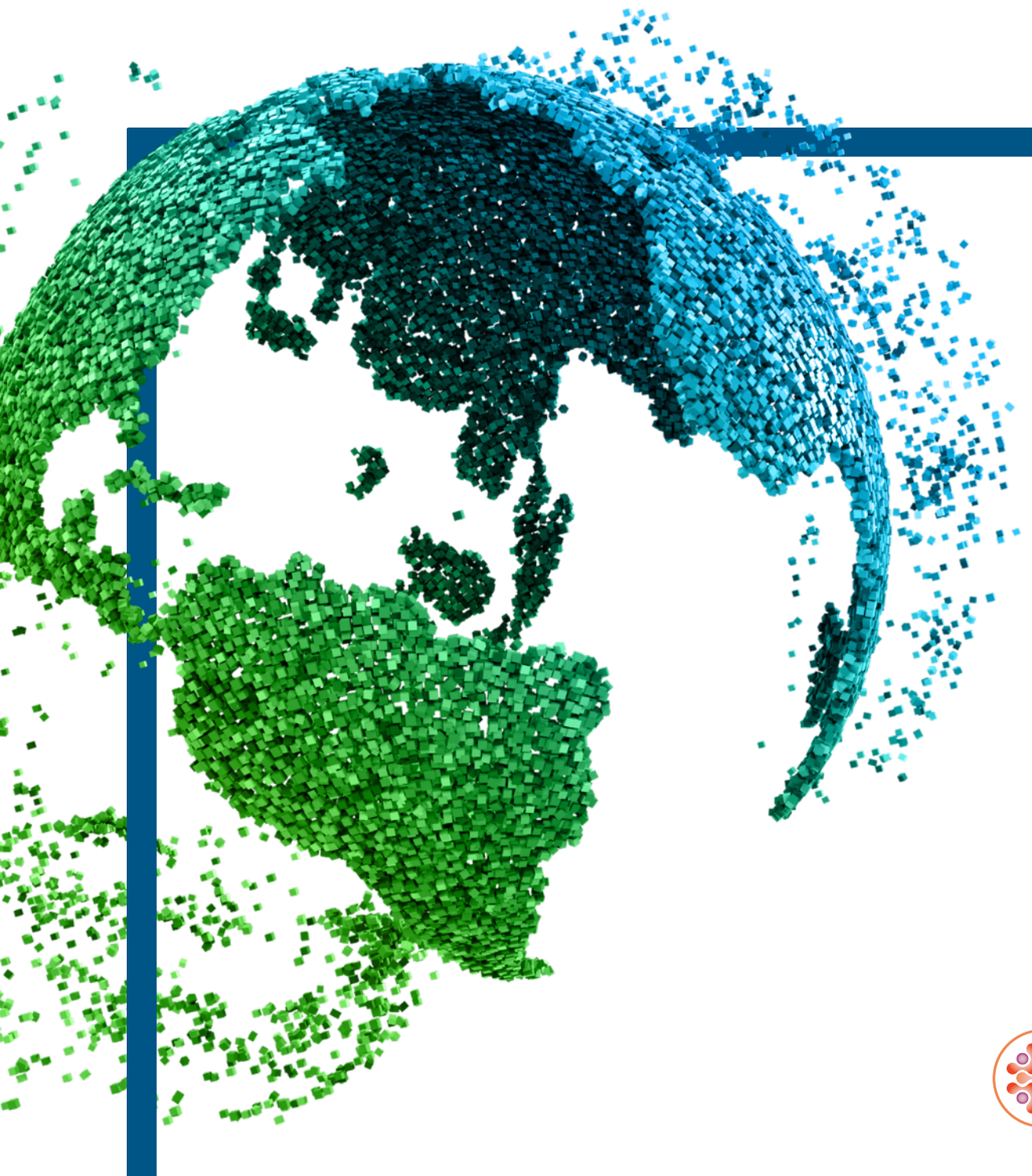


FIRST OF ITS KIND

Economic Impact Landscape
Analysis of regenerative medicine advanced therapy

ARM Foundation *for* Cell & Gene Medicine

IMS Health & Quintiles are now IQVIA™

This analysis includes a review of published academic literature, health technology assessments, and value frameworks related to the global health economic impact of cell and gene therapies. Performed by IQVIA on behalf of the ARM Foundation Economic Impact Working Group, the landscape analysis is the initial step in the Foundation's broader Economic Impact Project, which will ultimately provide a framework to measure and forecast the effect that breakthrough and potentially curative therapies will have on national and global healthcare economies.

ARM Foundation *for* Cell & Gene Medicine

IMS Health & Quintiles are now IQVIA™

Table of Contents

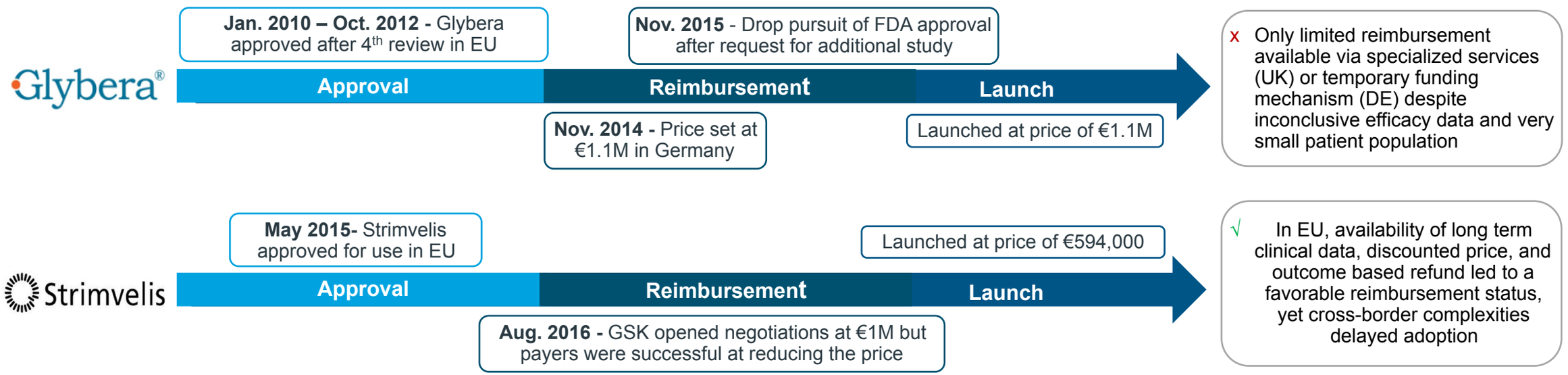
Project Overview

RM/AT therapies face suboptimal consideration of value throughout development and lifecycle management

The reimbursement and market access landscape of regenerative medicine and advanced therapies (RM/ATs) is not well defined

> RM/ATs have struggled to meet requirements for successful HTAs and stakeholders face unique challenges in assessing these therapies

> The unclear reimbursement landscape has led companies to pursue various approaches that largely impact price and access



To reframe the economic argument, RM/AT specific economic model is needed

Project Objective: Build RM/AT specific economic model and being to identify the benefit (cost impact) to the entire healthcare system (e.g. payers, patients, hospitals, etc.) associated with RM/ATs

