Working with Regulatory Bodies to Demonstrate the Role of Real-World Evidence in Quantifying a Patient’s Path to Achieving Overall Wellbeing

James Harnett, PharmD, MS
Sr. Director, Global Health & Value Real World Data & Analytics, Pfizer Inc.
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THIS PRESENTATION PROVIDES THE VIEWS OF THE SPEAKER AND IS NOT INTENDED AS COMPANY VIEWS OR POSITIONS
Objectives

• Identify challenges and emerging trends for regulatory consideration of real-world evidence

• Provide updates on how regulators (with a focus on the FDA) are considering utilizing real-world evidence generated from use of electronic health records

• Discuss how the industry may collaborate with the FDA to help realize the added value of real-world evidence

• Review learnings about the potential to leverage RWE to support regulatory assessments for improved patient-centered outcomes and recent developments in EHR driven trials
Challenges for Pharmaceutical Innovation: Time, Costs, Attrition, Access

- 95% of experimental medicines studied in humans fail to be both effective and safe
- Companies spend $5B per new medicine (2)

- Average of 4.6 months delay trial
- 6% of clinical trials are completed on time, 72% of trials run over schedule by more than one month (3)

- 40% of NICE reviews in 2000-13 resulted in unfavorable decisions (4)
- 80%+ generic dispensing (5)

Trend 1. Evolution of Longitudinal RWD sources

Real World Data is healthcare data not collected through RCT and used for decision making\(^1,2\)

- **Claims**
  - Large/low cost
  - Tx patterns/ costs
  - Follow-up across healthcare settings (inpt/outpt/ER)

- **Registry**
  - Set up for research
  - Deeper clinical information for condition of interest
  - Expensive, usually indirect access
  - Smaller #s
  - Biased sample

+ **6 mo lag**
  - No clinical information
  - Coding

TODAY IS THE PAST...

Trend 2. Focus on Patient-Centered Outcomes & Intersection with RWD&E

• In 2012, FDA's Patient-Focused Drug Development initiative under PDUFA V focuses on collecting patient perspective on condition and therapies (1)

• In July 2015, 21st Century Cures Act requires processes for use of patient experience data in the risk-benefit assessment (2)

• Also requires consideration of clinical experience evidence for new indications

• Acceleration in patient driven RWD collection (wearables, apps, social media)

• Use of RWD associated with improvement in patient health and well-being

• RWD can facilitate patient centeredness by:
  • Focusing on broader populations and outcomes than in RCTs
  • Promoting precision medicine
  • Better informing and engaging patients
  • Supporting patient-centered medical home with better coordination of health information
  • Facilitating identification of patients and ease participation in clinical trials
  • Accelerating access to needed medications

1. Available at: http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm368342.htm
2. Available at: https://www.congress.gov/bill/114th-congress/house-bill/6

Available at: http://jaha.ahajournals.org/content/5/9/e003058.full.pdf+html
Payers and Growing Use of RWD&E

- Actuarial analyses
- CER (2010 WellPoint guidance)
- Outcomes based agreements
- Indication based pricing/reimbursement
- Coverage with Evidence Development for Medical Device in US and Pharmaceuticals outside the US
  - Oncology examples in EU
Evolving US Regulatory Landscape for RWE

- Post-marketing surveillance (Mini-Sentinel)
- FDAMA Section 114 on Healthcare Economic Information
- Real world efficacy/effectiveness TBD
A Framework for Regulatory Consideration of Real World Efficacy/Effectiveness

- **What:** pragmatic RCTs (pRCTs) instead of traditional P3 confirmatory RCTs
  - Prospective clinical studies randomizing patients to ≥2 interventions and treated/ followed per usual practice
  - Representative of real-world patients
  - Leverage EHRs for data capture

- **Why:**
  - RCT requirements (protocol adherence) deter patient enrollment
  - 3%-7% of patients meet trial inclusion criteria & RCT populations are typically homogeneous
  - Limited practice resources
  - Guidelines are more comprehensive vs. P3 RCT.

