HSP0146-2020 - Farmacoepidemiologia

Wearables & World Data

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Background

Epidemiologia Clínica:

Ciência de se fazer previsões sobre pacientes individuais, contando eventos clínicos em grupos de pacientes similares usando métodos científicos fortes para garantir que as previsões são precisas.

Clinical Epidemiology - The Essentials 4th ed. - R. Fletcher, et. al., (Lippincott, 2005)

Medicina Baseada em Evidências

É o uso consciente, explícito e criterioso das melhores evidências atuais na tomada de decisões sobre o atendimento de pacientes individuais.[2]

Evidence based medicine: what it is and what it isn't BMJ - Sackett David L, et. al.

Clinical Trial (Ensaios clínicos):

Um estudo em que um ou mais participantes humanos são prospectivamente designados para uma ou mais intervenções (que podem incluir placebo ou outro controle) para avaliar os efeitos dessas intervenções nos resultados biomédicos ou comportamentais relacionados à saúde. Ensaios clínicos são estudos clínicos de intervenção.

Estudo Observacional:

Um desenho de estudo clínico não-intervencionista que não é considerado um ensaio clínico. O EO não randomiza o tratamento, mas "observa" diferenças nos desfechos que ocorrem após a tomada de decisões sobre o tratamento, sem garantir que pacientes em diferentes braços de tratamento tenham características semelhantes relacionadas aos resultados.

Estudo Observacional, Prospectivo:

Um estudo no qual a população de interesse é identificada no início do estudo e os dados de exposição/tratamento e desfechos são coletados a partir desse ponto. O início do estudo é definido como o momento em que o protocolo de pesquisa para a questão específica do estudo foi iniciado.

Estudo Observacional, Retrospectivo:

Um estudo que identifica a população e determina a exposição/tratamento a partir de dados históricos (ou seja, dados gerados antes do início do estudo). As variáveis e desfechos de interesse são determinados no momento em que o estudo é projetado.

CLASSIFICAÇÃO DA EVIDÊNCIA
NÍVEIS DE INFORMAÇÃO

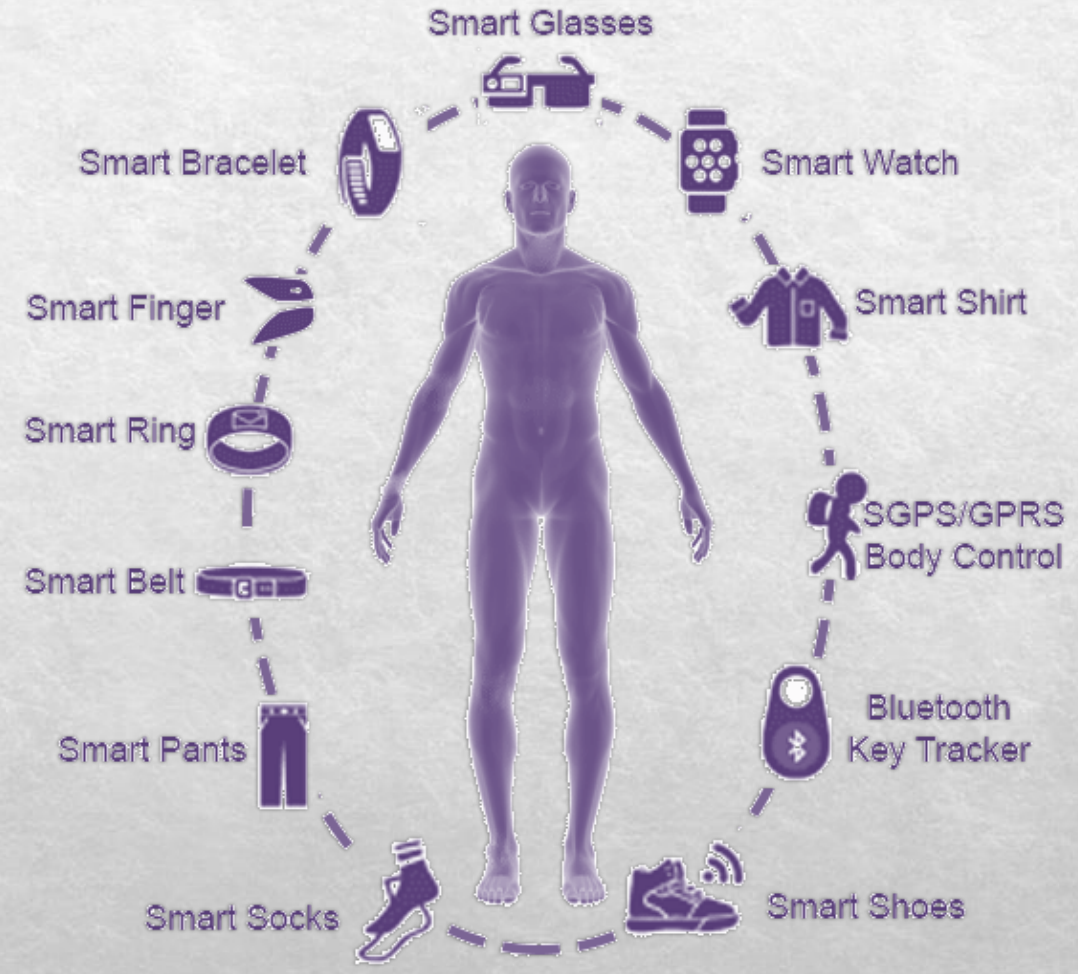
Diferentes tipos de evidência clínica ordenados de acordo com a 'força' de independência de vieses (*bias*) que obstruem a pesquisa médica.

Conceitos e Definições

O que são wearables?

Embora o termo wearable já dê pistas de como funciona um dispositivo do tipo, a nomenclatura não conta todos os detalhes. A tecnologia em questão não somente pode ser usada como uma peça de roupa ou um acessório, como também tem que possuir características que a conectem a outros aparelhos ou à internet.

Em outras palavras, aquele fone de ouvido de última linha ou um relógio digital não necessariamente são wearables — embora eles também possam se encaixar na categoria. A geração mais recente de gadgets é conhecida por trazer uma série de sensores que ajudam a aumentar sua organização, incentivar a prática de exercícios ou acompanhar programas de perda de peso, entre outras possibilidades.



Real-World Data:

Real-world ***data*** are the data relating to patient health status and/or the delivery of health care routinely collected from a variety of sources.

RWD can come from a number of sources, including but not limited to:

- ✓ Electronic health records (EHRs)
- ✓ Claims and billing activities
- ✓ Product and disease registries
- ✓ Patient-generated data including in home-use settings
- ✓ Data gathered from other sources that can inform on health status, such as mobile devices

www.fda.gov/science-research/science-and-research-special-topics/real-world-evidence

Healthcare Data Types

Wearable Devices Required for Acquiring 24-Hour Data

- Wearable devices that can be used for a long period of time and cause little burden are required in order to make measurements 24/7
- Diabetes-related wearables are representative devices in the medical treatment field; fitness trackers representative in the disease prevention field

Types of Wearable Devices for 24-Hour Measurement

Diabetes-Related

Blood Glucose Level

Insulin Pump

Heart Rate Monitor

Blood Pressure Monitor

Thermometer

Fitness Tracker (Amount of Physical Activity)