	1 Regenerative Medicine Landscape Analysis	2 Economic Model Development and Validation	3 Application of Model to Case Studies
Project Approach	• Conduct detailed literature review of existing resources on RM/ATs economic impact • Conduct primary market research with KOLs to refine understanding of current RM/AT economic impact models • Synthesize findings and identify preliminary inputs for RM/AT economic impact model	• Use inputs from Phase 1 to develop initial economic model • Validate economic model with relevant stakeholders (payers, providers, and patients / patient advocates) via primary market research • Review and revise economic model based on PMR and present findings to ARM	• Leverage internal IQVIA databases to collect data for one existing and one pipeline regenerative medicine therapeutic as finalized inputs • Enter data into economic model to calculate overall current/ projected cost-savings associated with selected therapeutics when compared to the current SoC
Key Deliverable	Readout of current landscape of RM/ ATs economic impact models Preliminary inputs for economic model	Refined and robust economic model	Further validation of model through calculation of net economic impact of regenerative medicine therapeutics across two case studies

Executive Summary

Executive Summary

Key Findings

- There is a **need for a more robust framework to demonstrate the value of RM/ATs stakeholders**
- Our research across 52 publications uncovered **additional economic considerations needed for a robust RM/AT framework:**
  - HTA models identified **societal burden during treatment and patient population** size as inputs
  - Academics suggested to include **innovative payment / contracting models, patient / caregiver non-medical and indirect medical costs, expanded time horizon, and mnf costs**
  - Based on SCC expertise, **lifetime patient / caregiver non-medical costs, system-wide impact, and patient-centered endpoints should also be included**

The SCC is now positioned to translate findings and insights from RM/AT economic framework landscape work into a white paper in collaboration with ARM team

Additional considerations from research:

1. *Lack of RM/AT-specific evidence base*
2. *Need for real world evidence platform*

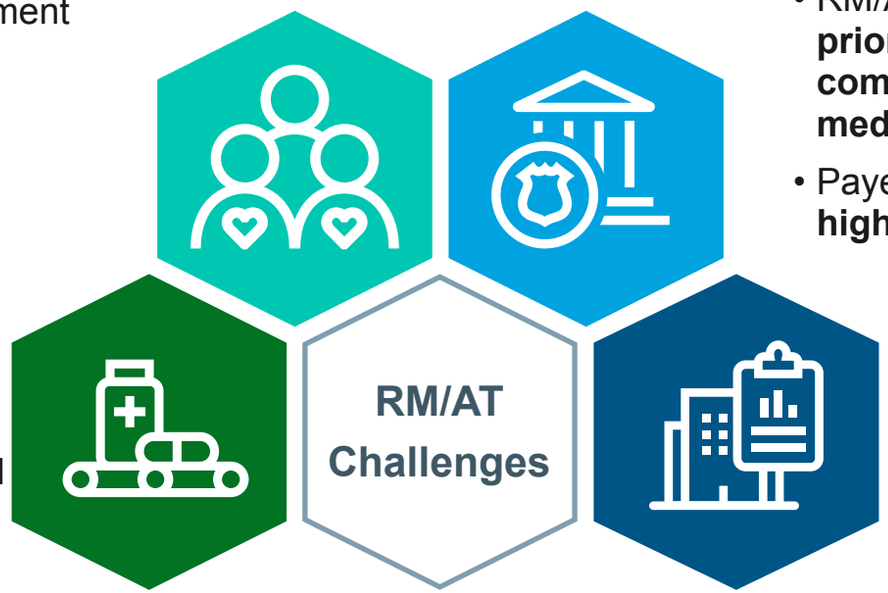
RM/AT therapies are facing specific challenges to demonstrate value to stakeholders

Patient / Caregiver

- Patients face **high access barriers** due to **enormous co-pays** for RM/ATs and **small number of accredited centers** for treatment

Manufacturer

- Difficult to **demonstrate clinical superiority** as **small** target **patient populations** make it **difficult** and **expensive** to conduct **RCT**, **head-to-head** studies
- Difficult to **demonstrate short-term cost-effectiveness vs. non-curative comparators**



HTA / Payers

- Payers **skeptical** of **long-term clinical efficacy** due to **lack of statistically significant, head-to-head trials**
- RM/ATs often not cost-effective as payers typically **prioritize short-term, direct impact**; they **do not completely capture long-term, indirect / non-medical benefits** of RM/ATs
- Payer **3-5 year budgetary cycles cannot handle high upfront cost** of RM/ATs

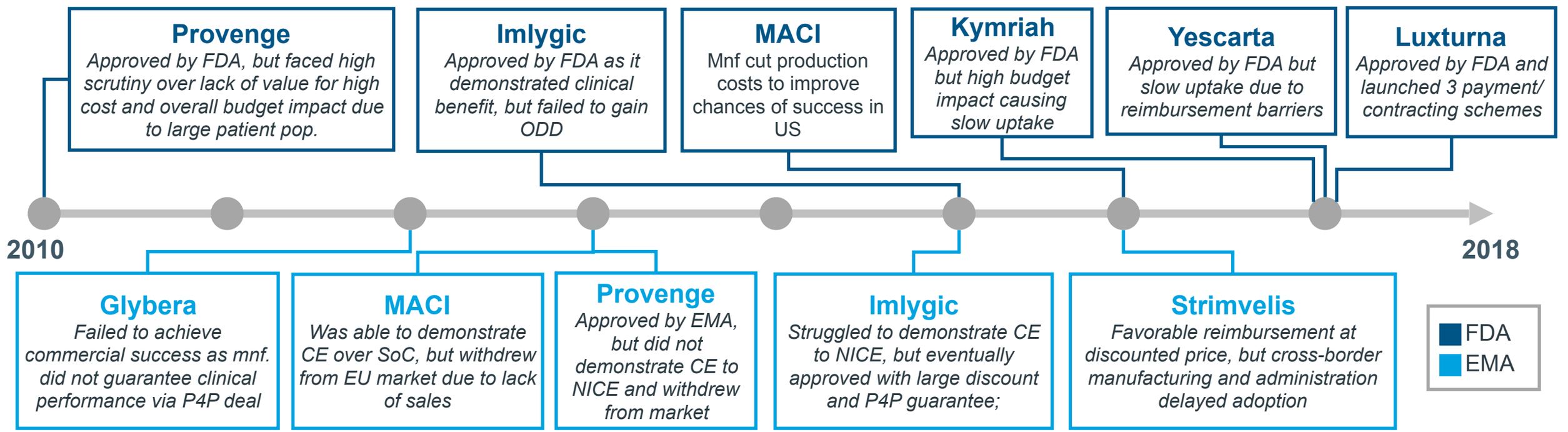
Providers / Hospitals

- **Lack of uniform assessment** of RM/ATs causes hospitals / providers to **struggle to obtain reimbursement**
- Hospitals **assume high financial risk** of RM/ATs due to **prolonged reimbursement timelines** caused by payers struggling to absorb budget impact of RM/ATs

RM/AT therapies have been unable to meet market expectations due to challenges in value determination

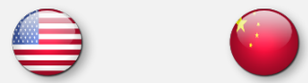
Common challenges across RM/AT commercial success considerations include

- Stakeholder skepticism of high upfront costs for RM/AT therapies with uncertain economic value
- Unclear models and inputs for economic assessments by regulators and payers
- Suboptimal patient access and reimbursement schemes compared to traditional therapies
- Unclear long-term therapy benefit of potentially curative therapies



Most countries have leveraged traditional archetypes and frameworks that are not suitable for RM/ATs

