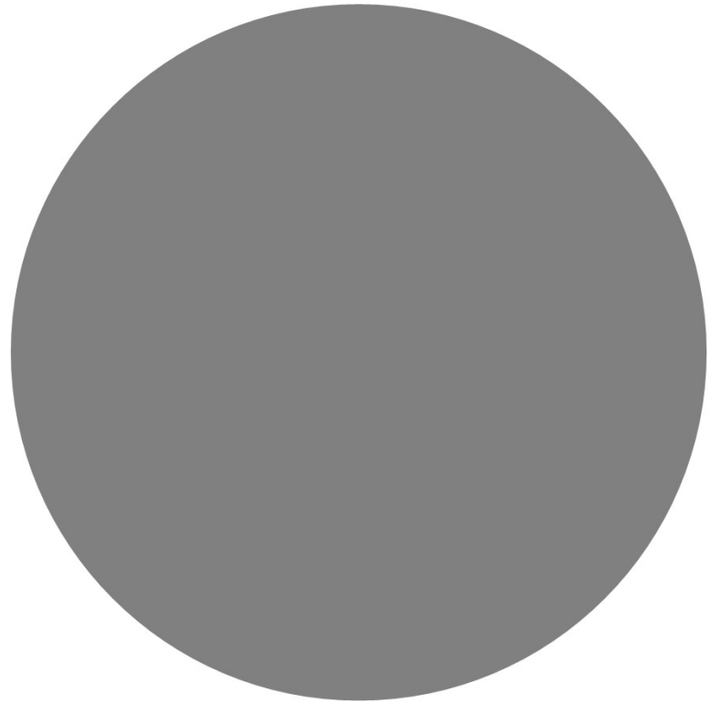
Using Historical Control for Regulatory Approvals in US

A Practical Review Focusing on Diseases in Small Population



2020 ASA Biopharmaceutical Section Regulatory-Industry Statistics Workshop

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Overview

- This is a continuation of previous work based on collaboration with the DIA-ADSWG NEED subteam[1]
  - Expand the cases from original pool of 22 to 50

- Focus on drug development programs using historical control as the comparator in the pivotal study(ies)
  - Many of these programs had 1 pivotal study to support efficacy claim

- Identify good practices and pitfalls based on reviewing FDA's reviews
  - Learn from the *real-world experience*

[1] Ghadessi, M., Tang, R., Zhou, J. et al. A roadmap to using historical controls in clinical trials – by Drug Information Association Adaptive Design Scientific Working Group (DIA-ADSWG). *Orphanet J Rare Dis* 15, 69 (2020).

Historical control: not a new concept

Compared to a different group of people with similar situation treated in a different manner – **Historical Control**

Or compared to the same group of people previously untreated – **Self-control**

Randomized clinical trial was widely recognized.