- **When:**
  - Drugs with early signs of exceptional activity and a strongly favorable benefit:risk ratio
  - And for additional indications in the same tumor (different combination regimen or line of therapy)

Available at:
http://annonc.oxfordjournals.org.proxy1.athensams.net/content/27/7/1342.full.pdf
Recent Developments in Bringing together FDA, Industry, Patients and Others on potential Use of RWE

- Highlight from Friends of Cancer Research Meeting (June 16, 2016)
  - Dr. Califf suggested “a lot of phase III and beyond that really should be done in an entirely different way” and “place need to go is randomization within real world practice” (1)
  - Dr. Pazdur suggested need for real world outcomes like symptom relief and control vs. progression on x-ray; Time to next treatment vs. time to treatment failure; response rate with lesser decrease in size of lesion vs RECIST (2)
  - Dr. Zhosin introduced INFORMED and real world data working group (3)
- Flatiron and FDA partnership in advanced non-small cell lung cancer patients treated with immunotherapy(4)

Another Recent Interaction with FDA on RWE (Duke-Margolis Center for Health Policy – FDA, March 2016)

• Discussion on whether data gathered from healthcare systems can supplement or support approval of new indications or label expansions

• Dr. Woodcock, Director of the Center for Drug Evaluation and Research (CDER) (1)
  • “randomize people within the healthcare system to do a trial inside the healthcare system utilizing the data collection methods of the healthcare system”
  • Could support expanded labeling (current off-label use)

• Examples of using RWD from Dr. Jarow, Chair of the medical policy council at CDER (2)
  • Rare Diseases
    • Lumizyme for Pompe disease – survival data from an international Pompe disease registry
    • Carbaglu for N-acetylglutamate synthase deficiency – case series data on plasma ammonia level reductions
    • Cholbam for bile acid synthesis disorders – case series data on growth, survival, and reduction in laboratory parameters of cholestasis
    • Glucarpidase for MTX toxicity - data on a ~20 patient subset NIH tx protocol
    • Metreleptin for Leptin deficiency/lipodystrophy- case series out of NIH, tx protocol

• Label Enhancements
  • High-dose influenza vaccine versus standard dose (Medicare claims)
  • Rabies vaccine dose schedule (5 vs. 4 doses - change in CDC recommendations)

1. Available at: https://healthpolicy.duke.edu/events/enhancing-application-real-world-evidence-regulatory-decision-making
FDA guidance developments for RWE: Future Interactions with Industry

- EHR data in prospective clinical investigations of human drugs and biological products medical devices, and combination products.
- ONC-cert. EHR, audit trails, consent, privacy, security, inspection, recordkeeping, retention

- Expanded indications for use
- Post-market surveillance
- Post-Approval Device Surveillance as Condition of Approval
- Control Group
- Supplementary data
- Objective Performance Criteria and Performance Goals

Available at:

Available at:
PDUFA VI Commitment Letter (Raising importance of RWE)

6. Enhancing Use of Real World Evidence for Use in Regulatory Decision-Making

As we participate in the current data revolution, it is important that FDA consider the possibilities of using so-called “real world” data as an important tool in evaluating not only the safety of medications but also their effectiveness. To accomplish this will require an understanding of what questions to ask, including how such data can be generated and used appropriately in product evaluation, what the challenges are to appropriate generation and use of these data, and how to address such challenges. Towards this end, FDA will do the following:

a. By no later than the end of FY 2018, FDA will complete one or more public workshop(s) with key stakeholders, including patients, biopharmaceutical companies, and academia, to gather input into issues related to Real World Evidence (RWE) use in regulatory decision-making. The workshop(s) should address, among other things, the following topics:
   • Benefits to patients, regulators, and biopharmaceutical companies of RWE in regulatory decision making;
   • RWE availability, quality, and access challenges, and approaches to mitigate these;
   • Methodological approaches for the collection, analysis, and communication of RWE; and
   • Appropriate contexts of use of RWE in regulatory decision-making regarding effectiveness.

