Generate evidence for medical breakthroughs and unmet treatment needs in rare disease research

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Kathryn Starzyk, Senior Director of Epidemiology, Quintiles
Your Presenters

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Eric has 15 years of experience of focus on health technology assessment, product reimbursement and commercialization, health care management, and health policy analysis for medical devices, diagnostics, and biopharmaceuticals.

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Senior Director of Epidemiology, Quintiles

As Senior Director of Epidemiology in the Real World & Late Phase Research division of Quintiles, Kathryn is responsible for scientific study oversight, primarily in the areas of study design and development, regulatory compliance and patient safety. Since 2007, she has developed and implemented over 45 observational studies globally in multiple disease areas, including rare diseases, infectious disease, oncology and cardiology.
Agenda

- Rare disease research landscape: An overview Adaptive pathways and the unmet need in rare disease research
- Patient engagement and retention in long-term observational rare disease studies
- The Role of stakeholders in rare disease registries: Collaborating on study design to plan earlier in product development and meet multi-stakeholder needs
- New trends in rare disease research: Repurposing drugs under the US OPEN Act
- Q&A
Today’s Webinar Audience

- Academia
- Biostatistician
- Clinical Operations
- Risk Management
- Medical Affairs
- Market Access
- Health Economics/Health Outcomes
- Epidemiology
- Other
Rare Disease Introduction

It is estimated that **350 million people** worldwide suffer from rare diseases. If all of the people with rare diseases lived in one country, it would be the world’s **3rd most populous country**.

http://globalgenes.org/rarefacts

Approximately **50%** of the people affected by rare diseases are **children**. **30%** of children with rare disease will not live to see their **5th birthday**.

http://globalgenes.org/rarefacts
Increasing Worldwide Orphan Drug
Sales and Share of Prescription Drug Market (1998 to 2018)
Pressure for Change Influences Drivers of Innovation Uptake

Drivers
- Unsustainable spending
- Cost control pressures
- Quality improvement pressures
- Need for continuity/standardization
- Recognized delivery inefficiency
- Drive to identify appropriate subpopulations/focus treatment
- Patient choice meets affordability

Innovations
- Health reform
- Insurance structure changes
- Value-based payment
- Coding system reform
- HTA/EBM
- Comparative effectiveness
- Cost control/management mechanisms
- Pay for performance/risk sharing
- ACOs
- Home health & health disparities
Innovation is in the eye of the beholder

Retooling to meet multiple stakeholder needs

**Patient**
- Need to maintain health
- Benefit/risk tradeoffs
- Affordability of care

**Manufacturer**
- Incentives to develop evidence
- Reimbursement commensurate with value
- Return on investment
- Reward for innovation

**Laboratory**
- Better, faster, cheaper
- Staff resource requirements and turn around
- Managing with a budget

**Value**

**Policymaker**
- Balance of quality and cost
- Societal considerations
- Health system statutes and guidelines

**Payer & HTA**
- Balance of quality and cost
- Evidence-based care
- Provision of appropriate care to appropriate populations
- Balancing care across the population

**Provider & Hospital**
- Provision of appropriate care
- Provision of reimbursed services
- Financial efficiency & viability
- Managing with a budget

Addressing the “Value Challenge”

_The Devil is in the detail_

Companies can no longer create products that are simply safe and effective; they must develop medications providing superior results to those already on the market.


What is the Key Issue Facing Your Business?

- 36% Defining Value
- 64%

Particularly true for “niche agents” faced with changing acceptance drivers and rules of the road.

What are the biggest barriers to your company’s efforts to demonstrate the value of its products?

(% respondents)

- Different stakeholders define value differently: 56%
- Value considerations differ for different conditions being treated: 36%
- The same stakeholders in different geographies define value differently: 33%
- Inability to obtain or failure to generate data related to value during trials: 33%
- Lack of understanding of what stakeholders are seeking: 26%
How MUCH evidence is enough to support reimbursement of niche agents?

While we have generally reached consensus on factors like what “strength of evidence is,” the “rules of the road” are much less clear and rapidly changing for niche agents.

