AI in RWE: Key drivers for accelerating clinical development and patient access

Our agenda today

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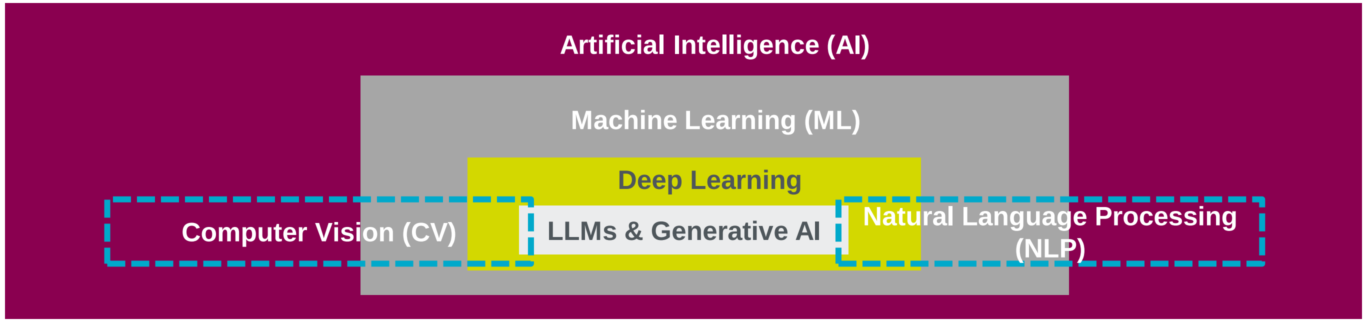
- **AI in focus**
  - **AI and potential applications**
  - **AI algorithm development**
  - **Sample AI use cases in clinical development and patient access**
- **Leveraging RWD**
  - **RWD/RWE and potential applications**
  - **The regulatory landscape**
- **Conclusions and key takeaways**
- **Q&A**

Overview of AI and potential applications

Level-setting on terminology: AI 101



Machine learning (ML):	Deep learning:	Computer vision (CV):	Natural language processing (NLP):	Large language models (LLMs):
Ability to learn from data and improve performance as they identify patterns and make predictions. Traditional machine learning requires some human intervention to correct mistakes.	Subset of machine learning that focuses on artificial neural networks to solve complex problems and discover intricate patterns in large datasets.	Enhances a machine's ability to interpret and understand images or videos; can tap into machine learning or deep learning.	Allows computer systems to interpret text and perform tasks including speech recognition, sentiment analysis, and automatic text summarization.	Trained on massive datasets of text and codes to learn patterns in human languages and make predictions.

Artificial Intelligence (AI): Development of computer systems capable of performing tasks such as text/speech recognition, decision-making, problem-solving, and data analysis. While capable of streamlining processes and driving efficiencies, these algorithms often require human oversight.

AI applications are set to accelerate clinical development

GenAI: Enabling next-gen search-and-retrieve and a step change in quality of content generation

- **ChatGPT and other LLMs are transforming the opportunity for AI/ML across the clinical development continuum**

- **Big bucket opportunities**
  - Search-and-retrieve
  - Content generation
  - Workflow automation

- **Considerations for businesses**
  - Access to talent with NLP skills
  - Need to re-engineer workflows
  - Staff training: selection of prompts (i.e., user queries) and need to check/confirm answers
  - User access to internal info and data assets via AI tooling
  - Regulatory and legislative compliance (emerging global legislation trends)

Evidence generation → Optimization → Access realization

Pre-clinical	Phase I	Phase II	Phase III	Launch	Post launch
Feasibility	Site / investigator selection	Reg. Strategy	Technical writing	Medical education execution	HEOR study design
Site activation and IRB submissions	Protocol / synopsis development	Dossier key document management	Label Management	Market access strategy support	HEOR study execution
Medical design and strategy	CRF prep / EDC formatting	Agency and internal inquiries	Regulatory intelligence	Medical document creation	Med info call center
Study startup planning and mgmt.	Site initiation	Operational and metrics reporting	Publishing	Medical, legal, regulatory review	Materials prep (FAQ, briefing, etc.)
Patient recruitment	Safety management	Dossier development	Quality analytics and reporting	KOL interactions	Scientific patient comms
Clinical monitoring	Data analysis and database build	Site audits	Compliance mgmt.	RWE driven studies	
Medical writing	CSR development	Safety case processing	Medical review		
Stat analysis and reporting	Site payments	Signal detection / surveillance			

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AI-enabled workstreams drive efficiencies in Market Access and HEOR evidence generation

Protocol development / approach	Data collection	Data extraction	Quality assessment	Report development
Defining the scope of the study	Literature search; primary and secondary data collection	Extraction of evidence; development of data file	QC; assessment of bias using industry-standard tools	Development of a technical summary report with key value messages
Optimizing protocols/developing search strategies; integrated evidence generation plans	Source screening/feasibility assessment/gap analysis	Data extraction/Dataset specification/EHR to EDC conversion /TLF development	Edit checks; parameter assessment based on industry standard tools	Developing content for standard report structure and visualizations

General data and project management

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AI applications in Market Access and HEOR – a sample

Literature reviews and cost effectiveness modelling

- Accelerating systematic reviews
- Enhanced data extraction and quality assessment
- Natural language processing and social listening
- Endpoint analysis and surrogate outcomes assessment
- Quantifying uncertainties and evaluating scenarios

RWD and algorithm development

- Patient identification and optimizing protocol design
- Supporting clinical trial feasibility and recruitment
- Identifying patterns and trends in RWD
- Machine learning DNA; deep learning techniques; digital twins
- Accelerating analysis of big data/data lakes

Reimbursement and pricing strategies

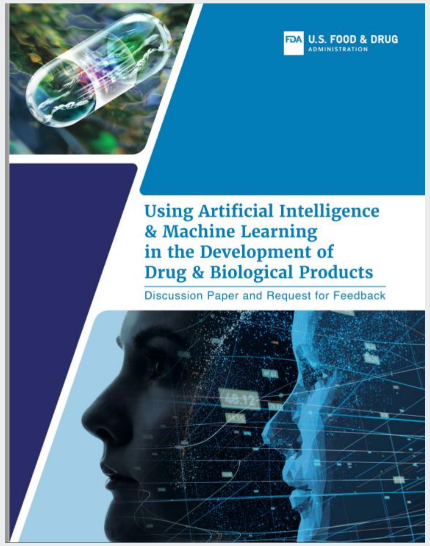
- Estimating the value of healthcare interventions
- Supporting value-based healthcare decision making
- Optimizing patient access to new therapies
- Enhancing affordability of healthcare services
- Supporting sustainable healthcare systems