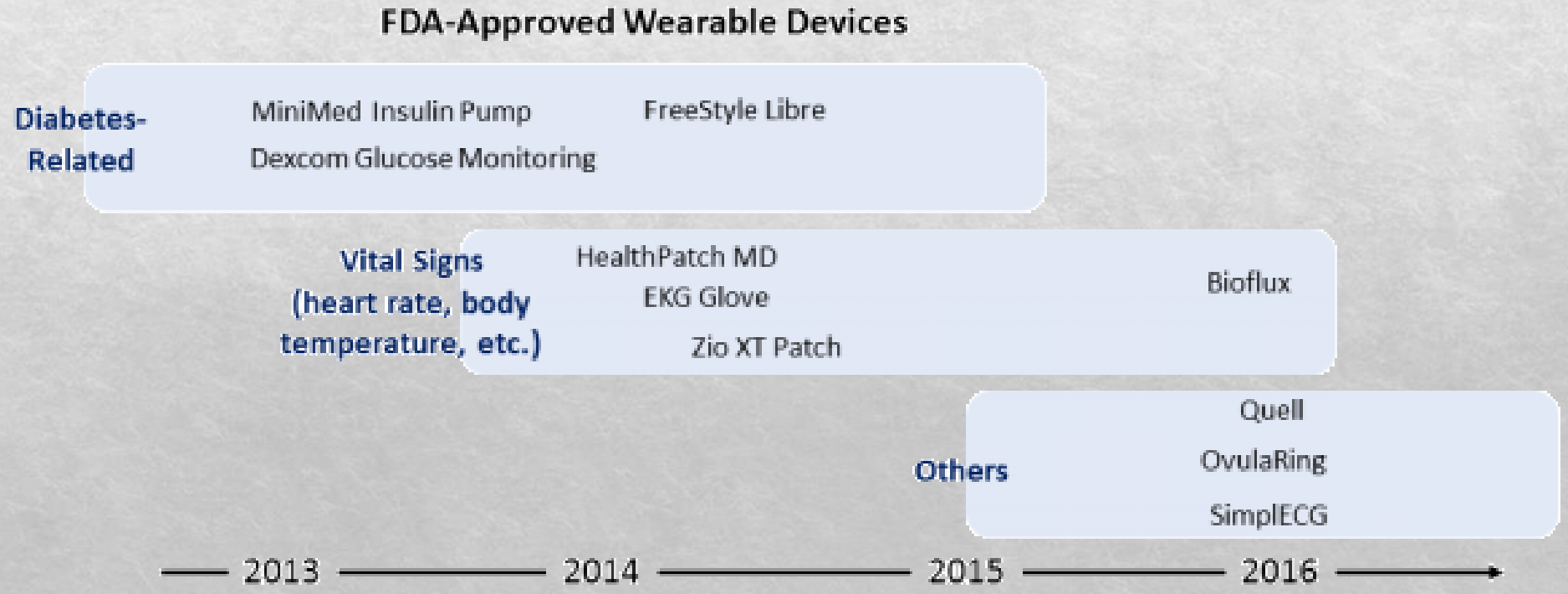
Sleep Monitor

Others

Wearable Devices for Medical Treatment

Increasing Number of FDA-Approved Devices for Medical Treatment

- In addition to the traditional diabetes-related devices, wearable devices for measuring vital signs, as well as those in new fields, have been obtaining approval from the FDA in recent years
- However, the range of proliferation for such devices is expected to be limited since many are for the purpose of medical treatment at hospitals



JAMA Cardiology | Original Investigation

Passive Detection of Atrial Fibrillation Using a Commercially Available Smartwatch

Geoffrey H. Tison, MD, MPH; José M. Sanchez, MD; Brandon Ballinger, BS; Avesh Singh, MS; Jeffrey E. Olgin, MD; Mark J. Pletcher, MD, MPH; Eric Vittinghoff, PhD; Emily S. Lee, BA; Shannon M. Fan, BA; Rachel A. Gladstone, BA; Carlos Mikell, BS; Nimit Sohoni, BS; Johnson Hsieh, MS; Gregory M. Marcus, MD, MAS

IMPORTANCE Atrial fibrillation (AF) affects 34 million people worldwide and is a leading cause of stroke. A readily accessible means to continuously monitor for AF could prevent large numbers of strokes and death.

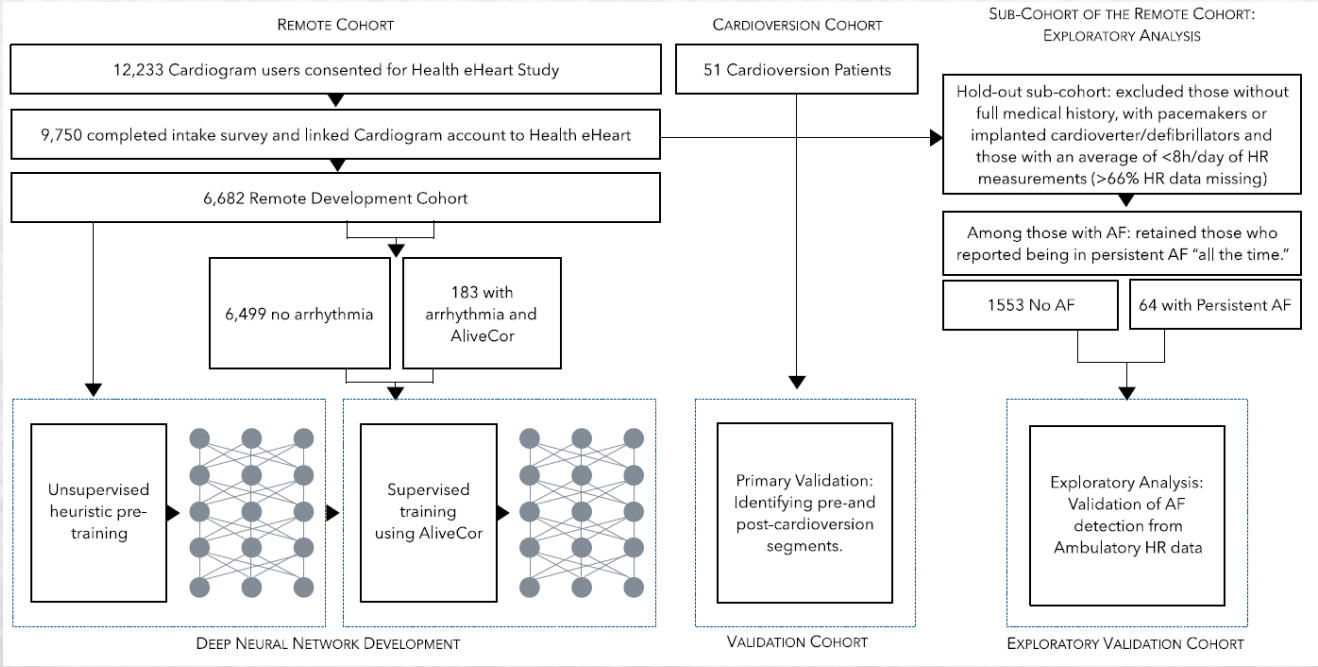
OBJECTIVE To develop and validate a deep neural network to detect AF using smartwatch data.

