Real - World Data for Regulatory Purposes in the Rare Disease Setting: generating decision grade evidence

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Disclosures

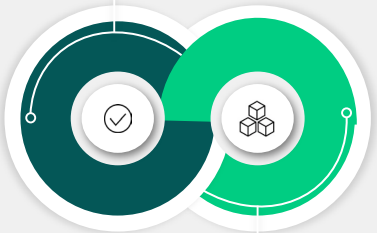
Dr. Gatto is an employee of and holds stock options in Aetion, Inc., a technology company that provides analytic software and services to the healthcare industry, and owns stock in Pfizer Inc.

“Substantial evidence” is required to demonstrate product effectiveness

Generally entails **two adequate and well - controlled** clinical investigations

“evidence consisting of adequate and well - controlled investigations…by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved…could fairly and responsibly be concluded by such experts that the drug will have the effect it purports… under the conditions of use prescribed, recommended, or suggested in the labeling or proposed labeling thereof”

– FD&C Act section 505(d) (21U.S.C. § 355(d))



Quality

Randomized (concurrently controlled, superiority) design with protocolized assessments provides most certainty in interpretation

Quantity

Mitigates possibility of a single investigation’s results being erroneous due to bias or chance

Source: FDA. Substantial Evidence of Effectiveness for Human Drug and Biological Products Guidance for Industry. Dec 2019.

FDA accepts an alternative evidentiary approach when…

The disease is life - threatening or severely debilitating with unmet medical need

&

No randomized concurrently controlled superiority trial is ethical or feasible

Even when true, the **substantial evidence** standard must be met

Pivotal RWE for label claims

Establish regulatory feasibility → **Establish scientific feasibility**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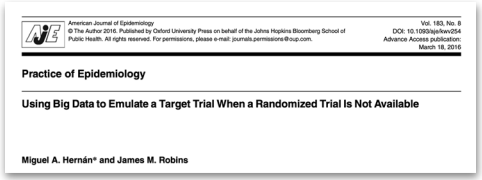
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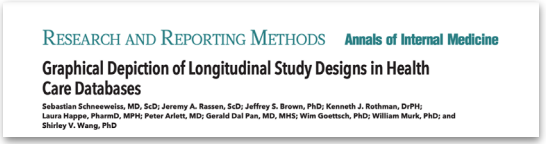
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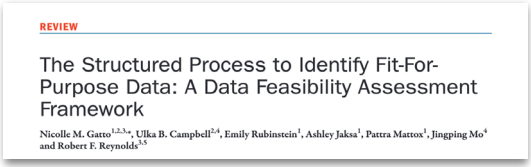
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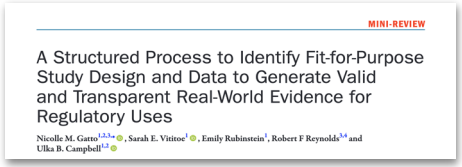
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OPEN ACCESS

Check for updates

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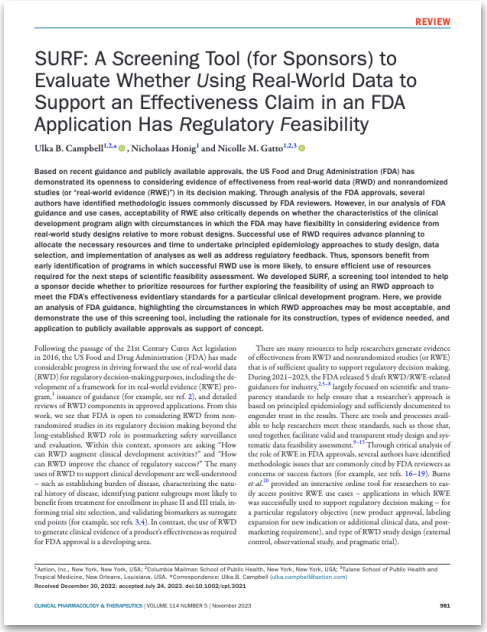
Establishing regulatory feasibility

Pivotal RWE for label claims

Establish regulatory feasibility → **Establish scientific feasibility**



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Based on recent guidance and publicly available approvals, the US Food and Drug Administration (FDA) has demonstrated its openness to considering evidence of effectiveness from real-world data (RWD) and nonrandomized studies (or "real-world evidence (RWE")) in its decision making. Through analysis of the FDA approvals, several authors have identified methodologic issues commonly discussed by FDA reviewers. However, in our analysis of FDA guidance and use cases, acceptability of RWE also critically depends on whether the characteristics of the clinical development program align with circumstances in which the FDA may have flexibility in considering evidence from real-world study designs relative to more robust designs. Successful use of RWD requires advance planning to allocate the necessary resources and time to undertake principled epidemiology approaches to study design, data selection, and implementation of analyses as well as address regulatory feedback. Thus, sponsors benefit from early identification of programs in which successful RWD use is more likely, to ensure efficient use of resources required for the next steps of scientific feasibility assessment. We developed SURF, a screening tool intended to help a sponsor decide whether to prioritize resources for further exploring the feasibility of using an RWD approach to meet the FDA's effectiveness evidentiary standards for a particular clinical development program. Here, we provide an analysis of FDA guidance, highlighting the circumstances in which RWD approaches may be most acceptable, and demonstrate the use of this screening tool, including the rationale for its construction, types of evidence needed, and application to publicly available approvals as support of concept.

Following the passage of the 21st Century Cures Act legislation in 2016, the US Food and Drug Administration (FDA) has made considerable progress in driving forward the use of real-world data (RWD) for regulatory decision-making purposes, including the development of a framework for its real-world evidence (RWE) program,[1] issuance of guidance (for example, see ref. 2), and detailed reviews of RWD components in approved applications. From this work, we see that FDA is open to considering RWD from nonrandomized studies in its regulatory decision making beyond the long-established RWD role in postmarketing safety surveillance and evaluation. Within this context, sponsors are asking "How can RWD augment clinical development activities?" and "How can RWD improve the chance of regulatory success?" The many uses of RWD to support clinical development are well-understood – such as establishing burden of disease, characterizing the natural history of disease, identifying patient subgroups most likely to benefit from treatment for enrollment in phase II and III trials, informing trial site selection, and validating biomarkers as surrogate end points (for example, see refs. 3,4). In contrast, the use of RWD to generate clinical evidence of a product's effectiveness as required for FDA approval is a developing area.

There are many resources to help researchers generate evidence of effectiveness from RWD and nonrandomized studies (or RWE) that is of sufficient quality to support regulatory decision making. During 2021–2023, the FDA released 5 draft RWD/RWE-related guidances for industry,[5–9] largely focused on scientific and transparency standards to help ensure that a researcher's approach is based on principled epidemiology and sufficiently documented to engender trust in the results. There are tools and processes available to help researchers meet these standards, such as those that, used together, facilitate valid and transparent study design and systematic data feasibility assessment.[9–15] Through critical analysis of the role of RWE in FDA approvals, several authors have identified methodologic issues that are commonly cited by FDA reviewers as concerns or success factors (for example, see refs. 16–19). Burns *et al.*[20] provided an interactive online tool for researchers to easily access positive RWE use cases – applications in which RWE was successfully used to support regulatory decision making – for a particular regulatory objective (new product approval, labeling expansion for new indication or additional clinical data, and postmarketing requirement), and type of RWD study design (external control, observational study, and pragmatic trial).

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SURF is a screening tool to help a sponsor determine whether it makes sense to explore the use of RWD to meet the regulatory effectiveness evidentiary standards for a particular clinical development program

Based on our analysis of FDA's guidance, learnings from review of use cases, and our experience

RWE experts (partnering with clinical and regulatory colleagues) apply SURF to a development program

Campbell, UB et al. Clin Pharmacol Ther. (2023) doi: 10.1002/cpt.3021.

Figure 1. SURF screening tool

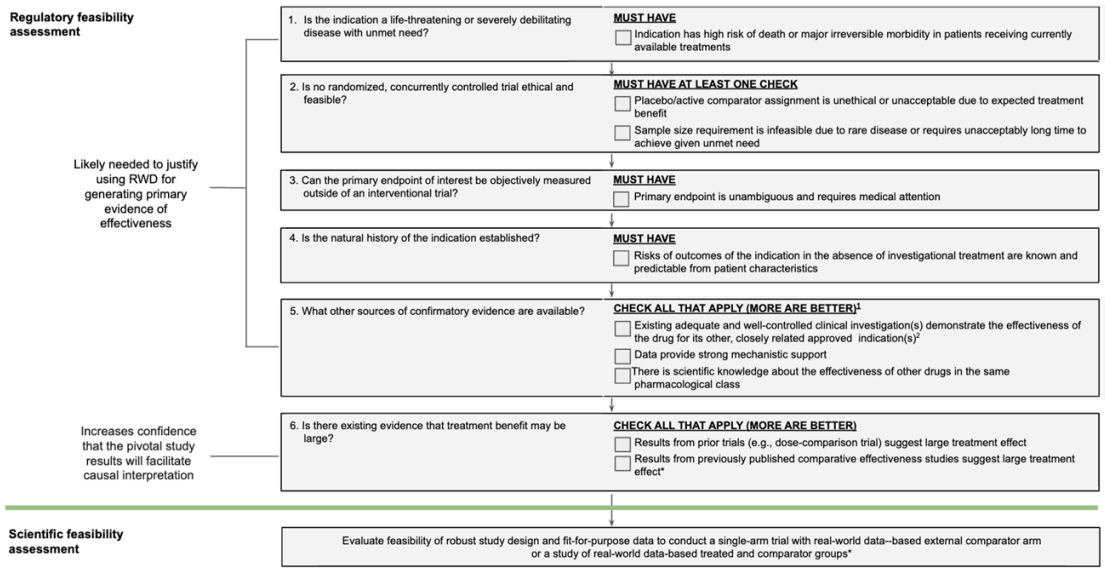

Figure 1 SURF screening tool for determining whether the use of RWD to contribute to substantial evidence of effectiveness within an FDA application for a particular clinical development program is justified based on the program's characteristics.[1] The evidence sources listed below are examples from FDA guidance; other evidence sources beyond those listed below may be acceptable based on clinical program characteristics, the strength of evidence, etc.[2] Applies to supplementary approvals only. FDA, US Food and Drug Administration; RWD, real-world data.

Campbell, UB et al. Clin Pharmacol Ther. (2023) doi: 10.1002/cpt.3021.

The SURF questions:

1. Is the indication a life-threatening or severely debilitating disease with unmet need?
2. Is a randomized, concurrently controlled trial unethical or infeasible?
3. Can the primary endpoint be objectively measured outside of an interventional trial?
4. Is the natural history of the indication well-established?
5. Are there other sources of robust confirmatory evidence?
6. Is the treatment expected to have a large effect?