Predictive analytics

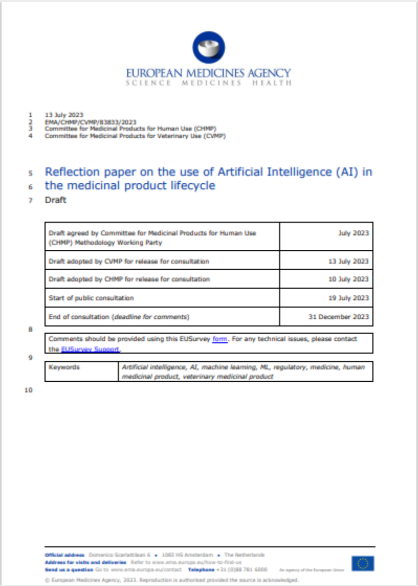
- Predicting patient outcomes and treatment response
- AI in disease prevention and management
- Early detection and intervention
- Optimizing treatment pathways
- Supporting clinical decision-making

Regulatory guidelines are being developed to help shape the applications of AI across the healthcare ecosystem

- There are concerns with opacity, potential for bias and error, negative or harmful impacts in use
- Regulatory and legislative compliance should be included in development pipeline from the outset



EMA: *"… the use of exceptionally great numbers of trainable parameters arranged in non-transparent model architectures introduces new risks that need to be mitigated both during model development and deployment to ensure the safety of patients and integrity of clinical study results. Also, as the overarching approach is inherently data-driven, active measures must be taken to avoid the integration of bias into AI/ML applications and promote AI trustworthiness.."*



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

13 July 2023
EMA/CHMP/CVMP/83833/2023
Committee for Medicinal Products for Human Use (CHMP)
Committee for Medicinal Products for Veterinary Use (CVMP)

Reflection paper on the use of Artificial Intelligence (AI) in the medicinal product lifecycle

Draft

Draft agreed by Committee for Medicinal Products for Human Use (CHMP) Methodology Working Party	July 2023
Draft adopted by CVMP for release for consultation	13 July 2023
Draft adopted by CHMP for release for consultation	10 July 2023
Start of public consultation	19 July 2023
End of consultation (*deadline for comments*)	31 December 2023

Comments should be provided using this EUSurvey form. For any technical issues, please contact the EUSurvey Support.

Keywords	*Artificial intelligence, AI, machine learning, ML, regulatory, medicine, human medicinal product, veterinary medicinal product*

FDA: *"There are also concerns with using algorithms that have a degree of opacity, or algorithms that may have internal operations that are not visible to users or other interested parties. This can lead to amplification of errors or preexisting biases in the data. We aim to prevent and remedy discrimination — including algorithmic discrimination, which occurs when automated systems favor one category of people over other(s) — to advance equity when using AI/ML techniques."*

Regulatory acceptability of AI: Current perspectives
By Stephen Pike, Chief Clinical Data & Digital Officer, RWE & AI Innovation & Strategy at Parexel and Mwango Kashoki, SVP, Global Head of Regulatory Strategy at Parexel

