ENABLING BETTER USE OF REAL WORLD EVIDENCE

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Engineering Systems / Political Science / NewDIGS
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Panel on New Data Models
Managing Uncertainty and Leveraging New Evidence
October 27, 2015
Cannon Caucus Room, Cannon House Office Building, Washington DC

MIT CBI
Center for Biomedical Innovation

ENABLING BETTER USE OF REAL WORLD EVIDENCE

ON WHAT ISSUES SHOULD COMMON STANDARDS OR RULES BE SET?

- Interoperability: data exchange, categorization, diagnostic criteria
- Curation: standards for verification and confirmation of data quality
- Allowed Uses: With IRB approval? With consent? Opt in or opt out?
  - Public Health Surveillance, surrogate validation
  - Research Effectiveness, discovery, repurposing, RCT recruiting
- Privacy: Anonymized/de-identified? Data security standards?
- Ownership: IPR on data, on tools, on protocols/standards

WHAT SCOPE OF HARMONIZATION IS NEEDED?

Global > Nation-Region > Dyad-Group > Public Agency-Private Firm

WHO SHOULD DECIDE? HOW? VOLUNTARY OR MANDATORY?

Issue / Scope	Interoperability Standards	Curation Standards	Allowed Uses Opt In / Opt Out	Privacy Identifiability	IPR on Data & Standards
Agency-Firm					
Dyad-Group					
Nation-Region					
Global					

DATA INTEGRATION AND CURATION

RWE based on many types of data, including administrative claims data, electronic medical records, and patient and product registries.

Continuous readouts from medical instruments, continuous monitoring from mobile apps and contextual info from social media available.

Data embody varying degrees of quality, accuracy, and completeness, which adds uncertainty to utility in evidence generation.

Integration of data sets with different diagnostic categories and outcome measures, merging genotypic and phenotypic information, based on different principles of organization, is a challenge.

Acceptable evidence generation requires ability to adjust for possible bias in data sources related to data completeness, data capture incentives, clinical data workflows, and other factors.

NOTE: WHEN DOES CURATION REQUIRE ACCESS TO PATIENT

DATA USE - OWNERSHIP AND CONSENT

- Small-n treatment groups => pool data across nations, organizations.
- Intellectual property rights conventions, patient consent, and privacy protections vary nation-to-nation and organization-to-organization.

OWNERSHIP

- Firms own trials data and some registries (US FDA, not EU EMA)
- Public and private payers own claims data
- Health care providers own medical records
- Patient ownership of medical records and genotypic information varies across jurisdictions and contracts

CONSENT AND PRIVACY

- Patient/subject informed consent (varied)
- Privacy and data protection standards (varied)
- Anonymized data and freedom to operate… but limits on value
- Public policies on data use affect willingness to participate (china)

DATA ANALYSIS – ANALYTICAL METHODS AND RESEARCH DESIGN

How combine observational interventional studies to accelerate evidence generation in a methodogically sound manner?

- New "causal Inference" literature jointly developed by social sciences, epidemiologists, clinical trials designers . . .

  Who? Gary King Harvard, Teppei Yamamoto / In Song Kim MIT
- New AI literature on signal detection methods and unstructured data

  Who? Ramy Arnout,Harvard; William Crown,Optum; Jeremy Rassen, Aetion; Peter Szolovits, Clinical Decision Making Group MIT CSAIL.
- New forms of clinical trials, working between observational studies that generate hypotheses on safety or effectiveness to use of smart tech to identify and enroll patients in confirmatory trials

  Who? Vicki Seyfert-Margolis My-Own-Med, Dennis Ausciello, Center for Technology Assessment and Continuous Health

NOTE: DO YOU NEED THE IDENTITY OF PATIENTS?

The Next Frontier: Fostering Innovation by Improving Health Data Access and Utilization

KA Oye[1], G Jain[2], M Amador[3], R Arnaout[4,5], JS Brown[6], W Crown[7], J Ferguson[8], E Pezalla[9], JA Rassen[10], HP Selker[11], M Trusheim[12] and G Hirsch[2]

Beneath most lively policy debates sit dry-as-dust theoretical and methodological discussions. Current disputes over the EU Adaptive Pathways initiative[1,2] and the proposed US 21st Century Cures Act[3] may ultimately rest on addressing arcane issues of data curation, standardization, and utilization. Improved extraction of information on the safety and effectiveness of drugs-in-use must parallel adjustments in evidence requirements at the time of licensing. To do otherwise may compromise safety and efficacy in the name of fostering innovation.