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Implications for RWD acceptability:

INCREASES REGULATORY FLEXIBILITY: Fills urgent public health need

INCREASES REGULATORY FLEXIBILITY: Gold standard design is not feasible

MITIGATES UNCERTAINTY: Must be measured in routine clinical care as a pre-condition to be captured in RW data sources

MITIGATES UNCERTAINTY: Predictable, well-known outcome risks in untreated patients

MITIGATES UNCERTAINTY: Corroborating evidence from other sources

MITIGATES UNCERTAINTY: More likely to overcome inevitable bias

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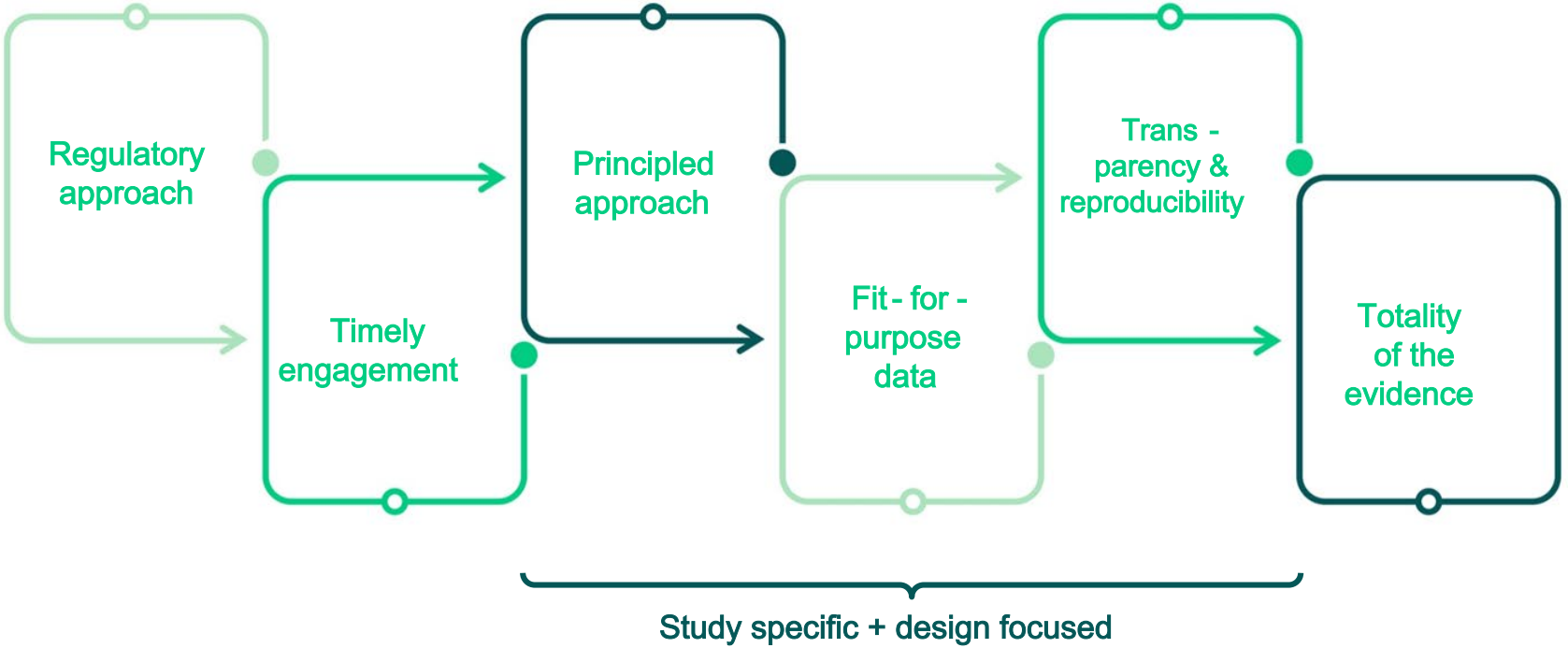
Generating decision - grade RWE

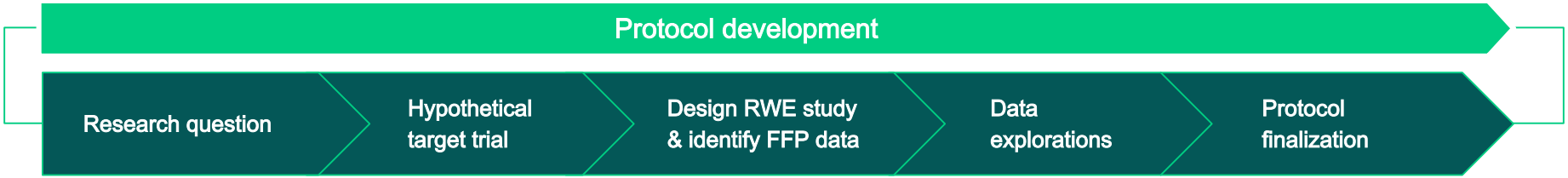
Key themes arising from FDA guidances



Study lifecycle

Study lifecycle

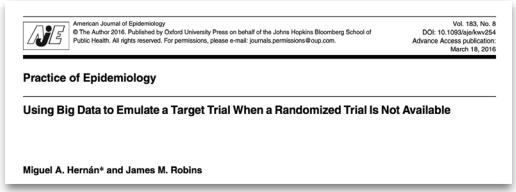
Published standards support decision - grade RWE



Published standards support decision - grade RWE

Protocol development

Research question → Hypothetical target trial → Design RWE study & identify FFP data → Data explorations → Protocol finalization



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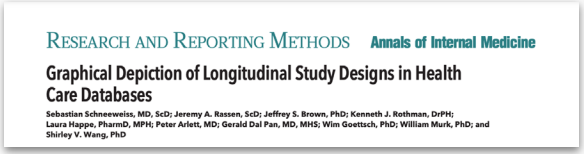

RESEARCH AND REPORTING METHODS Annals of Internal Medicine

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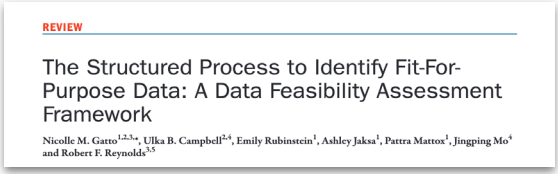

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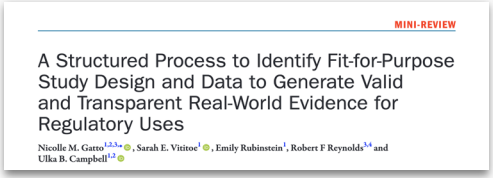

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SPIFD2 Framework

Combines and updates the predecessor SPACE and SPIFD frameworks to provide a step-by-step principled process for RW design & data selection

Step 1: State the research aim, question, and objectives
1a: Overarching research aim
1b: Research question
1c: Primary objective(s)
Step 2: Describe the hypothetical target trial
2a: Conceptual definition
2b: Target trial definition
Step 3: Describe RW emulation of the hypothetical target trial
Step 3a: Best-case operationalization under routine clinical care
(See SPIFD2 Table S2 for potential confounder identification)
Step 4: Identify a fit - for - purpose dataset
4a: Minimal criteria for valid operationalization in RWD source
4b: RWD minimal criteria ranking with regard to uniqueness and importance
4c: Detailed data source feasibility assessment findings and summary heat map
4d: Practical considerations
Step 5: Document final RW operationalization, rationale, validity concerns, & approaches to address these concerns
5a: Final RW operationalization in STaRT-RWE
5b:. Rationale for final operationalization of RW study design element or variable
5c: Validity concerns related to RW operationalization, selected RW data source and/or study design
5d: How these validity concerns are/will be addressed

Source: Gatto et al, CPT 2023

SPIFD2 template simplified view

Step 2 - Describe the hypothetical target trial

STEP 1: STATE THE RESEARCH QUESTION, AIMS, AND OBJECTIVES													
1a 1b 1c													
	STEP 2:DESCRIBEHTT		STEP 3: DESCRIBE RW STUDY EMULATION OF HTT	STEP 4:IDENTIFY FIT- FOR- PURPOSE RWD SOURCE						STEP 5: DOCUMENT FINAL RW OPERATIONALIZATION, RATIONALE, VALIDITY CONCERNSAND APPROACHES TO ADDRESS THESE CONCERNS			
Design Elements	2a	2b	3a	4a	4b	4c	Data Source 1	Data Source 2	Data Source 3	5a	5b	5c	5d
General													
Estimator Treatment group assignment, Time zero Length/frequency of follow-up Sample size needed													
Variable Related													
Inclusion & Exclusion Criteria Treatment & Comparator Group Primary Outcome Key Secondary Outcome(s) Subgroups Confounders													
Practical Considerations (4d)													
Budget Timeline Other													

Abbreviations: HTT (Hypothetical Target Trial)

Source: Gatto et al, CPT 2023

FDA approval use cases

Looking across FDA approval case studies: Rare diseases

	ZOLGENSMA® (onasemnogene abeparvovec -xioi)	PROGRAF® (tacrolimus)	RETHYMIC® (allogeneic processed thymus tissue -agdc)	ZOKINVY® (lonafarnib)	DOJOLVI® (triheptanoin)
Indication	Spinal muscular atrophy (TA: Neurology)	Organ rejection prevention in lung transplant patients (TA: Transplantation)	Congenital athymia (TA: Immunology)	Hutchinson-Gilford progeria syndrome and processing-deficient progeroid laminopathies (TA: Genetic disorder)	Prevention of major clinical events in patients with long-chain fatty acid oxidation disorders (TA: Metabolic disease)
RWD use	Benchmark	Benchmark + CS	Benchmark	ECA	ECA
Primary endpoint	Survival and independent sitting	1-year graft and overall survival	Death	Death	Major clinical events (rhabdomyolysis, hypoglycemia, or cardiomyopathy)
Comparator group	Historical untreated	Benchmark: historical untreated CS: concurrent active comparator-treated	Concurrent untreated, supportive-care patients	Concurrent untreated patients	Historical untreated patient time (self-matched)
Treatment group data source	Single-arm trial	US Scientific Registry of Transplant Recipients/ SSA Death Master File	Pooled data from 10 single-arm trials conducted over 28-year period	Secondary analysis of pooled data from two published investigator-initiated single-arm trials	Single-arm trial
Comparator data sources	Two published RW natural history studies	Benchmark: published natural history studies CS: concurrent cohort from same registry	Concurrent RW cohort referred to the same investigator who conducted the trials	Concurrent RW cohort from the Progeria Research Foundation international registry	Pre-trial RW data obtained from trial participants' medical records
Epi / stats methods	NA - Benchmark only	CS: multivariable Cox proportional hazards models used to estimate adjusted hazard ratio	NA	"Matching algorithm", "censor untreated"	"Retrospective vs prospective study periods"

ECA = external control arm; CS = cohort study

Source: Aetion analysis; FDA/EMA drug approval documents.

Looking across FDA approval case studies: Rare diseases

Key factor	ZOLGENSMA®	PROGRAF®		RETHYMIC®	ZOKINVY®	DOJOLVI®
Approval type	Full	Full		Full	Full	Full
RWD role in approval	Benchmark: Substantial evidence	Benchmark: Substantial evidence	CS: Not considered	Benchmark: Substantial evidence	ECA: Substantial evidence	ECA: Not considered

Source: Aetion analysis; FDA drug approval documents.

Looking across FDA approval case studies: Rare diseases

Key factor	ZOLGENSMA®	PROGRAF®		RETHYMIC®	ZOKINVY®	DOJOLVI®
Approval type	Full	Full		Full	Full	Full
RWD role in approval	Benchmark: Substantial evidence	Benchmark: Substantial evidence	CS: Not considered	Benchmark: Substantial evidence	ECA: Substantial evidence	ECA: Not considered
Clear unmet need						

Looking across FDA approval case studies: Oncology

	MONJUVI® (tafasitamab - cxix)	KOSELUGO® (selumetinib)	ABECMA® (idecabtagene vicleucel)	BALVERSA® (erdafitinib)	TALVEY® (talquetamab - tgvs)
Indication	Relapsed or refractory diffuse large B-cell lymphoma	Neurofibromatosis-1 with symptomatic, inoperable plexiform neurofibroma (TA: Oncology)	Relapsed, refractory multiple myeloma (TA: Oncology)	Advanced urothelial carcinoma with FGFR alteration (TA: Oncology)	Relapsed, refractory multiple myeloma
RWD use	ECA	ECA	ECA + Benchmark	ECA	ECA
Primary endpoint	Overall response rate	Tumor growth rate and progression-free survival	Overall response rate	Overall survival	Overall response rate and duration of response
Comparator group	Historical active comparator-treated	Contemporaneous therapeutic class-untreated	ECA: contemporaneous active comparator-treated Benchmark: other therapies	Contemporaneous active comparator-treated	Contemporaneous physician choice-treated
Treatment group data source	Single-arm trial	Single-arm trial	Single-arm trial	Single-arm trial	Single-arm trial
Comparator data sources	Historical patient records from clinical trial and compassionate use program sites	Sites engaged in National Cancer Institute-led natural history study	ECA: concurrent cohort (mix of trial sites, registries and research database) Benchmark: published studies	Flatiron-FMI database	Primary data collection from sites in multiple countries
Epi / stats methods	Propensity-score matching, with estimated odds ratio	Age-matching; adjusted estimates of growth rate derived from a random coefficient mixed model	ECA: trimmed stabilized inverse probability of treatment weighted propensity score	Propensity score-weighted analysis, with estimated hazard ratio	Adjusted analysis (method not specified)

ECA = external control arm; CS = cohort study

Source: Aetion analysis; FDA/EMA drug approval documents.

