Age of the Cure? - Challenges and Considerations for Managed Care from Regenerative Medicine and Cell Therapies

Presented by:
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Assoc. Director - Genomics, Biotech, and Emerging Medical Technology Institute, NAMCP
What is Regenerative Medicine?
What is Regenerative Medicine?
(with cell therapies as a subset)

Deals with repairing or replacing tissues and organs by using advanced materials and methodologies

- **Embryonic stem cells**
- **Allogeneic stem cells** – cells taken from one person and given to another person
- **Autologous stem cells** – cells taken from a person and given to the same person
- **Gene therapy**
- May also involve **biocompatible matrices and/or other systems to support the cells**
- **Sources of adult stem cells (multiple):**
  - Bone marrow & blood
  - Skeletal muscle
  - Adipose tissue
  - Liver, brain, cord blood, placenta and umbilical cord
What Steps Can be Involved in Provision of Regenerative Medicine?

While the cells may be treated as a biologic, the entire procedure may be multi-faceted and complex, involving one or more of the following steps:

1. **Mobilization or cell extraction**
   - Use of cell mobilizing agents such as Mozobil or Neupogen
   - Bone marrow aspiration

2. **Apheresis** to separate stem cells from other blood components

3. **Cell selection/purification** (e.g., CD4, CD8, CD34+, Mac-1, CD 146)

4. **Expansion of cells in culture** (does not always occur)

5. **Genetic manipulation of stem cells** (rarely occurs)

6. **Delivery/administration**
   - Surgical implantation
   - Intramuscular injection (e.g., critical limb ischemia)
   - Catheterization & injection (e.g., cardiac applications)
   - IV infusion or injections (e.g., physician admin. oncologics, cell therapy vaccines)
   - May include imaging guided administration
Exception from Biologic Regulations:
Qualifications for Autologous Stem Cells

Considerations that would not require an IND or BLA submission for cellular products

- The **cells are autologous** and are intended for **use for a specific clinical indication**
- The **cells are minimally manipulated**
- The device is solely responsible for the production of the autologous cells (i.e., no other manufacturing steps take place outside of the device other than the recovery of the source cells)
- The cells are used within a short period of time (i.e., cells are not stored or shipped);

The device and selected cells are only used at the point of care (i.e., cell processing is performed at and by the clinical site where cells are directly administered). The selection device is used in a location close enough to the patient that the recovery, processing, and direct administration of the cells will occur in a matter of hours (or less) and without the need for shipping

Other Key Considerations:

- Do existing procedure codes fit or pay enough?
- How will the procedure or biological be affected by inpatient vs. outpatient use?
- Will the cells be processed / manufactured off site like a biological or at the hospital?
- Are there safety or quality concerns with in-house models?
- Are there competitive cost and HTA disadvantages to having a separate and higher payment for a biological?

*Other eligibility criteria may apply; Sources: FDA.: http://www.fda.gov/OHRMS/DOCKETS/98fr/07d-0290-gdl0001.pdf, Quintiles analysis*
Demonstrating New Health Technology Value…Simple as Quantum Mechanics!

What clinical study design?

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?

What do HTA, payers, hospital admins. Physicians, and lab directors want to see?

Can competitors free-ride on our innovation dollars?

Do we fit into existing codes?

How do we secure additional payment if needed?

What comparator?
What’s Managed Care’s Perspective on Regenerative Medicine?
Technology types with greatest potential to impact quality & cost of care

- **Vaccine**
- **Biologic**
- **Personalized Medicine**
- **Small Molecule**
- **Molecular Dx**
- **Medical Device**
- **Cell & Gene Therapy**
- **Nanotech.**

- **Low or Very Low Impact**
- **Moderate Impact**
- **High or Very High Impact**

- **Vaccines, biologics, & personalized medicine were most frequently as high impact potential**
- **55% ranked cell & gene therapies as high or very high impact**
- **Nanotech ranked lowest...likely because few demonstration products**

Based on a US 2013 survey of the National Association of Managed Care Physicians, including 60% payer and 40% provider respondents. N = 20
Perspective on Regenerative Medicine Impact

Payer perspective on the degree of overall impact regenerative medicine technologies may have on the practice of care:

- 28%: Transformative, offering options not possible with conventional biopharmaceuticals
- 6%: Significant impact, but few may be transformative
- 6%: Comparable to existing standards of care
- 6%: No Impact
- 61%: No Impact

- 89% viewed regen. meds as being significant or transformative
- However, despite this optimism...scrutiny of these technologies is expected to be high because:
  - Novelty – truly new, unproven, not well understood
  - Concerns on long-term safety & efficacy
  - Concerns that they will be costly
  - Unclear how to assess value for a cure

Based on a US 2013 survey of the National Association of Managed Care Physicians, including 60% payer and 40% provider respondents. N = 20
Managed Care Dilemmas with Regenerative Medicine

- Which technologies & procedures are better than others? What are the differentiating characteristics among them?

