NORD
National Organization for Rare Disorders

Rare Disease Scientific Symposium

Alternatives to Placebo Controls and RCTs in Rare Disease Trials

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Regulatory Considerations for Externally Controlled Clinical Trials

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Disclaimer

- This presentation reflects the views of the author and should not be construed to represent FDA's views or policies.

Externally Controlled Trials

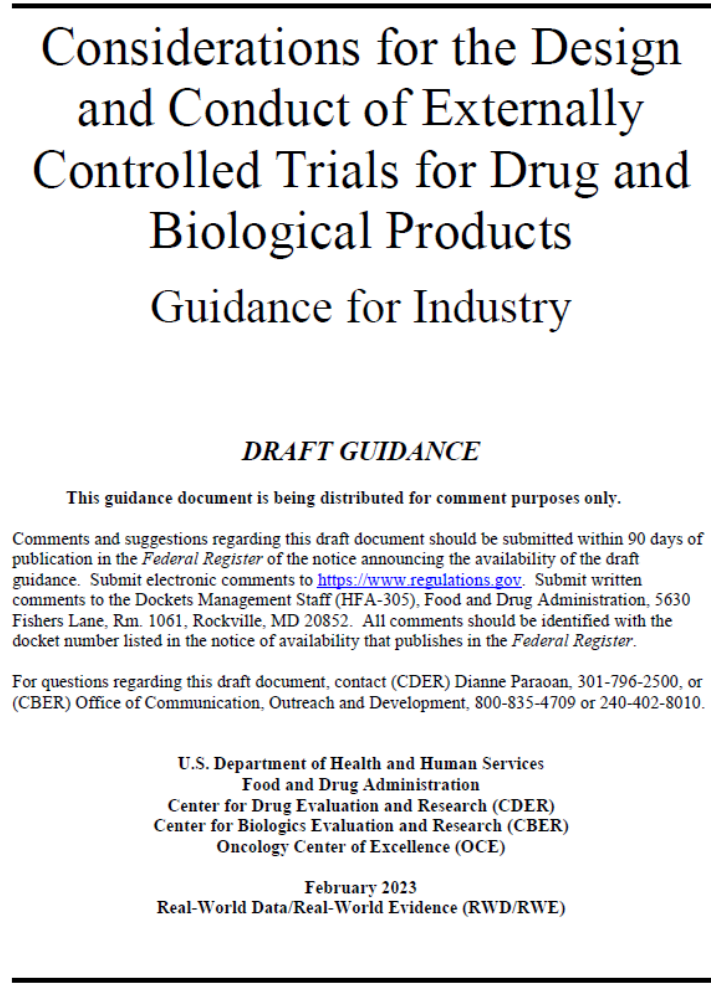
- Outcomes in participants receiving the test treatment according to a protocol are compared to outcomes in a group of people **external to the trial** who had not received the same treatment
- FDA draft guidance: Demonstrating Substantial Evidence of Effectiveness (Dec 2019)

  "Despite the limitations of externally controlled trials compared with concurrently controlled trials, **strong support for effectiveness can emerge from externally controlled trials, especially when**

  1) the natural history of a disease is well defined,
  2) the external control population is very similar to that of the treatment group,
  3) concomitant treatments that affect the primary endpoint are not substantially different between the external control population and the trial population, and
  4) the results provide compelling evidence of a change in the established progression of disease."

External Control Guidance

- Given the lack of randomization, treatment and control groups should be as similar as possible in terms of
  - Known factors that can affect outcome being measured
    - Demographic factors (e.g., age, sex, race, region)
    - Prognostic or predictive biomarkers
    - Disease characteristics (e.g., diagnosis, age of onset, severity, duration, specific signs/symptoms, comorbidities)
    - Prior and concomitant therapies/treatments, standard of care
  - Methods to measure/ascertain such factors
  - Methods to assess primary outcome
    - More suitable for well-defined and objective endpoints.
- Sponsors should consult with the relevant FDA review division early in a drug development program



Considerations for the Design and Conduct of Externally Controlled Trials for Drug and Biological Products

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DRAFT GUIDANCE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 90 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) Dianne Paraoan, 301-796-2500, or (CBER) Office of Communication, Outreach and Development, 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)
Oncology Center of Excellence (OCE)

February 2023
Real-World Data/Real-World Evidence (RWD/RWE)

https://www.fda.gov/media/164960/download

Design Consideration

- Reducing potential for bias is best addressed in the design phase
- Well-chosen design elements increase confidence in the interpretability of study results
- Usually required to finalize a study protocol before initiating an externally controlled trial, including selection of the external control arm and analytic approach.
- Specific design elements to prespecify in the protocol include:
  - Suitable data sources with justification
  - Baseline eligibility (inclusion and exclusion) criteria
  - Appropriate exposure definitions and windows
  - Well-defined and clinically meaningful endpoints
  - Adequate analytic plans
  - Approaches to minimize missing data and sources of bias

Data Consideration

- Externally controlled trials using real-world data (RWD) sources may result in substantial amount of missing data
  - RWD are often collected as part of routine clinical practice in which assessments often occur irregularly for selective outcomes/tests (unlike comprehensive assessment for predetermined set of outcomes/tests at regular interval in clinical trials)
  - This could lead to missing data on key prognostic factors, biomarkers, or even primary outcomes within specific time windows
- Sponsors should consider availability of data sufficient to permit comparability assessment (e.g., the amount of information available in known/likely prognostic factors)
- FDA generally expects that marketing applications include patient-level data (i.e., data on each patient) for both treatment and external control arms
- Sponsors should also ensure that FDA has access to source documents and source data for the external control arm as part of an FDA inspection

Example: Copper Histidinate in Menkes Disease

- **Menkes Disease (MD)**
  - Affects only 1 in 50,000-250,000 live male births
  - Neurodegenerative disorder caused by a genetic defect that impairs a child's ability to absorb copper
  - Classical MD (90%): most severe form with death often occurring before third year of life
- **External Control Design**
  - Two single-arm trials comparing 66 treated patients to 17 untreated patients from contemporaneous external control group
  - Primary endpoint: overall survival
  - Primary population: subjects with severe ATP7A mutations who were born after 1999
- **Results**
  - Early treatment (within 4 weeks of birth) showed 78% reduction in death risk, with nearly half surviving beyond 6 years versus no external untreated patients surviving past 6 years.
  - First approved treatment for MD

https://www.accessdata.fda.gov/drugsatfda_docs/label/2026/211241s000lbl.pdf
FDA Approves First Treatment for Children With Menkes Disease | FDA

Example: Copper Histidinate in Menkes Disease

Characteristics of external comparison that may support effectiveness

- Natural history of a disease is well-defined
- External control group very similar to treatment group
- Concomitant treatments impacting primary endpoint not substantially different
- The results provide compelling evidence of a change in progression of disease

Menkes Disease Example

- Death usually occurs before third year of life in Classical MD (90%)
- Similar between treatment and control groups in key factors; imbalances generally favorable to control
- No disease-modifying therapy impacting survival, contemporaneous external control
- Large treatment effect observed in survival (78% reduction in death risk)

Key Takeaways

- **Design stage is critical**
  - Should carefully assess whether an externally controlled trial is suitable (well-defined natural history, well-defined and meaningful endpoint, and large drug effect expected)
  - Address potential sources of bias through careful design, not just analysis
  - Finalize protocol and analysis plan before trial initiation
- **Comprehensive comparability assessment required**
  - External control data should include sufficient information allowing comprehensive comparability assessment
- **Early FDA engagement**
  - Consult with the relevant FDA review division early in a drug development program before initiating an externally controlled trial

Quantitative Systems Pharmacology-Based Virtual Twins Approach in Rare Disease Clinical Development.