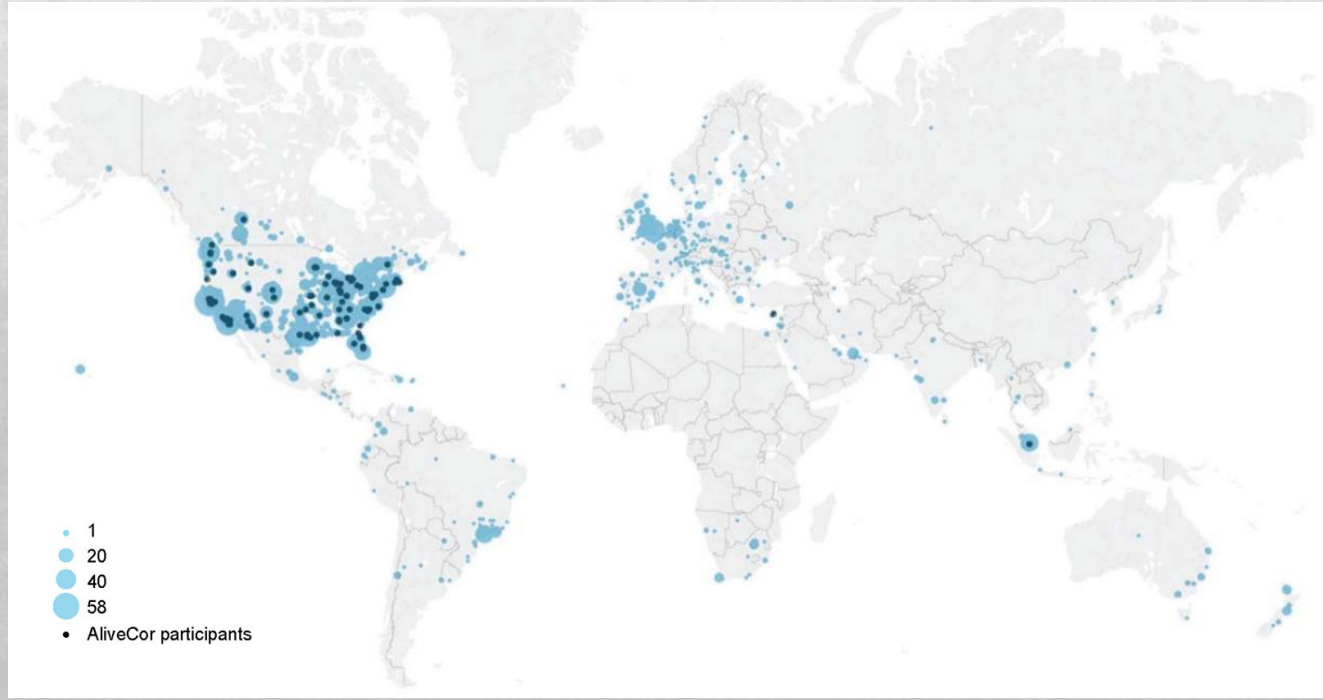
DESIGN, SETTING, AND PARTICIPANTS In this multinational cardiovascular remote cohort study coordinated at the University of California, San Francisco, smartwatches were used to obtain heart rate and step count data for algorithm development. A total of 9750 participants enrolled in the Health eHeart Study and 51 patients undergoing cardioversion at the University of California, San Francisco, were enrolled between February 2016 and March 2017. A deep neural network was trained using a method called heuristic pretraining in which the network approximated representations of the R-R interval (ie, time between heartbeats) without manual labeling of training data. Validation was performed against the reference standard 12-lead electrocardiography (ECG) in a separate cohort of patients undergoing cardioversion. A second exploratory validation was performed using smartwatch data from ambulatory individuals against the reference standard of self-reported history of persistent AF. Data were analyzed from March 2017 to September 2017.

MAIN OUTCOMES AND MEASURES The sensitivity, specificity, and receiver operating characteristic C statistic for the algorithm to detect AF were generated based on the reference standard of 12-lead ECG–diagnosed AF.

RESULTS Of the 9750 participants enrolled in the remote cohort, including 347 participants with AF, 6143 (63.0%) were male, and the mean (SD) age was 42 (12) years. There were more than 139 million heart rate measurements on which the deep neural network was trained. The deep neural network exhibited a C statistic of 0.97 (95% CI, 0.94-1.00; $P < .001$) to detect AF against the reference standard 12-lead ECG–diagnosed AF in the external validation cohort of 51 patients undergoing cardioversion; sensitivity was 98.0% and specificity was 90.2%. In an exploratory analysis relying on self-report of persistent AF in ambulatory participants, the C statistic was 0.72 (95% CI, 0.64-0.78); sensitivity was 67.7% and specificity was 67.6%.

CONCLUSIONS AND RELEVANCE This proof-of-concept study found that smartwatch photoplethysmography coupled with a deep neural network can passively detect AF but with some loss of sensitivity and specificity against a criterion-standard ECG. Further studies will help identify the optimal role for smartwatch-guided rhythm assessment.

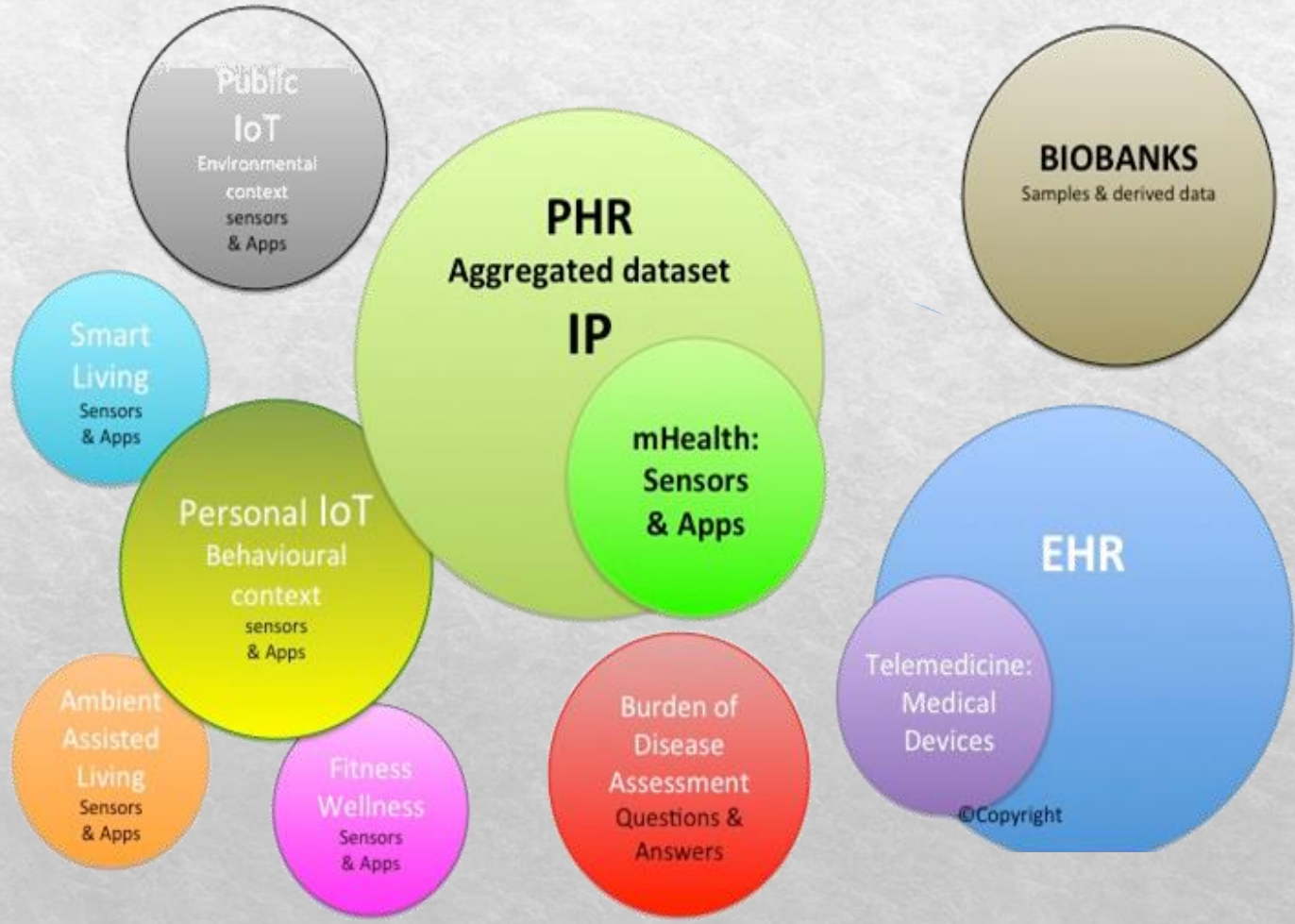




Classificação Conforme a Forma de Captação

- **Primária:** coletados ativamente para perguntas de pesquisa em que dados de interesse precisos e confiáveis não estão disponíveis

- **Secundária:** coletados para outros fins que não o desenho de estudo em questão. Os dados secundários podem ser capturados através de registros de dados de saúde ou bancos de dados específicos de doenças.



