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SECOND PLENARY: Real World Evidence in Asia Pacific: Are We Ready? Is It Helpful for Decision Makers?

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Real World Evidence in Asia Pacific:

Are We ready?

Is It Helpful for Decision Makers?

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ISPOR 8th Asia Pacific Conference Tokyo September 10, 2018

Potential Conflict of Interest disclosure

- Received partial support to attend this meeting
- Employee of a public university and affiliated hospital
- I conduct public domain research sponsored by medical product companies
- I do consulting for private industry
  - Free for Taiwan companies as part of a government program

Key issues from my perspective

- Ready as users to make decisions?
  - Regulators
  - Health insurance agencies
  - Clinicians
  - Patients and families
- Ready and capable to generate relevant evidence?
- Barriers

healthpolicy.duke.edu/sites/default/files/atoms/files/ rwe_white_paper_2017.09.06.pdf

- "We define Real World Data as data relating to patient health status and/or the delivery of health care routinely collected from a variety of sources."
  - Electronic medical records
    - Including health monitoring devices (blood pressure, blood sugar, blood oxygen, spirometry …)
  - Health insurance claims
  - Patient reported outcomes (web-based, apps …)

Real World Data (RWD) has been used for a long time …

Journal of Formosan Medical Association 2002; 101: 632-41

COST-EFFECTIVENESS ANALYSIS OF INTERFERON-α THERAPY IN THE TREATMENT OF CHRONIC HEPATITIS B IN TAIWAN

Raoh-Fang Pwu and K. Arnold Chan[1]

- RWD from Taiwan + efficacy data from foreign clinical trials

Pwu & Chan *J Formos Med Assoc* 2002;101:632-41

- Funded by a manufacturer of interferon-α
  - Wong et al. Cost-effectiveness of Interferon-α2b Treatment for Hepatitis B e Antigen-Positive Chronic Hepatitis B. Ann Intern Med 1995; 122: 664-75 (treatment would be cost saving in the USA)
- Markov model, transition probability derived from Taiwan data, health care expenditure and utility associated with different health states, …
- Incremental Cost-Effectiveness Ratio was US$14,200/QALY from societal perspective, but the results were probably not considered in reimbursement decision ☹

Pwu & Chan *J Formos Med Assoc* 2002; 101: 632-41

- Real World Data
  - Disease epidemiology
  - Health care expenditure
- Utility associated with different health states
  - Hepatologists interview
- Limited efficacy data, as trials were mostly conducted in North America / Western Europe
  - Different ethnicity
  - Different disease detection and management approaches, resulting in different case mix

10+ years later, health insurance claims as RWD

- PLoS One 2015 https://doi.org/10.1371/journal.pone.0122860

RESEARCH ARTICLE

Clinical Outcomes in Low Risk Coronary Artery Disease Patients Treated with Different Limus-Based Drug-Eluting Stents - A Nationwide Retrospective Cohort Study Using Insurance Claims Database

Chao-Lun Lai[1,2,3], Ching-Fen Wu[4], Raymond Nien-Chen Kuo[5,6], Yen-Yun Yang[6], Ming-Fong Chen[7], K. Arnold Chan[8,9], Mei-Shu Lai[3,6]*

- Head-to-head comparisons of different stents

- Strengths

Lai et al. doi.org/10.1371/journal.pone.0122860

  - Large study size
  - Population-based (national health insurance)
  - Linkage with national mortality data
- Limitations
  - Same as that with other health insurance claims systems – limited clinical information, no life style factors, …
  - Local reimbursement guidelines
  - Lag time between market approval and reimbursement
- Were the Taiwan FDA and National Health Insurance Administration aware of the study?
  - Probably not ☹

An extension of the prior study, funded by Taiwan FDA

- Identify patients who received coronary stents from a hospital Electronic Medical Records system
- Link clinical data, National Health Insurance data, and mortality data
- Best of both worlds?
  - If done right …
  - Other medical centers in Taiwan?

