AMCP

PARTNERSHIP FORUM

No. 3 — 2021

Addressing Evidence Gaps in the Expedited Review Process: Payer Perspectives

NOV. 18–19, 2021

Moderator Welcome

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AMCP Partnership Forums
Collaboration for Optimization

- Provide a voice for stakeholders
- Find common ground and gain consensus
- Identify actionable results
- Amplify to raise visibility

Goals of this Partnership Forum

- Identify the gaps between FDA accelerated approval requirements and treatment outcomes valued by payers.
- Explore opportunities for an evidence ecosystem to address gaps
- Develop policy recommendations to facilitate communication, reduce financial uncertainty, and potentially shorten the time to coverage decisions.

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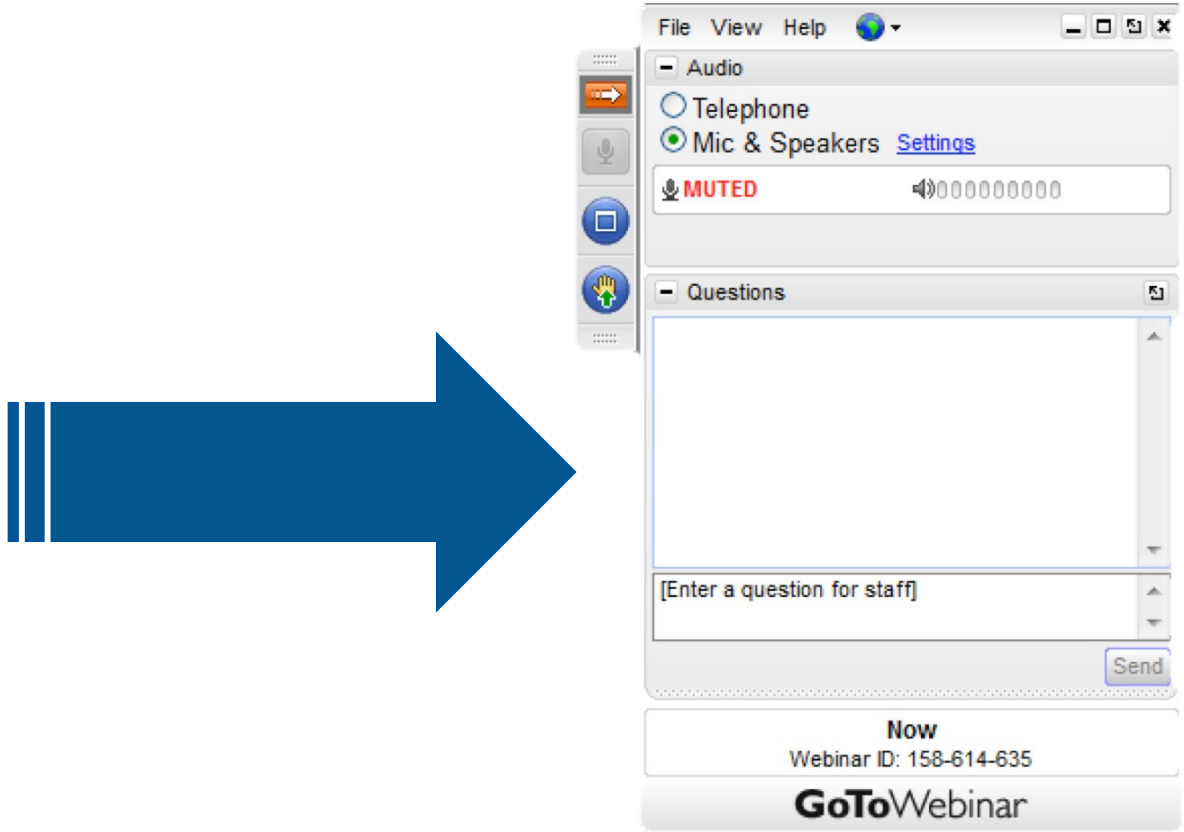
How to Ask Questions



Audience Polling: How would you rate the need for accelerated drug approval?

1. Extremely necessary
2. Very necessary
3. Somewhat necessary
4. Not very necessary
5. Not at all necessary

Audience Polling: How confident are you to apply surrogate endpoints used for accelerated approvals to formulary decisions?

1. Extremely confident
2. Confident
3. Not very confident
4. Not all confident
5. Not applicable

Our Faculty

Vivien Chan, PharmD
General Manager
Director of Formulary & Contracting
Costco Health Solutions

Paula Eichenbrenner MBA, CAE
Executive Director
AMCP Foundation

Lilian Ndehi-Rice, PharmD, MBA, BCPS
Associate Vice President, Pharmacy Clinical and Specialty Strategies
Humana Inc.

Agenda

- Background on Accelerated Approval Pathway
- Managed Care Perspectives
- Forum Findings
  - Clarify Accelerated Approval Criteria
  - Correlate Surrogate Endpoints with Meaningful Outcomes
  - Bridge the Evidence Gaps with Enhanced Evidence Ecosystem
  - Advance Potential Policy and Practice Solutions to Reduce Financial Uncertainty
- What's next?

