A Practical Review of Real World Data for Effectiveness Decisions

Case Studies of Using Historical Data in Developing Novel Therapies by DIA NEED

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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

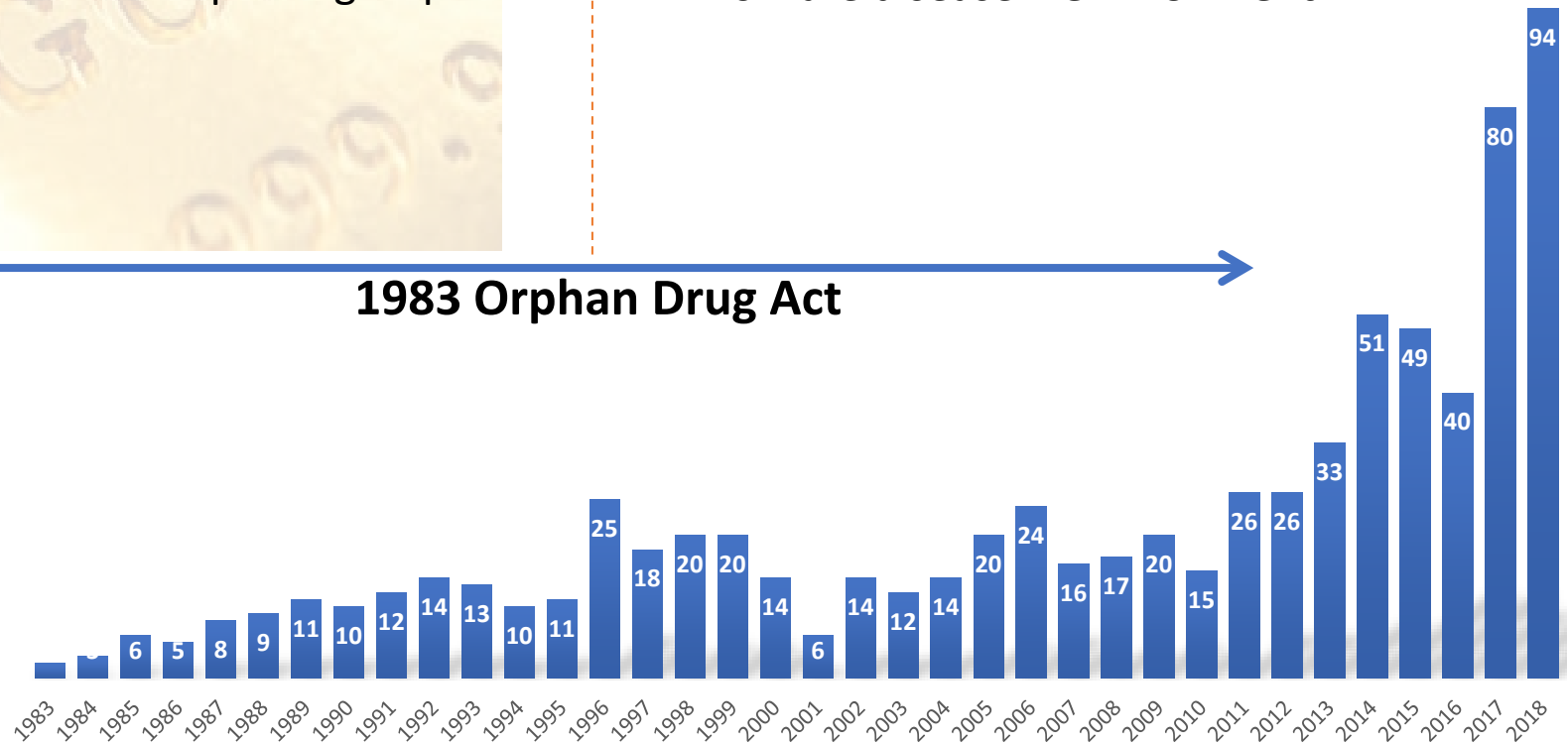
- Remove the potential bias
- Produce compared groups

Back to "historical control" ?

