Use and Applications of Real World Evidence in HTA Processes: Lessons Learned from ICER’s Experience

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Institute for Clinical & Economic Review (ICER)

• Independent non-profit research institute in Boston in its 10th year
• Multidisciplinary staff of ~30
  • External commissioning of economic models
• Mission: Improve use of evidence throughout the health care system to improve patient care and integrate considerations of value into practice and policy
• Goal to produce reports on highest impact new drugs near time of US Food & Drug Administration (FDA) regulatory approval
  • Comparative clinical effectiveness, cost effectiveness, potential budget impact for health system
  • Debated in public with voting on evidence of effectiveness & value
ICER Value Assessment Framework

Purpose:

• Takes a population-level perspective
  • NOT trying to serve as a shared decision-making tool used by individual patients and their clinicians

• Within its population-level focus, ICER’s value framework seeks to encompass and reflect experiences and values of patients.
Applications & Perspective of Use of Real World Evidence (RWE) to Support Decision-Making
Definition of “Real World Evidence”

• Evidence derived from data generated during or as a by-product of the delivery of health care in realistic settings
  • Evidence about whether interventions “work,” for whom, and in what contexts
  • Evidence explaining how and why the intervention works, and how a model can be amended to work in new settings

• Typically observational, but can also include pragmatic clinical trials, or the application of treatment effects measured in conventional RCTs to other, “real world” settings or populations

From: Green Park Collaborative Real World Evidence Project Methods Workgroup
RWE Provides Useful Information for HTA

- Fill gaps rarely addressed by clinical trials
  - Populations not represented in RCTs or standard care settings
  - Care settings not included in RCTs
  - Important long-term or cost-related outcomes
- Informing rare disease topics where RCTs difficult or not likely to occur
- Data related to implementation in actual practice
  - Understanding how context affects how a health care intervention can work in various settings

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Real world research in Latin America: Opportunities, sources and barriers

Y. Gregory, M. Barbeau, G. Machnicki, Z. Volo, O. Heisel, P. Keown
Institute for Clinical and Economic Review Publishes Guidance on Improving the Development and Use of Real World Evidence for Drug Coverage and Formulary Decisions

BOSTON – April 10, 2018 – The Institute for Clinical and Economic Review (ICER), in collaboration with the Office of Health Economics (OHE), has released two new white papers to provide guidance to payers and manufacturers on the development and use of real world evidence for drug coverage and formulary decisions. The papers were generated as part of the annual ICER Policy Summit, where life science and payer organizations meet to develop collaborative approaches to addressing key policy issues related to the generation and application of evidence to improve value in the US health care system.

"Both manufacturers and payers share common goals in applying real world evidence to decision-making," noted Steve D. Pearson, MD, MSc, President of ICER. "However, discussions at our Policy Summit highlighted the need for a common framework to help all parties gain a mutual understanding of how to tailor the entire evidence development process to achieve the best fit with key contextual factors that determine the level of evidentiary certainty decision-makers will require. There is no doubt..."
ICER Guidance on Improving Development & Use of RWE for Drug Coverage & Formulary Decisions

- Two white papers in collaboration with UK Office of Health Economics (OHE)
- Goal to provide guidance to payers & manufacturers on use of RWE
- Generated as part of ICER Policy Summit
  - Life science and payer organizations met to develop collaborative approaches to address key policy issues related to generation & application of RWE.
- RWE will play larger role in coverage and formulary decisions in the future
- Need for common framework to help all parties gain mutual understanding of how to tailor the entire evidence development process to achieve best fit with key contextual factors
- Find common ground to maximize positive role RWE can play in guiding decisions that will improve patient outcomes and overall value for the health system
RWE for Coverage Decisions: Opportunities and Challenges

- Developed as background for December 2017 ICER Policy Summit
- Sets out potential opportunities & important challenges & limitations that must be addressed in considering options for using RWE to inform insurance coverage decisions
- Highlights challenges associated with wider use of RWE, including:
  - increased potential for bias,
  - risks of incomplete data, and
  - lack of universally accepted methodological standards.
- Leaders from 22 payer and life science organizations convened to share perspectives on challenges and opportunities for RWE
Topic of Increasing Interest in Health Care Systems Globally