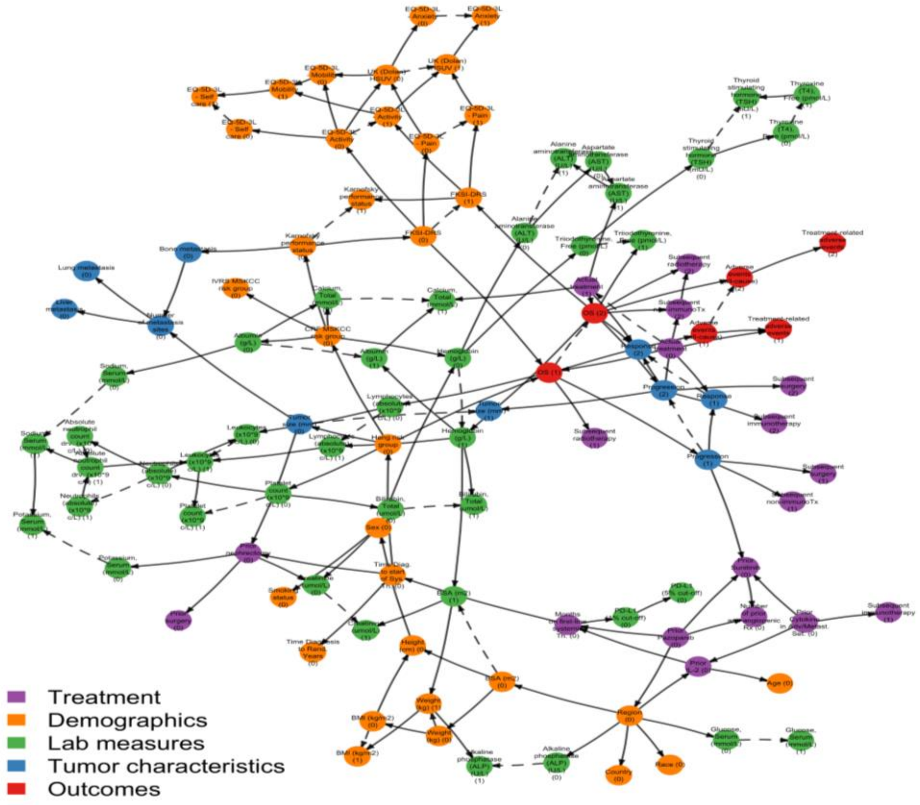
Overview of AI algorithm development

HEOR typically focuses on machine-learned algorithm development methods

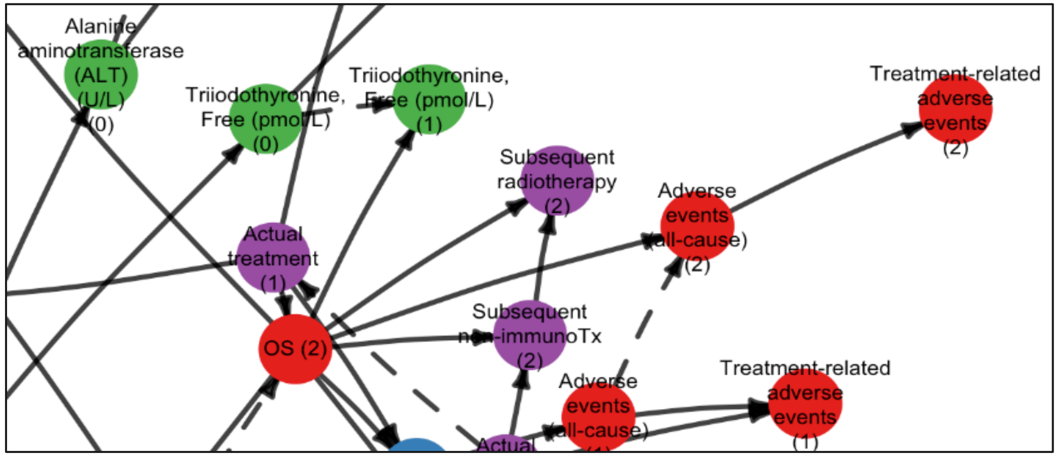
- **Traditional**
  - **Supervised** – specification of an outcome variable to perform classification, ranking, or prediction
  - **Unsupervised** – focused on dimension reduction and identifying the underlying structure of the data without specifying outcomes
- **Representation learning methods**
  - **Deep learning models** – extract features directly from the data to enhance understanding of the structure or relationship between causes and effects

Classification and regression	**Tree-based methods and ensemble learners**
Clustering and deep learning	**Data specific approaches**

Advancements in AI methods to enhance transparency: Bayesian network ML methods



- Applying informative priors and Bayesian methods in machine learning
- The output illustrates the interdependencies between the variables of interest



Bayesian networks are a novel risk prediction method that uses "networks of data" to reduce uncertainty and increase predictive power

Advancements in AI methods to enhance causal inference: TMLE as a bridge to statistical methods

Targeted Learning (TMLE)

- Addresses causal inference assumptions
- Focuses in on the question, e.g., "what is the improved outcome in the treated population"? (especially important in high-dimensional space, where traditional methods get worse with big data)
- Applies innovative "Targeting Step" (analytically, a second chance to get estimate right)
- Optimizes bias/precision tradeoff for the target

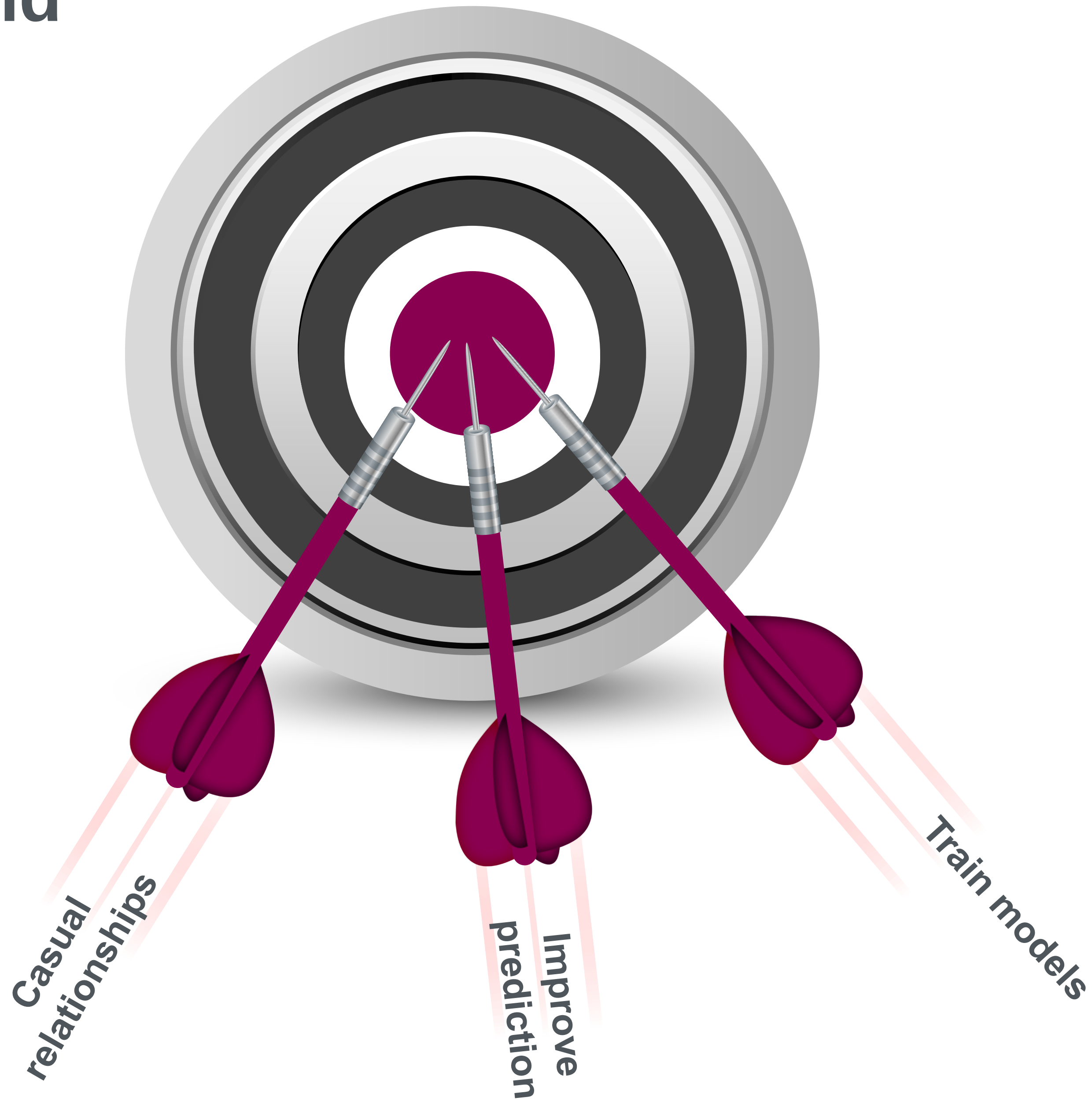
Super Learning (SL)

- Works on a collection of input models
- Builds data-adaptive composite model
- Cross-validates to guarantee best overall fit

AI algorithm development use cases

What can we do with ML and data (RCT & RWD)?

