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Accelerating Gene & Cell Therapy Trials With Real-World Evidence

David Schwicker (MA)
CEO
ORPHA Strategy Consulting

22 June 2020 | 14:00 CET | Free webinar

Rare Diseases at a Glance

Source: Adapted from EURORDIS RARE DISEASES EUROPE

OVER
7.000
distinct rare diseases

Each one affects fewer than
1 IN 2.000
PEOPLE

Affect between
6% AND 8%
of the population in the course of their lives

NO CURE

For the vast majority of diseases – treatments available for only 600 – chronic multisystemic dysfunction requiring complex care

80%

of rare diseases have identified
GENETIC ORIGINS

Between
20% AND 30%

ULTRA RARE
conditions, affecting < 1 in 50.000

30 MILLION PEOPLE
are living with a rare disease in Europe

300 MILLION worldwide

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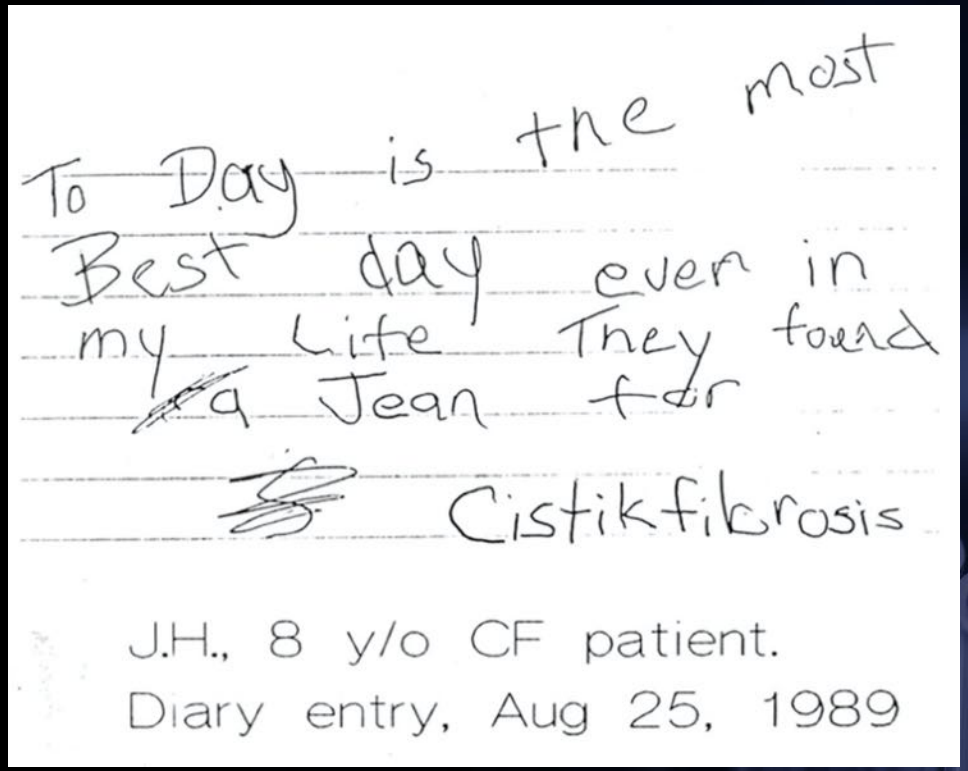
Half of Those Affected are Children

Diary of a Child with Cystic Fibrosis



Source: FS Collins. N Engl J Med 2019;381:1863-1865.

The NEW ENGLAND JOURNAL of MEDICINE

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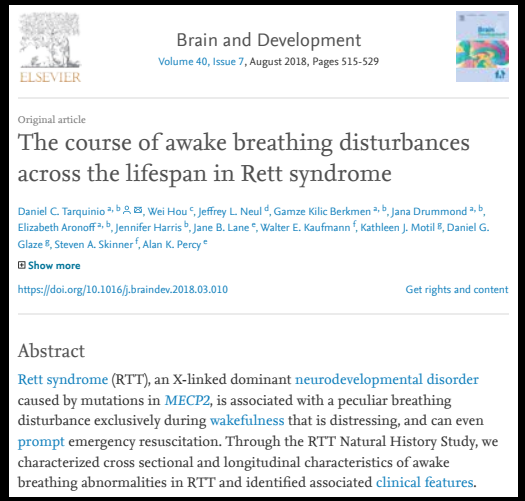
Patient-Led Research

Rettsyndrome.org
ACCELERATING RESEARCH. EMPOWERING FAMILIES.



ELSEVIER

Brain and Development
Volume 40, Issue 7, August 2018, Pages 515-529

Original article

The course of awake breathing disturbances across the lifespan in Rett syndrome

Daniel C. Tarquinio [a, b], Wei Hou [c], Jeffrey L. Neul [d], Gamze Kilic Berkmen [a, b], Jana Drummond [a, b], Elizabeth Aronoff [a, b], Jennifer Harris [b], Jane B. Lane [e], Walter E. Kaufmann [f], Kathleen J. Motil [g], Daniel G. Glaze [g], Steven A. Skinner [f], Alan K. Percy [e]

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https://doi.org/10.1016/j.braindev.2018.03.010

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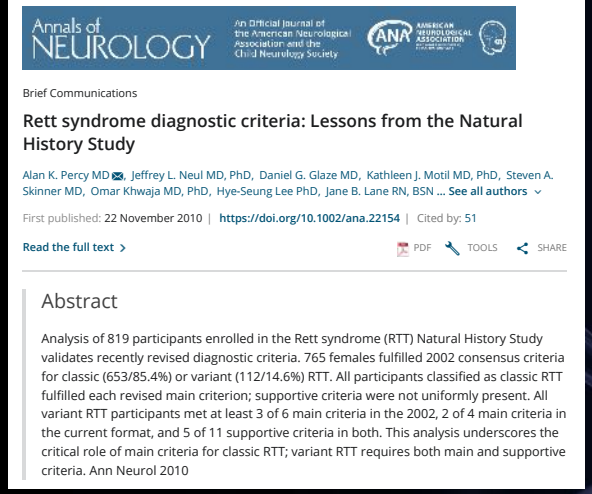
Abstract

Rett syndrome (RTT), an X-linked dominant neurodevelopmental disorder caused by mutations in *MECP2*, is associated with a peculiar breathing disturbance exclusively during wakefulness that is distressing, and can even prompt emergency resuscitation. Through the RTT Natural History Study, we characterized cross sectional and longitudinal characteristics of awake breathing abnormalities in RTT and identified associated clinical features.



Annals of NEUROLOGY
An Official Journal of the American Neurological Association and the Child Neurology Society
ANA American Neurological Association

Brief Communications

Rett syndrome diagnostic criteria: Lessons from the Natural History Study

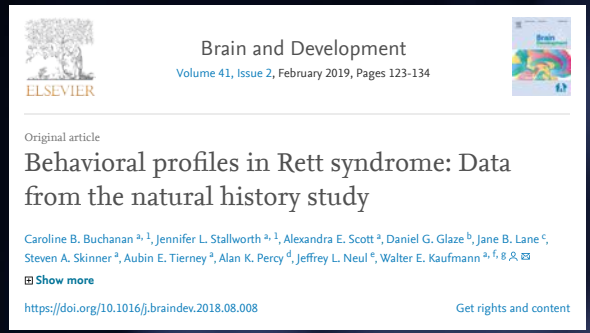
Alan K. Percy MD, Jeffrey L. Neul MD, PhD, Daniel G. Glaze MD, Kathleen J. Motil MD, PhD, Steven A. Skinner MD, Omar Khwaja MD, PhD, Hye-Seung Lee PhD, Jane B. Lane RN, BSN ... See all authors

First published: 22 November 2010 | https://doi.org/10.1002/ana.22154 | Cited by: 51

Read the full text > PDF TOOLS SHARE

Abstract

Analysis of 819 participants enrolled in the Rett syndrome (RTT) Natural History Study validates recently revised diagnostic criteria. 765 females fulfilled 2002 consensus criteria for classic (653/85.4%) or variant (112/14.6%) RTT. All participants classified as classic RTT fulfilled each revised main criterion; supportive criteria were not uniformly present. All variant RTT participants met at least 3 of 6 main criteria in the 2002, 2 of 4 main criteria in the current format, and 5 of 11 supportive criteria in both. This analysis underscores the critical role of main criteria for classic RTT; variant RTT requires both main and supportive criteria. Ann Neurol 2010



ELSEVIER

Brain and Development
Volume 41, Issue 2, February 2019, Pages 123-134

Original article

Behavioral profiles in Rett syndrome: Data from the natural history study

Caroline B. Buchanan [a, 1], Jennifer L. Stallworth [a, 1], Alexandra E. Scott [a], Daniel G. Glaze [b], Jane B. Lane [c], Steven A. Skinner [a], Aubin E. Tierney [a], Alan K. Percy [d], Jeffrey L. Neul [e], Walter E. Kaufmann [a, f, g]

Show more

https://doi.org/10.1016/j.braindev.2018.08.008

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RTT Natural History Studies

Inform study design, e.g. population, duration, biomarkers

Incorporate patient-relevant endpoints

Address patient needs in research, support recruitment

De-risk programs through patient collaboration

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“As most individuals with rare disease will not be cured in their lifetimes, identifying ways to improve quality of life is crucial to patient-centered care.”