To take stock of the current state of the art, this essay identifies sources of demand for better utilization of real-world medical data, highlights the need for improved data quality, data access, and analytic methods, and evaluates the US Sentinel Initiative and Optum Labs as examples of distributed and centralized data initiatives.

To engage with emerging needs, this essay offers an integrated research and policy agenda. Academic research topics focus on improving data quality and access and on developing hybrid observational and interventionist methods to enhance causal inference under less-than-ideal conditions. Policy agendas focus

tional and "precision medicine"; 3) growing demands from payers and health technology assessment officials for quantifiable measures of relative effectiveness of new drugs. Defining the path forward requires an understanding of each of these trends, and how they are shaping the evolution of evidence requirements.

First, with the advent of adaptive approaches to drug licensing, the need to leverage observational data to reassess licensing decisions is expanding from a few drugs that target life-threatening unmet needs to many drugs addressing a wider variety of medical needs.[5] Calls for rapid access to new treatments originally came from advocates for patients with fast-progressing conditions such as HIV, cancer, and many orphan conditions. Patients with chronic, slowly progressing diseases with unsatisfactory treatment options are now making the same plea for rapid access. The EU Adaptive Pathways initiative and the US 21st Century Cures initiative both seek to address patients' demands for early access to a broadening array of treatments, with an associated need for reassessment of initial licensing decisions in light of evolving real-world evidence (RWE) on drug safety and effectiveness.

For these initiatives to succeed, regulators must strike an appropriate balance between addressing needs through early

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PATIENTS, PROVIDERS, PAYERS WANT EFFECTIVENESS NEED RWE

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STATE OF THE ART

see COMMENTARY page 131

A Proposal for Integrated Efficacy-to-Effectiveness (E2E) Clinical Trials

HP Selker[1,2], KA Oye[3], H-G Eichler[4], NL Stockbridge[5], CR Mehta[6], KI Kaitin[1,7], NE McElwee[8], PK Honig[9], JK Erban[1,10] and RB D'Agostino[11,12]

We propose an "efficacy-to-effectiveness" (E2E) clinical trial design, in which an effectiveness trial would commence seamlessly upon completion of the efficacy trial. *Efficacy trials* use inclusion/exclusion criteria to produce relatively homogeneous samples of participants with the target condition, conducted in settings that foster adherence to rigorous clinical protocols. *Effectiveness trials* use inclusion/exclusion criteria that generate heterogeneous samples that are more similar to the general patient spectrum, conducted in more varied settings, with protocols that approximate typical clinical care. In E2E trials, results from the efficacy trial component would be used to design the effectiveness trial component, to confirm and/or discern associations between clinical characteristics and treatment effects in typical care, and potentially to test new hypotheses. An E2E approach may improve the evidentiary basis for selecting treatments, expand understanding of the effectiveness of treatments in subgroups with particular clinical features, and foster incorporation of effectiveness information into regulatory processes.

EFFECTIVENESS AND RWE

Classic RCT provide a valid basis for inferring safety and efficacy of a drug for strictly adhering confounder-cleansed populations over limited periods of time . . .

…. But limits on use of RCT as basis for predicting safety and effectiveness for general populations with comorbidities taking other drugs with limited adherence over longer periods of time.

Observational studies based on real-world data can provide insights into the safety and effectiveness of drugs . . .

…. But the presence of selection effects, biases in data capture, and variable data completeness limit internal validity of such studies.

How move from Efficacy-to-Effectiveness?

- Combine RWE and targeted interventional studies
- Going backwards from observation to targeted trials

SEEK EARLIER ACCESS, BETTER RISK MANAGEMENT - NEED RWE!

STATE OF THE ART

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See COMMENTARY page 378

Adaptive Licensing: Taking the Next Step in the Evolution of Drug Approval

H-G Eichler[1,2], K Oye[2,3,4], LG Baird[2], E Abadie[5], J Brown[6], CL Drum[2], J Ferguson[7], S Garner[8,9], P Honig[10], M Hukkelhoven[11], JCW Lim[12], R Lim[13], MM Lumpkin[14], G Neil[15], B O'Rourke[16], E Pezalla[17], D Shoda[18], V Seyfert-Margolis[14], EV Sigal[19], J Sobotka[20], D Tan[12], TF Unger[18] and G Hirsch[2]

Traditional drug licensing approaches are based on binary decisions. At the moment of licensing, an experimental therapy is presumptively transformed into a fully vetted, safe, efficacious therapy. By contrast, adaptive licensing (AL) approaches are based on stepwise learning under conditions of acknowledged uncertainty, with iterative phases of data gathering and regulatory evaluation. This approach allows approval to align more closely with patient needs for timely access to new technologies and for data to inform medical decisions. The concept of AL embraces a range of perspectives. Some see AL as an evolutionary step, extending elements that are now in place. Others envision a transformative framework that may require legislative action before implementation. This article summarizes recent AL proposals; discusses how proposals might be translated into practice, with illustrations in different therapeutic areas; and identifies unresolved issues to inform decisions on the design and implementation of AL.

