Real World Evidence and Implications for Emerging Technologies

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clinical | commercial | consulting | capital

Real-World Evidence: What is it and Why is it Important?
Cycle of Evidence Development

It’s a Journey & NOT a Destination

Evidence development is increasingly a CYCLE

Different stakeholders have different info needs

"Real world", comparative, and continuous value demonstration approaches emerging

Evidence development is increasingly a CYCLE

RCT | Observational

- Investigate and catalogue evidence of asset value
- Communicate CER profile of agent stratified by patient and disease severity to various stakeholders
- Perform gap analysis and refine clinical development accordingly
- Explore effectiveness profile of comparative agents in various settings and populations using real-world data
- Research epidemiology and treatment patterns to understand and meet medical needs of patient population

However...system incentives & infrastructure do not "embrace" or optimize this cycle...particularly for emerging biologicals, orphan products, devices & diagnostics

Limitations...Trial Sample May Not be Representative

"A clinical trial is the best way to assess whether an intervention works, but arguably the worst way to assess...who will benefit"

Evidence-based medicine, heterogeneity of treatment effects, and the trouble with averages

From Kravitz et al. Milbank Quarterly. 2004;82:661-687
“Real-World” Evidence: What is It?

Real world data = data used for decision-making that are not collected in conventional randomized controlled trials (RCTs), includes clinical and economic data reported by patient registries, claims databases, electronic health records, patient-reported outcomes, and literature review.

Real-world evidence = organized information informing a conclusion or judgment based on real-world data.

Outcomes

- Clinical: Biological measures of morbidity and mortality
- Economic: Estimated measure of medical and non-medical resources used or saved
- Patient Reported: Any measure or report coming directly from the patient

Sources

- Supplement to RCTs: Suplemental data gathered during RCT alongside core data
- Registries: Observed cohorts of patients with disease or treatment of interest
- Surveys: Surveys sent to patients in hospital or at home
- Medical Records: Reviews of paper or electronic medical charts of patients
- Large Simple Trials: Observed trials with larger populations but less control than RCTs
- Claims Database: Records of treatments and procedures billed to payers, as well as of associated events

Decisions Impacted by RWE Throughout the Lifecycle

- Evidence gaps & “need to know” exist at all stages of the product lifecycle. Impossible to fill all gaps in pivotal study

Impact RWE can have here?

- Regulatory Approval: RWE can confirm alignment of trial outcomes with real-world practice
- Clarification of value message, especially where RCT evidence is unclear or insufficiently powered
- Initial Decision on Access and Pricing: RWE can strengthen initial push for further RCT evidence
- Efficacy, effectiveness, and economic outcomes with focus on off-label settings where available
- Comparative effectiveness, adverse events profile, economic outcomes (similar to initial access and pricing decision)

Types of outcomes measured?

- Safety, efficacy
- Comparative effectiveness, adverse events profile, economic outcomes
- Efficacy, effectiveness, and economic outcomes (similar to initial access and pricing decision)

Source: Quintiles Research
**Managed Care Dilemmas** Associated with RWE

- How can we best ensure the right product is targeted to the right patients?
- Which technologies & procedures are better than others? What are the differentiating characteristics among them?
- Is the coding system in the US sufficiently granular to track & alter management strategies?
- What are the right incentives & levers to support innovation and appropriate access, while limiting marginal or ineffective technologies?
- How do we manage the array of technologies that end up being “additive” in terms of budget impact when things don’t “fall off the conveyor belt”?
- Do regulations or policies prevent us from doing the “prudent thing”?

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**Setting the Stage for RWE Discussion**
Focus Shift: Products to Systems & Episodes of Care

Health System: the organization of people, institutions, and resources to deliver health care services to meet the health needs of target populations

Issues & Characteristics
- Organization/stakeholders are co-dependant BUT are driven by different incentives
- Incentives & interactions among stakeholders do NOT by design optimize quality & cost from the systems perspective
- Different incentives = different evidence requirements & decision drivers for technology uptake

How and to what extent do we need to rethink evidence development to reflect health system requirements, including different stakeholder needs?

