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AI state-of-play around clinical research

A white paper written by the AI joint task force from the European CRO Federation and the eClinical Forum

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About AI Task Force

The European CRO Federation New Technologies Working Group (EUCROF NTWG) and the eClinical Forum launched the Task Force on AI. It has the purpose to monitor the evolution of AI/ML technologies in the Life Sciences domain and address relevant topics of major interest for clinical research.

About EUCROF

The European Contract Research Organisation Federation (EUCROF) consists of members from most European countries and partner members from nearby countries with the aim of promoting clinical research of high quality in Europe in general and in the European Union in particular. EUCROFs objectives include supporting discussions with European bodies (EMEA/EU Commission), promoting discussions on selected topics with representatives of the pharmaceutical industry to enhance business relations and identify common concerns, and endeavouring to develop transcontinental relationships with other associations e.g., with the Association of Clinical Research Organizations (ACRO) in the USA and Japanese Clinical Research Organization Association (JCROA) () in Japan. For further information visit the website at www.eucrof.eu.

About the eClinical Forum

The eClinical Forum (eCF) is a global, technology independent group representing members of industries engaged in clinical research. The eClinical Forum's mission is to serve these industries by focusing on those systems, processes, and roles relevant to electronic capture, handling, and submission of clinical trial data. The eClinical Forum has sought out opportunities to promote electronic Clinical Trials since its inception in 2000. The cross-industry forum has a broad view of research with members - Sponsors, Contract Research Organizations (CROs), Technology vendors (both clinical research and healthcare), Academia, and Investigators - and with invited outreach opportunities with global Regulatory representatives. For further information visit the website at www.eclinicalforum.org.

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The information presented in these works draws upon the combined current understanding and knowledge of EUCROF and the eClinical Forum on this topic and is provided as an aid to understanding the environment for electronic clinical research. The opinions of the author(s), EUCROF and the eClinical Forum do not necessarily reflect the position of individual companies. Users should assess the content and opinions in the light of their own knowledge, needs and experience as well as interpretation of relevant guidance and regulations.

For additional Disclaimer and License information, see Appendix 1.

Executive summary

This position paper provides information about the state-of-play of artificial intelligence (AI) and machine learning (ML) for clinical research.

The regulatory overview presented in this paper shows that while regulations are far from final for all use cases, the US and Europe have made the biggest steps toward monitoring and facilitating the use of AI, and regulations are in development in other regions around the globe.

Use cases presented include AI to enhance clinical trial operations, feasibility exploration according to inclusion/exclusion criteria for recruitment, patient and site recruitment, applications to improve trial operations, risk-based monitoring and data management, task automation, applications for Real World Evidence (RWE), medical coding, and more.

The paper presents clinical evaluation challenges for the development and validation of AI, focusing on data acquisition and selection, AI modelling, change management, and monitoring and evaluating trends.

The paper offers the UK Information Commissioner's Office (ICO) toolkit for AI risk mitigation as a best practice for compliance and the basis of validation.

The paper concludes with the positions of the AI Task Force, including the promise for improving treatments and clinical research, the risks, and the challenge for using AI given the current state of evolving regulations.

Abbreviations and Terms

Abbreviation	Term
AI	Artificial Intelligence
ATMTV	Automated Total Metabolic Tumor Volume
CE	Conformité Européenne
CoE	Center of Excellence
CRO	Contract Research Organizations
CSV	Computer System Validation
DHT	Digital Health Technology
DL	Data Lake
DPIA	Data Protection Impact Assessment
DW	Data Warehouse
eCOA	electronic Clinical Outcomes Assessments
EFPIA	European Federation of Pharmaceutical Industries and Associations
EMA	European Medicines Agencies
ETL	Extract, Transfer Load
eTMF	electronic Trial Master File
EDC	Electronic Data Capture
FDA	Food and Drug Administration
GxP	Good x Practice
HMA	Heads of Medicines Agencies
ICO	Information Commissioner's Office
IoT	Internet of Things
IRB	Institution Review Board
IVDR	In Vitro Diagnostic Regulation
MDR	Medical Device Regulation
RTSM	Randomization & Trial Supply Management
RWD	Real World Data
MD	Medical Device
ML	Machine Learning
NLP	Natural Language Processing
SaMD	Software as Medical Device
SDQ	Smart Data Query
SME	Subject Matter Expert
URS	User Requirements Specifications
US	United States

1 Introduction

The evolution of AI is starting to impact the life sciences industry, and many applications with clinical, operational and medical benefit. Unlike other industries, life sciences have the challenge to ensure patients' safety and privacy, with the attendant increased regulatory interest in how the technology is developed, validated and implemented.

In this environment, the New Technologies Working Group of EUCROF and the eClinical Forum initiated the AI Task Force with the purpose to monitor the evolution of AI technologies and development of related regulations in life sciences and address relevant topics that are of major interest for clinical research.