INTRODUCTION

Public and political trust in the current drug development and approval process is frequently challenged by the controversy over timely access to new therapeutics, product withdrawals, and postapproval modifications to labels. Partly in response to consumer advocates and the medical community,[1,2] and to advances in regulatory, bench, and clinical sciences, there have been increases in the amount of up-front data required to market a new drug. Current scientific and regulatory approaches to marketing authorization generally utilize randomized controlled trials (RCTs) to provide information on safety and efficacy, yet data on real-life comparative effectiveness are required to inform clinical decisions and those of payers.[3] Taken together, these issues have led to more data being required during the initial development of a new product. To meet this demand, pharmaceutical firms have increased their investment both in research and development and in the number, size, duration, and design complexity of clinical trials. Yet, despite the near universal increase in effort and investment from all stakeholders in the health-care system, including regulators, the number of newly approved drugs per year has remained flat. Costs of medicines are increasing, and there are few truly innovative treatments. As a result, the rising cost of incremental gains in health benefits is unsustainable within an environment of strained budgets.

Under the traditional regulatory paradigm, the life span of a drug is divided into two distinct phases: prelicensing and postlicensing. During the prelicensing phase, patients are exposed to a new drug only if they enroll in clinical trials with informed-consent procedures, meet specific enrollment criteria, and are randomized to the investigational product. The situation changes abruptly upon licensure. Often, this single event expands the exposure of a new drug from a relatively small number of highly selected trial subjects to millions of real-world patients who might not fit treatment eligibility requirements as specified in the label. At this point, drugs are generally perceived to be "safe and effective." The unpredictability of the confounded real-world populations and usage combined with the unrealistic expectation of perpetual safety based on the extrapolation of limited data is not generally acknowledged in the current regulatory-decision framework. Such unrealistic expectations

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PERSPECTIVES

CONFERENCE PROCEEDINGS

Legal Foundations of Adaptive Licensing
3 April 2012
European Medicines Agency, Canary Wharf, London, UK

Legal Foundations of Adaptive Licensing

K Oye[1], LG Baird[1], A Chia[2], S Hocking[3], PB Hutt[4], D Lee[5], L Norwalk[6] and V Salvatore[7]

In April 2012, MIT's Center for Biomedical Innovation and the European Medicines Agency (EMA) cosponsored a workshop on legal foundations of adaptive pharmaceuticals licensing. Past and present attorneys from the US Food and Drug Administration (FDA), the EMA, and Health Sciences Agency Singapore (HSA) found that existing statutes provided authority for adaptive licensing (AL). By contrast, an attorney from Health Canada identified gaps in authority. Reimbursement during initial phases of adaptive approaches to licensing was deemed consistent with existing statutes in all jurisdictions.

Background on adaptive licensing

In March 2012, Eichler *et al.* published "Adaptive Licensing: Taking the Next Step in the Evolution of Drug Approval" in this journal.[1] The article contrasted traditional binary approaches to drug licensing with adaptive approaches that emphasize stepwise learning under conditions of acknowledged uncertainty. It summarized recent comprehensive proposals for AL, discussed how proposals might be shaped to fit different therapeutic areas, and identified unresolved issues associated with design and implementation of AL. The article spurred debate over whether existing statutes and regulations provided authority for AL, with reference to elements of early and late stages.

Initial authorization. Traditional accelerated approval–conditional marketing authorizations (CMAs) provide early access to a limited number of drugs. AL would provide earlier access to more drugs in an initial authorization stage with novel measures to manage risks. Access to a drug would be limited to a restricted population, defined on the basis of knowledge about benefits and risks at the time of initial approval. Off-label use would be limited. Drugs would be labeled as initially authorized, and patients and physicians would be informed on knowns and unknowns about the drug. Reimbursement would be provided with rates as yet to be determined.