- Is the coding system in the US prepared for novel procedures or sufficiently granular to track & alter management strategies for cell therapies?

- How to ensure the right product is targeted to the right patients?

- What are the right incentives & levers to support innovation and appropriate access, while limiting marginal or ineffective technologies?

- How to appropriately price and manage risk for therapies that are “curative”?

- Do regulations or policies prevent us from doing the “prudent thing”?

Sample target indications currently *not covered* by leading US payers:

<table>
<thead>
<tr>
<th>Conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myocardial infarction</td>
</tr>
<tr>
<td>Congestive heart failure</td>
</tr>
<tr>
<td>Critical Limb Ischemia / Peripheral Artery Disease</td>
</tr>
<tr>
<td>Multiple sclerosis</td>
</tr>
<tr>
<td>Systemic lupus erythematosus</td>
</tr>
<tr>
<td>Systemic sclerosis</td>
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<tr>
<td>Rheumatoid arthritis</td>
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<tr>
<td>Juvenile rheumatoid arthritis</td>
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<tr>
<td>Osteonecrosis</td>
</tr>
<tr>
<td>Orthopedics / cartilage repair</td>
</tr>
<tr>
<td>Idiopathic thrombocytopenic purpura</td>
</tr>
<tr>
<td>Dematomyositis</td>
</tr>
<tr>
<td>Polymyositis</td>
</tr>
<tr>
<td>Autoimmune cytopenia</td>
</tr>
<tr>
<td>Diabetes mellitus (type I)</td>
</tr>
<tr>
<td>Systemic vasculitis</td>
</tr>
<tr>
<td>Celiac disease</td>
</tr>
<tr>
<td>Crohn's disease</td>
</tr>
<tr>
<td>Oncology (select indications/applications)</td>
</tr>
</tbody>
</table>

**Implications for Regenerative Medicine:**

- US payers are concerned about unproven, hospital-based cell therapies
- Policies will change as evidence for tested products matures in the marketplace

Source: Indications identified through evaluation of multiple US MCO coverage policies.
On a scale of 1 to 10 (where 1 = lowest and 10 = highest), please rate the following factors in terms of level of importance regarding assessment of regenerative medicines for coverage:

- Effectiveness – based on hard endpoints...not surrogates
- Durability of treatment effect
- Evidence of safety (including...
- Comparative effectiveness vs...
- Established scientific rationale for...
- Cost of the cell/gene therapy...
- Overall procedure costs
- Quality of life impacts
- Availability of long-term data
- Effectiveness – based on...
- Physician/medical society support

Results also suggest that a comprehensive value story is necessary for success.
Global Evidence Pitfalls for Regenerative Medicine

- Study design quality is key. Device-like studies = high rejection potential
- Long-term evidence is key and plan for post-market data collection
- Rigorous outcomes are key

N = 48 HTAs and reimbursement policies from Australia, Canada, France, Spain, Sweden, the UK and US

Source: “HEOR for Regen Med and Cell Tx” Faulkner & Spinner, ISPOR 2011
Common US Evidence Pitfalls for Regenerative Medicine

Nearly 90% of US HTAs noted a lack of comparator

Almost 50% of HTAs noted that studies did not include the right endpoints

US HTAs focused much more on safety

Insufficient #/quality of studies, Lack of comparative data, Lack of long term data (>1 yr), Inconclusive/inconsistent studies, Inappropriate endpoints, Concerns regarding safety, Insufficient efficacy, Insufficient cost-effectiveness

N = 48 HTAs and reimbursement policies from Australia, Canada, France, Spain, Sweden, the UK and US

Source: “HEOR for Regen Med and Cell Tx” Faulkner & Spinner, ISPOR 2011
• Experience over the past 10-12 years suggests that 12 months is the minimum acceptable trial timeline
• Payers prefer 2 years+
• Manufacturers may be required to also add a registry to follow patients as a condition of reimbursement, depending on disease severity, treatment risks and costs

Based on a US 2013 survey of the National Association of Managed Care Physicians, including 60% payer and 40% provider respondents. N = 20
Payers Willing To Pay For Long-term Value

Degree of payment increases for regenerative medicines compared to existing standard of care

- Disease is cured [permanently]
- Prolonged duration of therapeutic effect 2-3 years longer than any established alternative
- Prolonged duration of therapeutic effect 6-12 months longer than any established alternative

