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Strategic Planning for Orphan Drugs:
Maximizing Asset Value Through Evidence-Generation Planning

7 June, 2022

Presenters

Kati Copley-Merriman, MBA

Vice President, Market Access and Outcomes Strategy

Jin Yang, PhD

Associate Director, Market Access and Outcomes Strategy

Sheryl Warttig

Director, Market Access and Outcomes Strategy

Vijay D'Souza, PhD

Senior Associate, Market Access and Outcomes Strategy

Learning Objectives

What are strategic planning considerations for orphan drugs?

What is a market access evidence plan for orphan drugs?

What are key country requirements and innovative funding mechanisms to consider for orphan drugs?

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What is a Market Access Evidence Plan (Roadmap) for Orphan Drugs?

Kati Copley-Merriman
Vice President,
Market Access and Outcomes Strategy

Orphan Drugs Treat Rare and Very Rare Diseases, but Definitions Differ by Country

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Rare disease

- ≤ 6.5 in 10,000 (WHO)[1]
- < 5 in 10,000 in Canada (CADTH)[2]
- ~ 7 in 10,000 in the US (FDA)[3]

Orphan

- < 5 in 10,000 in the EU (EMA)[4]
- < 5 in 10,000 in the UK (MHRA)[5]
- < 5 in 10,000 in Australia[6]
- < 4 in 10,000 in Japan[7]

Ultra-orphan

- ≤ 1 in 50,000 in Scotland (SMC)[8]
- ≤ 1 in 50,000 in England and Wales (NICE)[9]

Ritchter et al. (2015)[10] identified 296 definitions related to rare diseases from 32 international jurisdictions

CADTH = Canadian Agency for Drugs & Technologies in Health; EMA = European Medicines agency; EU = European Union; FDA = Food and Drug Administration; MHRA = Medicines and Healthcare products Regulatory Agency; NICE = National Institute for Health and Care Excellence; SMC = Scottish Medicines Consortium; UK = United Kingdom; US = United States; WHO = World Health Organisation.

Orphan Drugs – Challenges With Standard HTA Approaches

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Challenges

Evidence

- **Lack of evidence**
- Low patient numbers
- Surrogate endpoints
- Single arm trials

Condition

- Poorly understood
- Lack of natural history
- No or unclear comparators/ standard of care

Other

- **High cost of the orphan drug**
- Ethical considerations
- Drugs with more than 1 rare indication

Leads to uncertainties in the clinical and economic evidence → Uncertainties can lead to long appraisal times by HTA agencies and fewer positive outcomes → If not reimbursed, the opportunity to collect real-world efficacy and safety data for "pay per performance" schemes is diminished

HTA = health technology assessment.

How Can a Market Access Evidence Plan (Roadmap) Support the Value of a Pipeline Product? Plan for Success

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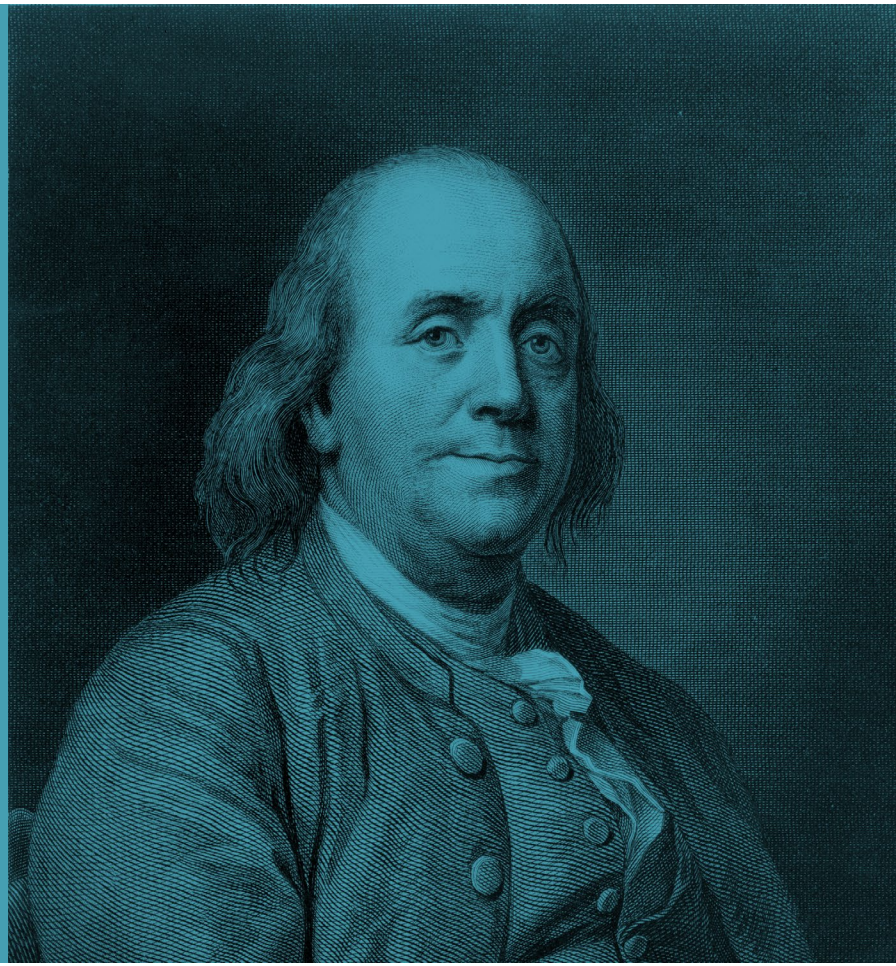
"If you fail to plan,
you are planning to fail!"

BENJAMIN FRANKLIN



Market Access Evidence Plan (Roadmap) Timing

- For products that might be approved based on phase 2 data, which is common for orphan drugs, the Market Access Evidence Plan should start prior to beginning phase 2 trials
- Ideally for all other products, the Market Access Evidence Plan would begin prior to phase 3, in time to influence the study design

Orphan drugs are commonly approved using single-arm phase 2 trials, so comparator arm(s) need to be generated by indirect comparisons

Market Access Evidence Plan Creation Process Overview

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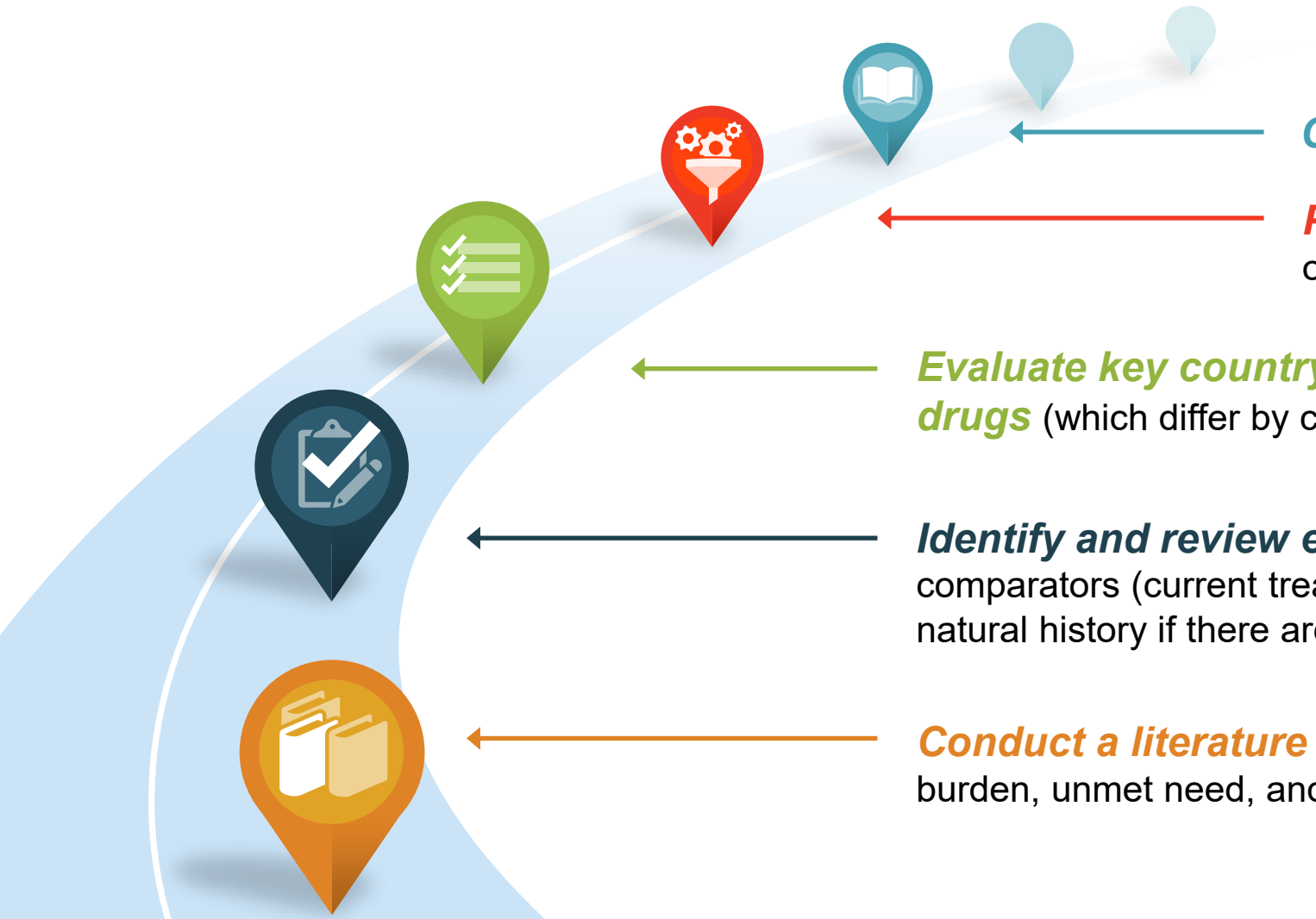