History of ‘Expedited Programs’

- Tension of drug development/review timeline perceived as ‘too long’ by the patient community and ‘too short’ by others
  - HIV-AIDS in the early 1980s
    - Limited access to experimental drugs
    - Review standard largely ‘survival’
  - In the late 1980s
    - Increased access to experimental drugs
    - Institutionalization of Accelerated Approval
      - Allowing approval based on surrogate clinical endpoints transitioned from ‘survival’ to ‘reasonably likely to predict clinical benefits’

- Tension exists today
  - New goal for some: unfettered access to investigational drugs
  - Recent approval for new medications for ALS

Four Expedited Programs: Focus on Accelerated Approval

Fast Track *Designation*

- Section 506(b) of the FD&C Act 1988
- Features
  - Expedited development and FDA review
  - Can be rescinded

Priority Review *Designation*

- Prescription Drug User Fee Act of 1992
- Feature
  - Shorter clock for FDA review of marketing application

Breakthrough Therapy *Designation*

- Section 506(a) of the FD&C Act 2012
- Features
  - Intensive guidance from FDA
  - Rolling review
  - Can be rescinded

Accelerated Approval ***Pathway***

- Section 506(c) of the FD&C Act of 1992
- 21 CFR part 314, subpart H
- 21 CFR part 601, subpart E
- Feature:
  - Approval based on an effect on a surrogate endpoint or an intermediate clinical endpoint that is reasonably likely to predict a drug's clinical benefit
  - Confirmatory trials required
  - Approval may be withdrawn

Accelerated Approvals Based on Surrogate Endpoint is Common

Total Approvals (or ‘market access’) : 269

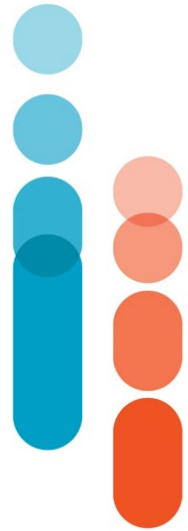
> 85% of accelerated approvals in last 10 years are in oncology

Converted to full Approval: 132

Indication Withdrawn: 5

Application Withdrawn: 15

Not Yet Converted: 117



CDER Drug and Biologic Accelerated Approvals Based on a Surrogate Endpoint As of June 30, 2021

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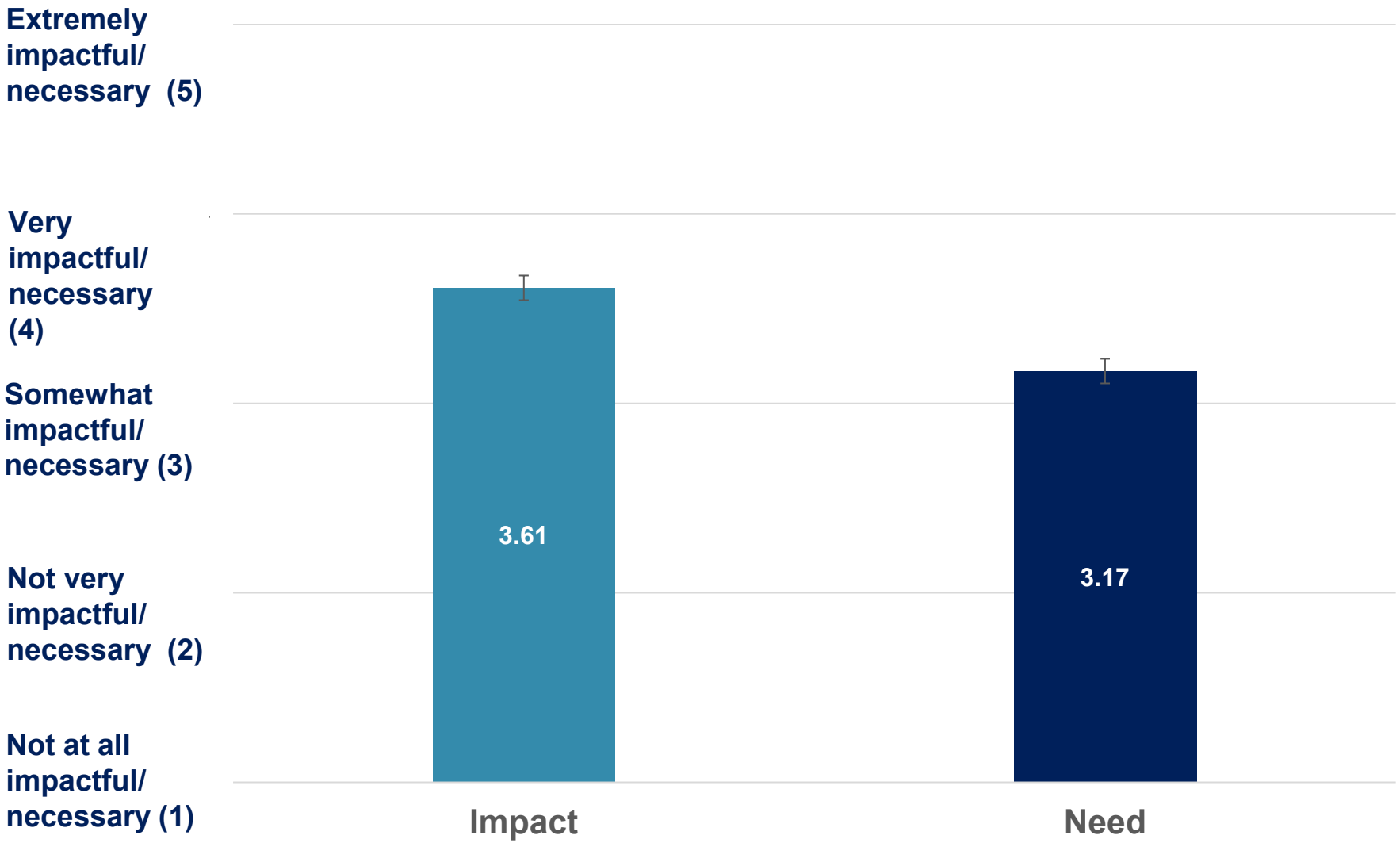
Payer Perspectives on Expedited Reviews