Looking across FDA approval case studies: Oncology

Key factor	MONJUVI®	KOSELUGO®	ABECMA®		BALVERSA®	TALVEY®
Approval type	Accelerated	Full	Full		Accelerated	Accelerated
ECA role in approval	ECA: Supportive benchmark	ECA: Supportive benchmark	ECA: Not considered	Benchmark: Supportive benchmark	ECA: Not considered	ECA: Not considered

Source: Aetion analysis; FDA drug approval documents.

Key factor	MONJUVI®	KOSELUGO®	ABECMA®		BALVERSA®	TALVEY®
Approval type	Accelerated	Full	Full		Accelerated	Accelerated
ECA role in approval	ECA: Supportive benchmark	ECA: Supportive benchmark	ECA: Not considered	Benchmark: Supportive benchmark	ECA: Not considered	ECA: Not considered
Clear unmet need						

Source: Aetion analysis; FDA drug approval documents.

Summary

- Regulatory acceptance of RWE in lieu of the "two RCT" approach hinges on:
  - Establishing circumstances in which there is more regulatory flexibility and tolerance of uncertainty
  - Mitigating uncertainty with robust RW study design / data fitness and corroborating evidence
- Existing frameworks, tools and templates are available to facilitate RWE regulatory feasibility evaluation and enable validity through fit-for-purpose design and data selection

Thank you.

Studying Rare Diseases With External Controls: Opportunities, Challenges And A Case Example

Andrea Gross, MD
Pediatric Oncology Branch
Society for Clinical Trials Annual Conference
May 21, 2024

NIH NATIONAL CANCER INSTITUTE
Center for Cancer Research

Disclosures

- No financial disclosures
- Unpaid advisory roles for Alexion/AstraZeneca and Springworks Therapeutics

Why Study Rare Diseases?

- Rare Disease:

  Disease or condition that **affects less than 200,000 persons in the U.S**

  and

  Disease or condition for which there is no reasonable expectation that the cost of developing and making available a drug for it will be recovered from sales of drug

- 300 million people in the world with rare diseases
  - 3.5 – 5.9% of the world's population

ARTICLE 'ESTIMATING CUMULATIVE POINT PREVALENCE OF RARE DISEASES: ANALYSIS OF THE ORPHANET DATABASE, EUROPEAN JOURNAL OF HUMAN GENETICS (2019)

https://www.rarediseaseday.org/what-is-a-rare-disease/

Insights from Studying Rare Diseases

- "Two-Hit" hypothesis of tumor suppressor genes from Knudson's work with hereditary retinoblastoma (1971)
  - Require a new "de novo" mutation in second allele to develop cancer
  - Has led to a greater understanding of development of all cancers (hereditary and sporadic)

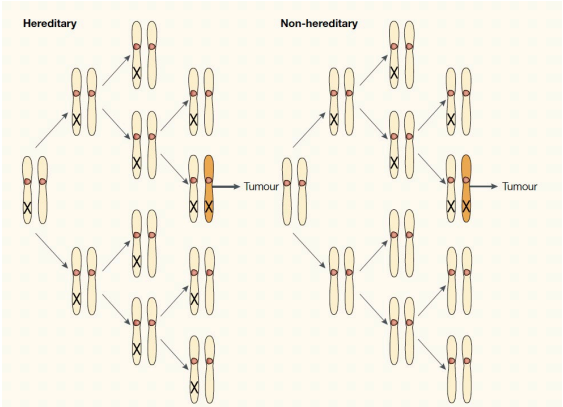


Figure 4 | **Two-hit tumour formation in both hereditary and nonhereditary retinoblastoma.** A 'one-hit' clone is a precursor to the tumour in nonhereditary retinoblastomas, whereas all retinoblasts (indeed, all cells) are one-hit clones in hereditary retinoblastoma.

(Knudson, Nature Reviews, 2001)

Clinical Trials for Rare Disease

- **Opportunities in Rare Disease Research**
  - ***Unmet medical need***
  - Genetic diseases and tumor predisposition syndromes can offer unique biological insights
  - Patient advocacy organizations

- **Challenges with clinical trial design and endpoints**
  - Small patient population & young age; large randomized controlled trial often not feasible
  - Need for long-term tolerability of investigational agents
  - Lack of validated outcome measures

Are Randomized Trials Always Necessary?

- Randomized controlled trials (RCTs) are the “gold standard” for drug approval
  - Not always feasible in rare diseases with small populations
- If probability of outcome is high a RCT may not be appropriate
- Externally Controlled Trial:
  - Compares treatment patients to a group of patients external to the study, such as those treated at an earlier time (historical control) or a group treated during the same time period but in another setting

Parachute use to prevent death and major trauma related to gravitational challenge: systematic review of randomised controlled trials

Gordon C S Smith, Jill P Pell

Parachutes reduce the risk of injury after gravitational challenge, but their effectiveness has not been proved with randomised controlled trials

(Smith 2003)

(FDA Guidance E10 Choice of Control Group and Related Issues in Clinical Trials)

Sources of Real World Evidence

Real World Data (RWD): Data relating to patient health status and/or the delivery of health care routinely collected from a variety of sources (Examples: Electronic health record, disease registries, insurance filing data)

Prospective Observational Study (Natural History Study) Pre-planned observational study intended to track the course of the disease and are likely to include data of persons who are receiving standard of care for a disease

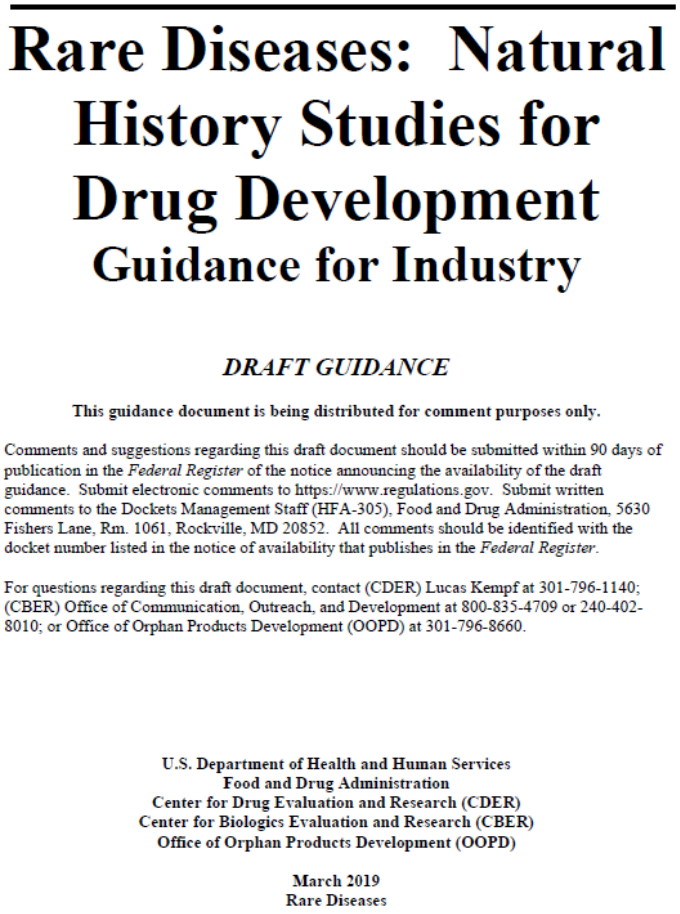
Retrospective Observational Studies: Retrospective non-interventional study which identifies the population and determines the exposure/treatment from historical data

Real World Evidence (RWE): Clinical evidence about the usage and potential benefits or risks of a medical product derived from analysis of real world data

(Framework for FDA's Real-World Evidence Program, 2018)

FDA Guidance: Natural History Studies in Rare Diseases

- 2019: Intended to "inform the design and implementation of natural history studies that can be used to support the development of safe and effective drugs and biological products for rare diseases"
- Potential uses of a natural history study for drug development in rare disease:
  - Identifying the patient population
  - Identification/development of clinical outcome assessments
  - Identification/development of biomarkers
  - Use of natural history study data as an external control



Rare Diseases: Natural History Studies for Drug Development

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) Lucas Kempf at 301-796-1140; (CBER) Office of Communication, Outreach, and Development at 800-835-4709 or 240-402-8010; or Office of Orphan Products Development (OOPD) at 301-796-8660.

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)
Office of Orphan Products Development (OOPD)

March 2019
Rare Diseases

When to Use an External Control for a Trial?

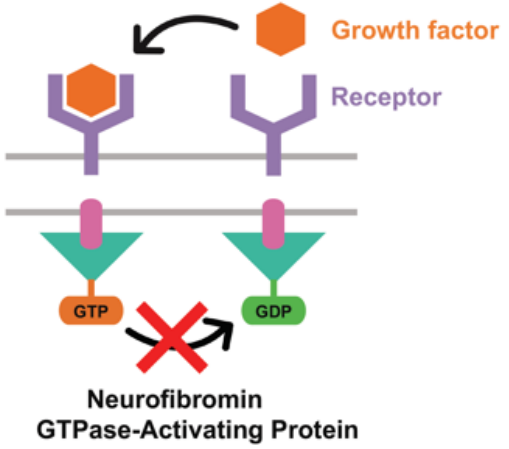
- ❑ Not possible or ethical to run placebo control
- ❑ No available therapy for comparison
  - ❑ Absence of a standard therapy
- ❑ Disease progression is well understood or predictable
- ❑ The outcome measure is objective
- ❑ The effect of the treatment is:
  - ❑ Large/dramatic
  - ❑ Not affected by investigator motivation or choice of subject
  - ❑ Strong temporal association with drug/administration/intervention
  - ❑ Consistent with effect in animal models
- ❑ Control group: well documented, access to individual patient data
- ❑ Results provide compelling evidence of change in established progression of disease

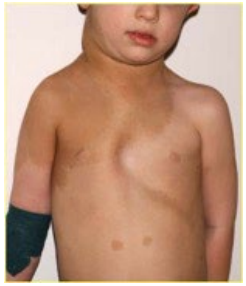
(Jahanshahi M et al.: Therapeutic Innovation & Regulatory Science, 2021)

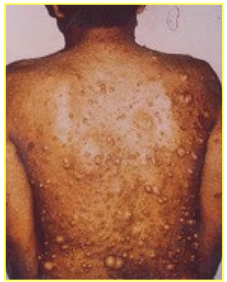
Case Example: Neurofibromatosis Type 1

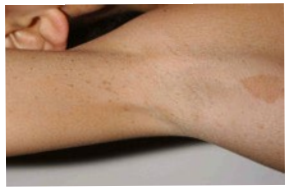
Neurofibromatosis Type 1 (NF 1)

- Single gene disorder (1:3500)
  - Neurofibromin,17q11.2, RAS pathway activation
- Cutaneous Findings:
  - Café au lait macules, cutaneous neurofibromas, skin freckling
- Involvement of all organ systems
- Tumor development:
  - Peripheral Nerve Sheath Tumors (PNST):
    - Plexiform neurofibromas (PN)
    - Atypical neurofibroma (AN)
    - Malignant peripheral nerve sheath tumors (MPNST)
  - Optic pathway and low-grade gliomas
  - Other tumors (GIST, Pheochromocytoma, JMML)



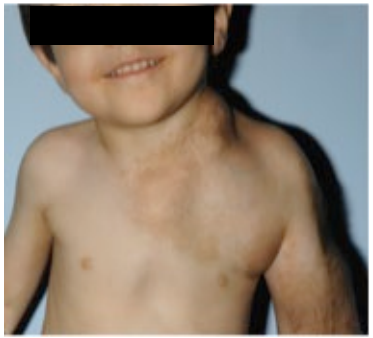




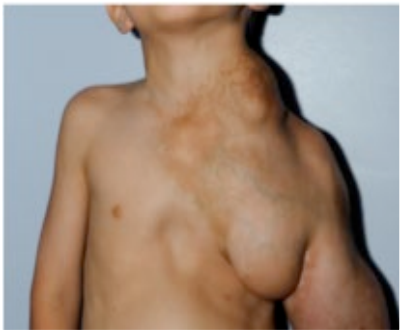


Plexiform Neurofibromas (PN)