Susana Zaph, PhD

Senior Director, Head of QSP-US

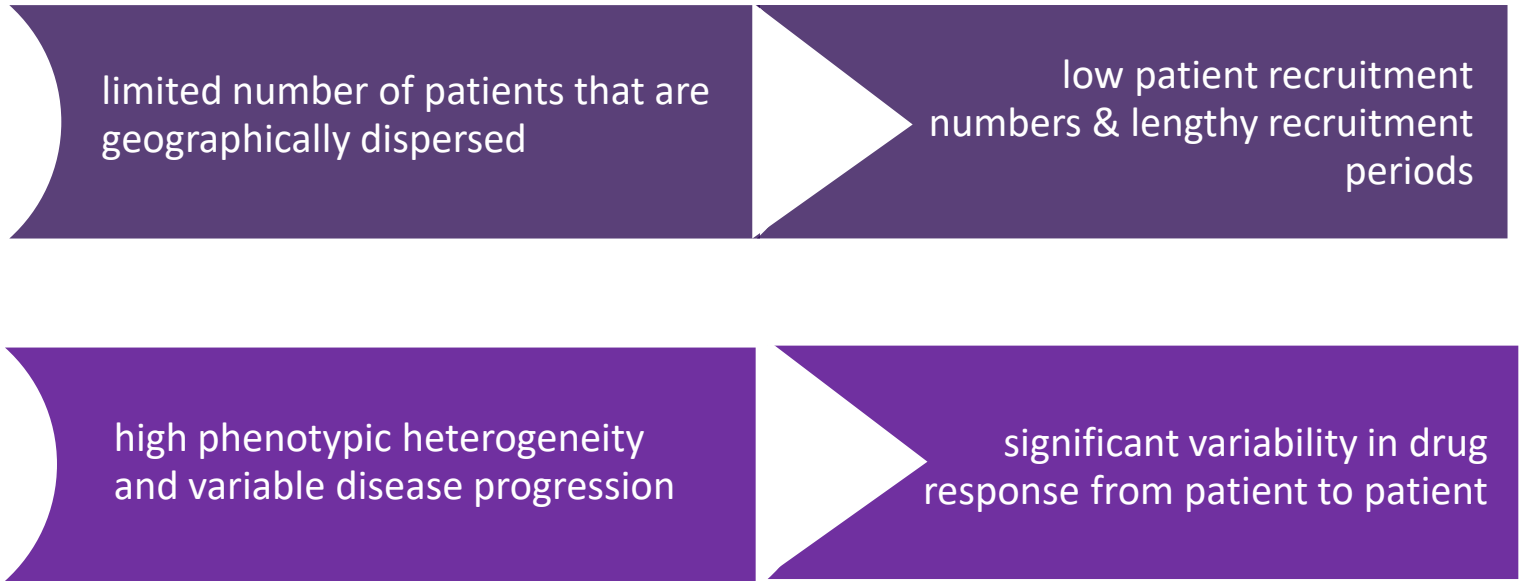
R&D

Sanofi

Susana Zaph is a Sanofi employee and may hold shares and/or stock options in the company.

MAT-US-2603660 v1.0 – P
Expiration Date: 04/01/2028

Drug development in rare diseases is challenging



These factors often make the efficacy data of clinical trials in rare diseases difficult to interpret using traditional approaches

Quantitative System Pharmacology (QSP) modeling has been recognized by health authorities as a valid approach that can help overcome these factors[1]

1. Bai J, et al., Quantitative Systems Pharmacology for Rare Disease Drug Development. Journal of Pharmaceutical Sciences, 2023; 112, 2313-2320

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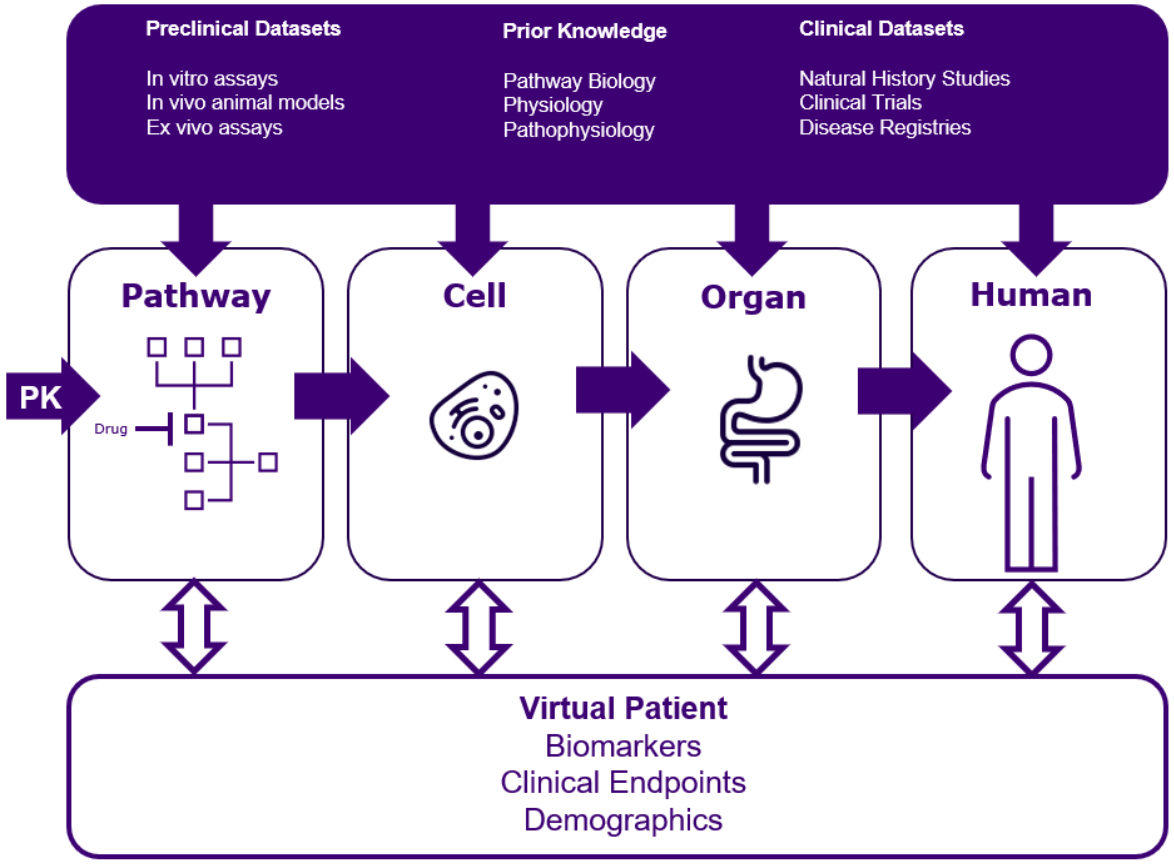
QSP models connect known pathophysiology and drug's MoA to observed biomarkers and clinical endpoints