Evidence generation and learning. At present, the treatment experience of most nontrial patients does not contribute significantly to evidence generation. AL would make fuller use of all sources of information to update regulatory and treatment decisions. Evidence generation, particularly in later stages of the drug life cycle, would not be limited to conventional randomized controlled trials but would encompass a broader methodology spectrum, including pragmatic clinical trials, clustered randomized controlled trials, observational studies based on electronic medical records, registries, and other forms of active and passive surveillance.

Workshop findings

The workshop was organized to assess whether existing statutes in the European Union, United States, Canada, and Singapore provide adequate authority for AL. Conclusions included the following.

United States. Authority currently exists in statutes and regulations for all elements of AL, but regulators are not obligated to pursue AL approaches. Private and public payers may reimburse for drugs during initial authorization.

European Union. Authority can be identified with enactment of pharmacovigilance legislation in July 2012,

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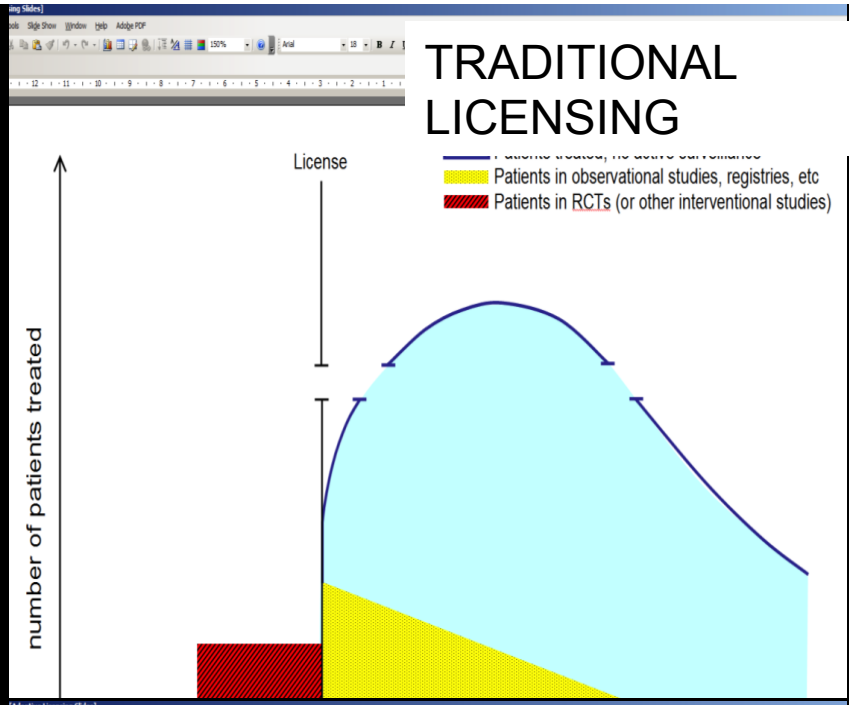
ADAPTIVE LICENSING
Patient experience contributes to evidence development

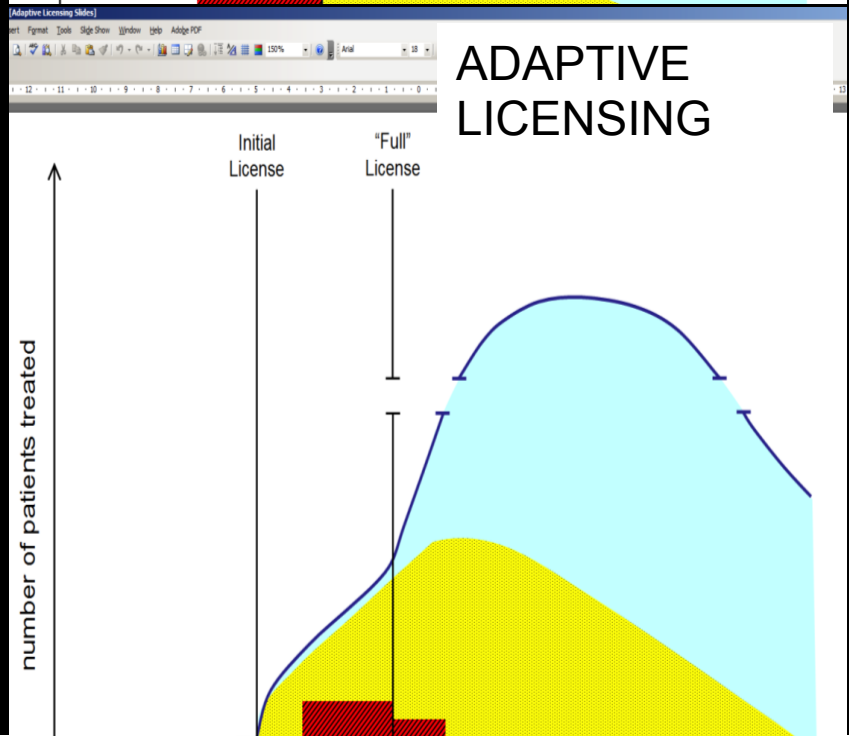
FRONT END – PRE MARKET
Earlier approval
Conditional
Limit to patients on benefit/risk

