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Regulatory and Statistical Considerations for Externally Controlled Clinical Trials

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Disclosures

- I have no financial relationships to disclose
- This presentation reflects the views of the author and should not be construed to represent FDA's views or policies

Outline

- Introduction
- Considerations for including external control data in clinical trials
  - Selecting data that is fit-for-purpose
  - Importance of study design
  - Brief discussion of analysis
- Regulatory examples of use of external control data
- Conclusions

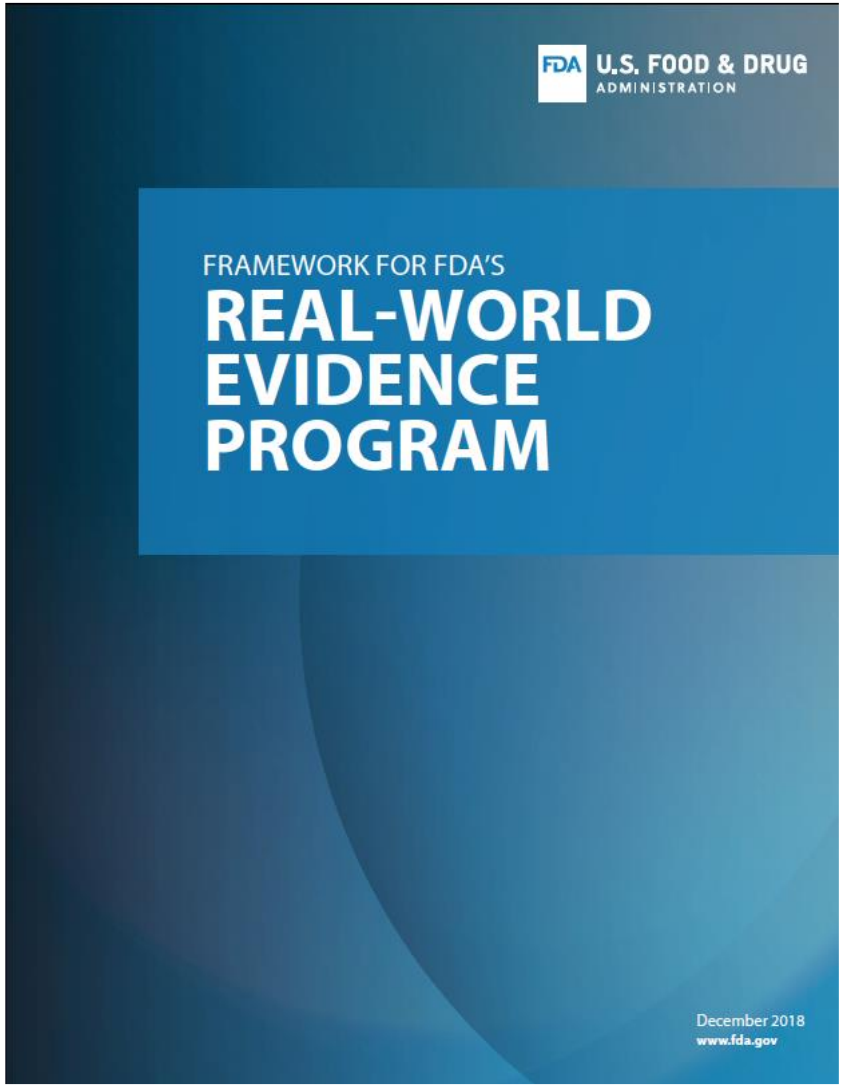
Introduction

- In general, randomized trials are preferred for providing evidence of drug efficacy
  - RCTs are gold standard for comparing treatments as the process of randomization removes confounding by known and unknown factors

- In the case that a randomized control arm is not possible, an external control (EC) arm may be an option for estimating comparative treatment effect or providing supportive evidence where the disease area is well characterized with respect to natural history and the expected effect size is large on an outcome that can be precisely measured

Regulatory Guidance and Resources

- FDA has provided many resources for the design of non-traditional clinical trials
- May 2001: E10 Guidance for Industry[1] describes strategies for choosing a control group for clinical trials intended to demonstrate efficacy
  - Considerations for using external controls are described in Section E
- December 2018: FDA provided the Framework for the Real-World Evidence Program[2], which includes some information on how real-world data and evidence will be incorporated into regulatory decision making



[1] https://www.fda.gov/downloads/guidances/ucm073139.pdf
[2] https://www.fda.gov/downloads/ScienceResearch/SpecialTopics/RealWorldEvidence/UCM627769.pdf