QSP models

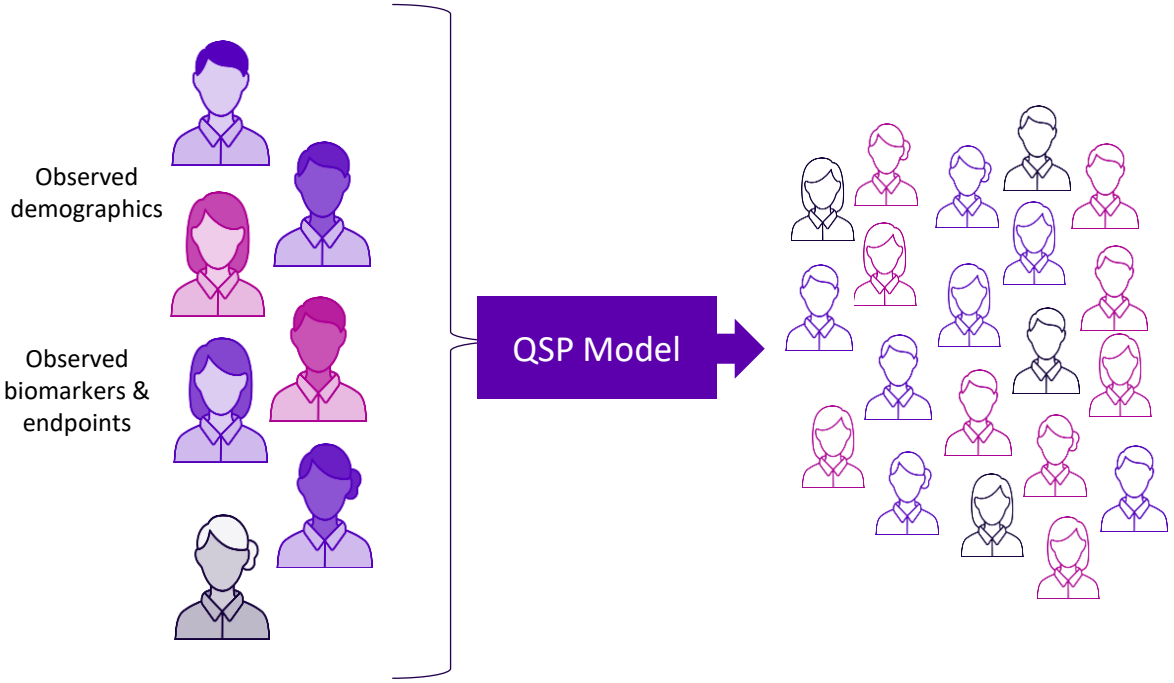
- Often span multiple biological scales
- No black boxes
- Can be informed by diverse datasets
- Describe how the effects of drugs propagate throughout the pathophysiology to gain insight into drug response



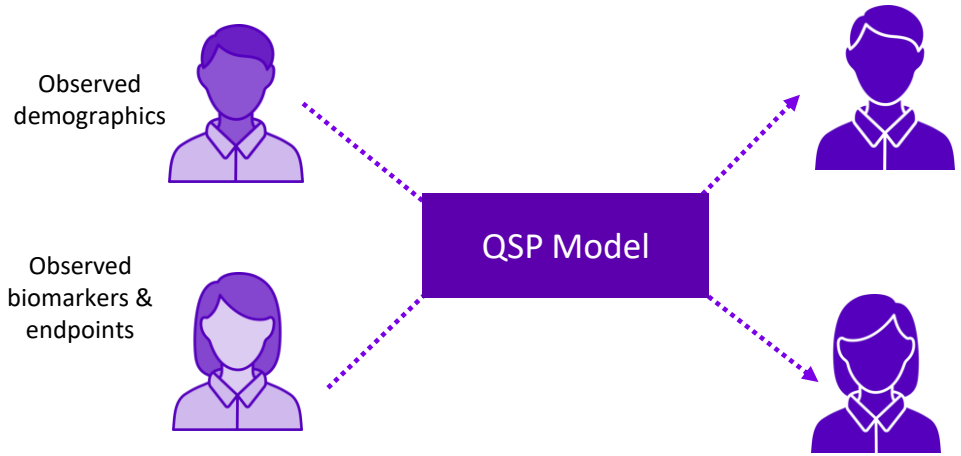
Original images.

QSP models can generate virtual patients and digital twins

Virtual patient populations represent the variability observed in real patient populations



Digital twins are model derived replicas of key features of real patients



Original images.

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Olipudase alfa: a case study in QSP-based pediatric extrapolation

Clinical Development

Evidence of Safety and Efficacy

→One Ph2 open label adult trial[1,2]

→One placebo-controlled Ph3 pivotal adult trial (ASCEND)[3]

→One pediatric trial with an open-label design (ASCEND-Peds)[4]

Substantial evidence of effectiveness was established with the adult pivotal trial

M&S Objective: Partial pediatric extrapolation from pivotal ASCEND adult trial

→QSP based analysis to quantify disease and response similarity in pediatric and adult ASMD patients

1. Wasserstein, M. P. et al. Mol. Genet. Metab. 116, 88–97 (2015). 2. Wasserstein, M. P. et al. J. Inherit. Metab. Dis. 41, 829–838 (2018);
3. Wasserstein M,, et al. Genet Med. 2022 Jul;24(7):1425-1436.; 4. Diaz, G.A.,. et al. Genet Med 23, 1543–1550 (2021).

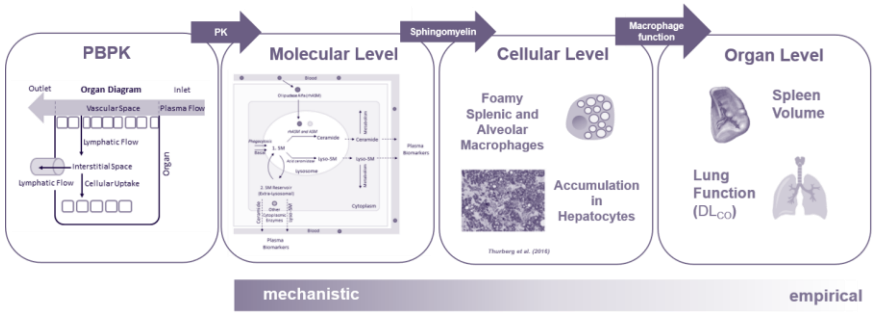
Digital twins can quantify degree of disease and response similarity between adult and pediatric patients to support extrapolation

Observed individual patient data

Adult Patients

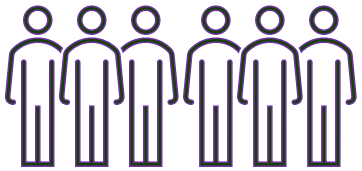
Pediatric Patients

individual patient calibrations of QSP model to generate digital twins



Subset of personalized parameters to generate virtual twins, along with BW, and age

Digital twins



Adult Digital Twins

Pediatric Digital Twins

Quantify mechanistic similarity of virtual twins

Adult Virtual twins

?