Payer Archetypes

	Pharmacoeconomic	Therapeutic Referencing	Willingness-to-pay
Definition of value:	***Value is considered in the context of utility that a treatment brings to stakeholders and/or the ability to implement that treatment with constrained resources***	***Value is considered as the therapeutic benefit that a product brings over the standard of care and/or other therapeutic alternatives***	***Value is influenced by the complex dynamics of competition on both the supply and demand side of the payer equation, reflecting both willingness and ability to pay***
Countries:			
Key test of value:	• *Cost-effectiveness (usually by ICER)*	• *Clinical benefit relative to comparator(s)*	• *Clinical and non-clinical benefit; unmet need* • *Cost / budget impact*
Issues for RM/ATs:	• ***Difficult to meet current QALY thresholds*** *due to small patient populations*	• *Challenging to compare* ***clinical superiority*** *and* ***cost savings against non-curative comparator***	• *Difficult to* ***justify non-clinical benefit to payers focused on clinical value*** • ***Fragmented systems make it difficult to pay upfront***

With regulatory requirements varying across geographies for RM/AT therapies…

	Country	Clinical Evidence	Comparative Clinical Evidence	Cost Effectiveness Analysis	Budget Impact Assessment	Company Costing Information
Pharmaco-economic	United Kingdom				*Budget impact considered at the CCG level	
	Canada					
	Brazil					
Therapeutic Referencing	Germany					
	France			*For products with ASMR rating I – III only		
	Italy					
	Spain					
	Japan			*Starting in Oct 2016, CEA required for certain drug candidates		*Only if “cost-plus” pricing method is used
Willingness-to-pay	United States					
	China	*No dossier submission required				

Required evidence

Optional / required only circumstantially

Not required

…there is substantial variation on which HTA bodies manufacturer's pursue, and on HTA outcomes

	Regulatory / HTA Agency				
Therapy	NICE	IQWiG / GBA	AIFA	HAS	ICER
Glybera					
Strimvelis					
Imylgic					
Kymriah					
Yescarta					
Luxturna					
Provenge					

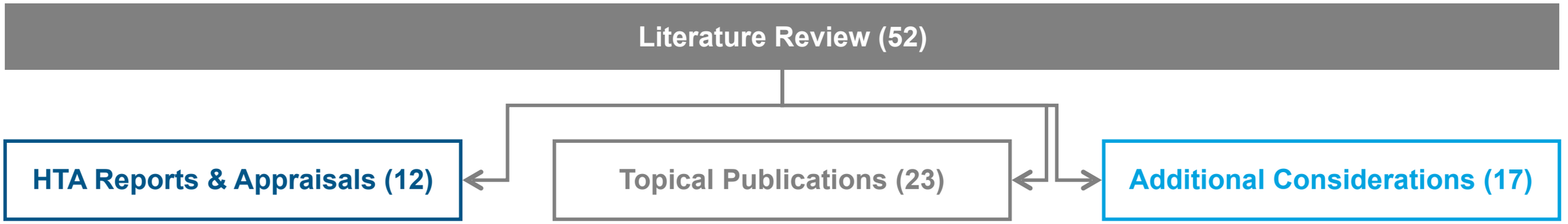
Approved / Favorable Assessment

Approved / Favorable Assessment with Exceptions

Not approved / Unfavorable Assessment

Not assessed by HTA or currently under review

The SCC team conducted a literature review to identify existing and suggested economic considerations for RM/ATs



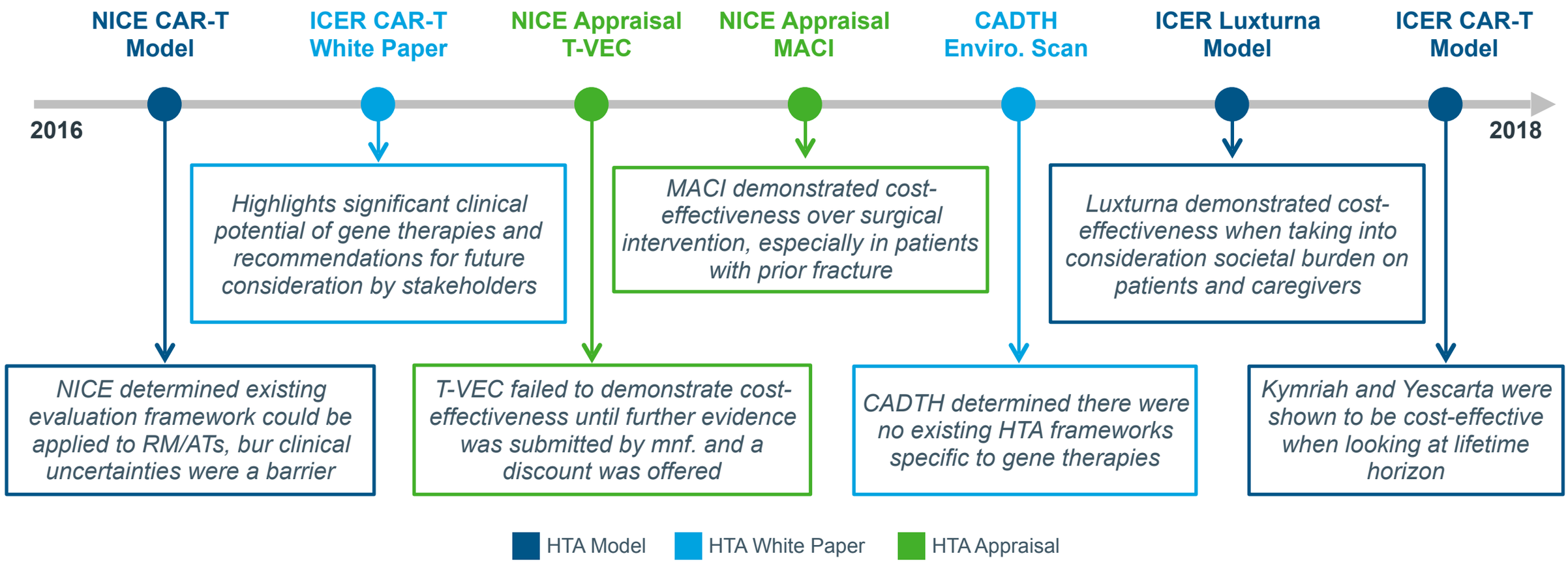
HTA reports and appraisals to understand economic considerations in prior evaluations of existing RM/ATs by HTAs

Team identified literature that provided broader perspective on economics related to RM/ATs

Academic insights on additional economic considerations that should be incorporated into existing valuation approach

SCC team utilized findings from literature review to generate additional economic considerations to more comprehensively capture value of RM/ATs

Although there is no specific valuation framework for RM/ATs, major agencies have conducted initial studies into their value



HTA Reports & Appraisals

NICE and ICER cost-effectiveness models begin to demonstrate importance of expanding economic inputs taken into consideration during evaluation of RM/ATs

Emerging HTA models begin to demonstrate value by including a more comprehensive set of metrics on RM/AT economic impacts

HTA Models and Economic Inputs				
Framework Inputs	**Pivotal Stakeholders**	**NICE CAR-T (2016)**	**ICER Luxturna (2018)**	**ICER CAR-T (2018)**
Cost of acquisition				
Healthcare utilization costs				
Population size				
Administration and monitoring				
Health-related QoL				
Lifetime horizon				
Hospital markup				
Innovative payment models / contracting				
Loss of productivity (during treatment)				
Nursing home care				
Caregiver burden				
Non-medical costs (during treatment)				

Patient and caregiver inputs are less commonly considered than other considerations