Real-World Evidence:

Informações sobre cuidados em saúde (health care) derivadas de múltiplas fontes fora das configurações típicas de pesquisa clínica, incluindo registros eletrônicos de saúde (EHRs), dados de reembolso e cobrança, *registries* de produto e doença e dados coletados por meio de dispositivos pessoais e aplicativos de saúde.

"Real-World Evidence — What Is It and What Can It Tell Us?" - Rachel E. Sherman et al. - n engl j med 375;23 - December 8, 2016

Real-World Evidence:

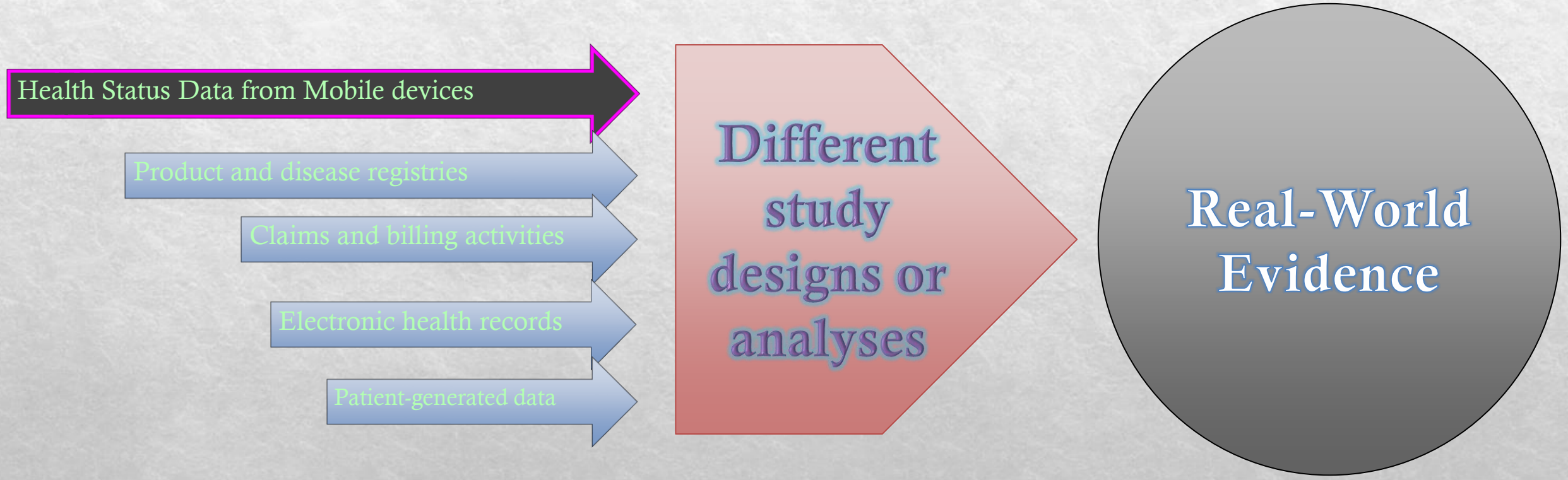
Real-world ***evidence*** is the clinical evidence regarding the usage and potential benefits or risks of a medical product derived from analysis of RWD.

RWE can be generated by different study designs or analyses, including but not limited to:

- ✓ large simple trials
- ✓ pragmatic trials
- ✓ observational studies (prospective and/or retrospective).

FDA - https://www.fda.gov/science-research/science-and-research-special-topics/real-world-evidence

Relação entre RWD e RWE

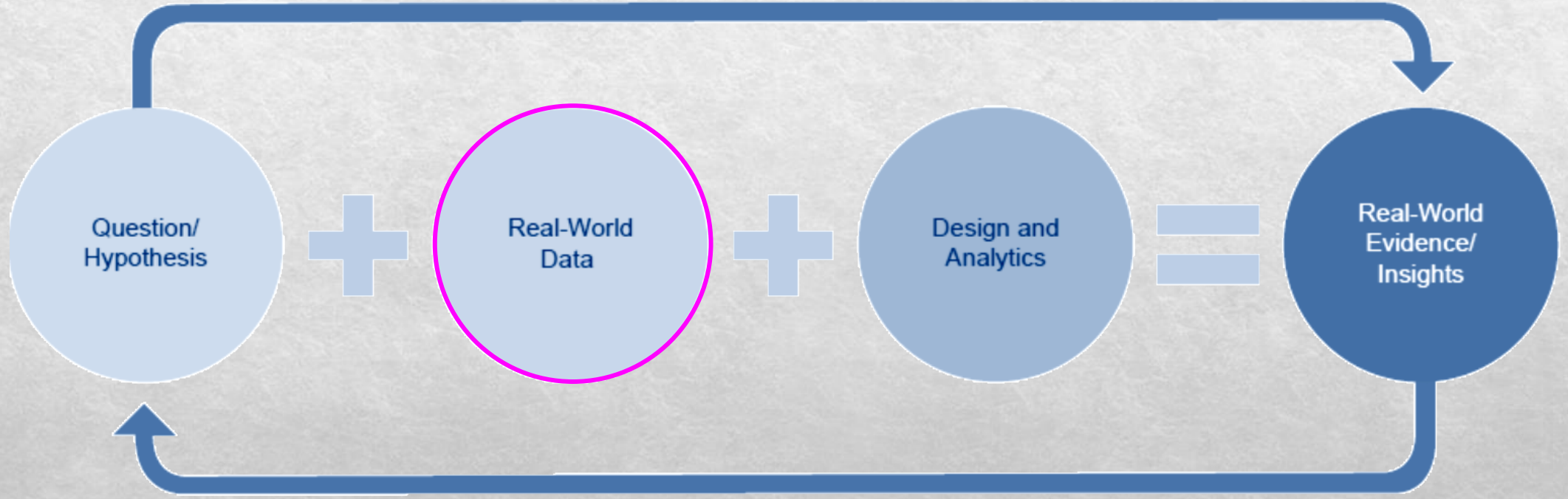


Fontes importantes de RWD para desenvolvimento de estudos

Data source	Data owners/curators	Typical coverage (patient records)	Typical time to data access
Administrative claims databases	HealthCore, Japanese Medical Claims Database, NHS, Optum, Truven,	> 10 million	Immediate
Electronic health/medical records	CPRD, Evidera, Flatiron Health, NorthWest eHealth, Optum, Parexel, PCORnet, QuintilesIMS	2–10 million	Immediate
Clinical registries	American College of Cardiology, SwedeHeart, CALIBER, CancerLinQ, Health Data Insight, Severe Asthma Registry	< 2 million	Within 1 year
Prospective studies and hybrid approaches	CROs/AROs, academic partnerships	> 1000	Over 1 year
Patient-generated data (e.g. social media or patient-powered research networks)	PatientsLikeMe, Carenity, PCORnet	> 100 000	Immediate[b]

ARO, academic research organization; CPRD, Clinical Practice Research Datalink; CRO, contract research organization; NHS, National Health Service; PCORnet, National Patient-Centered Clinical Research Network.