Pediatric Virtual twins

- Same model
- Similar Accuracy
- Similar parameters

Original images.

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QSP –based digital twins were applied successfully to support the partial pediatric extrapolation of olipudase alfa

FDA Conclusion of ASCEND and ASCEND-Peds Trials

Dose Selection of Olipudase alfa-rpcp in Adult and Pediatric Participants

Carefully performed dose selection studies contributed to the design of the ASCEND investigation, an adequate and well-controlled investigation demonstrating the efficacy of olipudase alfa-rpcp.

FDA concluded that the results were clinically meaningful because progressive loss of pulmonary function and liver failure are the most common causes of death in patients with ASMD. In addition, FDA allowed for partial extrapolation of positive adult ASCEND trial results to be used for pediatric populations due to similar disease pathogenesis, drug mechanism of action, and comparability of efficacy results (i.e., change from baseline for endpoints in common between the adult and pediatric studies).

https://www.fda.gov/ddrugs/CDERARC

"Review team conclude that the submitted QSP model provides insight on mechanism of ASMD progression and response to olipudase alfa treatment in pediatric and adult ASMD patients.

The simulation results supported the **mechanistic similarity of disease and response to olipudase alfa** between pediatric and adult ASMD patients. These results **support the approval of olipudase in pediatric patients**, in addition to the observations from clinical trials in pediatric and adult patients"

FDA integrated review 9-2022: feedback on QSP model

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Conclusions

QSP approach can:

- **Quantify the degree of mechanistic similarity** between pediatric and adult patients
- Evaluate the **validity of the extrapolation assumptions** across different populations
  - justify when extrapolation of efficacy is scientifically plausible given the known biology shared by pediatric and adult patients.

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The patients and their caregivers


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uniQure

AMT-130 CASE STUDY

External Comparators as an Alternative to Placebo

Presented by **David H Margolin, MD, PhD**
VP, Clinical Development, uniQure

NORD Rare Disease Scientific Symposium
Arlington, VA

April 14-15, 2026

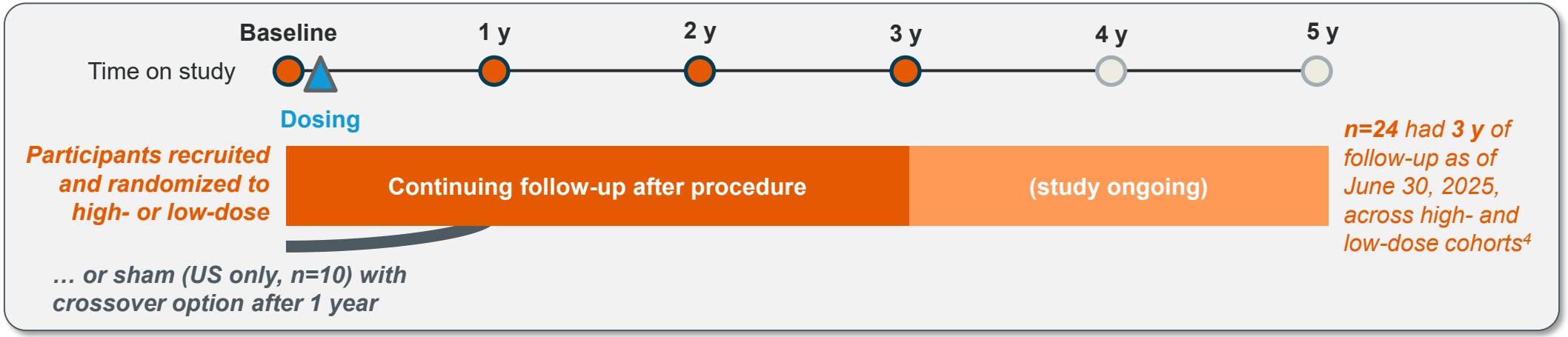
Speaker Disclosures

David Margolin is an employee of uniQure, Inc., and owns stock or stock options.

AMT-130 is an investigational agent currently being studied in the treatment of Huntington's disease. Its safety and efficacy have not been established, and it has not been approved by the FDA, EMA, or any other regulatory body. There is no guarantee that investigational agents will receive health authority approval or become commercially available.

EMA, European Medicines Agency; FDA, United States Food and Drug Administration

AMT-130 is a Surgically Delivered Investigational Gene Therapy Candidate for the Treatment of Huntington's Disease[1-3]



The challenge

Long-term sham controls pose an ethical challenge and are not patient-centric[5,6]

A potential solution

External comparators using natural history data may enable long-term efficacy/safety assessment without extended sham exposure[7-9]

1. https://clinicaltrials.gov/study/NCT04120493. Accessed April 1, 2026. 2. https://clinicaltrials.gov/study/NCT05243017. Accessed April 9, 2026. **3.** Sung V. Presented at: Huntington Study Group Annual Meeting; November 6–8, 2025; Tampa, FL. **4.** Margolin D. Presented at: CHDI Therapeutics Conference; February 23–26, 2026; Palm Springs, CA. **5.** Millum J, Grady C. *Contemp Clin Trials.* 2013;36(2):510-514. **6.** Bardakjian TM, et al. *J Huntingtons Dis.* 2019;8(1):79-85. **7.** Boareto M, et al. *Neurology.* 2025;104(10):e213646.**8.** Papoutsi M, et al. Presented at: HD Therapeutics Conference (HDTC); February 24-27, 2025, 2025; Palm Springs, California. **9.** Hooper G, et al. *J Neurol Sci.* 2019;405:312.

How External Comparators for the AMT-130 Trials Were Constructed

Candidate external dataset selection

Core Question: What are appropriate datasets?

Yes

Fit-for-purpose and TTE framework

Core Question: Is the dataset fit for purpose? Can a target trial emulation framework be applied?

Yes

Patient selection & covariate balancing

Core Question: Is covariate balance achieved?

Fit For Purpose Feasibility Assessment[1]

Dataset selection
- Enroll-HD
- TRACK-HD
- PREDICT-HD

Fit-for-purpose assessment
- Assess for relevance and reliability
- Regulatory guidance

Define T_0
- Index time zero
- Aligned baseline between treated and external participants

Patient matching
- Patient demographics
- Disease characteristics
- Baseline scores

Statistical adjustment
- Propensity score matching
- Can maximize matching ratio for more statistical power

Comparative analysis
- Long-term outcomes in treated groups vs matched external controls

CAG, cytosine-adenine-guanine; cUHDRS, composite Unified Huntington's Disease Rating Scale; HD, Huntington's disease; TFC, Total functional Capacity; TTE, Target Trial Emulation.

1.US Food & Drug Administration. Considerations for the Design and Conduct of Externally Controlled Trials for Drug and Biological Products: Guidance for Industry. 2023. Accessed April 1, 2026. https://www.fda.gov/media/164960/download.