- Capacity for rapid data accumulation and interpretation advancing exponentially
- Computer learning, natural language processing, and evolution of electronic health records revolutionizing potential availability and use of RWE to improve health.
- Traditional randomized controlled trial (RCT) evidence declining as smaller patient populations (personalized medicine) make it harder to design studies, and costs of conducting RCTs are rising (related to increases in complexity and external standards).
- Pragmatic clinical trials that combine randomization with more real world circumstances has grown.
  - Potential to use routine data sources to record patient events and outcomes, transforming the costs, size and feasibility of such trials.
- Changing environment is creating new opportunities for the use of RWE.
Current Uses of RWE and Related Initiatives

1. Drug development: Identify targets for development of new therapies
2. Regulatory approval decisions: Limited to circumstances where RCT not practical; but FDA guidance on RWE to support regulatory decisions for medical devices, expected to issue RWE guidance for drugs (21st Century Cures Act)
3. FDA safety monitoring & signals: FDA use of RWE to monitor post-approval drug safety is much more established, most recently via Sentinel Initiative.
4. HTA assessments & payer coverage decisions - initial: Payers use epidemiological data (e.g., insurance claims) to estimate potential population that could require treatment, and potential costs and cost offsets.
5. HTA assessments & payer coverage decisions – reassessments: Reconsider coverage, discounts & formulary tier based on how products perform.
Potential Payer Uses of RWE

(1) Effectiveness outside investigational setting
(2) Comparative effectiveness
(3) Long-term outcomes
(4) Safety, including rare or late-occurring adverse events
(5) Cost impacts
(6) Effectiveness in subpopulations
(7) Effectiveness and safety in populations not included in pivotal clinical trials
Challenges Associated with Use of RWE

• Some stakeholders see great value in RWE and are exploring ways to make use of these data sources, but there are inherent limitations and numerous challenges associated with RWE application to coverage decisions.

• Acceptance of expanded future role for RWE is not universal, particularly if seen as reducing the amount of RCT evidence available.

• Among challenges associated with RWE are:
  • bias and confounding;
  • incomplete data;
  • data mining;
  • access to data; and
  • lack of universally accepted methodological standards.
Key Opportunities for RWE: Improving Current Uses

• Evaluation of drug effectiveness, safety, and adherence in real-world patients
  • To evaluate durability of benefits and side effects over a longer period than studied in RCTs
  • Exploring population subgroups in which clinical benefit is (likely to be) greatest
  • Gaining comparable evidence on the new drug and on the comparator (“usual care”)
  • Evaluating benefits when used outside of the initial indication
  • Leveraging advantages of pragmatic clinical trials to inform all aspects of the evaluation of drug effectiveness and safety

• Evaluation of comparative effectiveness through indirect comparisons (network meta-analysis) enriched with outcomes from real-world patients

• Evaluation of outcomes that are not measured during standard drug development process, for example any “other benefits” or wider elements of value such as the impact on productivity

• Evaluation of budget impact and cost-effectiveness in a real world setting
Key Opportunities for RWE: Future Uses

• Innovative study designs such as nested trials within cohorts can combine benefits of collecting data from real world settings while incorporating best practice methods (e.g., randomization as in traditional RCTs).

• Real time monitoring of patients (e.g., wearables) will enable RWE collection to become routine, and could reduce cost of evidence generation, expand available datasets, and allow remote monitoring for better medication management.

• Developing adaptive regulatory pathways linked to coverage with evidence development to monitor safety and effectiveness of new treatments with the highest uncertainty.