2021 Survey: What and Who

- Cross-sectional survey
- 22 questions
- Piloted to assess content and face validity
- Fielded Sept. 22-Oct. 4
- **Respondents**
  - 178 respondents
  - 159 qualified payer respondents

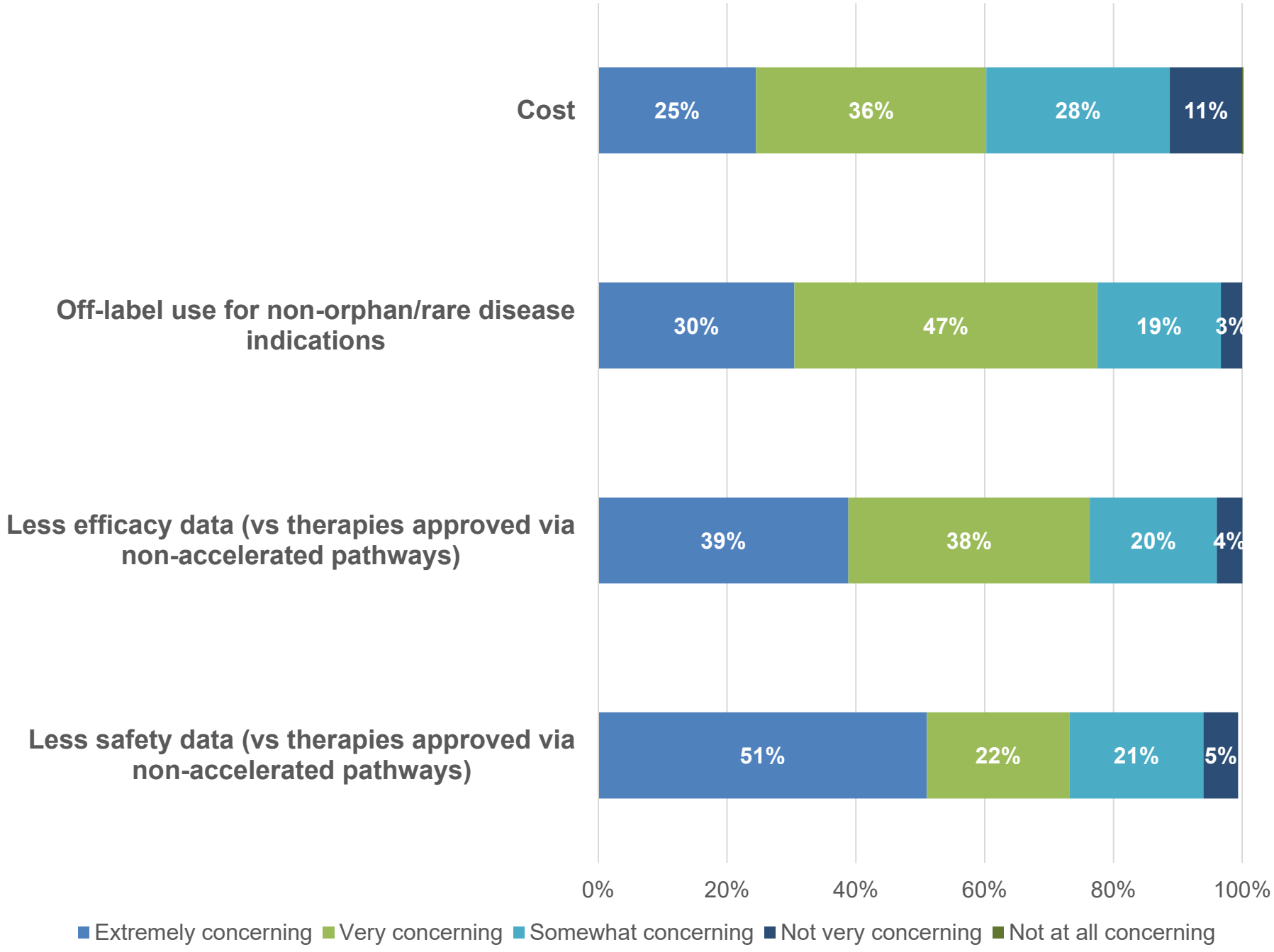
Employer Types	Job Functions	Expertise
• Payers • Pharmacy benefit managers • Specialty pharmacy	• Pharmacy director • Formulary management • Operations • Contracting	• Formulary • Commercial or exchange plan management



Payer perception of the impact of accelerated drug approval to the future of health care and perception of relative necessity

Q: How impactful do you think accelerated drug approvals is to the future of healthcare? (1 = Not at all impactful; 5 = Extremely impactful)
Q: How would you rate the need for accelerated drug approval? (1 = Not at all necessary; 5 = Extremely necessary)

Notes: Respondents that answered "Not sure/I don't know" were removed from the analysis. All respondents that endorsed a work organization type of "other" were also removed. Averages are presented.



