Enabling the Potential of Real World Data

Neil Corner, GM, IQVIA Canada
Nancy Dreyer, Chief Scientific Officer and SVP, IQVIA
Figuring out the correct hierarchy of evidence has refined researchers’ PowerPoint skills – but remains locked in a paradigm which ignores the fact that we have been studying the perfect patient in the perfect setting.

Source: Google image search October 2019, hierarchy of clinical evidence
Yet regulators are no longer tied to the old paradigm

Scott Gottlieb, Former FDA Commissioner

“Pre- and post market evaluations should be thought of as parts of a continuum rather than as two separate and distinct processes; in particular, he said, the “need for a point of regulatory accountability” should not preclude the possibility of evaluating products over their life cycle of use. RWE offers a way to better inform the benefit–risk profiles for medical products and is already used routinely by FDA to evaluate safety and emerging risk”

“FDA will uphold and promote the “gold standard” for evidence; however, the source of that evidence is not mandated”

Source: Examining the Impact of Real-World Evidence on Medical Product Development
I. Incentives Proceedings of a Workshop—in Brief February 12, 2018
Health Canada is embracing RWE in a structured logical way, challenging the traditional evidence generation paradigm

• “This project aims to improve our ability to assess and monitor the safety, efficacy, and effectiveness of drugs across the drug life cycle. It will do this by optimizing the use of RWE through stakeholder engagement”

• The project is expected to be complete in 2022 and anticipated outcomes include:
  - Increased use of RWE to enhance regulatory decision making/risk communications through drug lifecycle
  - Improved use and sharing of RWE with health care system partners
  - Increased clarity for stakeholders on where and how RWE can support regulatory decision making
  - Improved access to drugs through the use of new sources of evidence to support drug applications

The Government of Canada is excited by the potential of using high-quality, real-world evidence to increase timely access to new treatment options for all Canadians, particularly special patient populations.”

Ginette Petitpas Taylor, Minister of Health

Sources: Health Canada "Increasing access to new treatments for special patient populations 16-Apr-2019
Health Canada “Strengthening the use of real world evidence for drugs 22-Aug-2018
As part of the initiative, Health Canada with CADTH and INESS has begun
the project “optimizing the use of RWE to inform regulatory decision-making

Planned approach for implementation

1. Developing Guidance for Industry and Data partners
   • Publishing principles and guidance for industry and data partners on the key data elements needed for decision points across
     the product life cycle and how HC and industry can work together to optimize RWE use early on in submission discussion

2. Developing and Implementing a Transparent Approach to Assessing Quality of Evidence
   • Documenting the approach to assessing quality of evidence submitted across the life cycle
   • Aim to support data producers in collecting the right data of sufficient quality to inform regulatory decision making

3. A Phased Approach to Implementation
   • Health Canada already accepts RWE As part of submissions across life cycle, however with the guidance and quality of
     evidence (QoE) approach clarified, we will work with willing partners to phase in deliberate use of RWE starting with product
     lines for which use of RWE provides clear value-add to the health system and to Canadians. Lessons learned will be used to
     optimize the approach for future phases

4. Working with Partners to Optimize Data Availability
   • Collaborating with partners to support the development/sharing/optimization of sources with greatest return on investment for
     Canadians
   • Monitoring the safety and effectiveness ness of medical devices on the market requires data, both to identify signals and
     proactively assess for potential issues (regulatory/non regulatory solutions will be assessed)

Source: Adapted from Defining decision-grade real-world evidence and its role in the Canadian context: A design sprint
The workshop was held October 21, 2018 in Toronto, Ontario, as a satellite to the 2018 Annual Canadian Association for Population Therapeutics Conference.
The workshop was developed and delivered as a joint partnership between the Canadian Agency for Drugs and Technologies in Health (CADTH); Canadian Association for Population Therapeutics (CAPT), Health Canada, and the Institute of Health Economics (IHE). CADTH and Health Canada provided unrestricted grants to support the workshop; CAPT and the IHE provided in-kind support.
Health Canada is calling for RWE submissions now for certain situations to develop regulatory RWE policy

“We encourage RWE submissions:

1. That aim to expand evidence-based indications for populations often excluded from clinical trials (ex: children, seniors, and pregnant women)
2. For drugs/diseases where clinical trials are unfeasible such as may be the case with rare diseases
3. Where clinical trials are unethical, as may be the case during emergencies where dosages from animal studies may need to be extrapolated to treat humans potentially exposed to chemical or biological threats.”