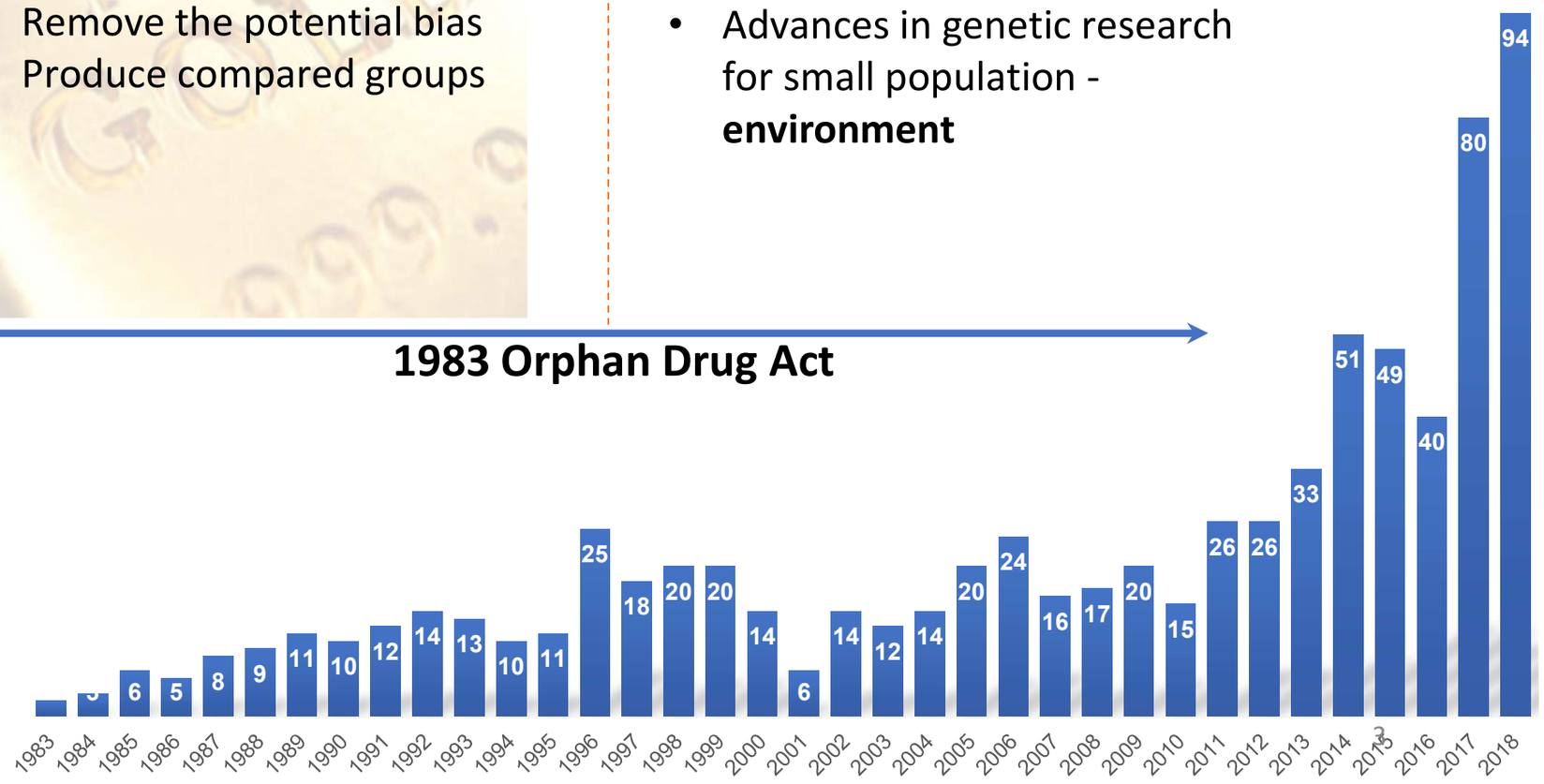
Gold standard of clinical trial
- Remove the potential bias
- Produce compared groups

Back to "historical control" ?

- Accessibility to massive historical data - **resources**
- Advances in genetic research for small population - **environment**

1950 **1983 Orphan Drug Act**

Number of Orphan Indications Approved in the United States 1983–2018:



Source: FDA. Search Orphan Drug Designations and Approvals. Available from: https://www.accessdata.fda.gov/scripts/opdlisting/oopd/