Providers / hospitals HTA / Payers Patient / caregiver Manufacturer

HTA Reports & Appraisals

HTA white papers highlight additional considerations due to the absence of a RM/AT-specific HTA framework

ICER Gene Therapy White Paper

ICER provided recommendations for mnfs. to overcome likely reimbursement and access hurdles

- Offset **high budget impact** by presenting **alternative payment strategies**, such as pay for performance or amortization, to payers
- Robust **registry studies** to **reduce uncertainty** where RCTs are not possible
- Present **evidence** demonstrating how overall **cost of therapy** is **linked to costs of development**

ICER highlighted the need to incorporate novel elements into manufacturers' strategy to clearly demonstrate value of gene therapies to payers

CADTH Environmental Scan: Gene Therapy*

CADTH aimed to identify existing frameworks or HTA approaches to evaluating gene therapies

- **NICE**, **GBA**, and **SBU** believe that **existing HTA framework is sufficient** to assess gene therapies
- **AHTA** is planning to **develop separate guidelines** for evaluation of gene therapies

From its current research, CADTH concluded that gene therapies often fail to meet evidence and pricing requirements when limited comparator data, long-term data, and health budgets are restricted

*CADTH paper still in progress, findings based on current draft
SBU: Swedish HTA, **AHTA:** Australian HTA

NICE appraisals for both T-VEC and MACI validate additional inputs taken into consideration for economic value assessment

NICE Appraisal T-VEC (2016)

- NICE agreed with the company's inputs to determine cost-effectiveness:

Cost-effectiveness inputs
Treatment costs
Administration costs
Routine care costs
On progression costs
BSC/ palliative care costs
Terminal care costs
Adverse events

Additional economic considerations including **reduced anxiety for patients with visible skin tumors**, and **caregiver-related cost** were <u>not included</u> in the cost-effectiveness model but were brought up during discussions

- NICE determined T-VEC clinically and cost-effective only after additional manufacturer submitted evidence, and implementation of a **patient access scheme** (PAS), **further discounting**, and a prior EMA agreement for additional **post-marketing studies** to address long-term safety

NICE Appraisal of MACI (2017)

- NICE used MACI's budget impact analysis and ChondroCelect's cost-effectiveness analysis for the appraisal:

Cost-effectiveness inputs
Development costs*
Microfracture
First TKR (PKR or TKR)
Further TKR
Outpatient visit
Rehabilitation
HrQoL and Adverse events

Health-related quality of life improvements and adverse event disutility scores were considered, but demonstrated either no difference than standard of care, or did not demonstrate sufficient data

- NICE determined cost-effectiveness for roughly half of the eligible patient population but noted that QALY gain estimates for the full eligible population would likely be greater than £20,000.

PSS=personal social services; TKR= total knee replacement; PKR = partial knee replacement
*Development costs include courier services and development of cell culture, cell harvesting procedures, ACI kit, staff time, and transporting the cells to and from the laboratory

A detailed review of current academic literature further identified new economic inputs that demonstrate value of RM/ATs (1/3)

Framework Comparison		Bubela et al. (2013)	Jorgensen et al. (2015)	McCabe et al. (2016)	Corbett et al. (2016)	Driscoll et al. (2017)	Mihos et al. (2017)	Hampson et al. (2017)
General	*Need novel valuation framework*	■			■			■
Inputs	*Innovative payment models / contracting*	■	■	■	■			■
	Real world evidence		■			■	■	■
	Population size	■	■	■		■	■	■
	Patient burden (indirect medical and non-medical costs)	■					■	■
	Additional value for curative nature	■						
	Development and Operational costs	■		■				
	Lifetime horizon		■					

■ Suggested by authors ■ Not suggested by authors

Selected literature was prioritized based on content relevance; a comprehensive list of literature sources reviewed can be found in the supplemental capture sheet

A detailed review of current academic literature further identified new economic inputs that demonstrate value of RM/ATs (2/3)

Framework Comparison		Morrow et al. (2017)	Hanna et al. (2016)	Touchot et al. (2016)	Jorgensen et al. (2017)	Caplan et al. (2016)	Spoors et al. (2017	Daniel et al. (2017)
General	*Need novel valuation framework*	■	■	■		■	■	■
Inputs	*Innovative payment models / contracting*			■	■	■	■	■
	Real world evidence		■	■				■
	Population size							
	Patient burden (indirect medical and non-medical costs)							■
	Additional value for curative nature					■		
	Development and Operational costs	■						
	Lifetime horizon			■				

■ Suggested by authors ■ Not suggested by authors

Selected literature was prioritized based on content relevance; a comprehensive list of literature sources reviewed can be found in the supplemental capture sheet

Additional Considerations

A detailed review of current academic literature further identified new economic inputs that demonstrate value of RM/ATs (3/3)

Framework Comparison		Faulkner et al. (2018)	Gopalan et al. (2016)	Abou-El-Enein et al. (2017)	Senior (2017)	Poschen et al. (2017)	Aggregate*
General	*Need novel valuation framework*			■		■	58%
Inputs	*Innovative payment models / contracting*	■					58%
	Real world evidence		■				42%
	Population size						32%
	Patient burden (indirect medical and non-medical costs)	■		■			32%
	Additional value for curative nature	■	■		■	■	32%
	Development and Operational costs		■				21%
	Lifetime horizon	■					16%

■ Suggested by authors ■ Not suggested by authors

Selected literature was prioritized based on content relevance; a comprehensive list of literature sources reviewed can be found in the supplemental capture sheet
**Aggregate score is a composite score of suggestions across all 19 research reports*

Additional Considerations

Innovative payment models have been critical to help overcome HTA / payer uncertainties of high upfront costs

Payers skeptical of long-term efficacy of RM/ATs

- **Kymriah** — P4P contract with CMS
- **Imlygic** — P4P contract with NICE
- **Strimvelis** — P4P contract with AIFA
- **Luxturna** — P4P contract with Harvard Pilgrim and Express Scripts

Manufacturers are guaranteeing clinical efficacy of their products through outcomes-based contracting agreements

Payers unable to absorb large budget impact of high-cost RM/ATs

- **Luxturna** — Annuity-based contracting model with CMS, with payments tied to outcomes

Spark is reducing budget impact by allowing CMS to spread payment over several years

Although innovative contracting and payment models reduce payer skepticism and budget impact, issues remain:

- *Lack of infrastructure to track patients and link clinical outcomes to claims*
- *Innovative payment models reduce immediate budget impact and/or spread risk but do not improve long-term sustainability*

Real world evidence generation will play a key role in reducing stakeholder uncertainty over long-term clinical / safety of RM/ATs

Historical Challenges

- Amgen did not provide sufficient clinical comparison evidence to differentiate Imlygic from current SoC comparator
- Glybera did not accurately establish natural progression of disease and chose an incorrect primary endpoint
- Provenge demonstrated significant benefit for OS but not PFS; Dendreon did not identify subpopulations where benefit may be greater to improve overall value story

Historical Successes

- Kymriah leveraged RWE approaches to identify natural progression of disease and burden of illness in patients
- Kymriah compensated for a single-arm pivotal trial by leveraging RWE to highlight significant benefit to patients

Application of RWE Strategies to RM/ATs

Retrospective data analyses

- Define historical treatment landscape, patient journey, burden, and generate data for SOC / comparators
- RWE will characterize how product will address disease burden and fulfill gaps in treatment, differentiating it from SoC

Prospective observational studies (cohort)

- Track safety and effectiveness before, during, and after treatment of patients
- Identify potential subpopulation benefits to differentiate pdt
- Demonstrate durability of effect and safety after launch

