External Control Arm Planning for Rare Diseases

The Professional Society for Health Economics & Outcomes Research

ISPOR Europe: 12-15 November 2023

Workshop Purpose

Description of this Presentation

- **External control arms (ECAs)** are increasingly being used in rare disease applications to regulatory and health-technology assessment (HTA) agencies.
- The acceptance of ECA evidence depends upon:
  - *Identification of a well-characterized external cohort*
  - *Appropriate justification of sources and methods used*

We will guide you through planning considerations for the creation of ECAs for regulatory and reimbursement purposes

Dr. Raymond A. Huml and his daughter, Meredith L., on the campus of North Carolina State University for a Facioscapulohumeral muscular dystrophy (FSHD) fundraiser.

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Agenda

Topic	Speaker	Duration
Polling questions *(Upfront to get to know you)*	Interactive	5 minutes
ECA guidance and case studies	**Carla Vossen** Syneos Health	10 minutes
Data sources to consider for ECAs in neuromuscular disease	**Raymond Huml** Syneos Health	10 minutes
Industry experience with rare diseases ECA planning for regulatory purposes	**Tracy Mayne** Independent Consultant	10 minutes
Using external control arms to inform economic models	**Dawn Lee** PenTAG	10 minutes
Challenges and solutions	**Raymond Huml** Syneos Health	5 minutes
Interactive discussion between presenters and with the audience	Interactive	15 minutes

Audience Polling Questions

Questions to get to know the audience

Q1. What is your experience with external control arms in rare diseases?

a. Extensive experience
b. Minimal experience
c. No experience

Q2. What is your position on external control arms for rare diseases?

a. Only useful to support evidence from randomized controlled trials.
b. I have doubts but might consider this to replace randomized control arms in the future.
c. Can be used as comparator arms for single arm trials.

Navigate to this session in the meeting app to participate!

ECA Guidance and Case Studies

Carla Vossen
Syneos Health

Suitability Externally Controlled Trials

FDA[1], EMA[2], and NICE[3] regard external control arms suitable when:

- ✓ RCT not considered ethical or feasible:
  - ✓ *Patients may oppose randomization*
  - ✓ ***Rarity of condition / small sample size***
- ✓ Serious condition with high unmet medical need

FDA[1]- and EMA[2]-specific considerations:

- ✓ Natural history well understood
- ✓ Established clinical or surrogate endpoints
- ✓ Large expected effect size
- ✓ Availability of a well-characterized external cohort

NICE[3]-specific considerations:

- ✓ Financial or technical constraints on studies
- ✓ Treatment combinations cannot be directly assessed
- ✓ RCT not applicable to care pathway / setting NHS
- ✓ RCT uses unvalidated surrogate outcomes
- ✓ RCT has limited follow-up
- ✓ RCT excludes eligible patients (e.g., children)

References:

1 FDA Draft Guidance for Industry. Considerations for the Design and Conduct of Externally Controlled Trials for Drug and Biological Products. February 2023. Available at: https://www.fda.gov/media/164960/download

2 EMA ICH E10 Choice of control group in clinical trials - Scientific guideline. January 2001. Available at: https://www.ema.europa.eu/en/ich-e10-choice-control-group-clinical-trials-scientific-guideline

3 NICE. Real-World Evidence Framework. June 2022; Update July 2023. Available at: https://www.nice.org.uk/corporate/ecd9/chapter/overview.

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Guidance Externally Controlled Trials

Key Items	FDA[1]	EMA[2]	NICE[3]	HAS[4]	CADTH[5]	EunetHTA[6]
Communication	✓ Early communication/scientific advice recommended					
Design Justification	✓ Pre-specified protocol and analysis plan ✓ Address comparability, confounding and bias					
Suitability Assessment	✓ Assessed case-by-case in (inter)national or European context					
Transparency	✓ Access to data ✓ Plans and reporting		✓ Plans and reporting			
Missing items	✗ Assessment suitability data sources ✗ Recommendations analysis methods		✗ Evidence synthesis external data ✗ International data and transportability		✗ Recommendations data sources ✗ Assessment suitability data	

EU joint clinical assessment impact mostly on patient access, and regulatory and HTA evidence strategy alignment.

References:

1 FDA Draft Guidance for Industry. Considerations for the Design and Conduct of Externally Controlled Trials for Drug and Biological Products. February 2023. Available at: https://www.fda.gov/media/164960/download.

2 EMA Draft Reflection paper on establishing efficacy based on single-arm trials submitted as pivotal evidence in a marketing authorization. April 2023. Available at: SAT guidance.

3 NICE. Real-World Evidence Framework. June 2022; Update July 2023. Available at: https://www.nice.org.uk/corporate/ecd9/chapter/overview.

4 Vanier A, et al. Rapid access to innovative medicinal products while ensuring relevant health technology assessment. Position of the French National Authority for Health. *BMJ Evid Based Med*. 2023;bmjebm-2022-112091.

5 CADTH Guidance for Reporting Real-World Evidence. May 2023. Available at: https://www.cadth.ca/guidance-reporting-real-world-evidence.

6 EUnetHTA. D4.3 Direct and Indirect Comparisons. Practical and methodological guidelines. August 2022. Available at: https://www.eunethta.eu/d4-3/.

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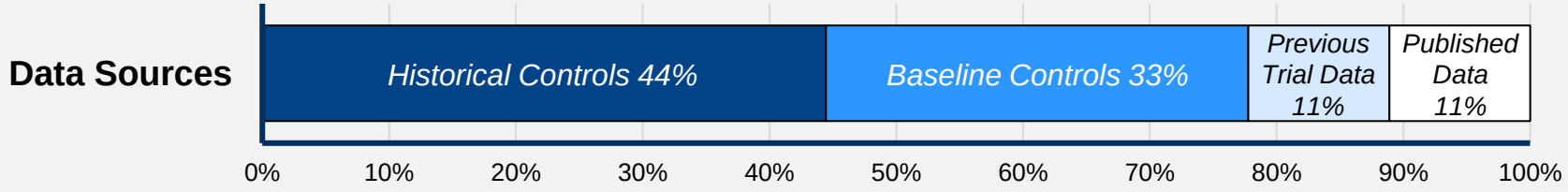
Regulatory Acceptance Externally Controlled Trials

EMA: external controls in 18 (17%) of 103 approved oncology submissions (2016–2021)[1]

- 63% of external control approaches accepted; but 0% that applied confounding adjustment
- 37% rejected due to:
  - *Heterogeneity populations*
  - *Missing outcome assessments*
  - *Inappropriate statistical analysis*

FDA: external controls accepted for 45 non-oncology submissions (2016-2021)[2]

- 80% were for rare diseases; 87% with an objective endpoint



References:

1 Wang X et al. Current perspectives for external control arms in oncology clinical trials: Analysis of EMA approvals 2016–2021. *J Cancer Policy*. 2023;35:100403.