Source: Optimizing the Use of Real World Evidence to Inform Regulatory Decision-Making
Health Products and Food Branch Notice
April 16, 2019
Real World Data sources are changing, today the model provides a detailed linked comprehensive view of the patient in the real world enabling regulatory standard data to support evidence generation.

Collectable over time for cohorts of patients:
- Medication
- Co-medications
- Diagnosis
- Co-morbidities
- Labs
- Diagnostics
- Vitals
- Patient Outcomes
- HCRU
- Quality of Life
- Productivity
- Presenteeism
- Absenteeism
- Re-admissions
- Mortality/Survival
- Etc.

Phase IV Studies including PROs
Academic Database Research
Literature Reviews
Registries

Year 2009

Year 2019

IC/ES
Physician eCRF
Registry
Wearable
eDiary/ ePRO
EMR
PSP
Nancy Dreyer, PhD, MPH
*Chief Scientific Officer & Senior Vice President, Real-World & Analytic Solutions*

Nancy Dreyer leads the Center for Advanced Evidence Generation, focusing on the use of real-world evidence using minimally interventional and non-interventional study designs. Her current interests focus on determining when real-world evidence is reliable enough for regulatory use and innovative study designs to advance understanding about treatment effectiveness and safety.

She has worked with the FDA and the European Medicines Agency and was recently appointed to the Clinical Trials Advisory Committee of the Patient-Centered Outcomes Research Institute. She also serves on the Science Advisory Council for DIA and has been a Standing Consultant to the NFL Health and Safety Executive Committee since 2013. She is a Fellow of both the International Society of Pharmacoepidemiology and DIA.

Highly noted publications include her work as co-editor of “Registries for Evaluating Patient Outcomes: a User Guide,” published by the US Agency for Research on Healthcare and Quality, and a highly downloaded 2018 publication on advancing a framework for regulatory use of real-world evidence. She is also known for creating the GRACE Checklist, the only validated checklist for measuring the quality of observational studies of comparative effectiveness.

She is an Adjunct Professor of Epidemiology at the UNC Gillings School of Global Public Health in North Carolina and a two-time recipient of *PharmaVOICE* magazine’s annual list of the 100 most influential and inspiring individuals in life sciences. In 2019, she received DIA’s Global Inspire Award for Author of the Year for “Advancing a framework for regulatory use of real-world evidence: When real is reliable,” the most downloaded publication in 2018 in *Therapeutic Innovation & Regulatory Science.*
Knowing when and how to use real-world data to support medical product approvals and use

Beyond the 1%

Nancy A Dreyer, Chief Scientific Officer
IQVIA Real-World Solutions
October 21, 2019
Toronto
<1% of the population participates in clinical trials

What does this mean for the rest of us?
Traditional hierarchy of medical evidence ranks RCT as better than non-interventional study designs

Strengths:
- Only treatment varies
- Randomization is used to minimize influence of known and unknown confounders

Limitations:
- Higher costs and resources
- Limited generalizability

- Traditionally used for post-market safety/surveillance
- Measures comparative effectiveness & safety (no placebo)

- Less confidence in the data, design and analysis
- No guidance exists as yet
Studying treatment effects – time to move beyond study design

The results of well-designed observational studies do not systematically overestimate the magnitude of the effects of treatment as compared with those in randomized, controlled trials on the same topic.

“Our results across all reviews (pooled ROR 1.08) are very similar to results reported by similarly conducted reviews. As such, we have reached similar conclusions; on average, there is little evidence for significant effect estimate differences between observational studies and RCTs…”

The problem…is that only some observational studies are misleading (just as some RCT are misleading), but that no one has devised a foolproof method for distinguishing those that are useful from those that are misleading.