- Accessibility to massive historical data **– resources**
- Advances in genetic research for rare disease – **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/

DIA-ADSWG Nature and Extent of Evidence Needed for Rare Diseases (NEED) Subteam

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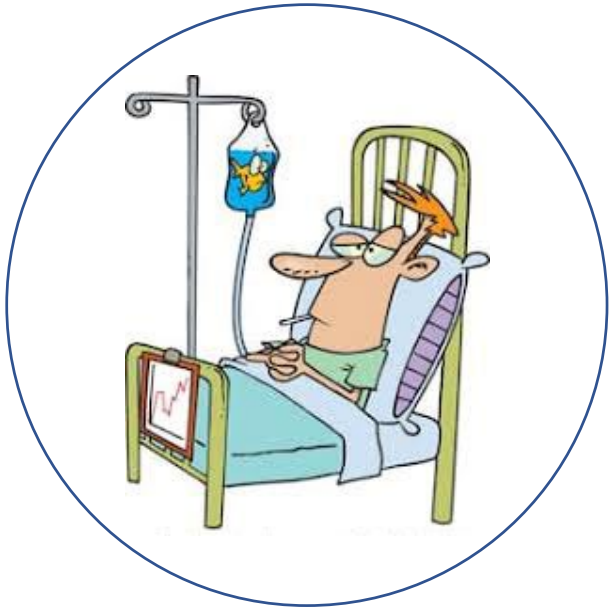
A Practical Roadmap