- We can more confidently identify causal relationships – the richer the data the closer we come to ‘truth’
  - Traditional statistical modelling can only infer association and cannot capture high numbers of interacting variables or large amounts of data
- We can improve prediction and support personalized medicine (identify patients at risk of disease, can optimize treatment selection)
- Can train models with RCT data, and also combine these together (including different types of RWD – EHR, claims data, physician notes…)
- **The more data we have the more confident we can be in the results**



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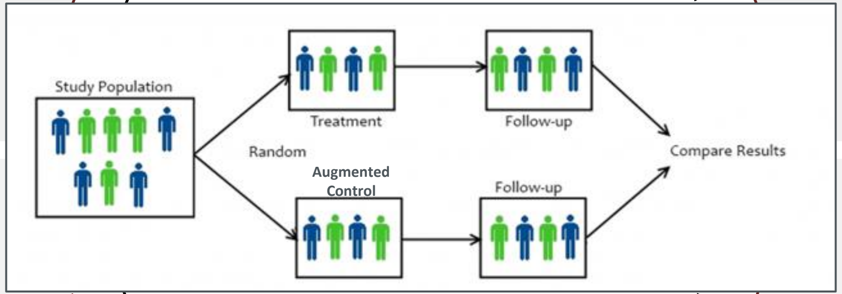
What can we do with ML and MORE data (RCT & RWD)?

We can design augmented RCTs (augment or replace the control arm with other RCT data or RWD)

Applying CV-TMLE (cross-validated targeted maximum likelihood estimator) to reduce bias introduced by augmenting control arm



With access to more RCT data, we can more frequently propose an augmented RCT option, and the process will be faster than using RWD alone, as data can be easily accessed

Saves time, money, and the method is approved by the FDA for regulatory submissions

AI algorithm development harnesses data to drive optimal clinical development

Sample use cases

- Identifying meaningful patient subgroups
- Prediction of clinical outcomes
- Derivation of patient phenotyping algorithm
- Synthetic data generation for external control arms
- Evidence-based feasibility and site identification
- Prediction of optimal treatment

Overview of RWE/RWD and potential applications

Level-setting on terminology: RWD/RWE 101

Primary data

Data collected in real time for a specific need

Includes prospective observational and interventional studies, and patient-reported data

Secondary data

Data that have already been collected for another purpose

Includes claims, EMR, disease registries, and other existing databases

Real-World Data (RWD)

Observational data collected from primary or secondary sources in non-randomized controlled trial (RCT) settings

Real-World Evidence (RWE)

Information derived from analyses using RWD regarding a medical product’s usage in the real-world and potentially associated risks and benefits to patients

Deployment of RWE across clinical development and life cycle management

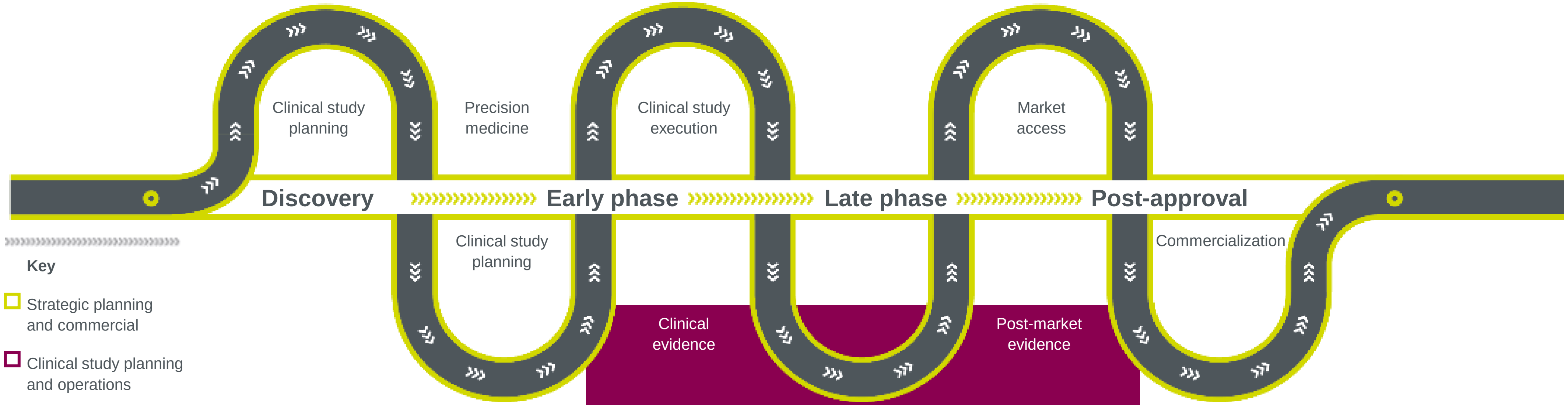
Strategic planning and commercial
Clinical study planning and operations

- Landscape analysis (epidemiology, treatment pathways, unmet need, endpoints, market)
- Advanced modeling and decision-making

- Biomarker discovery
- Responder population identification

- Real-time study monitoring
- Integrated RWD collection (eCOA, sensors/wearables)

- Comparative effectiveness research
- Health economic modeling



Key

- Strategic planning and commercial
- Clinical study planning and operations
- Regulatory grade RWE

- Protocol optimization
- Patient modeling and access
- Site selection
- Feasibility and risk modeling

- Hybrid studies and synthetic control arms
- Virtual and direct-to-patient trials