BACK END – ON MARKET
Strengthen observation
- Registries
- EHRs

Analyze safety and effectiveness
Adapt label and license

KEY
Patients in interventional studies
Patients treated but unobserved
Patients treated and observed





FROM PREDICTION TO OBSERVATION AND MONITORING
Credit: Eichler OECD presentation 2014

Year	Drug > Adverse Effect	Detection Threshold
1950-60s	Thalidomide > phocomelia	10000 cases
2005	Natalizumab > PML	3 cases
2009	Pandemrix > narcolepsy	6 cases

Note: phocomelia — low background / high visibility event

Note: MI in diabetics — high background / low visibility events

WEAK EXISTING POSTMARKETING FOLLOWUP AND CONTROLS

2005 Ed Markey staff study

- 91 required postmarketing studies
- 45% not completed, many not started

2013 Moore-Furberg study of 20 drugs approved in 2008

- 8 expedited approval based on average of 5.1 years of clinical testing
- 12 standard approval based on 7.5 years of clinical testing
- 60% of required follow-up safety studies not completed by 2013

2013 Carpenter "hodgepodge of exceptions to rigorous premarket review"

- Approval based on testing in limited patient populations
- Use not restricted to limited patient populations

REPURPOSING DRUGS – NEED RWE

SERENDIPITOUS REPURPOSING – NEW USES FOR OLD DRUGS

Sildenafil developed as treatment for angina, repurposed for erectile dysfunction, then repurposed for pulmonary arterial hypertension.

Phenothiazine originally developed as antimalarial, antihistamine, anesthetic. When used as anesthetic on psychotics, reduced psychosis.

Tricyclics originally developed for TB then repurposed as antidepressant when mood of TB patients treated with tricyclics improved.

EXAMPLES OF MORE SYSTEMATIC REPURPOSING

AZT tested and rejected as treatment for herpes simplex, and then used as treatment for HIV. NIH funding for screening of existing drugs as anti-retrovirals was key in repurposing.

Fluoexetine HCl was developed as Prozac for depression, then patented, licensed and marketed as Sarafem to treat PMS.

DRUG REPURPOSING THROUGH OBSERVATONAL INNOVATION?

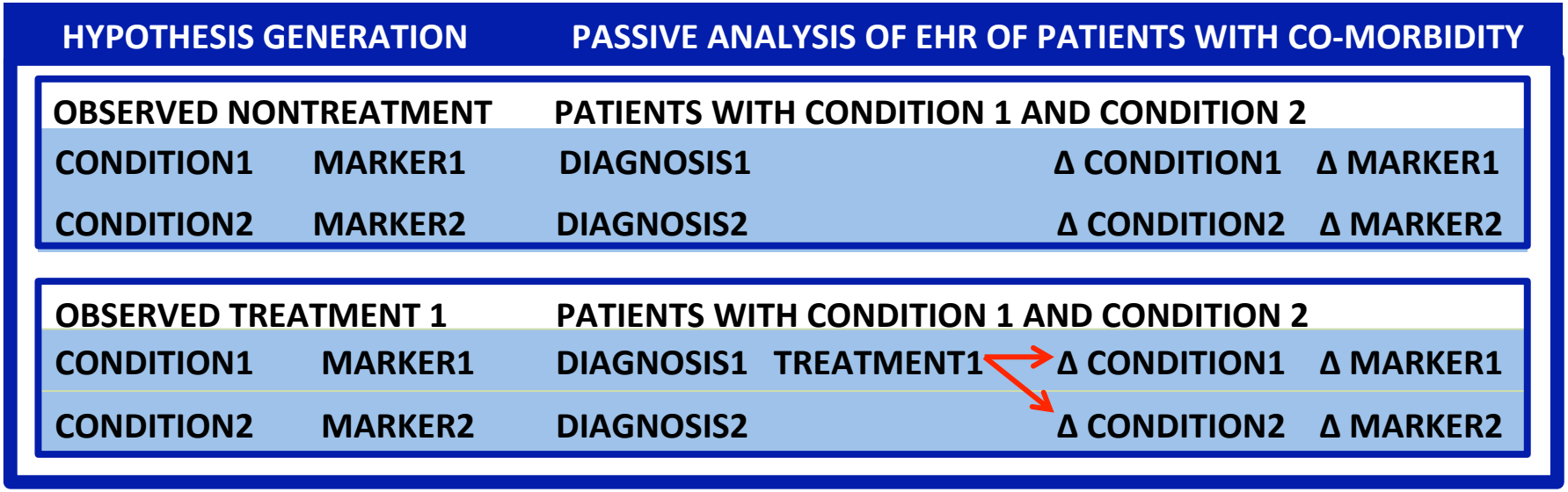
Fewer new drugs emerging from pipeline . . . .
. . . . interest in squeezing additional value from existing drugs.