• Ability to collect post-launch RWE is crucial for accelerated access arrangements to be successful from both payer and innovator perspectives.
Understanding the Context, Selecting the Standards: A Framework to Guide the Optimal Development and Use of RWE for Coverage and Formulary Decisions

- Addresses key issues that emerged from discussion during Summit
- Need for a common approach to tailor development of RWE to meet perceived evidentiary needs of decision-makers.
- Conceptual framework to guide generation and adoption of RWE via shared understanding of key contextual issues, such as:
  - whether RWE is intended to support an argument of superiority of a drug vs. similar comparators, or
  - whether RWE will be used to argue for increased drug spending in hopes of lowering overall health system costs.
Understanding the Context & Selecting Standards

- Efforts to design standards for prospective RWE analyses have convened manufacturers, payers, and patient groups to ensure that evidence generated is both rigorous and fully informed by what matters most to patients.

- Payers and manufacturers often perform analyses of RWE, with wide variation in scope and sophistication of efforts.

- Acknowledged ability of RWE to fill critical gaps in understanding about effectiveness and value, BUT...

- Some level of suspicion that analyses using observational data are less reliable and more open to manipulation than data from RCTs.

- Numerous white papers have addressed barriers to use of RWE by payers, or have outlined best practices in observational analysis methods, to create more transparency and generate more trust in results of manufacturer-driven analyses.
Understanding the Context & Selecting Standards

• ICER Policy Summit developed new conceptual framework and specific steps to help both manufacturers and payers meet the challenge of developing observational RWE through a transparent process that can be considered credible by all stakeholders.

• Framework addresses 3 elements largely missing from earlier efforts focused on defining “best practices” or “standards” for RWE:
  1) how to understand the role that contextual factors play in determining how high the evidentiary standard needs to be in each situation;
  2) how to tailor key process and methodological approaches to match that evidentiary standard; and
  3) how to ensure that broader process principles that support transparency are integrated successfully throughout the course of any RWE initiative.
Overview of Conceptual Framework

• To support communication and active collaboration on RWE, payers and manufacturers need clear understanding of various steps within the process of developing and using RWE, to increase validity of the analysis and ensure optimal application to coverage and formulary decisions.

• Specific steps range from measures to ensure data integrity, to ways to increase the transparency of analytic protocols, to mechanisms for testing the validity of the results.

• When these standards for producing high-quality RWE are ignored, high risk of being incomplete, clouded by confounding variables, and ultimately misleading.

• Meeting the most rigorous form of every standard that has been proposed for RWE takes substantial time and resources, creating a barrier that can stymie efforts to develop and use RWE.

• Need to strike right balance between rigor and feasibility to produce RWE that will be persuasive in coverage and formulary policy, by considering type of evidentiary assertion that it is intended to support and context surrounding the policy decision to be made.
Developing a Shared View of Evidence and Process Standards at the Start

Contextual considerations influence payer expectations and will suggest either a “High” or “Low” bar for the evidence and process standards necessary for RWE to be viewed as persuasive.

High Evidence Bar Situations
- Assertion of superiority over other Rx
- Will expand use within or beyond label
- Will increase drug spend
- Will conflict with existing RCT results
- Will require big shift in practice
- Counter-intuitive or lack of rationale to give face validity to results

Low Evidence Bar Situations
- Assertion of equivalent effectiveness of a lower cost agent
- Will not expand use
- Signal of new safety concern
- Will complement existing RCT data to fill gaps
- Will not require big shift in clinical practice
- Strong rationale supporting the face validity of results

Framing the Question
- Clarify how the question/hypothesis match the needs of decision-makers for the type of decision
- Define the PICOTS*

Curating Data
- Ensure that people who know the nuances of the data source are involved
- Perform rigorous cross-validation of data

Establishing Methods
- Post the protocol in advance
- Work before analyses begin to standardize eligibility and other criteria

Verifying Analyses
- Replicate results using different methods within same data set
- Replicate using different data sources
- Share analytic code

Making the Decision
- Integrate RWE with other evidence
- Disseminate RWE in justifying decision
- Manage potential impact on patients, clinicians, and health system

Grounding through transparency, collaboration, and communication

*PICOTS: Patients, Intervention, Comparators, Outcomes, Time Horizon, Setting
Developing a Shared View of Evidence and Process Standards: Determining the Evidence Bar

Before beginning RWE analysis, prospective research protocol should identify key contextual considerations to determine the evidence level and corresponding methodological and process standards that should be followed.