Architectural Considerations: “Gears” of Health Systems

The Players
- Payer
- Hospital
- Physician
- Manufacturer
- Laboratory

Gears of the System
- Operational Processes & Mechanisms
- Funding Flows & Financial Viability
- Decision Processes
- Policy

“Oil” that Keeps it Going
- Mission & Motivators
- Business Goals
- Incentives
- Standards & criteria
- “Feedback Loop” & Interconnectivity
- Patients
RWE Helps Address Needs of Stakeholders & Health Systems

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

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

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

**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

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

**Evolving Market Pressures**

*Challenge: Needs from a Broadening Array of Stakeholders*

**What is “must have” vs. “nice to know”***?

**How do we incorporate health systems thinking into value demonstration efforts?**

A Variety of Key Factors/Drivers
*Impact RWE & CER Development & Use*

**Sample Factors**
- Market Econ Pressure
- ↑ Focus on Value
- Payer Rejection & Restriction ↑
- ↑ Role of the Provider
- Manage Value Over Time
- Risk sharing
- Pressure to Health Costs
- Comparative effectiveness
- Reimbursement Re-Evaluation
- Health System Interconnectivity
- Conditional Coverage
- Shift to clinical pathways

**Strategic Implications:**
- Which factors are more or less important?
- What are the core drivers of near term business models around RWE?
- Which of the these factors are most important to drive ROI?
- How to prioritize “got to have” vs. “nice to know” RWE efforts?
- What are the strategic implications for RWE strategy & internal processes?
- Which factors require alteration of managed care business practices?

**Scope & intensity differs by stakeholder & market**

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Manufacturer’s Dilemma
Increased Economic Pressure = Increased Value Scrutiny by Stakeholders

**Value offered by RWE**
- Understand which technologies work & how well OUTSIDE pivotal studies
- Improves targeting of benefit & product alternatives to areas where it matters
- Enables more “fine tuned” business management decisions

**Potential Health System Integration Challenges for RWE**
- Educational learning curve influences uptake
- System infrastructure not “built that way” (yet)
- Evidence standards remain uncertain & highly variable across markets & stakeholders
- Pricing, reimbursement, & incentive structures
- Affordability? What does cost of generation outstrip management benefits?

Value Demonstration for New Health Technologies…Simple as Quantum Mechanics!

- What clinical study design?
- What do HTA, payers, hospital admins, Physicians, and lab directors want to see?
- Will we see ROI on additional evidence development?
- Will medical societies support our dossier submission?
- Are existing payment rates sufficient?
- What HTA pathway?
- What pricing latitude?
- Can competitors free-ride on our innovation dollars?
- Do we fit into existing codes?
- How do we secure additional payment if needed?
- What comparator?
France and Netherlands open-minded to real-world evidence and in separate cases provide conditional reimbursement until the supportive real-world evidence becomes available.

Real world data are not an absolute requirement in the UK. NICE advises that registry data can be useful for utility data mapping, defining baseline data for patient subgroups, etc. However, if data from registries/observation studies are supplied to show that effects from clinical trials can be replicated in the real world – it is not required.

IQWiG refers to the discussion on pragmatic trials and views RCTs as feasible means to generate real-world data, depending on the appropriate trial design. Hence, with regard to the benefit assessment as a precursor for the cost-benefit assessment, IQWiG is confined to RCTs if available but flexible with regard to the proximity of the trial design to routine care conditions. Real-world data generated by study designs other than the RCT are only taken into account by the institute if there is no alternative.