1 Resources of HD → 2 Should we use HC? → 3 Disadvantages of using HC → 4 Minimizing disadvantages

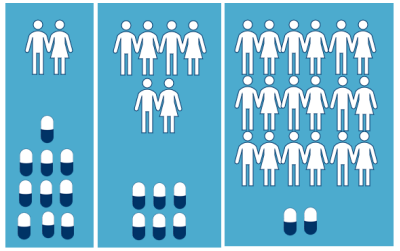
Medical chart



Patient registry

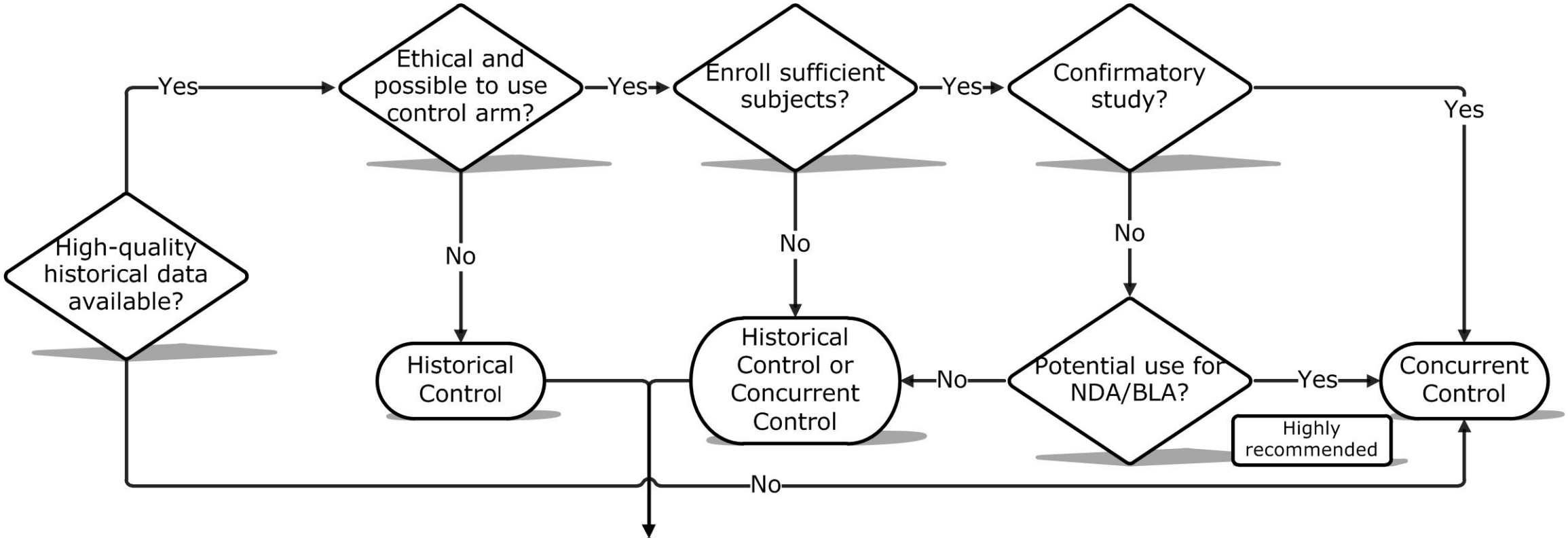
Claim data

Previous clinical trials



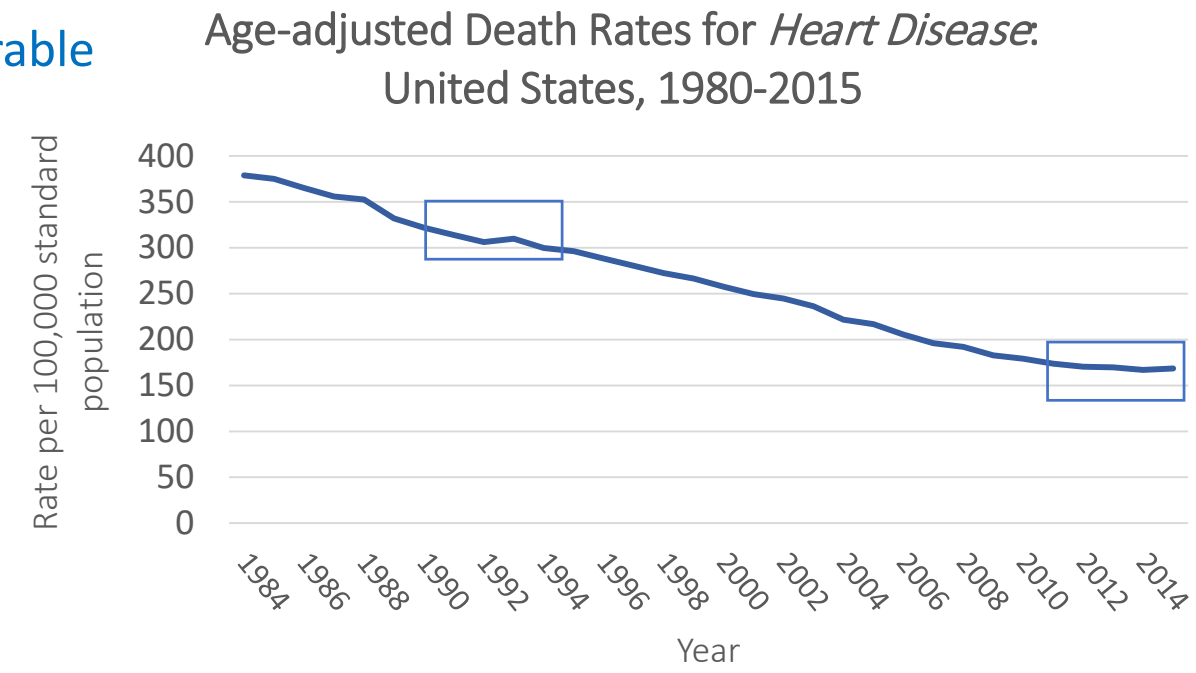
Natural history studies

1 Resources of HD → 2 Should we use HC? → 3 Disadvantages of using HC → 4 Minimizing disadvantages

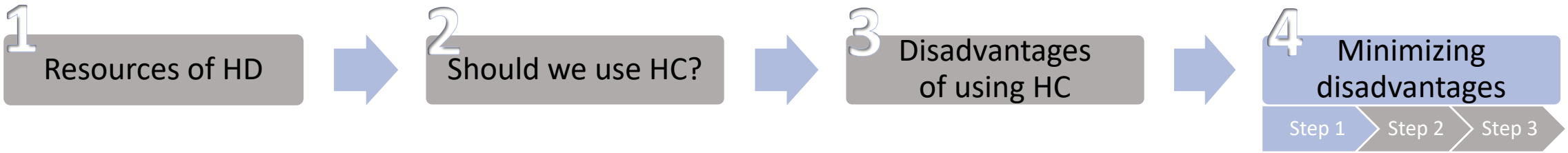


1 Resources of HD → 2 Should we use HC? → 3 Disadvantages of using HC → 4 Minimizing disadvantages

- Not randomized
  - Population between groups are not comparable
- Not concurrent
  - Improved standard care
  - More sensitive technology
- Data collection