Kathleen R. Bogart and Veronica L. Irvin, Orphanet Journal of Rare Diseases, 2017

https://patientengagementopenforum.org

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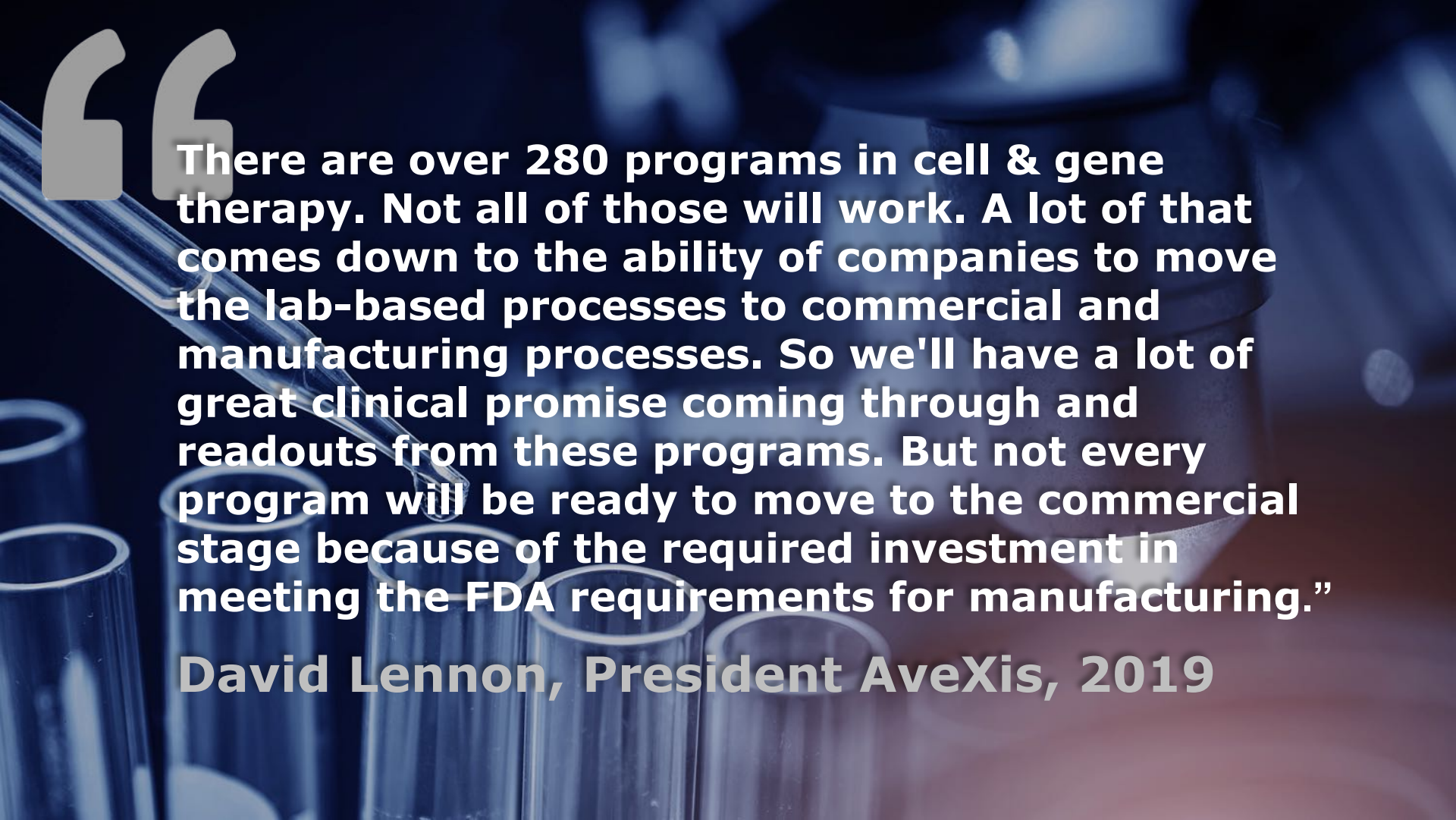
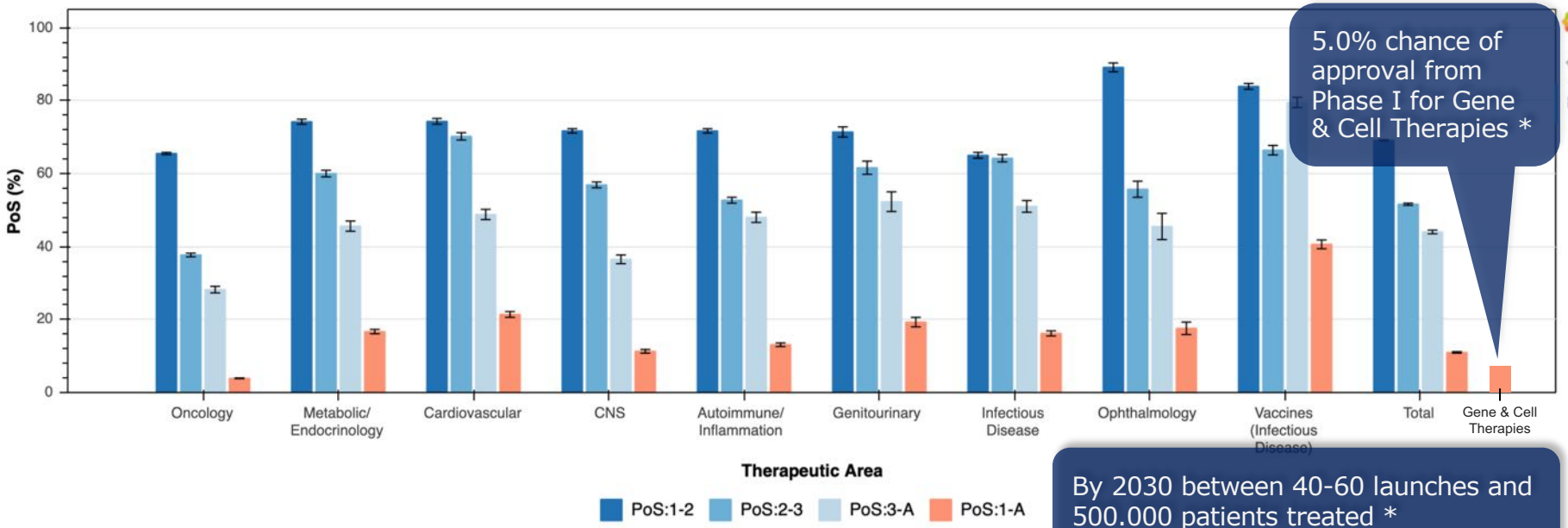


There are over 280 programs in cell & gene therapy. Not all of those will work. A lot of that comes down to the ability of companies to move the lab-based processes to commercial and manufacturing processes. So we'll have a lot of great clinical promise coming through and readouts from these programs. But not every program will be ready to move to the commercial stage because of the required investment in meeting the FDA requirements for manufacturing.”