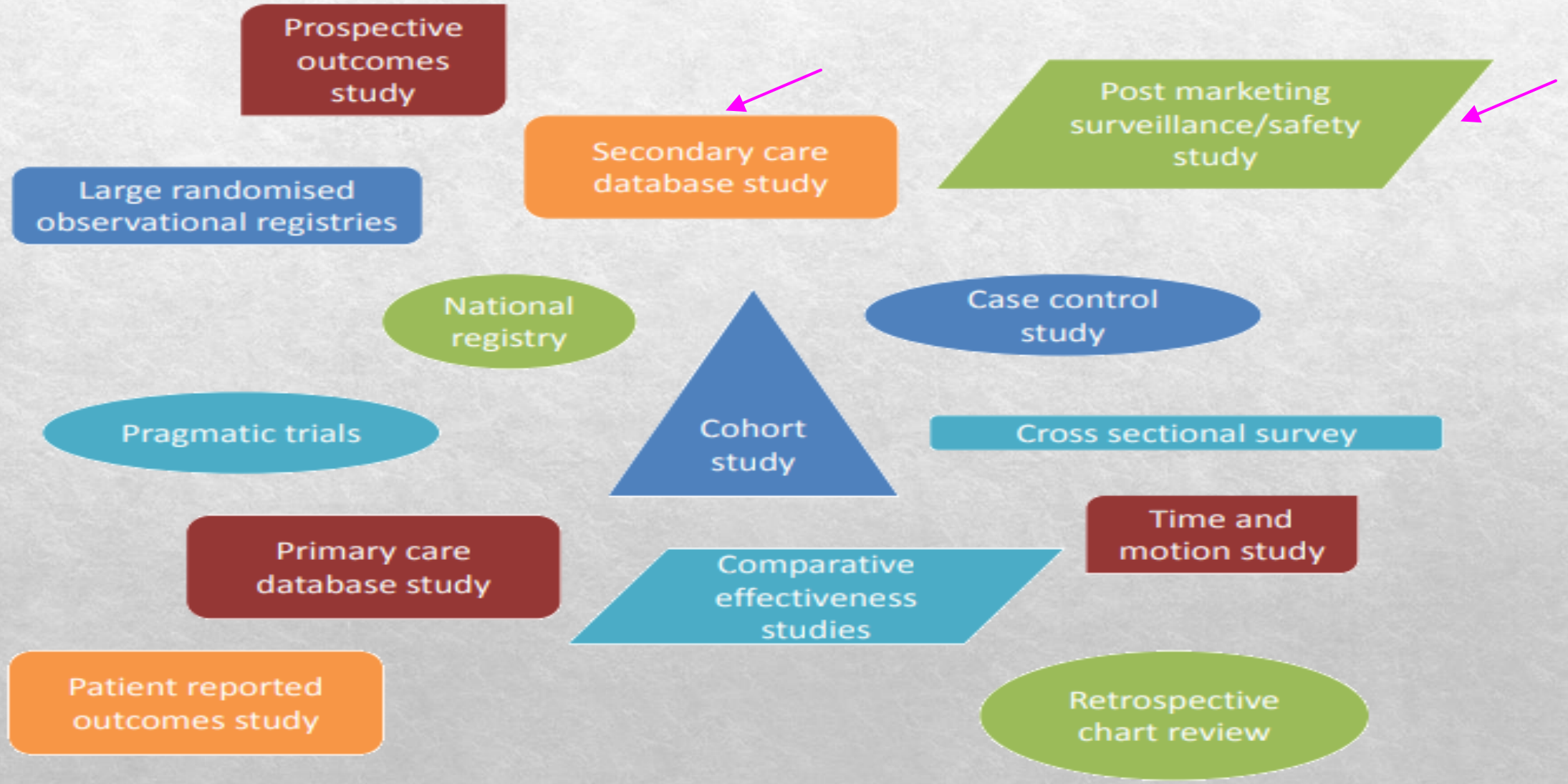
CONCLUSÃO


Question/
Hypothesis
Real-World
Data
Design and
Analytics
Real-World
Evidence/
Insights

RWE/RWD

Usos e Oportunidades

Exemplos de Estudos de Mundo Real



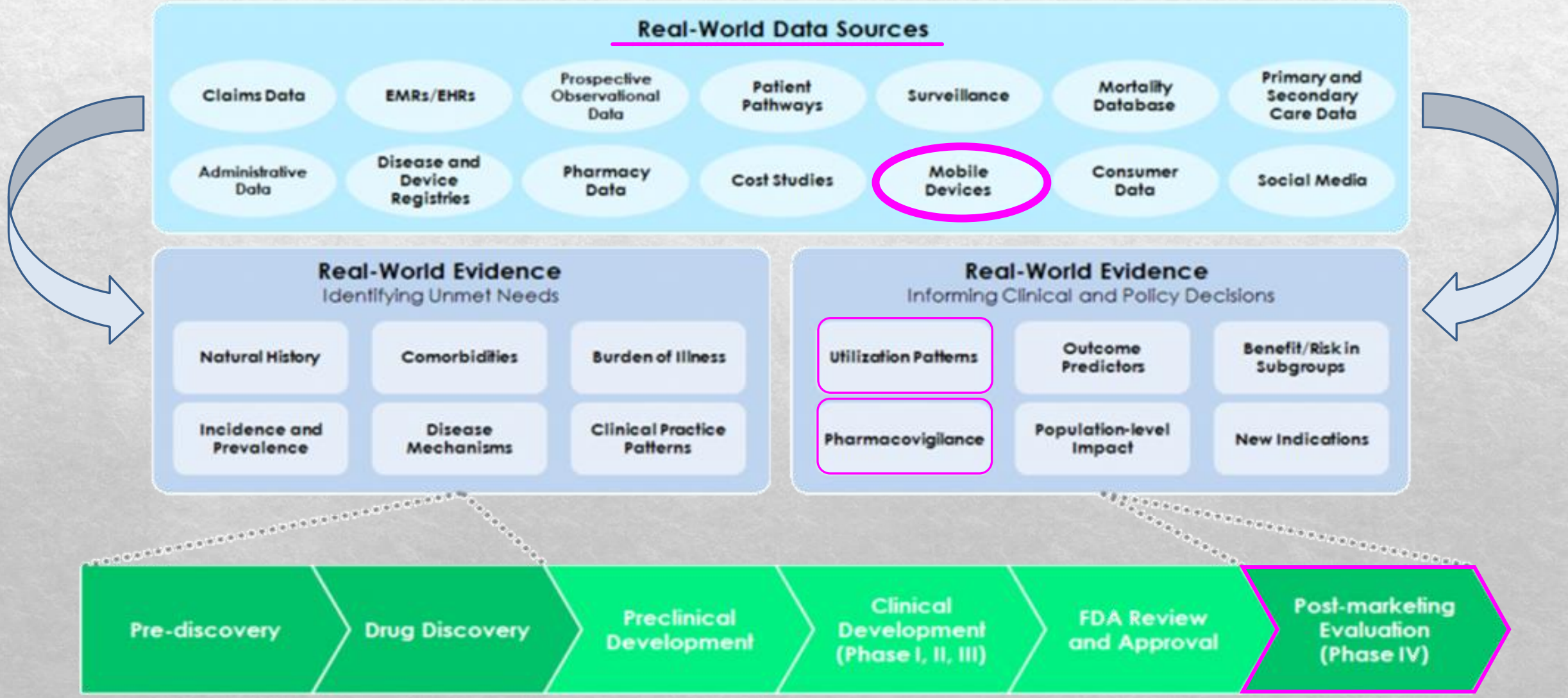
ABPI (Association of the British Pharmaceutical Industry) - ABPI Guidance 2011: Demonstrating Value with Real World Data