This position paper presents the state-of-the-art of AI in clinical research in four sections focused on the following topics:

- An overview of the status of regulations in the United States, Europe, Asia and the rest of the world
- A review of major use cases for the domain
- Recommendations for best practices in development and validation of AI in clinical research
- A statement of this task force's current positions and future work

2 Regulatory Landscape

The regulatory landscape for AI in clinical trials and drug and medical device development is emerging. This section summarizes current status of regulations in countries and regions around the globe.

For countries and regions with more regulatory activity around AI, following points are presented:

- Current regulatory thinking related to drug development.
- Current regulatory thinking related to medical devices.
- What is known about use of AI in clinical trials.
- Any approvals for treatments that include AI.
- Available resources to support organizations developing trials or submissions that include AI.
- Any country or region-wide regulations or regulatory work around AI beyond clinical trials.

For countries with less regulatory activity focused on AI, each section summarizes a brief current status.

2.1 United States

As of the time this paper was prepared, there was no regulation in place for AI or for AI in drug and device development in the United States. However, the United States Food and Drug Administration (FDA) has active initiatives exploring AI in drug and device development and is developing the groundwork for guidance and regulations with input from industry and other stakeholders. The FDA has approved over 100 medical devices which include AI, and are supporting development of new biomarkers and trial management technologies that include AI.

2.1.1 Current Regulatory Thinking and Stakeholder Input Related to Drug Development

In April 2023 the FDA issued two discussion papers on AI Using AI and ML in the Development of Drug and Biological Products [1] and AI in Drug Manufacturing [2] and requested industry feedback on possible frameworks and methods to achieve AI compliance. Both discussion papers are, as the authors of Using AI and ML in the Development of Drug and Biological Products state in the background and scope section, "…not FDA guidance or policy", but "an initial communication with stakeholders, including academic groups, researchers, and technology developers, that is intended to promote mutual learning and discussion."

The AI in Drug Manufacturing paper lays out a few example use cases, areas where industry may need guidance and policy on how to implement and validate systems using AI, and some questions for industry.

The Using AI and ML in the Development of Drug and Biological Products paper covers three topics:

- Landscape of current and potential uses of AI/ML
  - This section provides a useful summary covering a wide range of uses of AI in drug discovery, preclinical/nonclinical research including pharmacokinetics and pharmacodynamics (PK/PD), clinical trials, post marketing safety surveillance, and pharmaceutical manufacturing.
- Considerations for the use of AI/ML
  - This section covers standards and practices for using AI/ML, and specific considerations for use in drug development
- Next steps and stakeholder engagement
  - The conclusion notes: "Building on this discussion paper, FDA will continue to solicit feedback and engage a broad group of stakeholders to further discuss considerations for utilizing AI/ML throughout the drug development life cycle. These discussions and future collaborations with stakeholders may provide a foundation for a future framework or guidance."
  - The initial call for feedback accompanying the paper closed 09 August 2023.

2.1.2 Current Regulatory Thinking and Stakeholder Input Related to Medical Devices

The FDA established a Digital Health Center of Excellence (CoE)[3], whose strategic priorities include "Artificial Intelligence and Machine Learning in Software as a Medical Device." The agency has produced several documents to assist organizations exploring these technologies. For example, the FDA published "Artificial Intelligence/Machine Learning (AI)-Based Software as a Medical Device (SaMD) Action Plan" in January 2021 [4] outlining several steps the FDA plans to take in advancing AI development within Software based Medical Devices. One notable inclusion to the plan was how FDA plans to allow a Total Product Lifecycle (TPLC) approach, which enables manufacturers to make updates to their Medical Devices (MD) whilst in production. This TPLC approach demonstrates FDA's commitment to streamlining the use and maintenance of AI based algorithms in the real-world, whilst providing transparency and maintaining patient safety [5].

2.1.3 Status of Clinical Trials Using AI

At the time of this writing, a search for "artificial intelligence" on clinicaltrials.gov yields 1,111 results. Most are not associated with Phase I-IV trials, indicating that they are "exploratory" and while 206 of these studies are funded by industry, 869 are funded by academia, individuals, or organizations. It is interesting, though, that 469 of these studies are interventional, versus 642 observational trials.

2.1.4 Approvals of Devices Using AI

As of October 5, 2022, the FDA's non-exhaustive list of "AI-enabled devices across medical disciplines, based on publicly available information" included 178 such devices. Most of these analyze data derived from devices used for imaging, ultrasound, radiology, cardiology, and other areas to provide rapid results that would require an inordinate amount of time for humans to produce [6].

2.1.5 Resources to Support Submissions Using AI

The FDA's discussion paper "Using Artificial Intelligence & Machine Learning in the Development of Drug & Biological Products" noted the Center for Devices and Radiological Health's Center for Digital Excellence, has "…provided consults for drug submissions that involve AI/ML, and are developing a framework for AI/ML-based devices…as well as a foundation for Good Machine Learning Practices for medical device development".

