Disclaimer

Melanie Whittington

- My previous academic institution, the University of Colorado, received funding for CAR-T modeling from the Institute for Clinical and Economic Review. My comments are my own and do not represent the position of any organization I am associated with.

Judith Glennie

- I have no conflicts of interest to declare related to the contents of this presentation
- My comments are my own and do not represent the position of any organization to which I have belonged and/or consulted in the past

Fabrizio Gianfrate

- I have no conflicts of interest to declare related to the contents of this presentation

Maximilian Hunt

- I have no conflicts of interest to declare related to the contents of this presentation

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CB PARTNERS

PRICING FOR THE 'PROMISE' OF CURE

HOW RWE MAY BECOME THE NEW LEVER FOR PAYER RE-NEGOTIATIONS

WORKSHOP

For distribution to ISPOR International Attendees

MAY 20, 2020

CONFIDENTIAL

NEW YORK CITY
SAN FRANCISCO
LONDON

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We would like to first introduce our panellists, and welcome our audience.

Melanie Whittington

Kansas, USA

Assistant Professor, Department of Population Health, University of Kansas Medical Center

Judith Glennie

Toronto, CAN

President, J.L. Glennie Consulting Inc.

Former Assoc. Director, Drugs Programs Branch Ontario MoH

Fabrizio Gianfrate

Ferrara, ITA

Professor in Health Economics, University of Ferrara

Former AIFA member of Pricing and Reimbursement Committee

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New York City, USA

Senior Principal, CBPartners

Global Value Access & Pricing

AIFA: Italian Medicines Agency; MoH: Ministry of Health

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Workshop Objective and Goals

OBJECTIVE

To discuss the **evolving role** of **real-world evidence** (RWE) in **pricing and reimbursement** evaluations of **innovative one-time treatments**, such as CAR -Ts and gene therapies across **global markets**.

GOALS

- Highlight the relevance and importance of **RWE data collection** for innovative treatments such as **cell and gene therapies**
- Discuss **key issues** and considerations regarding the **collection and evaluation of RWE** in the context of **single or short-term treatments**
- Understand what **procedures** are **currently in place** to evaluate RWE and provide a **critical look** at the **future use of RWE** for evaluation of innovative single or short-term treatments
- Explore **challenges** from the **payer** and **manufacturer perspectives** and outline potential targeted **mitigation strategies**

CAR T: Chimeric Antigen Receptor T-cell; RWE: Real World Evidence

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AUDIENCE POLL

Audience members, please vote for answers through the Zoom Platform based on your perspective and experience with RWE and innovative one-time treatments.

QUESTION 1

What are the biggest challenges for health systems when making innovative one-time treatments available upon launch?

A. UNCERTAINTY OF LONG-TERM OUTCOMES

B. SIGNIFICANT BUDGET IMPACT

C. COST DENSITY OF ONE-TIME TREATMENTS

RWE: Real-World Evidence

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AUDIENCE POLL

Audience members, please vote for answers through the Zoom Platform based on your perspective and experience with RWE and innovative one-time treatments.

QUESTION 2

What are significant barriers associated with the collection and utilization of RWE to validate the long-term benefit of innovative one-time treatments?

A. IDENTIFICATION OF CLINICALLY MEANINGFUL ENDPOINTS

B. COST / LOGISTICAL BURDEN OF DATA COLLECTION

C. INCONSISTENT DATA COLLECTION ACROSS SITES

RWE: Real-World Evidence

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Agenda

1:50 – 2:05	2:05 – 2:20	2:20 – 2:35	2:35 – 3:45
THE ROLE OF RWE IN HEALTH ECONOMICS	**A CANADIAN PAYER PERSPECTIVE**	**THE EUROPEAN RWE LANDSCAPE**	**CONCLUSION**
1. Overview of the **uncertainties** surrounding innovative one-time treatments such as **CAR-Ts**	1. Canadian experience with **RWE and CAR-Ts**	1. How RWE is currently being used in **HTA and pricing decisions** in Italy and across the EU	1. Summary of the **key topics** covered during the discussion
2. Using **RWE** in **value assessment**	2. New **framework and assessment process** changes in Canada	2. How the use of RWE is expected to **evolve in the future**	2. Audience **Q&A**
3. Using **RWE** to **address uncertainties** surrounding innovative one-time treatments	3. Learnings for the **future evolution of RWE**	3. EU perspective on the **key opportunities and challenges** for payers and manufacturers	

CAR T: Chimeric Antigen Receptor T-cell; RWE: Real World Evidence; ICER: Institute for Clinical and Economic Review; HTA Health Technology Assessment

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CAR T: Chimeric Antigen Receptor T-cell; RWE: Real World Evidence; ICER: Institute for Clinical and Economic Review; HTA Health Technology Assessment

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Chimeric Antigen Receptor T-Cell Therapy (CAR-T)

CHIMERIC ANTIGEN RECEPTOR T-CELL THERAPY (CAR-T)