60% said >51%
45% said >26%
20% said 51%

0-25% 26-50% 51-100%

- Cell & regenerative medicine therapies that cure disease may command substantial premiums over existing therapies

  > Definition of a “cure” will vary by disease area

- Even prolonged duration of therapeutic effect would support significant premium pricing opportunities

  > Depends on “magnitude” of effect also…

Based on a US 2013 survey of the National Association of Managed Care Physicians, including 60% payer and 40% provider respondents. N = 20
Case Studies on Regenerative Medicine
## Case Comparison: Autologous Chondrocyte for Knee Cartilage Defects

### Clinical Rationale
- Lack of options for young patients
- Strong directional evidence of improvement
- Concern about lack of long term evidence
- Concern about lack of CER

### Economic Rationale
- Poor evidence
- Model extended for 50 years on cost of knee replacement and QoL

### Criteria | US (e.g., Aetna, BCBS, etc.) | NHS / NICE |
<table>
<thead>
<tr>
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</thead>
<tbody>
<tr>
<td>Decision</td>
<td>Recommended as medically necessary for 2nd line &amp; subpopulation</td>
<td>Investigational, not for use outside clinical trial</td>
</tr>
</tbody>
</table>
| Clinical Rationale | • Lack of options for young patients  
• Strong directional evidence of improvement  
• Concern about lack of long term evidence  
• Concern about lack of CER | • Few & poorly designed RCTs  
• Small sample size  
• Inconsistent design and results  
• Limited long-term outcomes & evidence was similar to SOC |
| Economic Rationale | | • Poor evidence  
• Model extended for 50 years on cost of knee replacement and QoL |

### Implications for Regenerative Medicine:
- Poor study design is at significantly increased risk for rejection
- Value demonstration for QoL-driven indications is difficult; align with payer expectations
- Focus on quality trial design & prepare for long-term follow-up
Case Study: PAD / CLI Bone-Marrow Stem Cell Therapy

**RECOMMENDATION:**

**Investigational**, for all indications including CLI & Buerger Disease

**Economic Rationale:**

- Extremely small, niche population with
  - High unmet need (need amputation with failed surgery and revascularization)
- No economic review included in the assessment

**Scientific Evidence Considered:**

1. Pain and functioning
2. Prevention or delay of limb amputation
3. Durability of treatment effects

**Clinical Criteria Scrutinized:**

Typical inclusion criteria: Patients with ABI<0.4 and failed surgical & revascularization treatment. Higher than normal rate of diabetes, hyperlipidemia, and ischemic heart disease. Outcomes:

- **Study 1:** Frequency of amputation 21% compared to 44% for control.
- **Study 2:** While no significant improvement in ABI, there was a significant improvement in ulcer size and pain at rest.
- **Study 3:** Significant improvement in ABI and rest pain sustained over 24 months.
- In an observational study, for a-PAD and TAO, 3-year survival rates were 80% and 100%, AFS was 60% and 91%, and significant improvement in pain and ulcer size.

**Key Takeaways:**

- Investigational because additional RCTs are needed to evaluate the health outcomes.
- Additionally, payers seek evidence on the safety and durability of the treatment is also needed

**Implications for Regenerative Medicine:**

- RCT-level data and appropriate outcomes are key to acceptance
- Establishing treatment long-term durability critical.
Case: Pancreatic Islet Cell Transplant After Pancreatectomy

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

**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
Case: Autologous Cell Transplant for Myocardial Infarction

RECOMMENDATION:
Further research required to determine long-term efficacy and safety (horizon scan report 2007)

Clinical Rationale:
• Review based on 10 RCTs and 4 noncomparative trials
• All studies at the time evaluated surrogate outcomes (e.g., LVEF) vs. changes in morbidity and mortality
• Lack of long-term data on “hard” and/or clinically discernable health outcomes
• Insufficient evidence on short- and long-term safety given risks associated with the procedure

Economic Rationale:
• Limited cost impact analysis evaluated incremental costs of relevant procedure steps via codes/payment rates in the Australian system
• Did NOT account for cost of cells as a commercial product, but as part of a hospital procedure

Key Takeaways:
• Focus on surrogate outcomes = perception not ready for “prime time”
• For high risk + high volume + high cost = highest level of payer scrutiny

Implications for Regenerative Medicine:
• Understand what payers view as most important value outcomes
• Evidence threshold for high risk/high cost indications will be HIGH
Takeaways
What does the Climate Look Like for Value Demonstration in Regenerative Medicine?