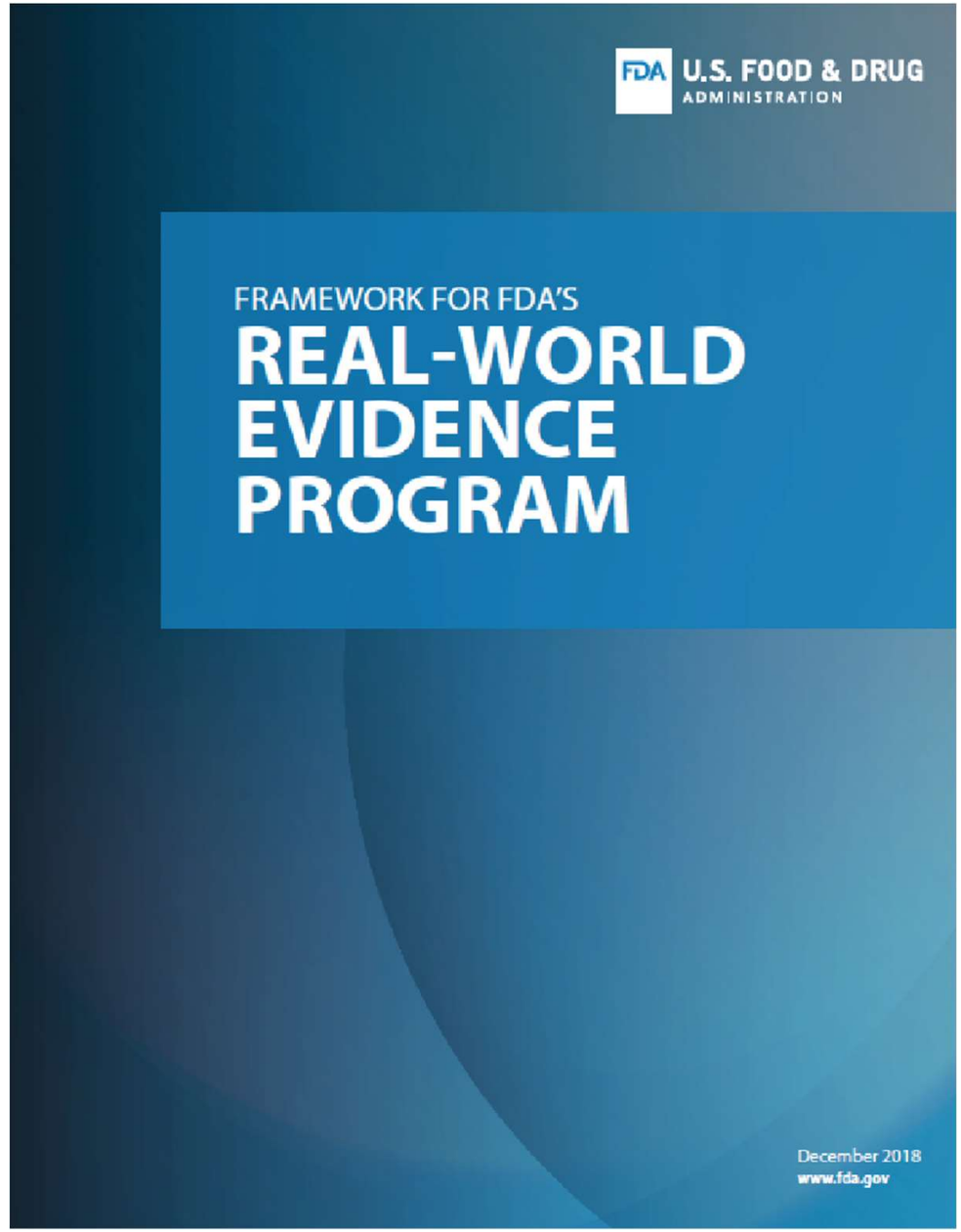
Guidance for Industry

E 10 Choice of Control Group and Related Issues in Clinical Trials

Rare Diseases: Natural History Studies for Drug Development

Guidance for Industry

DRAFT GUIDANCE



Guidance for Industry

E 10 Choice of Control Group and Related Issues in Clinical Trials

Section 1.C.5 Types of Controls (1.3)