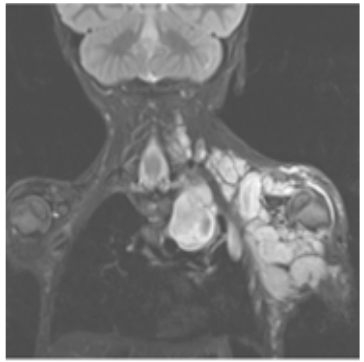
- Involve multiple nerve fascicles/branches
- Schwann cells, fibroblasts, mast cells, highly vascular
- Slow growth, large size, complex shape
- Disfigurement, pain, functional impairment, life-threatening
- Risk of transformation to malignant peripheral nerve sheath tumor (MPNST)



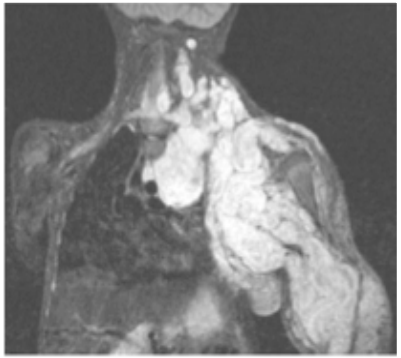
3 years



5 years



3 years



5 years

NCI NF1 Natural History

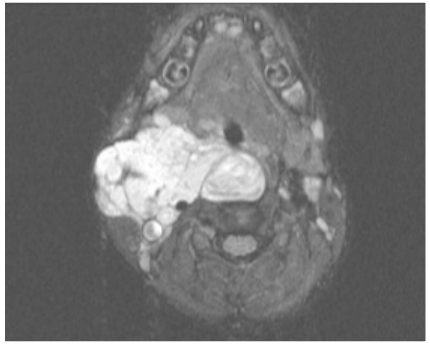
Dr. Brigitte Widemann

- Knowledge of the natural history of plexiform neurofibromas required for development of meaningful clinical trials
- Reproducible and sensitive measurement of PN required to measure activity in clinical trials
- Novel endpoints are required to measure efficacy
  - Function, patient reported outcomes, appearance
  - Response Evaluation in Neurofibromatosis and Schwannomatosis international working group (REiNS)

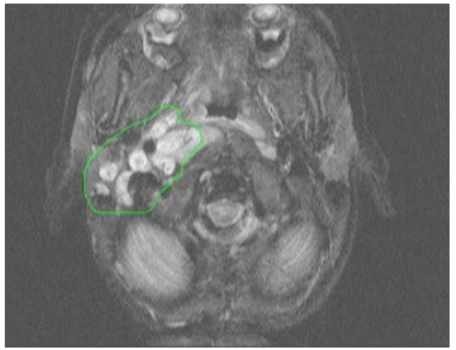
Volumetric MRI Analysis of PN

- Volumetric MRI is the standard methodology for measuring PN on clinical trials (REiNS)

STIR Sequence

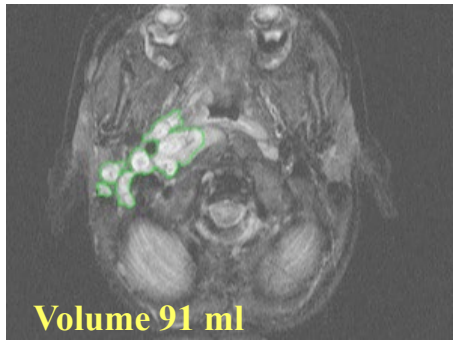


Region of Interest



- Response Criteria:
  - **Partial Response (PR)**: ≥ 20% decrease in tumor volume
  - **Progressive Disease (PD)**: ≥ 20% increase in tumor volume from best response

Tumor border identified



(Dombi, Neurology, 2013; Solomon J, Comput Med Imaging Graph, 2004; Gross AM, NEJM. 2020.

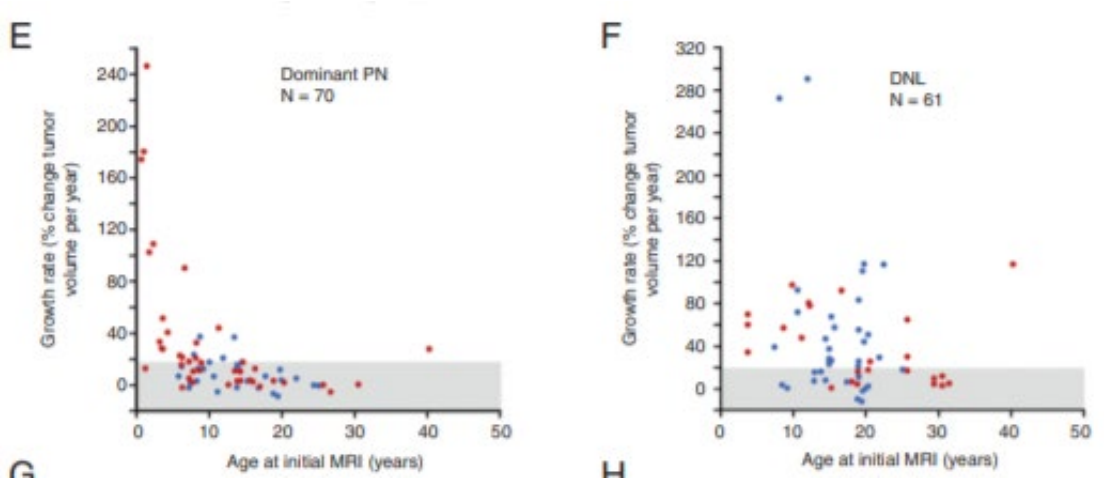
PN-Related Questions Addressed in the NHx Study:

- PN Growth Rate:
  - PN grow most rapidly in young children
  - Spontaneous PN shrinkage occurs BUT no patients with >20% shrinkage per year

Neuro-Oncology

XX(XX), 1–11, 2020 | doi:10.1093/neuonc/noaa053 | Advance Access date 10 March 2020

Longitudinal evaluation of peripheral nerve sheath tumors in neurofibromatosis type 1: growth analysis of plexiform neurofibromas and distinct nodular lesions



(Akshintala, Neuro-Oncology, 2020)

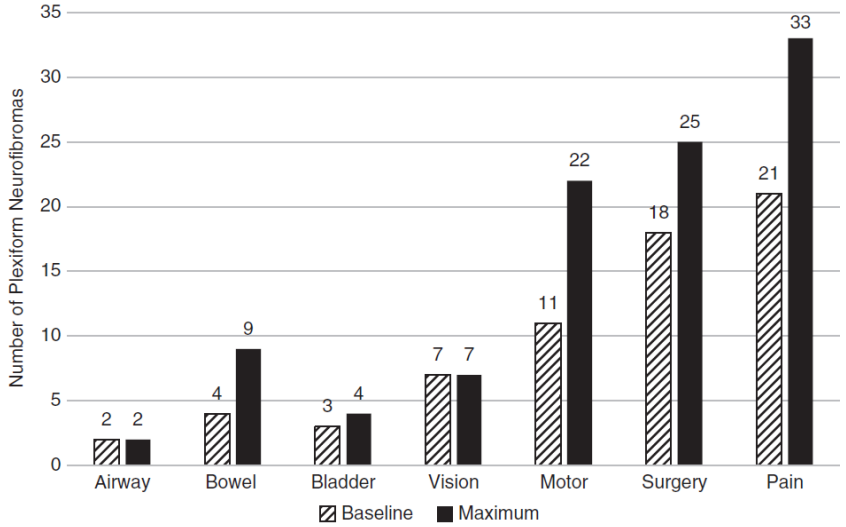
PN-Related Questions Addressed in the NHx Study:

- PN-Related Morbidity
  - Most PN causing some degree of morbidity at time of first assessment
  - Once a PN-related morbidity develops in patients with PN that are growing, it is extremely unlikely to resolve spontaneously
  - Larger tumors were more likely to have associated motor dysfunction
  - More rapidly growing tumors associated with increased need for pain medication

Neuro-Oncology

XX(XX), 1–9, 2018 | doi:10.1093/neuonc/noy067 | Advance Access date 28 April 2018

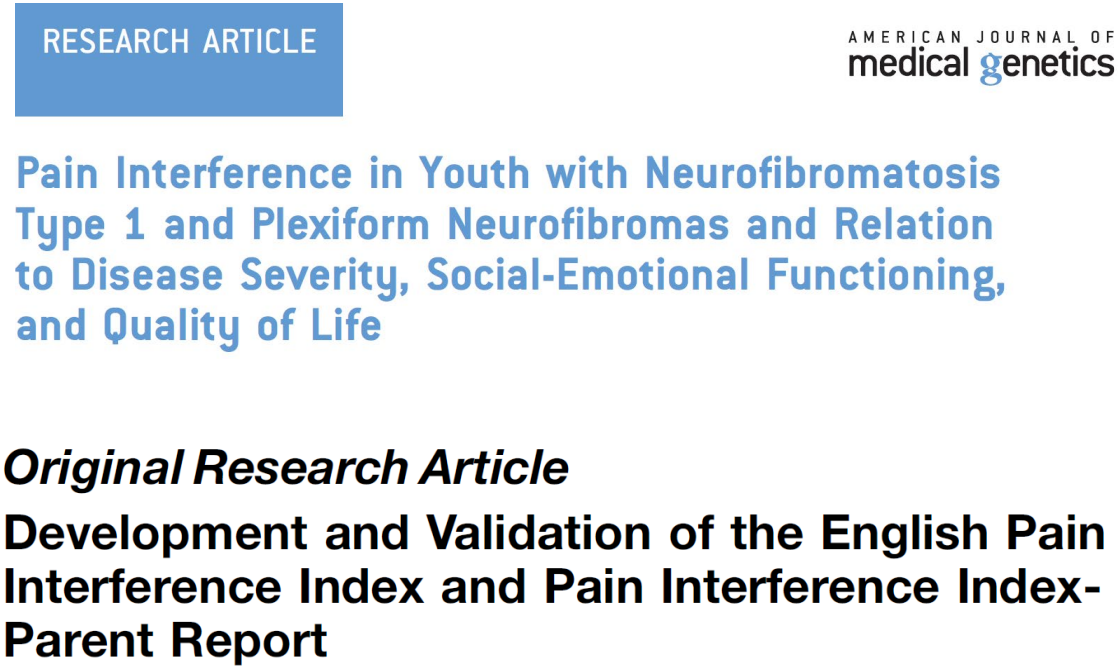
Association of plexiform neurofibroma volume changes and development of clinical morbidities in neurofibromatosis 1



(Gross, Neuro-Oncology, 2018)

PN-Related Patient Reported Outcome Measures

- Identified pain as a significant factor interfering with daily functioning and resulting in decreased quality of life for patients with NF1
- Validation of the Pain Interference Index in NF1


RESEARCH ARTICLE

AMERICAN JOURNAL OF medical genetics

Pain Interference in Youth with Neurofibromatosis Type 1 and Plexiform Neurofibromas and Relation to Disease Severity, Social-Emotional Functioning, and Quality of Life

Original Research Article

Development and Validation of the English Pain Interference Index and Pain Interference Index-Parent Report

(Wolters, AJMG, 2015)

(Martin, Pain Med, 2015)

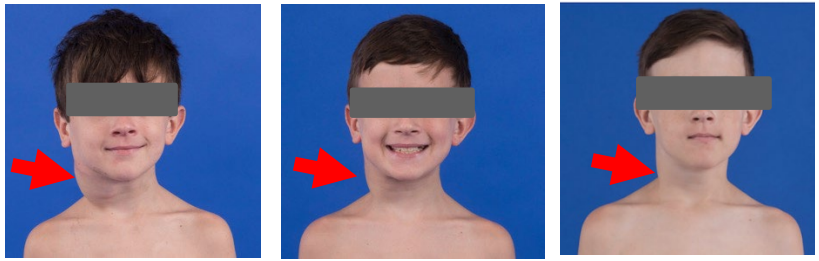
Applying FDA Guidance to NF1 Natural History Study