Create the value story

Product SWOT (strengths, weaknesses, opportunities, threats)

Evaluate key country HTA requirements for orphan drugs (which differ by country and change over time)

Identify and review evidence base for key comparators (current treatments or standard of care/ natural history if there are no approved treatments)

Conduct a literature review to understand the disease burden, unmet need, and disease data gaps (e.g., utility data)

Market Access Evidence Plan Creation Process Overview

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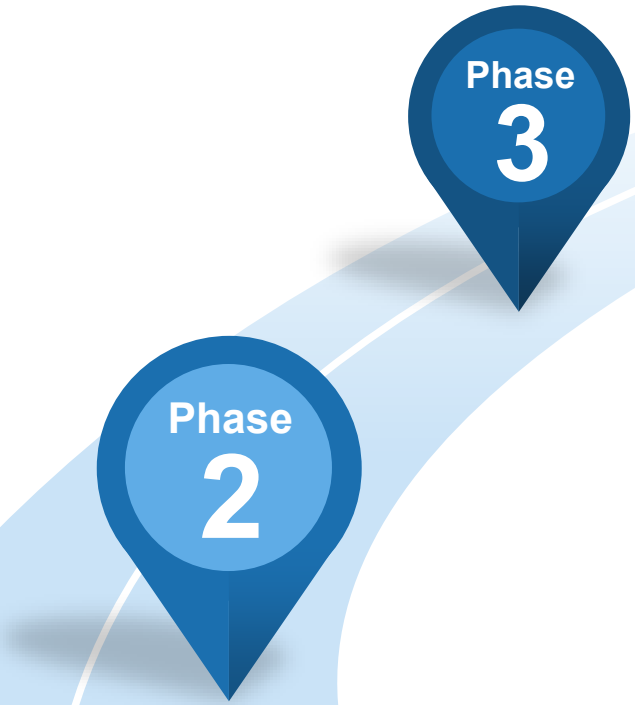
Create a market access evidence plan to address gaps and country requirements

Conduct payer research to assess perceptions of unmet need, payer evidence needs, and price expectations

Conduct a gap analysis for evidence to support the value story based on gaps identified in the literature, and for the product based on product and competitor study designs

Review existing data to support the value story, both in the literature and for the product

Special Considerations: Payer-relevant Comparators

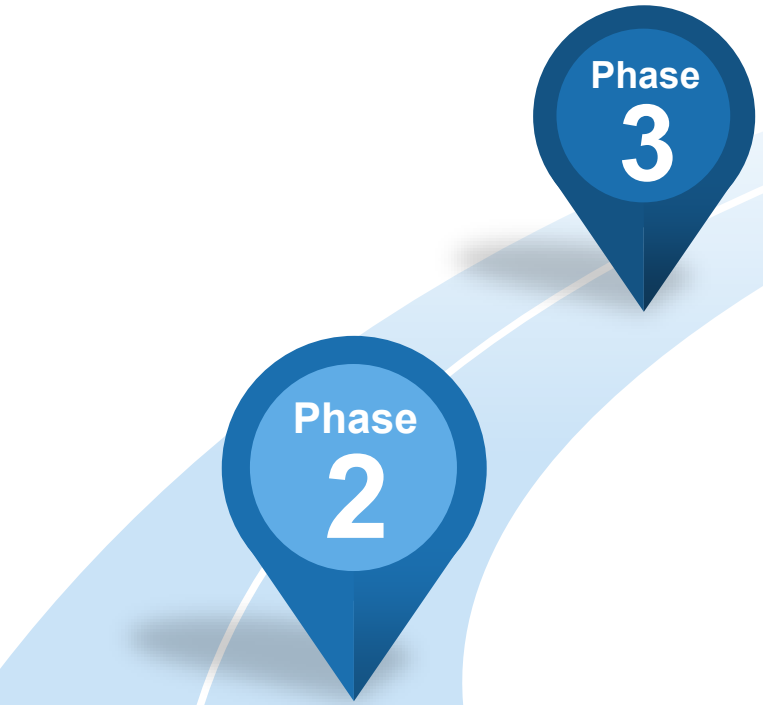


Consider payer-relevant vs. clinical benefit comparators

Identify comparators and study endpoints

- Prepare convincing evidence of comparative effectiveness (direct or indirect) vs. **all relevant comparators**
- Understand comparator trials, have indirect comparisons planned
- For single-arm studies, the comparator arm can be created using retrospective studies or disease registries

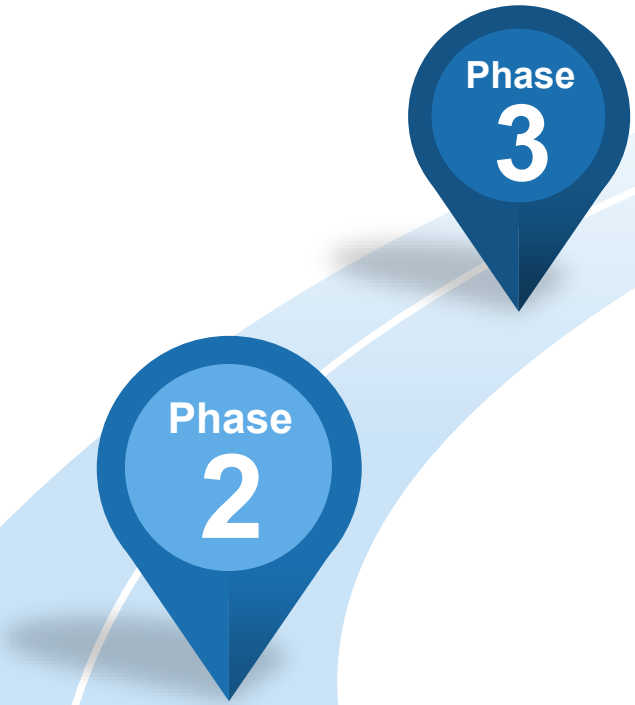
Special Considerations: Patient-reported Outcomes



Patient-reported Outcomes (PROs)

- PROs are often not included in clinical trials
- When included, the results fail to demonstrate change, capture domains important for patients, or are uncertain
- With a Roadmap, disease-specific measures can be planned and included

Special Considerations: Utility Measurement



Poor utility data can undermine price and reimbursement

Utility measurement

- Plan to collect utility estimates for cost-effectiveness models (quality adjustment)
- If not collected in a trial, it will cost more money for an additional utility study; this may lead to a price restriction as payer-relevant value (QALY gain) is uncertain
- Utility data is hard to collect in pediatric trials, which are common in rare diseases; methods being developed to address this are using parental scores or cross-matching with pediatric QOL measures

QALY = quality-adjusted life year; QOL = quality of life.

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What Are the Elements of a Market Access Plan Roadmap Specific to Orphan Drugs?

Jin Yang
Associate Director,
Market Access and Outcomes Strategy

Literature Review To Understand Burden of Rare Diseases

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A comprehensive literature review to understand the rare disease and the unique unmet needs patients face

- **Disease definition and diagnostic criteria**: diagnosis can be challenging
- **Natural history and clinical burden:** chronic and heterogeneous nature
- **Epidemiology:** limited and variable data
- **Humanistic burden:** lack of disease-specific PRO instruments
- **Economic burden:** lack of country-specific studies
- **Current treatment:** approved treatments and their HTAs, treatment guidelines, treatment patterns, pipeline drugs

Gap Analysis From the Literature Review: *Examples*

- **Epidemiology data are scarce in countries A, B, and C.**
- Lack of natural history data; unclear when clinical manifestations will occur.
- **Most studies used SF-36; disease-specific instrument is not validated.**
- Economic burden studies are all US-based and short-term; long-term data outside the US are needed.
- Treatment patterns are similar across studies for 1L therapies but vary in the 2L setting, likely due to product availability in different countries.

1L = first line; 2L = second line; SF-36 = 36 Item Short Form health survey.

Evaluation of PRODUCT X and Competitive Landscape

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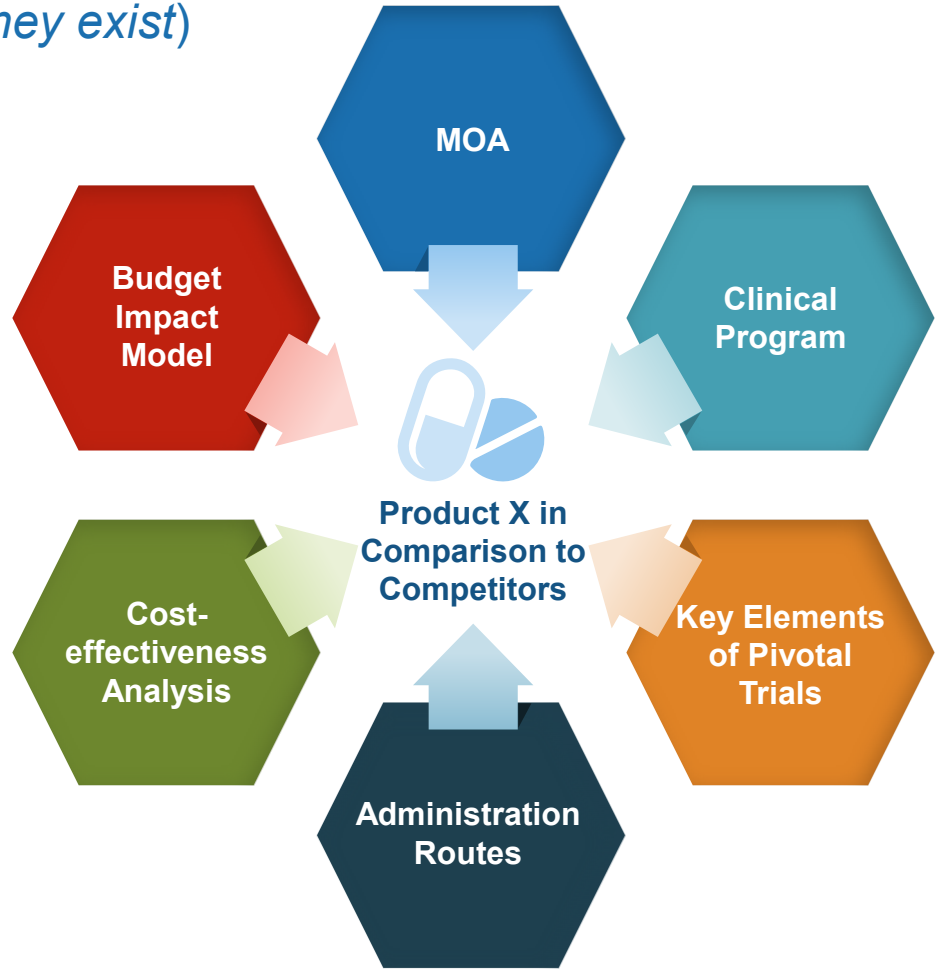
Assessing PRODUCT X in various aspects helps identify gaps in evidence collection, shape trial design, and differentiate the product from competitors (*if they exist*)