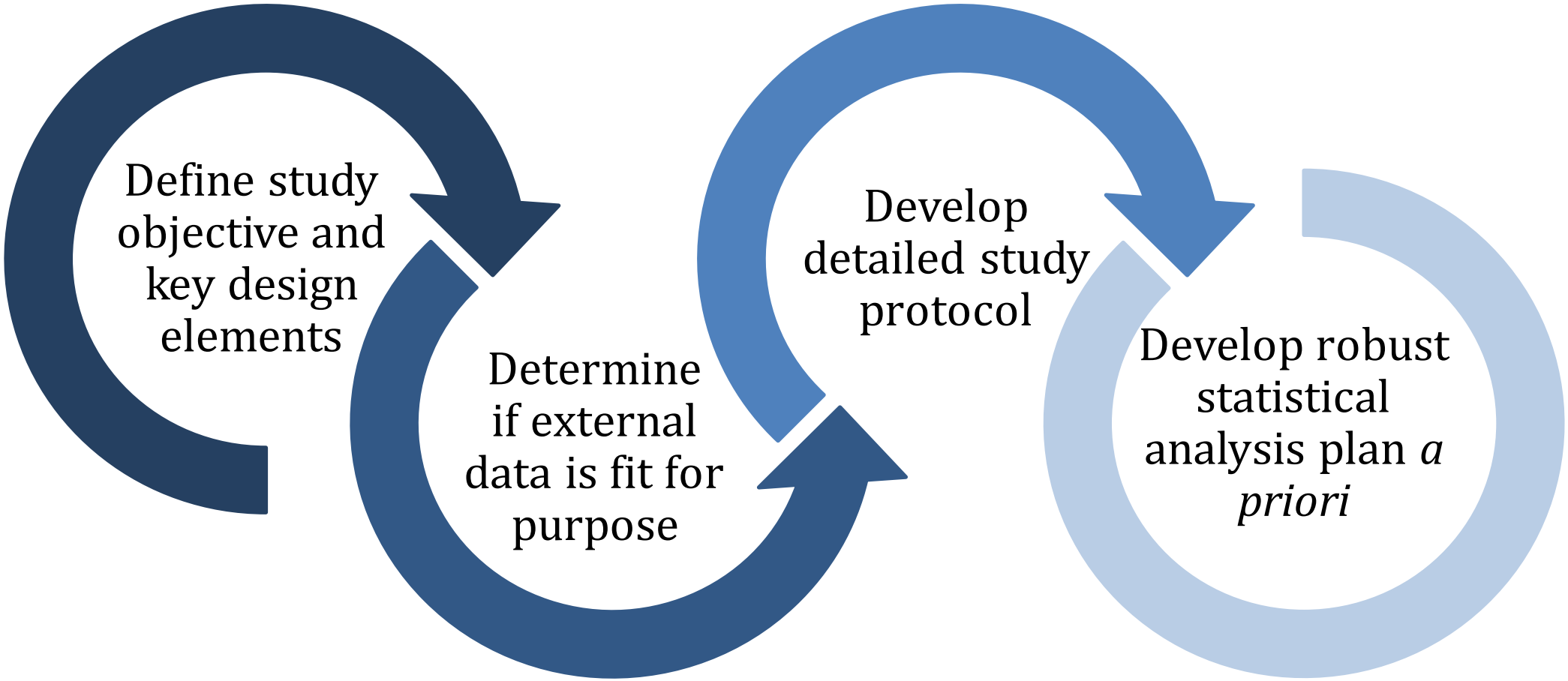
Additional Regulatory Guidance and Resources

FDA has published several draft Guidances related to Real-World Data and Real-World Evidence[1]:

- Assessing Electronic Health Records and Medical Claims Data To Support Regulatory Decision-Making for Drug and Biological Products
- Assessing Registries to Support Regulatory Decision-Making for Drug and Biological Products
- Considerations for the Use of Real-World Data and Real-World Evidence To Support Regulatory Decision-Making for Drug and Biological Products
- Data Standards for Drug and Biological Product Submissions Containing Real-World Data
- Submitting Documents Utilizing Real-World Data and Real-World Evidence to FDA for Drugs and Biologics
- Use of Electronic Health Records in Clinical Investigations
- Use of Real-World Evidence to Support Regulatory Decision-Making for Medical Devices

[1] https://www.fda.gov/downloads/ScienceResearch/SpecialTopics/RealWorldEvidence

Considerations for Including EC Data in Clinical Trials



Ref: Mishra-Kalyani PS, Amiri Kordestani L, Rivera DR, et al. External control arms in oncology: current use and future directions. Ann Oncol. 2022;33(4):376-383.