- Associated with understanding level of skepticism that will meet results of RWE
- Select more rigorous standards when skepticism is likely to be high.
- Begin with type of evidentiary assertion that RWE is intended to make.
  - High: Superiority for particular drug in comparison to others (indicator that payers will require a relatively high evidentiary bar), or
  - Low: Equivalent effectiveness of a lower-cost agent among two or more drugs.
Developing a Shared View of Evidence and Process Standards: High Evidentiary Bar

• Other contextual considerations that suggest a high evidentiary bar for RWE include:
  • Superiority for particular drug in comparison to others
  • Used to inform coverage or formulary decisions that would expand use of a drug and increase cost
  • Assertions that a more expensive drug would lead to lower overall costs across the health system
  • Suggesting need for substantial changes to clinical practice
  • Conflicts with findings from randomized controlled trials (RCTs)
  • Lacks a clear underlying rationale (i.e., a biomedical explanation for the results)

• Consider whether any RWE program of observational studies can achieve degree of trustworthiness required. When bar for evidence is very high, consider pragmatic clinical trials (PCTs) a potentially better option than observational RWE.
Developing a Shared View of Evidence and Process Standards: Low Evidentiary Bar

• Relatively low evidentiary bar is often satisfactory when:
  • Intended assertion will be that lower-cost drug offers equal effectiveness in real-world settings when compared to more expensive options
  • Assertion supported by RWE will not expand use of current treatments or require a large shift in clinical practice
  • Strong underlying rationale behind the findings (e.g., equivalent outcomes for drugs with similar mechanisms of action)
  • Findings complement existing RCT data to fill obvious gaps in knowledge (e.g., use in a population group not included in RCTs)
  • If signaling new safety concern, as payers (& regulators) are risk-averse and wish to take early steps to minimize potential harms to patients
Developing a Shared View of Evidence and Process Standards: Collaboration & Communication

• Develop shared view of data & process standards that can best meet evidentiary bar for specific analyses, before RWE effort begins

• Payers value perceived validity, regulatory requirement of RCTs to justify new approvals
  • Hesitant to use RWE if it could undermine incentives for manufacturers to conduct RCTs
  • Understand RCTs often fail to address longer term, comparative effectiveness, or patient & clinician acceptability, & see RWE as complement to RCTs, useful to fill in gaps in evidence
  • Generally drugs do not perform as well in practice as in RCTs, so RWE claiming otherwise viewed with skepticism

• Manufacturers need to understand how much scrutiny (& skepticism) payers will focus on data and methods
  • Should be mindful of these views when approaching payers to discuss contextual considerations relevant to their proposed generation of RWE
Developing RWE: Framing the Question

• RWE will have chance of meeting evidentiary bars and being fit for informing policy decisions only if decisions tailored to meet these within each step of RWE analysis.
• Frame research question & hypotheses to match intended evidentiary assertion
• Link with adequately curated data set, clear methods, & procedures for verification
• Consider whether observational study will meet evidentiary bar, or whether RCT or PCT needed
• Discussions about evidence, process standards and proposed RWE research questions between manufacturers, payers to ensure that RWE will be accepted by broad set of organizations.
• To make tangible, helpful to delineate specific PICOTS* for the analysis, to ensure full understanding of scope and intent of analysis and help avoid later misunderstandings.