- **MOA**: a unique MOA
- **Clinical program:** robustness of clinical evaluation
- **Study design and outcomes:** study arm, endpoints, PRO assessment, utility values, unique safety concerns
- **Administration route:** advantage versus SOC
- **Economic evaluation:** lessons learned from prior CEA or BIM



BIM = budget impact model; CEA = cost-effectiveness analysis; MOA = mechanism of action; SOC = standard of care.

Gap Analysis For Product X: *Examples*

- **Phase 2 trial for PRODUCT X does not collect utility values.**
- Competitor trials are similar but have additional PRO endpoints.
- No head-to-head trial between PRODUCT X and Competitor Y; but **indirect comparison is feasible**.
- Oral administration is an advantage, as SOC is administered via IV infusion.
- PRODUCT X has a novel mechanism of action, offering a new treatment option to patients who are refractory to SOC.

IV = intravenous.

SWOT Analysis: *Examples*

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Strengths

- PRODUCT X has a relatively higher response rate based on indirect comparison of trial data.
- PRODUCT X has a good safety profile similar to placebo.
- PRODUCT X trial showed evidence of improved PRO while no other competitors evaluated PRO.

Opportunities

- A high unmet need exists for patients with Disease X, who are refractory to SOC.
- Current treatment in 2L is a complex and risky procedure.
- PRODUCT X will be the first approved pharmacological treatment in the 2L setting.

Weaknesses

- Utility data, which are used in economic models, were not collected in the clinical trials of PRODUCT X.
- Administration is subcutaneous injection versus oral.
- Long duration of response is not established for PRODUCT X.

Threats

- Competitor Y has started phase 3 trials.
- Competitor Y is a once-daily oral tablet while PRODUCT X is administered subcutaneously.
- European markets have tougher reimbursement environments.

Implications For Product X: *Examples*

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	Literature-based Evidence Gaps	Priority To Address
Diagnosis	• **Diagnosis is based on exclusion of other secondary causes**.	**LOW: This is not something Company X could easily solve for PRODUCT X, despite a need for confirmatory diagnosis test.**
Epidemiology	• Epidemiology data on Disease X are available in France, Germany, Italy, Spain, and the UK.	**LOW:** Country-specific epidemiology data of Disease X are sufficient to support a budget impact model.
Humanistic burden	• Only a few studies were evaluated, all used the generic instrument SF-36.	**MODERATE TO HIGH:** The clinical trial for Product X used the SF-36, instead of the disease-specific instrument xxx.
Economic burden and prior modeling	• **All identified studies were US-focused analyses; data outside the US is lacking.**	**HIGH: Obtaining accurate country-specific economic burden data is required for economic modeling.**
Treatment pattern	• Treatment pattern data for both 1L and 2L therapies are available, showed similarities across countries in the 1L setting and variations in the 2L setting.	**LOW:** Adequate treatment pattern information was found for both 1L and 2L settings, all of which are recent (2020-2021).

Value Messages: *Examples*

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Value messages help you see the value of your product and position it in the market landscape

Efficacy Messages

- PRODUCT X reduced disease activity xx from baseline by xx% after 6 months of treatment; and the reduction is maintained for at least X months.
- XX% of patients responded to PRODUCT X by 2 weeks, and yy%, zz% responded by 6 weeks and 6 months, respectively.

Safety Messages

- Treatment with PRODUCT X over 6 months shows no clinically significant worsening in safety profile, compared with baseline.
- Treatment with PRODUCT X is well tolerated, and adverse events are mild; no increase in serious infection or risk of xx leading to discontinuation of Product X.

Economic Value Messages

- PRODUCT X is cost-effective compared with placebo (no treatment); incremental cost effectiveness ratio of PRODUCT X is $xx per QALY.
- PRODUCT X has a low budget impact ($xx per member per month) because the disease is rare.

HRQOL Improvement Messages

- Clinically meaningful improvement in QOL, as measured by XYZ instrument, has been shown after x weeks of treatment with PRODUCT X versus a worsening with no treatment.
- Time to deterioration is longer with PRODUCT X versus placebo.

Market Access Plan (Recommended Projects): *Examples*

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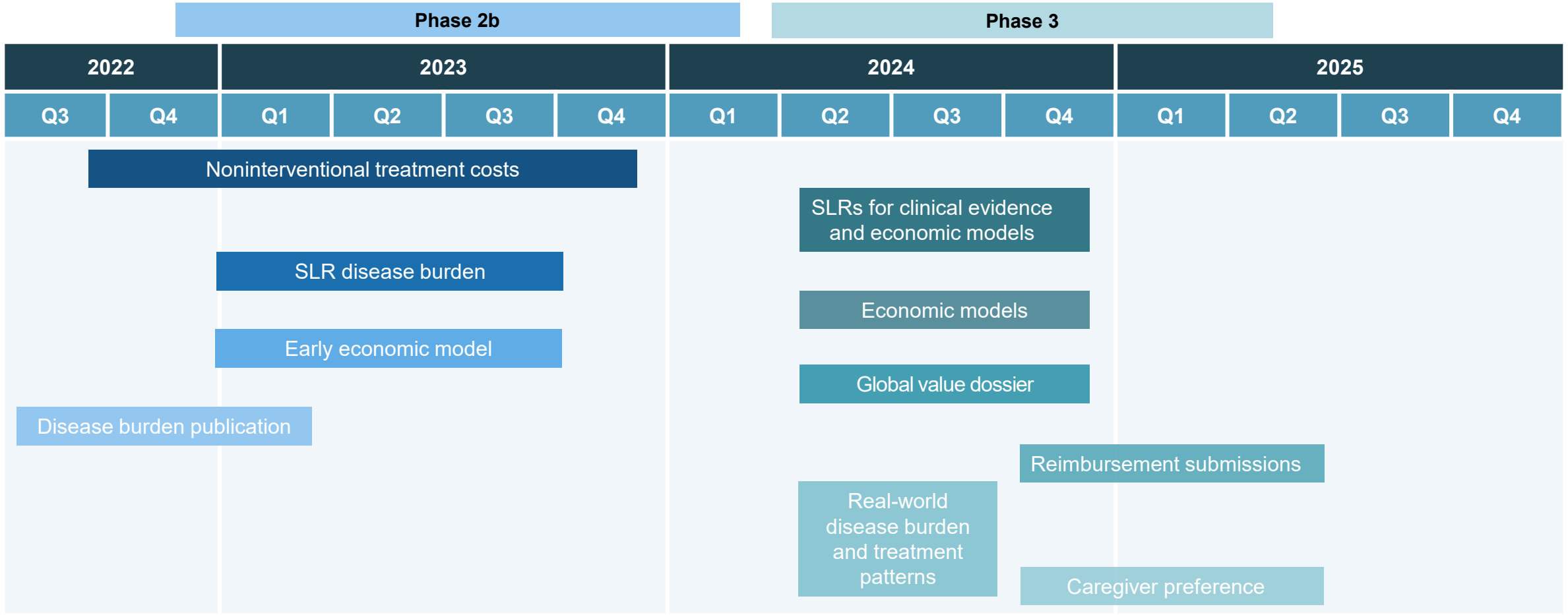
Assuming Phase x Study Completion Q# 20##; Launch Q# 20##

Evidence needed for gaps	Data source	Country	Start date/ study length/ price estimate	Rationale
Early HTA advice	Letter of intent 3 months prior to building economic models	Europe	Q3, 2022 6-8 months $XX,XXX	Gain strategic input from country HTAs
Real-world burden of disease and treatment patterns	Database study or disease registry/partner with disease associations	US, UK, and others	Q3, 2022 $XX,XXX	Understand the burden of disease and current treatments
Early economic model	Economic model	US	Q4, 2022 $XX,XXX	Understand model data gaps and pricing implications
Reimbursement submissions	Targeted and systematic literature reviews; country-specific economic models; global value dossier	US (AMCP), UK (NICE); IQWiG (Germany), etc.	Q1, 2024 6-9 months $XX,XXX per country	Meet reimbursement requirements

AMCP = Academy of Managed Care Pharmacy; NICE = National Institute for Health and Care Excellence.