2.2 Europe

As of the time this paper was prepared, there was no regulation in place for AI or for AI in drug and device development in the European Union. However, several proposals and whitepapers have been published as the region evolves toward settled policies.

2.2.1 Current Regulatory Thinking and Stakeholder Input Related to Drug Development

While no regulations on AI in drug and device development have yet been published in Europe, several documents recently published by regulators bodies in Europe focus on the use of AI drug development and clinical research, and are aimed at gathering stakeholder input as regulatory thinking evolves, and some provide guidance:

- Workshop Report: Joint HMA/EMA Workshop on Artificial Intelligence in Medicines Regulation
  This summary of a workshop held by the European Medicines Agency (EMA) and the Heads of Medicines Agency (HMA) in April 2021 gathers input from stakeholders as overviews of presentations delivered in the workshop sessions, and some recommendations for policy development [7].
- The Big Data Steering Group set up by EMA and the Heads of Medicines Agencies (HMA) has published an updated workplan that sets key actions to be delivered between 2022–25, two key actions which include the publication of an AI reflection paper and AI guidelines [8].
- The Danish Medicines Agency published a useful guide on key questions to address for critical AI GxP applications, "Questions to critical GxP AI applications (Draft V.0.9.4)" - Danish Medicines Agency, February 24, 2021[9]. This is not a formal guidance and is not a regulation.

- In July 2023 the EMA released an AI paper on the use of AI in the medical product Life Cycle. This paper is currently out for industry comment by the end of Dec 2023 [10].

2.2.2 Other Resources to Support Clinical Trials and Submissions Using AI

The Italian Medicines Agency (AIFA) released in May 2021, a guide of submission of requests for authorization of CT involving the use of AI or ML systems [11].

2.2.3 Regulations in Development for AI Across Industries

Several publications cover European regulators' current thinking on use of AI in all industries.

- European Commission Approach to Artificial Intelligence
  - In April 2021, the European Commission released a proposal to regulate AI, describing it as an attempt to ensure a "*well-functioning internal market for artificial intelligence systems*" that is based on "*EU values and fundamental rights*". A legal framework will provide major AI stakeholders clarity by intervening only in those cases that existing national and EU legislations do not cover. The legal framework for AI proposes a clear, easy to understand approach, based on four different levels of risk: unacceptable risk, high risk, limited risk, and minimal risk [12].
- A white Paper on Artificial Intelligence, A European approach to excellence and trust [13].
  - The European Commission published this paper in February 2020, concentrating on how AI can be trusted. It lays out and seven key requirements:
    - Human agency and oversight
    - Technical robustness and safety
    - Privacy and data governance
    - Transparency
    - Diversity
    - Non-discrimination and fairness
    - Societal and environmental wellbeing
    - Accountability
- The European Commission published a proposal for a new AI EU Regulation titled "Regulation of the European Parliament and of the Council Laying Down Harmonised Rules on Artificial Intelligence (Artificial Intelligence Act) and Amending Certain Union Legislative Acts COM/2021/206" in April 2021)[14].
  - This proposal by the European Commission sets out policy options on how to achieve the twin objective of promoting the uptake of AI and of addressing the risks associated with certain uses of such technology. This proposal aims to implement the second objective for the development of an ecosystem of trust by proposing a legal framework for trustworthy AI. The proposal is based on EU values and fundamental rights and aims to give people the confidence to embrace AI-based solutions, while encouraging businesses to develop them. AI should be a tool for people and be a force for good in society with the ultimate aim of increasing human well-being.
  - The proposal follows a risk-based approach and imposes regulatory burdens only when an AI system is likely to pose high risks to fundamental rights and safety. For other, non-high-risk AI systems, only very limited transparency obligations are imposed. AI systems whose use is considered unacceptable as contravening Union values, for instance by violating fundamental rights and or exploiting vulnerable people are prohibited from use.

2.3 Asia

Across Asia, China, Japan, Singapore, South Korea and Taiwan have all released guidance documents that support the use of AI in health technologies. Most notably, South Korea's Ministry of Food and Drug Safety (MFDS) have published no fewer than five guidance documents on the topic, ranging from validation to clinical evaluation, effectiveness and device classification.

2.3.1 Current Regulatory Thinking and Stakeholder Input Related to Drug Development

As of publication of this paper, there are no documents we found in our research published by regulators or organizations developing policy in Asia related to AI in drug development or clinical trials specifically.

2.3.2 Current Regulatory Thinking and Stakeholder Input Related to Medical Devices

Guidance documents developed to date by Asian regulators are all aimed at the medical device market, for products that include some form of AI algorithms. In Japan however, the Ministry of Health, Labour and Welfare (MHLW) have focused their initial efforts specifically on Medical Devices for Imaging systems used for diagnosis, suggesting that this is an area where the authority sees potential value in healthcare [15].

2.3.3 Resources to Support Clinical Trials and Submissions Using AI

As of publication of this paper, there are no documents we found in our research published by regulators or organizations in Asia offering support for or feedback on clinical research or regulatory submissions for new treatments.