- Safety and effectiveness surveillance
- Enhanced patient-registry value

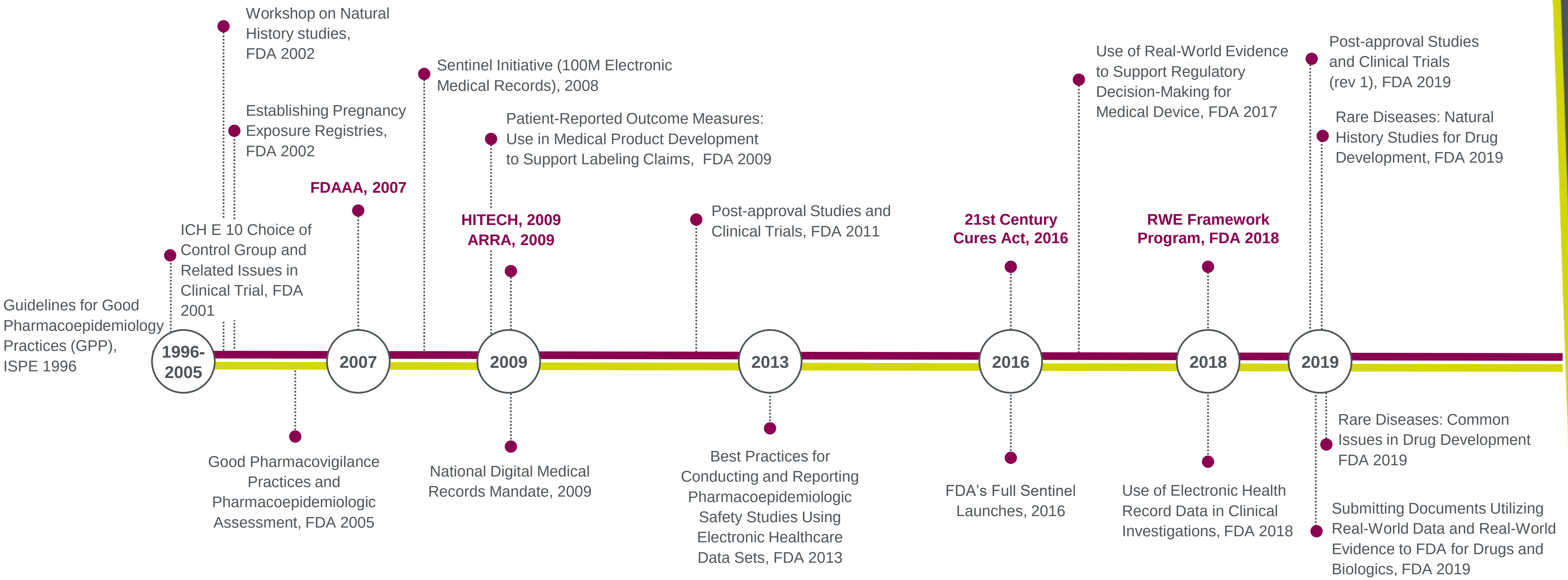
Regulatory-grade real-world evidence

- Performance assessment
- Payer requirements
- Budget impact and cost-effectiveness

Regulatory and legislative landscape

United States

Key US legislative and FDA regulatory actions



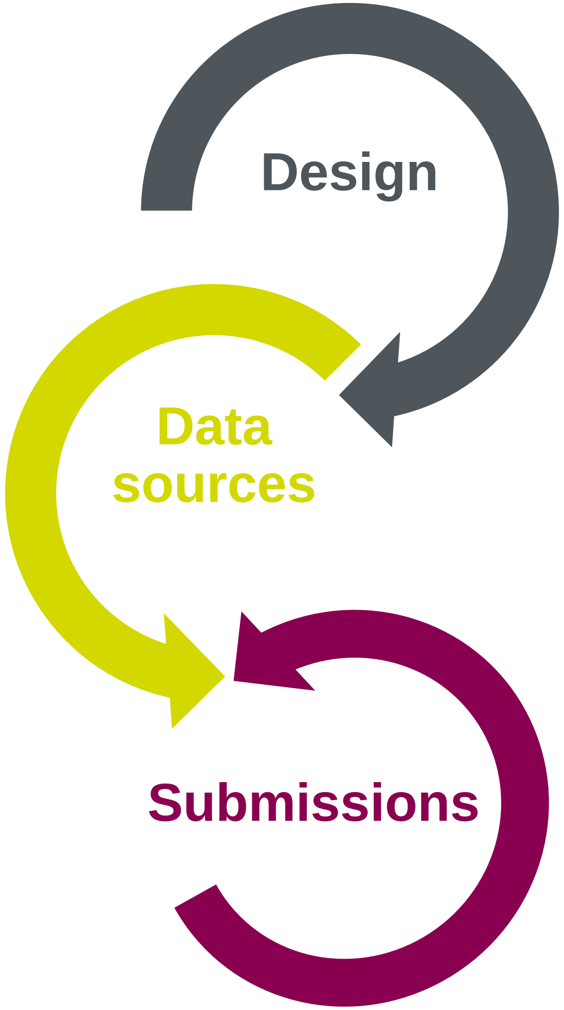
Recent RWE guidance

Design

- **Considerations for the design and conduct of externally controlled trials for drugs and biologic products :** Draft guidance for industry – Feb 2023
- **Real-world Evidence: Considerations regarding non-interventional studies for drugs and biologic products:** Draft guidance for industry – Mar 2024

Submissions

- **Data standards for drug and biologic submissions containing real-world data:** Draft guidance for industry – Oct 2021
- **Considerations for the use of RWD and RWE to support regulatory decision making for drug and biologic products:** Draft guidance for industry – Dec 2021



Data sources

- **Real-world Data: Assessing electronic health records and medical claims data to support regulatory decision making:** Draft guidance for industry – Sep 2021
- **Real-world Data: Assessing registries to support regulatory decision making:** Draft guidance for industry – Nov 2021

Limitations to consider when using RWD for regulatory

- Missing data
- Sample size
- Sources of bias (selection bias, confounding
- Comparability issues
- Uncertainties in covariate matching
- Lack of transparency
- No pre-specified protocol / statistical analysis plan

Communicate with regulatory agencies early and often to discuss the use of RWD/E in drug development programs

Key takeaways

Key takeaways and conclusions

- **AI transforms evidence generation** and **supports optimized delivery** across the clinical, access, and life cycle management spectrum
  - Evidence-based: Algorithms allow us to harness big data/RWD to generate evidence-based insights
  - Adaptive decision-making: Incorporating RWE into AI-enabled tools allows for real-time scenario testing and nimble decision-making
  - Faster: Streamlining processes drives faster insights, faster development, and faster patient access

- The **landscape is fast-evolving** and collaborative efforts between AI experts and healthcare professionals and other industry stakeholders can enhance outcomes
  - Training/grounding these algorithms with data still require human oversight
  - Adapting to evolving regulatory landscape ensures AI system safety and efficacy

- AI is positioned to **accelerate clinical development** and **enhance patient access** with **continued stakeholder collaboration** across the healthcare ecosystem

Questions?