- An **innovative**, **one-time treatment** indicated for select cancers of the blood
  - Harvest T cells from the patient, genetically engineer the T cells in the lab to express a TCR specific for CD19, manipulate the engineered T cells, and then re-infuse the engineered T cells into the patient
  - CAR-T cells proliferate and kill malignant B-cells within the patient

CURATIVE POTENTIAL

- Axicabtagene ciloleucel is one CAR-T that is approved for **diffuse large B-cell lymphoma**
  - Response rate of 82% from pivotal study
  - Overall survival at 6 months of 80%
  - Median follow-up 15.4 months
  - Maximum follow-up 24 months

UNCERTAIN LONG-TERM EFFICACY & SAFETY BENEFIT

- Potential for lifetime of benefits, but **limited follow-up data** available
  - In part because of US Food and Drug Administration's breakthrough therapy designation and consequent accelerated approval timeline

CAR-T: Chimeric Antigen Receptor T cell
TCR: T-Cell Receptor

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Uncertainties in Clinical & Economic Evidence around CAR-T

	DETAILS	RECOMMENDATIONS
CLINICAL UNCERTAINTIES		
LONG-TERM EFFICACY	**Long-term evidence** demonstrating curative effects of is **limited, leading to uncertainties** in the **durability** of benefit	**Longer follow-up** of initial patients treated and **evidence collection** from individuals receiving treatment in the **actual care setting** is necessary to **reduce these uncertainties**
LONG-TERM SAFETY & QoL	Lack of **long-term adverse event** profile, and limited **patient-reported outcomes**, including patient's **quality of life** during and after treatment	
LACK OF COMPARATIVE DATA	Evidence from **single-arm studies** and **lack of head-to-head evidence** between CAR-Ts within the same indication **limit comparisons**	
ECONOMIC UNCERTAINTIES		
ADMINISTRATION SETTING	**Costs and reimbursement varies** by **site of care** (i.e., inpatient vs. outpatient), leading to **uncertainties** in the **financial impact**	**Evidence collection** from individuals receiving treatment in the **actual care setting** is necessary to **reduce these uncertainties**
MANAGEMENT OF TOXICITIES	Costs associated with CAR-T **adverse events management** are **highly uncertain**, given the limited **long-term safety data**	

CAR-T: Chimeric Antigen Receptor T cell; QoL: Quality of Life

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Uncertainty in Cost-Effectiveness of CAR-T: Lifetime Time Horizon

Table 2. Discounted Costs, QALYs, and Cost-effectiveness for Each Survival Model, Public Payer Perspective

Model Outcome and Treatment	Standard Parametric[a]	Flexible Parametric[b]	Mixture Cure 1[c]	Mixture Cure 2[d]	Flexible Parametric Mixture[e]
Total costs, $					
Axicabtagene ciloleucel	459 700	519 400	529 900	554 700	474 500
Chemotherapy	108 600	143 500	147 600	151 200	126 400
Incremental	351 100	375 900	382 300	403 500	348 100
Discounted total LYs					
Axicabtagene ciloleucel	2.83	7.35	7.66	9.19	5.30
Chemotherapy	0.94	3.21	3.17	3.37	2.40
Incremental	1.89	4.14	4.49	5.82	2.90
Discounted total QALYs					
Axicabtagene ciloleucel	2.07	5.84	6.34	7.62	4.14
Chemotherapy	0.55	2.46	2.55	2.72	1.80
Incremental	1.52	3.38	3.79	4.90	2.34
Cost-effectiveness					
$/LY	185 800	90 800	85 100	69 300	120 000
$/QALY	230 900	111 200	100 900	82 400	148 800

[a] Fit a parametric function to the published curve and extrapolated the parametric function to a lifetime horizon.

[b] Introduced a knot in the parametric function at the point where the published survival curve flattened.

[c] Introduced a knot in the parametric function at the point where the published survival curve ended; assumed everyone alive and responding to treatment at end of trial follow-up was cured.

[d] Introduced a knot in the parametric function at the point where the published survival curve ended; assumed everyone alive at end of trial follow-up was cured.

[e] Introduced a knot in the parametric function at the point where the published survival curve flattened and modeled excess death among long-term survivors.