Payers are consistently concerned about safety and efficacy data in expedited reviews

Q: How concerning are each of the following with respect to accelerated drug approval? (1 = Not at all concerning; 5 = Extremely concerning)

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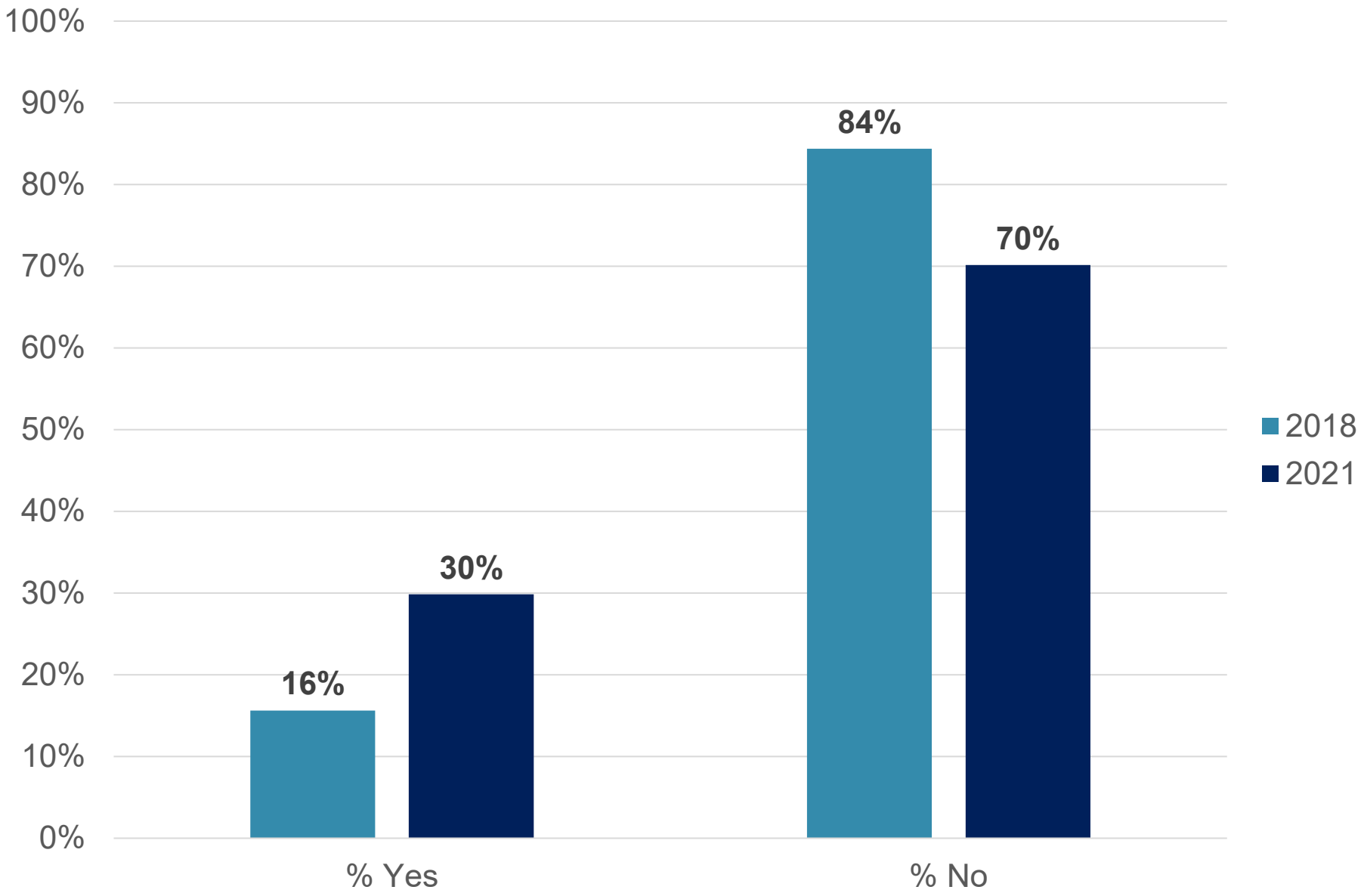
Expedited Reviews and Formulary Decision-Making