2.3.4 Regulations in Development for AI Across Industries Beyond Life Sciences

From our research, governments across the Asian region appear to have published little in terms of AI strategies in any sector at a national level, other than Singapore. In Singapore the "*Smart Nation National Artificial Intelligence Strategy*" defines for vision for "developing and deploying scalable, impactful AI solutions" across important sectors, which includes healthcare [16]. While this doesn't have an initial and direct impact on AI used within Clinical Research, it does pave the way for building trust in AI, which is a step in the right direction for future acceptance and enablement. Singapore also published a "Model AI Governance Framework" in January 2019, aimed at "translating ethical principles into practical recommendations that organisations could readily adopt to deploy AI responsibly" [17].

2.4 United Kingdom

The United Kingdom has defined a national approach for AI strategy, and is developing regulatory thinking on medical devices, with publications including:

- National AI Strategy - AI Action Plan, from 18th July 2022.
- The Medicines and Healthcare Regulatory Agency is working on mapping Good Machine Learning Practice to existing Device legal requirements [18].

2.5 Australia

While Australia has, as of this publication, not started developing regulations specific to drug and medical device development and clinical research, the Australian government has published the Artificial Intelligence Ethics Framework [19], which guides businesses and governments to responsibly design, develop and implement AI with emphasis on creating a trust environment about its safety, security and reliability.

The Australian government is addressing the challenges of promoting and protecting AI technology, developing and adopting AI, as well as aspects and considerations related to ethical AI [20].

2.6 South America

At present, no information relating to an AI regulatory framework related to clinical trials has been identified in South America.

2.7 Africa

No information relating to a regulatory framework related to AI in clinical trials has been identified in Africa either.

2.8 International Efforts: U.S. FDA, Health Canada, and U.K. MHRA Guidance

In a bid to provide more globally aligned guidance on the topics of AI and in particular Machine Learning, the U.S. FDA, Health Canada, and the United Kingdom's Medicines and Healthcare products Regulatory Agency (MHRA) have jointly identified 10 guiding principles that can inform the development of Good Machine Learning Practice (GMLP) [18]. These guiding principles aim to promote safe, effective, and high-quality medical devices that use Artificial Intelligence and Machine Learning.

2.9 International Efforts: IMDRF

The International Medical Device Regulators Forum, a voluntary group of medical device regulators from around the world, has prepared key definitions of Machine Learning - enabled Medical Devices [21].

2.10 Other Associations and Industry Forums

Several industry associations and forums have published resources and papers related to AI in healthcare, drug development, medical devices and clinical research:

- The European Federation of Pharmaceutical Industries and Associations (EFPIA), a group representing the biopharmaceutical industry operating in Europe in December 2020 published the "EFPIA Position Paper on Artificial Intelligence" [22]. The paper makes several recommendations, including support for:
    - Adapting regulations to include AI rather than creating new rules.
    - Following the European Commission's approach to regulate AI based on risk, acknowledging CE marking system for high-risk applications in healthcare which is already addressed by MDR/IVDR.
    - Developing of a center of excellence for AI in healthcare in the European Union
    - Increasing clarity and guidelines that enable innovation, adoption and acceptance of AI technologies.
- The International Coalition of Medicines Regulatory Authorities published the Informal Innovation Network Horizon Scanning Assessment Report – Artificial Intelligence 6 August 2021 [23].
    - This paper gives a good overview of where different Health Authorities are with AI regulation. Relevant for the EU is the proposed EU regulation as per point above. It also contains good example Case Studies of where AI could be used for GxP purposes and what controls different Health Authorities would expect. The main recommendations are to come up with cross Health Authority Guidance and then update regulations to cover the use of AI for GxP purposes.
- The International Society for Pharmaceutical Engineering (ISPE) recently updated their Good Automated Manufacturing Practice (GAMP 5) Guide [24], an industry guide on Computer System Validation to which Health Authorities refer to add AI into it to complement and to build onto its existing processes.

3 AI Use Cases

This section focuses on the uses of AI in conducting clinical trials. Drivers for the use of AI in research include:

- Ability to analyze great volumes of data, both structured and unstructured, more quickly and efficiently than humans (e.g., safety and pharmacovigilance data).
- Identifying correlations between data fields that may reveal clinical and/or operational issues (e.g. compliance information for patients in clinical trials, identifying "outliers" in clinical data that might indicate a need for on-site monitoring at one or more sites for specific issues).
- Development of AI assisted biomarkers (e.g., early detection of conditions long before human experts can recognize prodromal symptoms such as voice analysis data predicting Parkinson's Disease).

There are several areas where AI technologies are being used to enhance clinical trials, from planning through data cleaning and analysis. It is important to note, though, that when performing a search for "artificial intelligence and machine learning in clinical trials," many of the "hits" are disappointing as the terms AI and ML are certainly overused. For example, some websites claim AI-enabled study builds, but on reading the details it becomes clear that some of these are simply context-sensitive suggestions to assist in building electronic Data Capture (EDC) or electronic Patient-Reported Outcomes (ePRO) forms.