Modelos de estudos que podem prover RWE

Observational study designs	
Cohort	A cohort study follows a group of individuals over a period of time to consider associations between interventions received and outcomes.
Case-control	A study that examines associations between outcomes and prior exposures by comparing people with an outcome of interest to those without the outcome. These are not often used for interventions.
Cross-sectional	In a cross-sectional study, data are collected from a population or a representative subset of a population at one specific point of time or over a short period to examine associations between the outcomes and exposure to interventions.
Controlled before-and-after	Similar to a case series, in which observations are recorded on a series of individuals before and after receiving an intervention, but this study design includes a control group.
Case series, interrupted time-series or before-and-after	Recorded observations on a series of individuals before and after receiving an intervention. Does not typically provide evidence of relative effectiveness.
Case report	A detailed report on an individual patient, typically describing symptoms an unusual or new occurrence, including outcomes after a treatment. Does not provide evidence of relative effectiveness.

https://rwe-navigator.eu/use-real-world-evidence/generate-real-world-evidence/

RWE: da pré-descoberta à maturidade



Uso de RWE em decisões de *Health Care*

- O FDA usa o RWD e o RWE para monitorar a segurança no *postmarket* e eventos adversos e para tomar decisões regulatórias.
- A comunidade de saúde está usando esses dados para apoiar as decisões de cobertura e desenvolver diretrizes e ferramentas de suporte à decisão para uso na prática clínica.
- Os desenvolvedores de produtos médicos estão usando o RWD e o RWE para oferecer suporte a desenhos de ensaios clínicos para gerar abordagens de tratamento inovadoras.

RWE no Mundo e no Brasil

Panorama Atual, Tendências e Desafios

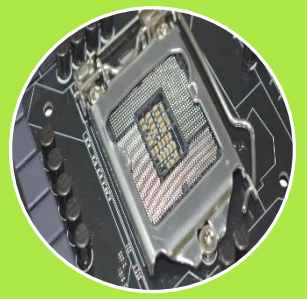
Fatores contribuintes para a "Revolução" RWE

Tecnológicos

- *Big data* / Cloud storage
- Capacidade de processamento
- IoT
- Vel. de Conexão (4G)

Regulatórios

- The 21st Century Cures Act (FDA 2016)



Econômicos

- $ de armazenamento de dados
- $ processadores

Metodológicos (data input)

- papel ➔ eletrônico (EHR)

Ministério da Saúde
Conselho Nacional de Saúde

RESOLUÇÃO Nº 510, DE 7 DE ABRIL DE 2016

O Plenário do Conselho Nacional de Saúde em sua Quinquagésima Nona Reunião Extraordinária, realizada nos dias 06 e 07 de abril de 2016, no uso de suas competências regimentais e atribuições conferidas pela Lei n o 8.080, de 19 de setembro de 1990, pela Lei n o 8.142, de 28 de dezembro de 1990, pelo Decreto n o 5.839, de 11 de julho de 2006, e

Considerando que a ética é uma construção humana, portanto histórica, social e cultural;

Considerando que a ética em pesquisa implica o respeito pela dignidade humana e a proteção devida aos participantes das pesquisas científicas envolvendo seres humanos;

Considerando que o agir ético do pesquisador demanda ação consciente e livre do

Considerando que a pesquisa em ciências humanas e sociais
direitos dos participantes, devendo ser concebida, avaliada e
participantes;

Art. 1
Parágrafo único. Não serão registradas nem avaliadas pelo sistema CEP/CONEP:
V - pesquisa com bancos de dados, cujas informações são agregadas, sem possibilidade de identificação individual;

Presidência da República
Casa Civil
Subchefia para Assuntos Jurídicos

LEI Nº 13.709, DE 14 DE AGOSTO DE 2018.

Mensagem de veto

Vigência

Texto compilado

Dispõe sobre a proteção de dados pessoais e altera a Lei nº 12.965, de 23 de abril de 2014 (Marco Civil da Internet).

O PRESIDENTE DA REPÚBLICA Faço saber que o Congresso Nacional decreta e eu sanciono a seguinte Lei:

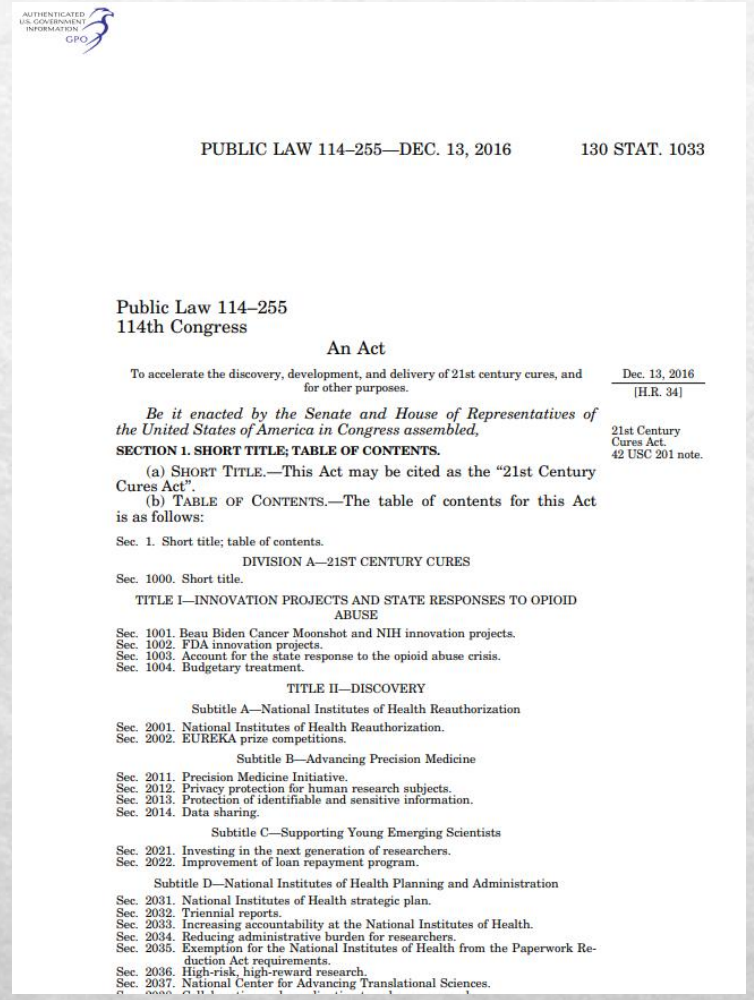
CAPÍTULO I
DISPOSIÇÕES PRELIMINARES

Art. 1º Esta Lei dispõe sobre o tratamento de dados pessoais, inclusive nos meios digitais, por pessoa natural ou por pessoa jurídica de direito público ou privado, com o objetivo de proteger os direitos fundamentais de liberdade e de privacidade e o livre desenvolvimento da personalidade da pessoa natural.

Art. 2º A disciplina da proteção de dados pessoais tem como fu

respeito à privacidade;

Art. 5º
Para os fins desta Lei, considera-se:
III - dado anonimizado: dado relativo a titular que não possa ser identificado, considerando a utilização de meios técnicos razoáveis e disponíveis na ocasião de seu tratamento;
IV - banco de dados: conjunto estruturado de dados pessoais, estabelecido em um ou em vários locais, em suporte eletrônico ou físico;



PUBLIC LAW 114–255—DEC. 13, 2016 130 STAT. 1033

Public Law 114–255
114th Congress

An Act

To accelerate the discovery, development, and delivery of 21st century cures, and for other purposes.