2 Jahanshahi M et al. The Use of External Controls in FDA Regulatory Decision Making. *Ther Innov Regul Sci*. 2021;55:1019-1035.

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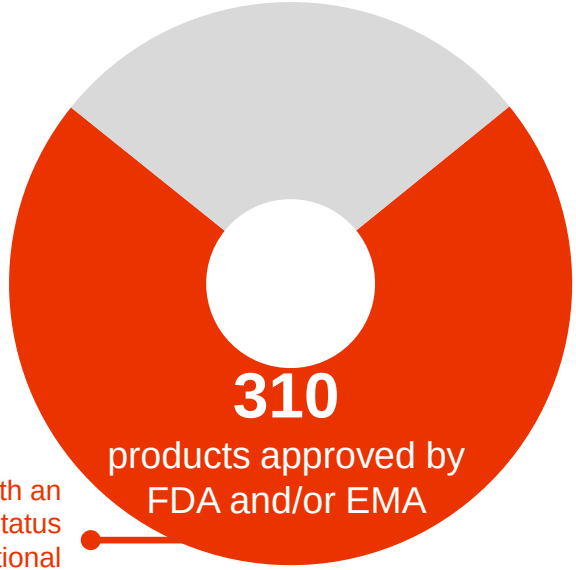
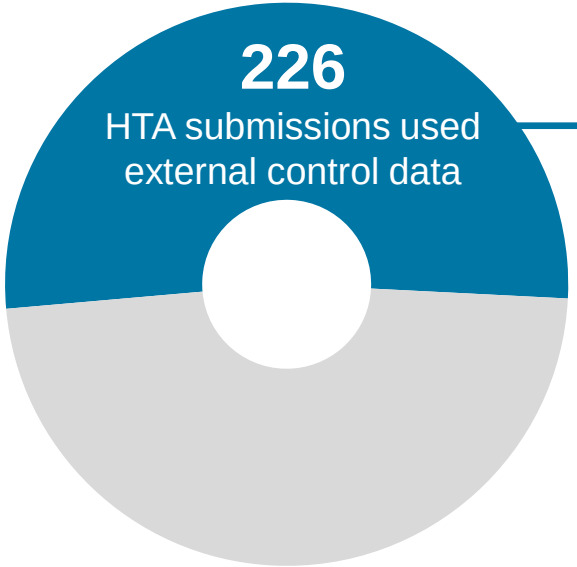
HTA Acceptance Externally Controlled Trials

433 HTA submissions including single-arm trial evidence in 21 countries (2011-2019)[1]



80% with an orphan status or conditional approval



- 29% used adjusted indirect treatment comparison
- 52% received positive recommendation
- Common data sources:
  - prior clinical trials (46%)
  - real-world data (39%)
  - both (15%)

Reference:

[1]Patel D, et al. Use of External Comparators for Health Technology Assessment Submissions Based on Single-Arm Trials. *Value Health*. 2021;24:1118-1125.

Selected Rare Disease Case Studies

All rare disease products below were approved by the FDA based on single arm data.

External control arms were rejected across agencies – mostly because of difficulties in finding suitable data.

Drug brand name *(generic name; year 1st approval)* Indication	Accepted for use by	Description external data *(patient-level data only)*	External control arm rejections across agencies					Reasons for external control arm rejection
			FDA	*EMA*	*NICE*	*HAS*	*G-BA*	
Abecma (idecabtagene vicleucel; 2021) Multiple myeloma	✓ FDA ✓ EMA ✓ G-BA	**Collated retrospective data from:** • Clinical sites • Registries • Research databases	✗	✗	N/A	N/A	✗	**Design justification:** × *Selection bias* × *Comparability* × *Missing data*
Exkivity (mobocertinib; 2021) NSCLC EGFR exon 20 mutation	✓ FDA ✓ NICE	• US database (Flatiron) • German charts	✗	✗*	✗	N/A	N/A	**Design justification:** × *Source selection approach* × *Comparability* **Suitability:** × *Large expected effect size* × *Well-characterized external cohort*
Rydapt (midostaurin; 2017) Leukemia, Mastocytosis	✓ FDA ✓ EMA ✓ NICE ✓ HAS ✓ G-BA	• German registry • Prior clinical trials	✗	✗	✗	N/A#	N/A#	**Design justification:** × *Selection bias* × *Comparability* × *Statistical planning and methods*

* Conditional marketing authorization application withdrawn by Sponsor after first feedback. ** Minjuvi not recommended for use in England

\# Submission was based on RCT data

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Data sources to consider for ECAs in neuromuscular disease

Raymond Huml
Syneos Health

Purpose: Description of this Presentation and Workshop

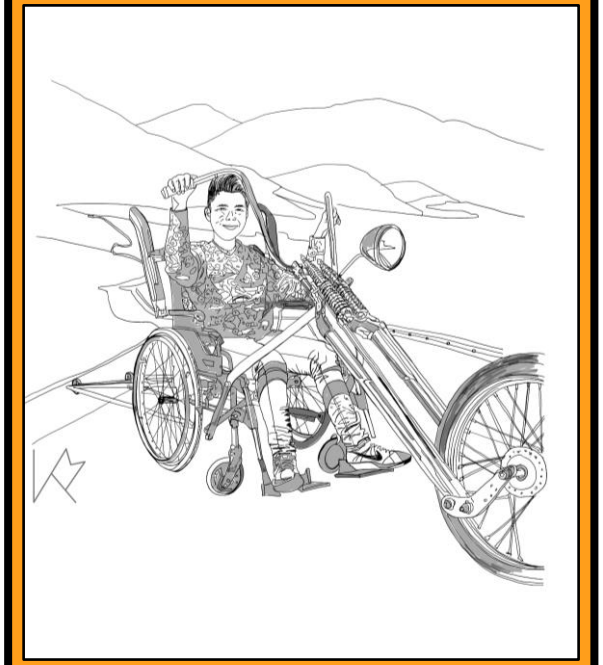

Illustration inspired by a photo of a boy in a modified “motorcycle” wheelchair on the front cover of the EURODIS 2015 Activity Report.