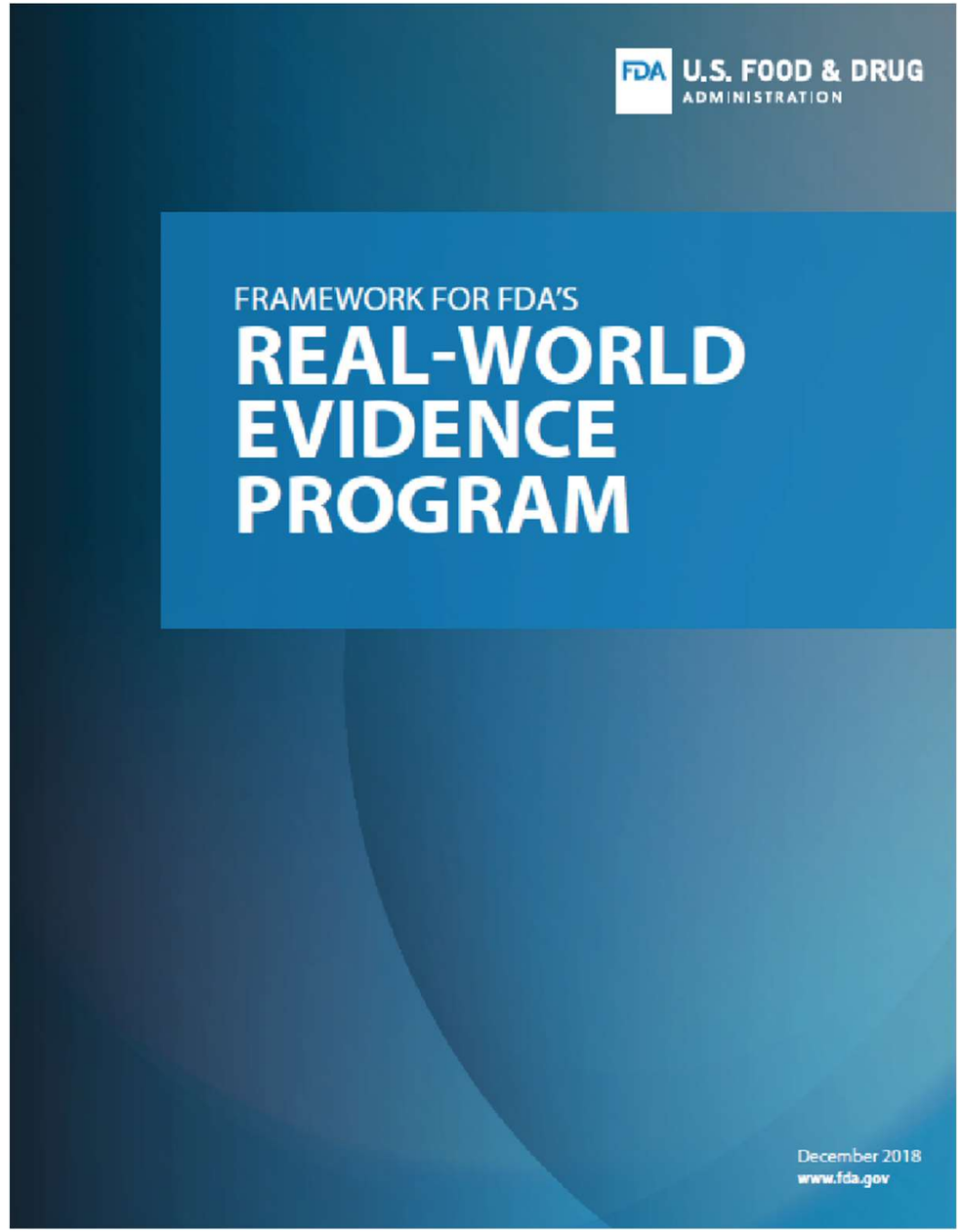
External (historical) control groups, regardless of the comparator treatment, are considered together as the fifth type because of serious concerns about the ability of such trials to ensure comparability of test and control groups and their ability to minimize important biases, making this design usable only in unusual circumstances.

Potential for Study Designs Using RWD to Support Effectiveness

External controls (e.g., historical controls) are a possible type of control arm in an adequate and well-controlled study.

…

Collection of RWD on patients currently receiving other treatments, together with statistical methods, such as propensity scoring, could improve the quality of the external control data that are used when randomization may not be feasible or ethical, provided there is adequate detail to capture relevant covariates.



Rare Diseases: Natural History Studies for Drug Development

Guidance for Industry

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Section B.1 Historical (external) controls

This situation generally restricts use of historical control designs to assessment of serious disease when

(1) there is an unmet medical need;

(2) there is a well-documented, highly predictable disease course that can be objectively measured and verified, such as high and temporally predictable mortality; and

(3) there is an expected drug effect that is large, self-evident, and temporally closely associated with the intervention.