Dec. 13, 2016
[H.R. 34]

Be it enacted by the Senate and House of Representatives of the United States of America in Congress assembled,

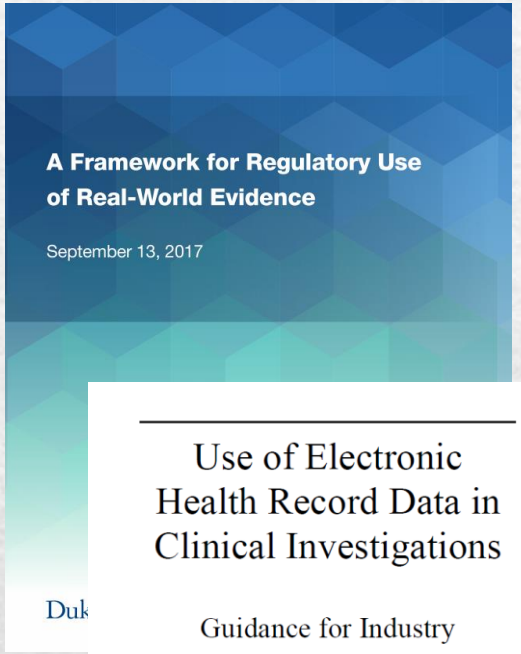
21st Century Cures Act.
42 USC 201 note.

SECTION 1. SHORT TITLE; TABLE OF CONTENTS.

(a) SHORT TITLE.—This Act may be cited as the "21st Century Cures Act".

(b) TABLE OF CONTENTS.—The table of contents for this Act is as follows:

The 21st Century Cures Act (FDA 2016)
"To accelerate the discovery, development, and delivery of 21st century cures, and for other purposes"



A Framework for Regulatory Use of Real-World Evidence

September 13, 2017

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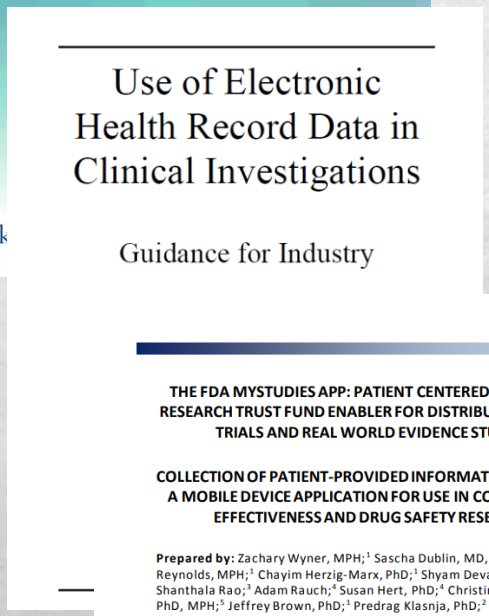
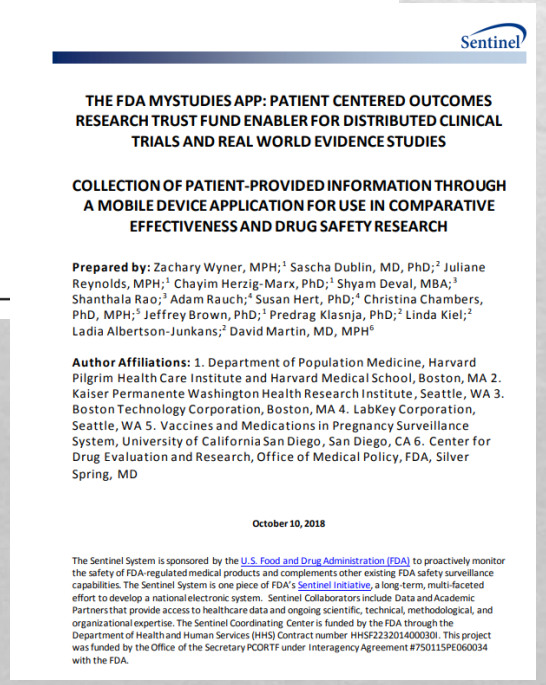


Use of Electronic Health Record Data in Clinical Investigations

Guidance for Industry



Sentinel

THE FDA MYSTUDIES APP: PATIENT CENTERED OUTCOMES RESEARCH TRUST FUND ENABLER FOR DISTRIBUTED CLINICAL TRIALS AND REAL WORLD EVIDENCE STUDIES

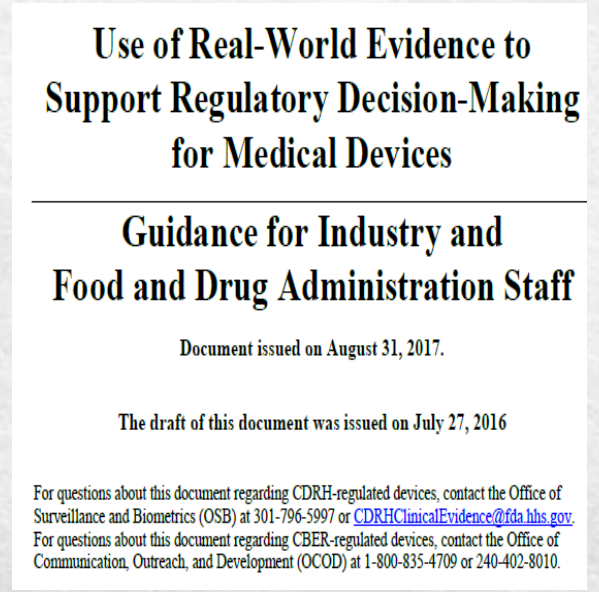
COLLECTION OF PATIENT-PROVIDED INFORMATION THROUGH A MOBILE DEVICE APPLICATION FOR USE IN COMPARATIVE EFFECTIVENESS AND DRUG SAFETY RESEARCH

Prepared by: Zachary Wyner, MPH;[1] Sascha Dublin, MD, PhD;[2] Juliane Reynolds, MPH;[1] Chayim Herzig-Marx, PhD;[1] Shyam Deval, MBA;[3] Shanthala Rao;[3] Adam Rauch;[4] Susan Hert, PhD;[4] Christina Chambers, PhD, MPH;[5] Jeffrey Brown, PhD;[1] Predrag Klasnja, PhD;[2] Linda Kiel;[2] Ladia Albertson-Junkans;[2] David Martin, MD, MPH[6]

Author Affiliations: 1. Department of Population Medicine, Harvard Pilgrim Health Care Institute and Harvard Medical School, Boston, MA 2. Kaiser Permanente Washington Health Research Institute, Seattle, WA 3. Boston Technology Corporation, Boston, MA 4. LabKey Corporation, Seattle, WA 5. Vaccines and Medications in Pregnancy Surveillance System, University of California San Diego, San Diego, CA 6. Center for Drug Evaluation and Research, Office of Medical Policy, FDA, Silver Spring, MD

October 10, 2018

The Sentinel System is sponsored by the U.S. Food and Drug Administration (FDA) to proactively monitor the safety of FDA-regulated medical products and complements other existing FDA safety surveillance capabilities. The Sentinel System is one piece of FDA's Sentinel Initiative, a long-term, multi-faceted effort to develop a national electronic system. Sentinel Collaborators include Data and Academic Partners that provide access to healthcare data and ongoing scientific, technical, methodological, and organizational expertise. The Sentinel Coordinating Center is funded by the FDA through the Department of Health and Human Services (HHS) Contract number HHSF223201400030I. This project was funded by the Office of the Secretary PCORTF under Interagency Agreement #750115PE060034 with the FDA.