*Population, Interventions, Comparators, Outcomes, Timing, Settings
Developing RWE: Curating the Data

- The higher the evidentiary bar is for specific RWE analysis, the more attention needs to be given to curating data sources to ensure they will meet agreed-upon standards.
- When prospective, data sources & definitions can be addressed collaboratively to maximize transparency and reliability of data.
- However, most RWE analyses use data previously gathered through routine mechanisms.
- Curating data sources therefore critical to enhance trustworthiness of retrospective RWE.
  - Ensure those who know nuances of data sources involved with analyses from earliest stages.
  - For example, drug utilization patterns are heavily influenced by benefit design and coverage policies; any RWE that evaluates cost needs to account for these factors, as results may differ in other data sets with different preferred agents and benefit designs.
- Without expertise in specific data sources, problems can be very difficult to spot.
  - Reason some payers more likely to believe their own data rather than analyses using other data sets, even well-respected sources.
Developing RWE: Establishing Methods

• Numerous efforts outline key approaches for RWE analytic methods to address perceived limitations (e.g., propensity score matching, other ways to reduce likelihood of confounders).

• Main point is that basic methodologic requirements should be core to RWE analysis, but additional focus and effort required when higher evidentiary bar.

• Steps to heighten transparency or rigor of RWE methodology include:
  1) engagement of outside academic experts;
  2) posting analytic protocol in advance of any work; and
  3) careful attention to all eligibility and outcome definitions, woven into curation of data sources and involving individuals deeply knowledgeable of source data.

• Manufacturers, payers & other organizations (e.g., ISPOR) should develop standard definitions for, e.g., adherence & other metrics, and deviation from these definitions should be accompanied by transparent justification.
Developing RWE: Verifying Analyses

• Critical step to assess credibility of RWE for informing coverage and formulary decisions
• Mechanisms to verify analyses offer broad set of choices to select tailored approach to evidentiary bar.
  • Options include efforts to replicate results using different methods within same data set (generally easier), or trying to replicate results using same methods applied to different data sources, including payer’s own data (likely needed when evidentiary bar is high).
• Analytic code sharing with external parties important, but concerns around “transfer of value” (needs regulatory clarification)
• Validation by independent party or peer-reviewed journal publication also add trustworthiness.
  • Academic consultants helpful in evaluating relative credibility of externally derived RWE.
  • However, if paid by manufacturers will always be viewed skeptically, especially with manufacturer-sponsored RWE.
  • In addition, third parties unlikely to have been involved in data curation, therefore may miss important nuances of data sources.
Developing RWE: Verifying Analyses

• Commitment to submit RWE for peer review should remain bedrock of verification.
• Payers often use publication in highly-respected journals as proxy for RWE quality.
• Positive social value to peer review & publication, including inherent check provided by external experts, broader sharing of methods and results, and fostering of ongoing dialogue around RWE among all stakeholders.

• However, some caveats should be noted:
  • Unlikely that journal reviewers will know nuances of data sources
  • Timeline for peer review and publication usually fails to meet needs of manufacturers or payers

• Given limits of peer review, uses of RWE to inform coverage and formulary decisions will need to rely on verification using more timely approaches, as a complement to eventual peer review.
Applying RWE: Making the Decision

• If contextual considerations have been discussed and clear understanding reached on type of assertion intended and related need for a high or low evidentiary bar, RWE produced should be fit for informing coverage and formulary decisions.

• Nonetheless, important to note that best practice in using RWE includes need to integrate transparently with other evidence sources, and to disseminate RWE evidence as part of justification for decisions.

• Clinicians, patients, & other stakeholders should be informed of the role RWE has played, including steps that payer and manufacturer have taken to ensure trustworthiness of results.
Process Principles: Transparency, Communication, Collaboration

• Underpinning each step of development process for RWE in HTA are several critical principles that must govern the entire process, requiring constant attention to transparency, communication, and collaboration.

• Methods to achieve transparency include posting RWE protocols in advance, sharing results and analytic code, and submitting work for peer reviewed publication.

• But also includes more subtle transparency required for effective discussion of contextual considerations that frame the entire RWE process.

• Ultimately, for benefits of RWE to outweigh limitations and risks in coverage and formulary decisions, all of these process principles must thoroughly infuse every part of the evidence generation process.
Conclusion

• In conclusion, it bears repeating that environment for RWE development and use has been changing rapidly in recent years.