Case Studies - Disclaimers

This is a **biased** sample of drug development programs

Numerous factors impact how the historical data are utilized in drug development

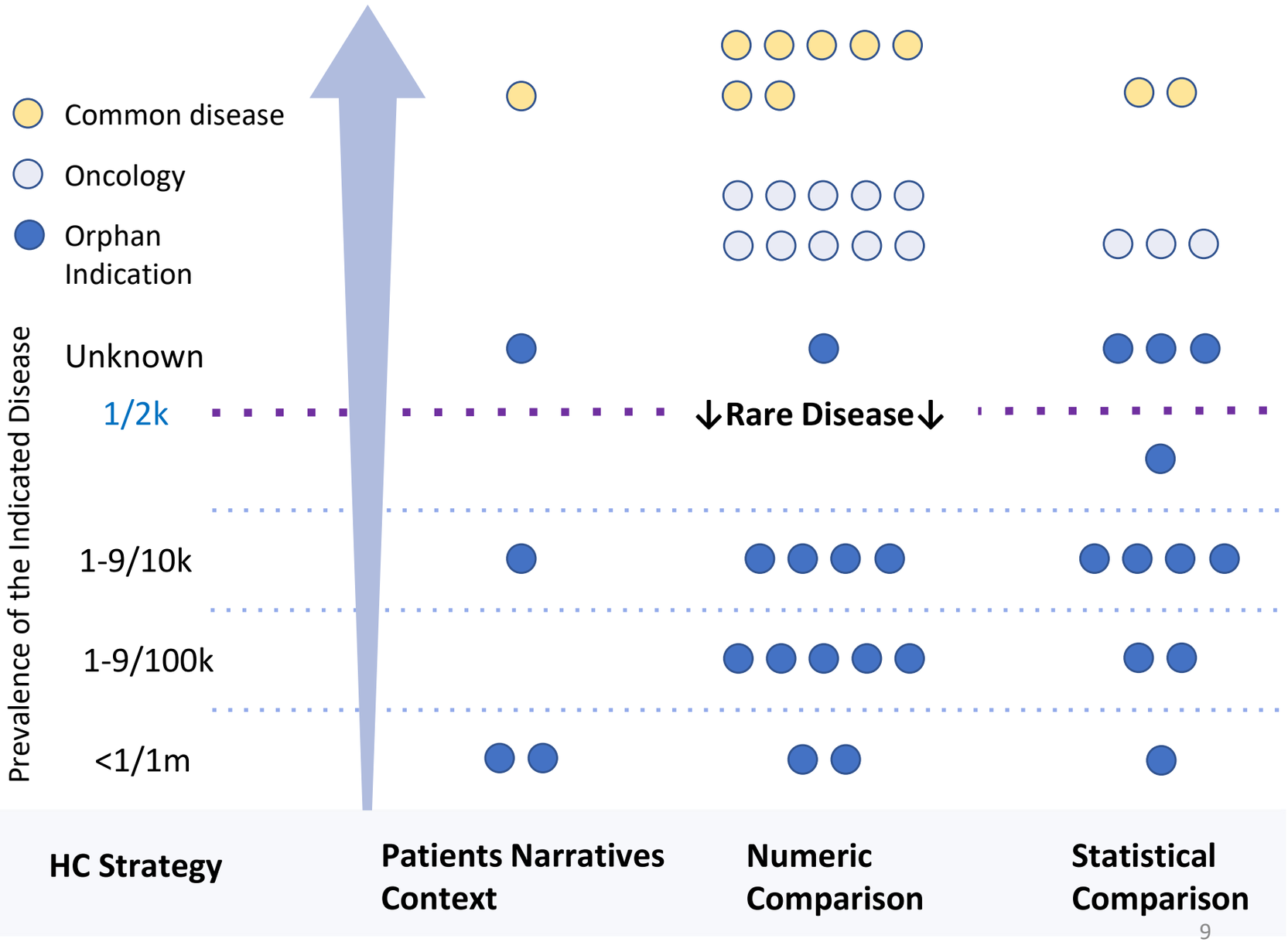
Historical data/RWD have a much broader spectrum of applications than filing

HC Strategy

Among the drugs reviewed, source of historical data include:

- Chart review, survey, publication, prior clinical trials / studies (27)
- Registry, database (9)
- Natural history study (7)
- Self-control (5)
- Implied control (1)
- Clinical judgement, consultation (2)
- Historical observation (2)

Strategy to form a “control” based on historical data varies.



Evaluating HC

How the quality of HC is evaluated?

The following texts appear in several recent reviews as *a prologue* to set expectation before FDA evaluated historical control as a comparator

- *The course of the untreated disease within a patient population is well understood to be uniform with outcomes that can be predicted reliably*
- *A valid historical control from a natural history study must have the same eligibility requirements, medical workup, and clinical evaluations as the clinical trial*
- *Using a historical control is most likely to be persuasive when the study endpoint is objective and when the outcome on treatment is markedly different from that of the historical control*

Predictable Course of Disease

Up-to-date understanding of disease progression

Compound	DRUG A	DRUG O	DRUG S
Pivotal Study	Phase 2, single-arm, international, multi-center	Phase 2/3 open-label, non-comparative	Ph2, open-label, single-arm with different dosing regimens
Source of HC	*Implied historical control*	International survey	Retrospectively natural history cohort
Strengths or Limitations	*Any anti-tumor effect observed must be attributed solely to the agent under investigation, as there is no precedent for any heavily pre-treated patients with [ ] whose disease is refractory to [ ] and [ ] ever experiencing a spontaneous regression of their disease to the point of meeting the protocol criteria for "partial response".*	Improved neonatal screening for patients with [ ] and earlier dietary intervention could possibly slow the natural progression of the disease. … part of the observed increase in survival rate in this clinical study could be due to earlier dietary treatment in addition to the new drug therapy with [ ].	Patients with [ ] show signs and symptoms after 6 mos and up to 18 yrs. These symptoms are heterogeneous in nature and are far less progressive relative to those associated with the [ ] patient population.