- Regenerative medicine is “on the payer radar” and an increasing focus
  - The “storm” has been sighted & decision makers are watching carefully

- Despite the promise, there is a “perfect storm” of factors converging that make global value demonstration more complex…particularly for ground breaking technologies
  - Driven by novelty, resource allocation pressures, and market health reform
  - Evidence is emerging for “homebrew”, device, and biologically classified cell therapies

- Early indicators may suggest storms ahead, but the key to success is planning and preparation. Focus on:
  - Solid study designs; appropriate patient targeting and sample size
  - Understanding the outcomes that matter on an indication-by-indication basis
  - Plans for longer-term data collection beyond the pivotal study
  - Characterizing benefits/cost balance vs. alternatives; economics matter

- Remember…for payers, saying “no” is easier than saying “yes”
  - Have your emergency kit well prepared to weather climate changes in HTA
Cell Therapy Value Demonstration and Reimbursement Considerations

- 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 of cell and persistence?
- How are the processes for cell collection, preparation and administration reimbursed?

- What are HTA agency and payers 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?

- Are available codes sufficient for key procedure steps?
- Do we need a new code? If so, what timing and info required?

- What outcomes are important in avoiding an investigational/experimental designation?
- What are the key coverage 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?

- 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?

- Payers will look at the balance of outcomes relative to cost of entire procedure
- How will evidence development differ from conventional therapies?
Consider the Reimbursement “Fit”

• Regenerative medicines often involve multiple procedural steps including:
  > **cell extraction** (bone marrow or other removal or mobilization)
  > **purification & preparation** (apheresis, cell purification, genetic manipulation, cell expansion)
  > **cell administration** (injection, infusion, catheter)
• **Fit into reimbursement systems may not be ideal** as cell therapy methodology may be beyond existing procedures
• Will market **reimbursement systems/payers view as a procedure/device vs. biological** (irrespective of regulatory)
  > Devices & drugs often have very different reimbursement pathways & evidence requirements
• Key strategic considerations include:
  > Site of care
  > Fit in coding systems
  > Bundled payment vs. separate components (including how cell component will paid for)
  > Appropriateness of existing payment mechanisms
  > Anticipated cost vs. alternatives
Multiple regenerative medicine technologies are moving into clinical development, but:

- They are truly novel and not yet understood/accepted by HTA, payer and physician decision makers: EDUCATE
- Reimbursement and commercial strategy is more complex due to combination procedure/surgery and cellular component; technologies can touch more than one payment system; EVALUATE – “measure twice & cut once”
- Manufacturing, distribution and market access channels are more complex than conventional biopharmaceuticals; NAVIGATE
- Early analysis of HTAs suggests that regenerative medicines will have to demonstrate strong clinical, economic and long-term follow-up data; DEMONSTRATE
- “Front-loaded” cost model and “episode of care” view can complicate economic and cost-effectiveness analysis; VENERATE – clearly understand economic drivers
- Need for strong educational efforts and clear communication of value proposition; COMMUNICATE – “multifaceted value…let me count the ways…”

Reverse engineer product plans targeting reimbursement requirements to optimize commercial potential so the pieces fit
Significant System Shocks are Likely to Further Impact Cell Therapy Potential

Myriad of additional factors complicate development, launch, market access and life cycle management planning for cell therapies.

**Technological**
- Next Gen Sequencing / Molecular Imaging
- iPS Cells / Transdifferentiation
- Cell and Tissue 3-D Printing
- Decision analytic tools & algorithms
- Health information technology & data resource development

**Clinical & Value-based**
- Clinical pathways & more rigid guidelines
- Comparative effectiveness
- Value-based reimbursement models
- Evolution of test evidence standards & development models

**Economic**
- Market economy collapse & “belt tightening”
- Regulatory & reimbursement reform
- Cost-effectiveness
- ACO models
- Conditional coverage/CED
Thank You!

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National Association of Managed Care Physicians
Appendix
Common Responses to Manage Cell Therapy

On a scale from 1 to 10 (where 1 is lowest and 10 is highest), please rate the likelihood of the following approaches to be applied to novel regenerative medicine technologies.