AI models are used in different areas to accelerate clinical trials from study start-up events to close out and data analysis and diagnostics. Good use cases of AI in clinical trials were presented by pharmaceutical companies and IT vendors both in the 1st annual ACDM symposium on AI in clinical trials held in London [25] and in the eClinical Forum Workshops held in Brussels and Uppsala. The following sections will describe some of these use-cases on a high level.

3.1 Feasibility and Recruitment

Large volumes of Real-World Data (RWD) are analyzed to explore the feasibility of the inclusion/exclusion criteria for a given condition. This allows sponsors to adjust these entry criteria to ensure realistic patient recruitment opportunities.

These same data sets may be explored to match potential patients and sites to clinical trials. This often involves using Natural Language Processing (NLP) to curate high-volume data sets to match patients to trials.

There are some systems in place that use AI for patient recruitment and enrollment. These systems use Real-World Data (RWD) or data/metadata from other clinical trials to find subjects for the trial. This is especially helpful for oncology trials that study rare diseases.

3.2 Study Start-Up

Some vendors and Contract Research Organizations (CROs) are using AI technologies for the initial setup of clinical operations systems, such as EDC, Randomization and Trial Supply Management (RTSM), electronic Clinical Outcomes Assessments (eCOA), electronic Trial Master File (eTMF) and other operational tools. For example, more complex EDC solutions read and digitize a study protocol, then use a combination of standards, data libraries and past study designs to implement the first draft of the clinical trial system(s). Next, a human subject matter expert (SME) makes any necessary adjustments and corrections and also rates or scores the initial implementation. This allows the system to learn and continually improve the initial design.

EDC is a logical target for AI solutions because there is great consistency in the data fields, forms and visit flows from study to study, especially within a given therapeutic area. Technologies such as eCOA and RTSM tend to be more nuanced. Even so, some vendors are using structured specification forms that do allow NLP processes to consume the specification and produce the initial system, often requiring little to no modification.

One of the biggest challenges for these design tools is change management. Consider the typical case of a protocol amendment. While intelligent systems may be able to compare the original protocol to the updated

one and produce a report showing the changes, there is risk associated with allowing AI to implement changes automatically. Such changes could easily over-write any modifications made by human experts after the initial design. Therefore, there is usually significant human intervention to review any recommended system changes before implementation.

Additional challenges to AI design tools include having adequate training materials, such as high-quality historical protocols, data standards and corresponding designs. Further, these materials may vary by therapeutic area or by patient population combined with the substantial volume of data typically required to train AI models increases the difficult of these solutions. There is still a need for subject matter experts to act as curators of these training inputs and of the AI designer itself.

Some pharmaceutical companies use AI for suggesting a study design and/or detecting protocol deviations. The application uses data from previous designs for similar studies and reads the study protocol to suggest an EDC design. Some of the challenges include the protocol documents not being in a machine consumable format, and inconsistent design and quality depending on human experience.

3.3 AI in Clinical Trial Operations

While a clinical trial is running, there are a few AI-enabled solutions that are gaining traction. One of these is monitoring patient compliance and issuing appropriate reminders to patients. Content and implementation of such messaging can be reviewed by patients and clinicians at design phase, as well as Institution Review Boards (IRBs) and/or Ethics Committees. Intelligent systems use predictive analytics to see how compliant individual patients are with activities such as taking medication and completing patient-reported outcomes. Then reminders are issued according to individual patient behaviors. If the application determines that an individual is highly compliant, then the number of reminders may be reduced. On the other hand, if the system sees indications of poor compliance, the reminders and other motivators are presented. In this way, those needing additional motivation receive it and those who would be annoyed by unnecessary reminders are spared excessive messaging.

Another helpful smart solution is automated eTMF indexing. As necessary trial documentation is scanned or sent into the system by other means, the system determines what type of document it is and where it should be stored in the eTMF. It may also produce a confidence score so that human reviewers can ensure that low scores are reviewed quickly to ensure accuracy and to further teach the system.

When it comes to reports and dashboards, there is still much that can be done to automate operational changes on the fly. Most analytics simply show where issues may be occurring, either currently or in the near future. More intelligent solutions can make changes on the fly. A good example is in clinical supply chain strategies. Traditionally, an RTSM system may classify sites around the globe as high, medium and low recruiting and then set a corresponding supply strategy for each of these classifications. For example, high recruiting sites may receive ten doses of medication at the start and then when need resupplies, six doses may be sent. The initial supply and resupply figures for a low recruiting site may be four and two, respectively. A medium site would fall somewhere in between these figures. However, an AI-enabled solution may constantly monitor the actual need at individual sites and set many more classifications to make much more efficient use of the study supplies, while at the same time, minimizing the number of expensive shipments that must be made.