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Thank you

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Appendix I

AI algorithm development use cases

1 Bayesian networks predictive modelling: Machine learning approach for individualized risk prediction

Situation and client challenge

- The client’s product was an immunotherapy drug in mRCC
- Trials were characterized by heterogenous treatment response
- The client was interested in developing a “personalized” risk prediction model to identify subsets of patients who respond better to therapy

Parexel approach

- Apply a novel risk prediction tool to understand variation in patient response to immunotherapy in mRCC
- Predicted OS, all-cause AEs and treatment-related AEs based on patient characteristics. Assessed model performance using logistic regression

Results and impact

- Risk scores (MSKCC and Heng), biomarkers (hemoglobin, albumin) and performance status were most prognostic for predicting OS, with ideal patient responders having high EQ-5D-3L scores and health state utility values

Client and geography

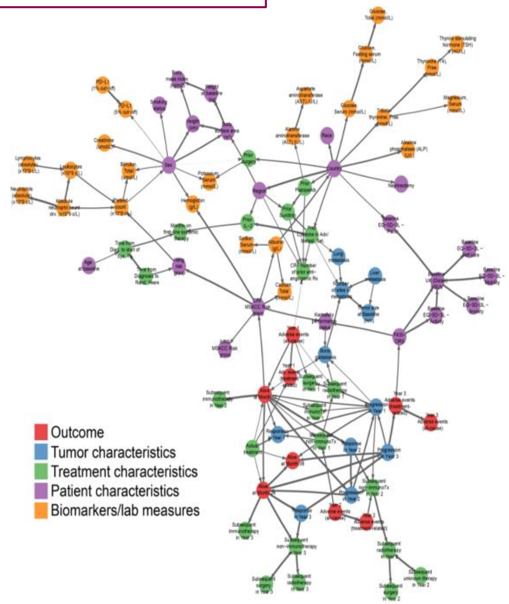
- Large Pharma company
- Oncology
- EU-5

Parexel key value

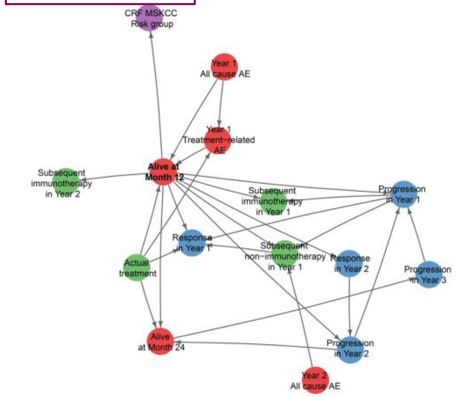
- Innovative approach
- Technical expertise in machine learning and disease expertise

Example of key output

Bayesian network model



OS at month 12



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Causal Machine Learning for Assessing Pneumococcal Vaccine Effectiveness: Innovations in Real-World Data Analysis and Confounding Pathway Adjustment

Situation and client challenge

- Determining real-world effectiveness from observational data requires careful consideration of the data generation process to account for confounding to compare treatment groups properly.
- This is especially true when estimating effects in situations with strong health behavior aspects, such as in vaccine effectiveness.

Parexel approach

- We used real world dataset MIMIC IV - a deidentified electronic health records dataset with 299,712 patients.
- To estimate causal effect of vaccination on pneumococcal disease, we employed directed acyclic graphs (DAG) to identify potential biasing pathways and then applied targeted maximum likelihood estimation (TMLE) to calculate the estimates.

Results and impact

- Propensity score matching (with enforced caliper matching) was necessary to achieve cohort balance. When accounting for imbalance and leveraging TMLE, data revealed a significant protective effect of the vaccine against pneumonia; TMLE-adjusted OR = 0.78 (95% CI: 0.72-0.84).
- …

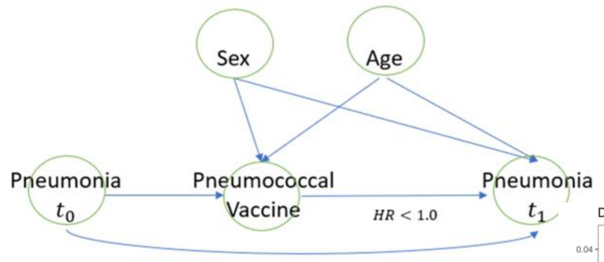
Client and geography

- USA - Beth Israel Deaconess Medical Center, Boston
- ISPOR EU poster 2023

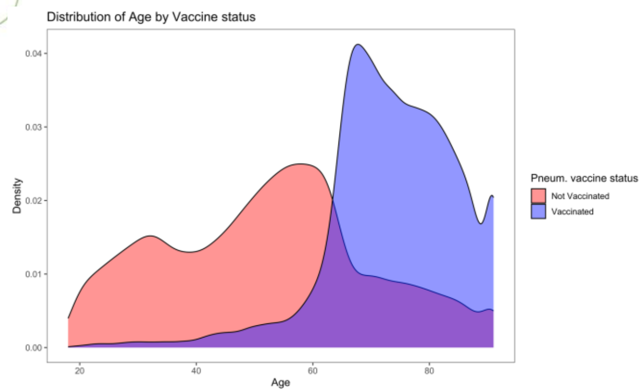
Parexel key value

- *Without Machine Learning (ML) to balance the cohort, result were paradoxical, showing high risk of disease in vaccinated group*
- *Further analysis with ML and various data sources (which ML methods allow for) will advance our understanding of vaccine effectiveness in real world settings.*

Example of key output



DAG



After cohort balancing

3 Developing an award-winning algorithm to support client access objectives in MS research

Situation and client challenge

Lack of specific terms in EHR data and use of a common ICD9 340 code in claims data to distinguish MS sub-types limits research using RWD

- Relapsing remitting MS
- Primary progressive MS
- Secondary progressive MS

Parexel approach

1. Created a retrospective cohort of patients with Multiple Sclerosis (MS)
2. Developed and ran EHR clinical notes-based and claims-based algorithms
3. Validated the algorithms with independent clinicians KOL review and random-sample manual chart extractions

Results and impact

- 94-99% positive predictive value obtained
- Algorithm deployed in subsequent client study, aimed at building outcomes evidence for their key asset
- Client and Parexel positioned as thought leaders in MS

Client and geography

- Client is a key player in MS
- Evidence initially required in US
- Subsequent application to EU markets