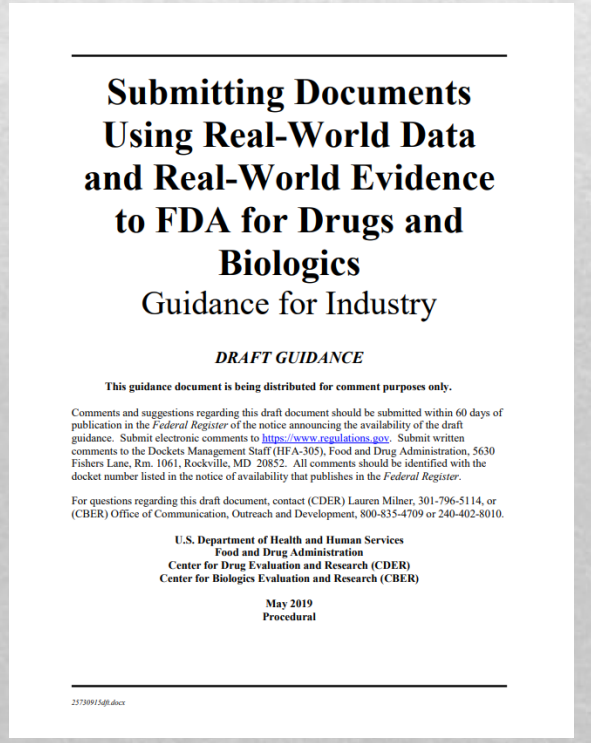
Use of Real-World Evidence to Support Regulatory Decision-Making for Medical Devices

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

For questions about this document regarding CDRH-regulated devices, contact the Office of Surveillance and Biometrics (OSB) at 301-796-5997 or CDRHClinicalEvidence@fda.hhs.gov. For questions about this document regarding CBER-regulated devices, contact the Office of Communication, Outreach, and Development (OCOD) at 1-800-835-4709 or 240-402-8010.



Submitting Documents Using Real-World Data and Real-World Evidence to FDA for Drugs and Biologics

Guidance for Industry

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to https://www.regulations.gov. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document, contact (CDER) Lauren Milner, 301-796-5114, or (CBER) Office of Communication, Outreach and Development, 800-835-4709 or 240-402-8010.

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)

May 2019
Procedural

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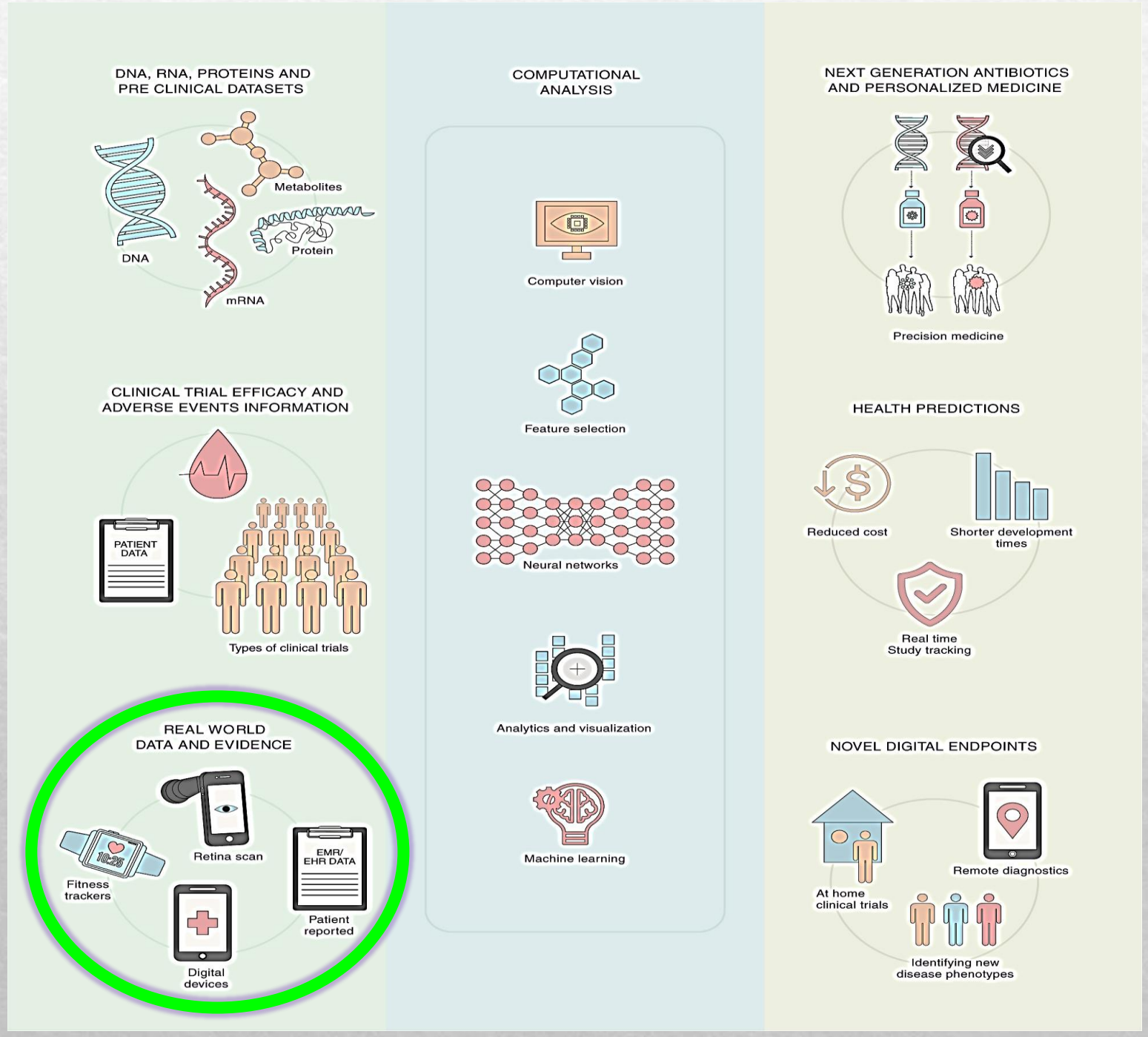

Estado da arte no uso da Analise Computacional

Challenges and considerations

Limitations of current computer science deep learning models to generalize to complex medical data sets and tasks.

Necessities of high volumes of labeled data sets for training deep learning algorithms

Strategies and regulatory framework for dealing with relevant ethics issues (e.g., patient privacy, retaining anonymity, securing data) and de-risk use of AI- and ML-based clinical prediction and decision support in health care.

Artificial intelligence and machine learning in clinical development: a translational perspective
npj Digital Medicine **volume 2**, article number: 69 (2019)

Jannet Woodcock - FDA CDER Director


Dankon
Maake
Ua Tsaug Rau Koj
Mochchakkeram
Terma Kasih
Multumesc
Merci
Raibh Maith Agat
Juspoaxar
Chokrane
Grazie
Cam on ban
Kiitos
Mamana
THANK YOU
Obrigado
Asante
Matondo
Dank Je
Nirringrazzjak
Spasibo
Multumesc
Obrigado
Grazie
Raibh Maith Agat
OBRIGADO
Merci
Multumesc
Mochchakkeram
Grazie
Vinaka
Obrigado
Thank You
Merci
Arigato
Welalin
Multumesc
Spasibo
Cam on ban
Kiitos
Raibh Maith Agat
Merci
Mochchakkeram
Chokrane
Grazie
Mochchakkeram
Merci
Spasibo
Matondo
Salamat
Nirringrazzjak
Matur Nuwun
Chokrane
Raibh Maith Agat
Salamat
Obrigado
Mochchakkeram
Ua Tsaug Rau Koj
Kiitos
Maake