b. By no later than the end of FY 2019, FDA will initiate (or fund by contract), appropriate activities (e.g., pilot studies or methodology development projects) aimed at addressing key outstanding concerns and considerations in the use of RWE for regulatory decision making.

c. By no later than the end of FY 2021, considering available input, such as from activities noted above, FDA will publish draft guidance on how RWE can contribute to the assessment of safety and effectiveness in regulatory submissions, for example in the approval of new supplemental indications and for the fulfillment of postmarketing commitments and requirements. FDA will work toward the goal of publishing a revised draft or final guidance within 18 months after the close of the public comment period.
Real-World Evidence Based on Patient Experience and Pharmacoeconomic Information Can Improve Understanding of Health Outcomes and Costs

• “Many health care organizations, including insurance providers, managed care organizations, pharmacy benefit managers, government health care programs, hospital systems, accountable care organizations, and integrated delivery networks make decisions on health care delivery across large populations. These organizations possess patient data relating to real-world uses of approved medicines, conduct their own research on such data, and may wish to collaborate with biopharmaceutical companies to determine the overall impact of medicines in specific patient populations.

• Real-world evidence—evidence derived from data gathered from actual patient experiences—can help improve our understanding of disease and health. For example, modeling long-term endpoints and effects on different populations can help payers and health systems understand expected benefits for patients.

• So long as the research methods are sound and well-described, companies should be able to communicate truthful and non-misleading information about analyses of real world data with payers and health systems. These organizations are very sophisticated about such analyses and can evaluate the significance and limitations of the results”
What about RWD & EU Regulators: An update on Adaptive Pathways

- Adaptive pathways - market authorization earlier in development cycle for very small population with additional evidence generation to support use in wider populations

- EMA Pilot launched in March 2014; 62 applications
  - 23% SMEs, 1/3 oncology (others include ID, respiratory, neurodegenerative, hereditary genetic disorders)
  - 18 accepted for assessment of suitability, others rejected due to development programs did not afford scope for expansion/iteration, Areas without unmet need, No changes to plan

- All 18 had RWD plans:
  - Use of existing disease registries to identify natural history of the disease, current standard of care, resource utilisation, adherence to treatment;
  - Single arm studies for rare diseases compared with outcomes and time-points inferred from disease registries;
  - Open label salvage studies in patients with no therapeutic options remaining, with the purpose of obtaining an expansion of the indication;
  - Collection of efficacy and safety data from early access/compassionate use programs to supplement RCTs in small populations;
  - Post-authorisation drug registries for effectiveness, long-term outcomes, drug utilisation, Patient Reported Outcomes (PROs), time to treatment failure, diagnosis confirmation;
  - Linking drug registries to risk-sharing schemes for reimbursement (pay-per-performance, annuity payments)
  - Expansion of the indication based on a mixture of disease registries and compassionate use data (for rare, severe diseases, where RCT data were available for less severe forms of the disease);
  - Post authorisation studies to investigate biomarkers’ (or other subpopulation selection criterion) status of an all-comer population;
  - Investigation of non-serological outcomes for vaccines.

- By 2 years, 6 applications progressed to EMA-HTA parallel advice
Are we Ready to Leverage EHR to Evaluate Real World Efficacy/Effectiveness?
Proof of Concept. Example of Concordance of RWE and RCT Outcomes

- Retrospective chart review of 212 patients in US/Canada
- ORR: 66% vs. 61-74% in 4 P3 trials
- 1-year survival in first-line 85% vs. 84% in RCT of tx naive
- Median PFS 9.5 mos vs. 7.7-10.9 mos in RCTs

Addressing Critical Gaps for Use of EHR in Oncology

Case Study #1: compare structured data only vs. structured and unstructured data to identify patients in a nationally representative EHR-based dataset with advanced squamous NSCLC.

• Using the combination of structured and unstructured data, 8324 patients were identified with advanced NSCLC.
  • Of the 8324 patients, only 2472 were also in the cohort generated using structured data only.
  • Furthermore, 1090 patients would be included in the structured data only cohort who should have been excluded with unstructured data elements.