When it comes to clinical trial optimization, there are some challenges in collecting and using the so-called secondary data in clinical trials. The secondary data is a one part of the RWD and is collected from sources like:

- Activity trackers to detect the lifestyle (e.g., activity, nutrition) of subjects.
- Geographical environment they live in.
- Emotion recognition models that look at social media texts posted by the subjects to detect their mood.

There are a lot of barriers to collecting and using this data, for example, low consumer appeal or subject burden, and dependency on slow regulatory processes.

Sponsors and vendors have presented systems that involve clustering and modeling of subjects into cohorts to increase the efficiency of the clinical trial, by simplifying patient management for the sites. AI also be used to detect if there is a risk of a subject having an adverse event and alert the site to take the necessary precautions. Other systems using NLP models that can review free text fields in the EDC and help data managers by suggesting queries that can be raised to the sites. The statistics show time savings increase over time of up to 75% compared with trials that do not use SDQ.

3.4 Risk Based Monitoring

Some vendors offer statistical and AI monitoring which can identify outlier patterns in data, which may indicate an issue that can be followed up with action from trial monitors [26][27].

3.5 Data Management

Several vendors mention the use of AI for activities around data management, such as mapping data to standards, and data cleaning, using a system that automatically generates specific edit checks or that flags outliers in the data. These solutions do not replace data managers and data scientists; rather, they are tools to help them identify anomalies, reduce errors and to get to database lock faster.

3.6 RWE and the use of RWD as AI enabler

Real-World Data (RWD) is any data relating to a patient's health status, collected during the routine delivery of care [28], as opposed to data collected within the controlled setup of clinical trials. Hence RWD does not differ so much in its type, but in the process and population involved in its collection. The first and mandatory step towards RWD collection is to notify patient about the data privacy terms and obtain his/her consent, while additional privacy and security measures must be taken into consideration to comply with privacy regulations, e.g., GDPR. The different types and sources of RWD can be, according to [29], Clinical data from electronic health records (EHRs) and case report forms (eCRFs), patient-generated data from patient-reported outcome (PRO) questionnaires or measurements from wearables, medical claims data, data from registries, and public and government data including cost and utilization data. Such information can be used to create algorithms for risk stratification or to gain insight into associations between exposures, interventions, and outcomes[30].

While clinical trials continue to be the main tool for studying the safety and efficacy of a new medicine, their controlled environment and well-defined cohorts constitute experimental conditions that do not represent real-world settings. RWD is a much better tool for understanding how patients react to a medicine once approved and made available in the market, i.e., in routine medical care. The lack of highly controlled settings usually results in lower levels of confidence, but the outcomes represent a wider population of subjects. Such outcomes are better suited for understanding and taking decisions in everyday medical care [31], in broader settings than the controlled ones in clinical trials.

There can be a huge quality difference between RWD vs data collected in a clinical trial, especially when using RWD collected by patients in everyday settings. In a clinical trial the process is carried out by professionals, with subjects following strict guidelines (like time and method of collection, or diet prior to collection). Real world data collected in a clinic is collected with the primary intent for records for payment as well as case history for the patient record and likely does not meet the collection standards and methods used by trained sites in clinical trials. In the everyday setting, the process is continuous, and carried out by subjects themselves. Whether the data is reported by the subjects, or is measured by devices they subjects operate, the continuous nature and the self-supervision can lead to low quality due to device failure (usually uncharged devices, wearables not worn when they should have been, or mobile applications left unused for too long and

automatically closed down) and lack of adherence (forgetting to answer instances of repeating questionnaires, amplified decline of interest in the process). Also, clinical data can be much more specialized to the medical conditions at hand, compared to the mostly behavioral data collected in an everyday setting.

But no matter these shortcomings when dealing with data collected in an everyday setting, it is now well-established that behavior is part of the intervention. The high specialization and quality of the sporadic clinical data is complemented by the continuous nature of the behavioral, every-day data, in much the same way a low-resolution film complements the understanding offered by the occasional high-resolution photo.

Beyond EHR records, behavioral RWD collected between visits to a clinic are categorized in terms of collection method and content. The following collection options are used: Patient-reported via questionnaires and automatically reported by wearables and other medical devices. Using any of the above methods, the following every-day RWD types are collected: physiological (e.g., physical activity, vital signs, sleep), psychological (e.g., emotions), social Interactions (e.g., phone calls, social media), and environmental (e.g., living and working environment conditions).

At a raw level, RWD can lead to decisions about individuals and cohorts via analytics visualizations. But full understanding of the context of subjects is gained via processing, using machine learning techniques. Supervised algorithms facilitate learning biomarkers, while unsupervised ones lead to phenotypes.

AI methods can be used to standardize RWD from the “messier” sources described above, allowing the data to be used for some types of clinical research and evidence for payers.

RWD facilitates learning digital composite biomarkers. Biomarkers are quantities characterizing some disease or outcome. Digital refers to their attributes being ubiquitously available, not only as clinical data. Composite refers to the combination of multiple attributes in the attempt to predict some outcome. ML algorithms are used to learn outcome predictors as non-linear combinations of the attributes into the digital composite biomarkers.