Development of higher quality EHR . . . .
. . . . enable search for secondary benefits as well as adverse effects.

Development of pattern recognition methods in artificial intelligence . . .
. . . . provide tools to detect secondary benefits, distinguish from noise.

Adaptive licensing uses observational with credibility . . . .
. . . . provides regulatory framework integrating observation and RCT.

REPURPOSING ON-MARKET GENERIC OR NEAR-GENERIC DRUGS



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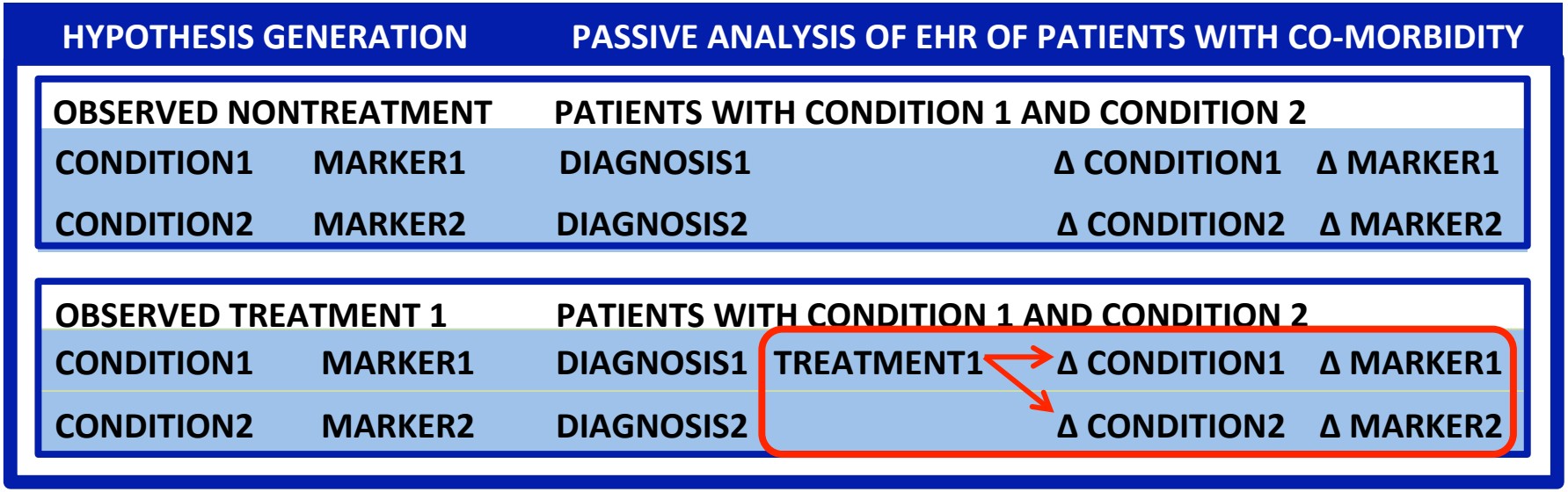

