External Controls in Cancer Clinical Trials – Challenges and Opportunities

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Potential Use of External Controls

- External controls could be considered to:
  - Understand natural history of disease
  - Designing future studies by establishing SOC effect
  - Used in place of randomized control arm (historical control)
  - Compare efficacy across treatment arms by supplementing concurrent controls in a prospective trial

- Source of data for the external control determines potential use

Regulation and Guidances

- 21CFR 314.126

"…historical control designs are usually reserved for special circumstances. Examples include studies of diseases with high and predictable mortality (for example, certain malignancies) and studies in which the effect of the drug is self-evident (general anesthetics, drug metabolism)"

- ICH E10 (2001)

Describes strategies for choosing a control group for clinical trials intended to demonstrate efficacy. Considerations for using external controls are described in Section E:

"The inability to control bias restricts use of the external control design to situations in which the effect of treatment is dramatic and the usual course of the disease highly predictable"

21st Century Cures Deliverables

- **FDA shall establish a program <u>to evaluate</u> the potential use of real world evidence (RWE) to:**
  - **Help support approval of new indication for a drug approved under section 505(c)**
  - **Help satisfy post-approval study requirements**
- **Program will be based on a framework to be issued by - 2018**

- **Real-World Data (RWD) are data relating to patient health status and/or the delivery of health care routinely collected from a variety of sources.**
- **Real-World Evidence (RWE) is the clinical evidence regarding the usage and potential benefits or risks of a medical product derived from analysis of RWD.**

Real world evidence means data regarding the usage, or the potential benefits or risks, of a drug derived from sources other than *traditional clinical trials*