Demonstrating Real-World Value

Payers opinions differ globally – Nordics among leading supporters of real world data

Trend: Comparative Effectiveness

Moving Beyond Placebo & into Real World

Source of the “Push”

Government Supported
- Accelerated by Affordable Care Act
- Uncertain flow through to govt. decision making as health reform evolves
- Targeted to high impact areas, so not yet applicable to everything

Commercial Payer
- Private payers have always done this implicitly, leveraging internal data
- Not yet an explicit requirement but moving in that direction in some TAs
- Some taking a “watch-n-wait” approach & other considering pilots

Manufacturer-driven
- Historically focused on post-market differentiation
- Increasingly considered pre-launch, including due to ex-US requirements

Strategic Considerations:

- When do we go there? For which TAs & scenarios?
- What are the risks of NOT going there?
- When are direct vs. indirect approaches acceptable?
- Part of the pivotal study & acceptability in sub-studies? Marketing implications?
- How do we get there? What are the right methodological approaches?

Applying CER:

- Payers & providers will increasingly look for differentiating information to inform access & management decisions
- Consider that decisions go beyond individual products and often focus on care pathways
- Consider applications beyond marketing, including as support for contracting & provider negotiations
Trend: Mind the Pathways
Shift Towards Evidence-based Clinical Pathways

Factors Influencing Clinical Pathway Development
- Pressures to channel care to patients that will benefit most
- Availability of a broadening array of evidence on products and care pathways
- Continued expansion of HIT networks
- Movement towards performance management of care pathways
- Health plan purchases of provider networks

Provider Education
- In-person & electronic outreach to providers
- Recruitment of network physicians
- Implementation Coordination & management
- Incentives to follow pathway (P4P)
- Reimbursement limits (step therapy, restrictions)
- Copay or co-insurance alterations
- Re-review and updating

Network Development
- Series of Meetings
- Validation
- Final Approval
- Update Pathway
- Recruitment of network physicians
- Implementation Coordination & management
- Incentives to follow pathway (P4P)
- Reimbursement limits (step therapy, restrictions)
- Copay or co-insurance alterations
- Re-review and updating

Enforcement
- In-person & electronic outreach to providers

Sample BCBS of Michigan Oncology Pathway
Not yet implemented, but potential evolutionary next step

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Strategic Considerations:
- Future evidence must go beyond the individual product to characterize “fit” and “position” within the care pathway and potential to improve overall value
- Care pathway evidence is by default comparative
- May require early engagement & collaboration with payers, providers & medical societies

Trend: Phasing Evidence Development
RWE development is not one Step-It’s a continuum

Coverage with Evidence Development (CED) is a form of conditional reimbursement where patients are provided initial coverage with the promise of developing additional real-world evidence to further characterize the benefits of medical technology

Adaptive Licensing involves iterative phases of data gathering aligned with regulatory review and licensing decisions over the life of the asset

Premises:
- Not for everything – mainly high unmet need & cost impact
- Evidence is not binary and develops over time
- Initial regulatory approval and coverage can in some cases be phased over technology lifecycle
- Front-end involves limited RCT and back-end evolves obs studies, registries, & databases

Possible Vehicles:
- FDA-CMS Parallel Review
- Revamping Medicare CED Guidance/Approach
- PCORI

Considerations:
- Limited acceptance by private payers
- Who funds?
- Is this more restrictive than what we have now?
- Which technologies?
Trend: Manufacturer/Payer Partnerships
Addressing Implications of Consolidation & Reform

Manufacturers have been seeking strategic partnership with payer organizations to better characterize the real-world value of innovative products.

RWE Current & Future States
Key Factors & Influence on Business Models

- What does the real world evidence (RWE) landscape in key markets look like now & in the future?
- Do we need to pursue RWE and what do competitor models look like? What works/what doesn’t?
- When is the right time to develop evidence to align with key decision points?
- What are the acceptable study designs or approaches? How does RWE integrate into existing lifecycle efforts & teams?
- What is the risk to an asset of not having a RWE plan?
- How and to what extent will RWE impact market access and availability?