“*We have no good standard for [reimbursement] decisions. We say, ‘you need more evidence,’ but there’s no unit of evidence. You don’t measure evidence in cubic feet or in meters. We say ‘you need more evidence,’ but against what standard? There’s absolutely none.*”

–Dr. Bruce Quinn, Foley Hoag LLP, former Medicare medical director, IOM report on policy issues in personalized medicine, 2010
Rare disease and Orphan drugs

Growing Concern Over High Per Patient Costs

There are a broad range of prices for orphan drugs and rare disease treatments, with the average range hovering between $200K to $400K per year.

Sample of products shows US price ranging from ~$100K to $>500K

While individual BI is in the “pennies” in terms of per-patient per-month cost, the aggregate BI is becoming a growing concern as a significant wave of new niche products, including personalized medicines enter the market.

When does cost outstrip other drivers, irrespective of value and ability to address unmet need?
Number of Orphan HTAs in select markets Increasing

- Difficult to say that number of rejections is increasing – a possibility – but they hover around 20% to 40%
- “Full” recommendations appear fairly constant around 20% to 30%
- Remainder recommended for reimbursement restrictions
What HTA agencies look for varies from market to market

- Criteria evaluated for orphan products by market is heterogenous
- “Common threads” include what you would suspect – unmet need, strength of evidence, effectiveness, safety and cost implications (some markets)
- However, the devil is in the detail in terms of “threshold of acceptability” and “magnitude of effect”

Adapted from Chawla, Shih, Spinner, Ransom, Tao, Duong, White, Faulkner, Doyle. Clinical & Economic Requirements for Orphan Drugs. ISPOR International Meeting, 2013. New Orleans, LA.
HTA/Payer Dilemmas Associated with Niche Populations

• Under what circumstances could we or should we say NO? There is not threshold or rule of thumb here

• How do we handle limitations study designs and gaps in evidence vs. broader agents? What approaches are appropriate? What yardstick is right?

• What is the potential for indication expansion out of the orphan area to broader indications?

• Do we handle orphan vs. ultra orphan any differently? How do I handle so called specialty products differently from broader products?

• How do we manage the array of technologies that end up being “additive” in terms of budget impact but have ↑ unmet need and limited per-patient costs?

• Do we need to change policies for what qualifies as orphan given the flood of new technologies en route to market? How so?
Manufacturer evidence challenges for Orphan/Rare/Specialty populations

Sample key issues for orphan populations

- Picking appropriate indications
- Limited epi. information
- Limited patient availability
  - Sometimes prohibiting RCTs and supporting single arm approaches…other “control” challenges
  - Difficulties in trial recruitment
- Challenges in patient ID
  - Easier with biomarkers
  - Some patients fall through cracks
  - How to educate?
- Lack of secondary evidence
  - Limited ability to leverage longitudinal data sources
- Study design selection
- Comparator selection
- Acceptable degree of benefit

Common Evidentiary Elements of Value Defense

- Biomarker status/response potential
- Efficacy (e.g., overall survival/progression free survival) & Safety
- QoL

- Value-based pricing & cost-effectiveness
- Patient population/epi data/unmet need

- Evolving evidence for changing payer & provider bus. models
- Subpopulation differentiation

- Comparative effectiveness
- Duration of effect

- Reimbursement & Re-evaluation
- Adherence/compliance

- Economic implications for payers, providers, patients
- Surrogate outcomes

- Defense vs. in-line & pipeline comparators

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Key questions/issues on RWE for niche-targeted therapies

RWE development represents a conundrum for targeted treatment applications given that a significant development cost is still involved…how do you triangulate how much is enough?

Common Questions for Targeted Populations

• If it is clear that the patient population is small, clear & targeted…how much RWE do we really need?
• If relevant, what questions are we trying to answer (e.g., epidemiology/patient population, comparative effectiveness, patient reported outcomes)…that may not be addressed pivotal study?
• Do different stakeholder types have different RWE information needs for decision making?