Defining Study Objectives and Key Design Elements

- External controls could be considered to demonstrate:
  - Natural history of disease
  - Established efficacy from prior trials for study assumptions (e.g. benchmark rate)
  - Comparing efficacy across treatment arms by supplementing or replacing concurrent controls in a prospective trial

- Along with initial study objectives, major design elements must be established in order to select external control data that are fit-for-purpose

Selecting Data That Is Fit For-Purpose

- Characteristics of potential EC data for would determine if it is fit for purpose for intended use
- If we want to compare efficacy endpoints, then high-quality and complete patient-level data is required

Ref: Mishra-Kalyani PS, Amiri Kordestani L, Rivera DR, et al. External control arms in oncology: current use and future directions. Ann Oncol. 2022;33(4):376-383

Data Sources

Clinical Trial Data

- Clearly defined population per eligibility criteria
- Exposure(s), prognostic factor(s), and endpoint(s) generally well defined and captured
- Data may not be contemporaneous to experimental trial data

Prospective Cohort/Registry Data

- Data in these sources are generally collected with scientific research intent, which improves likelihood of higher quality and completeness of data collection
- Data definitions may differ from clinical trial data, increasing the chances of misspecification and differences in comparability

Patient Level RWD (Claims/EHR)

- May be able to select contemporaneous cohort from from a relatively large pool of patients
- Availability and ascertainment of key data elements dependent on type of RWD
- Reliability and relevance should be evaluated. Misspecification, misclassification, and other data-related bias are major concerns

Literature or Summary Level Data

- Not appropriate for direct comparison as external control to establish safety or effectiveness
- May provide a good understanding of natural history, provide clinical context, or establish a benchmark for comparison for single arm experimental trial data

Ref: Mishra-Kalyani PS, Amiri Kordestani L, Rivera DR, et al. External control arms in oncology: current use and future directions. Ann Oncol. 2022;33(4):376-383.

Importance of Study Design

- Good study design when using external controls can help to avoid many of the pitfalls of using non-concurrent or non-randomized data

- What are the principles of good study design for a study utilizing external control data?
  - **Design established iteratively considering estimand and identifying fit-for-purpose data**
    - Comparable endpoints by definition and measurement
    - Similarities in key aspects of data (temporality, follow-up, etc)
    - Ascertainment of key variables (e.g. treatment, biomarkers, etc)
  - Minimize the need for analytic tools to deal with bias or confounding

Study Design Elements

- More on minimizing bias
  - Define an appropriate index or baseline date
  - Avoid bias induced by differential selection/confounder distributions
  - Use same eligibility criteria for prospective trial and EC
  - Can take measures to reduce probability of misclassification
  - Ascertainment of variables of interest should be blinded to endpoint assessment

- Other design considerations
  - Prespecify as much of analysis plan in design stage as possible
  - Formal sample size calculations are still relevant (and you can prespecify a stringent alpha)
  - Consider **hybrid designs** (can consider Bayesian methods) to supplement concurrently randomized controls with EC

Analytical Considerations

- Careful selection of the **primary estimand and corresponding attributes** (population, variable/treatment, intercurrent events, and summary measure) is essential for both the trial design and analysis plan

- At a minimum, a statistical analysis plan should include:
  - Sample size and power calculations
  - Methods to balance two populations and account for confounding and bias in the estimation of treatment effect when using EC, including a primary method and sensitivity/supportive analyses
  - A proposed metric to assess balance of the experimental arm and the EC (before and after methods to control for confounding/selection bias)
  - Methods for missing data

Some Major Types of Bias

Type of Bias	Description	Example
Selection Bias	• Failure of EC to resemble clinical trial population at baseline • Unbalanced selection over time (differential censoring)	EC patients choose their treatment, and this choice may be affected by health status
Confounding	• Induced by characteristics associated with treatment and endpoint • Difficult to know true confounders (potential differences on unmeasured characteristics)	Underlying supportive care may be different for EC and prospectively enrolled patients
Misclassification	• Inaccuracies in reported data • Data entry/coding error/uncaptured information • Endpoint assessment from incomplete/different information or at inconsistent intervals	Measurements of tumor response may not be at the same intervals in EC as a prospective trial

