Current Methodological Practices to Define Within-Patient Meaningful Change in Rare Diseases: A Targeted Literature Review

CO67

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INTRODUCTION

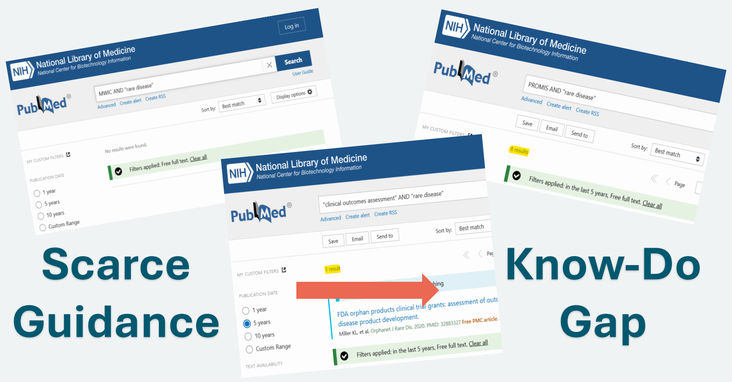
- Rare disease research faces challenges in measuring meaningful change due to small patient populations, heterogeneous phenotypes, and limited validated endpoints.
- Patient-centered evidence is increasingly emphasized, yet methodological guidance for clinical outcome assessment (COA) in rare conditions remains sparse.
- Defining meaningful within-individual change (MWIC) is critical for interpreting treatment impact in rare disease trials.
- Statistical approaches to COA development and MWIC determination vary widely, reflecting both innovation and lack of standardization.
- Understanding current practices can inform best-practice frameworks and improve trial design and endpoint selection in rare diseases.

OBJECTIVE

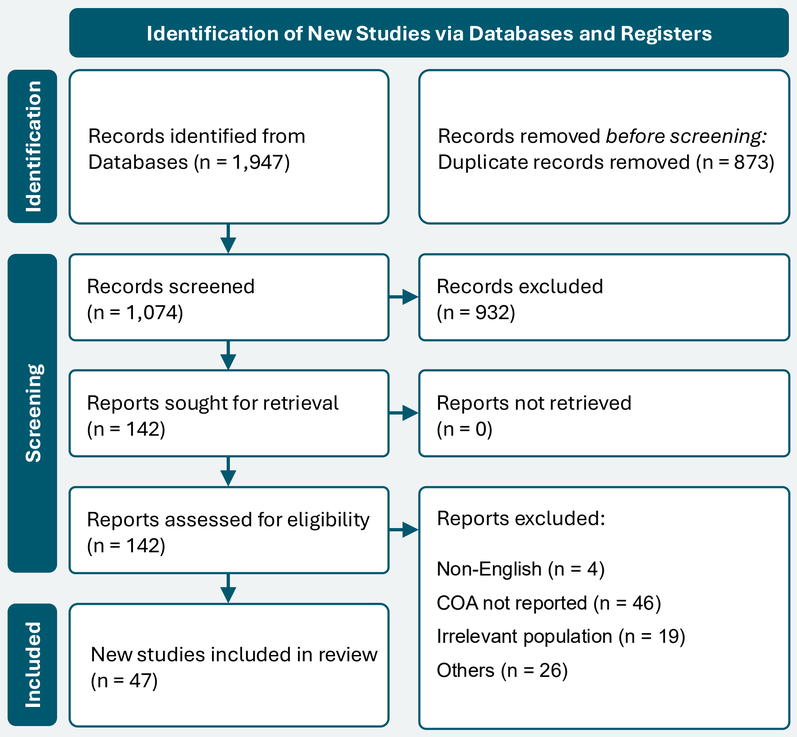
This study systematically explores MWIC methodologies and trends in statistical strategies applied to rare disease COAs.

METHODS

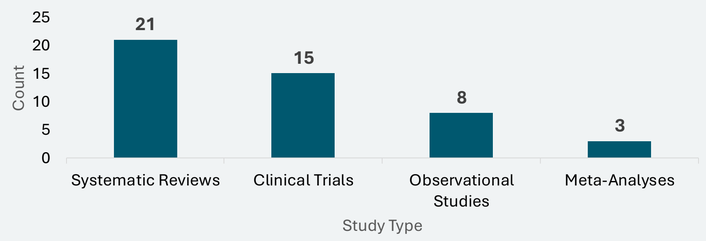
- Targeted literature review in PubMed (2020–2025) of English-language studies.
- Included clinical trials, systematic reviews, and observational studies on rare diseases and COA methodologies.
- Focused on MWIC definitions and statistical designs (anchor-based, distribution-based).
- Search used terms: “rare disease,” “meaningful change,” “MWIC.”
- Two-stage PRISMA screening applied; eligible full texts reviewed for data extraction.