Timeline of Activities for the Market Access Plan: *Examples*



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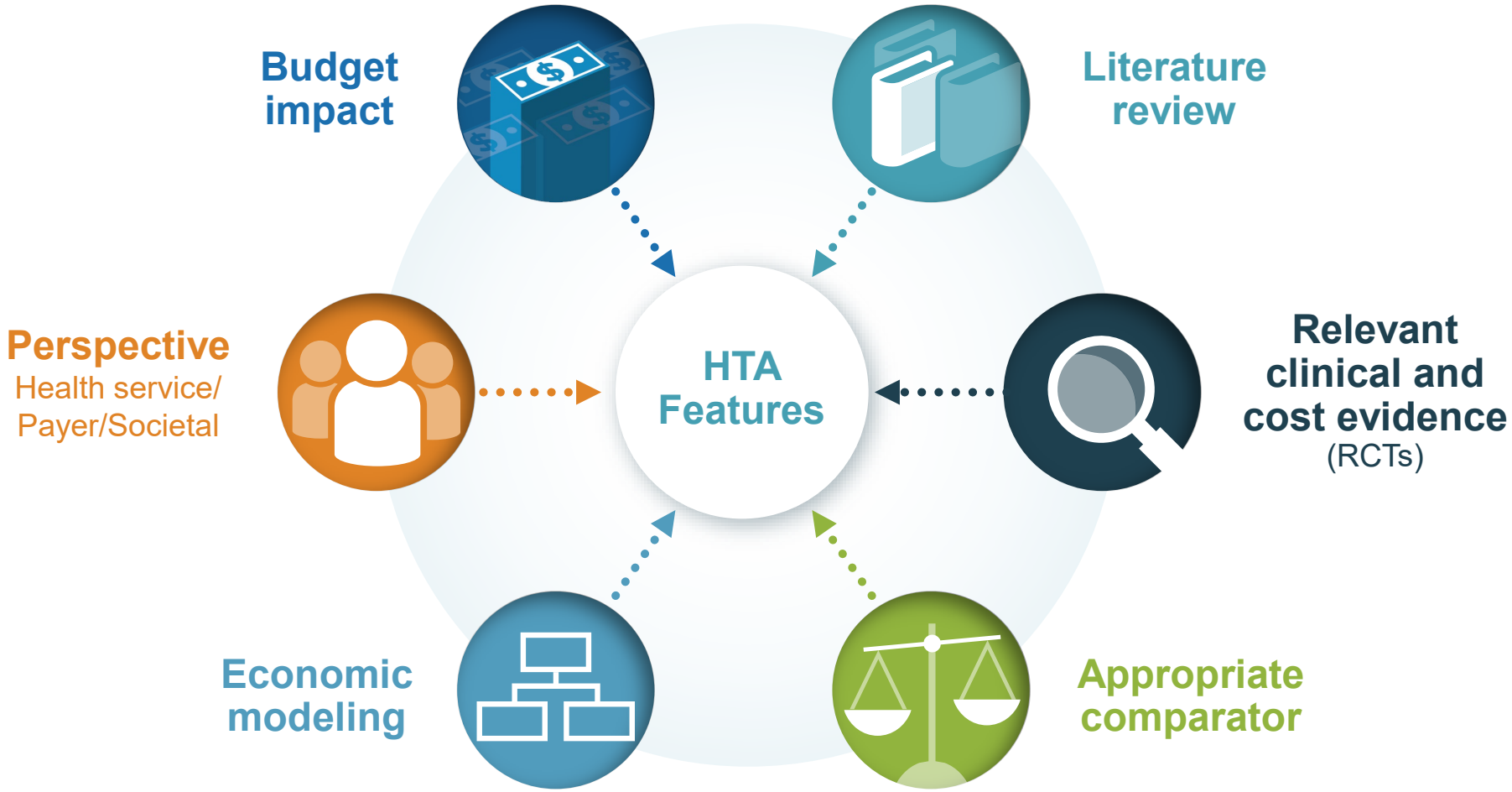
HTA for Orphan Drugs

Sheryl Warttig
Director,
Market Access and Outcomes Strategy

What is Health Technology Assessment (HTA)?



RCT = randomized controlled trial.

HTA for Orphan Drugs

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Same HTA methods

Most orphan drugs cannot be recommended/ approved

Some agencies allow flexibilities for orphan drugs

Orphan Drugs – Challenges With Standard HTA Approaches

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Challenges

Evidence	Condition	Other
• Lack of evidence • Low patient numbers • Surrogate endpoints • Single-arm trials	• Poorly understood • Lack of natural history • No or unclear comparators/SOC	• High cost of the orphan drug • Ethical considerations • Drugs with more than 1 rare indication
Solution: Accept greater uncertainties	**Solution:** Use specialist committees/advisors	**Solution:** Accept higher prices (higher willingness-to-pay thresholds)

Also:
- Conditional decisions (based on discounts, risk-sharing agreements, or managed access/entry)
- Exemption from HTA

NICE HTA for Orphan Drugs

Orphan drugs can be considered in 2 pathways:

- HST: for drugs that meet all 4 HST criteria
- TA: for drugs that do not meet the HST criteria
  - **Most orphan drugs go through this route!**

HST criteria

1) The disease is very rare < 1 in 50,000 (< 1,100 people in England)
2) The number of people in England eligible for the drug is < 300 (single indications) or < 500 (across all its indications)
3) The very rare disease significantly shortens life or severely impairs QOL
4) There are no other satisfactory treatment options, or it will offer significant benefit over existing options

HST = highly specialised technologies; TA = technology appraisals.

NICE HTA - TA Versus HST

Flexibilities that are common to both TA and HST

Decision-making flexibility for:

- Nature and quality of evidence
- More uncertainty is acceptable for rare diseases, children, innovative or complex technologies
- Benefits and adverse effects
- Position in the care pathway and alternatives
- Conditional recommendations (restricted population, discount, managed access)

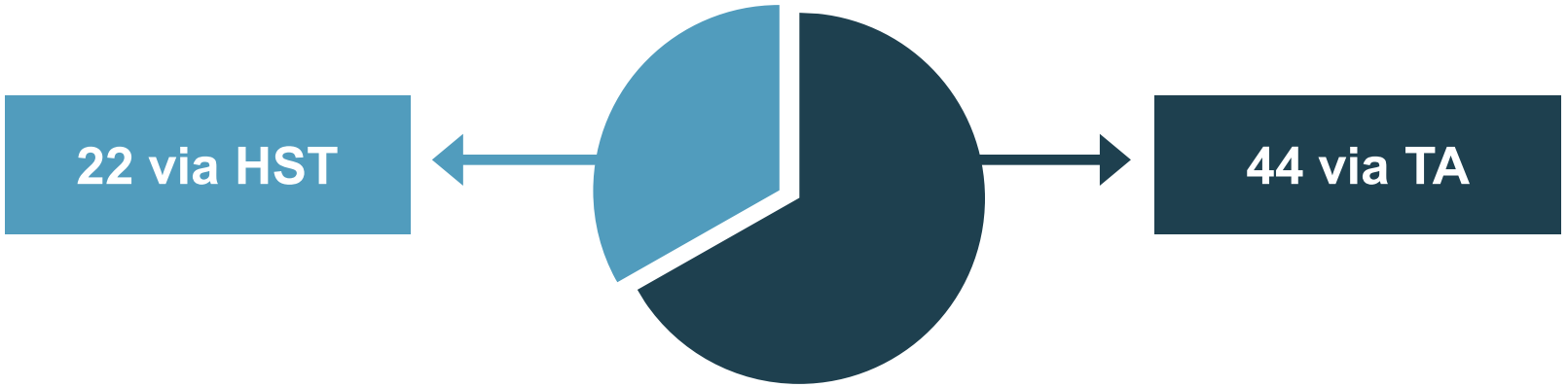
NICE HTA - TA Versus HST

Flexibilities that are different

	Technology appraisal	Highly specialised technologies
Decision-making flexibility	As per previous slide	*As per previous slide,* ***plus*** • The overall size of health benefits to patients/carers. • Robustness of the current evidence and the contribution the guidance might make to strengthen it. • Extent of morbidity and disability with current SOC
Willingness-to-pay threshold	£20,000 - £30,000	£100,000
Quantitative decision 'modifiers'	QALY weight of x1 to x1.7 can be applied for severe conditions	QALY weight of x1 to x3 can be applied for large QALY gains (gains of 10-30 QALYS)

NICE HTA for Orphan Drugs

Between 2015 and 2020 **66 orphan drugs** were selected by NICE[1]



Why?