Sacks, H. Letter to Editor, NEJM Volume 343 Number 16 · 1195, 2000
Oncology drugs are often approved using surrogate endpoints but few show any survival benefit

Source: Kim C, Prasad V. Cancer drugs approved on the basis of a surrogate end point and subsequent overall survival: an analysis of 5 years of US FDA approvals. JAMA Internal Med 2015; 175(12):1992-1994

50% of all cancer drugs approved with surrogate endpoints showed no overall survival benefit

Figure 2. Overall Survival Results for Cancer Drug Approvals Granted on the Basis of a Surrogate End Point

FDA approvals for oncology drugs from 1/2008 to 12/2012
Digitization of health care provides new opportunities to close the divide between research and clinical care

- Improve efficiency of clinical research -- capitalize on data that is being captured every day by getting information from more diverse settings and populations

- Big data – potential for detection of infrequent events, long-term but infrequent outcomes

- Lower resource intensity – more questions answered

Sources: Adapted from Jacqueline Corrigan-Curay, FDA, presented August 26, 2019 at Int'l Conf of Pharmacoepidemiology
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- When RWE is good enough to be reliable
- New designs that maximize value of RWE
- Future state
When are RWD good enough?
21st Century Cures Act is intended to enable rapid modernization


Current scope of 21st Century Cures Act is to formalize and systematically expand use of RWE to support changes to labeling about drug product effectiveness, including

- adding or modifying an indication, such as a change in dose, dose regimen, or route of administration
- adding a new population, or
- adding comparative effectiveness or safety information

Many methods are discussed, including pragmatic trials and external comparators, but no guidance provided yet

“As the breadth and reliability of RWE increases, so do the opportunities for FDA to make use of this information”


Sources: FDA Framework for FDA’s Real-World Evidence Program_December 2018
**Japan echoes growing interest in regulatory use of RWD**

*Pharmaceutics and Medical Devices Agency guidance on RWD submissions scheduled for release in 2020*

- The envisaged use in regulatory submissions would be first seen in limited areas such as rare diseases …or to establish safety measures.
- PMDA has already launched pilot-based regulatory consultation services for the use of registry data in new drug applications.
- Guidelines planned for March 2020 will be shaped by learnings from the pilot consultation services. They will include the agency’s basic position on RWD use in submissions and “points to note” to ensure integrity.
- Draft guidelines will be put up for public comments, with the final version expected to be announced in the next fiscal year.
Big Data Report from EMA
February 13, 2019

• Summarizes taskforce reports on regulatory acceptability of big data

• Big data offers evidence which may be derived from unstructured, heterogeneous and unvalidated data of unknown provenance and unknowns around potential bias with additional uncertainties of accuracy and precision

- Data are generated under different scenarios and for different purposes which rarely includes medicines regulation

- Data ownership resides with multiple stakeholders many of which have no need to engage with the regulatory system

Sources: http://www.hma.eu/506.html
### Same interests and challenges everywhere

**Synopsis of the results from the industry survey in the EMA Big Data Report**

<table>
<thead>
<tr>
<th></th>
<th>Companies (&gt; 250 employees)</th>
<th>SMEs (&lt; 250 employees)</th>
</tr>
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<tbody>
<tr>
<td><strong>Greatest impact of big data:</strong></td>
<td>• Target identification • Patient stratification and personalised medicines • Post-authorisation safety</td>
<td>• Outcome identification • Informing on patients reported outcomes • Diseases prevalence</td>
</tr>
<tr>
<td><strong>Highest concerns on the validity of big datasets:</strong></td>
<td>• RWE data sets • Social media</td>
<td>• “-omics” • Imaging datasets</td>
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<tr>
<td><strong>Key challenges in the use of big datasets:</strong></td>
<td>• Data access • Data privacy • Data harmonisation</td>
<td>• Data security • Data validation • Data reproducibility</td>
</tr>
<tr>
<td><strong>Greatest international challenges:</strong></td>
<td>• Harmonisation on many aspects within and between countries including on access rules, data protection/privacy, data standards, collection, validation. • Data quality • Data access</td>
<td></td>
</tr>
<tr>
<td><strong>Regulatory measures to address these challenges:</strong></td>
<td>• Need for clear regulatory guidance (including on usability of big data in regulatory decision) for better harmonisation (see above row) • Facilitation of access to the data, fostering data sharing</td>
<td></td>
</tr>
</tbody>
</table>