External Comparators for HD Trials

Core Question:
What are appropriate datasets?

Study	Population	Duration	Location
ENROLL-HD[1]	N>30,000 (target=35,000)	Start: 2012 Completion (est): 2062	Europe, North America, Australasia, Latin America
TRACK-HD[2,3]	366	Start: 2008 Completion: 2011	Canada, France, Netherlands, UK
TRACK-ON[3,4]	239 continued from TRACK-HD	Start: 2012 Completion: 2014	
PREDICT-HD[5,6]	1700 (est)	Start: 2002 Completion: 2016[a]	US, Australia, Canada, Germany, Spain, UK

External comparators for HD trials

- Well-characterized natural history datasets enable contextualization of outcomes[7-9]
- AMT-130 leverages: Enroll-HD, TRACK-HD, and PREDICT-HD[10-12]

[a]The data cut off date was 2016 for AMT-130 external comparators, however PREDICT-HD continued until 2025.

HD, Huntington's disease.

1. CHDI Foundation Inc. Enroll -HD: A Prospective Registry Study in a Global Huntington's Disease Cohort. 2026. Accessed April 1, 2026. https://clinicaltrials.gov/study/NCT01574053. **2.** Tabrizi SJ, et al. *Lancet Neurol.* 2009;8(9):791-801. **3.** Neurodegeneration Research. TRACK-HD and TrackOn-HD. Neurodegeneration Research website. Published November 4, 2017. Accessed April 2, 2026. https://neurodegenerationresearch.eu/cohort/track-hd-and-trackon-hd/. **4.** Kloppel S, et al. *EBioMedicine.* 2015;2(10):1420-1429. **5.** Jordan Schultz. Neurobiological Predictors of Huntington's Disease (PREDICT-HD). 2026. Accessed April 1, 2026. https://clinicaltrials.gov/study/NCT00051324. **6.** Enroll-HD. PREDICT-HD 2020 Data Set Overview. Published March 15, 2021. Accessed April 2, 2026. https://enroll-hd.org/enrollhd_documents/PREDICT-HD/PREDICT-HD_2020_Data_Set_Overview.pdf. **7.** Boareto M, et al. *Neurology.* 2025;104(10):e213646. **8.** Papoutsi M, et al. Comparison of two natural history studies as part of the HD-IH consortium: a use case for historical external control group matching in clinical trials. Presented at: HD Therapeutics Conference (HDTC); February 24-27, 2025, 2025; Palm Springs, California. **9.** Hooper G, et al. *J Neurol Sci.* 2019;405:312. **10.** Sathe S, et al. *Front Neurol.* 2021;12:667420. **11.** Tabrizi SJ, et al. *Lancet Neurol.* 2009;8(9):791-801. **12.** Biglan KM, et al. *Front Aging Neurosci.* 2013;5:12.

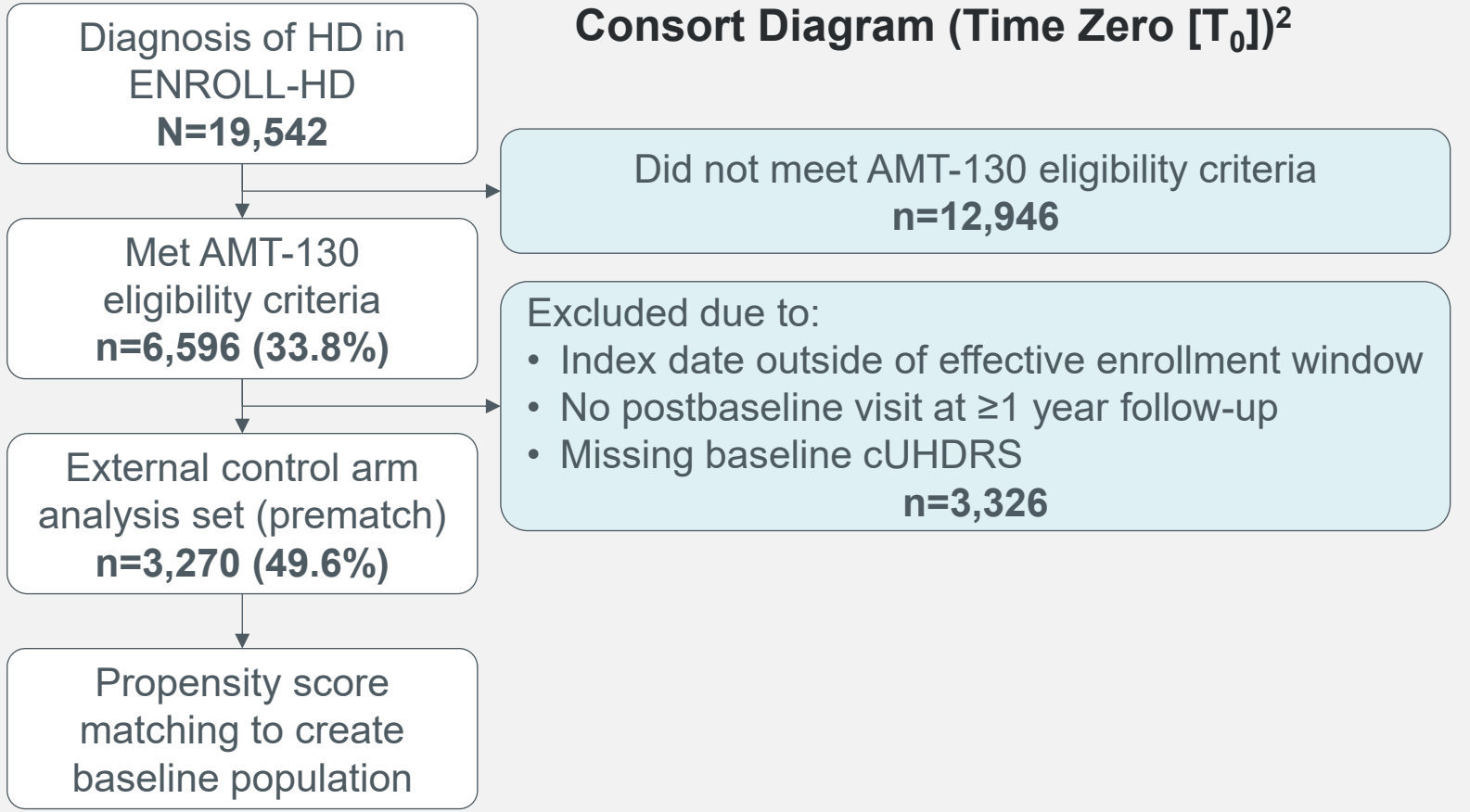
Applying Target Trial Emulation (TTE) Framework to AMT-130 3-year analysis

Core Questions:
Is the dataset fit for purpose?
Can TTE framework be applied?