Personalized Med & Companion Dx
• Epidemiology of biomarker
• Addressing patient comorbidities/confounders
• Comparative effectiveness
• Longer term efficacy & safety
• Patient reported outcomes
• Cost savings & offsets

Orphan & Rare Disease Indications
• Patient population/demographics
• Patient diagnosis/algorithm for ID
• Longer term efficacy & safety
• Patient reported outcomes
• Aggregate budget impact
• Cost offsets vs. no treat
Key Considerations for Optimizing Value Demonstration & Access
Key considerations for optimizing niche population value demonstration & access

1. Understand Your Flavor
2. Finding the Needle in the Haystack
3. Differentiation Amidst a Sea of Rarity
4. Balancing “Got to Have” vs. “Nice to Know”
5. Balancing Pricing Perception vs. Restriction Realities
6. Dare to be Different
7. Coming Up to Speed…Rolling Out Stakeholder Education
8. Finding a Seat at the Table
Understand Your Flavor

Not all niche populations are built the same…

<table>
<thead>
<tr>
<th>Category</th>
<th>HTA/Payer Perspective</th>
<th>Access Implications</th>
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</thead>
<tbody>
<tr>
<td>Precision Medicine - Broad Disease Area</td>
<td>• Viewed as similar to other broad disease area treatment:</td>
<td>• Addressed as a broad area treatment; salami slicing</td>
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<tr>
<td></td>
<td>• Even if subpop hits orphan size…not orphan</td>
<td>• Still value of targeting responders, but expectations of “better”</td>
</tr>
<tr>
<td>Precision Medicine - Limited Pop/Orphan Area</td>
<td>• More limited populations still viewed as similar to conventional scenario</td>
<td>• Addressed as conventional drug</td>
</tr>
<tr>
<td></td>
<td>• PM may differentiate vs. other orphan or alternatives</td>
<td>• True orphan indication = orphan pathway</td>
</tr>
<tr>
<td>Rare Disease/Orphan</td>
<td>• Many bubbling up &amp; getting more “picky” about endpoints</td>
<td>• HTA process vary by market depending on how they handle orphan…but generally different expectations</td>
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<td></td>
<td>• Some markets manage &amp; some don’t; some processes tightening</td>
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<tr>
<td>Specialty</td>
<td>• Niche agents can be valued if they hit a strong unmet need</td>
<td>• Most often addressed as conventional drug</td>
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<td></td>
<td>• Not generally special treatment</td>
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<tr>
<td>Ultra Orphan</td>
<td>• High unmet need and lack of alternatives</td>
<td>• HTA process vary by market depending on how they handle orphan…but generally different expectations</td>
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<tr>
<td></td>
<td>• Sometimes special provisions exist for this category in some markets</td>
<td>• Compassionate use can apply</td>
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</tbody>
</table>
Finding the needle in the haystack

Key for both value demonstration & commercialization

- **Finding patients is one of the most challenging aspects** for clinical development & commercialization for niche populations
  - **Precision medicine** – rarer biomarkers meet complex inclusion/exclusion criteria
  - **Orphan** – many patients may fall through cracks if the phenotype is not readily identifiable
- **Integrated clinical/HEOR approach key** – a most common HTA criticism for niche populations = lack of sufficient evidence about the target population
- **Leveraging clear Dx can help in either case (where feasible)** …for orphan is it possible to develop and algorithm or leverage Dx?
- **Lessons** from patient recruitment & epidemiology research **should be shared with commercial early** to help characterize education needs & field outreach campaigns

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**Example: Gaucher Disease**
- ultra orphan inherited metabolic disease w/Dx test
- although risk factors known, can be difficult to find patients outside of high risk geographic areas
- identification of non-metropolitan patients or those w/out clear family risks remains a challenge commercially

**Example: Thalassemia**
- blood disorder may be missed or misdiagnosed
- difficult to build an algorithm to specifically ID patients in data sources
- educational efforts require more specific approach to help physicians find affected patients that may be considered anemic or other issues
Differentiation amidst a sea of rarity

What makes orphan/rare /specialty products stand out?

- “Flying under the radar”…no longer an option
- Clarity of patient population – diagnosis & target population
  - Patient epidemiology & disease characterization
  - Diagnostic definition if challenging to identify; scope of population
  - Clear unmet need vs. rare but less impactful unmet need; limited or insufficient SOC alternatives
- Demonstration of outcomes that matter – hard outcomes vs. surrogates…including outcomes that move the needle vs. current scenario to justify the cost
  - Including longer-term/duration of therapy value demonstration plans
  - Regenerative approaches may be strong if prolonged duration of therapeutic effect or a cure vs. lifelong treatment scenarios
- Characterization of patient-centric considerations
- Clear economic story that resonates with payers, providers and policy makers
- As the space becomes more crowded…including in specific TAs…broader therapy tools such as risk sharing, CED, and contracting strategies become more important to overall value
Differentiation amidst a sea of rarity
Eculizimab…Considerations from Sir Andrew Dillon…

• “Eculizumab **radically improves the quality of life** of the small number of people with aHUS. Until it became available, people with aHUS were at risk of kidney failure needing dialysis, other organ failure, and early death.