In an externally controlled trial, outcomes in participants receiving the investigational treatment under a study protocol are compared to outcomes in a group of people external to the trial who did not receive the same treatment.

The external arm can be a historical control from an earlier time, or a concurrent control of people during the same time-period but in a different setting.

This presentation will discuss how data from different sources can be used for creating comparator data for clinical trials for novel neuromuscular treatments, what challenges can be faced and what solutions can be implemented.

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MDA's neuroMuscular ObserVational Research Data Hub (MOVR)

Accelerating Therapeutic Advancements in Muscular Dystrophies through Shared Registry Platforms

Patient registries can be effective tools for understanding the natural history of disease, measuring quality of care, identifying patients for clinical trials, and assessing the safety and effectiveness of new treatments. Continuing advancements in health information technology – including the adoption of electronic medical record systems and data standards – hold the promise of helping rare disease stakeholders overcome some of the barriers to collecting and using clinical data that have hindered the development of broad-based national or international patient registry programmes in the past. The use of a shared registry platform may be especially timely given the growing interest in patient registries for neuromuscular disorders among patient advocacy organisations, researchers, pharmaceutical companies, and regulatory authorities. This article discusses the relevance of registries for the treatment of muscular dystrophies (a subset of rare diseases), major obstacles to the development of large registry programmes, features of a technology platform for collecting clinically rich information in the digital age, and other issues that need to be addressed in order to spur the formation of shared-platform registry partnerships.

The Relevance of Registries for Neuromuscular Diseases

A registry is defined as an organised system that uses observational methods to collect uniform data on specified outcomes in a population defined by a particular disease, condition or exposure.[1] Registries that aggregate data from medical records and/or directly from patients themselves can be used to understand the natural history of disease, measure quality of care for persons receiving health services, find patients for clinical trials, and assess the safety and effectiveness of approved therapies. The type of registry and the data it collects will usually be determined by the research questions being answered. Exposure or product-based registries include patients based on an exposure to a particular treatment. Disease or condition-based registries assess the impact of various treatments, which is useful for developing treatment algorithms or guidelines and helping elucidate choices for patients and clinicians. Registries can also vary in sophistication and scope, from simple spreadsheets that are set up by a single physician to complex databases that are accessed online across multiple institutions around the world.

Organisations initiate rare-disease registries for different purposes and can change or revise their programmes over time. For diseases where patients are few, research agendas do not exist, standard case guidelines are absent, and patient communities have not yet formed, patient registries can be a first step in trying to understand the number of people affected, their geographical distribution, and the basic demographic and clinical characteristics of the disease.[2] In areas where disease-modifying treatments already exist or where the drug pipeline looks promising, the business case may be stronger for investing in the collection of detailed information from clinicians and patients. According to the Agency for Healthcare Research and Quality, the objectives of rare disease registry programmes fall into four main categories: connecting patients, families, and clinicians; learning about the natural history, evolution, risk, and outcomes of specific diseases; supporting research on the genetic, molecular, and physiological basis of rare diseases; and establishing a patient base for evaluating drugs, medical devices, and related orphan products.[3]

Although data from registries are not a substitute for controlled trials, in the case of rare diseases where treatment options are limited, registry data may be the only source of information available regarding a specific product's use at a population level. Pharmaceutical companies and regulators consider disease registries a valuable source of comparator data that can help "fill in the blanks" about outcomes that were not addressed in limited controlled trials.[4] There may also be situations when a randomised controlled trial is not ethically possible and so comparator data from a registry may be the only option.

Globally, several muscular dystrophy patient communities have been established to share rapidly evolving scientific advances, provide a platform for patient advocacy, and offer opportunities to advance scientific knowledge so that viable treatment options can be found. To advance scientific knowledge, some communities have established registries collecting data useful for research such as patient demographics, genetic profiling and drug treatment.[5] For example, Parent Project Muscular Dystrophy (PPMD), a company located in the US, established DuchenneConnect, a registry for individuals with Duchenne and Becker muscular dystrophy (DMD and BMD) and in Europe, Action Duchenne has a curated registry for the same diseases.[6] The overall goals of these programmes are to expand the knowledge base of these muscular dystrophies, to connect patients with actively recruiting clinical trials and research studies, and to educate patients and families about DMD and BMD research.[7]

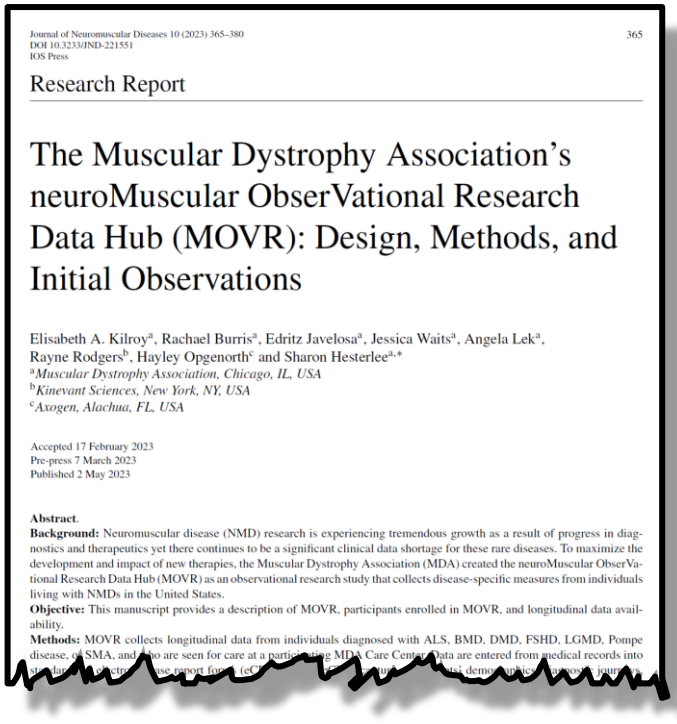
Regardless of whether or not a treatment has been approved by regulatory authorities, registries can also be used to assess the quality of care provided to patients with a rare disorder. This information can be given to healthcare providers to drive quality improvement and to families, who want objective information in deciding where to take their loved one for care. Data on quality measures and outcomes can also be used to document the evolving standard of care, as treatments change over time. The Muscular Dystrophy Association (MDA), for example, established the US Neuromuscular Disease Registry programme in 2013 to collect longitudinal patient data to benchmark best clinical practices and implement a clinical quality improvement programme for MDA Care Centers across the country.[8] Similarly, the Centers for Medicare and Medicaid Services (CMS) has established rules for qualified clinical data registries (QCDRs) as a way to help physicians drive quality improvement as part of the Quality Payment Program under Medicare.