TTE Framework Components[1]

- **Eligibility criteria**
- **Time zero**
- **Treatment strategy**
- **Outcome definition**
- **Follow-up period**
- **Casual contrast**
- **Analysis plan**

Consort Diagram (Time Zero [T_0])[2]

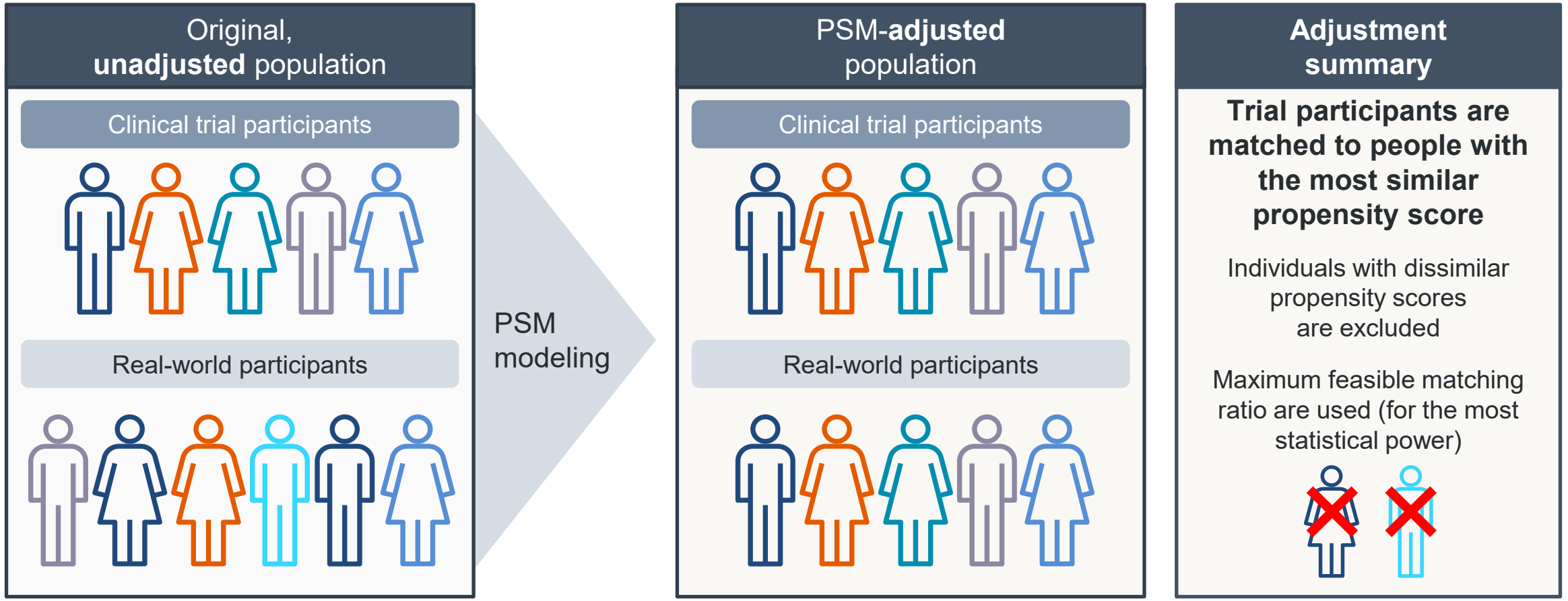


cUHDRS, composite Unified Huntington's Disease Rating Scale, HD, Huntington's disease; PSM, propensity score matching; TTE, target trial emulation.

1. Riggi E, et al. *J Comp Eff Res.* 2026:e250180. **2.** Margolin D. Presented at: CHDI Therapeutics Conference; February 23–26, 2026; Palm Springs, CA.

Propensity Score Matching is a Statistical Method to Balance Baseline Characteristics Using Known Prognostic Covariates

Core Question:
Is covariate balance achieved?



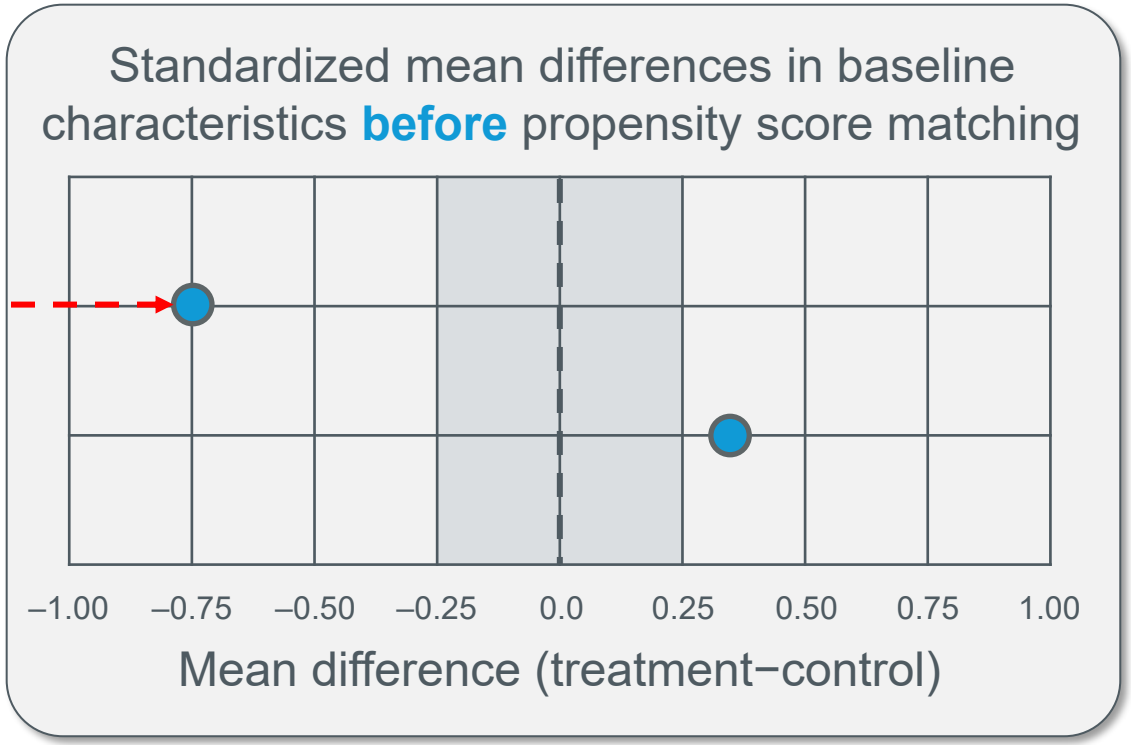
PSM, propensity score matching.

Liau MYQ, et al. *World J Methodol*. 2024;14(1):90590.

In the TTE Framework, Propensity Score Analyses Help Us Get From the "Screened" Population to the "Baseline" Population

Core Question:
Is covariate balance achieved?