David Lennon, President AveXis, 2019

Clinical Development PoS

Overall Estimates of PoS by Therapeutic Area – 2019Q4 Update



5.0% chance of approval from Phase I for Gene & Cell Therapies *

By 2030 between 40-60 launches and 500.000 patients treated *

Source: MIT-LFE Project ALPHA, 2019 https://projectalpha.mit.edu/pos/
PoS = Probability of Success; * Source: MIT NEWDIGS FoCUS, 2018

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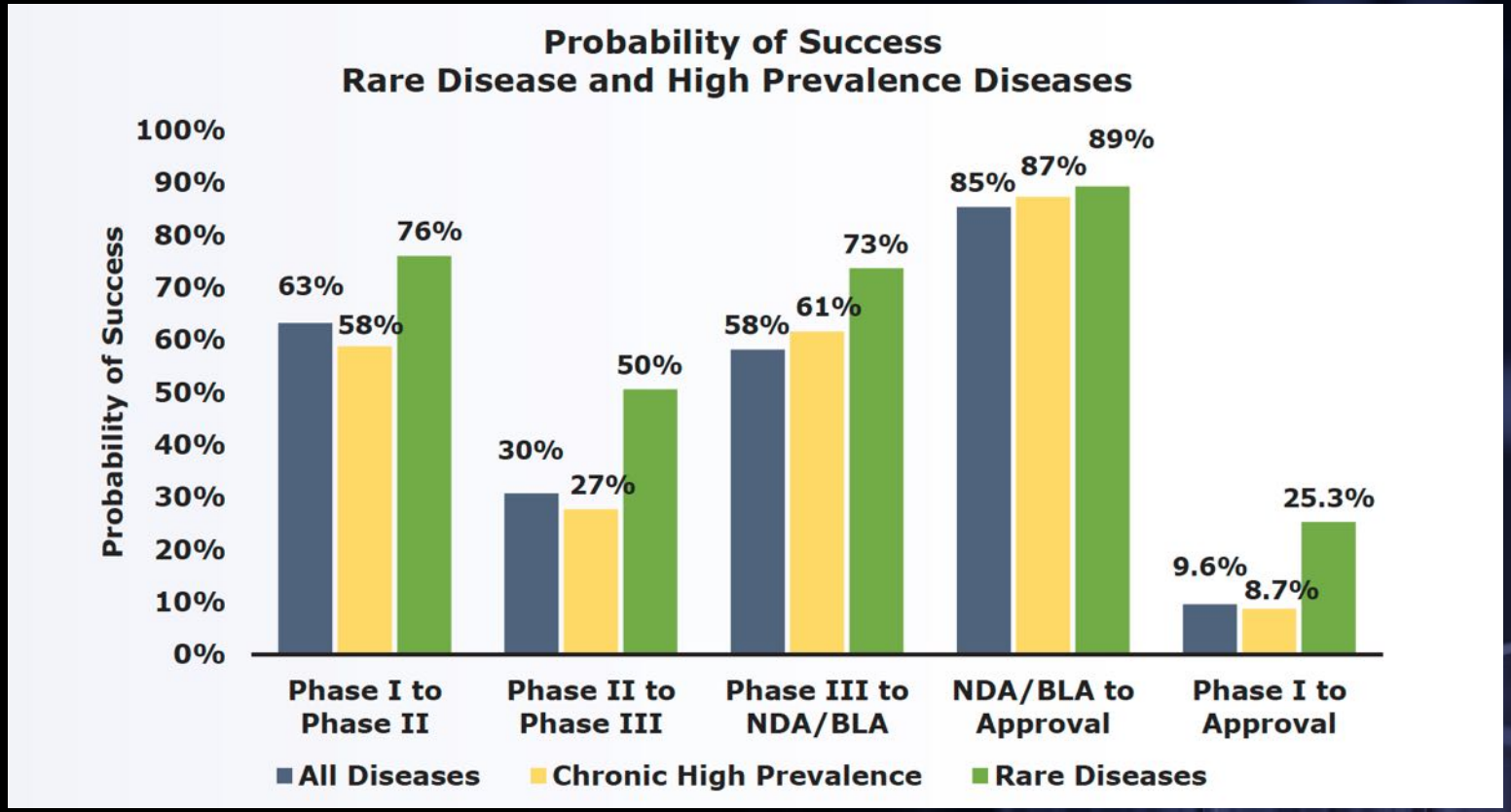
De-Risking Clinical Development



Source: Clinical Development Success Rates 2006-2015, BIO Industry Analysis, Biomedtracker, www.bio.org, 2017

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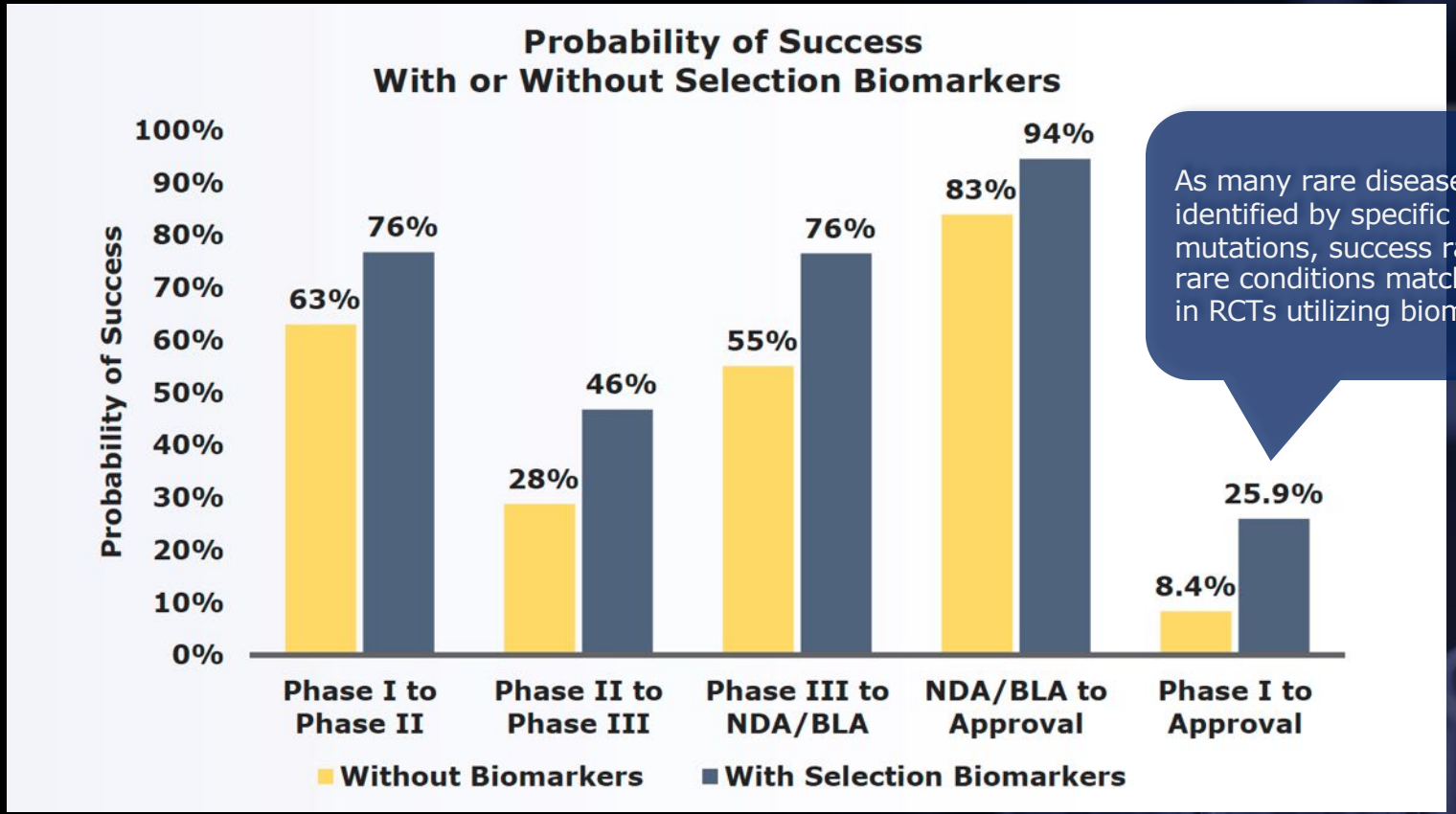
De-Risking Clinical Development



As many rare diseases are identified by specific genetic mutations, success rates in rare conditions match those in RCTs utilizing biomarkers

Source: Clinical Development Success Rates 2006-2015, BIO Industry Analysis, Biomedtracker, www.bio.org, 2017