• “The drug offers people with the disease **the possibility of avoiding end-stage renal failure, dialysis and kidney transplantation**, as well as other organ damage. [**SOC has substantial negative impacts on QOL**].”

• “The **drug is, however, very expensive**. In making its decision the independent Evaluation Committee needed to **take into account the total fixed budget for highly specialised services as a whole**”

• “The draft guidance recommends that eculizumab is funded only if important conditions are met. These include:
  › **Site of care**: use of eculizumab through an **expert centre**
  › **Population, dosing & duration**: putting in place **systems for monitoring how many people are diagnosed with aHUS**, how many receive the drug, **at what dose** and for **how long**. T
  › **Stopping rules**: develop **protocols for starting and stopping** treatment with eculizumab
  › **Conditional coverage**: introduce a **research programme to collect data to evaluate when stopping treatment or adjusting the dose** of the drug might occur.”
Navigating Uncertainty
Systematically balancing “Got to Have” vs. “Nice to Know”

- Evidence “asks” for orphan products are increasing as scrutiny increases, particularly EU
- Requires rethinking orphan value proposition development; emphasis = differentiation & value
- How to differentiate in a world where orphan budget may be fixed in aggregate?
- Requires a systematic evidence optimization approach, stakeholder testing, and requirements monitoring to “get it right”

<table>
<thead>
<tr>
<th>Country (Number of HTAs)</th>
<th>Agency</th>
<th>Clinical Burden</th>
<th>Clinical Evidence</th>
<th>Comparator</th>
<th>Safety</th>
<th>Quality of Life</th>
<th>HE Analysis/ Cost Effectiveness</th>
<th>Budget Impact</th>
<th>Cost</th>
<th>Strength of Evidence</th>
<th>Clinical Guideline Referenced</th>
<th>Patient Access Scheme</th>
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<td>France (23)</td>
<td>HAS</td>
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<td>Germany (4)</td>
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<td>Italy (3)</td>
<td>UVEF</td>
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<td>Netherlands (7)</td>
<td>ZINL</td>
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<td>Poland (2)</td>
<td>AHTAPol</td>
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<td>Portugal (3)</td>
<td>INFARME</td>
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<td>Scotland (10)</td>
<td>SMC</td>
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<td>Spain (7)</td>
<td>ACQAS/ SESC</td>
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<td>Wales (9)</td>
<td>AWMSG</td>
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</table>

- 80% - 100% of HTAs
- 60% - 80% of HTAs
- 40% - 60% of HTAs
- 20% - 40% of HTAs
- 0% - 20% of HTAs

The Price is Right

*Balancing pricing perception vs. restriction realities*

When does cost outstrip other drivers, irrespective of value and ability to address unmet need?

- Rising prices + aggregate volume raising questions of overall affordability, value criteria and pricing
- Critical to shift to value-focused approaches & novel mechanisms to ensure affordability
The Price is Right
Correlating Criteria to Pricing…Multi-criteria Decision Approach Example

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Price Differential</th>
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<tr>
<td></td>
<td>Low</td>
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<tr>
<td>Rarity</td>
<td>1:2,000 - 1:20,000</td>
</tr>
<tr>
<td>Uncertainty of effectiveness</td>
<td>Immature, but promising data</td>
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<tr>
<td>Manufacturing complexity</td>
<td>Not complex – small molecule</td>
</tr>
<tr>
<td>Follow-up measures</td>
<td>Moderate to none</td>
</tr>
<tr>
<td>Disease Severity</td>
<td>Morbidity</td>
</tr>
<tr>
<td>Available alternatives/unmet need</td>
<td>Alternatives with similar characteristics</td>
</tr>
<tr>
<td>Level of impact</td>
<td>Low</td>
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<tr>
<td>Broadness of use</td>
<td>Existing orphan or non-orphan indications for the same molecule</td>
</tr>
</tbody>
</table>
Dare to be different