Answers differ by technology type, application, competition/unmet need, population volume & cost.
Building an Evidence Toolkit to Address New Health Trends

Yesterday’s Toolkit

Example Health Care Trends (Some Markets)

1. Comparative Effectiveness
2. Accountable Care & Pay for Performance
3. Personalized Medicine
4. Value-based Reimbursement
5. Health Plan Consolidation
6. Clinical Pathways
7. Coverage w/ Evidence Development
8. Risk Sharing Agreements

New Health Toolkit

- Stakeholder research
- RCTs
- Observational studies
- Practical clinical trials
- Registries
- Claims & EMR data
- Budget impact model
- Value message testing
- Value dossier
- Cost-effectiveness model
- Time-in-motion studies
- Social media/patient data collection/surveys

Implications for Emerging Technologies:
Personalized Medicine & Orphan Products
Significant Wave of Growth on Horizon for Targeted &Rare Disease Therapies

Refocusing on targeted indications in response to increasing limitations on broader populations = shifts in the pipeline
Areas of low budget impact will grow in tandem
Just < 50% growth rate since 2000

16.7% worldwide growth rate

Biomarker Markets by Geographical Region 2007-2012 ($m)

Source: "Opportunities in Orphan Drugs" Peter Thornton. 2010.

Rare Diseases and Orphan Drugs
High Price Per Patient

There are a broad range of prices for orphan drugs and rare disease treatments and the most expensive drugs generally face the greatest out-of-pocket costs (OPC) for patients.

PMPM costs may be in the pennies...but the aggregate impact will catch up over time...

- Access to reimbursement difficult as drugs may not meet the strict interpretation of cost-effectiveness laid down by HTAs
- Increasingly attractive to replace the loss of revenues as products lose patent protection.
Key Questions/Issues on RWE for Targeted Applications

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

Case Study: Evidence Development Meets Evidence Scrutiny

While development for Xalkori was superior, costing 30% less, requiring 2,000 fewer patients, and 3 years quicker for regulatory approval, the drug was initially rejected for reimbursement.

Core Outcomes

Median PFS increased by of 4.7 months compared with chemotherapy, non-significant OS difference

Initial HTA Rejection

Core Rationale:
• Insufficient comparative effectiveness evidence vs. best supportive care
• Methodological issues making interpretation difficult

Key Questions:
• When is expedited clearance a market access risk?
• What degree of efficacy is “differentiated” currently?
• How could additional RWE development have helped avoid outcome?
• What are the implications for personalized medicine business models?
Case Study: Netherlands Conditional Reimbursement for Orphan Drugs

- Orphan drugs can be funded in The Netherlands through the policy “Expensive (orphan) drugs” (Beleidsregel dure (wees)geneesmiddelen). New process involves re-evaluation for funding
- The policies were created to allow additional governmental funding for hospital only drugs that would otherwise be difficult for hospitals to fund from their annual allocated budgets

CVZ evaluation criteria
- Indicated for disease occurring in less than 1 in 150,000 population
- No other treatment is available in The Netherlands for this indication
- The efficacy of the drug is scientifically proven and it has demonstrated therapeutic added value for patients

Expensive drugs
- The total net purchase costs of the drug are estimated to be at least € 2.5 million per year in all hospitals, for its reimbursed indication

Expensive orphan drugs
- The total net purchase costs of the drug are estimated to be at least € 600,000 per year per academic hospital, for its reimbursed indication

First planned re-evaluations

Expensive drugs
- Infliximab (psoriasis)
- Omalizumab (persistent allergic asthma)
- Ranibizumab (macular degeneration)

Expensive orphan drugs
- Alglucosida alpha (Pompe disease)
- Agalsidase beta / alpha (Fabry disease)
- Galsulfase (Mucopolysaccharidosis VI)

The Dx Dilemma: How do We Balance Evidence NEEDS with Development REALITIES?

“Setting the evidence threshold too high could keep genomics from clinical practice for years. It could also be a disincentive for investments in research and development.”