Unclear, probably because of size of eligible population

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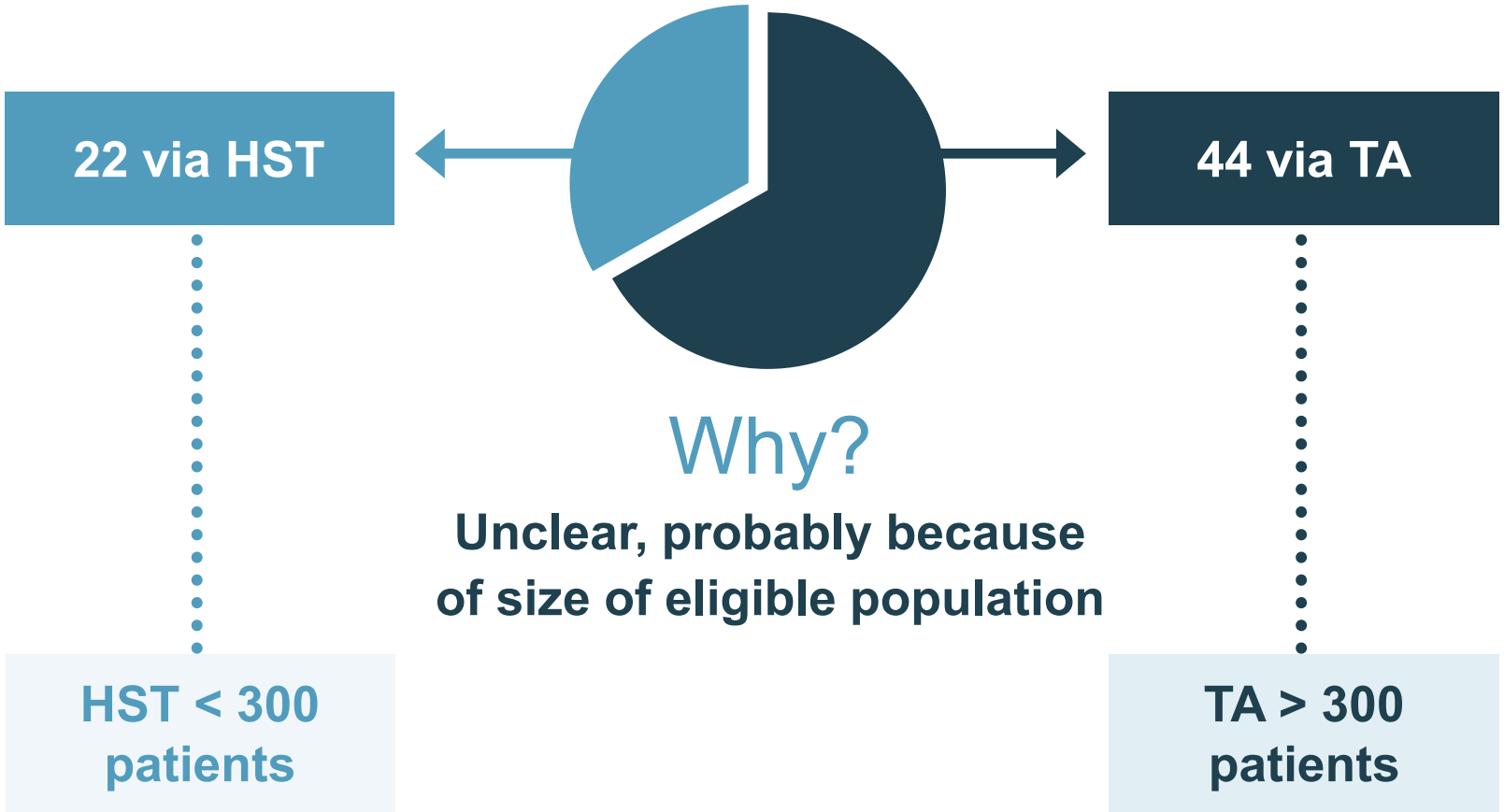

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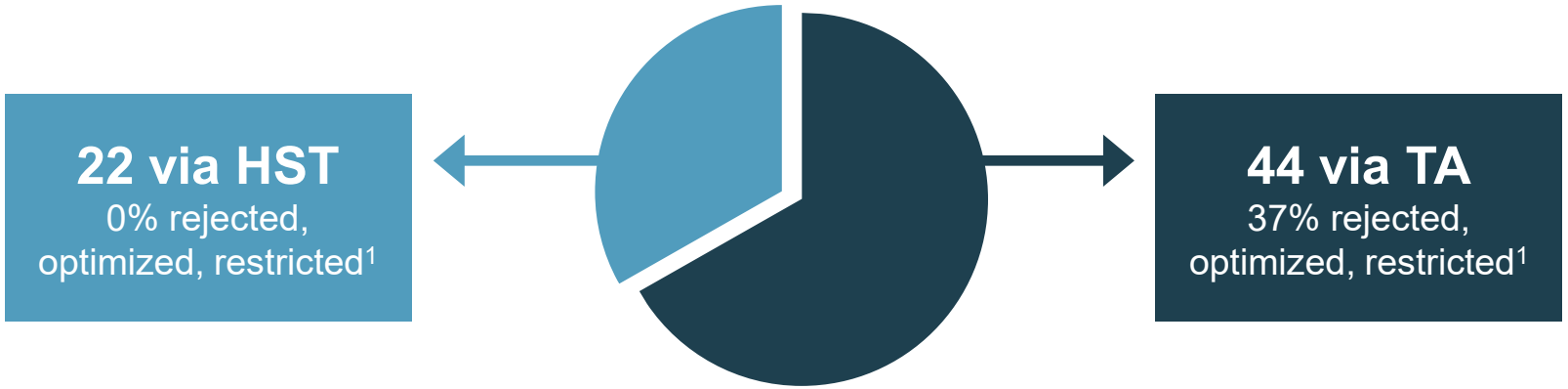

Why?

Unclear, probably because of willingness to pay threshold

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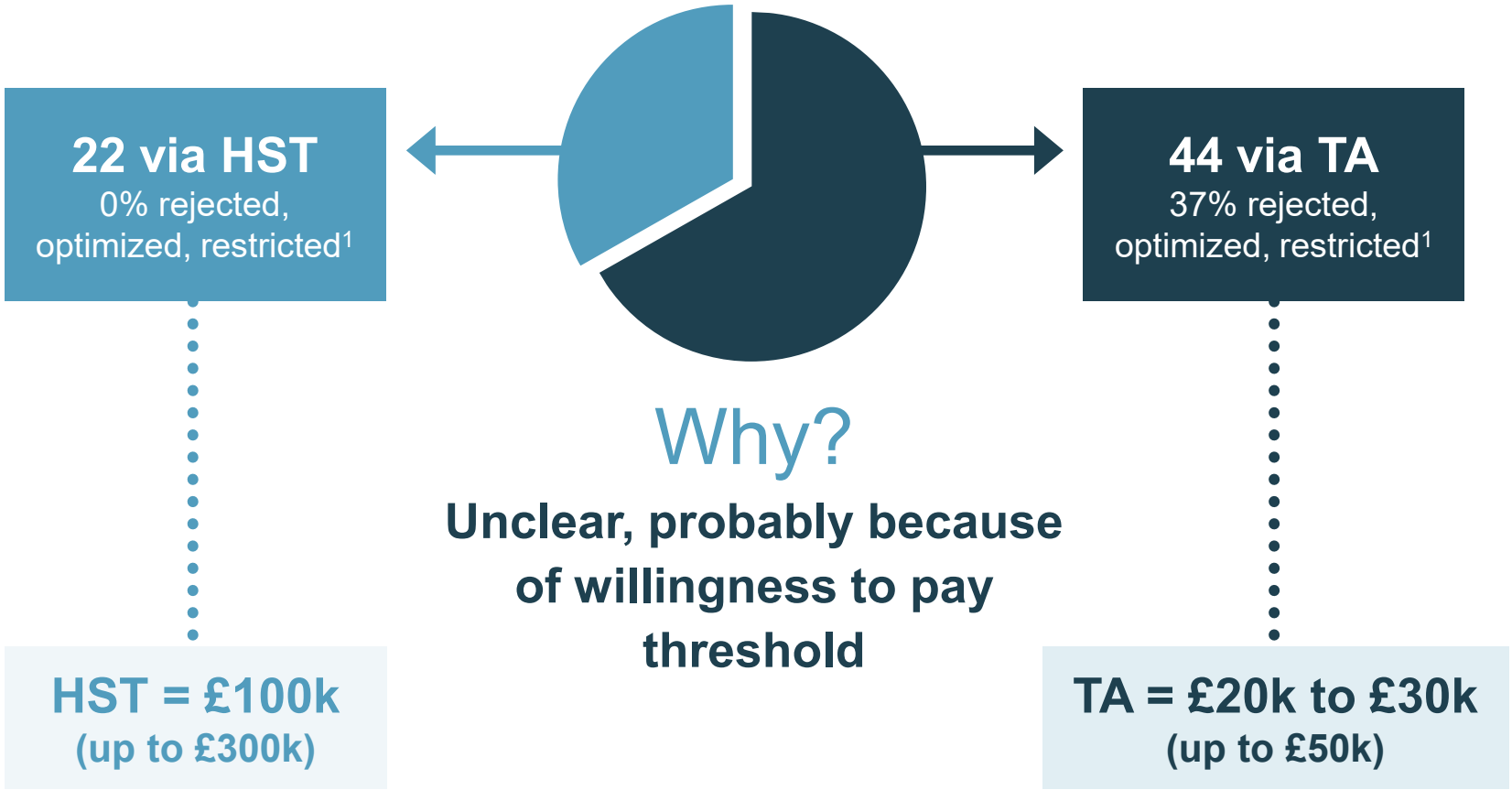

US Institute for Clinical and Economic Review (ICER): Ultra-Rare Diseases

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- Adapted approach for ultra-rare condition treatments if:
  - < 10,000 patients
  - Future expansion of the indication to > 20,000 patients is unlikely
  - Offers major gains in quality and/or length of life
- Adapted approach contextualizes the challenges of generating evidence
  - Same approach to standards of evidence and rating evidence will be used

Recent ICER White Paper Summary of Policy Options (April 2022)