- Comparative effectiveness
- Limits on repeat administration
- Coverage w/ Evidence Dev't
- New patient copay/coinsurance models
- Risk Sharing Agreements

1-2 3-4 5-6 7-8 9-10
# Qualifications as Implantable Biological

<table>
<thead>
<tr>
<th>Considerations</th>
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<tbody>
<tr>
<td><strong>Product must be</strong> relatively new to the outpatient setting (i.e., not recognized as an outpatient service prior to 1997)</td>
</tr>
<tr>
<td><strong>Technology must be</strong> reasonable and necessary for treatment of the Medicare beneficiary</td>
</tr>
<tr>
<td><strong>Associated cost of the technology must meet the definition of “not insignificant”</strong> in relation to the APC rate for the service</td>
</tr>
<tr>
<td>“Not insignificant”: the expected reasonable cost of a product must exceed by 25% the portion of fee schedule with which it is associated, and the difference between the reasonable cost of the product and its portion of the fee schedule must exceed 10% of the total fee-schedule reimbursement for the service</td>
</tr>
<tr>
<td><strong>Will the device substantially improve the treatment of an illness or injury or improve the functioning of a malformed body part</strong> compared to all available treatments?</td>
</tr>
<tr>
<td><strong>Will there be FDA approval?</strong></td>
</tr>
<tr>
<td><strong>The biologics may not be used to replace human skin</strong></td>
</tr>
<tr>
<td><strong>Cells must be:</strong></td>
</tr>
<tr>
<td>a. Be an integral and subordinate part of the service furnished;</td>
</tr>
<tr>
<td>b. Be used for one patient only;</td>
</tr>
<tr>
<td>c. Come in contact with human tissue; and</td>
</tr>
<tr>
<td>d. Be surgically implanted or inserted whether or not the device remains with the patient when the patient is released from the hospital</td>
</tr>
</tbody>
</table>
## Outpatient Biologic Scenario: Qualifications for J Code

<table>
<thead>
<tr>
<th>Considerations for Cell Therapies</th>
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</thead>
<tbody>
<tr>
<td>Drug is <strong>physician administered</strong></td>
</tr>
<tr>
<td>Will the application be both complete and timely?</td>
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<tr>
<td>Is HCPCS II proper designation? (That is, <strong>not equipment</strong>, not inpatient, not CPT, etc.)</td>
</tr>
<tr>
<td>Will the cells be medical in nature?</td>
</tr>
<tr>
<td>Will the cells be <strong>reasonable and necessary for the treatment</strong> or diagnosis of the illness or injury for which they are administered?</td>
</tr>
<tr>
<td>Will there be <strong>FDA approval</strong>?</td>
</tr>
<tr>
<td>Is there a need for national program operation? (Medicare, Medicaid, Commercial Providers)</td>
</tr>
<tr>
<td>Will the cells perform a different function than items already categorized in HCPCS II? (OR) If they operate differently, will there be <strong>therapeutic distinction from existing coded products</strong>?</td>
</tr>
<tr>
<td>Will the cells meet volume and marketing criteria?</td>
</tr>
<tr>
<td>Will the cells receive <strong>FDA approval as a biologic</strong>? Per payers, J-code needs regulatory approval as a biologic.</td>
</tr>
</tbody>
</table>

*Other eligibility criteria may apply; Sources: CMS, reimbursementcodes.com, Quintiles analysis*
Table 1: Key Evidentiary Criticisms Cited for Regenerative Medicine Products

<table>
<thead>
<tr>
<th>Evidence Consideration</th>
<th>AU</th>
<th>CA</th>
<th>FR</th>
<th>DE</th>
<th>IT</th>
<th>ES</th>
<th>SE</th>
<th>UK</th>
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<tbody>
<tr>
<td>Insufficient evidence of value</td>
<td>S</td>
<td>S</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>S</td>
<td>Y</td>
<td>S</td>
<td>S</td>
</tr>
<tr>
<td>Insufficient number/quality of studies</td>
<td>S</td>
<td>S</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>Y</td>
<td>Y</td>
<td>S</td>
<td>S</td>
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<tr>
<td>Lack of comparative data</td>
<td>S</td>
<td>S</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>Y</td>
<td>Y</td>
<td>S</td>
<td>S</td>
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<tr>
<td>Lack of long term data (&gt;1 year)</td>
<td>Y</td>
<td>Y</td>
<td>N</td>
<td>NA</td>
<td>NA</td>
<td>Y</td>
<td>Y</td>
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<tr>
<td>Inconclusive or inconsistent outcomes</td>
<td>S</td>
<td>N</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>N</td>
<td>S</td>
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<tr>
<td>Focus on surrogate outcomes</td>
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<td>NA</td>
<td>NA</td>
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<td>S</td>
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<td>Inappropriate endpoints</td>
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<td>Y</td>
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<td>Concerns regarding safety</td>
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<td>Insufficient efficacy</td>
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<td>Insufficient cost-effectiveness</td>
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<td>N</td>
<td>Y</td>
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Source: “HEOR for Regen Med and Cell Tx” Faulkner & Spinner, ISPOR 2011