Sources: [http://www.hma.eu/506.html](http://www.hma.eu/506.html), table 1
Framework for Evaluating RWD/RWE for Use in Regulatory Decisions

- Are the RWD are fit for study purpose?
- Is the trial or study design likely to provide adequate scientific evidence to answer or help answer the regulatory question?
- Does the study conduct meets FDA regulatory requirements?
RWE: Guidance for Evaluating the Quality of Observational Studies of Comparative Effectiveness

A Validated Checklist for Evaluating the Quality of Observational Cohort Studies for Decision-Making Support

Citation
Dreyer NA, Bryant A, Velentgas P. The GRACE Checklist: A Validated Assessment Tool for High Quality Observational Studies of Comparative Effectiveness. *Journal of Managed Care & Specialty Pharmacy* 2016; 22(10) 1107-1113

Recommendations

- **International Society of Pharmacoepidemiology (ISPE)**
  Citation: *Guidelines for Good Pharmacoepidemiology Practice*. *Pharmacoepidemiology & Drug Safety* 2016 25:2-10

- **Journal of Managed Care and Specialty Pharmacy (JMCP)**
  Citation: Happe LE: Announcing New Article Categories. *J Manag Care Spec Pharm*, 2015 Dec;21(12):1102-1103

- **National Institute for Health and Clinical Excellence**

- **National Pharmaceutical Council (NPC)**

- **European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP)**
  Citation: *Guide on Methodological Standards in Pharmacoepidemiology (Revision 5)*. EMA/95098/2010

www.graceprinciples.org
GRACE Checklist for RWE: 11 questions on data & methods

Classification & Regression Tree (CART) of expert raters: example

- Were concurrent comparators used?
  - Yes, sufficient quality for purpose.
  - No/not enough information, insufficient quality.

- Was the primary outcome(s) measured or identified in an equivalent manner between group(s)?
  - Yes, sufficient quality for purpose.
  - No/not enough information, insufficient quality.

- Were important covariates that may be known confounders or effect modifiers available and recorded?
  - Yes, sufficient quality for purpose.
  - No/not enough information, insufficient quality.

- If YES, sufficient quality for purpose.
  - Were sensitivity analyses conducted?
    - Yes, sufficient quality for purpose.
    - No/not enough information, insufficient quality.

Dreyer NA et al. The GRACE Checklist: A Validated Assessment Tool for High Quality Observational Studies of Comparative Effectiveness. J Managed Care & Specialty Pharmacy 2016; 22(10) 1107-1113
Classification & Regression Tree (CART) analysis

GRACE Checklist for RWE: 11 questions on data & methods

Single best quality predictor (71% sensitivity; 81% specificity) for composite endpoint of

- expert assessments,
- impact factor of journal where published and
- number of article citations

Were concurrent comparators used?

If NO/NOT ENOUGH INFORMATION is reported, the article is considered insufficient quality.

Were important covariates that may be known confounders or effect modifiers available and recorded?

If NO/NOT ENOUGH INFORMATION is reported, the article is considered insufficient quality.

Were sensitivity analyses conducted?

If YES, the article is considered sufficient quality for purpose.

If YES, sufficient quality for purpose.

If NO/NOT ENOUGH INFORMATION is reported, insufficient quality.