Comparability

Comparable populations, instruments and assessments

Compound	DRUG V	DRUG B	DRUG E
Pivotal Study	Phase 2/3, prospective, single-arm, open-label	Ph1/2, first-in-human, single-arm, open-label, dose-escalation	Ph2 randomized, placebo-controlled study followed by OLE
Source of HC	Natural history study	Baseline matched natural history cohort based on registry data	*Post hoc* historical cohort identified using 5 relevant baseline factors from registries
Strengths or Limitations	The control group chosen was appropriate for comparison to the current study population for the following reasons: (1) comparable key IE criteria; (2) patients were enrolled, and all data was collected, prospectively, and (3) patients were enrolled during a similar time period and were treated following the same guidelines	The applicant submitted evidence is not sufficiently strong regarding the [ ] rating scale comparability between HC and pivotal study • FDA's efficacy assessment focused only on the [ ] domain and ignored the [ ] domain score	Performance on [ ] can be improved by motivation in a clinical trial setting, but limited in real life due to concerns of failing or injury. … [ ] collected in the historical control group was not performed in the same investigative site or same investigator.

Objective Endpt w/ Large Effect

Statistical methods matter

Compound	DRUG P	DRUG C	DRUG X
Pivotal Study	Phase 3, single-arm	Phase 2, randomized, open-label, dose finding	Ph2b single-arm, open-label study
Source of HC	Literature review and a matched historically cohort.	Retrospective longitudinal study	Retrospective historical cohort
Strengths and Limitations	Matched historical control favorable outcome was 11% compared to 89% in the [ ] trial, with relative risk of 64.5, 95% CI [9 to 472], p <0.0001 …, historical controls can provide convincing evidence of efficacy when the outcomes with currently available treatment options are poor and the treatment effect is too large to be easily explained by confounding factors.	Between groups difference in [ ] at Week 64 were assessed in 4 different methods: • Observed data analysis • Inverse probability of treatment weighting • PS matching w/o replacement • PS matching w/ replacement	Sponsor analysis: HR 0.41 with 95% CI (0.26, 0.65) FDA's analysis: HR 0.63 with 95% CI (0.25, 1.58)

Other Observations

- Within the cases reviewed, the degree of unmet medical needs often outweighs the strength of (statistical) evidence in the regulatory decision
  - A particular HC strategy worked before, does not mean it will work again
- Advanced statistical methods, e.g., matching based analyses, play an increasingly important role when HC is utilized
  - Historical (treatment) effect will improve overtime, demanding more efficient and comprehensive analysis techniques
- Significant data attrition occurred as historical data were pruned using current I/E criterion to match the clinical trial population
  - Yet it does not guarantee a “matched” historical cohort
  - What if the pivotal study is prospectively planned to match and adapt to historical data?

Should we use HC

Data, Disease and Darn a lot more …

Many other factors impact the drug development program, take (Type 1) spinal muscular atrophy as an example.

Compound	US Approval Year	Modality	Source of HC	Method to utilize HC
SPINRAZA	2016	Intrathecal injection	Natural history study[1]	Served as external control in a Ph2 open-label dose-ranging study intended as the basis for NDA[3]
ZOLGENSMA	2019	Gene Therapy	Natural history study[1,2]	Characterized disease progression to support the pivotal study
EVRYSDI (risdiplam)	2020	Oral		Establish an efficacy threshold[4]

[1] Finkel RS, et al. *Neurology*. 2014;83:810-7.

[2] Kolb S, et al. *Amer Neuro Assoc* 2017; 883-891

[3] https://www.accessdata.fda.gov/drugsatfda_docs/nda/2016/209531Orig1s000MedR.pdf, https://www.accessdata.fda.gov/drugsatfda_docs/nda/2016/209531Orig1s000Admincorres.pdf

[4] Reid and Burger. 3rd EFSPI Workshop on Regulatory Statistics, 2018.

Summary

- Review selected NDA/BLA submissions which utilized historical control to support primary efficacy claim
- PERSONAL OPINION: proper characterization of the outcome from a newly enrolled patient if not treated or treated with SOC, is the single most important factor to the success of using HC
- In small population disease area, statisticians should use our expertise to help team design better natural history study that suits the development need