BACKGROUND:

- *Seven of 43 ongoing neuromuscular indications (including Facioscapulohumeral muscular dystrophy); can be used to determine natural history insights, endpoint selection, patient- and caregiver- reported outcomes research, and health economics outcomes analysis*

PREMISES:

- *Clinical trial data (randomized, controlled, double blind trials) are still gold/platinum, but real-world data / evidence (RWD/E) can augment both regulatory dossiers (pre-approval) and payer systems (pre- or post-approval)*
- *RWE can be gleaned from patient registries and natural history studies*



Journal of Neuromuscular Diseases 10 (2023) 365–380
DOI 10.3233/JND-221551
IOS Press

Research Report

The Muscular Dystrophy Association's neuroMuscular ObserVational Research Data Hub (MOVR): Design, Methods, and Initial Observations

Elisabeth A. Kilroy[a], Rachael Burris[a], Edritz Javelosa[a], Jessica Waits[a], Angela Lek[a], Rayne Rodgers[b], Hayley Opgenorth[c] and Sharon Hesterlee[a,*]
[a]*Muscular Dystrophy Association, Chicago, IL, USA*
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Accepted 17 February 2023
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Abstract.
Background: Neuromuscular disease (NMD) research is experiencing tremendous growth as a result of progress in diagnostics and therapeutics yet there continues to be a significant clinical data shortage for these rare diseases. To maximize the development and impact of new therapies, the Muscular Dystrophy Association (MDA) created the neuroMuscular ObserVational Research Data Hub (MOVR) as an observational research study that collects disease-specific measures from individuals living with NMDs in the United States.
Objective: This manuscript provides a description of MOVR, participants enrolled in MOVR, and longitudinal data availability.
Methods: MOVR collects longitudinal data from individuals diagnosed with ALS, BMD, DMD, FSHD, LGMD, Pompe disease, SMA, and Myo are seen for care at a participating MDA Care Center. Data are entered from medical records into

Genentech's Evrysdi®

Well-defined Endpoints Fortify Evrysdi® External Controls

- Externally controlled Firefish study allowed inclusion of infants with Type 1 spinal muscular atrophy (SMA) in indication for Genentech, Inc.'s Evrysdi® (risdiplam)
  - *Included a placebo-controlled trial, the Sunfish study, in children and adults with the less severe Type 2 or 3 SMA*
- Use of external controls for Firefish was controversial within agency
  - *Biometrics review team concluded "the evidence from Firefish, though impressive on face compared to the reported natural history, is not well controlled."*
- Clinical and upper-level reviewers disagreed, asserting "although Study BP39056 [Firefish] was open-label, it is a well-controlled study" that was "rigorously conducted"
- Revies stated "the study endpoints of sitting unsupported and ventilator-free survival were well-defined, with a low potential for bias." "Importantly, the results were clearly outside the natural history of the disease course for Type 1 SMA."

Kevin Schafer, who lives with Type 2 SMA, said that people regularly mistake him for Tony Stark, the fictional superhero of the movie, "Ironman", because of his intellect and advanced technological equipment.

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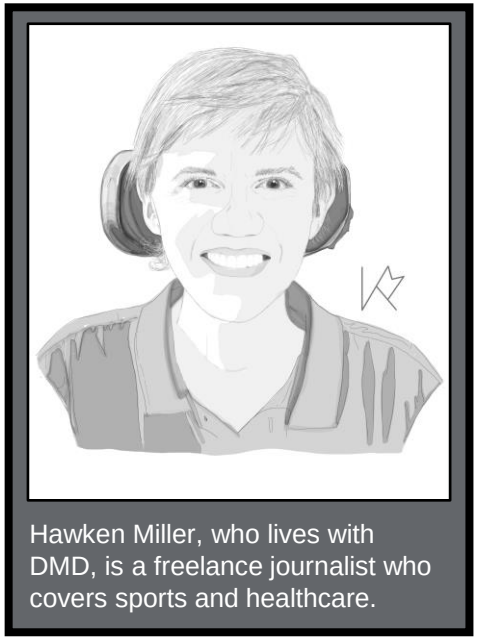
External Controls: Sarepta's DMD Gene Therapy

Compared with Novartis' Zolgensma®

- Sarepta conducted study-level and integrated-level comparison analyses of SRP-9001-treated patients and external controls
- Heterogeneous nature of Duchenne Muscular Dystrophy (DMD) and the potentially moderate treatment effect of SRP-9001 distinguish it from Novartis' SMA treatment, where natural history data were used to support single-arm trial results
- Sarepta Therapeutics, Inc.'s bid to use external control data to contextualize the clinical efficacy results for SRP-9001 in DMD fell flat with the FDA but found a receptive audience with some advisory committee members
- Cellular, Tissue and Gene Therapies Advisory Committee & agency review staff said DMD is too heterogeneous a disease, and any potential treatment effect with SRP-9001 is too moderate
- The FDA's view of Sarepta's analyses shows the high bar the agency has set for use of external controls to demonstrate efficacy.