Dreyer NA et al. The GRACE Checklist: A Validated Assessment Tool for High Quality Observational Studies of Comparative Effectiveness. J Managed Care & Specialty Pharmacy 2016; 22(10) 1107-1113
When RWD are good for regulatory use

This must be a contextual exercise as no simple formula will work

Considerations for determining suitability of RWD

• Data elements must meet major study objectives
• Data do not need to be 100% complete or accurate, since sensitivity analyses and modeling can be used to address missing data and quantify likely impact of bias.
• Data needs to be reasonably curated and the process should be documented
Establishing real-world endpoints: Overall Survival

Comparing RWD to RCT in advanced NSCLC patients treated with immune checkpoint inhibitors

Presented July 10, 2018,

Treatment patterns are often different in RW settings

**Time to treatment discontinuation:** comparing RWD to RCT in advanced NSCLC treated with immune checkpoint inhibitors

![Chart showing time to treatment discontinuation for different RWD sets and RCT results.](chart.png)

Establishing the validity of patient-reported medication use

Case study funded by the European Commission under the Innovative Medicines Initiative PROTECT

**Objective:** Assess medication use and other potential risk factors throughout pregnancy as reported by pregnant women, and the suitability of such data for research purposes

**Methods:** Self-reported medication use compared with data from electronic health records, national prescription data, and regional prescribing practices

**Results**
- 83% took ≥ 1 non-pregnancy-related med during pregnancy or prior month; 24% only used non-prescription medications; 7% reported not using prescribed meds
- Added information on potential risk factors, including recreational drug use, alcohol, smoking, education.
- Compared DK National Prescription register, 83% agreement for prescription meds for chronic conditions; 54% for meds indicated for short-term use

**Key Lessons**
- Direct to consumer studies can provide important data not found in EHR or prescription databases
- Validation of clinical outcomes of special interest may be warranted

Dreyer et al. Direct-to-patient research: piloting a new approach to understanding drug safety during pregnancy Jmir Public Health & Surveillance 2015; 1(2); e22. doi:10.2196
Data quality should be examined in the following terms:

- Provenance
- Structure
- Integration
- Rate of accumulation
- Curation

“Data quality is considered the biggest challenge for the use of big data for regulatory decision-making … across Europe and the ultimate validation of the derived evidence.”

HMA-EMA Joint Big Data Task Force Report, 13 Feb 2019

Recognizing RWD that is Fit for Purpose

Professor Miriam Sturkenboom, 2018 International Conference of Pharmacoepidemiology and Therapeutic Risk Management

Nancy Dreyer accepted DIA Inspire Award for Best Author, 2019 for publication on “Advancing a framework for regulatory use of RWE: When real is reliable”
Relevance: are there sufficient details on exposure, covariates, outcomes for study purpose? RWD should be representative of patients with the target condition and have sufficient size and follow-up to be able to demonstrate benefit.

Reliability of RWD via data accrual, data assurance stemming from minimizing data collection errors, RWD analyses prospectively defined.

Reporting: RWD sources should follow reporting standards and document data elements and definitions, data aggregation methodology and data collection time windows.

Transparent source verification and auditing procedures for completeness and consistency.

Common data model with common terminologies, vocabularies, coding schemes is needed to work with RWD across multiple sources.

Addressing RWD gaps requires a variety of RWD sources.

Study designs that rely on innovative use of RWD
Linking study-specific data collection with big data

LINKED RWD is the foundation
Innovative study design that use RWE

**INNOVATIVE EXTENSION**
Follow patients after RCT completion
The goal is to determine long-term value

Can reduce study cost by < 60%
compared conventional approaches

**EXTERNAL COMPARATOR**
Provide information on clinical benefit when a control group may not be feasible or ethical

Can lead to cost and time savings.
Increases the value of single-arm studies

**PRAGMATIC**
Pragmatic trials evaluate effectiveness of a randomized intervention in real-life conditions

Can lead to cost reductions on the order of 50%

**ENRICHED**
Combine primary and secondary data

Can lead to both cost and time savings, access to more information
Extending follow-up after a clinical trial

Understanding long-term benefits of treatment through direct-to-patient research

Approach

• Direct to patient follow-up for effectiveness (up to 10 years)
• Follow both treated and placebo patients
• Consent patients for new study before trial ends
• Single investigative site per country where possible
• Selected clinical validation for events of special interest - here, Major Adverse Coronary Events, (MACE)