Health data environment in other Asia Pacific countries that could generate RWE

- In no particular order …
  - South Korea
  - Japan
  - Hong Kong
  - …
- (Described in a short course on Sept 8)

HIRA data in South Korea

- PLoS One 2015; 10(5): e0124287
- N = 349,476

RESEARCH ARTICLE

Differential Cardiovascular Outcomes after Dipeptidyl Peptidase-4 Inhibitor, Sulfonylurea, and Pioglitazone Therapy, All in Combination with Metformin, for Type 2 Diabetes: A Population-Based Cohort Study

Jong-Mi Seong[1,2☯], Nam-Kyong Choi[3,4☯], Ju-Young Shin[5], Yoosoo Chang[6], Ye-Jee Kim[7], Joongyub Lee[3], Ju-Young Kim[8], Byung-Joo Park[1,2,5,7*]

1 Office of Drug Safety Information II, Korea Institute of Drug Safety & Risk Management, Seoul, Republic of Korea, 2 Department of Preventive Medicine, Seoul National University College of Medicine, Seoul, Republic of Korea, 3 Division of Clinical Epidemiology, Medical Research Collaborating Center, Seoul National University College of Medicine/Seoul National University Hospital, Seoul, Republic of Korea, 4 Medical Research Center, Seoul National University, Seoul, Republic of Korea, 5 Office of Drug Utilization Review, Korea Institute of Drug Safety & Risk Management, Seoul, Republic of Korea, 6 Department of Occupational and Environmental Medicine, Kangbuk Samsung Hospital, Sungkyunkwan University, School of Medicine, Seoul, Republic of Korea, 7 Office of Drug Safety Information I, Korea Institute of Drug Safety & Risk Management, Seoul, Republic of Korea, 8 Department of Family Medicine, Seoul National University Bundang Hospital, Seoul, Republic of Korea

Environmental Health and Preventive Medicine 2017; 22: 51

STUDY PROTOCOL Open Access

Analysis of the evidence-practice gap to facilitate proper medical care for the elderly: investigation, using databases, of utilization measures for National Database of Health Insurance Claims and Specific Health Checkups of Japan (NDB)

Takeo Nakayama[1*], Yuichi Imanaka[2], Yasushi Okuno[3], Genta Kato[4], Tomohiro Kuroda[5], Rei Goto[6,11], Shiro Tanaka[7], Hiroshi Tamura[5], Shunichi Fukuhara[8], Shingo Fukuma[8], Manabu Muto[9], Motoko Yanagita[10], Yosuke Yamamoto[8] and on behalf of BiDAME: Big Data Analysis of Medical Care for the Elderly in Kyoto

BMJ 2016; 352: h6926

Cardiovascular outcomes associated with use of clarithromycin: population based study

Angel Y S Wong,[1] Adrian Root,[2] Ian J Douglas,[2] Celine S L Chui,[1] Esther W Chan,[1] Yonas Ghebremichael-Weldeselassie,[3] Chung-Wah Siu,[4] Liam Smeeth,[2] Ian C K Wong[1,5]

- Based on Electronic Medical Records in Hong Kong
- Clarithromycin users (n=108,988) and amoxicillin users (n=217,793)

We are following what's happening in USA / Europe

N Engl J Med 2016; 375: 2293-7

SOUNDING BOARD

Real-World Evidence — What Is It and What Can It Tell Us?

Rachel E. Sherman, M.D., M.P.H., Steven A. Anderson, Ph.D., M.P.P., Gerald J. Dal Pan, M.D., M.H.S., Gerry W. Gray, Ph.D., Thomas Gross, M.D., M.P.H., Nina L. Hunter, Ph.D., Lisa LaVange, Ph.D., Danica Marinac-Dabic, M.D., Ph.D., Peter W. Marks, M.D., Ph.D., Melissa A. Robb, B.S.N., M.S., Jeffrey Shuren, M.D., J.D., Robert Temple, M.D., Janet Woodcock, M.D., Lilly Q. Yue, Ph.D., and Robert M. Califf, M.D.

- All US FDA officers

www.fda.gov/downloads/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm513027.pdf

Contains Nonbinding Recommendations

Use of Real-World Evidence to Support Regulatory Decision-Making for Medical Devices

Guidance for Industry and Food and Drug Administration Staff

Document issued on August 31, 2017.