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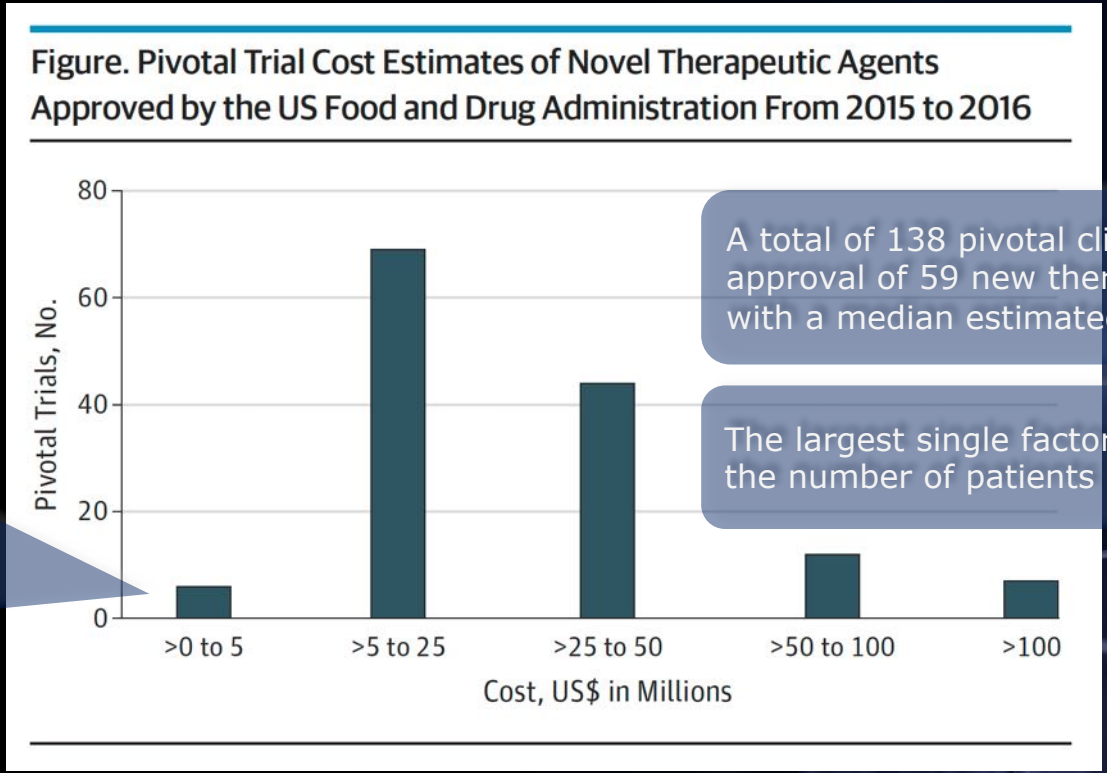
De-Risking the Cost of Pivotal Trials

Estimated costs of <$5 m for trials without a control group for 3 orphan drugs (< 15 patients each)



A total of 138 pivotal clinical trials for approval of 59 new therapeutic agents, with a median estimated cost of $19.0m

The largest single factor driving cost was the number of patients

Source: Moore TJ et al, Estimated Costs of Pivotal Trials for Novel Therapeutic Agents Approved by the US FDA, 2015-2016, JAMA Intern Med. doi:10.1001/jamainternmed.2018.3931

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Gene & Cell Therapy Investment

- "Tractability" of the (often rare) condition for development
- Good understanding of natural history and potential endpoints
- Ideally monogenic disease and well-established biomarkers
- Early data providing confidence in the MOA, good animal models
- Multiple disease targets ("pipeline in a product")
- Well established patient advocacy groups and contacts
- Serious condition(s) and high unmet needs
- Identified & diagnosed patients and expert site contacts
- Limited scope of clinical program > smaller = faster trials

Affordability Challenges

- Little consensus on what constitutes "value"
- Cumulative budget impact
- Less mature data at launch
- Uncertainties in long-term effectiveness and safety
- High upfront costs vs. downstream health benefits
- How to evaluate a "one and done" cure

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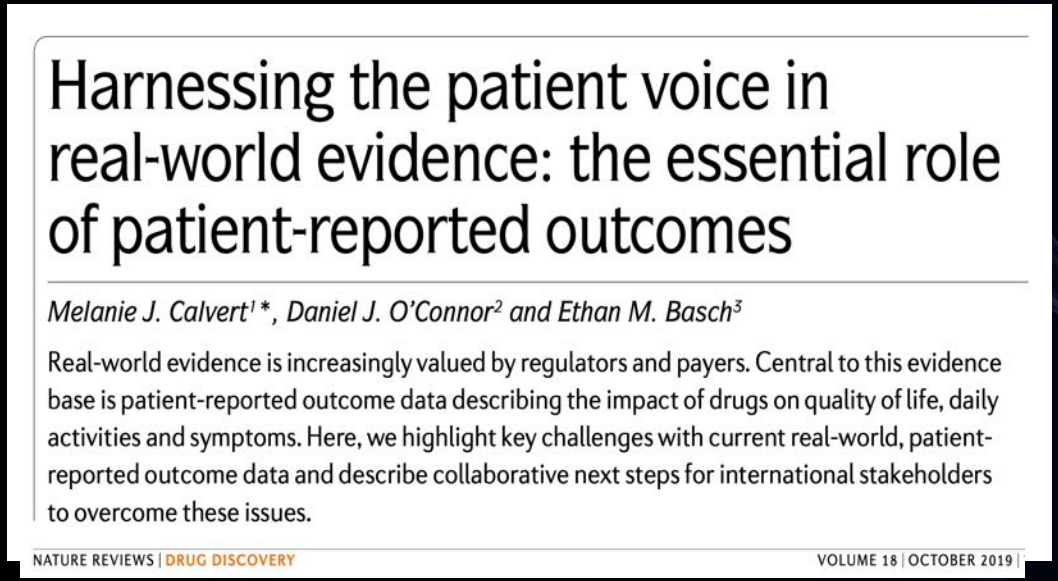
Why Accelerate Trials with *PC-RWE*?

- Reduce the number of participants exposed to experimental treatment and those exposed to placebo/sham procedures
- Understand disease progression and burden to identify biomarkers, patient-relevant endpoints and identifying inclusion/exclusion criteria
- Use natural history to produce historical control data for comparisons in single arm trials (external controls)
- Many-to-one matching methodologies, allowing comparison of one study participant with several historical controls
- Randomized real-world enrichment approaches to define a narrower patient population, reducing variability and improving the probability of detecting a treatment effect
- Incorporate patient needs, reduce barriers to participation, accelerate recruitment and enhance retention

Patient-Centred Real-World Evidence



Harnessing the patient voice in real-world evidence: the essential role of patient-reported outcomes

Melanie J. Calvert[1], Daniel J. O'Connor[2] and Ethan M. Basch[3]*

Real-world evidence is increasingly valued by regulators and payers. Central to this evidence base is patient-reported outcome data describing the impact of drugs on quality of life, daily activities and symptoms. Here, we highlight key challenges with current real-world, patient-reported outcome data and describe collaborative next steps for international stakeholders to overcome these issues.

NATURE REVIEWS | DRUG DISCOVERY VOLUME 18 | OCTOBER 2019 |

PROs capture how a patient feels and functions – quality of life, daily activities and symptoms

Without PRO data, RWE will not actually reflect how real patients experience real therapies in the real world