Hawken Miller, who lives with DMD, is a freelance journalist who covers sports and healthcare.

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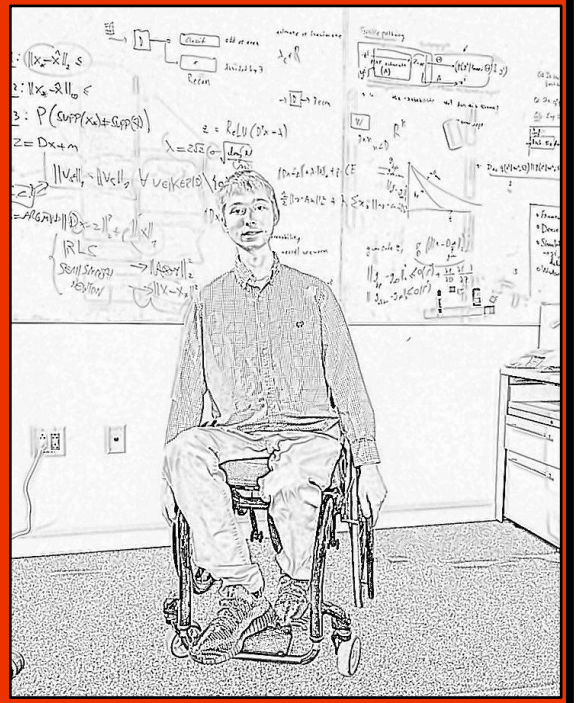
External Controls: Sarepta's DMD Gene Therapy II

External Control Sets Problematic

Jonathan R. Huml in his office at Harvard University's John A. Paulson School of Engineering and Applied Sciences complex.

Jonathan graduated with his MSE in Computational Science from Harvard University in May 2023.



- In a sensitivity analysis, this comparison was repeated with the predicted control analysis technique on a distinct and independent external control pool, and the results were directionally consistent and similar in magnitude
- In its meeting briefing document, FDA cited various limitations and weaknesses with Sarepta's external controls comparison:
  - *Disease course of DMD is highly heterogeneous across this age range, increasing likelihood of noncomparable patients across data sources*
  - *Intended treatment effect unlikely to be more than moderate*
  - *External control analysis would not be able to provide results persuasive enough to overcome potential biases*

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External Controls: Sarepta's DMD Gene Therapy III

FDA Contrasted Sarepta DMD Gene Therapy Data Set with Novartis AG Zolgensma® Data Set

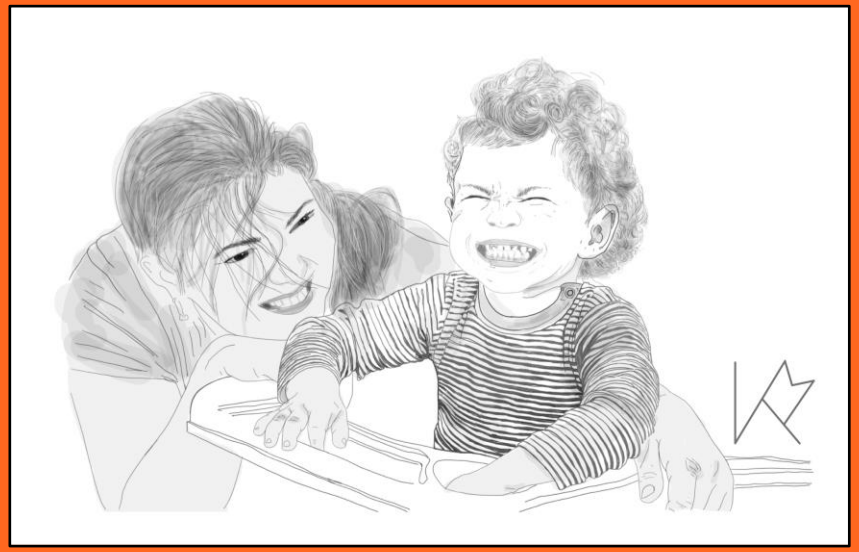

Illustration of Daniel, from Russia, who has Williams syndrome – a rare neurodevelopmental disorder. This illustration is from the 2014 EURODIS Photo Contest where it received the Expert's Choice Award.

Due to critical limitations of external control comparisons, integrated analysis and other study-level analyses "can only serve as exploratory and do not provide confirmatory evidence to support clinical benefit of SRP-9001," agency's briefing document states.

"In situations where we're looking at a disease where progression is heterogeneous for individual patients, where a treatment effect may be moderate, which would be an important clinical advance but is difficult to detect in a clinical studies … using an external control is very challenging to be able to draw any conclusions"

Mike Singer, FDA

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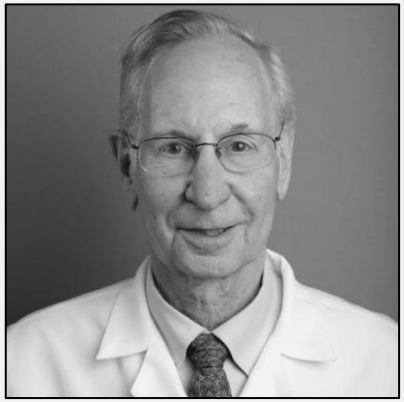
External Controls: Sarepta's DMD Gene Therapy IV

Although the FDA summarily dispatched with Sarepta's external controls analyses, some advisory committee members found the data persuasive.
The committee voted 8-6 in favor of accelerated approval.



Raymond Roos, MD
FDA Panelist

"One could be critical of this. There aren't a lot of subjects. There's no hypothesis tested, and individuals that are 6-7 years old didn't show any improvement.

"However, I'm impressed by the external controls that Sarepta showed, which suggest that the gene therapy, even in age 6–7-year-olds, is helpful. And perhaps the difference in the lack of improvement in the 6–7-year-olds is because they started at a different level, or maybe we need a second year to examine the effects of gene therapy."