FRAMEWORK FOR FDA'S
REAL-WORLD EVIDENCE PROGRAM
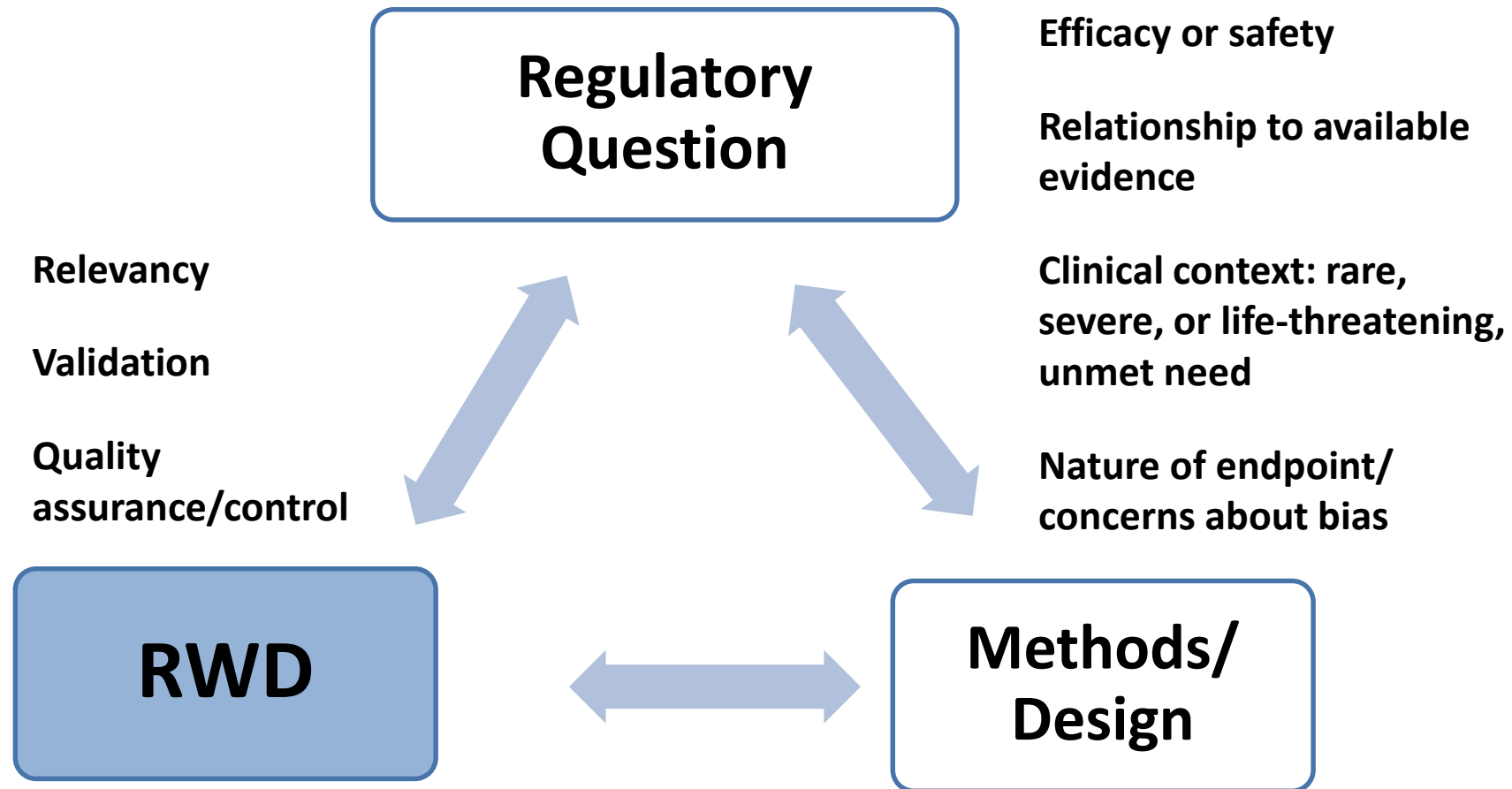
U.S. FOOD & DRUG ADMINISTRATION

December 2018
www.fda.gov

- Published Dec. 2018

- Intended for drug and biological products

- Outlines FDA's plan to implement the RWE program

- Multifaceted program
  - Internal process
  - Guidance development
  - Stakeholder engagement
  - Demonstration projects

Incorporating RWE Into Evidence Generation

Many factors must be considered at the same time

Efficacy or safety

Relationship to available evidence

Clinical context: rare, severe, or life-threatening, unmet need

Nature of endpoint/ concerns about bias

Relevancy

Validation

Quality assurance/control

Regulatory Question

RWD

Methods/ Design

Sridhara CTAC 2019

Framework for Evaluating RWD/RWE for Use in Regulatory Decisions

- **The study conduct meets FDA regulatory requirement**
  - Informed consent, appropriate oversight and monitoring,
  - Appropriate data standards for integration from various sources

Framework for Evaluating RWD/RWE for Use in Regulatory Decisions

- The trial or study design used to generate RWE can provide adequate scientific evidence to answer or help answer the regulatory question

  - Randomized designs using RWD (explore pragmatic RCT),

  - Non-randomized, single arm trials with <u>external control</u> (guidance in development),

  - Observational studies (retrospective, prospective, role of existing evidence (e.g.: <u>natural history of disease</u> – guidance under development))

Rare Diseases: Common Issues in Drug Development
Guidance for Industry

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to https://www.regulations.gov. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document, contact (CDER) Lucas Kempf at 301-796-1140 or (CBER) Office of Communication, Outreach, and Development at 800-835-4709 or 240-402-8010.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

February 2019
Rare Diseases
Revision 1

- Addresses importance of several aspects including adequate description and understanding of natural history of the disease, adequate understanding of pathophysiology of the disease and drug's mechanism of action, nonclinical pharmacotoxicology and human toxicology considerations and selection of outcome assessments and endpoints.
- Natural history studies can be retrospective or prospective and cross-sectional or longitudinal studies
- Historical/external controls can be considered in serious rare diseases with unmet medical need provided disease is predictable, such as high mortality, and the drug effect is large and self-evident.

Rare Diseases: Natural History Studies for Drug Development

Guidance for Industry

DRAFT GUIDANCE

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- Natural history studies that systematically and comprehensively capture data can help identify or develop biomarkers as a diagnostic biomarker, prognostic biomarker and useful in guiding patient selection and dose selection in drug development programs

Use of natural history study data:

- Adequate control to discriminate outcomes caused by new drug from outcomes caused by other factors. Historical controls may be used as controls; however, may not control certain biases.
- Use of external control assumes similarity between treated and control group with respect to disease severity, duration of disease, prior treatments, and other aspects that could affect outcomes and the timing of outcomes.
- Epidemiological approaches can be used to reduce bias. However, critical disease characteristics may not have been assessed in the historical/external control and standard of care may have changed over a period of time.