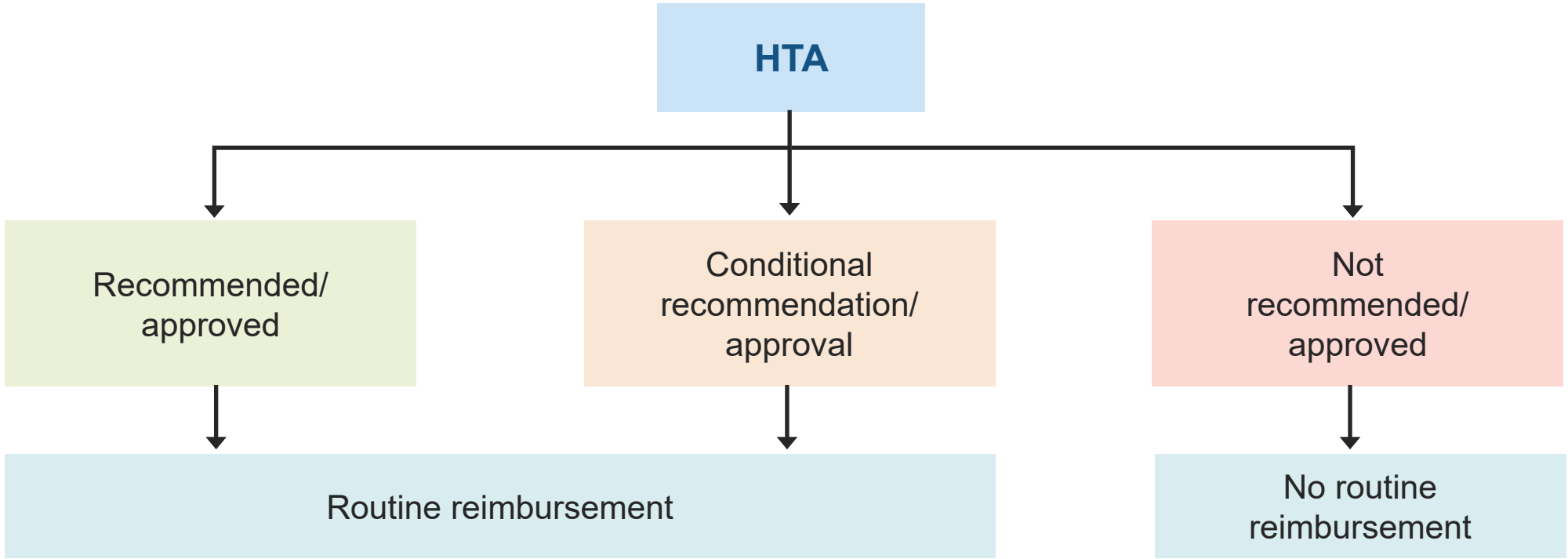
Strengthen Evidence Generation:

- Update ICD-10 codes to reflect the rare disease
- Fund patient registry development
- Clarify evidence expectations

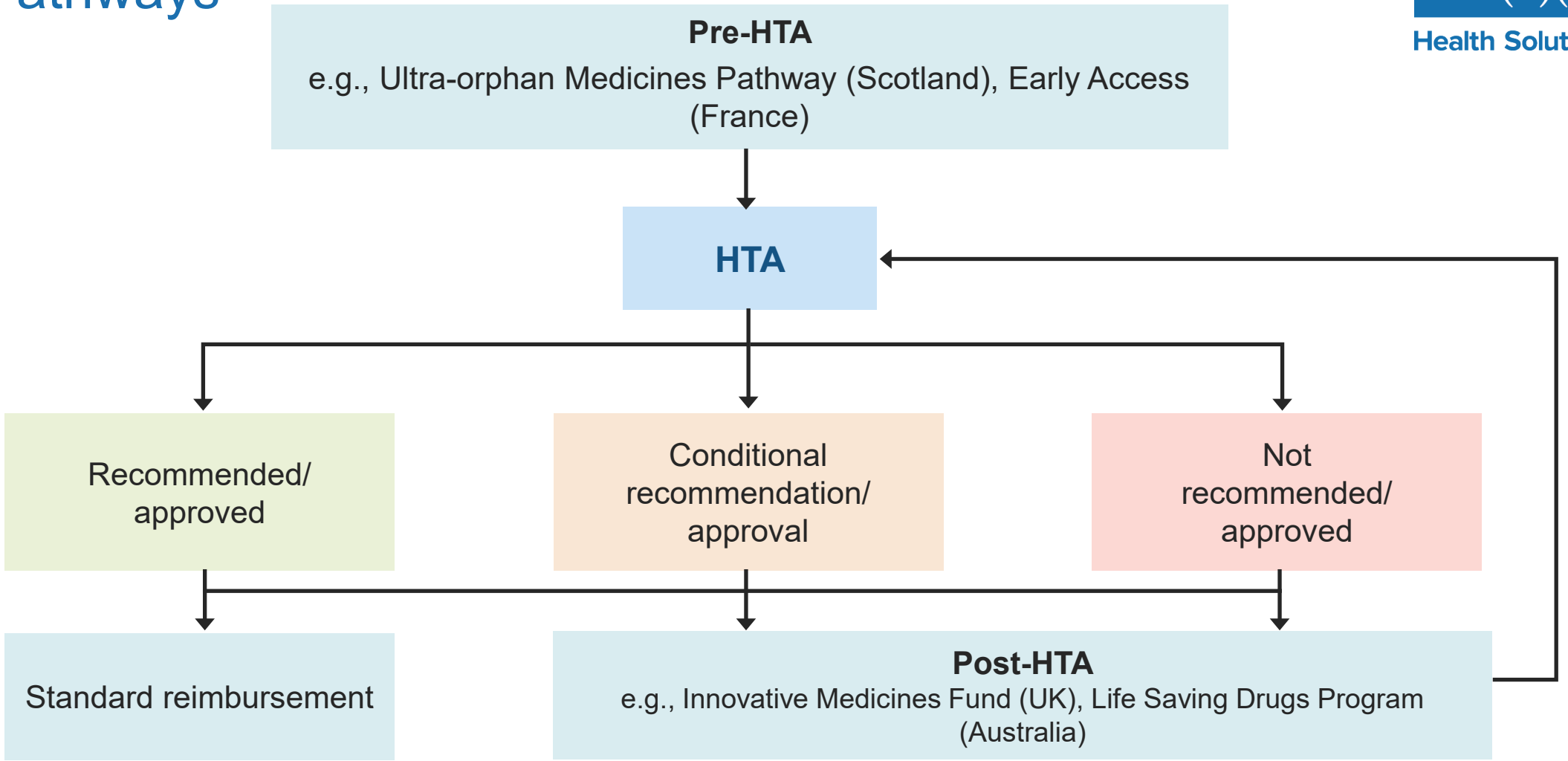
Pricing Options:

- Consider outcomes-based or volume-based contracts
- Consider indication-based pricing
- Pursue value-based pricing

HTA Pathways



HTA Pathways



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Innovative Funding Mechanisms for Orphan Drugs

Vijay D'Souza
Senior Associate,
Market Access and Outcomes Strategy

Innovative Payment Mechanisms

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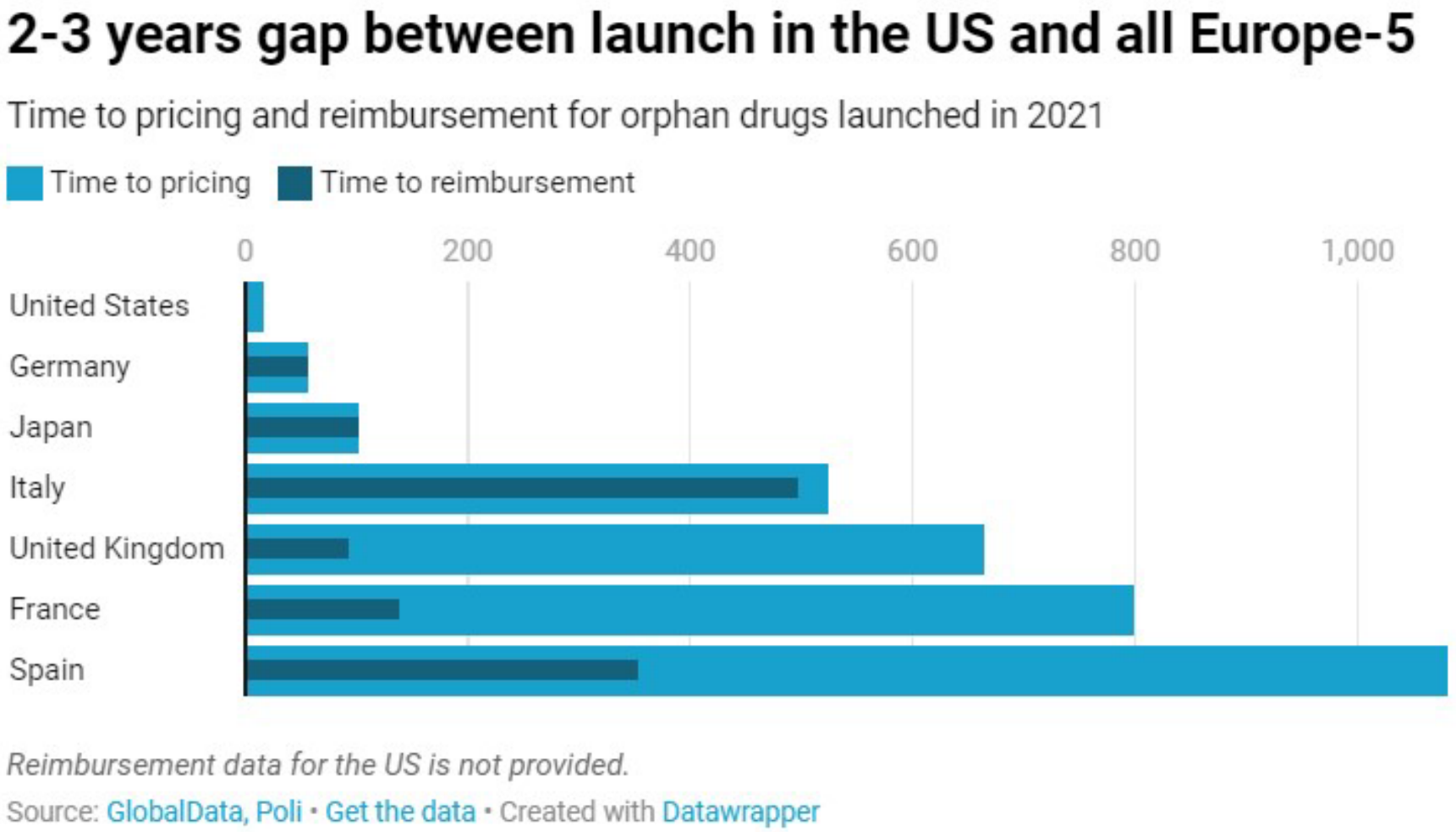
Payment models support equitable access to orphan drugs