Source: Whittington et al., 2019, JAMA Network Open, doi: 10.1001/jamanetworkopen.2019.0035.
CAR-T: Chimeric Antigen Receptor T cell; LY: Life-Year; QALY: Quality-Adjusted Life-Year

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Deliberating the Value of CAR-T

	ICER (USA)	NICE (ENG)
CLINICAL EVIDENCE	Moderate certainty of a small or substantial net health benefit, with high certainty of at least a small net health benefit	Meaningful overall and progression-free survival; however, evidence is uncertain
ECONOMIC EVIDENCE	Cost-effectiveness below commonly cited value thresholds over a lifetime time horizon but sensitive to time horizon and long-term benefit forecasting	Some cost-effectiveness estimates are higher than the thresholds considered an acceptable use of resources and are associated with a degree of uncertainty
VALUE DELIBERATION	Results of panel were split between low and intermediate long-term value for money	Recommended for use within the Cancer Drugs Fund if conditions in managed access agreement are followed; has potential to satisfy criteria for routine use if uncertainty is reduced

CAR-T: Chimeric Antigen Receptor T cell; ICER: Institute for Clinical and Economic Review
NICE: National Institute for Health and Care Excellence

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Real-World Evidence for Innovative One-Time Treatments

ADDITIONAL SUPPORTIVE EVIDENCE

- **Reduce uncertainties** in evidence
- **Confirm / refute** evidence available
- Provide **additional evidence** on data elements not previously collected

VALUE BASED AGREEMENTS

- Promote **value-based payments**
- Policy Implication from ICER CAR-T Review: *"For novel therapies approved with limited evidence, manufacturers and payers should consider a lower launch price with potential for increase if clinical benefits are confirmed from real-world, or a higher initial price tied to requirement for refunds or rebates if real-world evidence fails to confirm high expectations."*

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Use of Real-World Evidence in a Value Assessment

KEY CONSIDERATIONS	ADDITIONAL DETAILS

REAL-WORLD EVIDENCE AS SUPPORTING DATA	• As a **complement evidence** for:
	  • Comparative effectiveness
	  • Other benefits and contextual considerations
	• As **inputs in an economic model**

SOURCES OF REAL-WORLD EVIDENCE	• Sourced from **existing literature** or as **primary data collection**:
	  • **ICER** has previously collaborated with **patient** and **other stakeholders** to obtain new patient and caregiver **survey information**, generating real-world evidence de novo
	  • **De novo evidence** generation could include administering patient-reported outcome **surveys** or analyzing **claims data**

*"Particularly helpful under certain circumstances such as when **long-term safety** of a treatment or **durability** of a medication's **effect** is **unclear**" [ICER Value Assessment Framework Update 2020-2023]*

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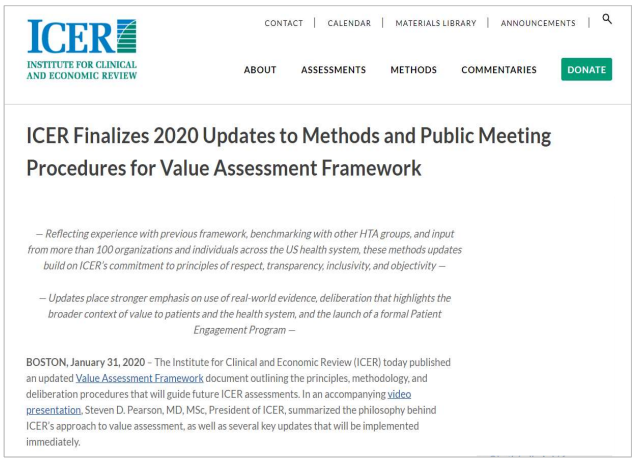
Key Update to ICER's Value Assessment Framework



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INSTITUTE FOR CLINICAL AND ECONOMIC REVIEW

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ABOUT ASSESSMENTS METHODS COMMENTARIES DONATE

ICER Finalizes 2020 Updates to Methods and Public Meeting Procedures for Value Assessment Framework

— Reflecting experience with previous framework, benchmarking with other HTA groups, and input from more than 100 organizations and individuals across the US health system, these methods updates build on ICER's commitment to principles of respect, transparency, inclusivity, and objectivity —

— Updates place stronger emphasis on use of real-world evidence, deliberation that highlights the broader context of value to patients and the health system, and the launch of a formal Patient Engagement Program —

BOSTON, January 31, 2020 – The Institute for Clinical and Economic Review (ICER) today published an updated Value Assessment Framework document outlining the principles, methodology, and deliberation procedures that will guide future ICER assessments. In an accompanying video presentation, Steven D. Pearson, MD, MSc, President of ICER, summarized the philosophy behind ICER's approach to value assessment, as well as several key updates that will be implemented immediately.

AUGMENTING EFFORTS TO USE REAL-WORLD EVIDENCE

- Ongoing commitment to use **existing** real-world evidence
- Commitment to exploring **new collaborative relationships** with organizations to generate real-world evidence that can **complement published sources**
- For treatments approved under **accelerated approval** pathways, ICER will **pilot** a **formal update process** after the treatment has been on the market for **24 months**
- In **response** to the most common **suggestion** from **patient advocacy groups**

ICER: Institute for Clinical and Economic Review

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ICER's 24-Month Real-World Evidence Update Pilot

PURPOSE

Generate **new real-world evidence** to inform updated assessments of therapies approved by the FDA under **accelerated approval pathways**

GOAL

Supplement the comparatively **limited evidence** base that often accompanies accelerated approvals with real-world evidence to provide stakeholders with a more **comprehensive understanding** of the early impacts of these therapies