“On the other hand, an undefined or excessively low threshold could encourage innovations that provide poor value [and have] adverse consequences for the health system and patients.”

“Where should the line be drawn between research and practice on the basis of evidence?”

Also...how do we keep “expectation bleedover” from companion Dx for setting misaligned perspectives for “stand alone” diagnostics not affiliated with a particular drug?

Key Questions/Issues on RWE for Diagnostics

Existing system for rewarding value for Dx makes it difficult for test manufacturers to develop evidence to explore every "nook & cranny" in evolving a comprehensive evidence base.

**Key RWE Considerations**

- How clear is evidence characterizing the association between the biomarker & target disease state?
- How to characterize differential value & outcomes given that most IVD tests (for now) have nondescript coding?
- How and to what extent is characterizing role and use of the test in patient management?
- What evidence around clinical utility for standalone tests may need to be filled outside of a pivotal validation study?
- How to address evidence gaps for lab developed tests vs. FDA approved tests? How will pressure mount for this and what are the rules of the road?
- How to balance additional evidence "asks" given lack of value-based reimbursement?

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Implications for Emerging Technologies: Medical Technologies
“Asks” for RWE in Devices...Driven by Many Factors

Some examples:

• Level of invasiveness & risk
• Longevity of effect (therapeutic devices)
• Type and nature of alternatives (i.e., surgical vs. drug vs. device)
• Level of competition (e.g., stents, orthopedic implants = multiple alternatives)
• Regulatory pathway (510(k) vs. PMA approval)
• Role in clinical pathways & episode of care

Common Complicating Factors in Evidence Generation for Devices

• Ability to conducted “blinded” assessments (e.g., artificial heart, troponin testing)
• Device use is “baked” into procedural codes = “black box” effect & difficulties distinguishing “signal from noise” (e.g., orthopedic implants, IVD diagnostics)
• Lack of accepted unique identifiers for device & test brands
• IT, claims, EMR systems not built to capture differentiation information
• No clear mechanisms to reward additional or “out of the box” evidence generation to demonstrate value
Case Study: Orthopaedic Registries

- Orthopedics represent a significant & growing cost driver in patient care...while addressing key patient needs
- **Challenge:** given lack of coding "tagged" to individual devices...difficult to understand how & to what extent some implants offer differential value & durability
  - Post-procedural complications & infection
  - Revision
- Multiple orthopedic registries, both domestic & international (e.g., GLORY) have been established to characterize a variety of efficacy & safety metrics for implanted knees & hips – to address uncertainties
- **Registries provide a RWE solution...BUT** remains uncertain how & to what extent expectations for (a) new implant evidence will evolve and (b) how this information may influence clinical development & management going forward

Key Questions/Issues on RWE for Medical Devices

*Given over 100K marketed medical devices of different types, how do we hone in on RWE requirements AND how would we implement that information into decision making*

**Common Questions for Devices**

- What different information do payers, providers, & patients need to know that is not generated in pivotal studies?
- If RWE is developed, **how would this be used to inform decision making** different from baseline today?
- Which technology applications most warrant additional RWE generation? (e.g., novel, invasive, high volume & cost, multitude of alternatives?)
  - Are some devices at risk for “elimination”?
- **How will hospital use of RWE change** for devices in the advent of:
  - ACO models
  - Changes in benefit structures (including in exchanges & managed Medicaid or Medicare populations)
  - Movement towards episode of care thinking

Destination apparent...journey uncertain
Implications for Emerging Technologies: Regenerative Medicine

What Does the Global Regenerative Medicine & Cell Therapy Market Look Like?