Phenotypes characterize the way internal conditions of subjects manifest themselves for external observation. The different RWD attributes measured constitute the observation, and clusters of the observations correspond to different phenotypes. The clusters are learnt from RWD using unsupervised ML algorithms. The clusters are then modelled for efficient representation of the phenotypes.

3.7 Task automation

AI/ML based algorithms and ruled based decision-making systems can assist today radiologists in the context of a clinical trial. An example of the use of AI for task automation in oncology is where AI is used as a digital pathology tool to assist in generating prognostic scorecard and as a clinical imaging tool to assist in calculating total metabolic tumor volume.

By applying advanced imaging analytics, radiological assessments can be improved by:

- Generating automated, accurate, and reproducible tumor burden and response assessment (e.g., RECIST, Lugano) for radiologist review
  - Reduce time and cost associated with quality checks of images prior to reader review.
  - Reduce reader variability.
  - Increase quality of reads if the system is able to identify tumors readers might miss.
  - Decrease cost and increase speed of reads with automated segmentation.
- Enabling new imaging-based insights
  - Provides additional imaging-based information, including total tumor burden and tumor location.
  - Potential to develop improved response metrics.

- Potential to further define subpopulations.

The intended use of a fully automated total Metabolic Tumor Volume is where an AI-based digital pathology algorithm, ATMVT (Automated Total Metabolic Tumor Volume) is used in the form of a Software as a Medical Device (SaMD) and a Digital Pathology Tool based on an AI digital pathology algorithm to assist in generating prognostic risk scorecard, which can deliver risk screening results.

Benefits of the fully automated Metabolic Tumor Volume are: a) no additional testing; b) fast turnaround; and c) easy integration.

3.8 Medical Coding

Mapping medical concepts described in free text to entries in standardized terminologies, such as ATC, MedDRA, RxNorm, SNOMED CT or WHODrug Global, allows the representation of semantically identical or related concepts by the same entry during data analysis; thereby limiting the number of distinct concepts considered [32][33]. In clinical trials, medical coding consists of coding reactions to MedDRA, concomitant medications to WHODrug [34] and selecting ATC classes based on the intended use of the medication [35].

Medical coding can be automated or supported by computer systems, thereby not only saving time and resources but also improving consistency. Most commonly, medical coding is automated by tools automatically coding direct matches of the verbatim (free-text description of the concept), with or without transformation, to the terminologies. This is referred to as auto-coding or auto-encoding[34][36]. Additionally, synonym lists are created by organisations to store and reapply coding decisions made during manual coding. Automation of medical coding faces different challenges: regularly evolving terminologies, presence of extraneous information in verbatim terms, misspellings, ambiguous medical concepts, multiple distinct medical concepts reported together, or concepts reported in the wrong field. While a synonym list can handle and solve most of these challenges, it is easily understood how they can grow considerably in volume while requiring extensive manual maintenance work and adjustment to terminology updates. For example, previously unseen misspellings cannot be handled by rigid synonym lists. On the contrary, AI using natural language processing, rules and machine learning can extract the right information, detect misspellings and utilize contextual information to select the appropriate entry in the terminology. However, their performance needs to be carefully evaluated to ensure high coding accuracy and consistency.

Nevertheless, the state of implementation of AI-based medical coding in clinical trials is still limited. In scientific literature, some approaches to automating medical coding for other fields such as pharmacovigilance or drug orders are presented [37][38][39][40]. For clinical trials, some companies have built their own tools [41] and some commercial solutions exist [42][43], but not all are based on machine learning and only one solution exists for ATC selection per intended use [43].

3.9 Other potential Use Cases

Other potential use cases related to the use of AI in clinical trials are:

- Drug Adherence
- Patient Recruitment via Trial Matching [44]
- Predicting fast progressors [45]
- Predicting phase transitions (i.e. phase 2 to phase 3 and increase PoS) [46]

3.10 Consideration for success

Despite these drivers and many other applications, there are potential barriers, including:

- User and public concerns/hesitancy with AI acceptance (concerns such as: inaccuracies, imbedded bias, discriminatory outcomes, privacy and security concerns
- Data governance challenges

- Substantial volume of reliable data needed to train the AI
- The need for transparent algorithms to meet drug development regulations
- Recruiting data science professionals
- Breaking down data silos
- Streamlining electronic records
- Substantial volume of reliable data needed to train the AI

It is encouraging to see the FDA continuing its efforts to communicate with researchers to address these barriers and to help realize the many benefits of AI in clinical trials.

4 AI Validation

This section focuses on validation, presenting challenges, validation steps and best practices.

The main challenges of the use of AI in clinical research can be grouped into 2 categories:

1. AI may introduce risks to patient safety.
2. Solutions that involve AI can be non-compliant with the regulations that are currently under creation.