Parexel key value

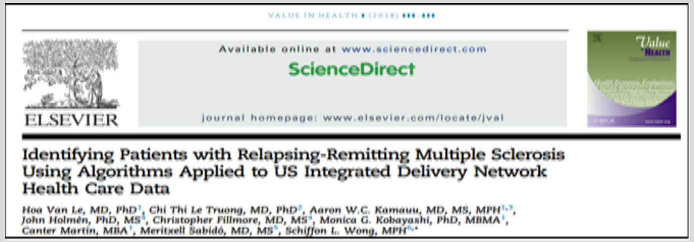
- Parexel's rigorous algorithm development process readily adaptable to other markets
- Advanced analytics expertise applicable across any therapy area

Key impact

Algorithm Workshop
ISPOR EU 2017

Relapse Measurement

- ECTRIMS 2017 Posters (x2)
- ACTRIMS 2018 Poster



VALUE IN HEALTH ▮ (2018) ▮▮▮-▮▮▮

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Identifying Patients with Relapsing-Remitting Multiple Sclerosis Using Algorithms Applied to US Integrated Delivery Network Health Care Data

Hoa Van Le, MD, PhD[1], Chi Thi Le Truong, MD, PhD[2], Aaron W.C. Kamauu, MD, MS, MPH[1,3], John Holmén, PhD, MS[4], Christopher Fillmore, MD, MS[4], Monica G. Kobayashi, PhD, MBMA[1], Canter Martin, MBA[1], Meritxell Sabidó, MD, MS[5], Schiffon L. Wong, MPH[6,]*

Case Ascertainment for *Highly Active* RRMS Patients

- ECTRIMS 2017 Poster
- ACTRIMS 2018 Poster

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4 Machine learning augmented RCT for rare disease treatments where limited patients are available for RCT

Situation and client challenge

- Client has a product for a rare disease- the patient population is small, making the possibility of a randomized trial infeasible.
- The client is able to identify and recruit enough patients to satisfy half the needed sample size for an RCT

Client and geography

- Large Pharma company
- Rare Disease
- US, Global

Parexel key value

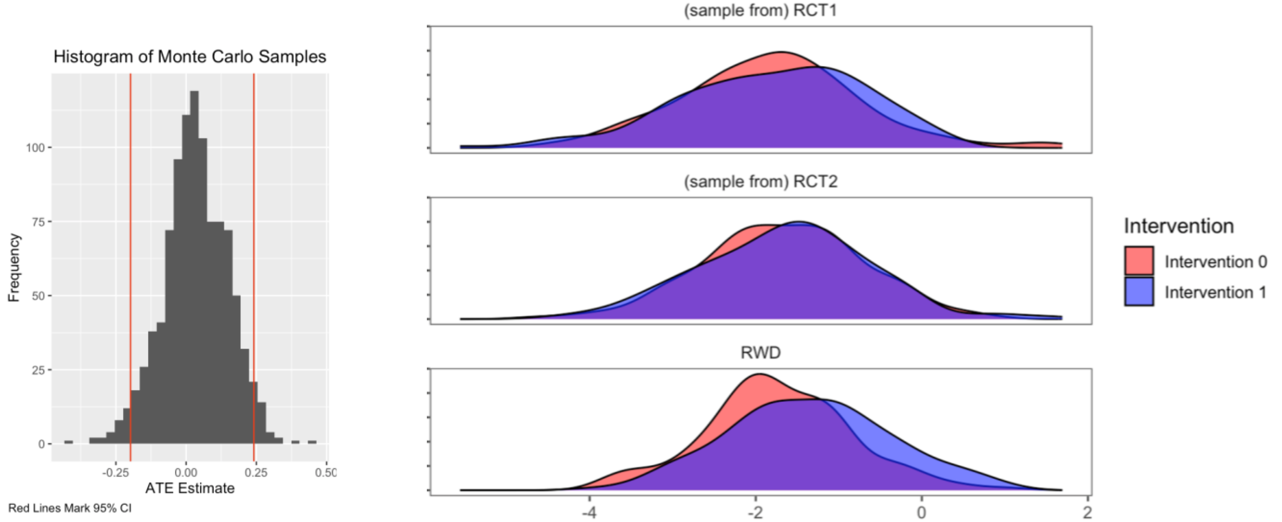
- Parexel is a leader in machine learning
- Augmented RCTs are less expensive and less time consuming than traditional RCTs

Parexel approach

- Augment or replace the control arm of the study with data from other RCTs and if needed RWD
- Access the Parexel Data Kitchen (a database of clinical trial data from other RCTs in the rare disease area)
- To minimize bias introduced by augmenting the control arm use cross-validated targeted maximum likelihood estimator (CV-TMLE)

Example of key output

Weight and aggregate data fusion estimate from RCT & RWD: can also pull only external controls from RWD: experiment selector (cross-validated) tmle ES-CVTMLE optimizes balance between RCT & RWD to minimize bias and maximize efficiency



Results and impact

- The client is provided with robust results from an augmented RCT that is aligned with the regulatory approval methods and process in the US (FDA allows for augmented RCTs in submissions)
- All stakeholders (client, regulatory bodies, and patients) can be confident in the results of the augmented RCT and people with rare disease can have access to life saving/improving treatments that would otherwise not be available due to lack of participants needed for traditional statistical methods.

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5 Machine learning augmented site Identification for rare disease treatments where limited patients are available for RCT

Situation and client challenge

- Client has a product for a rare disease- the patient population is small, making recruitment challenging
- Client needs support with site selection

Client and geography

- Large Pharma company
- Rare Disease
- US, Global

Parexel key value

- Parexel is a leader in machine learning
- Site identification support – providing evidence to assist in decision making (site selection)

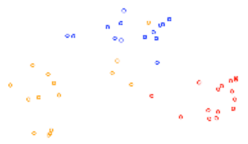
Parexel approach

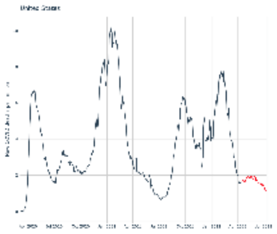
- Site recommender: ensemble of a meta mode, 3 model types, 1) super learners for forecast 2) site performance, and 3) country features
- Feature engineering to identify ‘best’ sites for recommendation
- Historic site performance, e.g. percent of successful study start up

Results and impact

- Site ranking, offering client insights into sites with optimal sites: high numbers of patient candidates and good historic site performance