The draft of this document was issued on July 27, 2016

- Implications for other regulatory agencies

www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm501068.pdf

Use of Electronic Health Record Data in Clinical Investigations

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
Center for Devices and Radiological Health (CDRH)

Guidance for Industry

July 2018
Procedural

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

www.ema.europa.eu/docs/en_GB/document_library/Presentation/2017/05/WC500227703.pdf

Use of Real World Data in Development Programmes

Dr Alison Cave and Dr Francesca Cerreta

Industry Stakeholder Platform on Research and Development Support

25 April 2017

An agency of the European Union

healthpolicy.duke.edu/sites/default/files/atoms/files/rwe_white_paper_2017.09.06.pdf

A Framework for Regulatory Use of Real-World Evidence

September 13, 2017

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Sean Tunis
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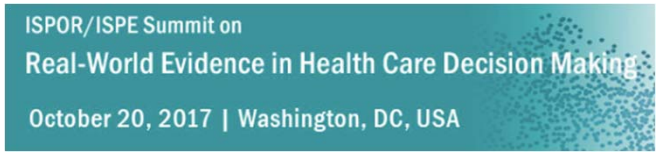
HealthCore

Taiwan FDA is interested, so far …



Organizing Institutions

- Methodology
  - Transparency & Reproducibility
- Regulatory agency (US FDA)
- Payer / Health Technology Assessment
  - EuNetHTA
  - Private health insurance companies
- Academia, patients, registries, industry, academic journals
- Similar discussion in Asia Pacific?

Potential barriers – not insurmountable

- Regulatory agency - GMP and GCP oriented
  - Clinical trial data (clean and structured) vs. observational data (messy …)
  - Clinical trial statistics vs. methods for observational studies
- Health Insurance agency
  - Explicit guidelines?
  - In some countries, budget impact seems to be more important than Incremental Cost-Effectiveness Ratio

Historically, some unfortunate dichotomy

- Randomized trials vs. Non-randomized studies
- Primary data vs. Secondary data
- Prospective vs. Retrospective
- Pre- vs. Post-marketing
- Validity vs. generalizability

- Ideally, different types of data complement each other – fit for purpose

All sorts of erroneous inference could be drawn from secondary health care data (just like other studies …)

- The large study size (nation-wide !) could be misleading
- RWD is generalizable, only if the study is valid
- Scientific journals should be the rigorous gate-keepers
- Training, training, training !!!

How to overcome these barriers?

- National laws and regulations
  - Like the 21st Century Cure Act in the USA
- Research methods
  - Existing methods are valid and robust
  - Ongoing development of new methods
- Data
  - Transparency in data development
  - Validation
  - Ethics review, privacy, and confidentiality
- Best practices and guidelines

Two health insurance claims-based studies

Funded by US FDA

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

2011; 365: 1896-904

ADHD Drugs and Serious Cardiovascular Events in Children and Young Adults

William O. Cooper, M.D., M.P.H., Laurel A. Habel, Ph.D., Colin M. Sox, M.D., K. Arnold Chan, M.D., Sc.D., Patrick G. Arbogast, Ph.D., T. Craig Cheetham, Pharm.D., Katherine T. Murray, M.D., Virginia P. Quinn, Ph.D., M.P.H., C. Michael Stein, M.B., Ch.B., S. Todd Callahan, M.D., M.P.H., Bruce H. Fireman, M.A., Frank A. Fish, M.D., Howard S. Kirshner, M.D., Anne O'Duffy, M.D., Frederick A. Connell, M.D., M.P.H., and Wayne A. Ray, Ph.D.