• Payers actively analyzing their own RWE to seek understanding of value for money that new (＆old) interventions provide.

• Researchers & manufacturers have new methodological tools to address some acknowledged RWE limitations, in a health care environment that is eager for data to distinguish best way to care for patients while controlling health system costs.

• Manufacturers & payers share goals in application of RWE to decision-making, but priorities often differ and mismatch between methods and purposes or perspectives of decision-makers is common.
Conclusion

• Conceptual framework presented here focuses on critical element of contextual considerations in setting the stage for successful RWE development and application.

• Contextual considerations, best addressed through discussion between manufacturers and payers, help define type of evidentiary assertion that RWE will attempt to make, and associated evidentiary bar that RWE will need to reach to be viewed as helpful.

• Guided by shared understanding of contextual considerations, supported by principles of transparency, collaboration, and communication, RWE can be developed and applied as a vital complement to other evidence in improving care for patients.
Knowledge & Experience from ICER Assessments
Examples of ICER’s Use of RWE in Evidence Assessments

- Net price: as derived from net sales and revenue (SSR Health Database)
- Non-intervention health care costs: from claims analyses when available
- Ex.: Abuse-deterrent formulations (ADF) of opioids – Claims analyses used for:
  - Incidence of abuse with opioids
  - Discontinuation of therapeutic use
  - Opioid and other health care costs
  - Opioid use prevalence in Massachusetts
ICER Value Assessment Framework

Goal: Sustainable Access to High-Value Care for All Patients

Long-Term Value for Money
- Comparative Clinical Effectiveness
- Incremental Cost-Effectiveness
- Other Benefits or Disadvantages
- Contextual Considerations

Short-Term Affordability
- Potential Budget Impact
Comparative Clinical Effectiveness

• ICER evaluates evidence from multiple sources, not just RCTs, useful in judging comparative clinical effectiveness of options.
  • Patient groups inform what outcomes are important, differences across severity, time in disease course, etc.
  • Patient groups inform opportunities for using or generating real-world evidence

• Whenever possible from available observational data or data provided by manufacturers, ICER includes an evaluation of the heterogeneity of treatment effect for key clinical outcomes.

• RWE can confirm magnitude of comparative net health benefit and the level of certainty in the evidence on net health benefit
Incremental Cost Effectiveness

• RWE may be useful for:
  • Costs/offsets from current treatments
  • Real world effectiveness data
  • Data on discounts/rebates (current & anticipated)
  • Productivity effects, other costs
Other Benefits or Disadvantages

• Benefits or disadvantages not considered as part of evidence on comparative clinical effectiveness:
  • Methods of administration that improve or diminish patient acceptability and adherence
  • Public health benefits, e.g., reducing new infections
  • Treatment outcomes that reduce disparities across various patient groups
  • More rapid return to work or other effects on productivity (if not considered a benefit as part of comparative clinical effectiveness)

• Not usually captured in RCTs, so rely on RWE, discussions with patients, etc.
Contextual Considerations

- Contextual considerations include ethical, legal, or other issues that influence the relative priority of illnesses and interventions.

- Quantitative RWE needed for issues to be considered:
  - Is this a condition of notably high severity for which other acceptable treatments do not exist?
  - Are other equally or potentially more effective treatments nearing introduction into practice?
  - Would other societal values accord substantially more or less priority to providing access to this treatment for this patient population?

- Information may be obtained from literature & discussions with clinicians, patients, manufacturers, payers, policy makers, etc.
Potential Budget Impact

• Estimated net change in total health care costs over an initial (5-year) time-frame

• Need for RWE on interventions potentially displaced, including market share, prior interventions’ utilization patterns, especially if related to Rx/condition/market criteria:
  • Magnitude of improvement in clinical safety and/or effectiveness
  • Patient-level burden of illness
  • Patient preference (ease of administration)
  • Proportion of eligible patients currently being treated
  • Primary care vs. specialty clinician prescribing/use
  • Presence or emergence of competing treatments of equal or superior effectiveness
Thank you