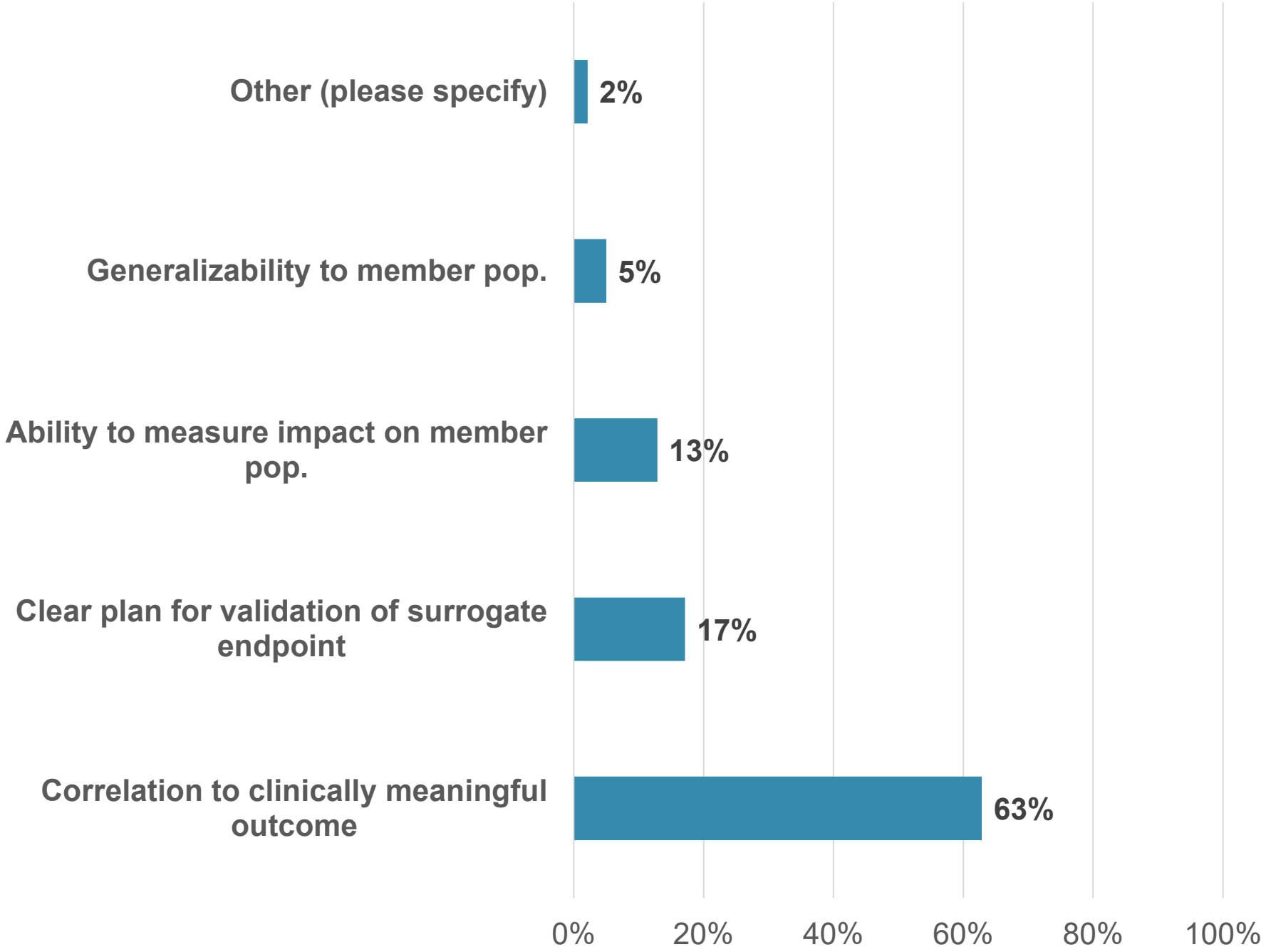


Statistical test: X^2 (1, 198) = 4.64; p = .03

Notes: Respondents that answered “Not sure/I don’t know” were removed from the analysis. All respondents that endorsed a work organization type of “other” were also removed.