TIMING

Process will begin at the **24-month anniversary** of the **Final Report posting**, and will span a period of **several months**, depending on the nature of the evidence to be generated

FDA: U.S. Food and Drug Administration; ICER: Institute for Clinical and Economic Review

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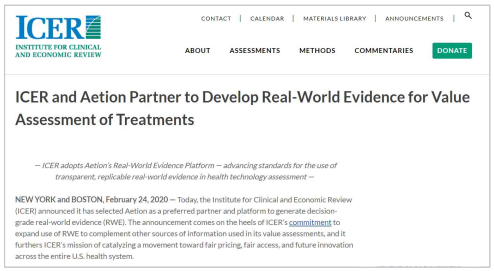
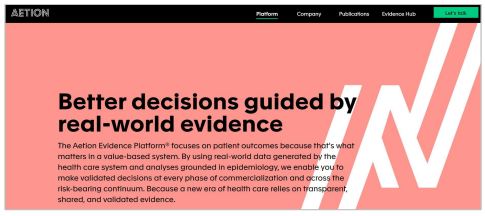
Recent Development - ICER & Aetion Partner to Develop Real-World Evidence for Value Assessment





ICER & AETION CASE STUDY

- In February 2020, ICER published a press release stating they were **adopting Aetion's Real World Evidence Platform** to advance the use of **transparent**, **replicable** real-world evidence in **value assessment**
- Aetion will be a **preferred partner and platform** to generate **decision-grade** real-world evidence
- Aetion will provide **rapid-cycle analytics** to allow ICER to quickly generate evidence with **rigor and transparency**

ICER: Institute for Clinical and Economic Review

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Agenda

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1. Overview of the **uncertainties** surrounding innovative one-time treatments such as **CAR-Ts**
2. Using **RWE** in **value assessment**
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1. Canadian experience with **RWE and CAR-Ts**
2. New **framework and assessment process** changes in Canada
3. Learnings for the **future evolution of RWE**

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1. How RWE is currently being used in **HTA and pricing decisions** in Italy and across the EU
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2:35 – 3:45
CONCLUSION

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2. Audience **Q&A**

CAR T: Chimeric Antigen Receptor T-cell; RWE: Real World Evidence; ICER: Institute for Clinical and Economic Review; HTA Health Technology Assessment

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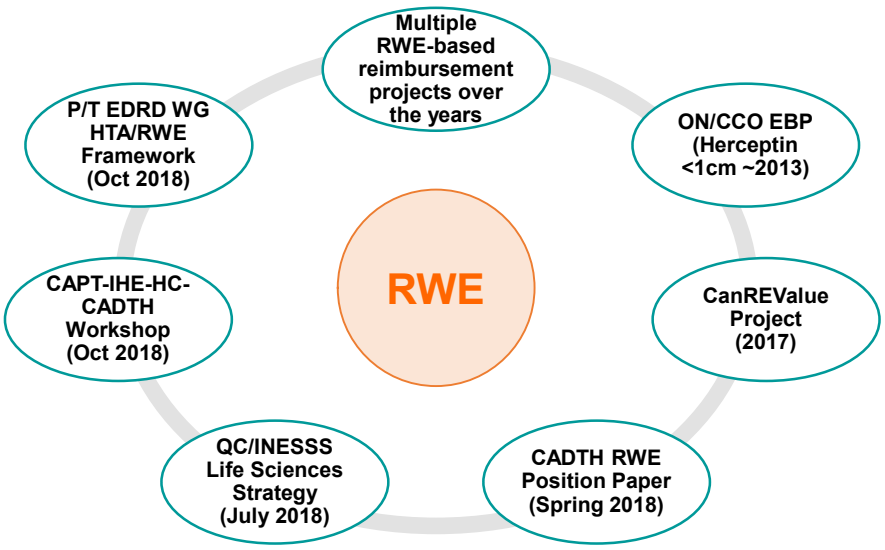
The Canadian Real-World Evidence Ecosystem



P/T EDRD WG: Provincial / Territorial Expensive Drugs for Rare Diseases Working Group; HTA: Health Technology Assessment; RWE: Real-World Evidence; CAPT: Canadian Association for Population Therapeutics; IHE: Institute of Health Economics; HC: Health Canada; CADTH: Canadian Agency for Drugs and Technologies in Health; INESSS: Institut National d'Excellence en Santé et en Services Sociaux; CCO: Cancer Care Ontario; EBP: Evidence Building Program

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Leveraging RWE for Payer Needs

INCREASING IMPORTANCE OF RWE

REGULATORY APPROVAL

- Inform **approval** and **on-going surveillance**

HEALTH TECHNOLOGY ASSESSMENT

- Support perception of **unmet need**
- Input into the **health economic analysis**

ACCESS OUTCOMES

- Product **listing agreements** (pCPA)
- **Value-based agreements** + verifying **real-world performance**