Registry Studies

- Continue to demonstrate real-world durability of effect / safety
- Capture outcomes to support innovative payment models / contracting agreements
- Identify potential subpopulations and follow-on indications

Additional Considerations

Internal SCC expertise identified additional economic inputs and considerations to maximize RM/AT value to stakeholders

Additional economic inputs

System-wide costs

- Looking at loss of economic productivity due to chronic illness from a broader perspective, such as the government

Lifetime non-medical costs

- Lifetime transportation costs, loss of earnings, loss of education

Patient-centered Endpoints

- Premiums for new patient-centered endpoints into clinical value consideration

Additional considerations for manufacturers

Delayed reimbursement codes

- Lack of reimbursement codes increases financial risk for hospitals / providers, with some unable to bear high costs of RM/ATs during interim before reimbursement is issued

Stakeholder Engagement

- Early engagement with payers to align on most meaningful clinical endpoints, real world evidence, pricing comparators to create most compelling value story

Inclusion of these additional economic considerations will allow HTAs / payers to better assess the net economic benefits of RM/ATs

Inputs from HTA Models*

Population size
Small patient populations lead to higher prices to offset development costs

Lifetime horizon
Shifting focus from traditional short-term budgetary cycles to assess long-term cost-effectiveness

Patient indirect costs (during treatment)
Costs associated with loss of productivity

Patient & caregiver non-medical costs (during treatment)
Costs associated with transport, home care, counseling, etc.

Inputs from Literature Review

Age of onset
Younger patients will gain significantly larger value from curative treatments across all inputs

Additional value for curative nature
Modifying CE thresholds or budget impact considerations for curative therapies

Patient & caregiver indirect medical costs (lifetime)
Costs associated with loss of productivity

Real world evidence
Valuing subpopulation data, indirect comparisons vs. SoC, follow-up data, etc. from RWE

Innovative payment models / contracting**
Reducing payer uncertainty surrounding high cost / budget impact

Inputs from SCC

Societal economic impact
Costs to employers, government, etc. due to loss of productivity and chronic care

Patient centered endpoints
Ascribing greater value to PCEs to better understand non-clinical / clinical benefit of RM/ATs for patients

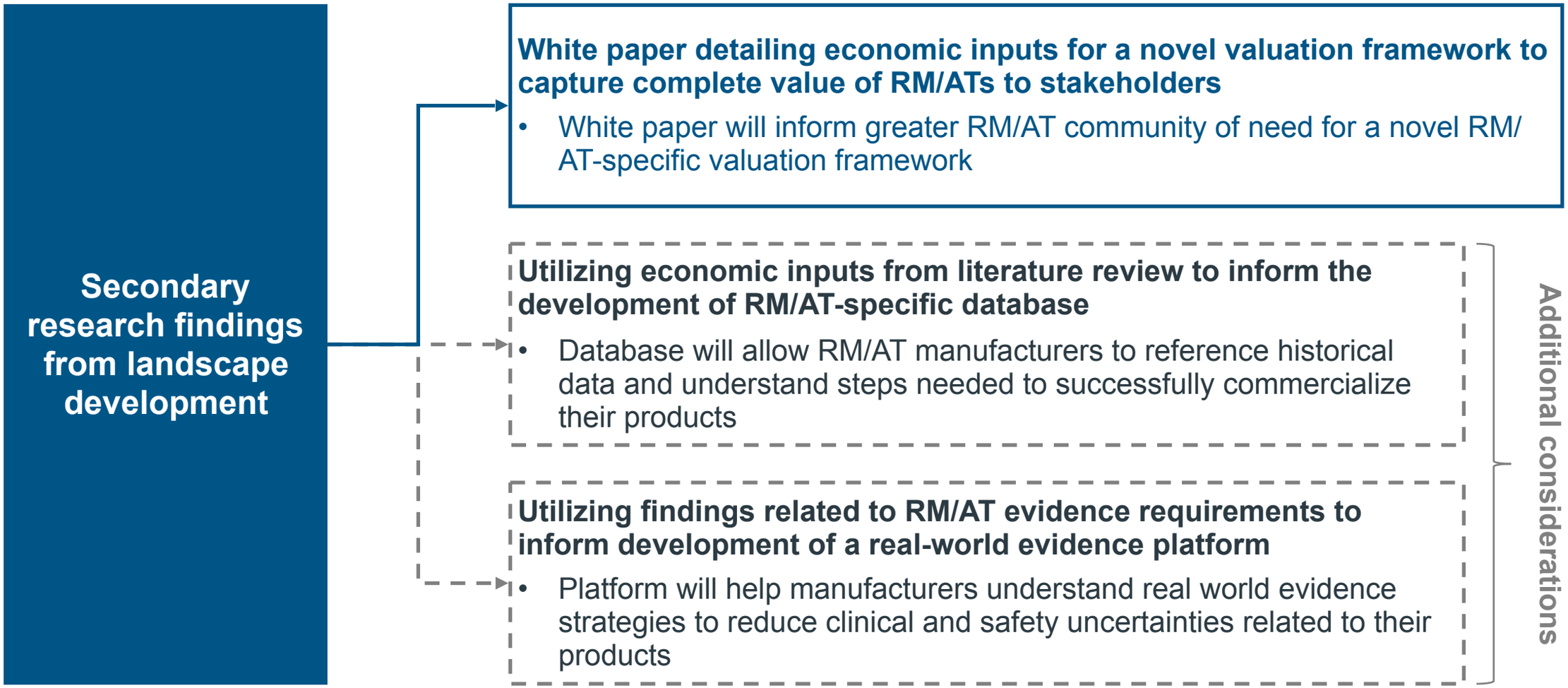
Patient & caregiver non-medical costs (lifetime)
Costs associated with transport, home care, counseling, etc.

Although these inputs will help uncover additional value of RM/ATs, they will require different levels of resource investment and involve different stakeholders across health systems

**These inputs are derived from assessments conducted by HTAs, however they are not currently included in most HTA / payer approaches*
***Will not impact value of overall product, but will reduce budget impact and improve market access*

Next Steps

Upon completion of secondary research the SCC team is positioned to translate findings into a white paper

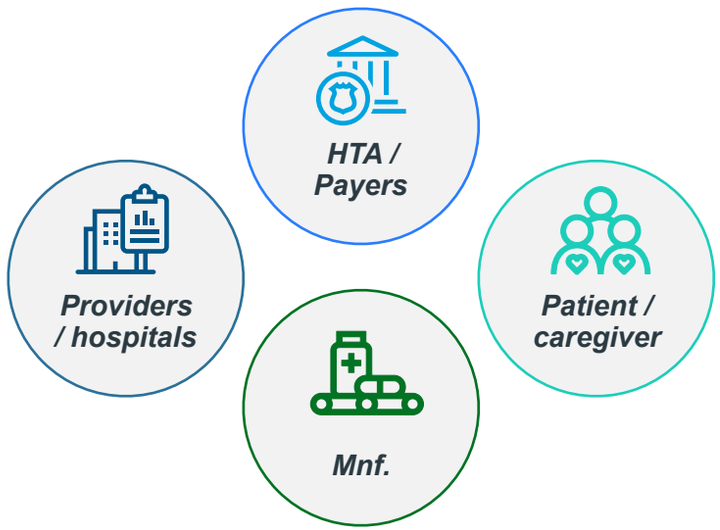


The whitepaper will give a holistic view of the RM/AT landscape, and will culminate in recommendations for a new framework