- <u>Potential uses of a Natural History Study for Drug Development in Rare Disease:</u>
  - ★ Identifying the patient population
  - ★ Identification/Development of Clinical Outcome Assessments
  - ❑ Identification/Development of Biomarkers
  - ★ Use of natural history study data as an external control

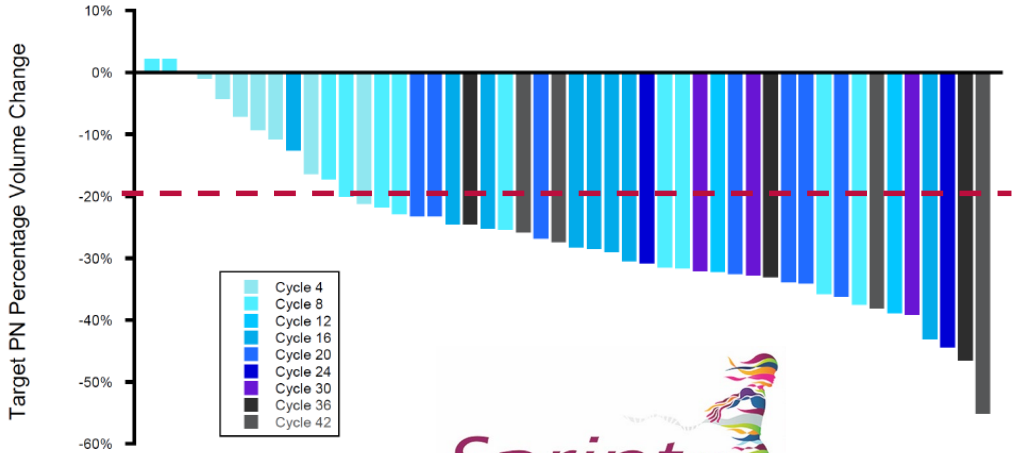
★ = Element confirmed/reinforced by data from the NF1 Natural History Study

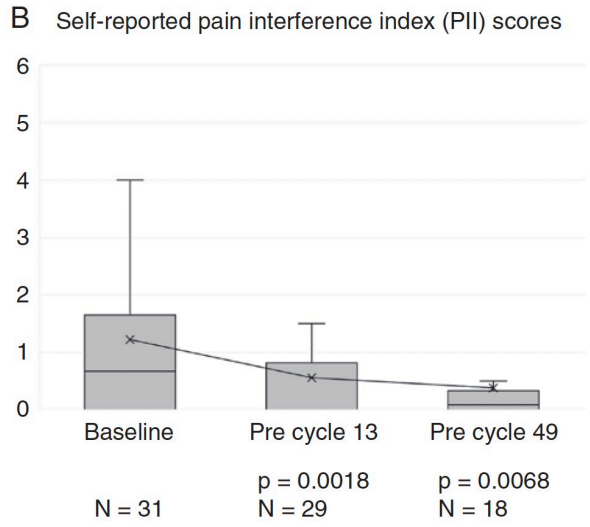
Phase 2 Trial: Selumetinib in Children with NF1 PN

- **Primary objective:** Overall Response Rate
- **Key Secondary Objectives:**
  - Functional and Patient Reported Outcomes
- **Results**:
  - Confirmed Partial response 34/50 (68%) patients
  - Clinical benefit with improvement in pain and function



Baseline | Pre-Cycle 13 | Pre-Cycle 37





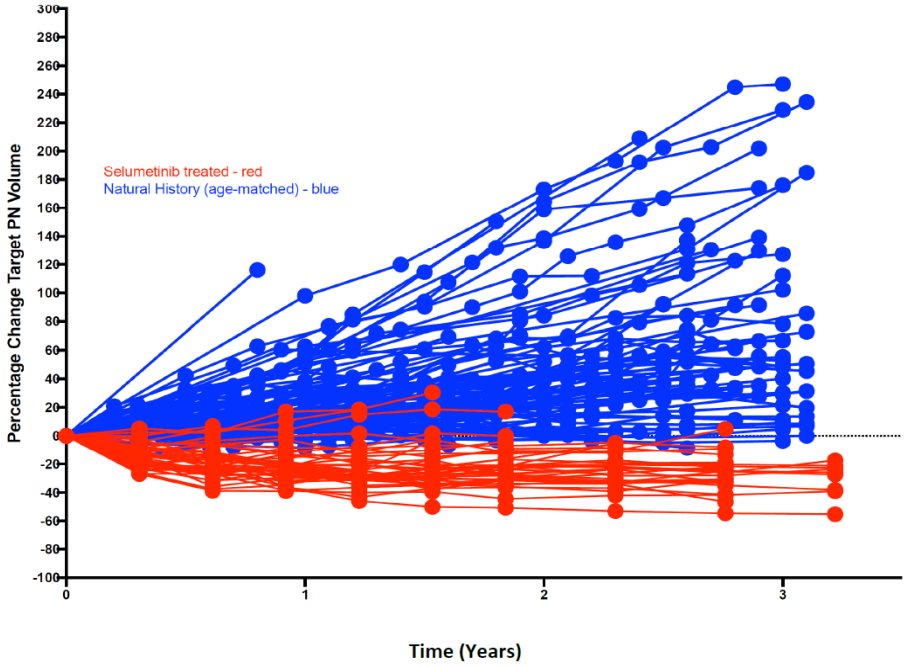
NIH NATIONAL CANCER INSTITUTE Center for Cancer Research

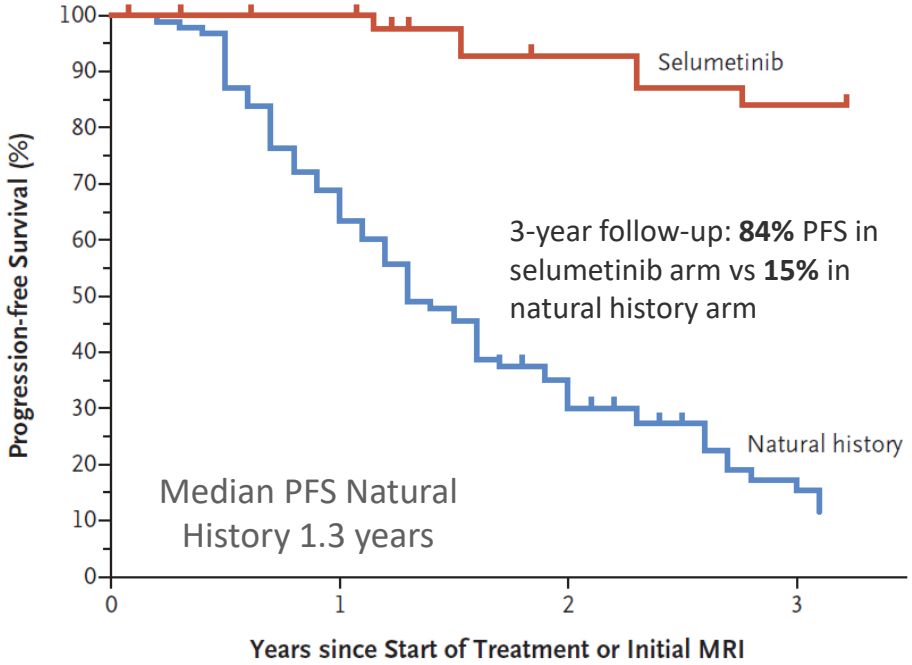
Sprint Selumetinib in Pediatric Neurofibroma Study

(Gross NEJM 2020) (Gross Neuro-Oncology 2023)

PN on Selumetinib vs Natural History

Age matched control: NCI Natural history and selumetinib

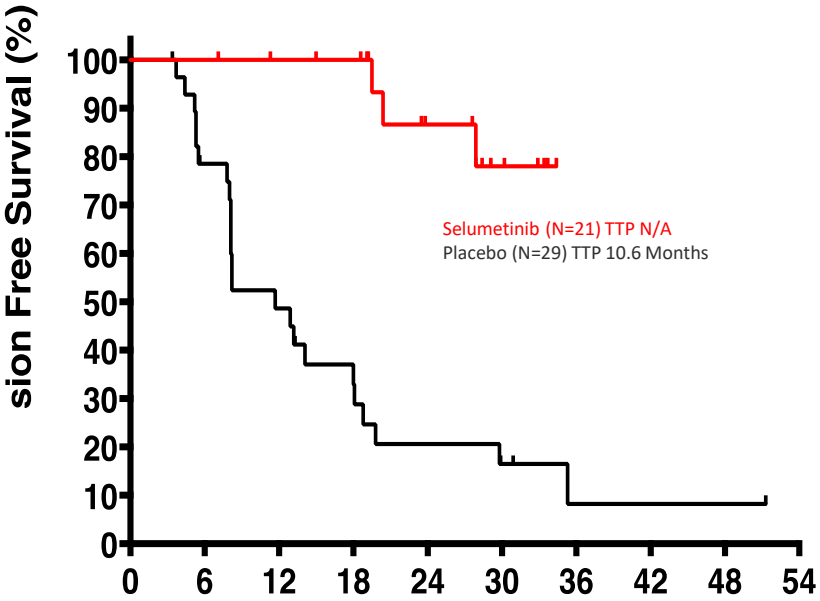




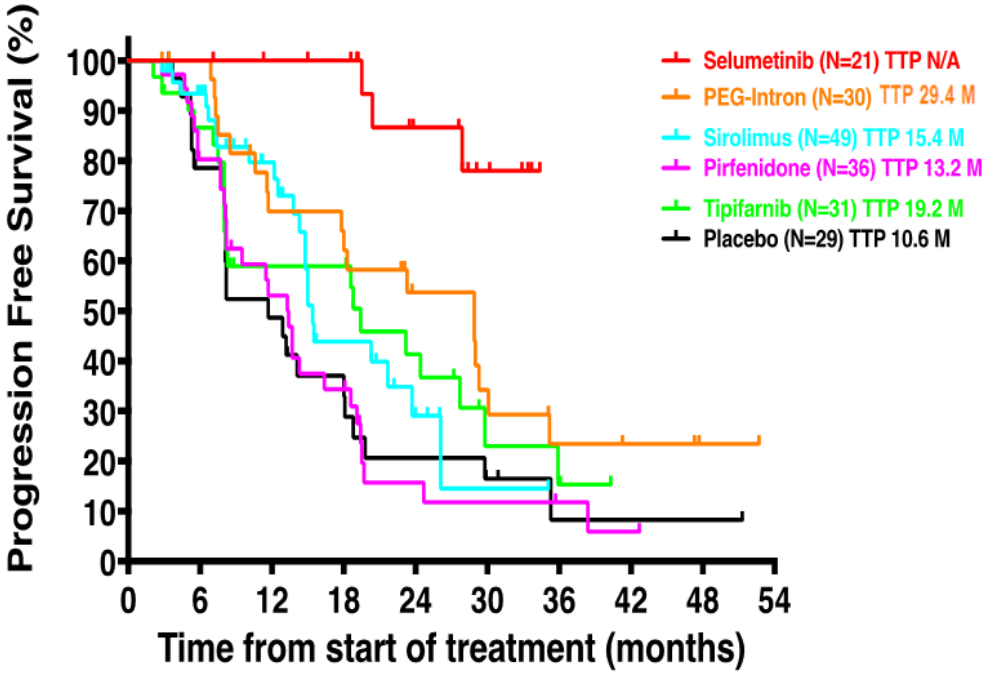
(Gross NEJM 2020)

PN on Selumetinib vs Prior Clinical Trials

Tipifarnib placebo/SPRINT progressive PN



Prior studies/SPRINT progressive PN



Gross AM, et al. N Engl J Med. 2020; Weiss BS, et al. *Neuro Oncol.* 2015; Widemann BC, et al. *Neurol Oncol.* 2014; Jakacki RI, et al. *Neuro Oncol.* 2017; Widemann BC, et al. *Pediatr Blood Cancer.* 2014.