RWE: Real World Evidence; pCPA: pan-Canadian Pharmaceutical Alliance

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Canadian Experience with CAR-Ts – Prior Assessment Process

HEALTH TECHNOLOGY EXPERT REVIEW PANEL (HTERP)

- Process announced **April 2018**
- **KYMRIAH** for pediatric Acute Lymphoblastic Leukemia and Diffuse Large B-Cell Lymphoma (January 15, 2019)
- **YESCARTA** for adults with Relapsed or Refractory Large B-cell Lymphoma (August 15, 2019)

KEY COMPONENTS

- **Protocols**
- **Clinical** systematic review
- **Economic review**
- Review of **implementation considerations**, **ethics**, and patient and caregiver **perspectives / experiences**
- Recommendations report

RECOMMENDATIONS

- **Conditional funding**, including a **reduced price**
- Promising patient outcomes, but **many uncertainties** due to **limited long-term data** (safety, effectiveness)
- **Challenges and opportunities**:
  - Managing adverse events
  - Collecting long-term data
  - Determining appropriate oversight of treatment sites
  - Providing access to treatment sites
  - Possible patient and caregiver travel
  - Need for clear and transparent patient eligibility criteria

TIMELINES

- **4-8 months HTA review process**
- CADTH review carried out in **parallel** with **INESSS review**
- Regulatory approval → HTA → negotiation → funding = **13 months +**

CADTH: Canadian Agency for Drugs and Technologies in Health; CAR-T: Chimeric Antigen Receptor T cell; HTA: Health Technology Assessment; HTERP: Health Technology Expert Review Panel; INESSS: Institut National d'Excellence en Santé et en Services Sociaux

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Canadian Experience with CAR-Ts – New Assessment Process

CADTH REVIEW PROCESS FOR CELL AND GENE THERAPIES

- Established **January 2020**
- Based on **learnings from experience** with first 2 CAR-T products
- Leverages components of both **drug and medical device evaluation processes**
  - Firm **performance targets and well-established processes** for conducting reviews and issuing recommendations (drugs)
  - Additional **ethical and implementation considerations** (devices)
- To date, **no reviews completed** under new process
  - **LUXTURNA** (voretigene neparvovec; inherited retinal dystrophy) submission pending; expected to be the **first product** to be evaluated through this **new process**

CADTH Pharmaceutical Reviews Update — Issue 12

Last updated: January 9, 2020

Product Line: Pharmaceutical Review Update

Issue: 12

Result type: Report

CADTH Program Updates

1. New CADTH Process for Cell and Gene Therapies

CADTH has undertaken an internal review of our processes for drugs and devices, and established a revised process for the review of cell and gene therapies that leverages the strengths of both programs. This new process will offer stakeholders the benefits of firm performance targets and well-established processes for conducting reviews and issuing recommendations for drug products, with the additional ethical and implementation considerations that are an important strength of CADTH's medical devices processes. The following document provides a brief overview of the new process:

- CADTH Review Process for Cell and Gene Therapies

CADTH: Canadian Agency for Drugs and Technologies in Health; CAR-T: Chimeric Antigen Receptor T cell; HTA: Health Technology Assessment

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Ontario Framework for CAR-T Patient Access

CAR-T THERAPY ENROLMENT PROCESS

- **Clinician criteria / responsibilities**:
  - Only an **oncologist, hematologist or CAR T-cell specialist** licensed to practice in a Canadian province or territory can enroll patients
  - Clinician must have **confirmation** from the CAR T-cell therapy center that they will treat the patient within a **clinically appropriate timeframe**
  - Complete the **application process**
- **Patient criteria**:
  - Patient must have a **valid health card** from their Canadian province or territory of residence
  - Patient must meet **eligibility criteria**

DESIGNATED CAR-T THERAPY CENTRES

- N=1 **pediatric**, N=2 **adult** (for Ontario population – 12 million + other provinces / territories not offering therapy)
- **Funded** to deliver CAR T-cell therapy for patients who meet the **eligibility criteria**

ELIGIBILITY CRITERIA

- Pediatric and young adult patients with relapsed / refractory B-cell **ALL**
- Relapsed / refractory **lymphoma**

ALL: Acute Lymphoblastic Leukemia; CAR-T: Chimeric Antigen Receptor T cell

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Ontario CAR-T RWE Initiative

ASSESSING THE REAL-WORLD CLINICAL AND ECONOMIC OUTCOMES OF EMERGING INNOVATIVE TECHNOLOGIES IN ONCOLOGY: CAR T-CELLS

RATIONALE

- CAR Ts are an **emerging innovation** with the potential to **significantly impact care** of cancer patients
- CAR T-cells have **limited comparative clinical data** to help evaluate **effectiveness and safety** against current treatment approaches
- Given the **limited Canadian experience** and the **substantial budget impact** associated with adopting emerging technologies, incorporating this innovation into the health system requires **thoughtful assessment** of the expected **health and resource impacts**

AIM

Evaluate the **real-world health outcomes** and **economic impact** of CAR-T cell therapy in **Ontario**

IMPACT

The **evidence generated** by these evaluations can be used to make **informed decisions** regarding the **real-world impact** of this new technology, and to **help develop proper policies** and **guidelines** to ensure the **best evidence-based** care for people with cancer

Funded by the OICR-CCO Health Services Research Network

CAR-T: Chimeric Antigen Receptor T cell; RWE: Real-World Evidence; OICR: Ontario Institute for Cancer Research; CCO: Cancer Care Ontario

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What have we learned so far?