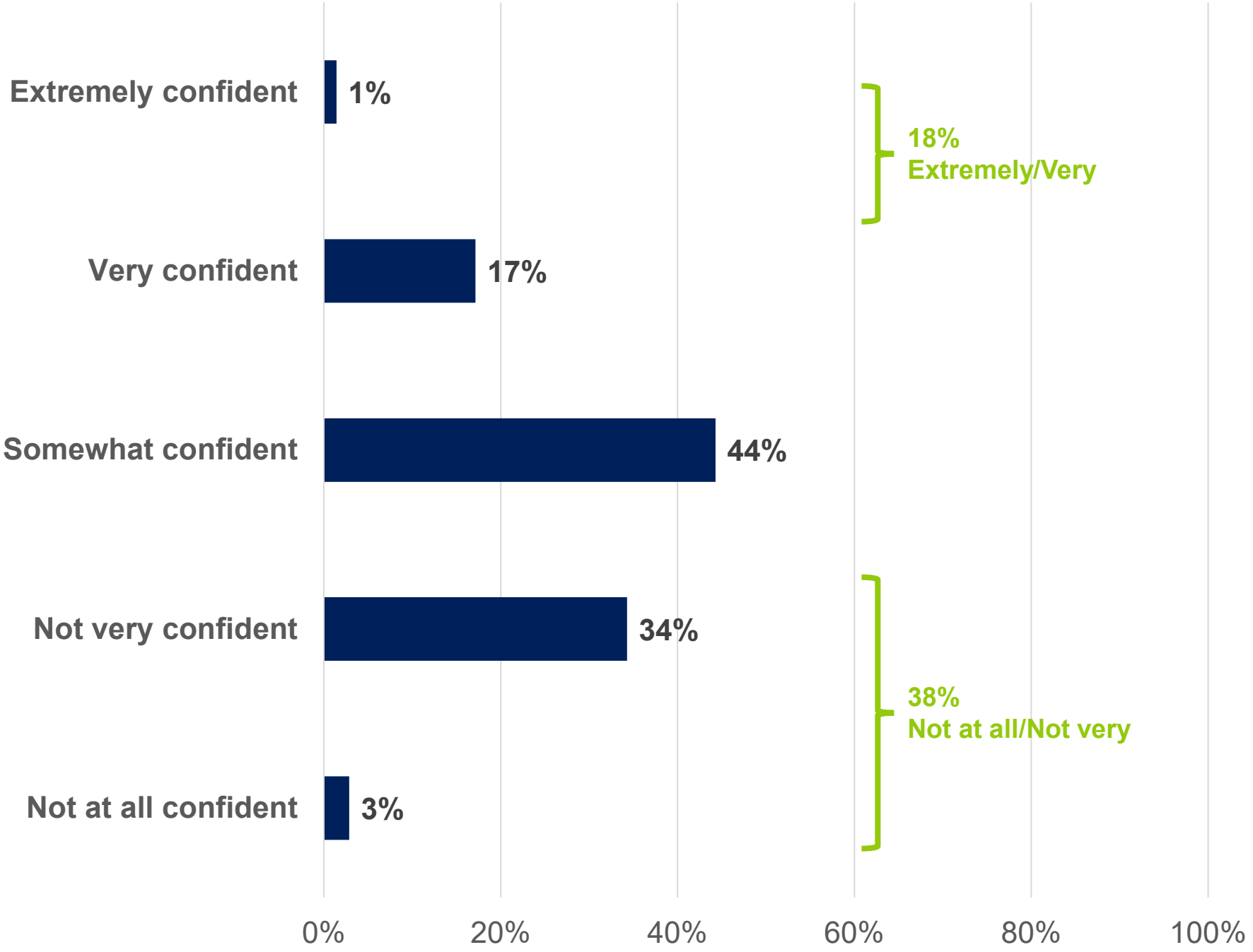
Payers were significantly more likely to have a separate review process for therapies receiving accelerated approval in 2021 compared to 2018 ($p < .05$)

Q: Does your organization have a separate and/or expedited review process for therapies receiving accelerated drug approval?



Payers seek correlation of surrogate endpoints to clinically meaningful outcomes for formulary decisions

Q: When your organization applies surrogate endpoints to your formulary decision-making process, what is the most important consideration?



Payers are **not confident** in applying surrogate endpoint data to formulary decisions

Q: How confident are you in applying surrogate endpoint data to guide formulary coverage decisions? (1 = Not at all confident; 5 = Extremely confident)

1. Clarify Terminology for Accelerated Approval Pathway

1. Clarify Terminology

"designed to facilitate the development and expedite the review of drugs to treat serious conditions and fill an unmet medical need"

Serious or life-threatening condition

Unmet medical need

Available treatments

U.S. Food and Drug Administration. Guidance for Industry: Expedited Programs for Serious Conditions – Drugs and Biologics. https://www.fda.gov/files/drugs/published/Expedited-Programs-for-Serious-Conditions-Drugs-and-Biologics.pdf.
U.S. Food and Drug Administration. Fast Track, Breakthrough Therapy, Accelerated Approval, and Priority Review. https://www.fda.gov/patients/learn-about-drug-and-device-approvals/fast-track-breakthrough-therapy-accelerated-approval-priority-review.

1. Unmet Need and Outcome Certainty Differ for Accelerated Approval Pathway

Traditional Approval	Accelerated Approval
Adequate and well-controlled studies	Adequate and well-controlled studies
As safe and effective **as existing therapies**	Meaningful therapeutic benefit…**over existing therapies**
Clinical benefit (e.g., "**prolongation of life or an established surrogate**")	Surrogate endpoint "**reasonably likely to predict clinical benefit** or an intermediate endpoint other than irreversible morbidity and mortality"

1. FDA Surrogate Endpoint Requirements

Causality	• Is there a compelling case for surrogate being on the single direct causal pathway to disease outcome, so less need for evidence of universality?
Biologic plausibility	• Is the biology of the surrogate so compelling that it adds to the weight of empirical evidence for acceptance?
Specificity/potential for complicating effects	• Other factors affecting disease outcome, including off-target effects of drugs
Proportionality	• To what extent does the magnitude of change in the surrogate explain the disease or the magnitude of change in disease status or burden?
Universality	• To what extent is there evidence across drug mechanisms or across different populations?

