UseTree Ascenian

COVID-19: AI can help.

The potential of Artificial Intelligence (AI) and Real-World Data (RWD) in medical regulatory, price and reimbursement decision making in the US and Europe

1. Introduction

Pre-COVID-19, the pharmaceutical, diagnostics and medical device industries were on the brink of large-scale disruption, driven by interoperable data, open and secure platforms, Artificial Intelligence (AI) systems, consumer-driven care, and a fundamental shift from health care to health. Yet the uptake of big data and use of information derived from AI in regulatory and payer decision making was slow, hampered by an attitude of skepticism in many quarters, as well as concerns about data protection and interpretation.

During the pandemic, big data and AI have become increasingly instrumental in predicting, mitigating and modelling patient behavior, health resource impact and spread of disease. In fact, AI is experiencing a kind of "Renaissance," wherein skepticism is gradually being replaced with trust, optimism and hope that big data and AI can deliver beneficial or even live-saving outcomes.

In this AI Renaissance, AI has the potential to improve the world's response to COVID-19, and to support evolution in both regulatory and reimbursement decision making. Now is the opportune time to investigate in more detail how AI, big data and more specifically Real-World Data (RWD), can improve decision making for regulatory approval, pricing of, and access to new treatments and diagnostics. To make the best use of AI and big data for regulatory and reimbursement purposes, it is important to not only collect the right data, from the right sources, but also to choose the most appropriate AI model for the objective at hand. In addition, we need to determine the most suitable data collection method and ensure transparency in data evaluation using commonly agreed methods.

2. Definitions

AI is defined as ...

(1) A branch of computer science dealing with the simulation of intelligent behavior in computers,

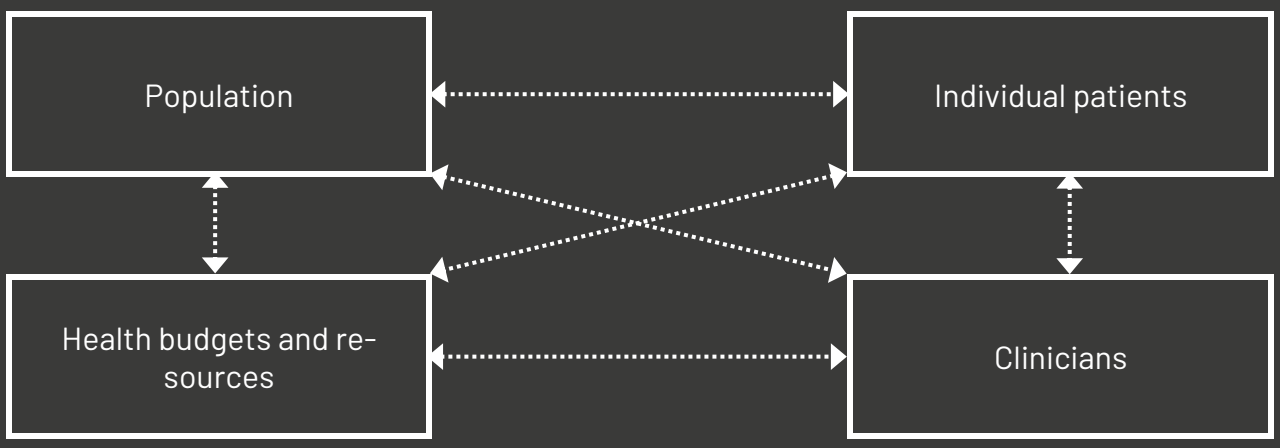
(2) The capability of a machine to imitate intelligent human behavior (Merriam-Webster, 2020).

Regulatory agencies have defined RWD. According to the US Food and Drug Administration (FDA), RWD is defined as: "The data relating to patient health status and/or the delivery of health care routinely collected from a variety of sources." The European Medicines Agency (EMA) defines RWD as, "routinely collected data relating to a patient's health status or the delivery of health care from a variety of sources other than traditional clinical trials." (Cave et al., 2019)

Real-World Evidence (RWE) is defined as the clinical evidence about the usage and potential benefits or risks of a medical product derived from analysis of RWD (US Food and Drug Administration, 2018).

Payers use RWD to assess the likely impact of a new treatment or diagnostic on population and subgroup health status, health budgets, and resource utilization.

Use of RWD to scope the value of a new treatment in health care service (George, 2015):



3. The potential of AI and RWD in regulatory decision making in Europe and US

The US 21st Century Cures Act, passed in 2016, puts some emphasis on RWD in regulatory decision making, including approval of new indications for approved drugs.

In December 2019, the FDA estimated that one-half of clinical trials will be replaced with computer simulations in coming years, to save money and increase productivity in drug development. A report in 2016 estimated that pharma companies could possibly save US$1 billion per year through use of RWE (Hughes et. al., 2018).