J Am Heart Assoc. 2017;6:e005362

Comparative Effectiveness and Safety of Dabigatran and Rivaroxaban in Atrial Fibrillation Patients

Chao-Lun Lai, MD, PhD; Ho-Min Chen, MS; Min-Tsun Liao, MD; Ting-Tse Lin, MD; K. Arnold Chan, MD, ScD

- Validation of cardiovascular outcomes was carried out in one study, but not the other

Validation

- System validation -- the whole data environment
  - Any “cleaning” process?
  - Apparent inconsistency?
    - Health care claims after death? Inconsistent gender? Duplicate National ID? Missing data? …
- Validation of Health Outcomes of Interest
  - www.sentinelinitiative.org/sentinel/surveillance-tools/validations-lit-review

ELSEVIER

Journal of Clinical Epidemiology 58 (2005) 171–174

Journal of Clinical Epidemiology

Health plan administrative databases can efficiently identify serious myopathy and rhabdomyolysis

Susan E. Andrade[a,*], David J. Graham[b], Judy A. Staffa[b], Stephanie D. Schech[c], Deborah Shatin[c], Lois La Grenade[b], Michael J. Goodman[d], Richard Platt[e,f,g], Jerry H. Gurwitz[a], K. Arnold Chan[e,h]

- Utilized a combination of diagnosis codes and laboratory order codes to identify potential cases
  - Casted a wide net, then reviewed medical records to confirm the event, not all potential cases were confirmed

Symposium 2
VALIDATION OF LARGE ADMINISTRATIVE DATABASES IN ASIA: METHODOLOGICAL AND PRACTICAL CHALLENGES

PACE Auditorium

Kiyoshi Kubota, NPO Drug Safety Research Unit, Japan
Cynthia de Luise, Worldwide Safety and Regulatory, Pfizer, USA

Validation studies of claims data in Japan – An overview and case study on the accuracy of Japanese claims data in identifying breast cancer
Izumi Sato, Kyoto University; The Keihanshin Consortium for Fostering the Next Generation of Global Leaders in Research, Japan

Taiwan experience and future developments
Arnold Chan, National Taiwan University, Taiwan

Validation in Hong Kong - challenges, opportunities and needs compared to other data sources
Ian C K Wong, University College London, United Kingdom; University of Hong Kong, Hong Kong

Panel discussion: Issues and themes on conducting validation studies in Asia
Izumi Sato, Arnold Chan, Ian C K Wong and Soko Setoguchi, Rutgers University, USA

Oct 30, 2017

Value in Health 2017; 20: 1003-8, 1008-22

Original Report

Good Practices for Real-World Data Studies of Treatment and/or Comparative Effectiveness: Recommendations from the Joint ISPOR-ISPE Special Task Force on Real-World Evidence in Health Care Decision Making

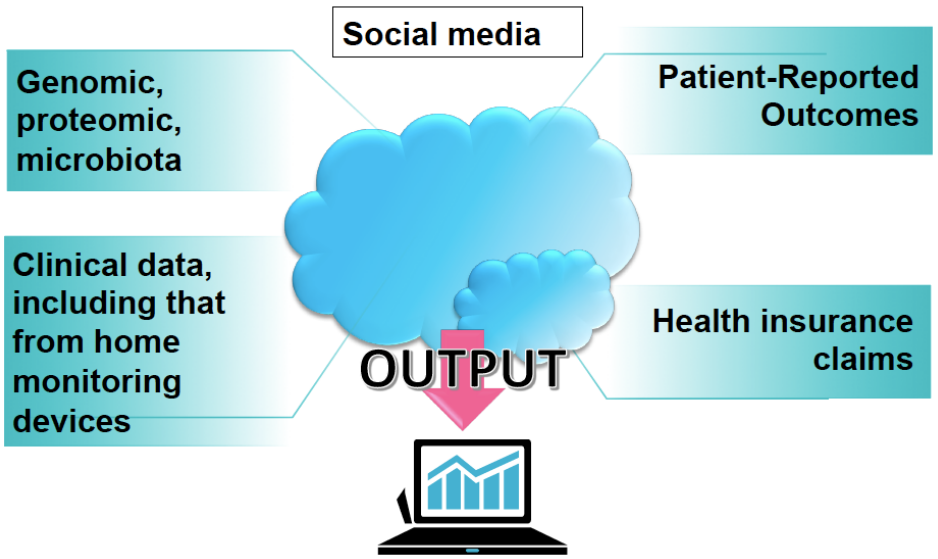
Marc L. Berger[1,], Harold Sox[2], Richard J. Willke[3], Diana L. Brixner[4], Hans-Georg Eichler[5], Wim Goettsch[6], David Madigan[7], Amr Makady[6], Sebastian Schneeweiss[8], Rosanna Tarricone[9], Shirley V. Wang[8], John Watkins[10], C. Daniel Mullins[11]*