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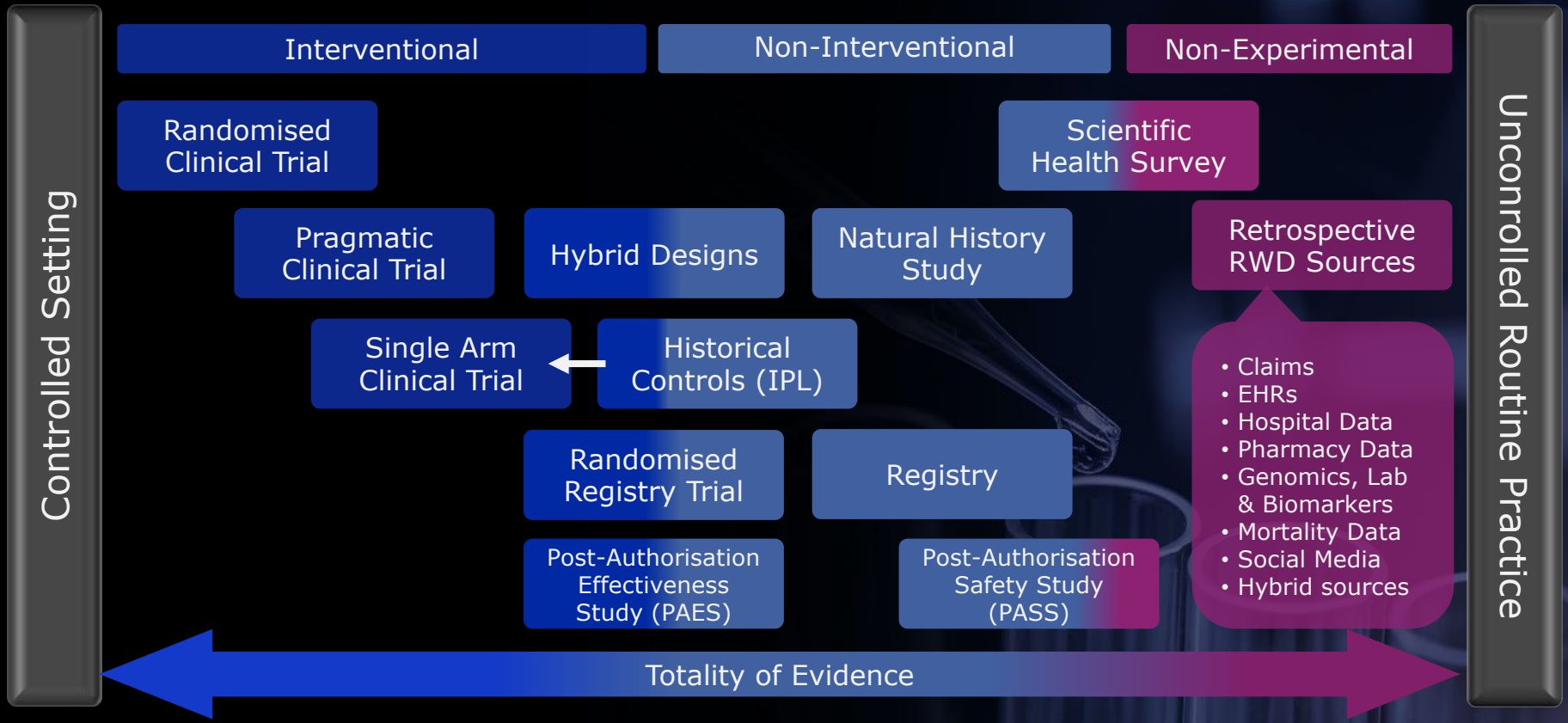
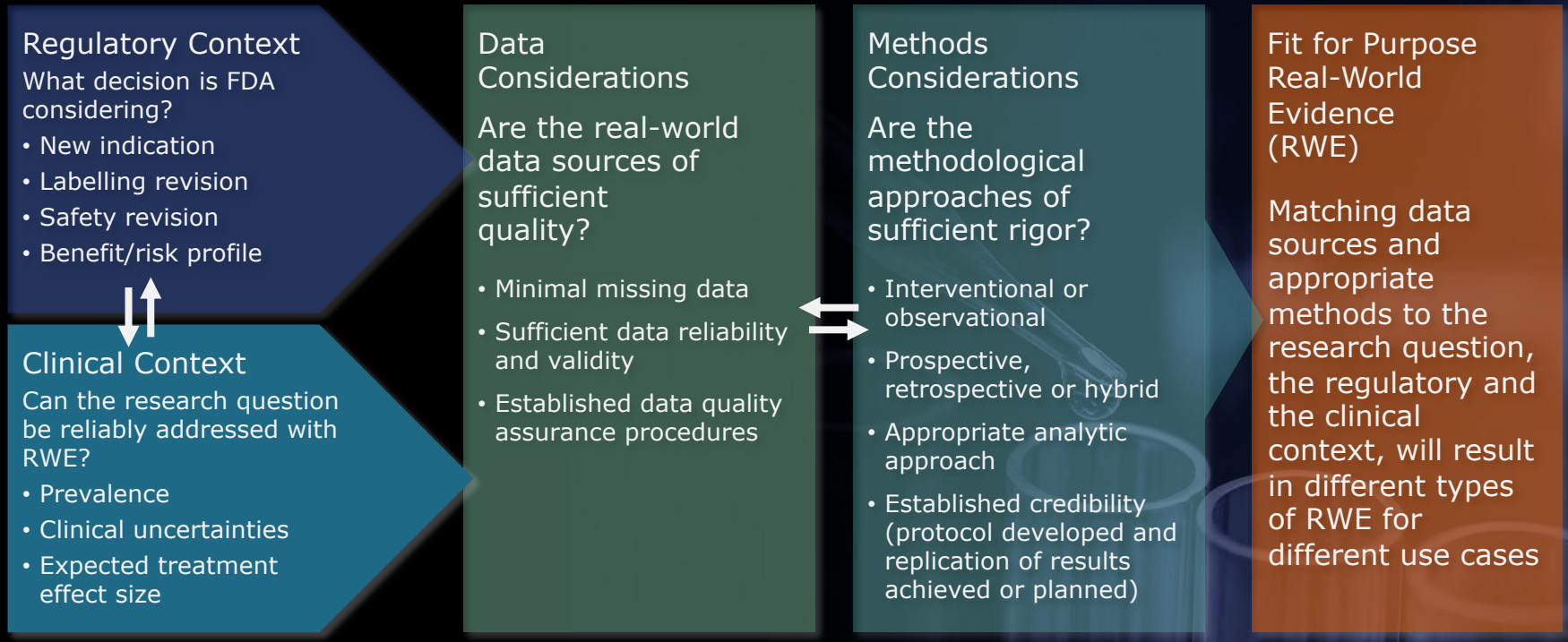
The RCT and RWE Continuum



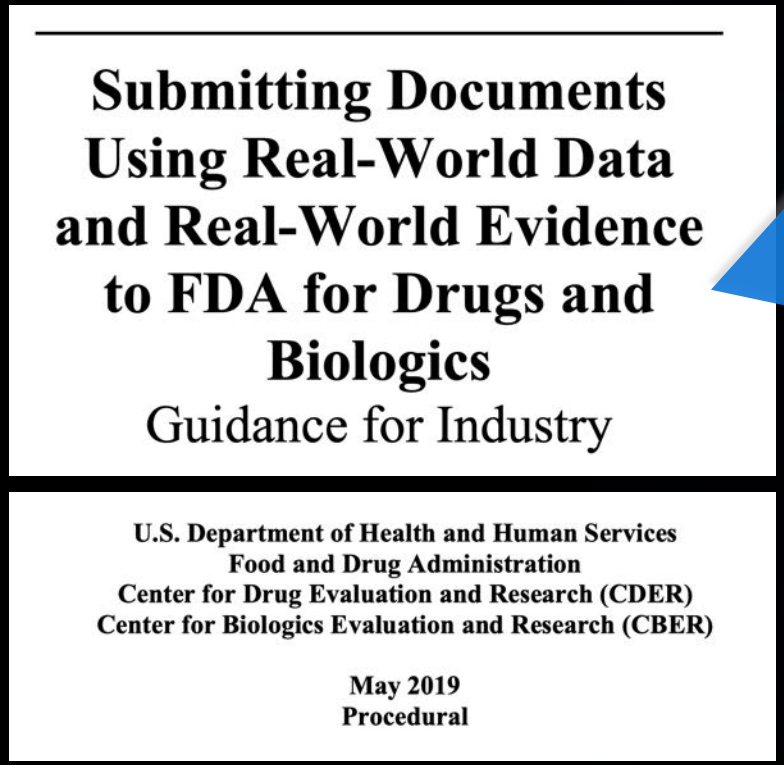
Source: Adapted from Makady A et al, What Is Real-World Data (RWD)? A Review of Definitions Based on Literature and Stakeholder Interviews. Value in Health 2017; 20 (7): 858-865

RWE in Regulatory Decision-Making



Source: Adapted from the RWE White Paper, Robert J. Margolis Center for Health Policy at Duke University, 2017

Draft FDA RWD/RWE Guidance



Submitting Documents Using Real-World Data and Real-World Evidence to FDA for Drugs and Biologics

Guidance for Industry

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

May 2019
Procedural

Example Submissions using RWD and/or RWE

- IND submissions for randomized clinical trials that use RWD to capture clinical outcomes or safety data, including pragmatic and large simple trials
- New protocols for single arm trials that use RWE as an external control
- Observational studies that generate RWE intended to help to support an efficacy supplement
- Clinical trials or observational studies using RWE to fulfill a post-marketing requirement to further evaluate safety or effectiveness and support a regulatory decision

Gene Therapy Guidance (2020)

Human Gene Therapy for Rare Diseases

Guidance for Industry

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research
January 2020

RCTs remain the standard, BUT:

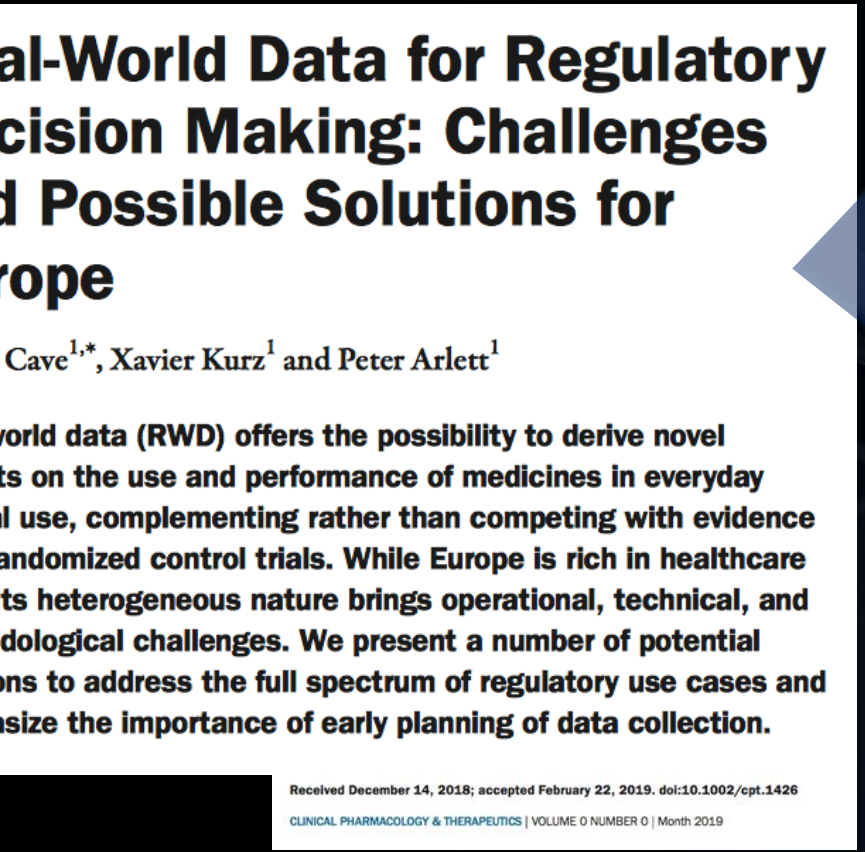
- Intra-subject control design may be useful
- Blinding, if feasible
- A single-arm trial using historical controls, if there are feasibility issues with conducting a RCT
- Knowledge of the natural history of disease is critical when using historical controls