Regulatory Examples of EC Data in Oncology

Drug	Disease Setting	Source of EC Data	Regulatory Use of EC Data
Selumetinib	Neurofibromatosis type 1 with inoperable plexiform neurofibromas (pediatric)	Previously conducted clinical trials	Establish natural history of disease
Erdafitinib	Unresectable urothelial cancer harboring select FGFR genetic alterations	Patient-level EHR data from US community-based cancer clinics	Establish natural history of disease
Pembrolizumab and lenvatinib	Advanced endometrial carcinoma that is not MSI-H or dMMR	Previously conducted clinical trials	Isolation of treatment effect
Several Immunooncology-combination therapies	Untreated, locally advanced or metastatic renal cell carcinoma	Previously conducted clinical trials	Isolation of treatment effect
Blinotumomab	Precursor B-cell ALL in complete remission with detectable MRD	Retrospective observational cohort study	Comparative efficacy analysis

Ref: Mishra-Kalyani PS, Amiri Kordestani L, Rivera DR, et al. External control arms in oncology: current use and future directions. Ann Oncol. 2022;33(4):376-383.

Regulatory Case Example: Establishing Natural History

- Selumetinib was approved by FDA in 2020 for the treatment of pediatric patients with neurofibromatosis type 1 (NF1) who have symptomatic, inoperable plexiform neurofibromas (PN)
  - Approval was based on the results of SPRINT Phase II Stratum 1 data, which demonstrated a durable response rate in 50 pediatric patients

- Given the rarity of the disease and uncommon occurrence of spontaneous regression of NF1 PN, 2 previously conducted trials were a submitted as supportive external control data to establish natural history:
  - A natural history study of NF1 in patients less than 35 years of age with a clinical diagnosis of NF1 or a confirmed NF1 mutation
  - The placebo arm of Study 01-C-0222, a multicenter, double-blinded, randomized, cross-over study comparing a different investigational in children and young adults (≥3 and ≤25 years) with a clinical diagnosis of NF1 and unresectable, progressive PN with the potential to cause significant morbidity

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Regulatory Case Example: Isolation of Treatment Effect

- The combination of pembrolizumab and lenvatinib was approved by FDA in 2019 for treatment of patients with advanced endometrial carcinoma that is not microsatellite instability- high (MSI-H) or mismatch repair deficient (dMMR), who had progression on systemic therapy and were not candidates for curative surgery or radiation
  - Approval was based on Study E7080-A001-111/KEYNOTE-146, a single-arm, multicenter, open-label, multicohort trial which demonstrated a durable response rate
- Monotherapy data from 3 previously conducted trials (Study204 for lenvatinib and KEYNOTE-158 and KEYNOTE-028 for pembrolizumab) were considered external control data to support contribution of components to treatment effect
  - Exploratory analyses included unadjusted cross-trial comparisons and adjusted analyses using propensity score methods to control for potential differences in baseline demographic and clinical characteristics
  - Results of both analyses were consistent and supported an improved ORR for the combination as compared to the individual therapies, but the adjusted analyses were limited by covariates that were measured in all four studies
  - Still the results provided supportive evidence for the supplemental indication approval of the combination therapy

Ref: Mishra-Kalyani PS, Amiri Kordestani L, Rivera DR, et al. External control arms in oncology: current use and future directions. Ann Oncol. 2022;33(4):376-383.

Regulatory Case Example: Comparative Efficacy

- Blinotumomab was granted accelerated approval for the treatment of adults and children with B-cell precursor acute lymphoblastic leukemia in first or second complete remission with minimal residual disease greater than or equal to 0.1%
  - Approval was based on BLAST Study (NCT01207388), a single arm, multi-center study that included adult patients with BCP ALL in complete remission with MRD at a level of ≥ 0.1% with a primary endpoint of complete MRD response rate

- The data from the BLAST study was compared to an external control arm that was derived from Study 2120148, a retrospective cohort study of patients outside the US with Philadelphia chromosome-negative BCP ALL in hematological complete remission with MRD
  - Populations for comparison were selected by matching important baseline patient clinical characteristics across studies, as well as by time from MRD measurement to start of therapy or relapse
  - Recurrence-free survival and overall survival were compared using stabilized inverse probability of treatment weights and adjustment for hematopoietic stem cell transplantation (HSCT)
  - Though the analyses favored Blinatumomab, there were several concerns regarding intercurrent events (differing transplant and subsequent therapy rates); these results were considered exploratory but supportive of the approval in this setting