Baseline characteristic	SMD pre-match, all observations (N=3,270)
DCL	−0.75
Sex	0.3

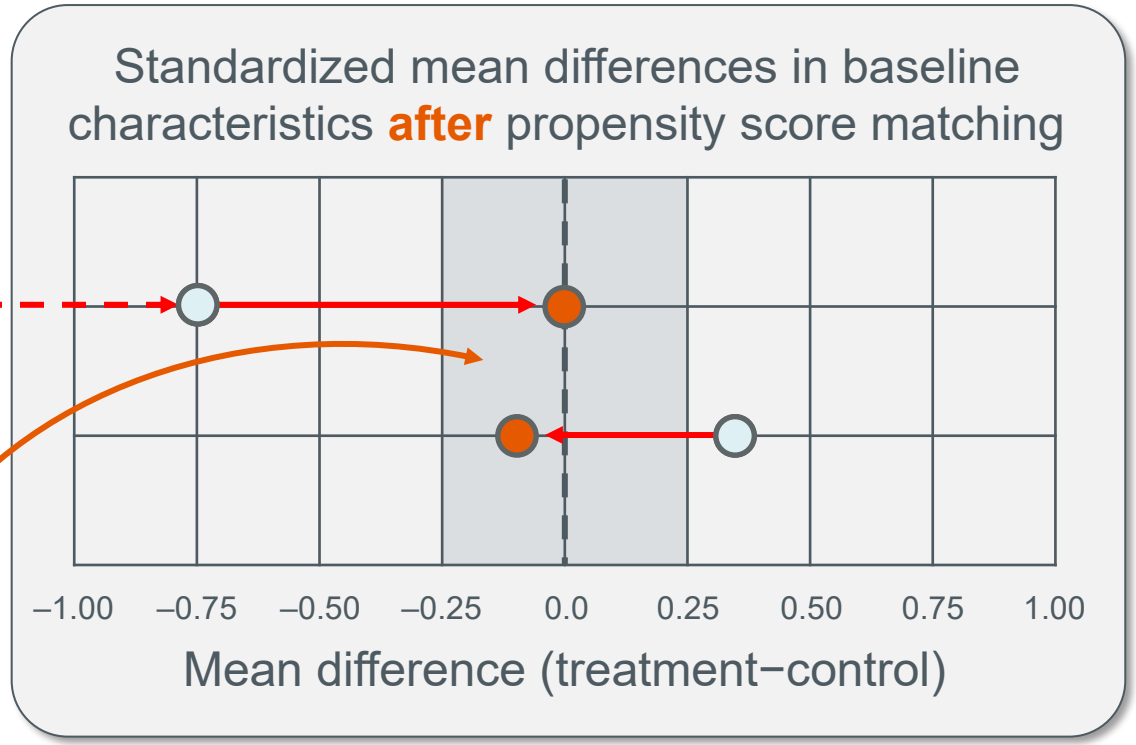


DCL, diagnostic confidence level; SMD, standardized mean difference; TTE, target trial emulation.

In the TTE Framework, Propensity Score Analyses Help Us Get From the "Screened" Population to the "Baseline" Population

Core Question:
Is covariate balance achieved?

Baseline characteristic	SMD pre-match, all observations (N=3,270)	SMD post-match (N=940)
DCL	−0.75	0.0
Sex	0.3	−0.1



The baseline characteristics are now similar enough to support robust statistical comparisons between the groups for clinical trial endpoints

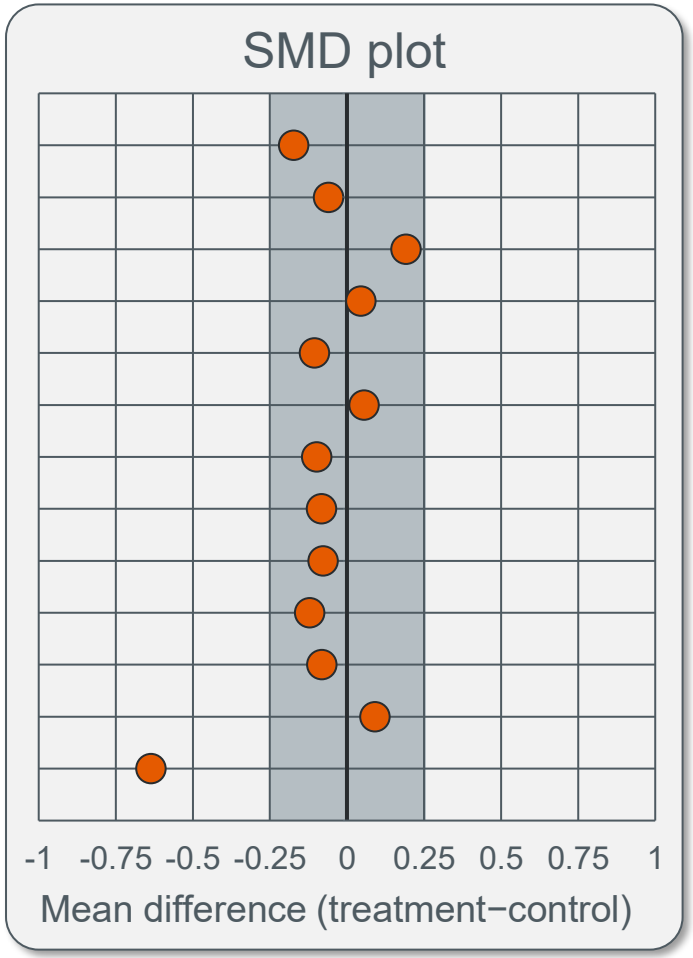
DCL, diagnostic confidence level; SMD, standardized mean difference; TTE, target trial emulation.

Baseline Characteristics are Generally Well Balanced Between Treatment Arm and PSM External Control

Core Question:
Is covariate balance achieved?

Propensity score covariates

Demographics and disease characteristics, mean	**AMT-130 high-dose (N=17)**	**PSM EC (Enroll-HD; N=940)**	**SMDs**
Sex, male (%)	47.1	55.6	–0.1723
Age, y	45.8	45.2	–0.0594
CAG repeats	42.4	42.8	0.1921
CAP100 score	86.2	86.8	0.0456
DCL = 3, 4 (%)	35.3, 64.7	30.5, 69.5	–0.1052
PIN score	0.77	0.81	0.0553
cUHDRS	14.9	14.7	–0.0977
TFC	12.2	12.1	–0.0819
SDMT	46.1	45.3	–0.0770
SWRT	89.9	87.6	–0.1209
TMS	12.1	11.6	–0.0813
HD-ISS stage 2, 3 (%)	47.1, 52.9	51.6, 48.4	0.0906
Region; North America, other (%)	58.8, 41.2	28.9, 71.1	–0.6361[a]



[a]Absolute SMD >0.25.

CAG, cytosine-adenine-guanine; CAP100, CAG-age product (scaled to 100); cUHDRS, composite Unified Huntington's Disease Rating Scale; DCL, diagnostic confidence level; EC, external comparator; HD-ISS, Huntington's Disease Integrated Staging System; PIN, prognostic index; PSM, propensity score matching; SDMT, Symbol Digit Modalities Test; SMD, standardized mean difference; SWRT, Stroop Word Reading Test; TFC, total functional capacity; TMS, total motor score.