To raise awareness, advance policy-making on modeling and simulation, and to further the acceptance and implementation of AI, the FDA has created a working group of more than 200 scientists (Morrison, T. 2018).

This initiative is matched in Europe by the EMA's own Modelling and Simulation Working Group, (Scientific Writing Team, 2018) whose aim is to "accelerate the implementation of a learning regulatory system based on electronic health records and other routinely collected RWD" (European Medicines Agency 2018), and to "deliver secure ethical patient-focused governance for accessing, managing, analyzing, and assessing real world data." (European Medicines Agency, 2019)

A suitable platform leveraging an agreed framework and aligned methodologies is needed to facilitate RWD collection by the agreed common standards and prepare RWE for use by regulatory agencies. The platform must comply with industry standards to ensure that it can store clinical data, data from wearables and sensors, patient- (PROs), clinician- reported outcomes (ClinROs), and administrative claims data and randomized clinicial trials. This data often exists in isolated (fragmented) databases in disparate, varying formats, stemming from different origins, such as research lab notes, medical journal articles, clinical trial results, patient's behavioral or lifestyle data, often collected using mobile or sensor-based e-health devices. A suitable platform should offer means to integrate and host all these disparate data sources from different stakeholders, to enable AI analysis of the data. A precondition for successful integration is to have a plan to implement data sharing while remaining cognizant and respectful of patient privacy, data security, and the protection of business interests (Wilson, 2019).

Developing such platform requires a multidisciplinary team with expertise in RWE strategy, regulatory assessment and decision criteria, commercial objective setting on how to use the results, big data technology, clinical trials, technical implementation, observation-nal research, and epidemiology.

In collaboration with the clinical trial community and patient groups, the FDA is developing scientific and technical

standards which aim to integrate new digital technologies into clinical trials. This approach aims to facilitate clinical trial designs which are more agile and accessible to patients and regulators.

Further, EMA recommends in its Regulatory Science to 2025 strategy to work with stakeholders, specifically with international partners, to facilitate collaborative clinical trials, e.g., with the Clinical Trial Transformation Initiative (CTTI) and similar. The aim is to innovate and accelerate patient identification. (European Medicines Agency, 2020)

By combining data from randomized clinical trials with data from multiple sources, such as:

- AI-enhanced mobile applications, wearables, biosensors and connected devices
- Electronic Health Records (EHRs)
- Publicly available content, for example, trial databases and social media

It will be possible to leverage new applications and uses of existing data, facilitating specific AI algorithms to data mine and analyze records according to requierements as set out by regulatory agencies in Europe and the US.

4. Translating the potential of AI for use in price and reimbursement decision making processes

RWE is playing an increasing role in supporting product value propositions, informing reimbursement decisions, and helping to manage data uncertainty from randomized controlled trials (RCTs).

While data collected in RCTs are the gold standard for internal validity, they bare uncertainties when interpreted by payers and health technology agencies against their evidence requirements. Uncertainties arise from insufficient demonstration of efficacy, unclear stratification of patient populations, treatment environment (before or after the new treatments) not reflecting treatment reality or statistical limitations. These uncertainties result in difficulties for payers to predict the likely impact on health care resource utilization, which patients may benefit most and how the treatment should be positioned in the disease pathway. RWE carries the potential to address some of the uncertainties by collecting additional evidence on outcomes, patient preference, quality of life and how patients access and move through the pathway within the health service. Using wearables, apps and sensors in conjunction with AI can facilitate collection of data from the patient population in a non-interventional way, through easy handling of the wearables. It can also provide near real-time feedback on treatment and effectiveness in a potentially much larger population than in RCTs. RWE has

the potential to augment the picture of efficacy that emerges from RCTs. Using RWE allows a more accurate reflection of how patients move through the health system and which treatment or diagnostic path patients travel in reality, including delays, waiting times and patients' own health decisions that influence health status (such as losing weight, adapting or increasing exercise routines, etc.), the addition of treatments by patients' own choice (such as over-the-counter medications) and other. This allows a more accurate assessment of budget impact, consumption of health care resources and how efficacy is translated into patient benefit. In conse-quence, price negotiations can be informed by more timely and accurate information.

For manufacturers, the use of AI to collect and interpret RWD is critical to determine early the potential product value. RWD in predictive AI models and analytics tools can accelerate and facilitate understanding of disease aetiologies and treatment pathways and improve identification of the fit of new treatments and diagnostics in current patient pathways. An agreed AI model would allow manufacturers to make such data relevant at the time of first health technology assessment/ payer evaluation. Manufacturers may also be able to improve clinical study design through prediction of the data that is most relevant to demonstrate benefit, identification of the most relevant clinical trial endpoints, optimization of study designs, and prediction of potential effect sizes. Altogether, use of AI should permit more targeted, better planned demonstration of value, oriented to the real-world health service setting.