HTA

We need a **different approach** to **evaluate** cell and gene therapies

IIMPLEMENTATION

We need a **different approach** to **manage the introduction** of cell and gene therapies into the **health system**

RWE

We need a **different approach** to assess the **value** of cell and gene therapies

INTEGRATED???

HTA: Health Technology Assessment; RWE: Real-World Evidence

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Summary of Status of RWE in Canada

While there are examples of Canadian RWE projects going back to 1995, payers have been reluctant to fully embrace the role of RWE as part of product negotiations

2019 RWE PAYER RESEARCH LEARNINGS

Payer stakeholders see only a **highly limited** and **well-defined** role for RWE in the context of **VBAs**

- For a **narrow range of products** (e.g., rare diseases, rare cancers)
- No more than **2-4 RWE-based VBAs** per year
- Support for **pilot projects** to test frameworks

FRAMEWORKS UNDER DEVELOPMENT

There are currently a number of **new frameworks** under development:

- Draft **Provincial / Territorial Supplemental Process** (Oct 2018; rare disease products only)
- **Health Canada / CADTH** (general)
- **CanReValue** (oncology only)

FUTURE EVOLUTION OF RWE

Future evolution of RWE will depend on:

- Creation of **frameworks**
- **Success of pilot projects** (e.g., ON CAR-T project, CanReValue)

RWE: Real-World Evidence; VBA: Value-Based Agreements;
CADTH: Canadian Agency for Drugs and Technologies in Health; CAR-T: Chimeric Antigen Receptor T cell

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CAR T: Chimeric Antigen Receptor T-cell; RWE: Real World Evidence;
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Scopes of Real World Evidence

1. **POPULATION LEVEL TRENDS:**
Characterise diseases and data populations by understanding epidemiology trends, treatment patterns, patient adherence and disease management opportunities

2. **NEW PRODUCT DEVELOPMENT:**
Develop new products and therapies more cost effectively by assessing the use of products already on the market, designing inclusion/exclusion criteria for clinical trials, performing predictive models on virtual trials, identifying new indications

3. **VALUE OF EXISTING TREATMENT:**
Assess the value of products and therapies already on the market by observing **drug safety**, comparing the **effectiveness of products** and designing **pay-for- performance criteria**

4. **TARGETED THERAPY:**
Better **target products and services** by identifying **underserved patient populations**, **high-cost areas for risk-based product pricing**, **subpopulations with superior product response** and **tracking message effectiveness** via prescribing behaviour

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Applications of Real World Evidence

RWE is used across the development cycle to highlight unmet need, competitively position a drug before launch, understand real-world treatment outcomes, and to build an evidence base in light of immature data at the time of Phase 3 reporting

RWE IS USED TO…

- Offer deeper insights into the **patient journey**, influence **treatment pathways**, inform **health policy** and **clinical guidelines**
- **Differentiate products** using both **clinical and economic evidence**
- Respond to **regulatory questions** about **product safety**
- Build the case for **market access and pricing**
- Proactively **monitor safety** and / or **comparative effectiveness**

RWE: Real World Evidence

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Sources of Real World Evidence (1 / 2)

KEY SOURCES	ADDITIONAL DETAILS
PRAGMATIC TRIALS	• Aim to test an intervention in a **study environment that is closer to real life** than a clinical trial in terms of study **population, intervention, comparator, and outcomes**
PATIENT REGISTRY	• An organized system that uses observational study methods to collect uniform data (clinical and other) to evaluate **specified outcomes for a population defined by a particular disease, condition, or exposure**, and that serves one or more predetermined **scientific, clinical, or policy purposes**
CLAIMS DATA	• Information gathered from the **medical bills** or **medical billing claims** forms filed on behalf of a group or population and submitted by **medical providers** to government and private health insurers
HEALTH SURVEYS	• A **survey of patients or clinicians** which is conducted to collect information concerning **health** and **health-related behaviour** (such as smoking)

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Sources of Real World Evidence (2 / 2)

KEY SOURCES	ADDITIONAL DETAILS
CHART REVIEWS	• A prospective or retrospective review and extraction of **data from patient medical records** following routine clinical care
CASE REPORTS	• A detailed report of the **symptoms, signs, diagnosis, treatment, and follow-up** of an individual patient or case series.
MANAGED ACCESS PROGRAMS	• A program that allows clinicians and **patients access to investigational drugs** either **prior to regulatory approva**l or based on **conditional approval** by regulatory or reimbursement authorities.