IQVIA-ARM RM/AT Whitepaper

- Executive summary
- Understanding of the cell and gene therapy
  - Current and future market
- Challenges and considerations for RM/AT value
  - Key gaps in RM/AT economic considerations
  - Recommendations for new inputs
  - Preliminary thinking around new economic model
- Implementation of new framework
  - Case study: value assessment of marketed RM/AT
  - Case study: value consideration of pipeline RM/AT
- Additional Considerations
- Conclusions

The whitepaper will introduce new economic considerations that should be taken into account by different stakeholders for value determination



Whitepaper

Prioritization of recommended inputs for RM/AT framework will take into account the variation in perceived product value

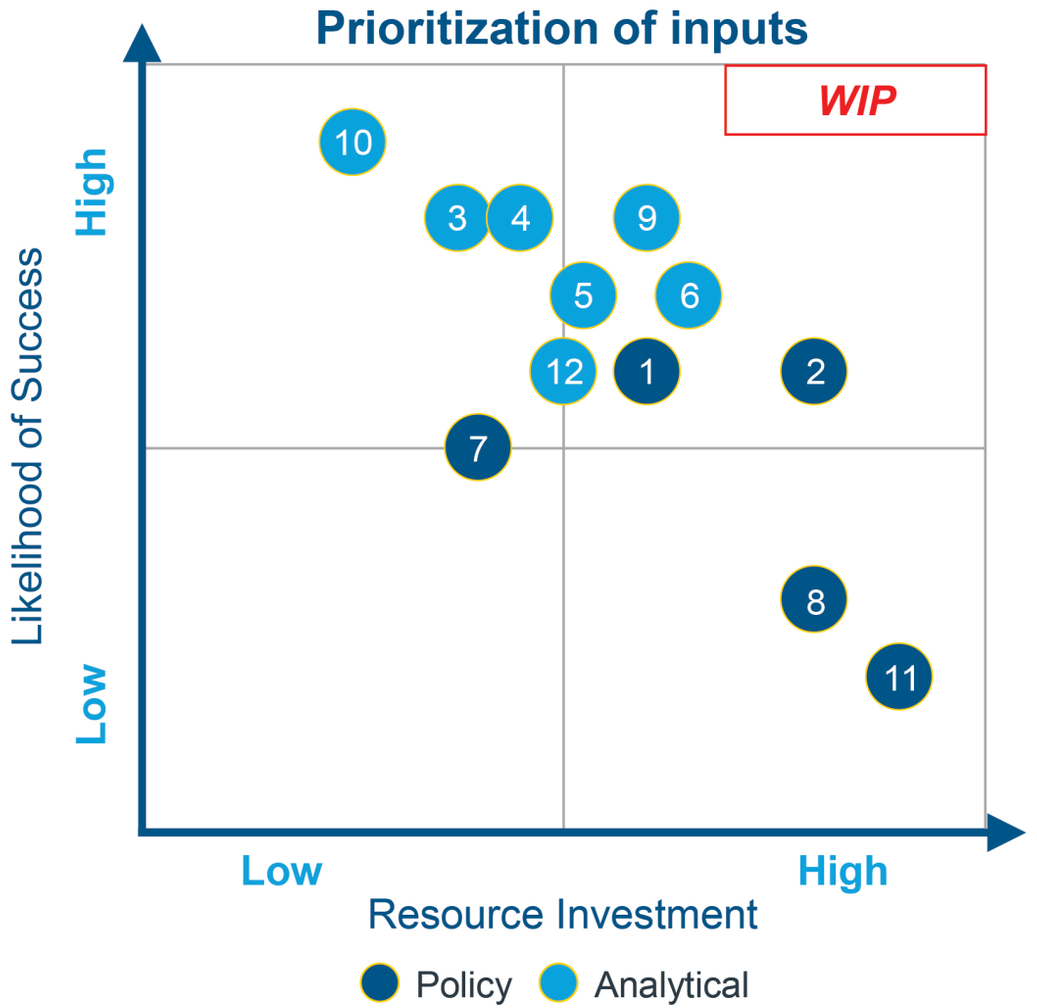
Factors Considered	Formal HTA / P&R					Value Frameworks						
	NICE	G-BA	HAS	CIPM	AIFA	ORPH-VAL	ICER-ODA	ICER	ASCO	ESMO	NCCN	MSKCC
Therapeutic benefit	✓	✓	✓	~	✓	✓	✓	✓	✓	✓	✓	✓
Patient benefit	✓	✓	✓	~	✓	✓	✓	✓	✓	✓	✓	✓
Cost effectiveness	✓	~	~	~	~	✓	✓	✓	~	~	~	~
Budget impact	✓	~	✓	~	✓	✓	✓	✓	~	~	~	~
Innovative characteristics	~	~	✓	~	~	~	✓	~	~	~	~	✓
Availability of therapeutic alternatives	✓	~	✓	~	~	✓	✓	✓	~	~	✓	~
Equity considerations	✓	~	~	~	~	✓	~	~	~	~	~	~
Public health impact/ Unmet need	✓	✓	✓	~	~	✓	✓	✓	~	~	~	✓

✓ **Greater ease of implementation** ~ **Lesser ease of implementation**

ODA= Orphan Drug Assessment; ORPH-VAL = European Working Group for Value Assessment and Funding Processes in Rare Diseases

Whitepaper

The white paper will further explore strategies and implications of different approaches for manufacturers



Implications for White Paper

- Highlight how curative nature of RM/ATs presents a unique challenge to approaching these inputs
- Explore strategies to bring inputs into stakeholder consideration, using historical analogues facing similar challenges
- Identify partners to engage in order to improve likelihood of success
- Utilize tradeoff between resource investment and likelihood of success to prioritize inputs RM/AT manufacturers should target

1. Population size **2.** Lifetime horizon **3.** Patient indirect costs **4.** Patient non-medical costs **5.** Caregiver indirect costs **6.** Caregiver non-medical costs **7.** Age of onset **8.** Additional value for curative nature **9.** Real world evidence **10.** Innovative payment models / contracting **11.** Societal economic impact **12.** Patient centered endpoints

Stakeholders will need to engage in various activities to improve uptake of a novel RM/AT valuation framework

Patient / Caregiver

- Patient advocacy groups will need to lobby payers and regulatory oversight agencies to incorporate patient and caregiver burden into RM/AT valuation process

Manufacturer

- Need to invest in real world evidence generation strategies to strengthen clinical / safety data
- Develop mechanisms to utilize innovative payment models and contracting strategies
- Generate compelling value story that demonstrates development and operational risks and costs assumed by mnf

HTA / Payers

- Pilot a uniform, novel valuation framework that takes into consideration RM/AT-specific economic considerations
- Develop data infrastructure to support innovative payment models and contracting strategies
- Initiate early dialogue with mnfs to shape clinical development of RM/ATs

Providers / Hospitals

- Engage public and private payers to create timely reimbursement plans for RM/ATs
- Work with mnfs to generate real world evidence to strengthen argument for RM/ATs