"The first-in-human study should be adequate and well controlled to support a marketing application"

Long-Term GT Follow-Up (2020)

- FDA may recommend that you establish a registry, or use an existing patient registry, to systematically capture and track data from treated patients
- It may be appropriate to establish a registry system to specifically capture adverse event data from treated patients who receive a GT product
- This registry system can be a part of the PVP plan and reviewed at the time of licensure

EMA – Historical Controls and LTFU



Real-World Data for Regulatory Decision Making: Challenges and Possible Solutions for Europe

Alison Cave[1,*], Xavier Kurz[1] and Peter Arlett[1]

Real-world data (RWD) offers the possibility to derive novel insights on the use and performance of medicines in everyday clinical use, complementing rather than competing with evidence from randomized control trials. While Europe is rich in healthcare data, its heterogeneous nature brings operational, technical, and methodological challenges. We present a number of potential solutions to address the full spectrum of regulatory use cases and emphasize the importance of early planning of data collection.

Received December 14, 2018; accepted February 22, 2019. doi:10.1002/cpt.1426

CLINICAL PHARMACOLOGY & THERAPEUTICS | VOLUME 0 NUMBER 0 | Month 2019

Publication by EMA Pharmacovigilance and Epidemiology experts (2019)

Focus on historical controls and post-authorisation registries for long-term follow-up

Case examples for EMA use of real-world data discussed:

- Kymriah and Yescarta
- Zalmoxis
- Strimvelis
- Spinraza

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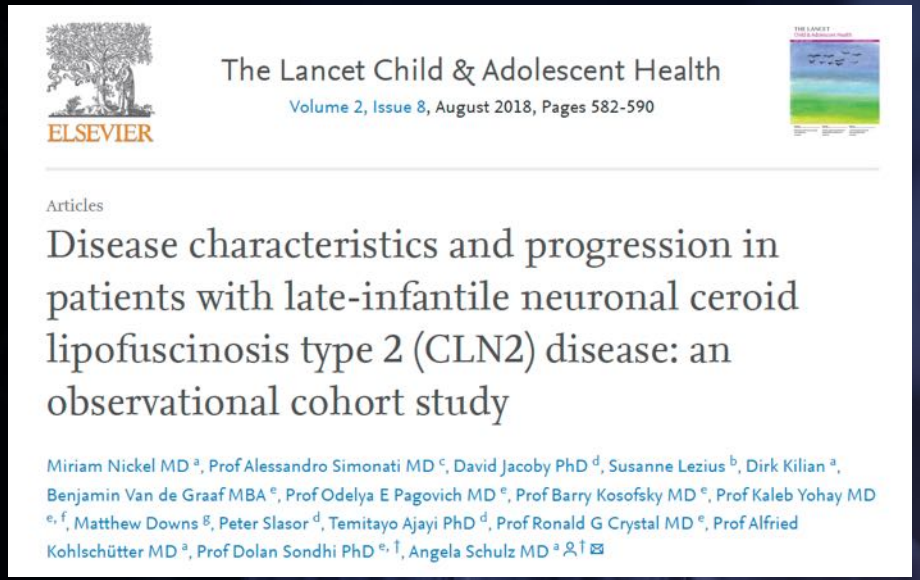
Case Example:
Natural History Supports Pivotal Study

- Data from two international datasets of patients with untreated genotypically confirmed CLN2 disease (Batten disease): the DEM-CHILD dataset (n=74) and the Weill Cornell Medical College (WCMC) dataset (n=66)
- Disease course was measured longitudinally in 67 patients: age of disease onset and diagnosis, disease progression, measured by the rate of decline in motor and language summary scores, and time from first symptom to death
- CLN2 disease has a largely predictable time course with regard to the loss of language and motor function (and shortened life expectancy)
- These data can serve as historical controls for the assessment of current and future therapies



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Case Example:
Natural History Supports Pivotal Study

- The pivotal CLN2 disease study was developed through close collaboration and communication between the sponsor and regulatory authorities, during which several methodological and statistical concerns were sequentially raised and addressed
- Questions arose regarding the comparability between the treated population and the natural history cohort regarding underlying differences in co-variables, such as age, sex, disease alleles, and baseline scores
- To address this concern, matching methodologies were incorporated, including adjustment for co-variables and use of many-to-one matching to compare one study subject with multiple historical controls
- Following these adaptations, all analyses consistently demonstrated a significant effect of cerliponase alfa

Pivotal study enabling Cerliponase alfa ERT (Brinuera, BioMarin) approval by the FDA and EMA in 2017

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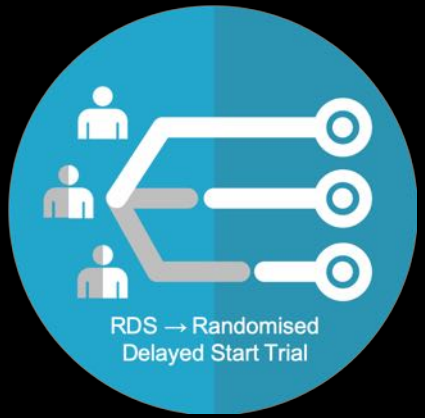
Randomised Delayed Start Trial (RDS)



- Suitable for patients with relatively stable disease condition over the duration of the trial
- Two stages: for stage 1, patients are randomized to receive a new treatment or a real-world control; for stage 2, patients who received control in stage 1 switch to the new treatment
- Analysis is based a combination of stage 1 inter-group and stage 2 intra-patient comparisons of treatment and control
- Enables assessments of outcomes that are effort-based, patient-reported or subjectively assessed by investigators
- Can reduce risk of bias vs. single-arm designs and maximize the assessment of multiple outcomes
- Blind start: initiate double-blind active therapy at different times from baseline, preceded by 0, 1, 2 intervals of placebo

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Randomised Delayed Start Trial (RDS)

LUXTURNA (voretigene neparvovec) pivotal Phase 3 trial (open label) in *RPE65* IRD

Multi-Luminance Mobility Test (MLMT) was a novel endpoint developed with FDA, experts and patients

