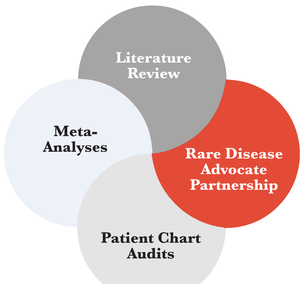
Missing Endpoints: The Path to Optimal Clinical Trial Endpoint Selection

"Begin With The End In Mind"[1]

Clinical trials in rare disease are complex and face unique challenges. Natural history is a critical element of any clinical development program; however, rare diseases inherently come with significant knowledge gaps.

Without sufficient natural history data, Industry will fail to identify clinically meaningful outcome measures that capture what patients' value most.

Available natural history studies identify:
- Incidence and prevalence;
- Phenotypic differences;
- Causes of morbidity and mortality;
- Impact on quality of life; and
- Cultural differences and other difficult-to-measure obstacles that may impact response to therapy



Natural history is available through multiple, equally important sources:

Creating A Successful RDA-Industry Partnership

Working with Rare Disease Advocates (RDAs) helps to mitigate the risks – delays or denied access to therapy – associated with clinical trial design in rare diseases. RDAs act as a bridge, bringing together Industry and Community to close the information gaps so often found in rare disease research.

An RDA partnership allows patients and other advocates to lend their voice to the clinical design process and help Industry avoid pitfalls when informing hypotheses that drive the selection of clinical trial outcome measures. This model leads to the identification of endpoints that offer the best chance of clinical success and community support.

The Industry-Advocacy partnership in *Figure 1* is very similar to the *FDA's Roadmap to Patient-Focused Outcome Measurement in Clinical Trials*[2], which is a simple three-step process:
- Understanding the disease through natural history;
- Conceptualizing the expected treatment benefit; and
- Developing and selecting outcome

We have added one additional step to this paradigm: *Testing Industry's hypotheses with patients and caregivers.* Qualitative interviews with the rare disease community provide the platform to test hypotheses prior to regulatory review. Access to the community is easy with an Industry-Advocacy partnership already in place.

Conclusion

The stakes are extraordinarily high for both orphan drug developers and rare disease communities. Trials often fail to measure functional outcomes that reflect patients' greatest unmet needs. Failure to identify outcome measures that capture what patients value most contribute to delays, or worse denials, to therapy. Industry-Advocacy partnerships are key to mitigating the risk of missing endpoints. Moving forward it is critical for Industry to adopt internal strategies to fill the empty chair at the table and allow RDAs to influence and support clinical trial design.

Protocol Design and Pre-Commercialization

Industry & Advocate Partnership–Figure 1

Pre-Trial: Identifying Optimal Clinical Trial Endpoints

Step 1 Develop the Partnership: Recognition by Industry of the value of partnering with Advocate(s) and Patient Community by allocating staff and budget to initiate and maintain partnership

START

Natural History (NH), Functional Outcomes Assessment	Discovery and Hypothesis Building	Endpoint Hypothesis Testing and Selection	Clinical Trial Execution
INDUSTRY / ADVOCATE	INDUSTRY / ADVOCATE	INDUSTRY / ADVOCATE	INDUSTRY / ADVOCATE
Methods: Assess available NH data, functional outcome measures available (both generic & disease-specific)	***Methods:*** Primary data collection (RWE, PROMs, qualitative interviews)	***Methods:*** Test endpoint hypotheses through primary data collection (qualitative interviews)	***Methods:*** Test draft educational materials through primary data collection (qualitative interviews)
Shared Goals: Identify need to collect additional NH data, develop new functional outcome measures	***Shared Goals:*** Identify risks, barriers & opportunities to trial recruitment and retention, market access scenarios, functional outcomes measures to test	***Shared Goals:*** Finalize selection of clinical trial endpoints	***Shared Goals:*** Finalize educational materials that Advocate can use to educate Community on clinical trial involvement, encourage participation and retention

Industry & Advocate Partnership–Figure 2

Pre-IND / FDA Approval Process

Step 2 Continue The Partnership: Preparation for commercialization through key stakeholder engagement

Payers	FDA	Patients and HCPs
INDUSTRY / ADVOCATE	INDUSTRY / ADVOCATE	INDUSTRY / ADVOCATE
Methods: Advocates /Community may opt to share information through written letters, video documentation/stories, social media tagging, and one-on-one meetings	***Methods:*** Advocates / Community may opt to start a social media campaign, share information through written letters, video documentation of PROs, and attend patient-focused (Patient Voice) or PFDD meetings	***Methods:*** Primary data collection
Shared Goals: Improve understanding of burden of disease and HEOR to reduce denials and improve access / retention	***Shared Goals:*** Regulatory buy-in and preparedness for IND review	***Shared Goals:*** Develop unbranded and branded education materials to improve awareness and adoption among patients and HCPs

Figure 1. illustrates the elements of a successful partnership during and after natural history review.

Commercialization and Beyond

Industry & Advocate Partnership–Figure 3

Commercialization

Step 3 Sustain The Partnership: Long-term success is dependent upon Industry's continuing its relationship with the Community

Reassess Community Needs / Collect RWE	Stay Involved
INDUSTRY / ADVOCATE	INDUSTRY / ADVOCATE
Methods: Primary data research, social media surveillance, video documentation	***Methods:*** In-person meetings, event attendance, share success stories
Shared Goals: Track patient outcomes on commercial drug, understand resources and support gaps, continued surveillance of unmet needs	***Shared Goals:*** Lasting partnership with Community

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WHITEPAPER:
https://www.rareadvocacymovement.com/missingendpoints

CITATIONS

1 Importance of Natural History Studies in Rare Diseases Anne R. Pariser, M.D. Associate Director for Rare Diseases Office of New Drugs Center for Drug Evaluation and Research US Food and Drug Administration
2 https://www.fda.gov/drugs/drug-development-tool-qualification-programs/roadmap-patient-focused-outcome-measurement-clinical-trials-text-version