Is it appropriate to use an external control for NF1?

- ☑ Not possible or ethical to run placebo control
- ☑ No available therapy for comparison
  - ☑ Absence of a standard therapy

No other agent with similar activity in NF1 PN

- ☑ Disease progression is well understood or predictable

NF1 NHx study characterized growth & morbidity

- ☑ The outcome measure is objective

Volumetric MRI analysis

- ☑ The effect of the treatment is:
  - ☑ Large/dramatic
  - ☑ Not affected by investigator motivation or choice of subject
  - ☑ Strong temporal association with drug/administration/intervention
  - ☑ Consistent with effect in animal models

Phase 2 Trial Data

- ☑ Control group: well documented, access to individual patient data
- ☑ Results provide compelling evidence of change in established progression of disease

(Jahanshahi, Therapeutic Innovation & Regulatory Science, 2021)

Regulatory Agency Approval of Selumetinib (Koselugo™)

April 10, 2020

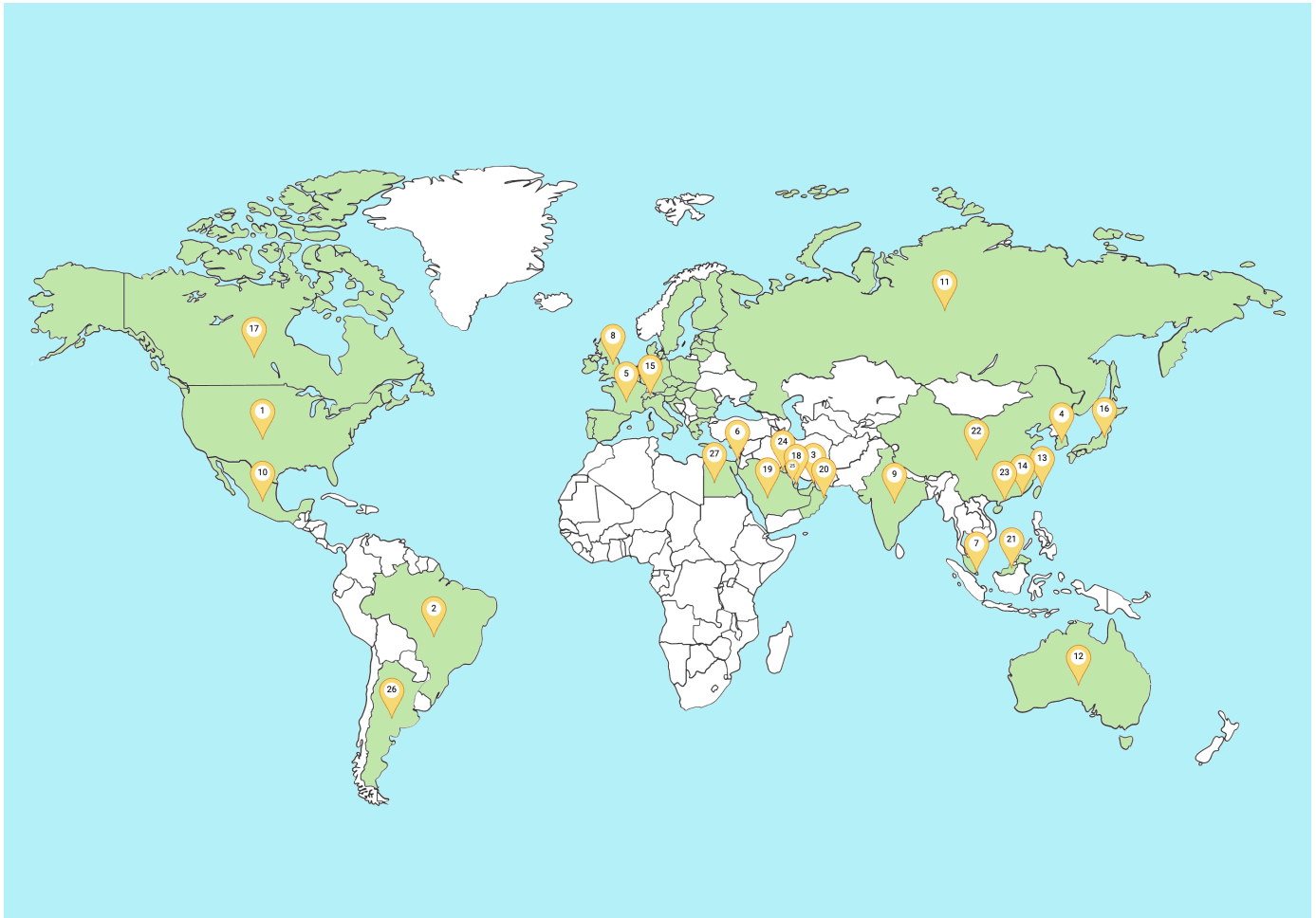
"The Food and Drug Administration (FDA) approved selumetinib for the treatment of pediatric patients 2 years of age and older with neurofibromatosis type 1 (NF1) who have symptomatic, inoperable plexiform neurofibromas (PN)."

April 22, 2021:

"Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion, recommending the granting of a conditional1 marketing authorisation for the medicinal product Koselugo2, intended for the treatment of paediatric patients with neurofibromatosis type 1 (NF1) plexiform neurofibromas (PN)."

FDA Prescribing Information; FDA Press Release, April 10, 2020.
https://www.ema.europa.eu/en/medicines/human/summaries-opinion/koselugo (April 22, 2021)

Regulatory Agency Approval of Selumetinib (Koselugo™)



1. USA
2. Brazil
3. United Arab Emirates
4. South Korea
5. European Union (27 member countries)
6. Israel
7. Singapore
8. United Kingdom
9. India
10. Mexico
11. Russia
12. Australia
13. Taiwan
14. Hong Kong
15. Switzerland
16. Japan
17. Canada
18. Qatar
19. Saudi Arabia
20. Oman
21. Malaysia
22. China
23. Macau
24. Kuwait
25. Bahrain
26. Argentina
27. Egypt

Key Points

- Rare disease research allows for insights into both rare and common conditions
- External controls can be used to support drug approval when the effect of treatment is large, temporally related to treatment and provides compelling evidence of change in established disease progression
- The NF1 model can serve as an example for other rare diseases and tumor predisposition syndromes

Acknowledgments

- Patients & Families who participate in trials
- Brigitte Widemann, MD
- NCI NF1 Team
- SPRINT Team
- CTEP
- REiNS
- Alexion/AstraZeneca

NATIONAL CANCER INSTITUTE
Center for Cancer Research

ccr.cancer.gov

Duke | MARGOLIS INSTITUTE *for* Health Policy

Assessing the Quality of Real-World Data for Regulatory Purposes in the Rare Disease Setting

Society for Clinical Trials
May 2024

healthpolicy.duke.edu

Disclosures

Director of the Board, Public Responsibility in Medicine & Research (PRIM&R)

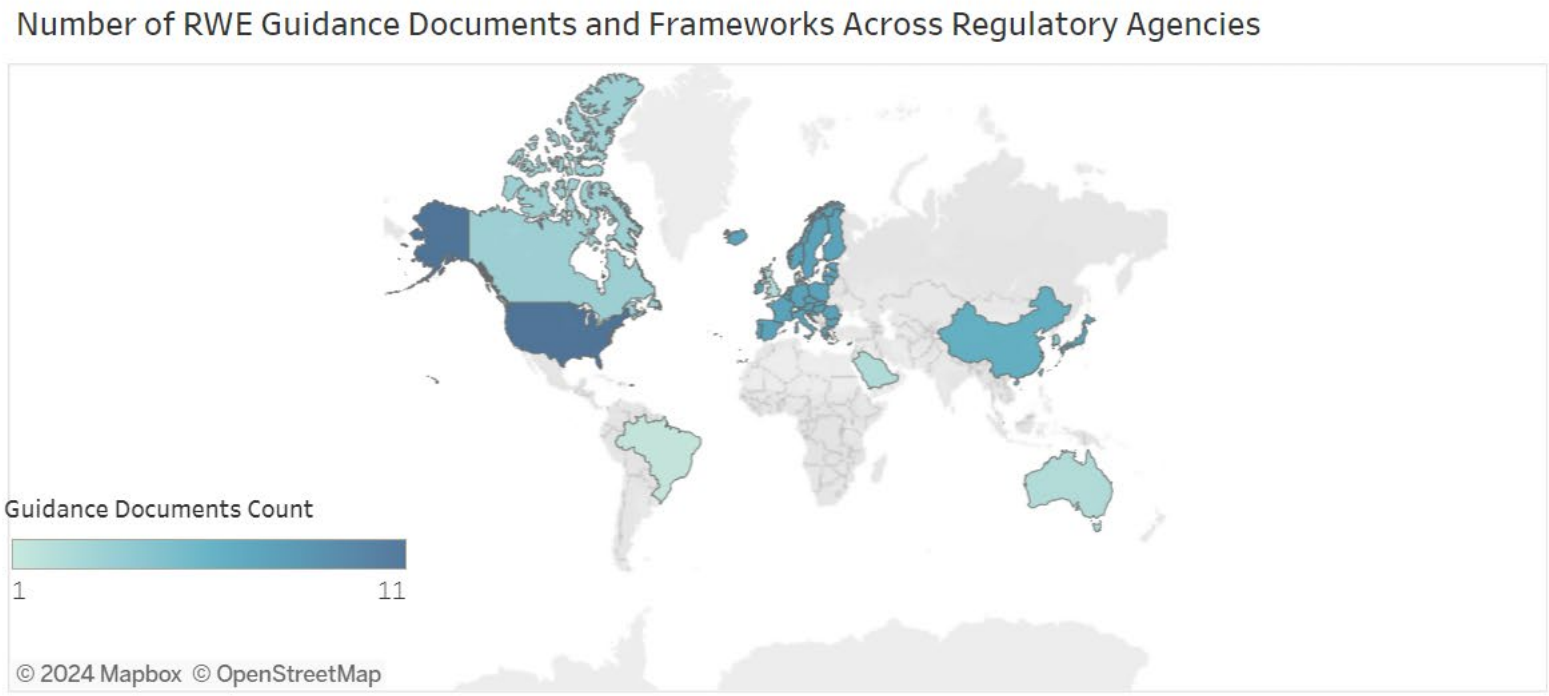
Editor in Chief, SAGE *Clinical Pathology*

Trust Scholar, AcademyHealth

June 2022 – International Coalition of Medicines Regulatory Authorities (ICMRA) Statement

Areas for Collaboration	Description
Harmonization of RWD and RWE terminologies	•Generating standardized definitions of RWD and RWE •Leveraging existing ICH activities
Convergence on RWD and RWE guidance and best practice	•Using common principles for RWD quality •Using metadata to characterize and discover RWD •Creating templates for study protocols and reports that can be used in several regulatory jurisdictions
Readiness	•Enable the rapid creation of international expert groups on specific topics of interest •Foster collaboration on governance and processes to allow for the efficient conduct of studies based on RWD from different countries
Transparency	•Promoting the publication of study results in open-source, peer reviewed journals •Defining common practices for systematic registration of pre-specified study protocols and results in public registries

International Harmonization of RWE Dashboard



The United States FDA is the only regulatory agency that has released a Real World Evidence Framework.

https://healthpolicy.duke.edu/projects/international-harmonization-real-world-evidence-standards-dashboard

International Regulatory Definitions of Quality

Definition: The evaluation of RWD data quality is made based on:
- ”the quality of data element population (e.g., whether abstracted from a verifiable source to assess transcription errors or automatically populated through a data extraction algorithm);
- adherence to source verification procedures and data collection and recording procedures for completeness and consistency;
- completeness (i.e., minimized missing or out of range values) of data necessary for specified analyses, including adjustment for confounding factors;
- data consistency across sites and over time
- evaluation of on-going training programs for data collection and use of data dictionaries at participating sites;
- evaluation of site and data monitoring practices; and
- the use of data quality audit programs” (page 16-17)

Regulatory Agency : Food and Drug Administration (FDA)

Term: Data Quality Use of Real-World Evidence to Support Regulatory Decision-Making for Medical Devices

International Regulatory Definitions of Quality, cont.