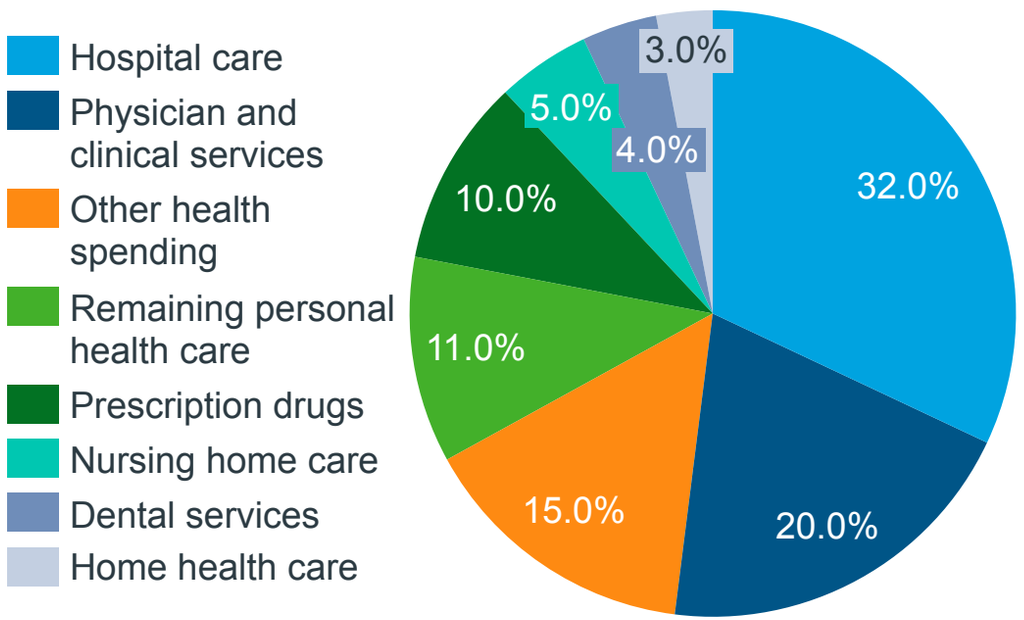
Detailed Findings

Emerging value considerations

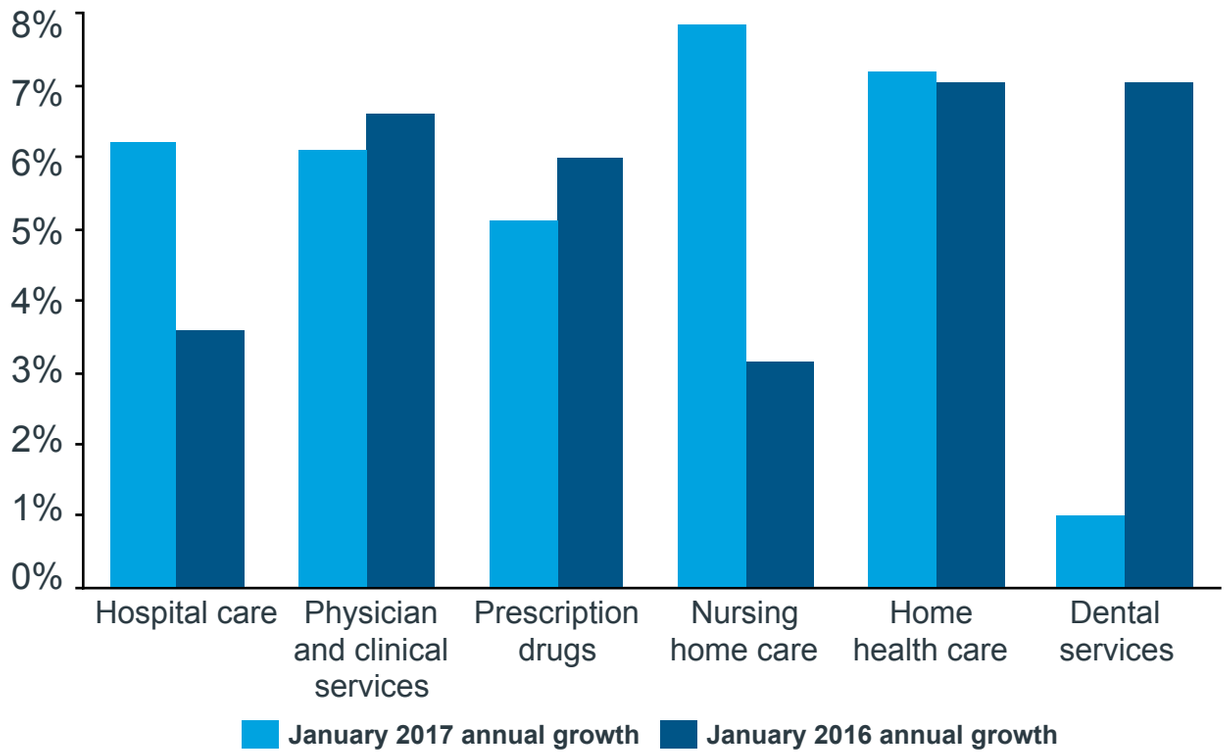
As healthcare spending spans well beyond prescription drug costs, it will be important to understand impact across categories

U.S. Example

U.S. Health Spending by Category (as of January 2017)



Health Spending Year-over-Year Growth for Selected Categories, January 2017 vs. January 2016



Source: Altarum monthly national health spending estimates; Center for Sustainable Health spending, Altarum Institute Spending Brief #17-03, January 2017 data

Major existing models have started to take a more holistic approach in assessing value, and have overlap in their economic inputs

Framework Comparison		NICE CAR-T (2016)	ICER CAR-T (2018)	ICER Luxturna (2018)
Inputs	*Cost of acquisition*	✓	✓	✓
	Hospital markup	✗	✓	✓
	Population size	✓	✓	✓
	Administration and monitoring	✓	✓	✓
	Health-related QoL	✓	✓	✓
	Healthcare utilization costs	✓	✓	✓
	Innovative payment models / contracting	✓	✓	✗
	Caregiver burden	✗	✗	✓
	Nursing home care	✗	✗	✓
	Loss of productivity (during treatment)	✗	✓	✓
Outputs	*Cost vs. benefit*	✓	✓	✓
	HTA outcome guidance	✓	✓	✓
	Recommended price	✗	✓	✓
Approach	*Adjustable weighting*	✓	✓	✓
	Complex, customized formula	✓	✓	✓

Using hypothetical CAR-Ts, NICE developed the first model to determine if their valuation framework was still valid for RM/ATs

Approach

- **NICE developed a model to understand how hypothetical CAR-Ts would perform with their typical CE framework**
- **Created two hypothetical TPPs:**
  - CAR-T as a bridge to HSCT treatment (~350k GBP, 7.5 QALY)
  - CAR-T is used with curative intent (~500k GBP, 10 QALY)
- **Tested outcomes under three hypothetical evidence sets:**
  - 60-80 patients with 10 month follow-up
  - 60-80 patients with 5 year follow-up
  - 120-140 patients with 5 year follow-up

Economic Considerations

- The model took into account:
  - **HSCT costs**
  - **Adverse events costs**
  - **Treatment administration and monitoring costs**
  - **Patient follow-up costs** (e.g. ongoing care and rehabilitation)
  - **Short-term HRQoL** (defined by relapse or remission)
  - **Long-term HRQoL** (defined by development of comorbidities)

Conclusions

- For the curative intent base case with minimum evidence set, assessments were borderline or favorable only when either given a **discount of 10% with lifetime leasing**, **reducing cost to same price as bridging to HSCT** (~350k GBP), or a **combination** of these strategies
  - Increased maturity of evidence had a significant impact by reducing uncertainty, and may facilitate traditional payments strategies
- **NICE conclusions: (1)** NICE appraisal methods are still applicable to CGTs, **(2)** quantifying and presenting clinical outcomes and decision uncertainty is a key factor in the assessment outcome, **(3)** Where evidence is immature but there is potential for substantial patient benefits, innovative payment methodologies will need to be developed to reduce budget impact and share risk