U.S. Food and Drug Administration. Surrogate Endpoint Resources for Drug and Biologic Development. https://www.fda.gov/drugs/development-resources/surrogate-endpoint-resources-drug-and-biologic-development

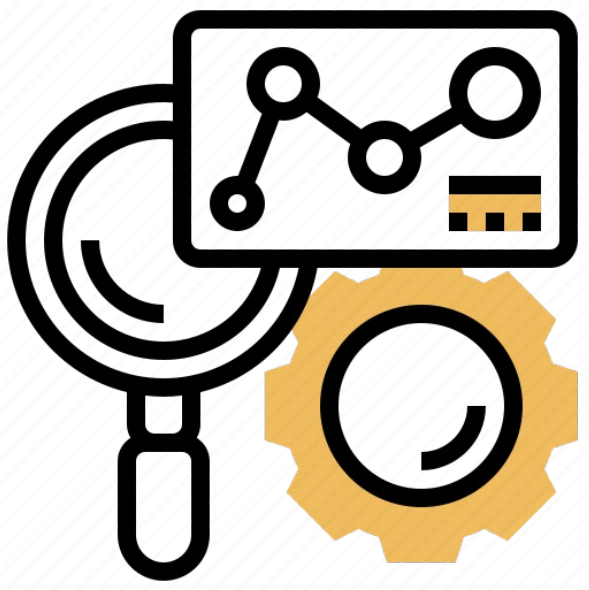
1. Sample Surrogate Endpoints Used in Accelerated Approval

Disease or Use	Surrogate Endpoint
Alzheimer's disease	Reduction in amyloid beta plaques
Chagas disease	Immunoglobulin G antibody negative or decrease in optical density
Chronic myeloid leukemia	Major hematologic response
Diffuse B-cell lymphoma	Durable complete response rate
Duchenne muscular dystrophy	Skeletal muscle dystrophin
Fabry disease	Reduction of GL-3 inclusion in renal capillaries
Methemoglobinemia	Serum methemoglobin
Nonalcoholic steatohepatitis (NASH)	Histopathologic findings or improvement of fibrosis
Pulmonary tuberculosis	Sputum culture conversion to negative
Sickle cell disease	Hemoglobin response rate

U.S. Food and Drug Administration. Table of Surrogate Endpoints That Were the Basis of Drug Approval or Licensure. https://www.fda.gov/drugs/development-resources/table-surrogate-endpoints-were-basis-drug-approval-or-licensure

2. Correlate Surrogate Endpoints with Meaningful Outcomes to Payers

2. Improve Understanding of Surrogate Endpoints and Correlate with Meaningful Outcomes



What	• Understanding of scales norms
Who	• Ability to differentiate disease severity, response, adverse events
How much	• Clinically important differences
When	• Changes can be expected
Why	• **Relationship to clinical or economic endpoints**

2. Accelerated Approval ≠ Payer Coverage. Payer Evidence Needs Differ

Overall Evidence

- More than 1 trial
- Randomized controlled vs. single arm trials
- Long-term follow up to assess durability of response

Surrogate Endpoints

- Clinical context of surrogate endpoints
- Guidance on when change is anticipated
- Correlation of results across subpopulations (e.g., more or less severe disease)
- Validation with clinical outcomes

Clinical Condition

- Improved understanding of disease course and patient impact (especially for rare conditions)
- Information on subpopulations (e.g., genetic subtypes and disease impact)

Economic Implications

- Resource use with worsening disease
- Number Needed to Treat
- Impact on total cost of care
- Budget impact for given plan membership

3. Bridge the Evidence Gaps by Building an Evidence Ecosystem

3. Bridge Gaps in with Evidence Ecosystem Data Networks, Analytics, and Infrastructure

3. Evidence Ecosystem Can Inform Payers

- Correlate surrogate endpoints to meaningful outcome measures
- Trust in surrogate markers
- Generalizability of benefits to sub-populations
- Treatment sequence
- Discontinuation criteria
- Patient Journey

4. Advance Potential Policy and Practice Solutions and Practices to Reduce Financial Uncertainty

4. Potential Policy and Practice Solutions Discussed

Payment Solutions	CMS National Coverage Decisions
	CMS Coverage with Evidence Development
	Require value-based contracts for Accelerated Approval pathway
Streamline Coding	Allow biopharmaceutical companies to concurrently apply for HCPCS code with breakthrough designation
Incentives for Confirmatory Trial Completion	Price at marginal cost until trial completed
	Create a differential rebate for AA products
Communication	Voluntary payer advisory committee to aid surrogate endpoint considerations

Coverage with Evidence Development

- Leverages existing authority
- Informs patient use criteria
- Encourages evidence development

- Potential to pay for ineffective treatments
- Evidence generation may be limited to patient use criteria
- Time and staff resources

Considerations:

- Spillover effect beyond Medicare?
- Would additional legislative authority be needed?
- Evidence development requirements and status would need to be transparent to build trust

Apply Marginal Cost Pricing to Incentivize Confirmatory Trials

- •Incentives for enrollment and study result disclosures
- Applicable to multiple lines of business
- Relative ease of administration

- •Disincentives for innovation for small or rare conditions due to revenue at launch
- •Limited long-term approach

Considerations:

- If marginal cost pricing is accepted, would coverage be mandatory?

Future of Accelerated Approval?

Increasing pressure to address:

1) ‘dangling indications’ and

2) incomplete confirmatory trials

3) product removal

4) FDA reforms?

Increasing pressure to provide:

1) direct access to investigational drugs, without any FDA involvement

2) access to medications with minimal evidence

3) expand approach within oncology

What’s Next?

Next Steps

AMCP PARTNERSHIP FORUM 2022

High-Investment Medications

EXECUTIVE SUMMARY

As novel therapies to address important medical needs are approved, the high costs for these medications — especially cell and gene therapies — can raise sustainability and affordability concerns for employers, payers, and patients. High short-term investments present clinical and financial challenges that are magnified when the long-term health benefits are uncertain, patients switch employers or enroll in different health plans, or complex care coordination is needed. New payment policies and the application of 21st century financial and technical tools can mitigate risk and affordability concerns.