Our Value

• Roughly 1/3 cost of using RCT framework for follow-up
• Bulk of budget is directed to following up potential MACE
The FDA granted Invega Sustenna a label expansion based on evidence from a pragmatic RCT

The first and only antipsychotic for which the inclusion of real-world data led to a label expansion by FDA (January 3, 2018)

Landmark Study Shows Once-Monthly Long-Acting Therapy INVEGA® SUSTENNA® (paliperidone palmitate) Significantly Delayed Time to Relapse in Patients with Schizophrenia Compared to Daily Oral Antipsychotic

First prospective, randomized clinical trial to reflect context of “real world” issues in treating schizophrenia, including recent incarceration and substance abuse

Study design

• 15 month, 50 site-randomized, open-label, active controlled study of 444 adults with schizophrenia
• Broad enrollment criteria
  – Mean age: 38 years
  – 60% of patients had comorbid substance abuse
  – Mean time since release from last incarceration: 42 days
• Primary endpoint: time to first treatment failure including psych hospitalization, arrest/incarceration, treatment discontinuation, increased psych services to prevent psych hospitalization, suicide, etc.

Patients enrolled from a registry, randomized and followed through standard registry data collection
- 7012 patients randomized from 11,709 eligible
- Also followed cohort that did not undergo randomization
- Primary end-point: all cause mortality at 30 days
- Followed entirely through existing record systems in a Swedish registry

Research question:
Does thrombus aspiration before PCI improve 30-day mortality?

Answer: No
# RWE in regulatory decisions about comparative effectiveness

**2017 - Q1 2019**

<table>
<thead>
<tr>
<th>Pragmatic RCT</th>
<th>Contemporary RW Comparators</th>
<th>FDA</th>
<th>EMA</th>
</tr>
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<tbody>
<tr>
<td>B-cell precursor acute lymphoblastic leukemia in 1st / 2nd complete remission with MRD ≥ 0.1%</td>
<td>B-cell precursor acute lymphoblastic leukemia in 1st / 2nd complete remission with MRD ≥ 0.1%</td>
<td>✓ (2018) Accelerated</td>
<td>✓ (2019)</td>
</tr>
</tbody>
</table>

- Pfizer's 2019 Ibrance approval for male breast cancer was based on reviews of EMR for safety

Legend: GEP-NETS: gastroenteropancreatic neuroendocrine tumor HER2: human epidermal growth factor receptor 2 HR: hormone receptor MRD: minimal residual disease SSTR: somatostatin receptor

RWE included in the label
Real world data comparators for single arm clinical trial – approval of NME for rare cancer indication

**Primary objective:** Assess overall response rate based on best objective response to standard chemotherapy

**Cohort:** Niche carcinoma patients being drug treated in 2nd line - from existing registry in Western Europe and EMR in USA

**Aim:** Use real world data as comparator for single arm clinical trial for novel mAb

**Results**

- Response to chemotherapy was very limited
- The primary outcome of standard chemotherapy was even worse than expected
- **Novel mAb confirmed as new treatment option by FDA and EMA in 2017**

<table>
<thead>
<tr>
<th>Response</th>
<th>N = 34</th>
</tr>
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<tbody>
<tr>
<td>Complete response, n (%)</td>
<td>0</td>
</tr>
<tr>
<td>Partial response, n (%)</td>
<td>3 (8.8)</td>
</tr>
<tr>
<td>Stable disease, n (%)</td>
<td>3 (8.8)</td>
</tr>
<tr>
<td>Progressive disease, n (%)</td>
<td>28 (82.4)</td>
</tr>
<tr>
<td>Objective response rate (95% CI), %</td>
<td>8.8 (1.9-23.7)</td>
</tr>
</tbody>
</table>
Real-world comparison data facilitates rapid drug approval

Real-world comparators provided context for regulatory filing of single arm Phase 2 trials

ORIGINAL ARTICLE
Blinatumomab vs historical standard therapy of adult relapsed/refractory acute lymphoblastic leukemia