*Be creative in addressing value demonstration requirements*

- Environment is now rapidly changing & evolving criteria
- Need to better define what “good” looks like for niche populations
  - Both in terms of clinical studies/value package & economic impact
  - This includes precision medicine, regenerative medicine, & orphan/rare therapies
- We have to rethink some conventional premises of EBM & HTA to get this right…it is becoming increasingly clear that “single yardstick” approaches are inefficient

- **Multi-criteria decision modeling**
  (e.g., Steven Simoens papers)

- **Adaptive Clinical Trials**
  (e.g., Pulmatrix's PUR118 trial for COPD)

- **Conditional Coverage**
  (e.g., CC in Belgium)

- **Registries**
  (e.g., Dutch Insurance Board for lysosomal storage disorders)

- **Policy Impact**
  (e.g., proposed budget limits & prioritization criteria in UK)

- **Risk Sharing Agreement**
  (e.g., Eculizumab in Australia)

The true sign of intelligence is not knowledge but imagination – Albert Einstein
Coming Up to Speed
Translating the value story to stakeholder education

Key Considerations

• Educational need around diagnosis and how to deploy?
• Identification & outreach to providers that will treat…and address gaps in patient ID
• Navigation of heterogeneous HTA & reimbursement channels
• Linking to advocacy to support outreach
• Patient affordability considerations (e.g., foundations)
• Alignment of value story & pricing with stakeholder-specific support around access & affordability
• Logistic complexities for treatments that may only be performed by handful of CoEs
Find a Seat at the Table

The “rules of the road” are being written…right now

Secretary’s Advisory Committee on Genetics, Health, and Society
Rare Diseases and Real World Evidence Generation

Overview

- Patient engagement and retention in long-term observational rare disease studies
- Role of stakeholders in rare disease registries
- Current trends in rare disease research
Role of Real World Evidence

Rare Disease Research

- Generate scientific evidence and publications
- Meet evolving coverage or reimbursement requirements
- Meet safety requirements and manage benefits-risk
- Contribute to treatment guidelines
- Demonstrate dedication to stakeholders/community
Patient Engagement & Retention
Challenges in Patient Engagement & Retention

**Potential Challenges**
- Loss of interest
- Change in provider over long term follow-up
- Competing studies
- Loss to follow-up

**Potential solutions**
- Direct patient engagement
- Flow of information
- Flexibility
- Core registry design
- Comprehensive plan for contact maintenance
Patient Engagement

Ensuring Success

• Good project planning with ongoing identification of potential recruitment and retention challenges – flexibility is key
• Tools to aggressively track and manage recruitment / retention activities
• Making it easy for sites and patients to participate
Stakeholder Engagement
Creating the Right Infrastructure

• Identification of key stakeholders – internal and external, changes over time

• Cooperative approaches
  › Amongst industry, associations, patient communities – when is it viable and when is it advisable?

• Hybrid approaches
  › Possibilities for synergy with existing local or international registries
  › Leveraging EMR and other existing data sources

• Registry governance
  › Important to establish formally and early
  › Role of advisory boards, patient advocates, others?
  › Multi-sponsor projects
Alignment of Registry Stakeholders

Foster more engagement amongst physicians, patients and communities

Think beyond natural history and treatment patterns –

Maximize returns

Create long-lasting, mutually beneficial relationships

What evidence is (or will be) needed to show value and to whom?

Mutually defined success
Current Trends in Rare Disease Research
The Changing World of Research

- Thinking globally
- Role of social media
  - Recruitment & organization
  - Data collection
  - Funding
Re-purposing of Existing Compounds

• Compounds abandoned during development or phased out post-approval
  » Example: analgesic properties of thalidomide potentially useful in the treatment of leprosy

• Off label use vs. Labeled indications: Why does it matter?

• Incentives: US Open Act (proposed)
  › Implications for real world evidence needs?
Thank you
Previous & Upcoming Events

Quintiles experts run regular webinars on Real-World & Late Phase services.

Topics include:

- PATIENT RETENTION & REPORTING
- VACCINES STUDIES
- HTA & MARKET ACCESS
- MAXIMIZING VALUE AND QUALITY IN PHASE IV
- HYBRID DESIGNS
- DATA MANAGEMENT
- PATIENT ASSOCIATIONS

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- DIA
- CHINA MEDICAL AFFAIRS SUMMIT
- AMERICAN ASSOCIATION OF MEDICAL SOCIETY EXECUTIVES

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