Strengths, Limitations, and Methodological Considerations

Strengths

- ✓ ENROLL-HD, TRACK-HD & PREDICT-HD comprehensive HD registries globally
- ✓ Prospectively collected, standardized assessments by trained raters reduces risk of measurement bias
- ✓ Prespecified matching and analysis plan seeks to mitigate retrospective selection bias

Source of potential bias	Mitigation Strategy
Population selection	PSM on key prognostic factors + sensitivity analyses
Calendar time	ENROLL-HD is contemporaneous with trial
Assessment measures	Use identical instruments (eg, cUHDRS, TFC) with harmonized timepoints
Time zero	Time zero was treatment initiation for AMT-130; controls anchored when first meeting eligibility at equivalent disease stage
Small AMT-130 study size and confounding	Pre-specified sensitivity analyses with varying matching and other parameters

cUHDRS, composite Unified Huntington's Disease Rating Scale; HD, Huntington's Disease; PSM, propensity score matching; SoC, standard of care; TFC, Total Functional Capacity; TMS, Total Motor Score.

Key Learnings and Take Aways

Potential benefits of external comparators

- Require the same level of methodological rigor as interventional studies
- Can provide scientifically robust context when built from high-quality natural history data
- Potential to enhance trial efficiency and reduce reliance on long-term control arms

Role of the rare disease community

- Progress depends on sustained investment in natural history studies and registries
- Organizations like NORD & CHDI play a critical role in enabling participation and sustaining longitudinal data collection
- Acceptance of thoughtful, fit-for-purpose design of external comparator analyses

HD, Huntington's disease; NORD, National Organization for Rare Disorders.

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HD GeneTRX1

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Principal Investigator: Paul Larson, MD

HD GeneTRX2

CT-AMT-130-02

Activated Sites:

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Cardiff University
Principal Investigator: Anne Rosser, MD, PhD

International Neuro Center
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Many other collaborators….

And to all the patients and their families…

THANK YOU!

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Rare Disease Scientific Symposium

When Randomized Trials Are Not Feasible: Clinical Decision-Making in Ultra-Rare Tumors

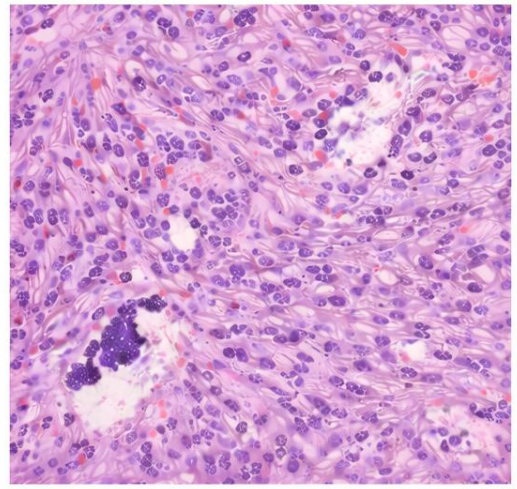
Oxana V Crysler, MD, MHS

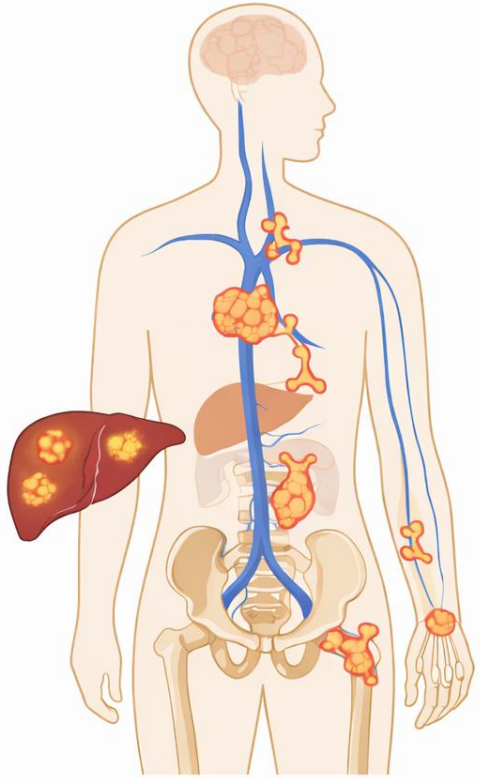
University of Michigan,

Rogel Cancer Center

Clinical scenario

- Decision-making in absence of randomized evidence
- Aggressive neoplasm, GI sarcomatoid carcinoma
- Widely metastatic disease: Liver, lymph nodes, bones
- No standard therapy
- No randomized trials, ultra rare cancers excluded based on pathologic diagnosis





AI-generated image for illustrative purposes (not derived from a real patient)

This case represents a composite clinical scenario. Details have been modified and do not correspond to any single identifiable patient.

What evidence do we have in non-RCT settings?

- **Research signals**

-Phase 1/2 clinical trials responders

-Case reports / small series/observational data

- **Biology**

- NGS / biomarkers / pathway targeting

- **Relevant data**

- Real-World databases

- Cross-disease extrapolation (same biology/pathology, different tumor of origin)

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Applying the framework to a clinical scenario

Evidence aggregation

Any reported responses?

Biology assessment

Immunotherapy target? Molecular target?

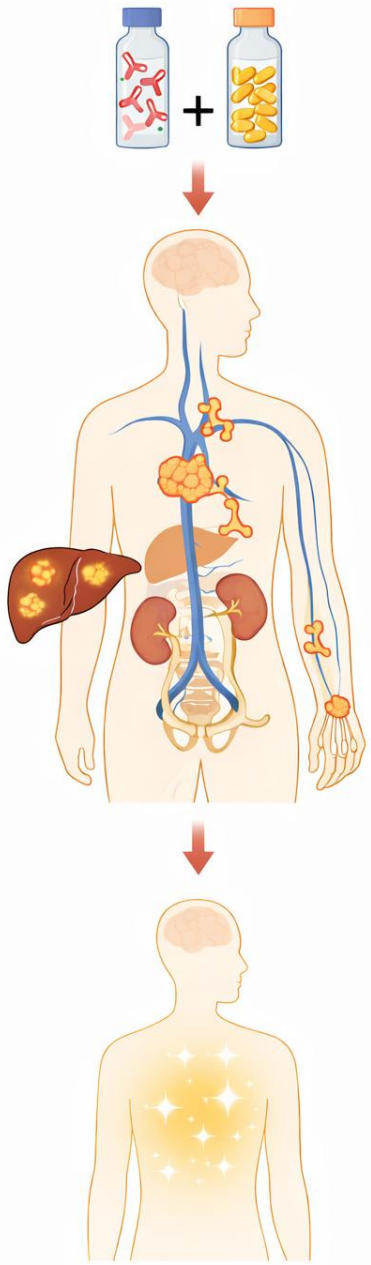
Disease prognosis

Aggressive disease course/Natural history of metastatic neoplasm

Consistency across reports? → Yes (uniformly poor outcomes)

A clinical decision-making model

- Cross-disease research: Sarcomatoid renal cancers -> response to Immunotherapy + TKIs
- Decision: Immunotherapy + TKIs
- Outcome: Durable complete response



Conclusions:

- Non-RCT ≠ non-evidence
- Structured decision making
- Need integration with AI/statistical models
- In ultra-rare tumors, we do not have the luxury of waiting for perfect evidence—we make risks/benefits decisions with imperfect data

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This is not a rare situation—it is the reality of ultra-rare tumors