Original Report

Reporting to Improve Reproducibility and Facilitate Validity Assessment for Healthcare Database Studies V1.0

Shirley V. Wang[1,2,], Sebastian Schneeweiss[1,2], Marc L. Berger[3], Jeffrey Brown[4], Frank de Vries[5], Ian Douglas[6], Joshua J. Gagne[1,2], Rosa Gini[7], Olaf Klungel[8], C. Daniel Mullins[9], Michael D. Nguyen[10], Jeremy A. Rassen[11], Liam Smeeth[6], Miriam Sturkenboom[12], on behalf of the joint ISPE-ISPOR Special Task Force on Real World Evidence in Health Care Decision Making*

Someday, after data security and ethics concerns are addressed … a data platform to generate useful evidence



2018.9.10

The NEW ENGLAND JOURNAL of MEDICINE 2016; 375: 454 - 63

REVIEW ARTICLE

THE CHANGING FACE OF CLINICAL TRIALS

Jeffrey M. Drazen, M.D., David P. Harrington, Ph.D., John J.V. McMurray, M.D., James H. Ware, Ph.D., and Janet Woodcock, M.D., *Editors*

Pragmatic Trials

Ian Ford, Ph.D., and John Norrie, M.Sc.

2016; 375: 1253-60

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Effectiveness of Fluticasone Furoate–Vilanterol for COPD in Clinical Practice

Jørgen Vestbo, D.M.Sc., David Leather, M.B., Ch.B., Nawar Diar Bakerly, M.D., John New, M.B., B.S., J. Martin Gibson, Ph.D., Sheila McCorkindale, M.B., Ch.B., Susan Collier, M.B., Ch.B., Jodie Crawford, M.Sc., Lucy Frith, M.Sc., Catherine Harvey, D.Phil., Henrik Svedsater, Ph.D., and Ashley Woodcock, M.D., for the Salford Lung Study Investigators*

- "There is a need for randomized trials to be conducted in conditions that are closer to usual clinical practice."
- "*Usual clinical practice*" varies across regions and countries

2018.9.10

JAMA 2018; 320: 146-55

JAMA | Original Investigation

Effect of a Home-Based Wearable Continuous ECG Monitoring Patch on Detection of Undiagnosed Atrial Fibrillation
The mSToPS Randomized Clinical Trial

Steven R. Steinhubl, MD; Jill Waalen, MD, MPH; Alison M. Edwards, MStat; Lauren M. Ariniello, BS; Rajesh R. Mehta, RPh, MS; Gail S. Ebner, BS; Chureen Carter, PharmD, MS; Katie Baca-Motes, MBA; Elise Felicione, MPH, MBA; Troy Sarich, PhD; Eric J. Topol, MD

JAMA 2018; 320: 137-8

EDITORIAL

Evaluating Health Technology Through Pragmatic Trials
Novel Approaches to Generate High-Quality Evidence

Eric D. Peterson, MD, MPH; Robert A. Harrington, MD

Steinhubl *et al*. JAMA 2018; 320: 146-55

- The mHealth Screening to Prevent Strokes (mSToPS) Trial
  - A randomized trial with an observational component
  - Embedded within existing healthcare environment
- "The trial was an investigator-initiated, randomized, pragmatic, siteless clinical trial involving a large health insurance plan's members throughout the United States.

RWE in Asia Pacific

- Are We ready?
- Is It Helpful for Decision Makers?
- Yes! and Yes!
  - Existing health care data environment (health insurance claims, electronic medical records, including home monitoring devices)
  - Prospectively collected registry data
  - Pragmatic trials
- Experienced investigators

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