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FDA Real-World Evidence

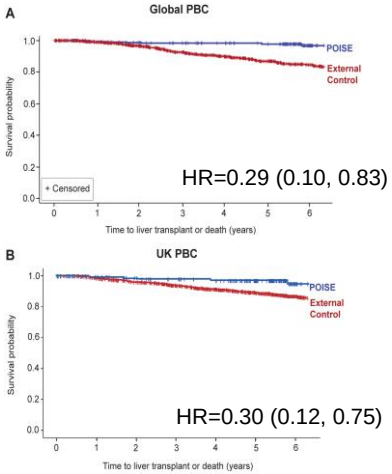
FROM THEORY TO PRACTICE

My Experience

Submission for PMR fulfillment and full approval

- 747-301 phase 3 with surrogate endpoint LTSE with 2 external controls
- 747-302 phase 3b/4 outcomes trial with external controls
- 747-405 phase 4 fully real-world nested trial emulation
- Design (with Alan Brookhart), protocol, analysis, CSR, sNDA, agency interactions

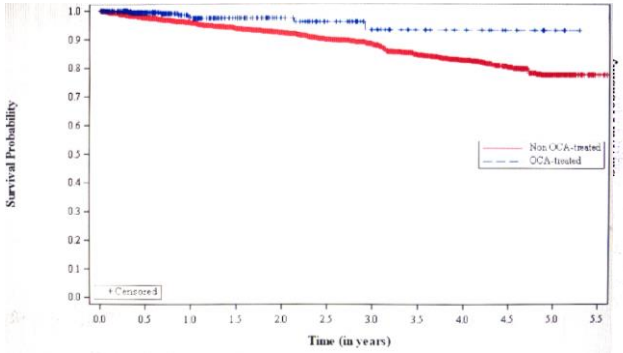
Phase 3 LTSE with EC



HR=0.29 (0.10, 0.83)

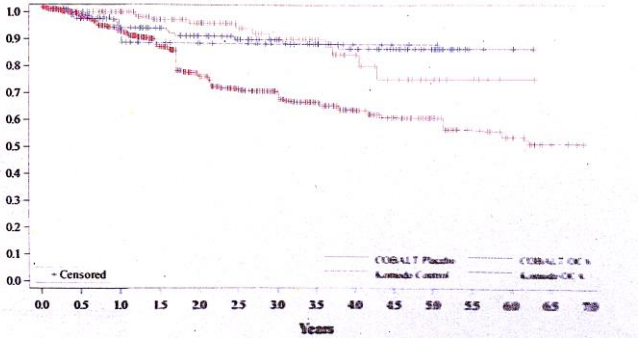
HR=0.30 (0.12, 0.75)

Phase 4 Nested Trial Emulation



HR=0.37 (0.14, 0.75)

Phase 3b/4 with EC



HR=0.39 (0.22, 0.69)

When Worlds Collide

Knows FDA regulations & requirements
Have appropriate SOPs

Knows RWD
Knows the analytic techniques

Major Areas

Selecting a RWE dataset

Selecting a vendor

Design

Medical writing

Clinicaltrials.gov

CDISC

Analysis and TLFs

Clean Room Committee

Adjudication

Audits

Submission

Selecting A Dataset

The FDA requires a patient-level dataset (deidentified is fine)

- GDPR privacy rules largely rule out EU data
- Few registries meet the strict FDA requirements (training, documentation, SDV…)
- EHR requires additional validation
- US claims data: standard collection, content and format, serious events well-recorded
- Merge with labs (LabCorp, Quest), government registries (SSDI, NDI, OPTN)

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Selecting A Vendor

Vendor needs regulatory SOPs (data collection, management, analysis, medical writing)

Vendor needs to create and maintain a TMF

Vendor needs to create traceable protocols and CSRs in regulatory format (Veeva)

Vendor needs Clin Dev + Regulatory + HEOR/RWE: YOU are the bridge

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Design

Only external control vs EC + PBO?

If EC + PBO: Full study PBO vs PBO for 1 year with index of dissimilarity and cross-over?

Selecting an index: random selection from all eligible (1st and last eligible for sensitivity) vs nested trial emulation

If sub-part H: include a fully real-world treated comparator to compare to trial, and to EC

Primary analysis: As-treated (censor at treatment cross-over) vs exposure-adjusted; ITT as sensitivity

Efficacy AND safety analyses

Efficacy endpoints

- Hard endpoints (hospitalization for an event)
- Death
- Adjudication

Safety

- ICD9 -> ICD10 (CMS but is not complete) -> MedDRA LLT (WHO mixed) -> MedDRA PT -> SOC
- You're going to need 2 physicians and a coder to complete mapping
- While major events well-captured in both, claims pick up much more than a CRF: how to compare for safety?

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Medical Writing

Need regulatory medical writers

Modify existing FDA formats

Veeva Vault: traceability

Consider a protocol + supplement

CDISC

The RCT data will be in CDISC format – need RWE data in the same, harmonized, compliant format

Include map in protocol/supplement

Need experienced CDISC programmers

Need experienced RWE coders (e.g., What do you do if units not included on lab results? What do you do if multiple tests on one day? What do you do if discover double claims submission?)

SDTM and ADaMs datasets

- 30 programmers 6 months
- Modifications: e.g., all claims visits are unscheduled

Define-XML

WARNING: Claims have NDC, trials use ATC, which includes generic name AND indication. Likely need to code just by generic drug name.

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Analysis And TLFS

Stringent regulatory standards (everything double-programmed, documented)

Propensity scores and SMR weights must be done BLINDED to outcomes (no access to ADTTE), with SOPs and good documentation of blinding and unblinding

All TLFs are pre-specified in the protocol. If not, it's ad hoc.

TLF strict conformance (including time and date stamps)

Need experienced RWE programmers who know how to work with claims, and with analytic techniques not used in RCTs (PSM, SDMs, weighting…)

WARNING: SAS PROC MEANS does not compute correct medians, SEs or ranges for weighted data

Include lots of sensitivity analyses (individual endpoints, subgroups… including full quantitative bias)

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Registration

Pre-submit to FDA (how long will you wait for feedback?)

Register on clinicaltrials.gov

Clean Room Committee

RCT has a DSMB; RWE has a CRC

What is a CRC?