RESULTS

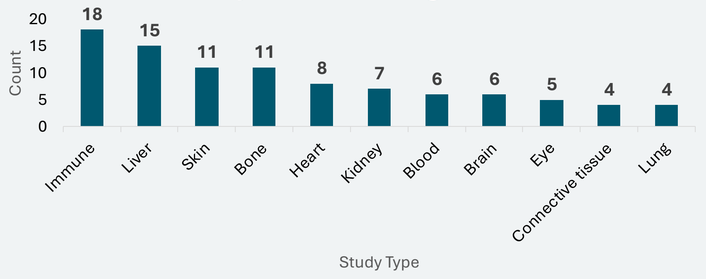


Distribution of Rare Diseases Publications by Broad Study Type



- **Systematic reviews lead the count**, reflecting reliance on evidence synthesis due to small sample sizes and limited trials in rare diseases.
- **Clinical trials are less frequent**, potentially highlighting challenges in conducting interventional studies for rare conditions (e.g., recruitment and cost constraints).

Distribution of Rare Diseases Publications by Anatomical Region

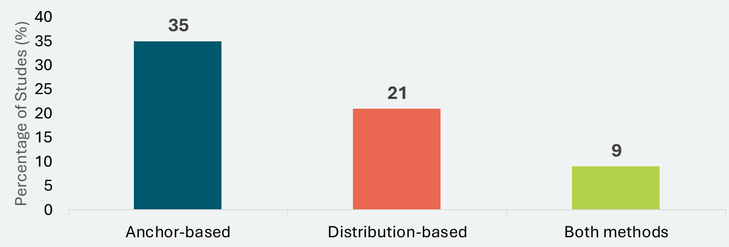


- **Immune system and skin dominate research focus**, indicating these areas have the highest burden or complexity among rare diseases.
- **Eye, lung, and connective tissue are underrepresented**, suggesting potential gaps in research or lower prevalence of rare conditions in these regions.

COA Distribution:

- **COA Endpoints (10/47, 22%):** Primarily PROs or functional scales capturing meaningful within-patient change.
- **Adapted Statistical Methods (5/47, 11%):** Employed anchor-based, distribution-based, or Bayesian approaches to improve interpretability in small, heterogeneous populations.
- **Limited COA Integration (37/47, 78%):** Focused on disease characterization, biomarkers, diagnostics, or treatment feasibility, with minimal use of standardized COA frameworks.
- **Conventional Analytics Predominate (42/47, 89%):** Relied on standard statistical methods—such as descriptive summaries, unadjusted comparisons, or basic inferential tests—without adaptations for small or variable samples, underscoring the need for tailored, fit-for-purpose analyses in rare-disease research.

COA Measurement Methods in Rare Disease Studies



Anchor-based methods were most frequently applied (35%), with fewer studies using distribution-based (21%) or combined approaches (9%), reflecting limited methodological overlap.

PROMIS* in Rare Diseases: Key Insights

PROMIS Customization
- Tailored for conditions like **FCS** and **TGCT**.
- Captures **disease-specific symptoms** (pain, fatigue).
- Reflects **impact on daily life** accurately.

Validity & Comparability
- Provides **validated, norm-referenced scores**.
- Enables **comparison with general population norms**.
- Example: **Osteogenesis Imperfecta**—effectively measures **physical & mental health** differences.

Integration in Clinical Trials
- Used in trials such as **Pompe Disease (PROPEL)** and **Hypophosphatasia studies**.
- Assesses **treatment impact** on **physical function & fatigue**.
- Supports **regulatory expectations** for **patient-centered endpoints**.

Enhancing RWE
- Integrated with **digital health tools** and **wearable devices**.
- Applied in studies like **Paroxysmal Nocturnal Hemoglobinuria**.
- Facilitates **real-world quality-of-life assessment**.

*Patient-Reported Outcomes Measurement Information System

DISCUSSION

- Nearly half the studies (47%) lacked robust methods to handle small sample sizes, reducing statistical reliability.
- Mixed-effects and Bayesian models were rarely applied (<12%), limiting consideration of inter-patient variability.
- Only 19% conducted phenotype-based subgroup analyses, restricting insights into disease heterogeneity and treatment response.
- Just 10% incorporated patient or caregiver perspectives, indicating limited patient-centered COA design.
- Integration of real-world data was minimal (<5%), reducing external validity and generalizability.
- Federated data-sharing approaches were scarcely utilized, constraining multi-cohort evidence generation.
- The observed gaps suggest incomplete alignment with evolving regulatory guidance on COA methodologies.

CONCLUSION AND RECOMMENDATIONS

- Significant gaps exist in rare disease COA development—limited use of advanced statistics, inadequate adaptation to small heterogeneous populations, and minimal patient input or RWE integration.
- Strengthening analytic approaches and RWE integration is essential to advance rare disease evidence generation.
- Innovative, patient-centered, and RWE-driven methods are urgently needed to generate robust, actionable evidence.
- Prioritize methodological rigor to enhance COA relevance and support informed decision-making.

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