We compared outcomes from a single-arm study of blinatumomab in adult patients with B-precursor Ph-negative relapsed/refractory acute lymphoblastic leukemia (R/R ALL) with a historical data set from Europe and the United States. Estimates of complete remission (CR) and overall survival (OS) were weighted by the frequency distribution of prognostic factors in the blinatumomab trial. Outcomes were also compared between the trial and historical data using propensity score methods. The historical cohort included 694 patients with CR data and 1112 patients with OS data compared with 189 patients with CR and survival data in the blinatumomab trial. The weighted analysis revealed a CR rate of 24% (95% CI: 20–27%) and a median OS of 3.3 months (95% CI: 2.8–3.6) in the historical cohort compared with a CR/CRh rate of 43% (95% CI: 36–50%) and a median OS of 6.1 months (95% CI: 4.2–7.5) in the blinatumomab trial. Propensity score analysis estimated increased odds of CR/CRh (OR = 2.68, 95% CI: 1.67–4.31) and improved OS (HR = 0.536, 95% CI: 0.394–0.730) with blinatumomab. The analysis demonstrates the application of different study designs and statistical methods to compare novel therapies for R/R ALL with historical data.

Blood Cancer Journal (2016) 6, e473; doi:10.1038/bcj.2016.84; published online 23 September 2016

Strong benefit evident in the trial (treated) population compared to the ‘control’ population

Figure 2. Comparison of complete response and overall survival between blinatumomab clinical trial patients and historical patients. Outcomes were analyzed using both the IPTW and sIPTW approaches: Odds ratio (OR) for achieving a CR/CRh (blinatumomab patients) or CR (historical patients) and hazard ratio (HR) for overall survival.
Rarity of BC in men limits the feasibility of randomized trials

Lifetime risk of developing invasive breast cancer

<table>
<thead>
<tr>
<th>Women</th>
<th>Men</th>
</tr>
</thead>
<tbody>
<tr>
<td>12.5%</td>
<td>0.1%</td>
</tr>
</tbody>
</table>

Women treatment guidelines recommended to men with BC

RWD was used to describe IBRANCE® (palbociclib) benefits for men with BC

- IQVIA
  - Pharmacy/medical claims
- flatiron
  - EMR
- Tx pattern and duration
- Real World clinical response

Confirmed clinical benefit from the addition of Ibrance to endocrine therapy

Evidence generated was accepted by the FDA

“We are expanding the indication for Ibrance to include male patients based upon data from postmarketing reports and electronic health records showing that the safety profile for men treated with Ibrance is consistent with the safety profile in women treated with Ibrance,”

- Richard Pazdur, MD, director of the FDA’s Oncology Center of Excellence

“The smart use of this innovative approach helped Pfizer expand its addressable market”

Sources: FDA, breastcancer.org, ASCO
Use of External Comparators For HTA Submissions

Key Findings

• 179 single arm submissions covering 102 drug/indication combinations

• Increase in submissions of single-arm clinical data packages to HTA bodies

• External comparators were used in 52% of submissions

• Positive HTA outcome was received for 61% of submissions with external comparators vs 50% without

Source: Patel D et al. Use of External Comparators for HTA Submissions – An Analysis of HTA Accelerator, Poster at 35th ISPE, August 2019, Philadelphia
Link of EHR and sports data are used for orthopedic injury research in professional sports

Lessons on Data Collection and Curation From the NFL Injury Surveillance Program

Nancy A. Dreyer, PhD,§† Christina D. Mack, PhD,§ Robert B. Anderson, MD,§§
Edward M. Wojtys, MD,§ Elliott B. Hershman, MD,§ and Allen Sills, MD§§

Background: "Research-ready" evidence platforms that link sports data with anonymized electronic health records (EHRs) or other data are important tools for evaluating injury occurrence in response to changes in games, training, rules, and other factors. While there is agreement that high-quality data are essential, there is little evidence to guide data curation.

Hypothesis/Purpose: We hypothesized that an EHR used in the course of clinical care and curated for research readiness can provide a robust evidence platform. Our purpose is to describe the data curation used for active injury surveillance by the National Football league (NFL).