- SMEs (RWE/Biostats/Clinical) blind to the data
- Any modification to protocol must go through CRC
- Can be binding or not: suggest binding
- Examples: We didn't include medically implausible ranges on labs and would like to add them; we need to add an unforeseen ICD10 code

Requirements (FDA will want ALL of this)

- Charter
- Submissions
- Meeting notes
- Decision log

In CSR, CRC protocol modifications are separate from protocol deviations

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Event Adjudication

Efficacy (outcomes)

- Death not well collected in claims (death on discharge imperfect; there can be late claims after death)
- SSDI incomplete (false negatives)
- Obituary search (false positives)
- Need to adjudicate: did event occur and is it valid
- 2 clinicians and 1 coder, blinded to treatment group
- Hospitalization for event: admission not discharge

Safety (causality)

- While not as rich as an RCT, RWE can be rich (visits, diagnoses, labs, com meds, procedures…)
- Need to clearly think through if/how this will be done for TEAEs (drug related)
- Important for DILI (DILI triggers and eDISH)

Need charter and good documentation

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Audits

Main CRO (and perhaps others) will need to be audited at least once

Audit usually done my Quality

You'll need to edit/create an audit form specific to RWE

- Verify data access
- Review SOPs
- Spot check on code
- Review TMF…

Documentation

- Audit form
- Remediation plan
- Sign off that plan was implemented

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Submission

Dataset size: could be a terabyte

- Too large for an FDA gateway
- Too large for Pinnacle 21
- Too large for publishing programs

How long will FDA keep data (data licensing agreements)?

You Are The Bridge

If you are Clin Dev/Regulatory

- Learn about RWE data and formats
- Learn RWE analytic constructs
- Realize: RWE has some inherent flexibility – take advantage!

If you're HEOR/RWE

- Read FDA guidances (you'll never have another sleepless night)
- Be ready for greater rigidity

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Using external control arms to inform economic models

Dawn Lee

PenTAG

Key Differences between HTA and Regulatory

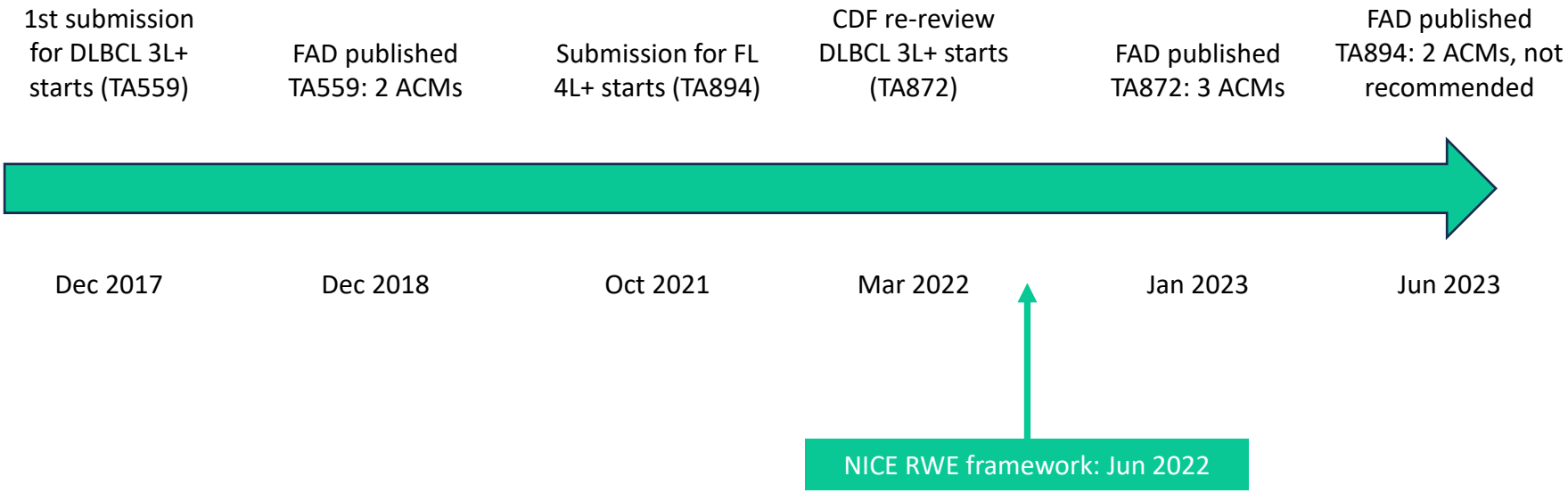
- Regulatory bodies seek to gain unbiased estimate of treatment effect
- HTA seeks to understand treatment effect and contingent estimate of cost-effectiveness **in decision problem population:**
  - *Decision problem population likely to differ from trial population*
  - *Decision problem may be different in different countries*
  - *Extrapolation required*
  - *Time on treatment important for costing*

NICE's recommendations

- **Emulate the RCT:**
  - *Target trial approach*
  - *Use same definitions for variables, match data collection processes where possible*
  - *Pragmatic: reflect routine care as closely as possible – tension here!*
  - *Pre-specify and publish protocol and analysis plan*
- **Identify potential confounders using systematic approach and clearly articulate causal assumptions (directed acyclic graphs)**
- **Use statistical method that addresses confounding considering observed and unobserved confounders**
- **Consider impact of bias from informative censoring, missing data, and measurement error and address appropriately, if needed**
- **Use sensitivity and bias analysis to assess robustness of results to main risks of bias and uncertain data curation and analysis decisions**

Ref: NICE RWE framework 2022

Example of Common Issues with Use of External Control: Axi-cel Submissions



Key Issues

Data identification

- Non-systematic method for identification of potential sources
- Rationale for preferred source weak
- Missing time on treatment data (and biased assumptions)
- Missing PFS data

Generalizability

- Differences in populations between trial, external control and expected practice
- No UK data

Analysis

- No matching analysis
- Adjustment methods complex and poorly explained
- Extrapolation not well justified

Common Problems and Potential Solutions

Lack of systematic identification of data sources (and confounders):

- *Structured review required*

Mismatch between treatments in practice / the data set and costings:

- *Effects and costs should match*
- *Sensitivity analysis subsetting to treatments used in practice in the relevant country*

Blended comparators:

- *In theory, not preferred by NICE, but precedent shows these are accepted, provided there is sufficient justification*

Common Problems and Potential Solutions (cont.)