Example of key output





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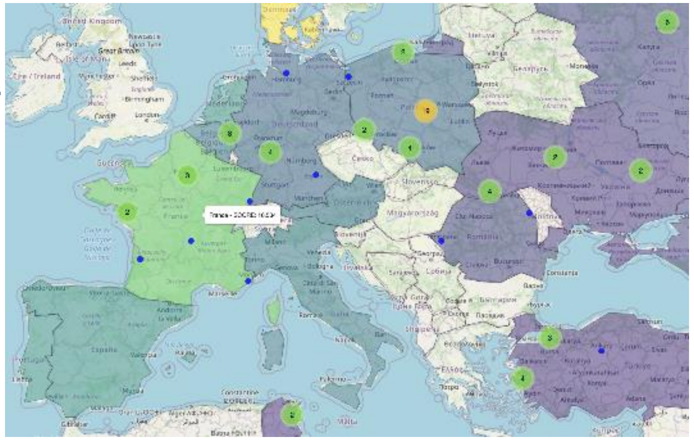
2	Andorra	0.8910470	0.0782128872	1
3	Austria	1.0234824	0.0010374422	1
4	Belarus	0.9870253	0.0019071650	1
5	Belgium	0.9955990	0.0030987981	1
6	Bosnia and Herzegovina	0.8743113	0.1505007849	1
7	Bulgaria	0.9786520	0.0189210633	1
8	Croatia	0.9784510	0.0134585893	1
9	Cyprus	1.0012382	0.0019405420	1
10	Czechia	1.0260633	0.0003106151	1



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Characterizing disease progression based on molecular data

Situation and client challenge

- *Alzheimer's disease (AD) has a complex etiology and several drugs have failed clinical trials*
- *One of the challenges in AD research is identification of patients who might progress faster under SoC, and who might show benefit from a drug modality*
- *Sponsor was interested in learning omics markers of AD disease progression*

Client and geography

- Big Pharma Sponsor
- Global study

Parexel key value

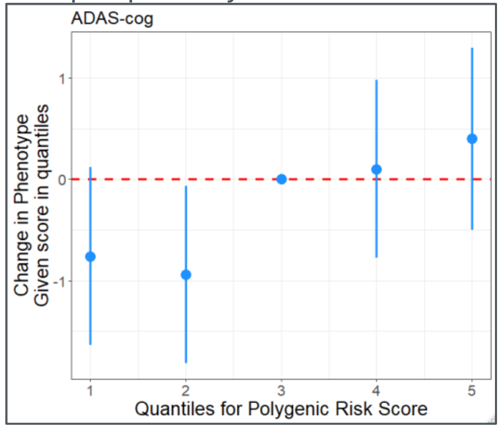
- *Parexel was able to deliver on a client's key study on AD using a large cohort of patients*
- *AD has a huge unmet medical need globally and Parexel ability to identify a marker of importance using RCTs will have reputational and economical benefits*

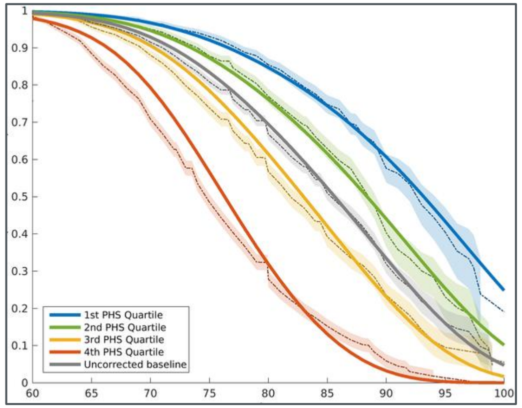
Parexel approach

- Using several clinical trials on AD, Parexel assembled cohort of population on AD along with their genotypes taken at enrollment
- Parexel used a machine learning approach, that combined various omics readouts including blood, CSF, and or clinical markers, for development of a biomarker of disease progression

Example of key output

- Creation of a mathematical model that demonstrates ability to classify AD patients based on risk of fast progression
- Demonstration of the accuracy of that model in an independent set, i.e., retrospective data, preferably real-world data
- Simulation and results of using that biomarker in an existing/completed clinical trial, (real or simulated through AI based on other trials), demonstrating the potential benefits in a real trial conducted prospectively





Results and impact

- The biomarker was subsequently validated in a separate real world study by the sponsor
- After validation, the sponsor used the omics + clinical biomarker for constructing a study that likely will elicit a tangible response in patients within the trial duration

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Appendix II

Machine learning methods and sample applications

ML methods with potential in HEOR - classification and regression

Method	ML Classification	Example applications
Bayesian belief networks	Supervised	Economic evaluation predictive analytics
Hidden Markov chains	Supervised	Economic evaluation: transition probability extraction, health state designations
Ridge and LASSO regression, elastic net	Supervised	Feature selection, predictive analytics, causal inference (propensity score, outcome regression, “double variable selection” to select confounders)

LASSO = least absolute shrinkage and selection operator.

ML methods with potential in HEOR – tree-based methods, ensemble meta-learners

Method	ML Classification	Example applications
Decision tree	Supervised	Economic evaluation: determining clinical pathways, structuring a decision model, predictive analytics
Random forests	Unsupervised or supervised	Predictive analytics, feature selection, causal inference (propensity score, outcome regression, causal forests for treatment effect heterogeneity)
Boosting	Supervised	Predictive analytics, causal inference
Bagging	Unsupervised or supervised	Feature selection, predictive analytics
Stacking	Supervised	Predictive analytics, causal inference (propensity score, outcome regression)

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ML methods with potential in HEOR – clustering, deep learning

Method	ML Classification	Example applications
Hierarchical clustering	Unsupervised	Cohort selection, feature selection
K-means clustering	Unsupervised	Cohort selection, feature selection
PCA	Unsupervised	Feature selection
Neural networks	Unsupervised or supervised	Feature selection, predictive analytics, causal inference

PCA = principal component analysis.

ML methods with potential in HEOR – data-specific approaches

Method	ML Classification	Example applications
Text: NLP	Unsupervised or supervised	Cohort selection
Imaging: Image recognition/ computer vision	Unsupervised or supervised	Predictive analytics, economic evaluation: transition probability extraction, health state designations
Audio: DSP	Unsupervised or supervised	Predictive analytics, causal inference, economic evaluation Health state designations

DSP, digital signal processing; NLP, natural language processing