Consequently, RWE – powered with AI-enabled analysis of RWD – could enable payer and health technology assessment organizations to make more realistic decisions on product value, budget impact, impact on the health service beyond budget, and scope of reimbursement.

The application of digital technology in oncology research will be a priority during the German EU presidency in Q2 2020 as announced by the German Federal Minister of Health, Jens Spahn (2020). After COVID-19, this unprecedented, European-level move to support clinical data development using digital technologies has the potential to improve decision making by regulators, health technology assessment agencies and payer organizations, by providing evidence that is enriched by RWD as well as resource consumption information in a timely fashion.

Case Study

Improving demonstration of resource utilization and overall survival (OS) in non-small cell lung cancer (NSCLC)

What: The use of web-based monitoring for lung cancer patients is of growing interest due to promising recent research suggesting improvement in cancer and resource utilization outcomes. A study in France recently investigated whether OS could be improved by using a web-mediated follow-up rather than classical, scheduled follow-up and imaging (Denis et. al., 2017).

How: Patients with advanced-stage lung cancer were randomly assigned to weekly symptom monitoring with a web-mediated follow-up algorithm to detect possible cancer progression (experimental arm), or routine follow-up with computed tomo-graphy (CT) scans scheduled every 3 to 6 months according to disease stage (control arm).

Outcomes: The intervention improved OS because of early relapse detection and better performance status at relapse.

5. Diagnostic and pharmaceutical manufacturers taking the lead

The value for diagnostic and pharmaceutical manufacturers teaming up with AI tech companies lies in the power of AI to store, process and analyze the overwhelming amount of trial data and RWD to be collected in every phase of drug development – including research, clinical trials, manufacturing, operations and finance.

Examples of partnerships between phar-maceutical and diagnostic manufacturers and AI companies

- Verily Life Sciences, a subsidiary of Google's Alphabet Inc., teamed up with Novartis, Otsuka, Pfizer and Sanofi to accelerate clinical trials and optimize patient recruitment and retention and improve data and evidence made available to payers and HTA agencies.
- On October 1st 2019 Microsoft and Novartis have agreed on a five-year collaboration to explore how Microsoft's expertise in advanced AI technology and Novartis' extensive expertise in clinical investigations can be combined to revolutionize the process of drug discovery and development. Across (Lee, 2019) disciplines such as research, clinical trials, manufacturing, operati-ons and finance.
- In December 2019, Trials@Home was launched officially by Europe's Innovative Medicines Initiative. Its aim is to investigate how remote decentralized clinical trials (RDCTs) using AI-enabled technologies may be able to include more diverse and remote populations to take part in clinical trials.

The use of AI will hugely support the process of collecting, organizing and analyzing huge amounts of data, as is the case in using RWD for evidence generation, thus facilitating fast, efficient innovation while reducing development costs.

6. Making best use of the AI experience in the COVID-19 pandemic

Global COVID-19-related RWD is created daily. RWD includes how COVID-19 patients access the health system, how they are treated, what OTC treatments patients are taking, monitoring remotely – when in quarantine at home - how the disease is evolving, and more. The AI community, diagnostic and treatment manufacturers, academia and regulatory and reimbursement agencies took the unique opportunity to explore how rapid analysis of this RWD data can be used to predict and

mitigate the impact of COVID-19. The use of AI is critical in the data analysis, because AI allows that collected data is either reinforced or benchmarked through learning from other sets of data (such as RCTs or literature insights from meta-analysis and other patient collected information). By using shared data and applying AI to this data, AI companies can empower patients, health workers, scientists, epidemiologists, regulators and policymakers to better understand, monitor and uncover patterns of disease spread, access needs, resource needs, best use of preventive interventions, and ultimately to make more informed decisions on how and where to allocate budgets for appropriate measures, new treatments, resource planning and communication of vital information to patients and the population more generally.

In the pandemic, there have been tremendous efforts to leverage AI and solve some of the challenges identified earlier in this paper. In the US, on March 16th the White House, the National Institutes of Health, and Georgetown University launched the "Open Research Dataset Challenge," making the CORD-19 dataset (US Government (2020), Allen Institute For AI et al. 2020) publicly available. This dataset contains tens of thousands of scholarly articles about COVID-19 and related coronaviruses. The initiative's aim is to have data scientists volunteer, applying recent advances in natural language processing and other AI techniques, to generate new insights that will support the fight against COVID-19. AI solutions will help medical researchers to find and extract the information they need to generate new insights, even as the number of publications grows so rapidly that researchers cannot realistically keep up with new developments in real time.