  - Lack of blinding
  - Accuracy
  - Missingness



Source: https://data.cdc.gov/NCHS/NCHS-Age-adjusted-Death-Rates-for-Selected-Major-C/6rkc-nb2q

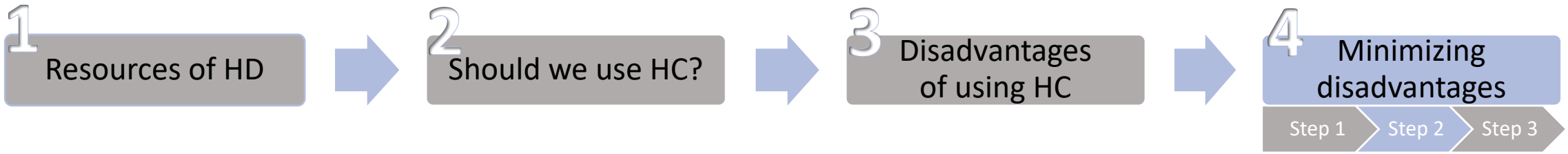


Step 1: At the design stage

- Choose high-quality historical control(s)
  - Checklists to evaluate real-world data
  - Flowcharts by Clinical Trials Transformations Initiative (CTTI) to evaluate registry data

- Design the current study closely to the selected historical control(s)

  Pocock's (1976) criteria
  - Inclusion/exclusion criteria for patient population
  - Type of study design
  - Exact definition of the outcome
  - Quality of study execution and management;
  - Potential biases due to time trends