To explore alternative payment models, financial tools, and policy initiatives to improve the predictability, affordability, and accessibility of high-investment treatments and ensure patients get the medications they need at a cost they can afford, AMCP held a multi-stakeholder Partnership Forum in Arlington, VA, April 26 and 27, 2022. Forum participants were asked to 1) identify stakeholder challenges associated with high-investment medications, 2) explore the challenges and opportunities related to financial tools to address predictability, affordability, and accessibility for high-investment medications, and 3) determine the challenges and opportunities of potential policy solutions to improve the predictability, affordability, and accessibility of high-investment treatments.

THEMES THAT EMERGED FROM THE PARTICIPANT DISCUSSION INCLUDED THAT:

- **High-investment medications do not yet raise significant sustainability or affordability stakeholder concerns but are expected to in coming years.** Among stakeholders, state Medicaid plans and employer groups are likely to have the most urgent need to address the predictability, affordability, and accessibility of these medications.

continued on next page

WATCH FOR FOLLOW-UP

This Partnership Forum was a valuable opportunity to evaluate the state of the evolving space of high-investment medications. AMCP's next steps will be to:

- **Publish a proceedings document** describing the findings and recommendations from the Partnership Forum in an upcoming issue of AMCP's *Journal of Managed Care + Specialty Pharmacy (JMCP)* and disseminate it widely to decision makers around the country.
- **Host a webinar** to report these findings and recommendations.
- **Continue to engage stakeholders** on this topic by sharing these findings and recommendations.
- **Create educational materials** providing background on the financial tools that may be utilized in the management of high-investment medications.
- **Explore opportunities** for the private and public sector to permit, test, and encourage new financial tools and policy solutions to meet market needs.

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Payer Perspectives on Expedited Reviews

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IN THIS ISSUE

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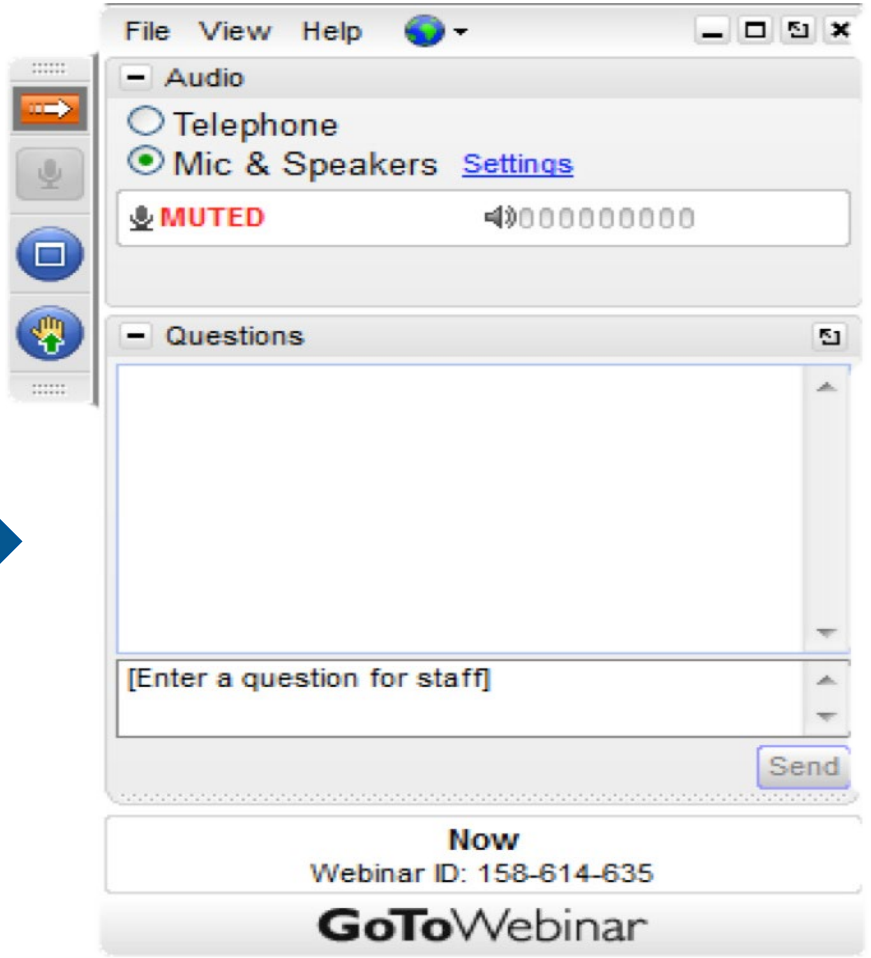
https://www.amcp.org/Resource-Center/meeting-proceedings-findings/addressing-evidence-gaps-expedited-review-process-payer-perspectives

Key forum takeaways

1. Support Speed of Innovation but Balance Needed to Aid Timely Coverage Determinations
2. Clarify Accelerated Approval Criteria
3. Correlate Surrogate Endpoints with Meaningful Outcomes
4. Bridge the Evidence Gaps with Enhanced Evidence Ecosystem
5. Advance Potential Policy and Practice Solutions and Practices to Reduce Financial Uncertainty



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