Lessons From Safety

FDA

- Appropriateness of data source
- Pre-specified study protocol and statistical analysis plan
- Selection of study population – explicit inclusion and exclusion criteria
- Exposure ascertainment
- Outcome ascertainment – validation, linkage
- Confounding adjustment – propensity score method
- Sensitivity analysis - robustness

Guidance for Industry and FDA Staff

Best Practices for Conducting and Reporting Pharmacoepidemiologic Safety Studies Using Electronic Healthcare Data

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

May 2013
Drug Safety

https://www.fda.gov/downloads/drugs/guidances/ucm 243537.pdf.

Consideration of using historical control arm

- Selection of patient population: blinded review; pre-defined eligibility criteria; contemporaneous patient cohort

- Endpoint ascertainment: prefer more objective endpoints; pre-specified criteria; blinded review

- Comparable assessment timing and methods

- Adequate size of the historical control data

- Pre-specify/include important prognostic & confounding variables in the data/analyses

- An adequate statistical analysis plan should be in place

Challenges for Drug Development in Rare Diseases

- Small number of eligible patients to participate in a given study

- Geographic distribution of patients

- Lack of knowledge about the clinical course/natural history of disease

- Dissimilar diseases

- Lack of appropriate comparator treatment

Sources and Challenges of External Control

Sources:

- Past clinical trials
- Registry Data
- Case Studies/Literature
- Real world data

Challenges:

- Collection of all confounders/factors that influence treatment assignment
- Unmeasured disease and patient characteristics
- Frequency of assessments (clinical trial vs. external control) and assessment method
- Time Lag
- Index date
- Survivor bias
- Follow-up time

Example 1: Blincyto supplemental approval

- Approved on 3/29/2018 for patients with precursor B-cell acute lymphoblastic leukemia (B-cell ALL), CR1 & CR2 with MRD+

- Supported by a single arm study MT103-203

  -- Primary efficacy endpoint: complete MRD response within the first

  cycle

- Supporting results (exploratory; not included in the label): Compare the single arm trial (Study MT103-203: reduce from n=113 to n=73) vs historical control arm (Study 20120148;n=182)

  - Efficacy Endpoints: RFS and OS

  - Propensity score adjustment

    - Selected baseline factors are balanced by using a weight function stabilized inverse probability of treatment weight (sIPTW)

Blincyto : Results in the label and Supportive Results comparing with a HC arm

- Label: Based on n=86

 -- % MRD - : 81.4% (95%CI: 72%, 89%)

-- Median hematological RFS : 22.3 months

- Sponsor's supportive results (FDA presented in 3/7/18 ODAC):