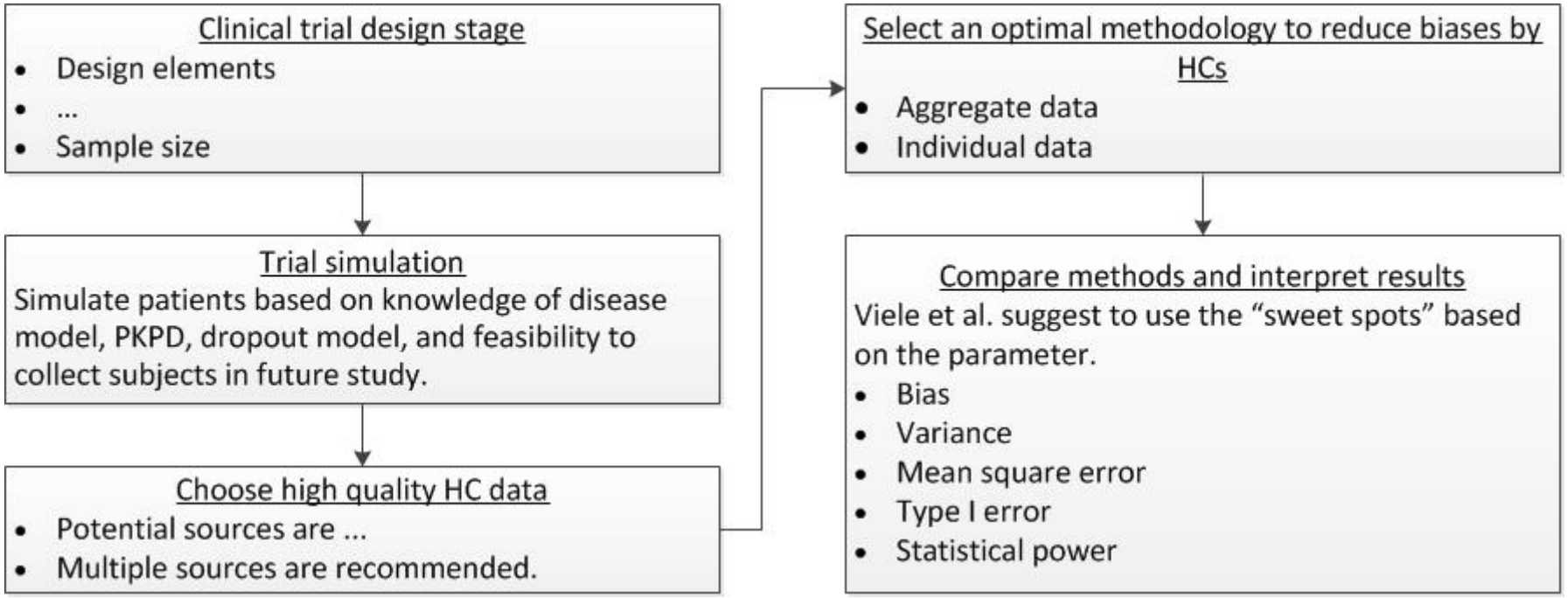
Step 2: At the analysis stage

Meta-analysis	• Network meta-analysis • Simulated treatment outcome • Matching-adjusted indirect comparison
Casual inference/ observational study	• Matching based on covariates or propensity score • Weighting by the inverse probability of treatment • Etc.
Historical borrowing	• Bias-variance (Pocock SJ, 1976) • Test-then-pool (Viele K, et al, 2014) • Power prior (Ibrahim JG, et al, 2000) • Meta-analytic Combined (Neuenschwander B, et al, 2010) • Meta-analytic Predictive (Neuenschwander B, et al, 2010) • Etc.