- Larger than you might think…
- Cell Therapy Group reports ~250 companies (globally) with >300 products in development*

<table>
<thead>
<tr>
<th>Phase</th>
<th>Count</th>
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<tr>
<td>Phase I</td>
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<td>Phase II</td>
<td>77</td>
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<tr>
<td>Phase III</td>
<td>32</td>
</tr>
<tr>
<td>Commercial</td>
<td>68</td>
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- Some therapies may be “home brew” in-hospital products and not commercial therapies
- Market entry by big pharma is beginning (Pfizer, Roche, J&J, Novartis)

Key Strategic Value Demonstration and Reimbursement Considerations for Cell Therapies

- Are available codes/tariffs sufficient for key procedure steps?
- Do we need a new code/tariff? If so, what timing and info required?
- What outcomes are important in avoiding reimbursement rejection?
- What are the key reimbursement limitations that we can expect for the therapy?
- Is payment level appropriate to support access for each step?
- What are our options for address inappropriate payment?
- How does site of care influence reimbursement potential for the therapy?
- Is special expertise required to provide the therapy?
- Are Centers of Excellence required?
- Payers will look at the balance of outcomes relative to cost of entire procedure
- How will evidence development differ from conventional therapies?
- Autologous or allogeneic?
- Type or cell and persistence?
- How are process for cell collection, preparation, and administration reimbursed?
- What are HTA agency and payer perspectives on cell therapies?
- How have payers and HTA agencies handled initial cell therapy entrants?
- What key criticisms of the value proposition have been cited for cell therapies?
- How flexible will payers be regarding patient access?
- Are there subpopulations that are best to target?
- What information will physicians require for adoption vs. conventional therapies?
- What outcomes are important in avoiding reimbursement rejection?
- What are the key reimbursement limitations that we can expect for the therapy?
- Is payment level appropriate to support access for each step?
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Regenerative Medicine
Evidence Criticisms from Global HTA Analysis

- Mixed treatment comparisons & other indirect assessments may gap fill
- Opportunity for RWE to fill gaps?
- Registry studies to address need for longer term data & safety/effectiveness


N = 48 HTAs and reimbursement policies from Australia, Canada, France, Spain, Sweden, the UK and US
**Case: Autologous Chondrocyte Implantation for Knee Cartilage Defects**

**RECOMMENDATION:**

NOT recommended, except in context of ongoing clinical studies

**Clinical Rationale:**

- Few RCTs; small sample sizes; poor trial design & controls
- Inconsistent study designs and outcomes reported
- Inconsistent evidence of clinical effectiveness
- Proportion of post-procedural complications
- Limited long-term outcomes data; when available, similar to standard of care
- No comparison with conservative management

**Economic Rationale:**

- Insufficient evidence to produce robust cost/QALY
- Methods for mapping QoL to economics not sound
- Long-term NICE model took into account cost of knee replacement + QoL for 50 yrs
- ICER for mosaicplasty dominated ACI in modeled scenarios
- Inconsistent model results based on “poor” evidence

**Key Takeaways:**

- Technologies reviewed as a bundle
- Limited discrimination between major technologies
- Poor study design = increased potential for rejection

**Implications for Regenerative Medicine:**

- Value demonstration for QoL-driven indications is difficult; align with payer expectations
- Focus on quality design
- Prepare for long-term follow-up

**Clinical Rationale:**

- Only case series were available, with study designs that NICE would generally not consider under ‘normal’ circumstances
- 24% to 85% of patients were insulin-free at 6-18 months
- In one study 75% remained insulin-free up to 5 years
- Accepted despite serious potential AEs, including vein thrombosis, liver failure, pancreatic infarct, and sepsis

**Economic Rationale:**

- Extremely small, niche population with
  - High unmet need
  - Limited budget impact
- No economic review included in the assessment

**Key Takeaways:**

- Poor study designs and even safety can be overlooked if:
  - Population is small with high unmet need
  - Outcomes are transformative or exceptional

**Implications for Regenerative Medicine:**

- Payers recognize clear, transformative outcomes
- Expect greater scrutiny for marginal, poorly differentiated outcomes

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**Case: Pancreatic Islet Cell Transplant After Pancreatectomy**