One of many collaboration examples: Ericsson, for example, responded and offered to participate, with 362 employee volunteers coming from an interdisciplinary background, including data scientists, data engineers, data visualizers, project managers, task managers, leaders, and writers (McLachlan, 2020). This interdisciplinary team will look at transmission, risk factors, virus make-up, ethics, diagnostics and therapeutics.

Other examples of publicly available data-sets related to the pandemic are (Godfried, 2020):

- Coronavirus Genome (Mooney 2020)
- Chemdiv Database Database (ChemDiv, 2020)
- GitHub Coronavirus (Haslett, 2020)
- COVID-19 Korea Dataset & Comprehensive Medical Dataset & visualizer (Lee, 2020)
- COVID-19 Vulnerability Index (DeCaprio, 2020)
- COVID-19 image data collection (Cohen, J.P., 2020)
- Coronavirus Tweets Dataset (Smith, S. (2020)

The rapid collection of RWD during the pandemic sets standards for how to collect consumption patterns of new treatments, how patients access health systems, how patients obtain diagnoses, and consequently how patients do or do not change their lifestyles. These are important sets of information for regulatory and reimbursement agencies.

7. Conclusions

AI has the potential to improve drug approval and pricing and reimbursement decisions. Significant work needs to be done on harmonizing standards, achieving academic alignment on methods and approaches, best route of communicating data to key stakeholders and how RWD analyzed by AI can inform the positioning of a new treatment in health service.

The following three insights are directed at pharmaceutical and diagnostic manufacturers' strategic and operational planning when developing AI systems integrating RWD and RCT data for use in regulatory and reimbursement settings:

1. Create a platform around an agreed set of standards to allow integration of data

Central to integration of RWD with RCT data is a standardized approach within a suitable platform, created with focus on either regulatory or reimbursement decision making. The manufacturer should be able to share, search, access, extract and analyze varied global data sources. Such a platform must provide:

- Unique, meaningful data related to the objective of the analysis, regulatory or reimbursement
- An easily accessible structure
- Ease of use, through user-centered design, so that new and expert users equally may use the platform in an effective and efficient way

- Clear communication of information, presented in a way that is easy to understand, process and use
- A method to facilitate smooth use of data for further processing and analyses
- Easy recovery from errors, with easily understood solutions

2. Match the regulatory and/ or reimbursement requirements for RWE and clinical trials

Each agency – regulatory and reimbursement – sets out requirements and methodologies for the design and execution of clinical trials and RWD collection. The platform should include filters designed based on these methods and requirements, to ensure that analyzed and presented data meets expectations of the key audiences and is relevant for decision making.

3. Create a perpetual learning and communication system

The value of connecting AI to RWD and clinical trial data only emerges if the following conditions hold:

- Integrate learnings from experience – such as during COVID-19
- Be sure to know the evidence requirements from payers, regulators and health technology agencies to define clearly your objectives when collecting, connecting and analyzing clinical

evidence and health care resource utilisation evidence with RWD through AI.

- Extend the audience to other key stakeholders – such as patients and physicians, but also to local budget holders in health services, ancillary health care services including long-term care, rehabilitation services and other
- Support data protection and data transparency through an agreed framework regarding what data is shared, what data is protected, and who owns what data
- Foster inter-disciplinary collaboration, to make data use from AI systems applicable to different competencies in health services

8. UseTree and Ascenian can support these efforts:

1. Align the development and use of RWD and AI to the requirements and criteria from regulatory and reimbursement agencies
2. Identify methods and evidence requirements relevant for price and reimbursement decision making
3. Identify key stakeholders and value messages emerging from the analyses, and align to the value proposition
4. Develop market-specific value outcome predictions and forecast models based on the data coming from AI – including clinical trial data and RWD
5. Assist in suitable data visualization, analysis and synthesis
6. Identify and create important touchpoints in interaction with the system
7. Define internal user groups that need to input to the development of a shared platform

8

Design user interactions to maximize the efficacy and efficiency of the system outputs

9

Design and conceptualize an easy-to-use interface to facilitate effective, efficient use, while preventing or allowing easy recovery from use error and complying with Norms and standards, for example (EN ISO 9241-210/110 & DIN EN 62366/60601, ANSI/AAMI/ISO 14971)

10

Provide a pleasant experience resulting in high user satisfaction with platform and process

11

Provide the user with confidence that results produced are reliable, valid and comport with regulatory and reimbursement agency requirements

If you are interested in using AI to support your regulatory or reimbursement work streams, please contact us.

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10. About Us

UseTree develops products based on a deep understanding of people. The interdisciplinary team of experienced experts advises international companies, as they strive to create products that are as catchy, useful and desirable as possible.

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