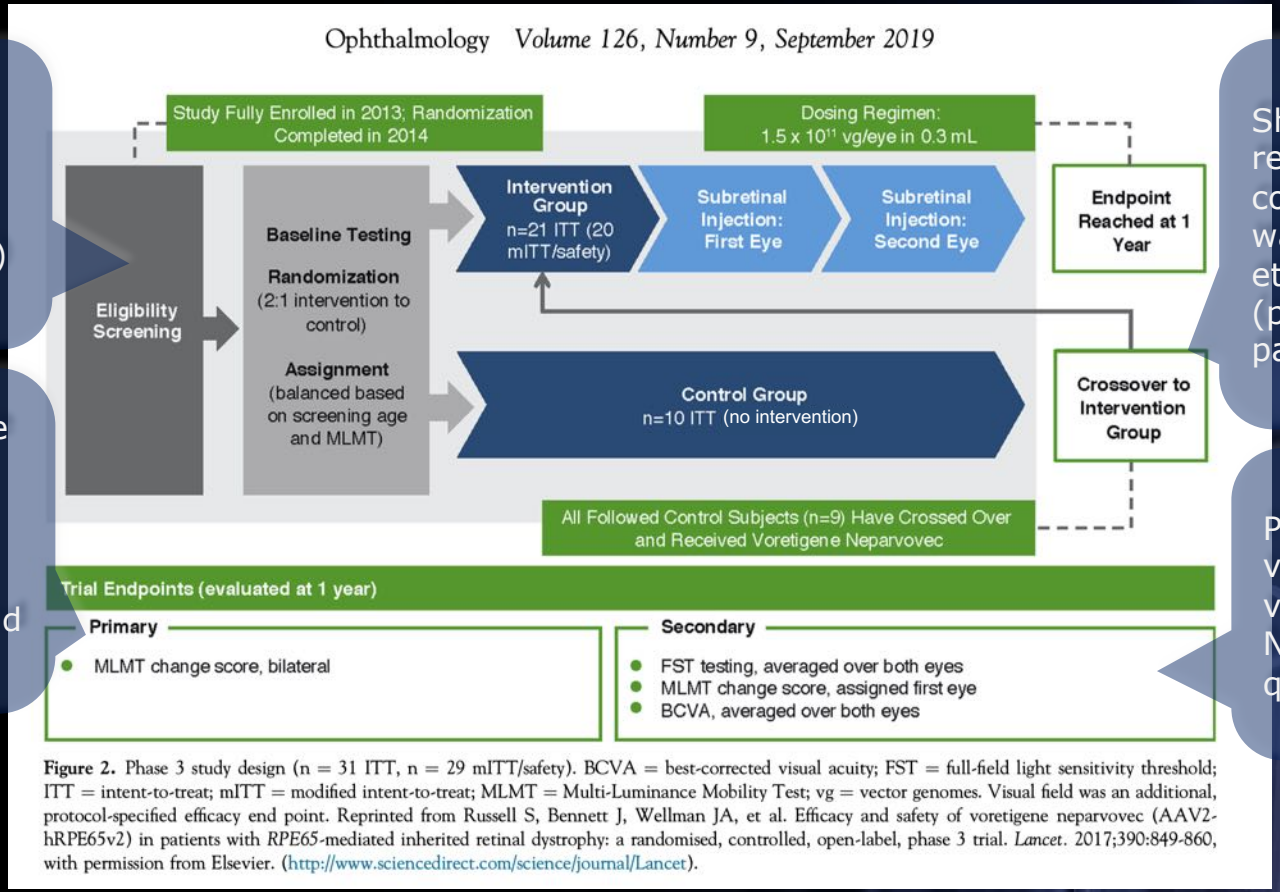

Figure 2. Phase 3 study design (n = 31 ITT, n = 29 mITT/safety). BCVA = best-corrected visual acuity; FST = full-field light sensitivity threshold; ITT = intent-to-treat; mITT = modified intent-to-treat; MLMT = Multi-Luminance Mobility Test; vg = vector genomes. Visual field was an additional, protocol-specified efficacy end point. Reprinted from Russell S, Bennett J, Wellman JA, et al. Efficacy and safety of voretigene neparvovec (AAV2-hRPE65v2) in patients with *RPE65*-mediated inherited retinal dystrophy: a randomised, controlled, open-label, phase 3 trial. *Lancet*. 2017;390:849-860, with permission from Elsevier. (http://www.sciencedirect.com/science/journal/Lancet).

Sham-sub-retinal surgery control group was rejected for ethical reasons (paediatric participants)

PRO: low-vision modified version of the NEI-VFQ-25 questionnaire

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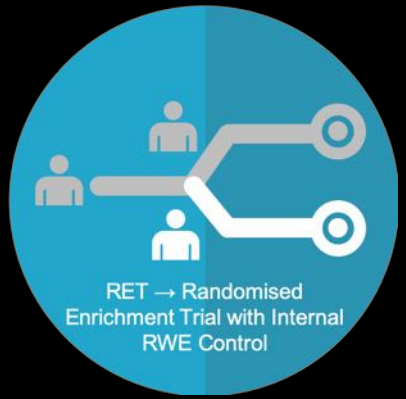
Randomized Enrichment (RW-RE) Design



- Two stages: the first stage is an open-label real-world observational study (SoC) over a suitable duration to quantify disease progression
- Patients from stage 1 who meet outcome- and/or biomarker-driven enrichment criteria are randomly assigned to receive a new treatment or remain on the Standard of Care (SoC)
- The primary endpoint may be based on difference in post- and pre-treatment progression or a difference of observed and predicted outcome
- If integrated into an existing registry (e.g. for a rare disease) also known as a Registry-Based Randomised Controlled Trial (RRCT)

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Case Example:
Registry-Based Randomised Controlled Trials (RRCTs)

Journal of Clinical Epidemiology
Volume 93, January 2018, Pages 120-127

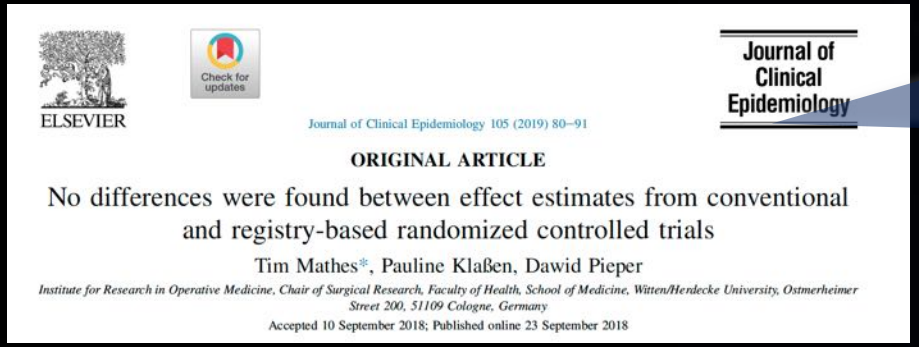
Review

Registry-based randomized controlled trials merged the strength of randomized controlled trails and observational studies and give rise to more pragmatic trials

Tim Mathes, Stefanie Buehn, Peggy Prengel, Dawid Pieper

RRCTs can provide valid (randomization, low lost-to-follow-up rates, generalizable) patient important long-term comparative-effectiveness data for relative little effort

Researchers planning an RCT should always check whether existing registries can be used for data collection



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Check for updates

Journal of Clinical Epidemiology

Journal of Clinical Epidemiology 105 (2019) 80–91

ORIGINAL ARTICLE

No differences were found between effect estimates from conventional and registry-based randomized controlled trials

Tim Mathes*, Pauline Klaßen, Dawid Pieper

Institute for Research in Operative Medicine, Chair of Surgical Research, Faculty of Health, School of Medicine, Witten/Herdecke University, Ostmerheimer Street 200, 51109 Cologne, Germany

Accepted 10 September 2018; Published online 23 September 2018

This meta-empidemiological study indicates that for objective outcomes, there is no systematic difference between effect estimates from RRCTs and conventional RCTs

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Master Protocols

The NEW ENGLAND JOURNAL of MEDICINE

REVIEW ARTICLE

THE CHANGING FACE OF CLINICAL TRIALS

Jeffrey M. Drazen, M.D., David P. Harrington, Ph.D., John J.V. McMurray, M.D., James H. Ware, Ph.D., and Janet Woodcock, M.D., *Editors*

Master Protocols to Study Multiple Therapies, Multiple Diseases, or Both

Janet Woodcock, M.D., and Lisa M. LaVange, Ph.D.