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Missing data

- *Imputation, sensitivity, analysis bias analysis*
- *Best- and worst-case scenario analysis*

EXAMPLE: Alectinib vs ceritinib in crizotinib-refractory, ALK-positive non-small-cell lung cancer?
Wilkinson et al. 2021

- *ECOG PS data missing for 47% of patients*
- *E-value approach used to estimate the relative risk of an unobserved confounder between intervention and mortality that would be needed to remove the treatment effect*
- *The estimated relative risk of 2.2 was substantially higher than for any observed confounders and considered unlikely given the estimated imbalance for important but poorly captured confounders*
- *For economic analyses would need to then estimate the e-value associated with lack of cost-effectiveness*

Common Problems and Potential Solutions (cont.)

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PFS measured differently in real-world (frequency of follow-up and what is classed as progression)

- Critical to understand differences between trial and real-life practice and likely impact on results
- OS less likely to be influenced by this (although less frequent follow-up may still impact on OS) but more impacted by differences in subsequent therapy mix
- Collect time on treatment data and time to next treatment data as well

Handling of multiple lines of treatment; different methods include:

- Looking only at first eligible line
- Use all lines
- Sample included lines at random to match trial characteristics
- Use all lines with weighting by line

Multiplicity of analytical choices:

- Lay person explanation of rationales and pros / cons of different options
- Scenario analyses
- Threshold analyses
- Consider use of end-to-end software (e.g., R) to more easily allow testing of different options

Assessing Data Quality

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NICE recommend use of DataSAT to assess data suitability:

- *Provenance*
- *Quality*
- *Relevance*

ROBINS-I recommended for assessing risk of bias in non-randomized studies, BUT:

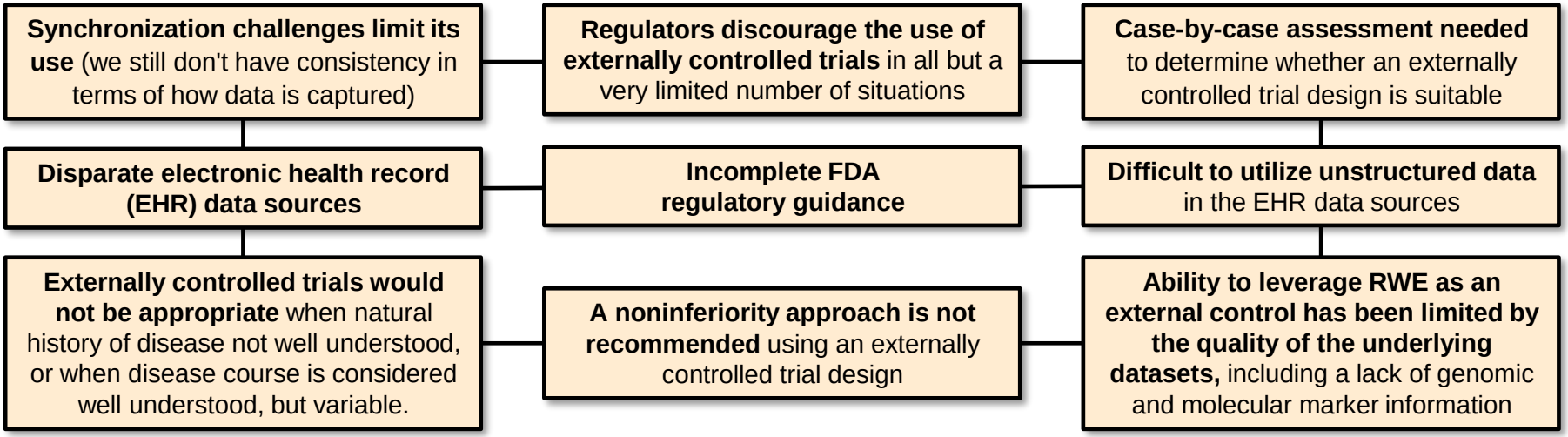
- *May not cover all risks*
- *NICE are clear that they do not expect uncertainty to be fully captured via statistical uncertainty in estimated intervention effect*

Challenges and Solutions

Raymond Huml
Syneos Health

Challenges: Using Control Arms

Confounding Factors Introducing Bias into Comparison between Investigator Treatment and External Control



"In many situations … the likelihood of credibly demonstrating the effectiveness of a drug of interest with an external control is low, and sponsors should choose a more suitable design, regardless of the prevalence of disease."

United States Food and Drug Administration

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Solutions…and Other Positive Attributes of ECAs

Gaining credence among regulators for decisions on drug approval and label expansion	Myriad of potential data sources	Multiple RWE FDA regulatory guidance exists	RWE / RWD cost effective
• Prograf® (tacrolimus) for new indication for prevention of lung transplant rejection in July 2021, demonstrates use of RWE to show efficacy for regulatory decision-making • SKYCLARYS™ for treatment of Friedreich's ataxia: used natural history study for additional confirmatory evidence of effectiveness • Brineura® for Batten disease: single-arm dose escalation clinical study compared to untreated patients from natural history study • SKYSONA® for treatment of ultra-rare childhood brain disease; used pooled efficacy data from two studies compared to external control of untreated retrospective natural history study	• Registries, Clinical Outcome Assessments *(e.g., PROs, Caregiver ROs, etc.)* • Digital media • Hospital systems *(MDA Care Centers associated with MOVR data hub)* • Published literature	• Though industry requests greater clarity from FDA	• RWE / RWD less expensive than clinical trial data

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Illustrations Courtesy of Dr. Maryna Kolochavina, as Referenced in #6 Below

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Everything we do is PERSONAL

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- ~25 years of experience working with rare diseases and patient advocacy groups
- Advanced Muscular Dystrophy Association's neuromuscular data hub
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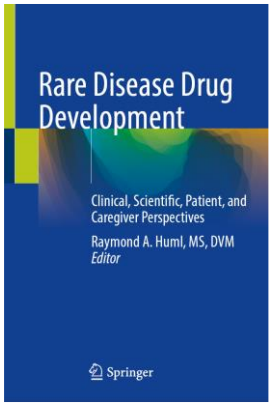

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