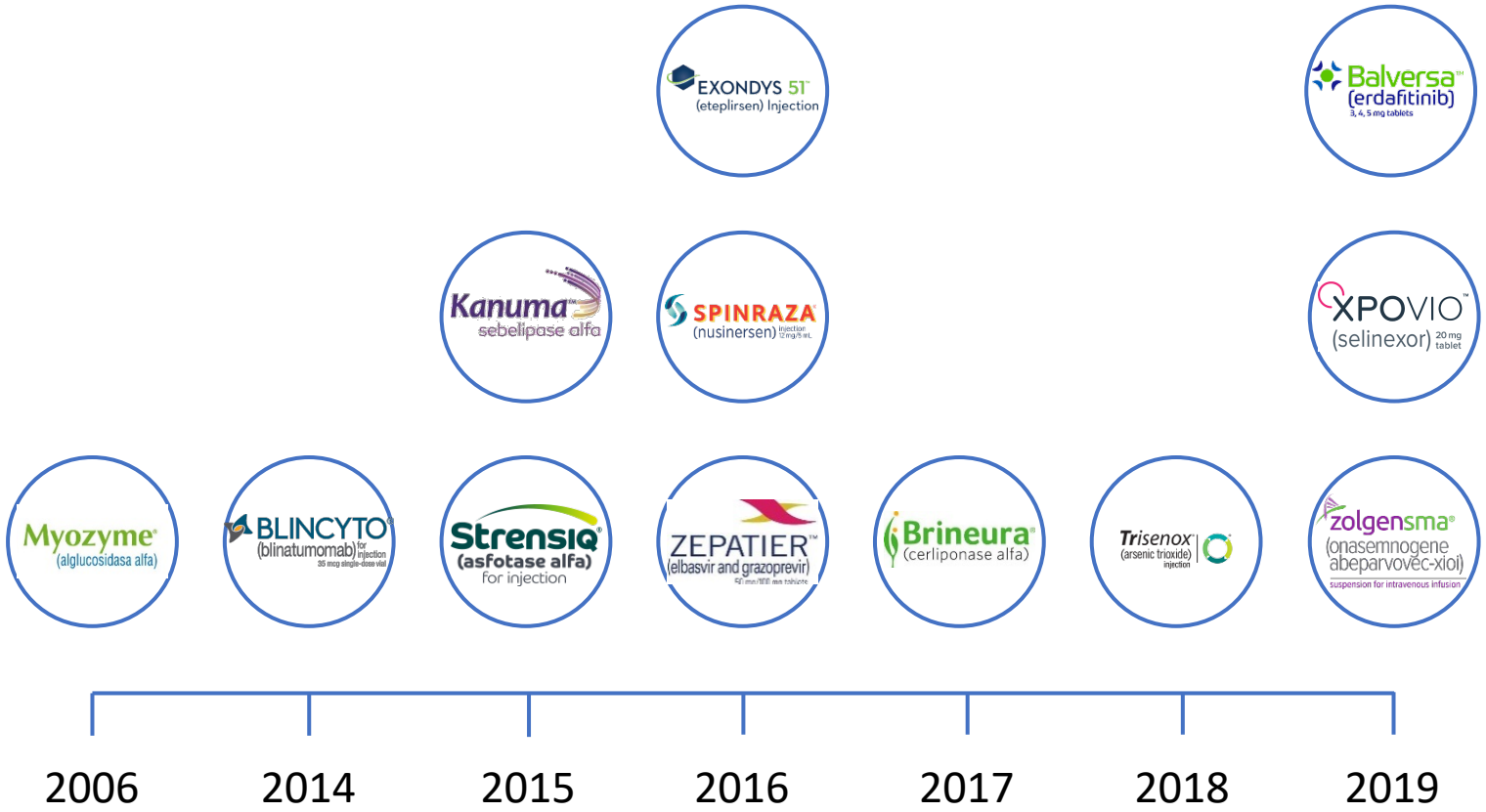
Step 3: Simulation and sensitivity analysis

No one solution that works in all situations.

The recommendation is to perform simulations as the following process:



Case Studies



Case Studies - Disclaimers

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

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

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

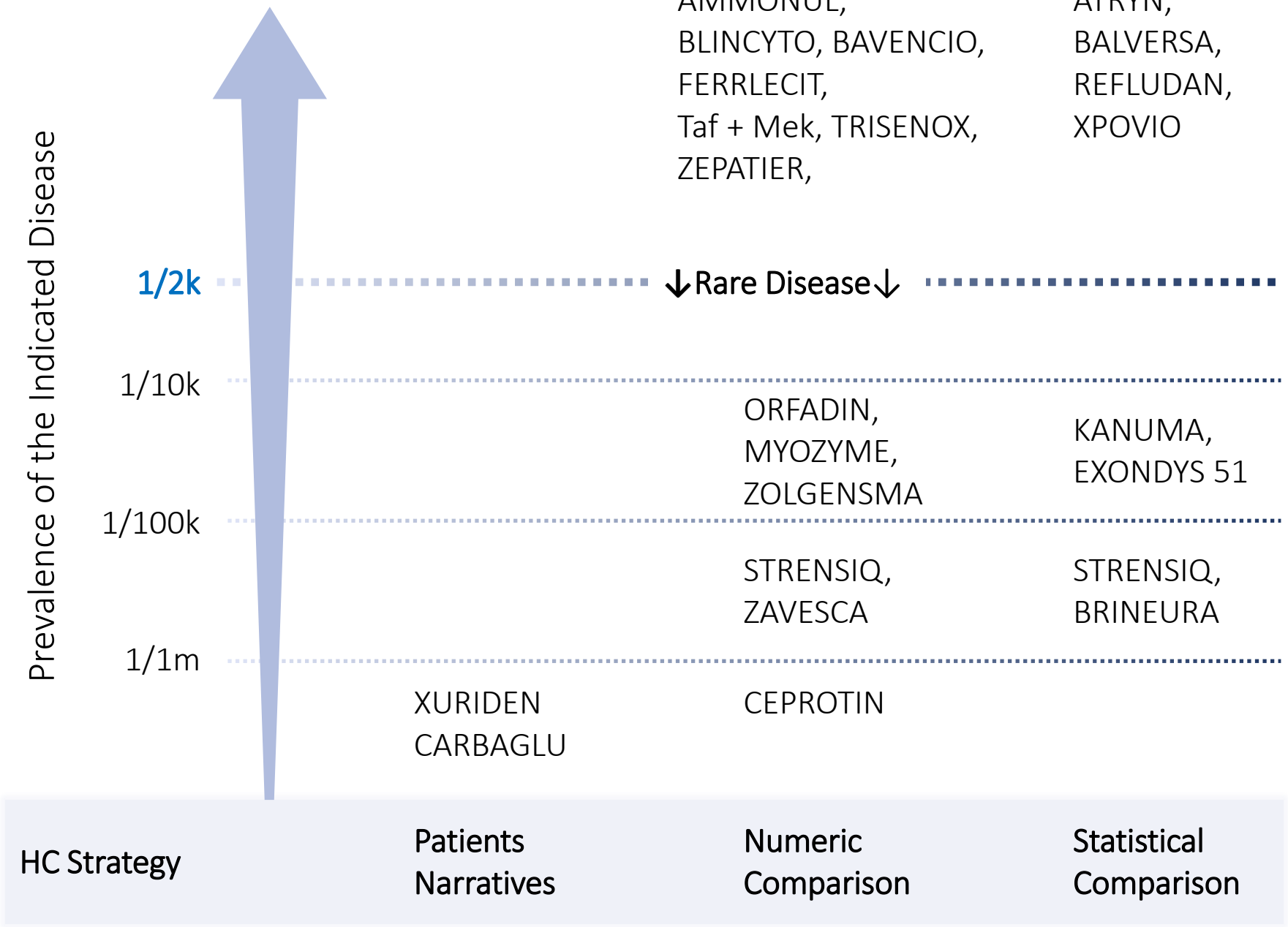
1+2 HC Strategy

NEED team reviewed filings from 22 drugs.

Source of HD:

- Chart review, database, publication (12)
- Registry (6)
- Previous clinical trials (1)
- Natural history (3)

Strategy to utilize historical data (to compare against IMP) varies.



1+2

HC Strategy

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

Drug	US Approval Year	Modality	Source of HC	Method to utilize HC
SPINRAZA	2016	Intrathecal injection	Natural history	Served as the control arm in a Ph2 dose-ranging study intended as basis for NDA[1]
ZOLGENSMA	2019	Gene Therapy	Prospective Natural history study[2]	Characterized disease progression to support the pivotal study
Risdiplam	In development	Oral	Natural history	Establish an efficacy threshold[3]

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

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

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

3+4
Working with HC

Selection Bias, and How to Minimize It

Compound	BLINCYTO	MYOZYME	XPOVIO
Pivotal Study	Ph2 fixed-dose single-arm study using a Simon 2-stage design with extension	Ph2/3 open-label, dose-ranging study in patients <6 mos with infantile-onset Pompe disease	Ph2b single-arm, open-label study in patients with relapsed/refractory multiple myeloma
Primary Endpoint	Complete remission or CR with partial hematological recovery (CR/CRh*) rate within first 2 cycles of treatment	Ventilator-free survival at 12 mos of age	Overall response rate (proportion of patients with a partial response or better)
Source of Historical Control	Retrospective historical database by combining existing databases from EU and US source	Retrospectively natural history cohort (identified based on entry criteria used in the pivotal study)	Retrospective historical cohort identified from Flatiron health analytic database
Limitations and Review Issues	• The estimated CR rate has accounted for important differences between patients in the HCs and MT103-211 • Each of the historical studies provided large # and variety of patients	• Patients were 'healthier' in the clinical study than HC given they need to survive long enough to enter the study and start treatment • Natural history study suggested improved survival overtime, the benefit of Myozyme is likely to be over estimated	• HC selection criteria systematically ensure that the clinical cohort will have longer expected OS compared to HC cohort (HC has 31% subjects with baseline ECOG missing) • Imbalances in baseline characteristics between the HC and clinical cohorts were noted