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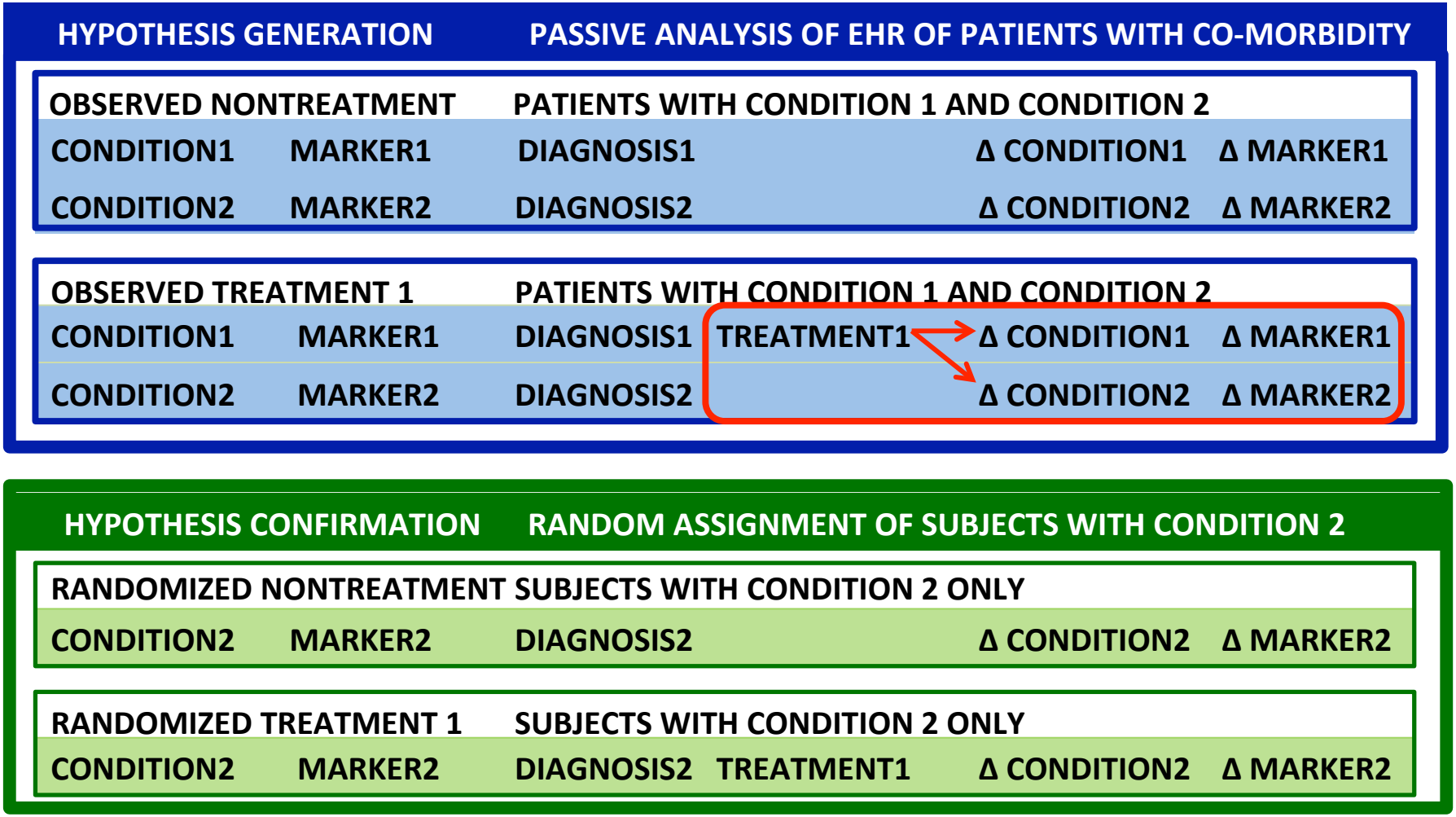

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Table 1 Illustrative examples of data initiatives

Name of data initiative	Lead/host organization	Lifespan stage			Data type					Target outputs				Geography		
		Discovery	Development	Delivery	Registry	Claims data	EMR	Clinical trials	Others	Biomarkers	Standards	Infrastructure	Methodology	US	EU	Other
Data Quality																
Clinical Data Interchange Standards Consortium (CDISC)	CDISC	x	x	x	x	x	x	x	x		x			x	x	x
Quality Metrics Initiative	International Society for Pharmaceutical Engineering	x	x						x		x			x		
Public Health Data Standards Consortium (PHDSC)	PHDSC		x	x	x	x	x				x			x		
Data Access																
CancerLinQ	American Society of Clinical Oncology		x	x	x	x	x	x		x		x		x		
Coalition Against Major Diseases (CAMD)	Critical PATH Institute		x			x				x		x	x	x		
ENCePP	European Medicines Agency		x	x			x	x				x			x	
European Medical Information Framework (EMIF)	Innovative Medicines Initiative			x	x	x	x				x	x	x		x	
Health Care Cost Institute (HCCI)	HCCI			x		x						x		x		
Optum Labs	Optum Labs		x	x		x	x		x			x		x		
PCORNet	PCORI		x	x		x	x	x				x		x		
Sentinel	US Food and Drug Administration		x	x		x						x	x	x		
Methods																
GetReal	Innovative Medicines Initiative		x	x	x	x	x					x	x		x	
Observational Medical Outcomes Partnership (OMOP)	Foundation of the National Institutes of Health		x	x		x	x					x	x	x		
PROTECT	Innovative Medicines Initiative		x	x	x	x	x	x					x		x	
Safer and Faster Evidence-based Translation (SAFE-T)	Innovative Medicines Initiative	x						x	x	x			x	x	x	