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Real World Evidence Accepted by Payers

ACCEPTABLE RWE SOURCES FOR MARKET ACCESS

- ✓ Patient and product **registries**
- ✓ **Electronic health records**
- ✓ Routinely collected **administrative data**
- ✓ Primary **patient level data** (prospective / retrospective)
- ✓ **Population health surveys**
- ✓ **Patient reported outcomes**
- ✓ **Early Access Programs** (EAP)
- ✓ **Compassionate Use**
- ✓ **Off-label use**
- ✓ Data from **other countries** reimbursing the product

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EU: Big Data Task Force (BDTF)

BDTF: Big Data Task Force

*A joint task force of the European Medicines Agency (**EMA**) and Heads of Medicines Agencies (**HMA**)*

PRIORITY RECOMMENDATIONS REPORT:

- Deliver a **sustainable platform** (DARWIN) to **access and analyze healthcare data** from across the EU
- Establish an **EU framework** for **data quality** and **representativeness**
- Enable **data discoverability**
- Develop **EU regulatory skills in big data**
- Strengthen EU regulatory processes for **big data submissions**
- Build EU regulatory capability to **analyze big data**
- Modernize the **delivery of expert advice**
- Ensure data are managed and analyzed within a **secure and ethical governance** framework
- Collaborate with **international initiatives** on big data
- Create an EU big data "**stakeholder implementation forum**"

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Real World Evidence in the EU5

GERMANY DEU

- Act for Greater Safety (August 2019)
- **G-BA** (Federal Joint Committee): RWE in rare diseases, drugs to be prescribed only in centers collecting data on registries
- **AMNOG**: Early benefit assessment, to include comparative RWE for assessing innovative therapies

FRANCE FRA

- **HAS** may request supplemental RWE to be examined by CT for revaluation (i.e., Myozime, Yervoi)
- Actual benefit and added value
- From ATU

UNITED KINGDOM GBR

- MHRA accept RWE observational as supplemental data to Ph II and III
- **NICE**: Guidance and statement of interest, extended sources E-health; concern on selection biases

SPAIN ESP

- Local issues, local use, local registries and databases
- Collaboration between communities

AMNOG: Pharmaceuticals Market Reorganisation Act; ATU: Temporary Authorization for Use; CT: Transparency Commission; GBA: federal Joint Committee; HAS: National Authority for Health; MHRA: Medicines and Healthcare products Regulatory Agency; NICE: National Institute for Health and Care Excellence; RWE: Real World Evidence

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Managed Entry Agreements in Italy

Brand	Brief Description
Afinitor	Novartis pays back 100 percent of the treatment cost of Afinitor in case of treatment failure after three-month re-evaluation.
Avastin	Roche offers 50 percent discount for first six weeks of treatment and total dosing of Avastin is capped at 11g/patient/year.
Erbitux	Merck reimburses 50 percent of the cost of Erbitux in case of no response.
Iressa	Astra Zeneca pays back 100 percent of the treatment cost of Iressa in case of treatment failure after three-month re-evaluation.
Javlor	Pierre Fabre pays back 100 percent of the treatment cost of Javlor in case of treatment failure after a three cycle re-evaluation.
Revlimid	Celgene pays back 100 percent of the treatment cost in case of Revlimid failure after a three cycle re-evaluation.
Nexavar	Bayer rebates the cost of Nexavar in full in case of treatment failure after three months.
Sprycel	Bristol-Myers Squibb provides the first month free and rebates 50 percent of the cost of Sprycel for non-responding patients.
Sutent	Pfizer provides Sutent with a 50 percent discount on first two cycles of treatment.
Tarceva	Roche provides Tarceva with a 50 percent discount on first two cycles of treatment.
Tasigna	Novartis provides 100 percent rebate for Tasigna for non-responding patients, while the first cycle is paid in full for all patients.
Torisel	Pfizer provides the first two months of Torisel treatment free while responders are identified.
Tyverb	GlaxoSmithKline pays back 100 percent of the Tyverb treatment cost in case of failure after a three-month re-evaluation.
Vectibix	Amgen and Dompe rebate the full cost of Vectibix therapy for non-responders after a three-cycle evaluation.
Velcade	Johnson & Johnson pays back 50 percent of Velcade's treatment cost for all eligible patients during the first cycle.
Vidaza	Celgene provides an 11 percent of discount for the first three cycles of Vidaza treatment.
Xeloda	Roche reimburses the cost of Xeloda treatment in case of treatment failure in mBC.
Yondelis	PharmaMar/Innovex rebate the full cost of therapy if patients do not respond after a two-cycle evaluation.