NICE developed a model to investigate the cost-effectiveness of ACI treatments compared to microfracture

Approach

- NICE developed a Markov model to understand how **autologous chondrocyte transplantation (e.g. MACI)** compared to **microfracture** (surgical alternative)
- Utilized two cases for analysis:
  - **Base case:** patient starting age of 33, lifetime horizon, procedure conducted as day case, and based on existing clinical evidence
  - **Sensitivity analysis:** patient starting age of 45 (increased likelihood of knee replacements), with varied time horizon, and based on potentially improved clinical evidence for ACIs

Economic Considerations

- The model took into account:
  - **Cost of procedure / treatment**
  - **Cost of knee replacement**
  - **Utility** (QoL based on patient-reported surveys of patient health)
  - **Mortality**

Conclusions

- For the **base case**, the models determined that there was a **14k GBP/QALY** gained through MACI vs. microfracture
- In patients who have **previously had knee repair**, the assessment determined **22k GBP/QALY** gained vs. microfracture
- In patients who have **not had previous knee repair surgery**, the assessment determined **8k GBP/QALY** gained vs. microfracture
- **NICE recommended use of MACI**, but limited use to patients (1) who have not had previous knee repair (2) have minimal osteoarthritic damage to the knee (3) articular cartilage defects over 2 cm^3

ICER developed a model to understand the cost-benefit profile of two approved CAR-Ts against the SoC in the US

Approach

- Created a model to determine **CE of Kymriah and Yescarta vs. SoC** (clofarabine and chemotherapy)
- Utilized a two part model consisting of a short-term decision tree and long-term patient survival model
- **Patient survival**, **quality-adjusted survival**, and **health care costs** from **payer perspective** were estimated across the lifetime horizon
- **Base case took only the payer perspective** (e.g. direct medical costs), but productivity loss was considered in a scenario analysis

Economic Considerations

- Economic inputs considered by the model:
  - **Treatment acquisition costs**
  - **Hospital mark-up costs**
  - **Healthcare utilization costs** (e.g. administration/monitoring)
  - **Adverse event costs**
  - **Lost productivity** during inpatient and administered treatments

Conclusions

- **Base case:** assuming outcomes-based contracting, the CE of each therapy fell below the commonly cited thresholds of $50-150k/QALY
- CAR-Ts were not CE when looking at a short time horizon but with a **longer time horizon** (7 years for Kymriah, 24 years for Yescarta), both fell below the $150k/QALY threshold
- Kymriah would have **acceptable budget impact** if it achieves $50-150k/QALY; Yescarta would do the same if it meets $50k/QALY threshold
- Societal case, considering loss of productivity during treatment, did not improve CE Ratio

ICER developed a model demonstrating significance of including indirect costs when evaluating cost effectiveness of Luxturna

Approach

- Created a model to determine **CE of Luxturna vs. SoC** (physician visits and supportive care)
- Utilized a Markov model with a population mirroring Luxturna's trial population
- Investigated two scenarios: (1) **base case** was the US payer perspective, which only includes direct medical costs and (2) **modified societal perspective** included direct and indirect costs
- Due to lack of QoL data, authors had to utilize outdated data from studies of other retinal disease populations, potentially biasing the study results

Economic Considerations

- **Cost of drug and surgery**
- **Adverse events**
- **Direct cost of medical care**
- **Direct cost of ophthalmic-related depression**
- **Direct cost of ophthalmic-related trauma**
- **Indirect cost of education**
- **Indirect costs of productivity loss**
- **Direct non-medical costs for caregivers, transportation, and nursing home care**

Conclusions

- Authors concluded that in the **base case,** due to the **high cost** of the Luxturna, it is **not cost-effective** compared to SoC
- Taking the **modified societal perspective**, however, authors concluded that Luxturna is **cost-effective for younger populations** when taking into consideration indirect costs
- Study suggested that in order to **achieve a $100k/QALY** threshold from the **base case**, Spark would need to reduce cost from $850k/patient to **$153k** for patients (**15 y.o.**) and **$348k** for patients (**3 y.o.**)
- Utilizing the **modified societal perspective**, Spark would need to reduce cost to **$363k** for patients (**15 y.o.**) and **$756k** for patients (**3 y.o.**)

HTAs released white papers to explore approaches towards RM/ATs and their associated challenges

ICER Gene Therapy White Paper

Key challenges

- **Small patient population** and **serious** / progressive **symptoms** of patients raise **ethical** and **financial barriers** to **RCTs** and **generating robust clinical evidence** for decision-makers
- It is **challenging** to assess the **value** of potential **"cures"** as **limited data** make it **difficult** to **guarantee long-term efficacy / safety**
- If **curative** effect is assumed, **traditional QALY** valuation may justify **immense prices**, raising **affordability issues** under existing **payment models**

Mechanisms to address affordability

- Most promising strategies include **outcomes-based agreements**, **reinsurance**, and forms of **amortization**

Recommendations

- Report details multiple **recommendations for mnfs.** (e.g. engaging in early dialogue with payers and patient groups) and **payers** (gaining a better understanding of RM/ATs and creating a classification system)

CADTH Environmental Scan: Gene Therapy*

Understand regulatory / HTA definition of gene therapy

- Widespread **variation in definition** of gene therapies, such as the **EMA** groups gene therapies with cell therapies under **ATMP** designation but **FDA** believes gene therapies fall under umbrella of **regenerative medicinal therapy**

Identify HTA guidelines / frameworks specific to gene therapy

- Literature results and survey **did not identify any HTA guidelines specific to gene therapies**
- **NICE**, **GBA**, and **SBU** believe that **existing HTA framework is sufficient** to assess gene therapies
- **AHTA** is planning to **develop separate guidelines** for evaluation of gene therapies

Study regulatory and reimbursement decisions for gene therapies

- **Recent regulatory approvals** of Strimvelis, Yescarta, and Luxturna, suggest that **mnfs.** are improving their ability to **compensate** for **uncertainties underlying clinical data**

*CADTH research in progress, results from draft report
SBU: Swedish HTA, **AHTA**: Australian HTA

About IQVIA

IQVIA (NYSE:IQV) is a leading global provider of advanced analytics, technology solutions and contract research services to the life sciences industry. Formed through the merger of IMS Health and Quintiles, IQVIA applies human data science — leveraging the analytic rigor and clarity of data science to the ever-expanding scope of human science — to enable companies to reimagine and develop new approaches to clinical development and commercialization, speed innovation and accelerate improvements in healthcare outcomes. Powered by the IQVIA CORE™, IQVIA delivers unique and actionable insights at the intersection of large-scale analytics, transformative technology and extensive domain expertise, as well as execution capabilities. With more than 55,000 employees, IQVIA conducts operations in more than 100 countries.

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The ARM Foundation for Cell and Gene Medicine is an independent, 501(c)(3) non-profit organization dedicated to providing education and research that will accelerate patient access to safe, efficacious and potentially curative therapies. Its programs engage, educate and empower patients, caregivers, industry leaders and other stakeholders to help advance the science and benefits of gene therapy, gene editing, cell therapy, tissue-engineering and organ regeneration. By increasing understanding and acceptance of these transformative technologies, the Foundation hopes to involve more people in the clinical trial process and therefore help expedite the development of life-saving therapies. To learn more, visit http://www.thearmfoundation.org.