N Engl J Med 2017;377:62-70.
DOI: 10.1056/NEJMra1510062

Umbrella Trials

To study multiple targeted therapies in the context of a single disease

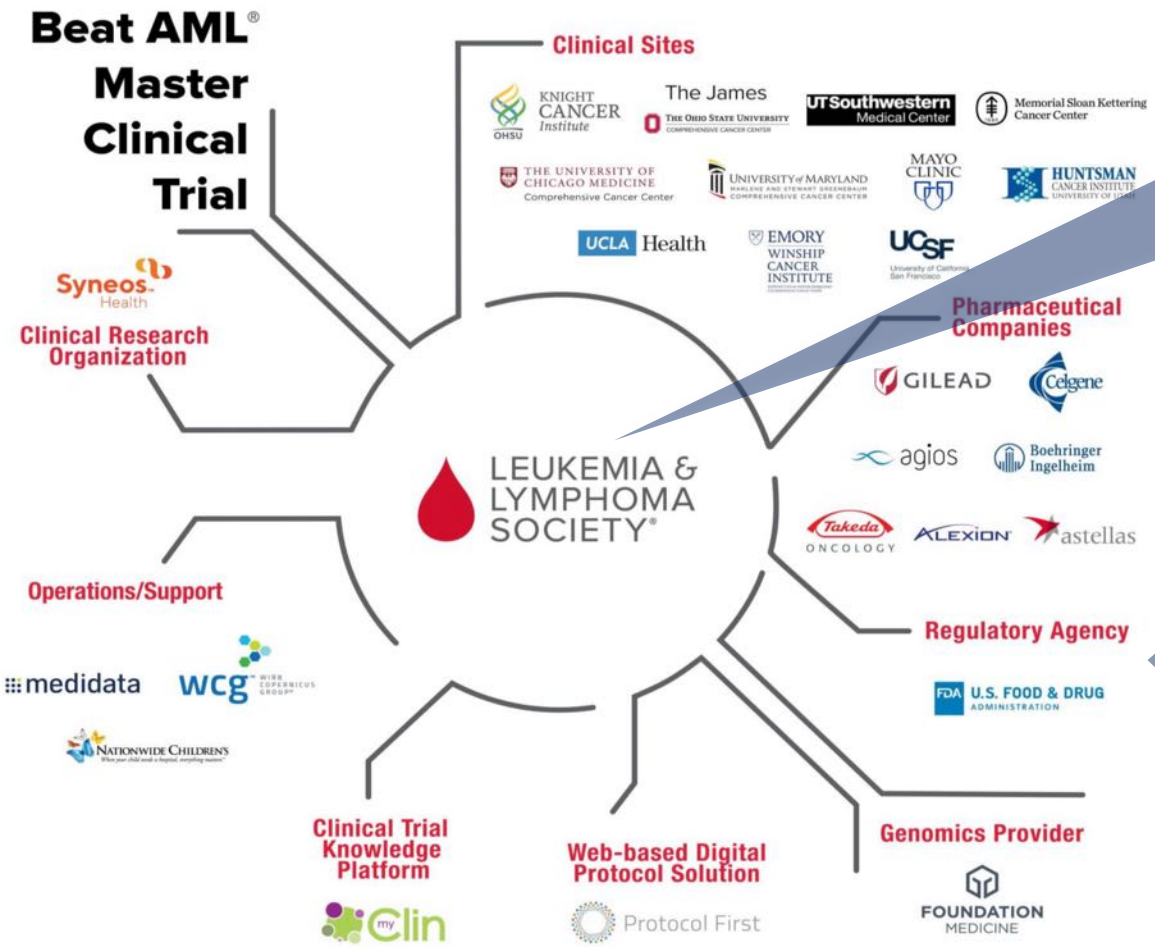
Basket Trials

To study a single targeted therapy in the context of multiple diseases or disease subtype

Platform Trials

To study multiple targeted therapies in the context of a single disease in a perpetual manner, with therapies allowed to enter or leave the platform on the basis of a decision algorithm

Collaboration is key



The patient organisation holds the IND and drives the project, provides central hub for funding

The vision is for drugs to directly graduate from the platform to Phase III registration trials, pre-approved by the FDA, dramatically shorter timelines

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Moving from Oncology to Neurology

Home - Neurology - ALS - Research

HEALEY ALS Platform Trial

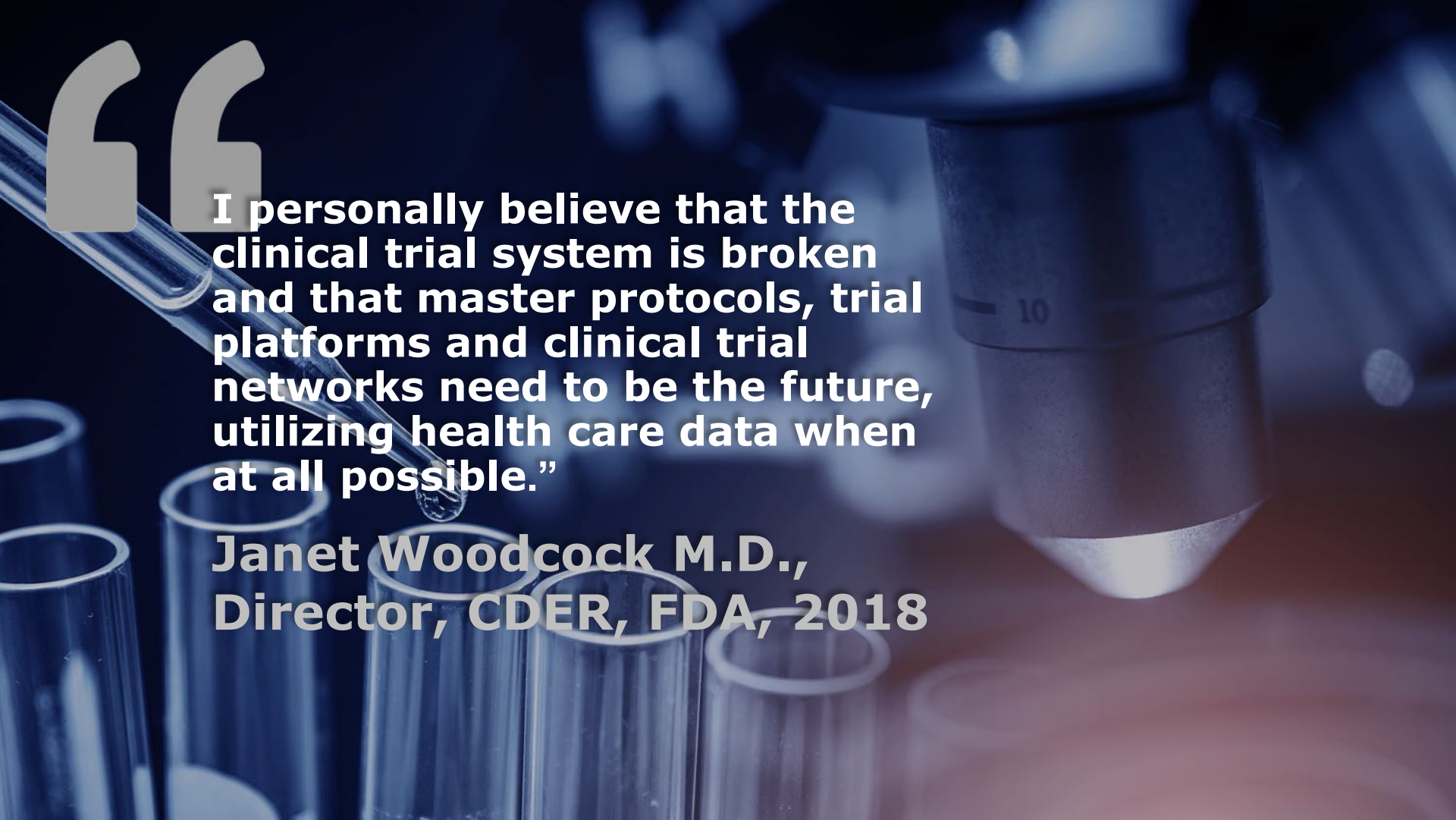
This is the first ALS platform trial, accelerating the path to new ALS therapies by testing multiple treatments at once, reducing the cost of research by 30%, decreasing the trial time by 50%, and increasing patient participation by 67%.

> *"This groundbreaking approach cuts the time to find an effective treatment in half, decreases costs by a third or more, and is supported by our patients, the FDA, ALS clinicians and scientists and our pharma colleagues."*

Merit Cudkowicz, MD, MSc
Director, Sean M. Healey & AMG Center for ALS

High industry interest, the first 5 therapies are ready to enter the trial; currently tailoring the arms to these experimental treatments in close collaboration with the companies (Spring 2020)

NCATS – Platform Vector Gene Therapy



I personally believe that the clinical trial system is broken and that master protocols, trial platforms and clinical trial networks need to be the future, utilizing health care data when at all possible.”

Janet Woodcock M.D., Director, CDER, FDA, 2018

Operationalizing RWE

- 90% of companies currently investing in building RWE capability across the entire product life cycle
- 70% building capabilities to conduct a greater proportion of RWE studies internally
- The data landscape is rapidly evolving: non-traditional data sources such as purpose-built linked data (e.g., clinical data linked to molecular data), connected devices, and health apps
- The future data landscape is likely to be shaped by an increase in strategic data partnerships and new ways of procuring data
- *Rare conditions: genetic testing initiatives, collaborations with patient groups, purpose-built natural history studies*

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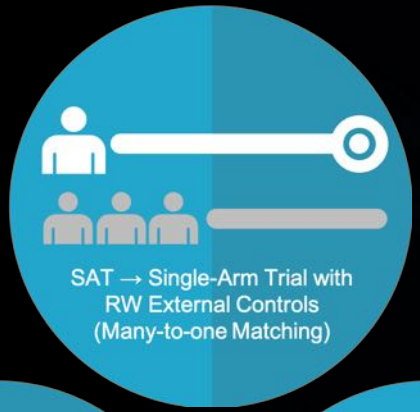
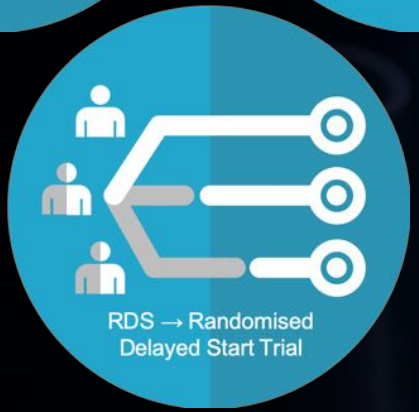
Study Designs Supported by RWE





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Thank you

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