Sources: http://espn.go.com/nba/story/_/id/15009403/cutting-edge-injury-prediction-prevention
Future state
## Right Source for the Right Data

### Patient Health Records
- Demographics, medical history, structured patient information
- Medication information
- Clinical measures
- Labs
*chart review or EHR

### Direct from Patient
- Additional demographics, medical information
- Treatment satisfaction, compliance
- Lost work productivity, activity impairment
- Patient diaries
- PROs

### Devices and Wearables
- Movement, sleep, heart rate
- Compliance with treatment, device use

### Insurance Claims Data / Billing Records
- 360° view of patient medical journey regardless of treatment center
- Objective evidence of health care system encounters/ resource utilization
- Outpatient prescription fills

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**KEYS TO SUCCESS**
- Investigate best place to find the patients
- Full feasibility for key data elements
- Don’t restrict to one data source

**Right data from the right place**
A continual process of evidence generation & product differentiation through use of linked data
More opportunities for insight into the patient experience

More is possible

More is acceptable

Enrich & augment
Add “voices” from patients and providers

Curate
Increase quality and usability in a systematic, effective manner

Link
Expand the value of data by linkage, while recognizing the challenge of quality, unbiased linkages
Combining new and existing RWD
FDA’s new App captures and integrates patient-generated data

MyStudies App Key features

- Open source customizable digital tool (for iOS and Android) that can be rebranded by researchers and developers
- Gateway capability: works for multi-site trials across multiple therapeutic areas and health outcome measures
- Ability for study sponsors to reconfigure app and patient data storage systems
- Backend architecture is secure and auditable, and compliant with necessary regulations such as 21 CFR Part 11 and FISMA

Sources: https://www.fda.gov/drugs/science-research-drugs/fdas-mystudies-application-app
During the pilot study, data elements were stored in multiple environments consistent with the storage architecture model.

**Data storage and access environment**

**Survey response data**
- LabKey stored the data
- LabKey, Kaiser Permanente could access the data

**Linked medical records data**
- Kaiser Permanente stored the data
- Only Kaiser Permanente could access the data. It was not released to LabKey, Harvard Pilgrim or FDA

Sources:
- [https://www.fda.gov/drugs/science-research-drugs/fdas-mystudies-application-app](https://www.fda.gov/drugs/science-research-drugs/fdas-mystudies-application-app)
Audit trails for the MyStudies app

A look towards evidentiary requirements?

• Mobile technology should record the date and time that the data are captured and this information should be transmitted or recorded in the durable database
• The first durable database should capture
  – Date and time that the data enter the durable database
  – Data originator for each data element
    ➢ Patient
    ➢ Mobile Technology (e.g., biosensor)
    ➢ EHR
• An audit trail should track modifications to the data and include data element identifiers that reflect the date, time, and data originator and the reason for the change
  – Modified or corrected data should not obscure previous entries
More linkage of RWD with clinical trial data

• Calibrate risk-factor Measurement between clinical trial participants and target patient population
• Use overlap between two groups for calibration

Make a stronger story for clinicians and payers through linkage of RCT and RW data

Changing data approaches to meet regulatory demands

**Study-driven primary data collection**

**Leveraging existing networks + registries**

- 80% less data needed for primary collection
- Significantly reduced HCP/site burden

**Opportunity**

- Combine and curate data from patients, physicians, etc. with transactional and other health data to assess effectiveness and safety of newly launched products compared to other available treatments over time.
- Data may come from pharmacies, wholesalers, providers, payers, claims processors, etc.

**Challenge**

- Reconciling de-identification goals and standards in research v. privacy
  1. Linking to de-identified data can compromise de-identification risk thresholds
  2. Patient consent does not trump data supply agreements

Case study is for illustrative purposes only. Results may vary.
“IN THEORY, THERE IS NO DIFFERENCE BETWEEN THEORY AND PRACTICE. BUT IN PRACTICE, THERE IS.”

-YOGI BERRA
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