Definition: "Data quality is defined as fitness for purpose for users' needs in relation to health research, policymaking, and regulation and that the data reflect the reality, which they aim to represent. Data quality is relative to the research question and does not address the question on what level is the quality measured e.g., variable, data source or institutional level. These aspects are addressed in the data quality determinants and dimensions of data quality" (page 39) as detailed in the Data Quality Framework. The Data Quality Framework restricts its scope to aspects of data quality relevant to regulatory decision-making.
Regulatory Agency : European Medicines Agency (EMA) Data Quality Framework for EU medicines regulation

Definition: Not formally defined but stated as having characteristics including "data completeness, validity of any data, cleaning algorithm(s), data extraction and transformation processess." (page 24)
Regulatory Agency : Health Canada/Canada's Drug and Health Technology Agency (CADTH)
Term: Data Quality Guidance on the use of real-world data in clinical studies to support regulatory decisions

Definition: "The quality of the source data should be understood including its accuracy, validity, variability, reliability and provenance."
Regulatory Agency : Medicines and Healthcare products Regulatory Agency (MHRA)
Term: Data Quality Guidance on the use of real-world data in clinical studies to support regulatory decisions

International Regulatory Definitions of Quality, cont.

Definition: "Not formally defined but the guarantee and management of data quality is described as considering:

- Quality of data element population
- Whether the data is extracted from sources that can verify any conversion error
- Whether source verification procedures and data collection and record procedures are complied with –
- Data integrity* necessary for analysis of disturbance factor adjustment, etc. shall be secured
- Omitted values or values out of range shall be minimized
- Data consistency between data generation sites shall be ensured
- Data consistency over time shall be ensured
- Whether data collection training program in progress is evaluated
- Whether a data glossary is used at data generation sites
- Whether data generation sites and data monitoring activities are evaluated
- Whether a data quality inspection program is used"

(translated) (page 24)

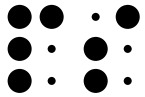
Regulatory Agency : Korea Ministry of Food and Drug Safety (MFDS) Guideline on RWE for Medical Devices

Term: Data Quality

Definition: "Data quality must take into account completeness, accuracy, consistency, and transparency of the data" (page 36)

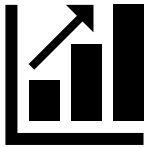
Regulatory Agency : Taiwan FDA (TFDA) Real-World Data - Relevance and Reliability Assessment Considerations

Term: Data Quality



Real-World Data

Data relating to patient health status and/or the delivery of health care routinely collected from a variety of sources (e.g., registries, wearables, EHRs, etc.)



Real-World Evidence

Clinical evidence about the usage and potential benefits or risks of a medical product derived from analysis of RWD.

Operationalizing EHR-Sourced Data for Quality, Relevancy, and Reliability

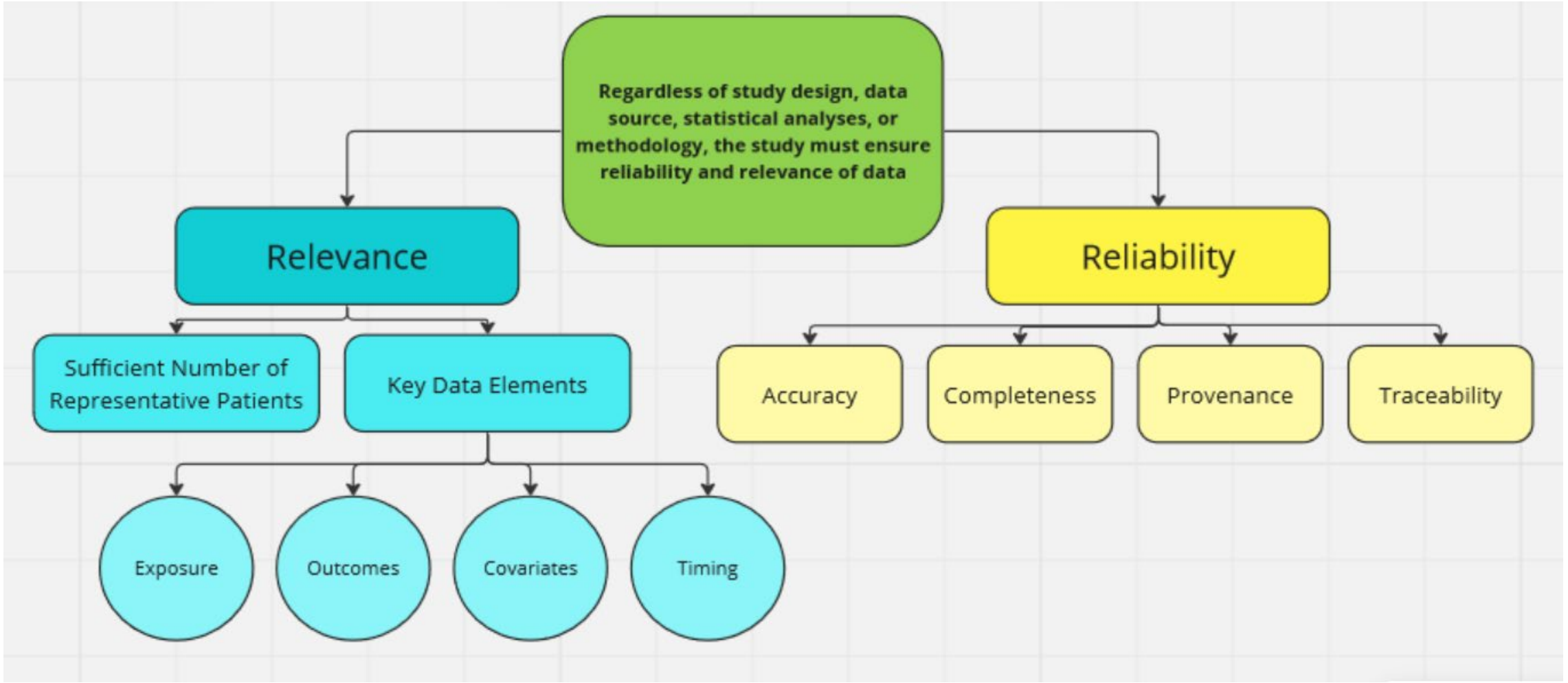
Generate actionable recommendations for stakeholders to improve the quality, relevancy, and reliability of data found in EHRs.

Operationalizing EHR-Sourced Data for Quality, Relevancy, and Reliability, cont.

- Structured text (e.g., ICD-10 codes)
- Unstructured/free text (e.g., clinical notes)
- PGHD uploaded through patient portals
- Lab data uploaded as pdfs
- Pharmacy data included in the EHR

- **Quality:** Accurate, complete, well-sourced, etc.
- **Relevancy:** Useful for the question and generalizable
- **Reliability:** Represents what it claims to represent

How does FDA determine if data are fit-for-purpose?



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Challenges with EHR-Sourced Data

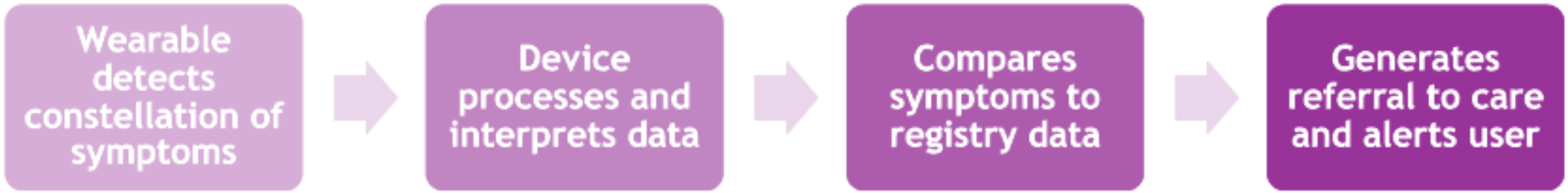
- EHRs are not a monolith. All considerations/recommendations are **context dependent.**
  - There is great **heterogeneity** in how data is collected and processed even within a single health system site.
- **Context lost** and **bias introduced** along the EHR data life cycle of source data, curated data, transformed data, and analytic dataset.
  - Lack of **standards** and lack of **data expertise** across stakeholders.
- **Takeaway:** The entire patient journey is not captured – especially for rare disease patients in the absence of natural history study data

2023 Patient-Generated Health Data (PGHD) Sub-Workstream

- Discuss the regulatory acceptability of patient-generated health data and genomic data
  - Digital health, wearables, decentralized trials, etc. (broadly considered patient-generated health data; PGHD)
  - Genomic data (i.e., pharmacogenomic biomarkers, poly- versus single-gene disease risk, pharmacokinetics, etc.)

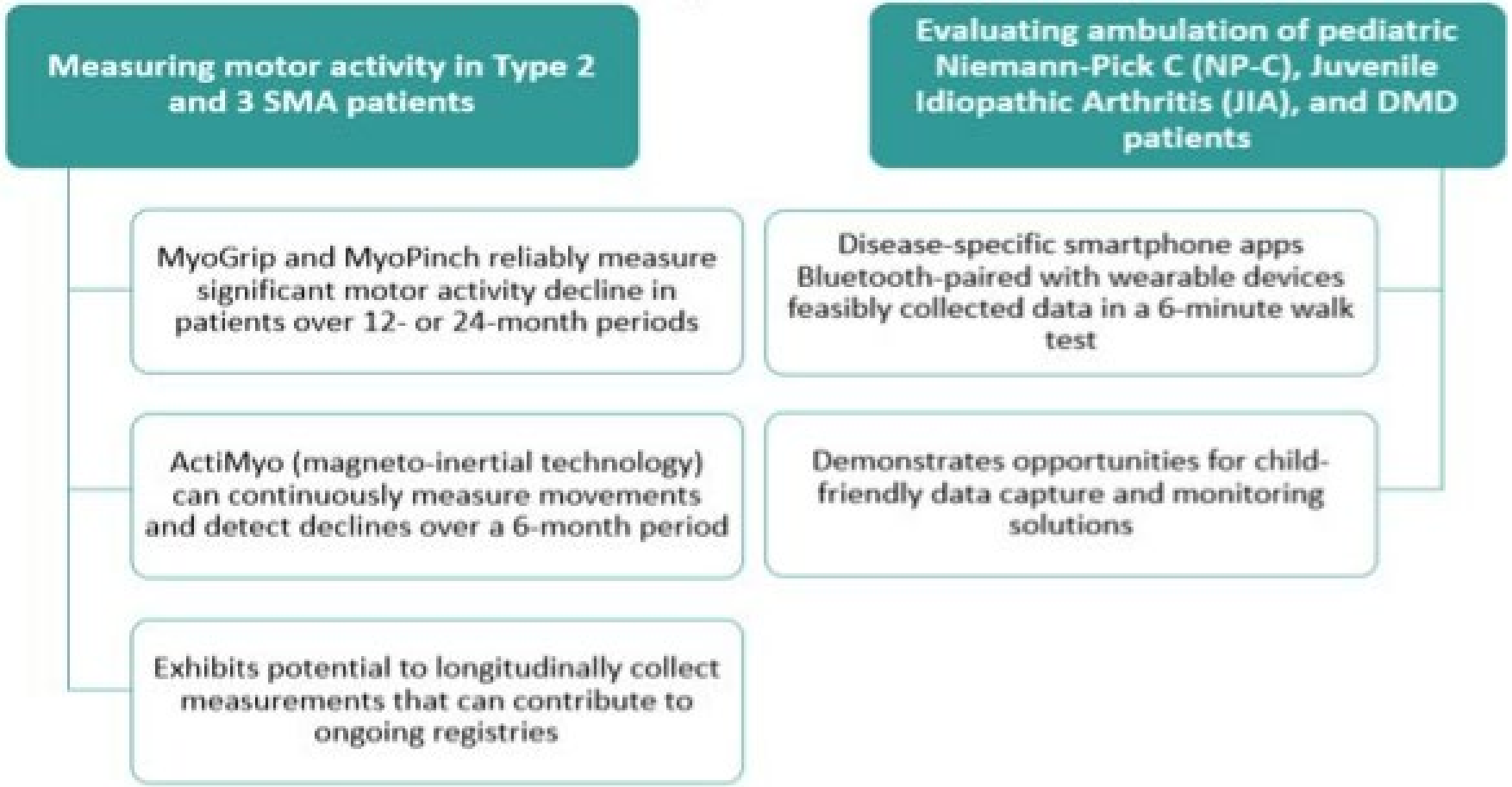
Example Use Case: Rare Disease and Wearables

- Utilizing technologies that passively monitor aspects of human health (e.g., sleep duration or heart rate) to detect infection symptoms or other health anomalies
- Like with infectious diseases, these could synthesize detection of multiple disease indicators in real time and serve as alarm systems to prompt the user to seek care
- Studies are exploring this multimodal sensing method for infectious disease monitoring; this model could translate to rare diseases as well



Example Use Case: Rare Disease, cont.