Non-orphan drug	Value metric	Orphan drug
Smaller	Incremental health gain	Larger
Lower	Cost	Substantially higher
Favorable	Cost-effectiveness	Unfavorable

- Cost-effectiveness metric in the HTA evaluation deems the orphan drug as not cost-effective
- New ways of funding are essential to enable patient access within the limits of funding by healthcare systems
- Alternative financing schemes facilitate access when the technology cannot be reimbursed by a routine commissioning pathway

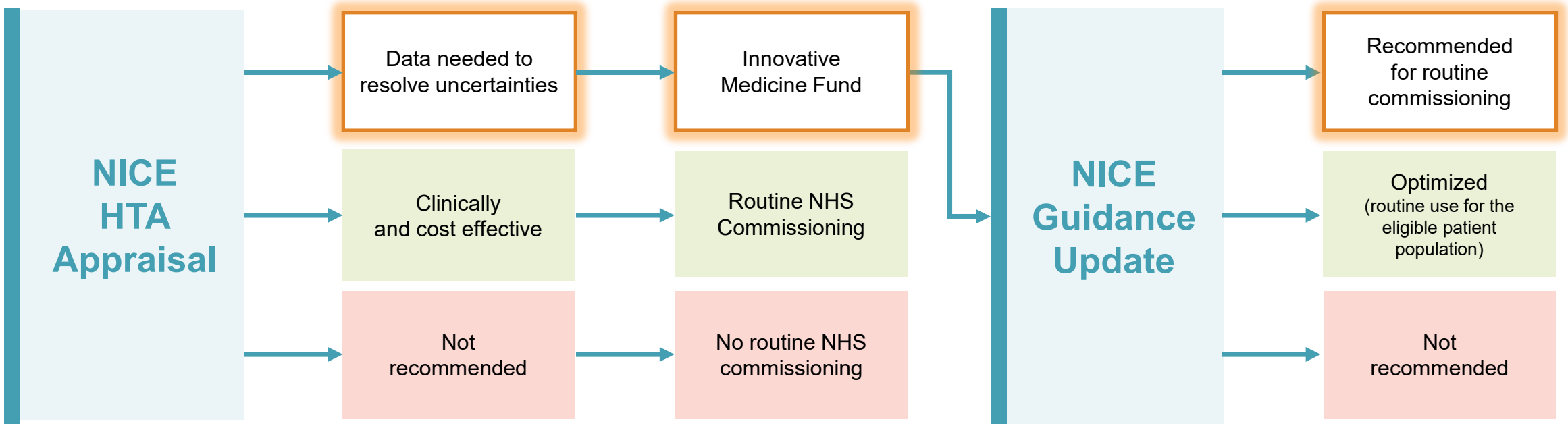
Orphan Drug: Time to Reimbursement



- Reimbursement and launch occur almost simultaneously in Germany, Japan, and Italy
- Average time pricing and reimbursement:
  - UK: 572 days
  - France: 660 days
  - Spain: 730 days

Innovative Funding for Rare Diseases – UK *(England and Wales)*

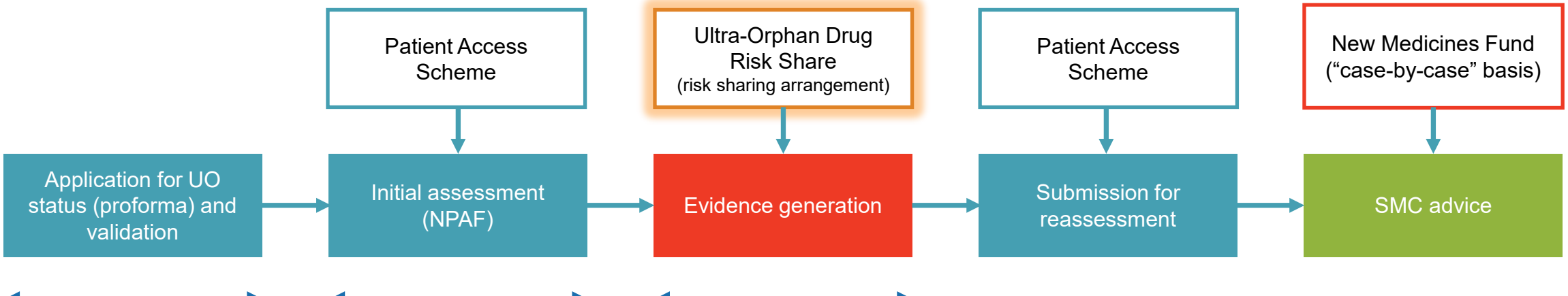
Alternative reimbursement pathway-Innovative Medicine Fund



NHS = National Health Service.

Innovative Funding for Rare Disease Medicines – Scotland

Ultra-Orphan Drug Risk Share and New Medicines Fund



- Early confirmation of ultra-orphan definition, even before CHMP opinion

- Assessment of clinical and cost effectiveness
- Highlights uncertainties within evidence-base and helps to inform the data collection stage

- The SMC will review the evidence and make a final decision on its routine use in NHS Scotland

CHMP = Committee for Human Medicinal Products; NHS = National Health Service; NPAF = New Product Assessment Form; UO: ultra-orphan.

Early Access for Rare Disease Medicines – France

Access to treat serious or rare diseases

Early Access Authorization

Company must commit to:

- Apply for MA within 2 years
- Respect the protocol for therapeutic use established for the drug
- Finance real-life data collection

Manufacturers request early access

1. Pre-MA early access
2. Post-MA early access

Consultation with ANSM on efficacy and safety

HAS assessment

Access granted

Compassionate Use

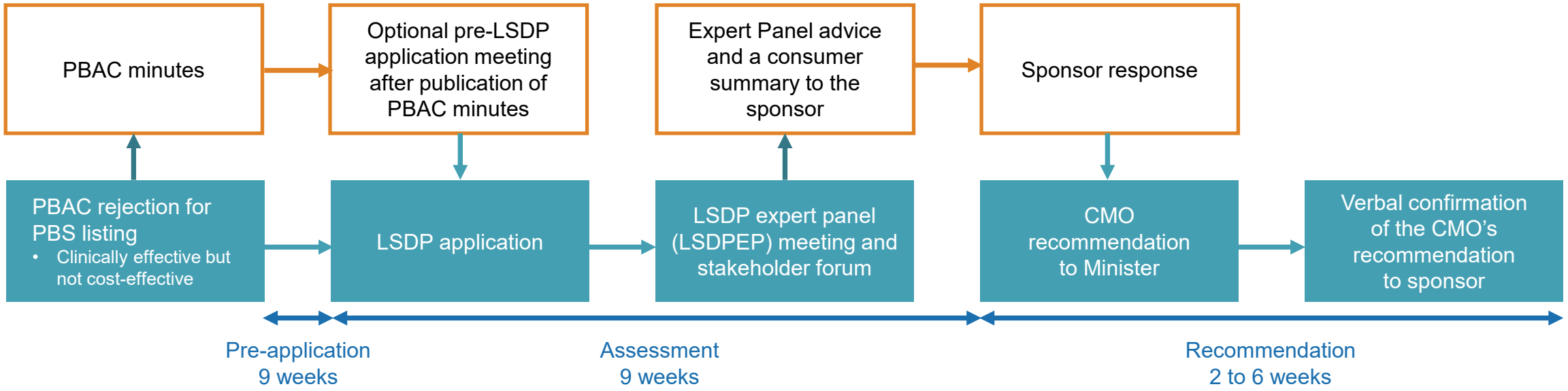
Compassionate access authorization	Compassionate prescription framework
Physician request for named patient	Company application
Access granted for 1 year, renewable	Access granted for 3 years, renewable

ANSM = Agence Nationale de Sécurité des Médicaments et des produits de santé (French National Agency for Medicines and Health Products Safety); HAS = Haute Autorité de santé é (French National Authority for Health); MA = marketing authorization.

Innovative Funding for Rare Disease Medicines – Australia

Alternative reimbursement pathway - LSDP

Listing a medicine on the LSDP



Pricing and review:

- Proposed price of the medicine versus the effective price of the medicine in comparable overseas markets compared
- Proposed cost of the medicine versus the cost of comparable medicines (that are already funded through the LSDP)
- Only cost of the medicine is subsidized
- Use and cost of new medicines on the list are reviewed after 2 years

CMO = Chief Medical Officer; LSDP = Life Saving Drugs Program; LSDPEP = LSDP expert panel; PBAC = Pharmaceutical Benefits Advisory Committee; PBS = Pharmaceutical Benefits Scheme

Planning for Alternative Funding

- Only 17% of orphan drugs reach marketing approval as per historical success rate; and nearly a third fail at the market access stage.[1]
- Lack of data on safety, efficacy, and additional benefit compared with existing treatments to support clinical effectiveness is the main cause of failure.
- Early engagement is recommended with each HTA body to discuss the evidence requirement for value assessment.
  - During the clinical development stage and before MA application, to help with type and amount of evidence required

Pathways to early engagement

Early engagement in France

- Clear timeframe for early engagement due to the nature of the early access application process in France.