**RECOMMENDATION:**

Recommended, but with stipulations for educating patients on procedure risk and stipulations on treatment selection

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Key Questions/Issues on RWE for Regenerative Medicine

Defining value for truly novel technologies where we don’t have a solid track record of experience + technologies span drug & device/procedural payment systems will be complex…anticipate additional asks & shape development approaches accordingly

Key Considerations

- Anticipate longer term “need to know” regarding efficacy & safety…anything truly new = ↑ scrutiny…prepare for registry “asks”

- Are the cells to be developed as a biological or via in-hospital purification approach. What are the implications for addressing hospital & operator variability? Will this impact surety of outcomes?

- What are the gaps in evidence that need to be filled to cover impact of the entire procedure?...its not just the cell component that stakeholders will ask for

- How important is comparative effectiveness in the target indication?

- Economic value demonstration & uptake requirements will vary markedly by site of care (i.e., inpatient vs. outpatient)

Conclusions
Consider How to Leverage RWE Across the Product Life Cycle

– Prelaunch (product not included):
  • natural history of disease
  • burden of illness
  • treatment patterns
  • competitor products
  • disease management
  – to inform development, launch strategy, and market access

– Post-launch:
  • brand usage (on and off-label)
  • safety & effectiveness
  • compliance, adherence, persistence
  • treatment satisfaction
  • competitor brands
  • comparative effectiveness
  • disease management

Consider Alternative & Hybrid Approaches for Evidence Generation

<table>
<thead>
<tr>
<th>Study Type</th>
<th>Consideration</th>
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<tbody>
<tr>
<td>Retrospective Database Studies</td>
<td>Able to assess extremely large populations Quick and relatively inexpensive Good for assessing rare outcomes and long latencies. Strong availability of US Claims data. Increasing availability of US electronic health data</td>
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<td>(EMRs, insurance claims)</td>
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<tr>
<td>Hybrid Studies</td>
<td>Augment routine data with new data solicited from healthcare providers and patients</td>
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<tr>
<td>Registries and</td>
<td>Able to assess extremely large populations More expensive than database studies although less expensive than clinical trials May form a backbone for country specific sub studies</td>
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<tr>
<td>Prospective Observational</td>
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<td>Cohort Studies</td>
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Real-world studies require specialist scientific design and analysis.
Understand Which Push/Pull Factors May Apply
*Variable in Terms of Evidence & Level of Acceptance*

- **Well Accepted**
  - Contracting Parameters
  - Formulary Placement
  - Coverage Limitations
  - Health Technology Assessment
  - Comparative Effectiveness
  - Clinical Pathways
  - CED/Conditional Coverage
- **Emerging**
  - Reference Pricing
  - Risk-sharing
  - Cost-effectiveness

Cost-effectiveness Reference pricing Coverage Limitations Contracting Parameters

Less evidence-based More evidence-based

Consider Investment vs. ROI Ratio
*Near vs. Longer Term Implications & Impact Potential*

<table>
<thead>
<tr>
<th>Trend Area</th>
<th>Likely Risk for MA (now)</th>
<th>Investment to Address</th>
<th>Anticipated ROI</th>
<th>Likely Risk for MA (future)</th>
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- **High**
- **Medium**
- **Low**
- **Depends on the Scenario**
- **Uncertain**
Moving Forward & Finding the Path

• RWE requirements are still evolving among various rates…still lots of uncertainty…still case-by-case & lack of standards
  o Some technologies won’t warrant RWE or if it is generated…it may not be used…though formerly “off radar” technologies may benefit from including RWE into value demonstration strategies
  o Need a better “roadmap” including alignment of study approaches/methods to key questions by technology type

• Important to anticipate which stakeholders need what information + impact on business models…including in terms of adapting to changing pressures
  o Accountable care models
  o Changing federal & state models

• Don’t forget the providers in the US…their role will be increasingly far-reaching…and they use evidence in different ways than payers

• Collaboration among stakeholders is key

Thank You!

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