Use cases for wearable sensors in measuring rare disease progress and producing PGHD:



Primary Limitations of PGHD for Rare Disease Populations

- Reconciling data from different devices
- Replicating data collection and accrual methods
- Protecting patient privacy
- Standardizing protocols for data quality, reliability, and validity
- **Takeaway:** Clinical uses of wearable devices and other digital modes of gathering data remains under development, and real-world experience using biometric data to address rare diseases warrants even further exploration.

PGHD Source	Data Quality Considerations
Wearables and mobile app data	Developers should continually check and improve upon the collection and processing of biometric data as collected by their innovations, and they should be **transparent** about how various pieces of health data are measured, either in discrete or ongoing settings via wearable devices and mobile apps.
Direct-to-consumer genetic testing data	The logical plausibility of the direct-to-consumer data (if the data points to a specific variant) needs to be considered. Sponsors need to evaluate direct-to-consumer tests according to specified data quality assurance plans and procedures.
Patient powered-registry data	Sponsors should be **transparent** about the provenance of data within patient-driven patient registries, as well as algorithmic transformations to the data.
Patient-reported outcomes (PROs) data	To ensure **data accuracy and completeness**, sponsors should ensure data is collected in a thorough and clear manner. Sponsors and patients/patient advocates should provide patients with education or other support needed to accurately capture and report their PRO data. Sponsors should balance the need for data **transparency** with patient privacy protection.

Thank You!

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ASSESSING THE QUALITY OF REAL-WORLD DATA FOR REGULATORY PURPOSES IN THE RARE DISEASE SETTING

2024 BOSTON

SCT | 45TH ANNUAL MEETING

Dr. Andrea Gross
National Cancer Institute

Organizer: Dr. Katherine Panageas
Memorial Sloan Kettering Cancer Center

Dr. Rachele Hendricks-Sturrup
Duke-Margolis Center for Health Policy

Chair: Dr. Audrey Mauguen
Memorial Sloan Kettering Cancer Center

Dr. Nicolle Gatto
Aetion

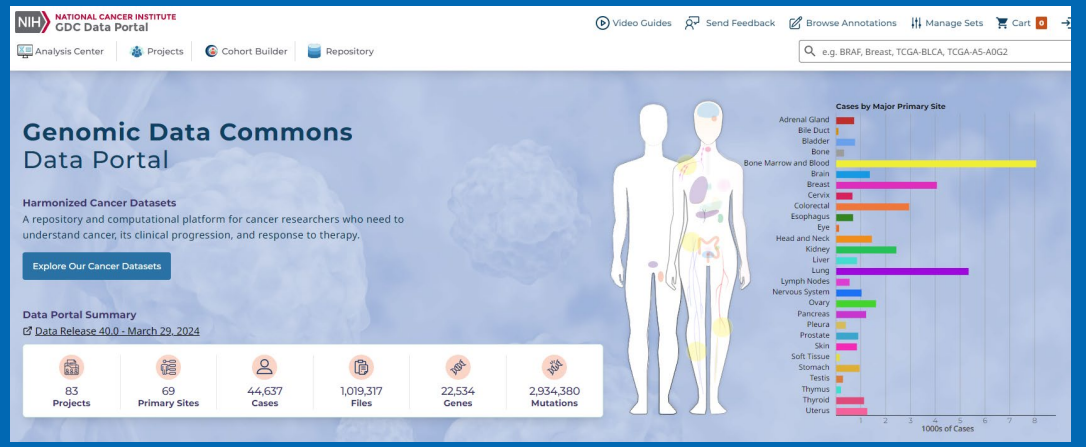
Discussant: Jessica Lavery
Memorial Sloan Kettering Cancer Center

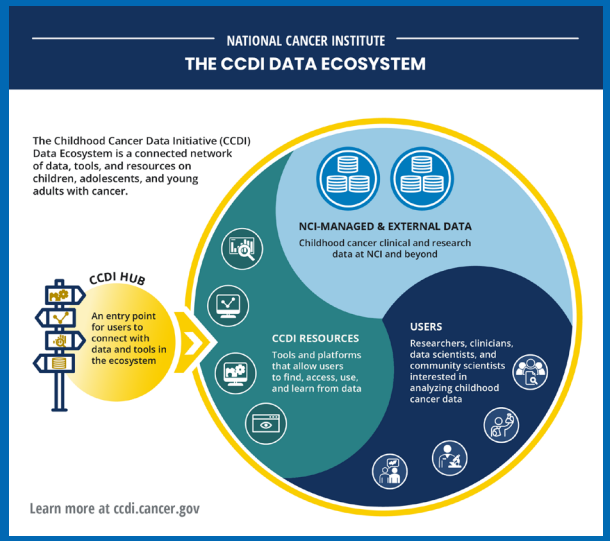
Real-World Data in the Rare Disease Setting

- Rare diseases defined as those affecting <200,000 people in the US
- Traditional randomized trials are not always possible in the rare disease setting
- Look to existing data:
  - What types of data are available (e.g., health records, registries, claims)?
  - How to operationalize study terms and endpoints to translate RWD into RWE?
  - Are the data of sufficiently high quality for regulatory purposes?
  - Are the data capable of addressing for the research question of interest, i.e., are they fit-for-purpose?
  - What are the methodological considerations for incorporating the available data into a regulatory application (e.g., natural history, synthetic control, pragmatic trials, etc.)?

Large-scale RWD

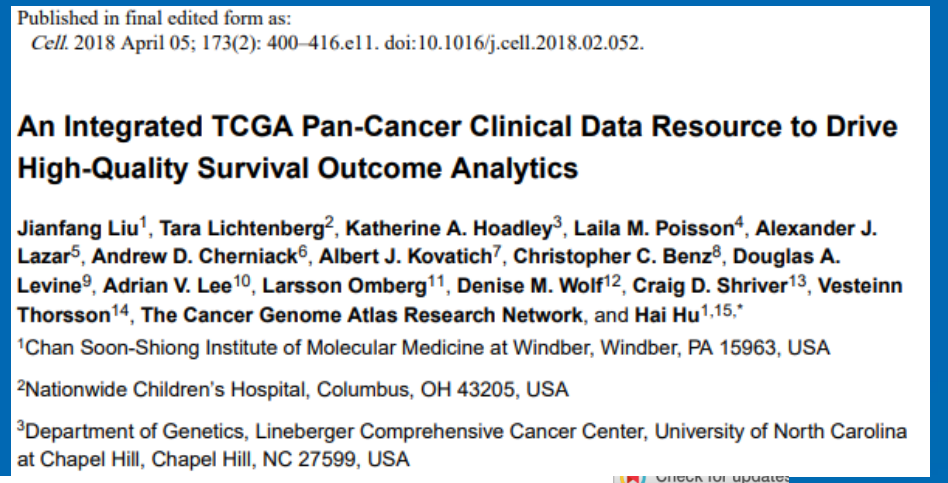
- Increasing availability of large-scale efforts to provide real-world data for multiple diseases
- Data collected from multiple institutions/organizations
  - Pros: Increased sample size
  - Considerations: Requires standardization of data collection & evaluation of potential variation across institutions and its implications





Overall Data Quality & Fit-for-Purpose Assessments

- Multiple definitions of quality
  - Completeness
  - Accuracy
  - Curation is repeatable
  - Face validity
  - *Relevance*
- Not all can be assessed by data user
- *"Regulatory-grade quality"* is a term without regulatory meaning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An Integrated TCGA Pan-Cancer Clinical Data Resource to Drive High-Quality Survival Outcome Analytics

Jianfang Liu[1], Tara Lichtenberg[2], Katherine A. Hoadley[3], Laila M. Poisson[4], Alexander J. Lazar[5], Andrew D. Cherniack[6], Albert J. Kovatich[7], Christopher C. Benz[8], Douglas A. Levine[9], Adrian V. Lee[10], Larsson Omberg[11], Denise M. Wolf[12], Craig D. Shriver[13], Vesteinn Thorsson[14], The Cancer Genome Atlas Research Network, and Hai Hu[1,15,*]

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Special Articles

Raising the Bar for Real-World Data in Oncology: Approaches to Quality Across Multiple Dimensions

Emily H. Castellanos, MD, MPH[1]; Brett K. Wittmershaus, BSE[1]; and Sheenu Chandwani, MPH, PhD[1]

DOI https://doi.org/10.1200/CCI.23.00046

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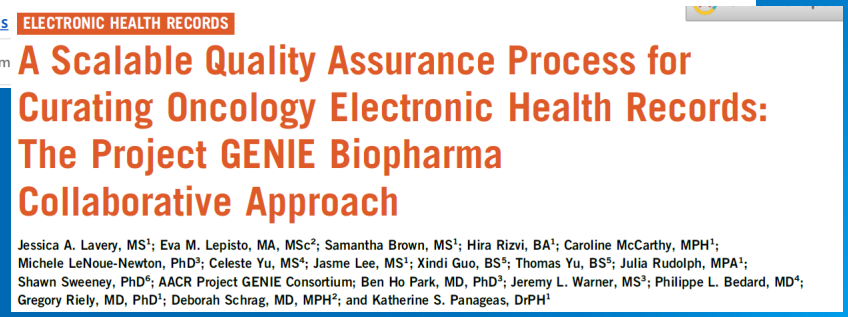
The Bar Is High: Evaluating Fit-for-Use Oncology Real-World Data for Regulatory Decision Making

Authors: Catherine C. Lerro, PhD, MPH, Marie C. Bradley, PhD, MPharm, MSc, Richard A. Forshee, PhD, and Donna R. Rivera, PharmD, MSc, FISPE

AUTHORS INFO & AFFILIATIONS

Publication: JCO Clinical Cancer Inform



Catherine C. Lerro et al., The Bar Is High: Evaluating Fit-for-Use Oncology Real-World Data for Regulatory Decision Making. *JCO Clin Cancer Inform* **8**, e2300261(2024).

On Assessing Data Quality & Fitness

- What are some of the pros & cons of having a specific checklist to assess whether data are fit-for-purpose?
- How early can the assessment of whether the data are fit-for-purpose be made (can it be made at the design stage, as opposed to after data are collected)?
- What options are available to researchers if, after evaluating the RWD quality and fitness, the data are deemed insufficient for use in the current study?
  - Can the data be utilized in any way for regulatory or non-regulatory purposes?

On Generating Real-World Data

- What types of efforts can be made (or have already been made), particularly in the rare disease space, to generate more robust RWD sources? *e.g., generating clinically-relevant common core data elements & shared endpoint definitions*
- Is there a role for natural language processing or other AI/machine learning tools in improving the efficiency of data collection and/or harmonization?
- What are the relevant considerations with respect to patient privacy, both with respect to incorporating AI tools and RWD access/sharing overall?

On Demonstrating Data Quality

- Who is responsible for demonstrating that data are of sufficient quality?
- Is there a responsibility of the group or organization generating or providing the RWD to demonstrate overall quality before an individual researcher assesses whether the data are fit-for-purpose?
- How does this differ in the ideal versus in practice?

Questions from the Audience

Thank you!