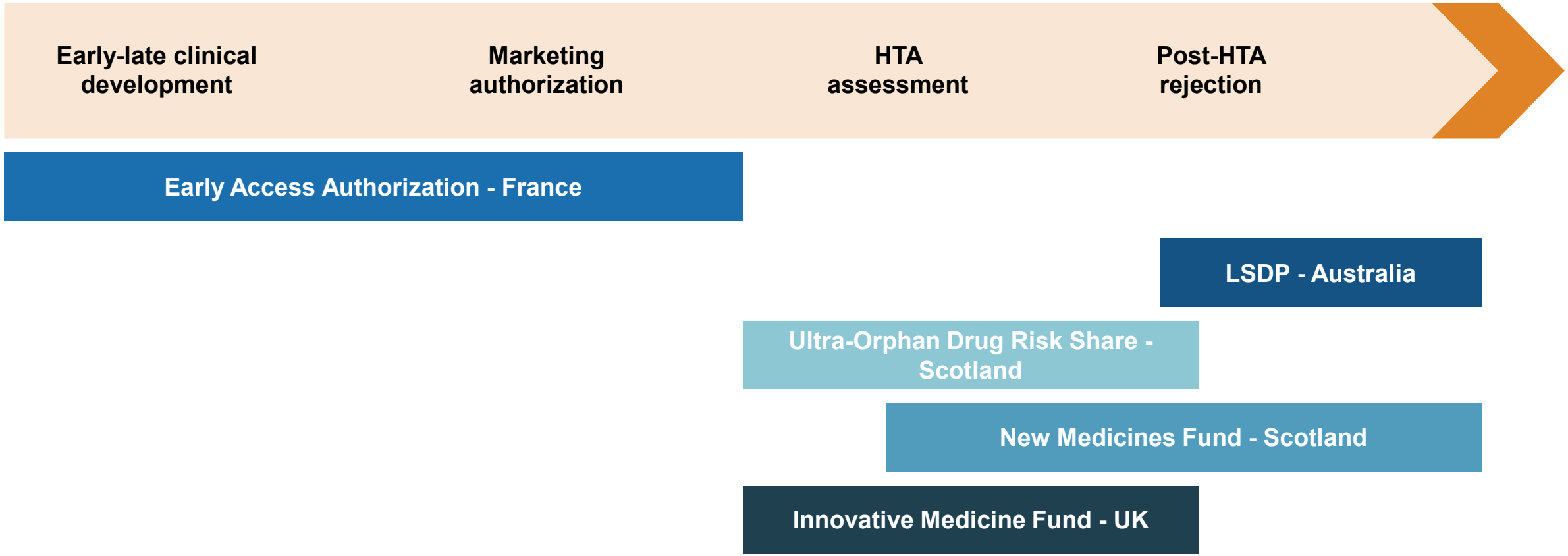
Early engagement routes in the UK

- Innovative Licensing and Access Pathway (ILAP)
- Promising Innovative Medicines (PIM) designation route for Early Access to Medicines Scheme (EAMS)

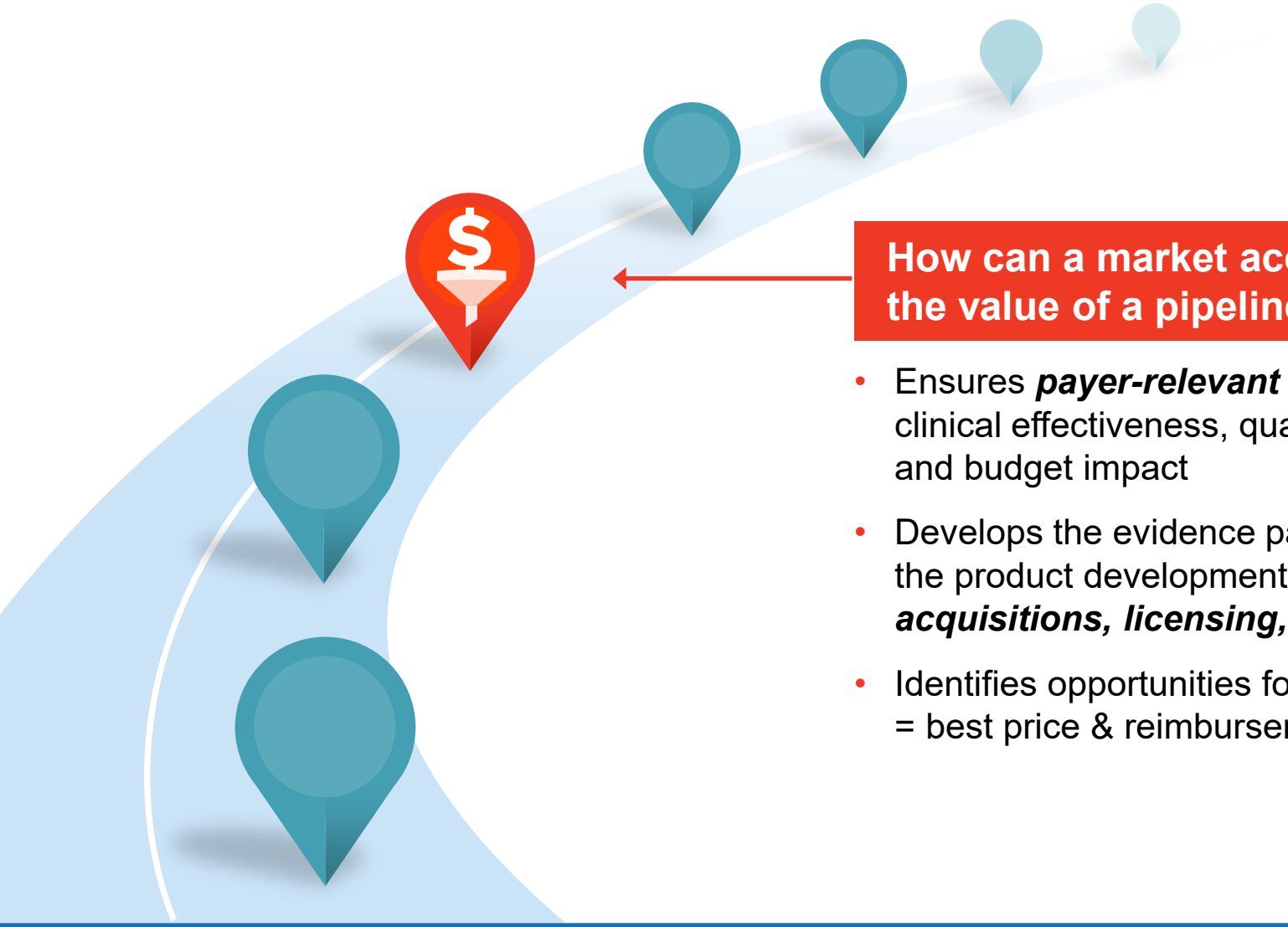
EAMS = Early Access to Medicines Scheme; ILAP = Innovative Licensing and Access Pathway; MHRA = Medicines and Healthcare products Regulatory Agency; PIM = Promising Innovative Medicines.

Innovative Funding – Summary

Variation in the evidence requirement between pre-market and HTA recommended access



Key Take-Home Messages



How can a market access evidence plan support the value of a pipeline product?

- Ensures ***payer-relevant*** evidence is generated demonstrating clinical effectiveness, quality-of-life benefit, cost-effectiveness, and budget impact
- Develops the evidence package in parallel with and throughout the product development process, so it is available to ***support acquisitions, licensing, and/or asset valuations***
- Identifies opportunities for ***highest value-added patient benefit*** = best price & reimbursement opportunity

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RTI Health Solutions

Kati Copley-Merriman
Vice President, Market Access and Outcomes Strategy
Email: kcmerriman@rti.org

Jin Yang
Associate Director, Market Access and Outcomes Strategy
Email: jyang@rti.org

Sheryl Warttig
Director, Market Access and Outcomes Strategy
Email: swarttig@rti.org

Vijay D'Souza
Senior Associate, Market Access and Outcomes Strategy
Email: vdsouza@rti.org

Peter Wirth
Vice President, Business Development
Email: pwirth@rti.org

Abbreviations

IL	first line
2L	second line
AMCP	Academy of Managed Care Pharmacy
ANSM	Agence Nationale de Sécurité des Médicaments et des produits de santé (French National Agency for Medicines and Health Products Safety)
BIM	budget impact model
CADTH	Canadian Agency for Drugs & Technologies in Health
CEA	cost-effectiveness analysis
CHMP	Committee for Human Medicinal Products
CMO	Chief Medical Officer
EAMS	Early Access to Medicines Scheme
EMA	European Medicines Agency
EU	European Union
FDA	Food and Drug Administration
HAS	Haute Autorité de santé é (French National Authority for Health)
HRQOL	health-related quality of life
HST	highly specialised technologies
HTA	health technology assessment
ILAP	Innovative Licensing and Access Pathway
IV	intravenous
LSDP	Life Saving Drugs Program
LSDPEP	LSDP expert panel
MA	marketing authorization

Abbreviations (con't.)

MHRA	Medicines and Healthcare products Regulatory Agency
MOA	mechanism of action
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NPAF	New Product Assessment Form
PBAC	Pharmaceutical Benefits Advisory Committee
PBS	Pharmaceutical Benefits Scheme
PIM	Promising Innovative Medicines
QALY	quality-adjusted life year
QOL	quality of life
RCT	randomized controlled trial
SF-36	36 Item Short Form health survey
SMC	Scottish Medicines Consortium
SOC	standard of care
TA	technology appraisals
UO	ultra-orphan
US	United States
WHO	World Health Organisation

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