3+4
Working with HC

Assessment Bias, and How to Minimize It

Compound	KANUMA	BRINEURA	EXONDYS 51
Pivotal Study	Ph1/2 open-label, single-arm study in infants with rapidly progressive disease due to LAL deficiency	Ph1/2, first-in-human, single-arm, open-label, dose-escalation	Ph2 randomized, placebo-controlled study followed by OLE
Primary Endpoint	Time to death from birth up to Month 12	% of patients with an absence of an unreversed (sustained) 2-point rate (slope) of decline or a score of 0 in the Motor total score over 96 weeks	% dystrophin positive fibers • 2nd endpoint: 6-minute walk test (6MWT)
Source of Historical Control	Retrospective natural history cohort (baseline matched)	Baseline matched natural history cohort based on registry data	*Post hoc* historical cohort identified using 5 relevant baseline factors from 2 DMD patients registries
Limitations and Review Issues	Sponsor took the recommendation from DGIEP and used survival as the primary endpoint	The applicant submitted evidence is not sufficiently strong regarding the CLN2 rating scale comparability between HC and pivotal study • FDA's efficacy assessment focused only on the motor domain and ignored the language domain score	• Performance on 6MWT can be improved by motivation in a clinical trial setting, but limited in real life due to concerns of failing or injury • 6MWT collected in the HC group was not performed in the same investigative site or same investigator

Missing Values, and How to Minimize It

Compound	ZEPATIER	BALVERSA	TRISENOX
Pivotal Study	Two trials with Placebo control and two trials without Placebo	Ph2 two-arm, open-label efficacy study	Ph2, single-arm, multicenter study Ph1, single-arm, single institution study
Primary Endpoint	% of subjects achieving SVR12 after 12-week treatment	% of subjects with objective response rate (complete response + partial response)	% of subjects with complete remission
Source of Historical Control	Previous clinical trials and publications	Real-world Flatiron-FMI clinic-genomic database	A case series from medical chart stored by a single institution
Limitations and Review Issues	Using data from previous clinical trials to form HC substantially reduce the impact of missing values	It may be not practical to use a multiple imputation approach due to small sample size (16-25 patients) in the control cohorts, as about one third of subjects did not have an ECOG value.	The data is limited in information and does not include significant information such as bone marrow biopsy results, drugs involved in prior treatments, dosages and laboratory data.

Other Statistical Considerations

For time-to-event endpoint, it is important to properly define the index date to enable a fair comparison between HC and clinical cohort

- The start time in clinical trial is often fixed, e.g., date of first dose
- Defining start time in HC could be tricky, e.g., date of diagnosis, last day of prior therapy, the first time a clinically relevant biomarker exceeding a threshold, etc.

➢ Avoid creating the 'immortal time' bias!

Slope of decline is often used as a measure of disease progression

- With repeated and scheduled assessments, slope can be estimated with precision in clinical trial setting
- Challenging to get the same precision in HC (irregular timepoint, insufficient duration)

➢ Responder analysis may be more robust

Some Commonalities in the Statistical Review

General *guidelines* when evaluating the use of 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

Summary

- A practical roadmap to design and analyze clinical trial for small populations using historical (external) control
- A brief review on case studies which utilized historical control (to support primary efficacy claim)
  - Different strategy to utilize historical data and/or historical control
  - Disadvantages when using HC and how to minimize them
- Future work/topics
  - Putting new methodologies to test
  - Forward looking: how to conduct good natural history/observation study to generate quality evidence