Source: IMS Health

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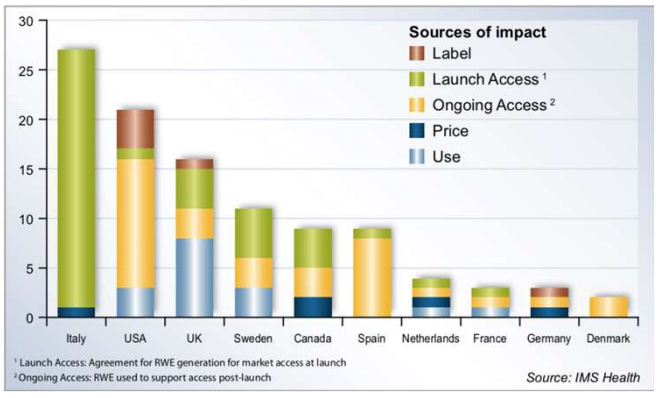
Real World Evidence Application Across Countries



- **LABEL:** influence of RWE on indications that can be legally marketed
- **LAUNCH ACCESS:** influence of RWE on enabling access at launch, including maximising a product's potential compared to its label
- **ONGOING ACCESS:** influence of RWE on enabling/restricting ongoing access for the product (e.g., formulary listing may be withdrawn based on unfavourable post-launch CE data)
- **PRICE:** extent to which RWE is used to negotiate a product's list or net price
- **USE:** influence of RWE on how a product is used in clinical practice

CE: Cost Effectiveness; RWE: Real World Evidence

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Real World Evidence Applications Across Product Lifecycle (1 / 3)

PRE-LAUNCH | LAUNCH | POST-LAUNCH

- Describe **current treatment patterns** to **understand main** competitors
- Understand the **natural history of the disease** or an aspect of the **disease course**
- Understand **current service structures** if they need to change to deliver the new medicine
- Understand **event rates, co-medication use and co-morbidities** to help inform study design
- Understand the **distributions and prognostic associations** of potentially **relevant biomarkers**

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Real World Evidence Applications Across Product Lifecycle (2 / 3)

PRE-LAUNCH | **LAUNCH** | POST-LAUNCH

- Document **clinical experience** and / or **safety surveillance** by setting up a registry or prospective study
- Demonstrate **real world outcomes achieved**, **reduction in resource use**, **patient acceptability**, and **clinical benefit**
- Identify **levels of untreated / undiagnosed patient subpopulations** to address restrictions

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Real World Evidence Applications Across Product Lifecycle (3 / 3)

PRE-LAUNCH | LAUNCH | **POST-LAUNCH**

- Support the need for a **licence extension**
- Support a **pricing and reimbursement review**
- Highlight the need for **change in practice or guidance**
- Demonstrate **suboptimal dosing or treatment**
- Identify appropriate **treatment subgroups**

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Market Access and Real World Evidence Scenarios

FUTURE SCENARIOS FOR RWE?

MORE RWE FOR…

CLINICAL TRIALS	• Fewer and Faster **Randomized Controlled Trials**?
MARKET ACCESS	• Adaptive **Regulatory Approvals** and **Market Access**? • **First Pricing & Reimbursement** based on **EAPs or Compassionate Use**? • RWE-based **Re-assessment** to Change Initial **Pricing & Reimbursement** Decisions? • Comparing Competitors for **Pricing & Reimbursement**? • RWE-based **Managed Entry Agreements**?
RWE SOURCES	• RWE by **Institutional sources**? • RWE Aggregated at **World-EU levels**?

EAP: Early Access Program; RWE: Real World Evidence

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Agenda

1:50 – 2:05	2:05 – 2:20	2:20 – 2:35	2:35 – 3:45
THE ROLE OF RWE IN HEALTH ECONOMICS	**A CANADIAN PAYER PERSPECTIVE**	**THE EUROPEAN RWE LANDSCAPE**	**CONCLUSION**
1. Overview of the **uncertainties** surrounding innovative one-time treatments such as **CAR-Ts**	1. Canadian experience with **RWE and CAR-Ts**	1. How RWE is currently being used in **HTA and pricing decisions** in Italy and across the EU	1. Summary of the **key topics** covered during the discussion
2. Using **RWE** in **value assessment**	2. New **framework and assessment process** changes in Canada	2. How the use of RWE is expected to **evolve in the future**	2. Audience **Q&A**
3. Using **RWE** to **address uncertainties** surrounding innovative one-time treatments	3. Learnings for the **future evolution of RWE**	3. EU perspective on the **key opportunities and challenges** for payers and manufacturers	

CAR T: Chimeric Antigen Receptor T-cell; RWE: Real World Evidence;
ICER: Institute for Clinical and Economic Review; HTA Health Technology Assessment

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Conclusion and Q&A

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Visit us at cbpartners.com for a summary of today's discussion and our other thought leadership posts

The panelists will now field any additional questions from the audience

Thank you for your participation!

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Thank you!

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AIFA: Italian Medicines Agency; MoH: Ministry of Health

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