collection of high quality data** à avoid many other biases.
- External controls:
  - No randomization.
  - Data quality heterogeneous.
- **ICH E10** discusses choice of control arm.

Bias

Bias	Description	Design limitation or potential adjustment method
Selection	• External control group: highly selected set of patients • Single-arm trial might enroll different patients compared to RCT	• Covariate-adjustment • Maybe propensity score
Assessment	• Lack of blinding • Heterogeneous assessment of endpoints	• Robust endpoints • Flatiron data?

Calendar time	• External controls not concurrent	• Statistical modelling:
		  • Time-dependent Cox,
		  • Time-effect via covariates,
		  • …
		• Flatiron data

Immortal	• Time origin difficult to determine • Patients in experimental group need to live «long enough» to be included	• Need clearly defined time origin
Regional	• Flatiron in US – implications for other regions? • TransCelerate's Placebo and Standard of Care	• Statistical methods for extrapolation • Build high-quality databases globally?

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

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

Focus on features of the data

- «RWD» terminology ambiguous.
- Focus on **features of data**, such as:
  - randomized or not,
  - concurrecy,
  - 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 à overwhelms potential bias(es).
- Single-arm trials routinely performed à external controls improve situation.

Considerations for regulatory approval framework

- Two-fully powered RCTs, both significant at $\alpha = 0.05$ à 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 à 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 à **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 à 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 à 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 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.

References

Beyer, U., Dejardin, D., Meller, M., Rufibach, K. and Burger, H. U. (2018). A multistate model for early decision making in oncology. https://arxiv.org/abs/1808.07221

Cave, A., Kurz, X. and Arlett, P. (2019). Real-World Data for Regulatory Decision Making: Challenges and Possible Solutions for Europe. Clin. Pharmacol. Ther., to appear.

Davies, J., Martinec, M., Delmar, P., Coudert, M., Bordogna, W., Golding, S., Martina, R. and Crane, G. (2018). Comparative effectiveness from a single-arm trial and real-world data: alectinib versus ceritinib. Journal of Comparative Eectiveness Research 7 855--865.

Nair, V. (1984). Confidence bands for survival functions with censored data - a comparative study. Technometrics 26 265--275.

Simon, R., Blumenthal, G. M., Rothenberg, M. L., Sommer, J., Roberts, S. A., Armstrong, D. K., LaVange, L. M. and Pazdur, R. (2015). The role of nonrandomized trials in the evaluation of oncology drugs. Clin. Pharmacol. Ther. 97 502--507.

Tang, H., Foster, N. R., Grothey, A., Ansell, S. M., Goldberg, R. M. and Sargent, D. J. (2010). Comparison of error rates in single-arm versus randomized phase II cancer clinical trials. J. Clin. Oncol. 28, 1936--1941.

Doing now what patients need next