*Note: This is not an exhaustive list of data initiatives

ENCePP: The European network of centers for pharmacoepidemiology and pharmacovigilance; PCORI: The patient-centered outcomes research institute; PROTECT: pharmacoepidemiological research on outcomes of therapeutics by a European consortium.

SENTINEL: DISTRIBUTED DATA SYSTEM SERVING FDA

Data Quality: Data partners, not Sentinel, retain patient-level data per the industry standard, maintain control of data behind firewalls, and respond to queries sent by the Sentinel operations center. Data curation is the responsibility of data partners. Sentinel leverages existing data standards used by insurers and clinicians in the US.

Data Access - Ownership and Consent: Data partners collect data for administrative, billing, and clinical care purposes, are responsible for protection and appropriate use of data, and must secure approval for research from their IRBs. Because Sentinel is part of a program of active surveillance for adverse effects of drugs, Sentinel queries are treated under a public health exception doctrine not requiring IRB approval. Only the FDA may initiate queries in Sentinel.

Analytical methods: The reliance on a distributed structure, with queries to data owners returning marginal counts or intermediate matrices rather than individual-level data, complicates the use of advanced analytical methods to control for selection effects and interaction effects, limits data curation, precludes follow-up queries for further information on individual cases.

OPTUM LABS – A CENTRALIZED SYSTEM SERVING UNITED HEATHCARE

Data Quality: Health care data from de-identified claims and clinical data from multiple health plans and provider groups.

- The data are integrated across care settings, longitudinally linked at the patient level, and stored in a secure central location.
- The centralized data facilitates rapid turnaround on analyses, and enables close investigation of rare events, small patient subgroups and other inquiries difficult to conduct with distributed data model.
- The centralized model also facilitates direct queries of the full database to test project feasibility and generate preliminary descriptive results without needing to distribute common protocols to remote data holders, obtain iterative approvals, and aggregate results across sites post analysis.
- All data from contributing plans and EMRs are subjected to numerous edit checks to cleanse the data to support research.
- Up to 85% of EMR clinical content originally resides in unstructured data. As a consequence, thousands of clinical data elements are extracted from EMRs through natural language processing (NLP), curated, normalized and then linked to claims at an individual level to add depth to the claims population breadth.

OPTUM LABS – A CENTRALIZED SYSTEM SERVING UNITED HEATHCARE

Data Access – Ownership and Consent:

- Optum obtains rights to use de-identified claims and EMR data for research from contributing health plans and provider groups under its business associate relationships with these organizations.
- Patient-protected health information is encrypted and double hashed into unique identifiers that enables data to be linked across sources in a completely de-identified manner.
- A statistical expert in de-identification approves all views and determines that the data elements in combination present a "very small" risk of re-identification, as specified by HIPAA.

Analytical methods:

- The reliance on a centralized structure, with direct access to anonymized individual data, permits the use of advanced analytical methods to control for selection effects and interaction effects and allows follow-up queries for further information on individual cases.
- But centralized architecture limits Optum access to a smaller set of data sources than the Sentinel.

SOME OPPORTUNITIES AND GAPS

DESIGNING AND REFINING ADAPTIVE LICENSING

- EMA Adaptive Licensing Pilot Projects
- Simulations using data from previously approved drugs
- Assessing payer based methods of controlling access

POOLING INTERVENTION AND OBSERVATIONAL DATA

- Multinational trials to capture sufficient N
- Exploit natural experiments (Singapore) to estimate biases
- IPR and licensing of data from registries, payers and EHR
- Privacy regulations and data sharing arrangements
- Cybersecurity and data protection
- Technical protocols and standards for interoperability
- Advanced methods for causal inference with large data
- Confirmation of associations on beneficial or adverse effects
- Going backwards from observation to intervention

POLITICAL ECONOMY

- Converting data owners (payers, providers, HMO) into developers?
- Drug licensing as pricing policy: creating competitive markets?

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