Case Study #2: Evaluate characteristics, healthcare resource utilization, and survival outcomes associated with early vs. delayed molecular diagnostic testing in metastatic NSCLC.

• 350 (249 early molecular diagnostic testing, 101 delayed molecular testing) patients identified, linked with resource utilization data from a claims data warehouse and with death data from the Social Security Death Index.
  • Cohorts were comparable in overall survival, progression-free survival and healthcare resource utilization.
• Demonstrates the need to link EHR data with other sources to evaluate resource utilization and outcomes.

What about EHRs for Other Therapeutic Areas? What about Patient Reported Data?

- How about in Rheumatoid Arthritis?
  - **PQRS Measure # 177 (1)**
    
    **Rheumatoid Arthritis (RA): Periodic Assessment of Disease Activity**
    
    Percentage of patients aged 18 years and older with a diagnosis of rheumatoid arthritis (RA) who have an assessment and classification of disease activity within 12 months

  - Inflammatory conditions #1 specialty spend PMPY (2)

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<th>2533 RA Patients in EMR Receiving two most commonly used biologics (3)</th>
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1. Available at: https://www.pqrspro.com/measures/pqrs_measures_groups_2016/2016-pqrs-rheumatoid-arthritis-ra-measures-group/
2. Available at: http://lab.express-scripts.com/lab/drug-trend-report
3. Data on File.
Moving forward to EHR-based pRCT for Development

The Salford Lung Study – first pre-approval pRCT

- Open-label, P3, pRCT in asthma and COPD
- Randomized to (1) continuation of usual treatment (2) QD fluticasone furoate/vilanterol for 12 months.
  - GPs prescribe as usual, patients order and collect repeat prescriptions in their usual way, and collect their study medication from their usual community pharmacist.
- Using an electronic health record for effectiveness (m-s exacerbations) and safety data (plus calls)
  - Additional data feeds added (out-of-hours services, health services and deaths)
  - All possible adverse events or study endpoints are verified in blind fashion
- Challenges:
  - GPs and practice nurses had to become responsible for recruitment of their own patients (ie, needed patients in practices collecting data)
  - Phase III informed consent was a challenge to recruitment
  - Investigators had limited experience of prelicense clinical research, need change in research culture
  - Intensive collaboration; ~150 GSK-funded healthcare workers are engaged in the study.
- Timing: 3/12-10/14 for recruitment; 3161 patients screened, 2802 randomized
- First COPD results reported in May 2016, epub Sept 2016

“GetReal aims to show how robust new methods of RWE collection and synthesis could be adopted earlier in pharmaceutical R&D and the healthcare decision making process.”

pRCTs are not the end goal => rapid learning system

- pRCTs are a big step forward, especially for development products

- pRCTs are part of developing a rapid learning health system

- What about observational research, specifically retrospective analyses for products already on the market?
  - To inform new indications/dosing/regimens/populations/outcomes

- To recognize a rapid learning health system, need a framework for evaluation of observational research including retrospective analyses that promotes:
  - Increased transparency
  - Replicating findings
  - Applying good standard research practices (ISPOR, ISPE, etc)
  - Using positive and negative controls
Where do we go from here…

- Need increased partnership to understand the application of different types of RWE for regulatory purposes
  - Salford lung study is groundbreaking for future development programs, but pRCTs still require significant time and resources.
    - Discuss ways to facilitate adoption of pRCTs (informed consent, training)
    - Consider appropriate use of observational research as well

- As EHR were intended for patient management and not designed for research, we need to:
  - Evaluate new technologies to accelerate abstraction from unstructured data
  - Facilitate more data linkages to provide more comprehensive picture of patient care and outcomes (partnership of data companies, HCPs/institutions, patients, employers, payers, others)
  - Ensure alignment of incentives and introduce technologies to improve and standardize capture of appropriate clinical information on ongoing basis
BIG DATA = BIG QUESTIONS