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Summary

- Data considerations when using EC
  - Capture/definitions of covariates and endpoints must be same
  - Temporality of data – even small lags may make a big difference with respect to treatment/disease/patient population idiosyncrasies
- Good study design can help to avoid many of the pitfalls of using non-concurrent or non-randomized data as external controls
  - Avoid differences in the populations that result in groups that not comparable
  - Minimize the need for analytic tools to deal with bias or confounding
- Regulatory case studies of the use of external control data in oncology clinical trials do exist, but thus far the evidence generated by the EC data have been supportive only

Some Final Thoughts on External Controls

- The burden of proof to demonstrate that external controls meet the bar for comparative analyses should not be underestimated
- When considering a trial design that includes external controls, other options that preserve principal of randomization should be considered:
  - N:1 randomization ratios
  - Pragmatic trials
  - Decentralized trials
- Hybrid trial design (with Bayesian or frequentist methods) offer a unique benefit of allowing for both external and concurrent controls, which minimizes risk
- If ultimately an externally controlled trial design is chosen, all operating characteristics and statistical methods should be prespecified

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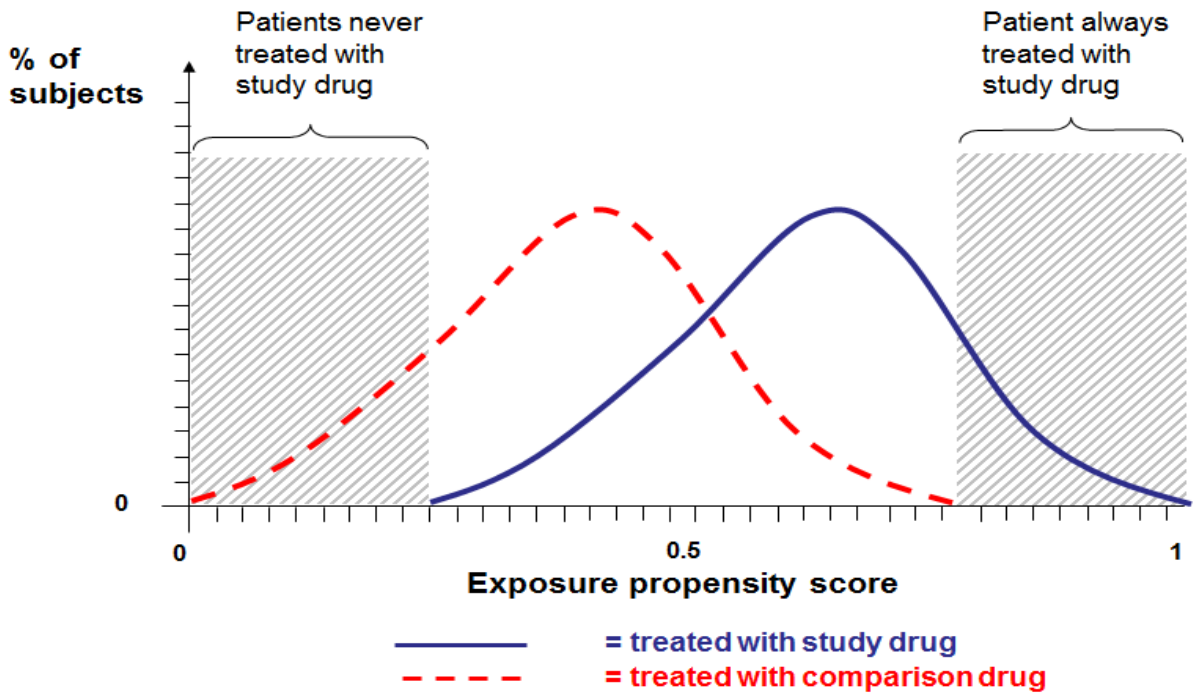
General Considerations for Balancing Scores

- Model the covariates that may affect group assignment (experimental treatment vs. external control) to create a balancing score

- After matching/stratification/weighting using the score, differences in outcomes between groups can be attributed to treatment effect if certain assumptions are held (no unmeasured confounding, sufficient overlap, correct model specification)



Some Statistical Methods to Control for Bias

Type of Bias	Statistical methods
Selection Bias	• Balancing scores, e.g. propensity scores (matching, weighting, stratification) • Inverse probability weighting
Confounding	• Balancing scores, e.g. propensity scores (matching, weighting, stratification) • Inverse probability weighting • Marginal structural models
Misclassification/ Measurement	• Measure misclassification or "validate" measurements of external data by measuring sensitivity, specificity, PPV, NPV