HR (95% CI)=0.50 (0.32-0.78)   HR (95% CI) =0.76 (0.47-1.24)
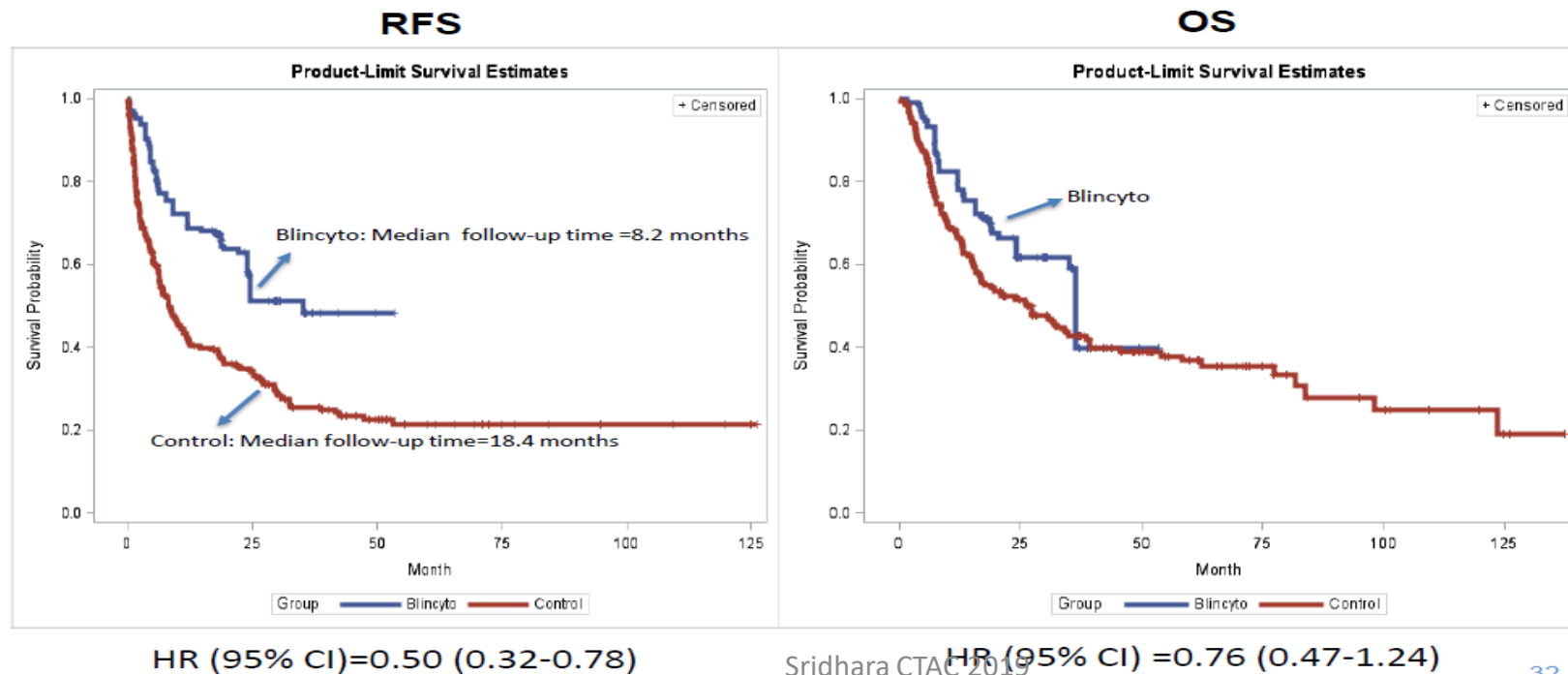
Limitation in Blincyto supportive results using the HC arm

3/7/2018 ODAC:

While RFS appears to be in favor of Blincyto treated arm, there are limitations of the propensity score adjusted analyses based on HC arm:

- 35% of Blincyto patient data excluded to match with external control group
- Confounding due to subsequent treatment, e.g. differential rates of HSCT and data are not contemporaneous
- Differential follow-up time between two arms

Example 2: Vistogard

- Approved on 12/11/2015 for patients who experience 5-FU or capecitabine over dose or early onset of severe or life-threatening toxicities within 96 hours after 5-FU or capecitabine treatment

- Studies report ~ 0.5% mortality among ~ 300,000 patients in U.S. receiving flurouracil due to toxicity

- This approval was supported by:
  - Two expanded access single-arm studies :
    401.10.001 (US; n=60) and WELL401 (US&EU; n=75)
  - Retrospective historical case report : n=25

- *Endpoint for the pivotal study:* Survival at day 30 or resumption of chemotherapy if the resumption occurred first prior to 30 days

- 96% vs. 16% (historical control) survival rate

Opportunities: Clinical Trial Design Options

FDA

Key consideration: reduce sample size and maximize allocation to investigation drug

Key feature: adaptive design

- RCTs 2:1 or 3:1 randomization allocation with decision criteria to stop early

- Supplement concurrent control in a RCT with external control

- Crossover design with each patient as his/her own control

- Single arm trial with external control

- Basket/Umbrella/Platform trials with a Master Protocol

International Collaborations? Others? – Possibility to conduct RCT

Regulatory considerations/flexibilities? – Depends on the disease and available options

Conclusion

- When feasible RCT is the best way to understand, evaluate a treatment effect – takes care of known and unknown confounding factors

- Single arm trials supported with historical controls in general reserved for special circumstances

- **If a historical/external control arm is used to support a submission, adequate data based on pre-determined patient selection criteria and pre-specified statistical analysis plan are required.**

- FDA's Framework serves as a roadmap for more fully incorporating RWD and RWE into the regulatory paradigm

- RWE remains a top FDA priority

- FDA is committed to understand its full potential; Multi-stakeholder effort