The main challenge is to avoid introducing a risk to the patient, which can happen in various ways, such as wrong diagnosis, false alarms and false alerts, and misleading automated recommendations. From a vendor's point of view, operation in a non-compliant manner is also a major challenge that needs to be mitigated. Both challenges can be addressed by proper validation, which should be adapted to the requirements set by the regulatory authorities.

Advanced data driven algorithms present technical and regulatory challenges over traditional rules-based programming and validation. The main challenges that are critical to quality and include:

- Ensuring that AI models are trained and tested with enough suitable data and processes.
- Demonstrating control during a highly iterative model development process.
- Demonstrating robust analytical performance prior to model deployment.
- Monitoring for ongoing post-deployment model performance reliability.
- Data integrity and privacy are guaranteed.

These fundamental differences to traditional "GxP" validation present challenges in demonstrating to health authorities how decisions were made. Companies must be able to demonstrate through objective design, development and testing evidence (documentation) that algorithms developed are fit for purpose (accurate and reliable). Note: If AI software/component is part of a Digital Health Technology (DHT), including software as a medical device or an AI component of a medical device:

- A clinical evaluation should be performed to verify the performance, safety and clinical benefits of the medical device.
- Clinical evaluation report should be prepared as required by the European Commission for all medical device approvals [47] for a medical device aims to show the device offers more benefit and/or poses less risk than state-of-the-art treatments or is at least comparable to state-of-the-art technologies
- The context of intended use within the clinical trial should be defined as well as the meaningful aspect of health (identification of measurement in clinical study).

In order to accomplish this, the algorithm development lifecycle process should address these challenges while also complementing the validation process of the core computer system (e.g., map expected AI validation activities and deliverables to the lifecycle phases of existing computerized systems and infrastructure development and validation procedures).

A GxP computerized system must be validated for its intended use. An AI model, as a component of a computerized system, should be validated as a sub-set process that links to, and complements the validation of the overall computerized system. Simply put, an AI model should be validated to meet its functional, regulatory and performance requirements in order to enable the overall computerized system to meet its overall user requirements and intended use.

The following are the high-level phases that cover the Validation of an AI model. See **Diagrams below** for an illustration of the process.

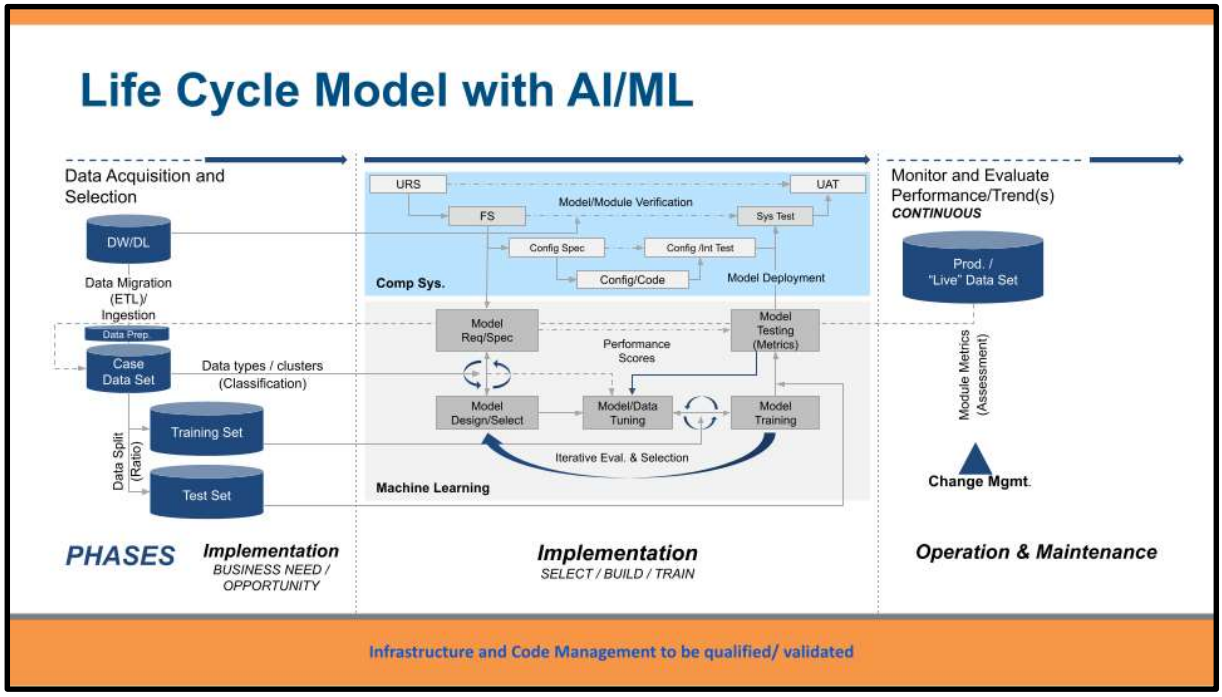

Figure 1: AI Validation Diagram Waterfall Model

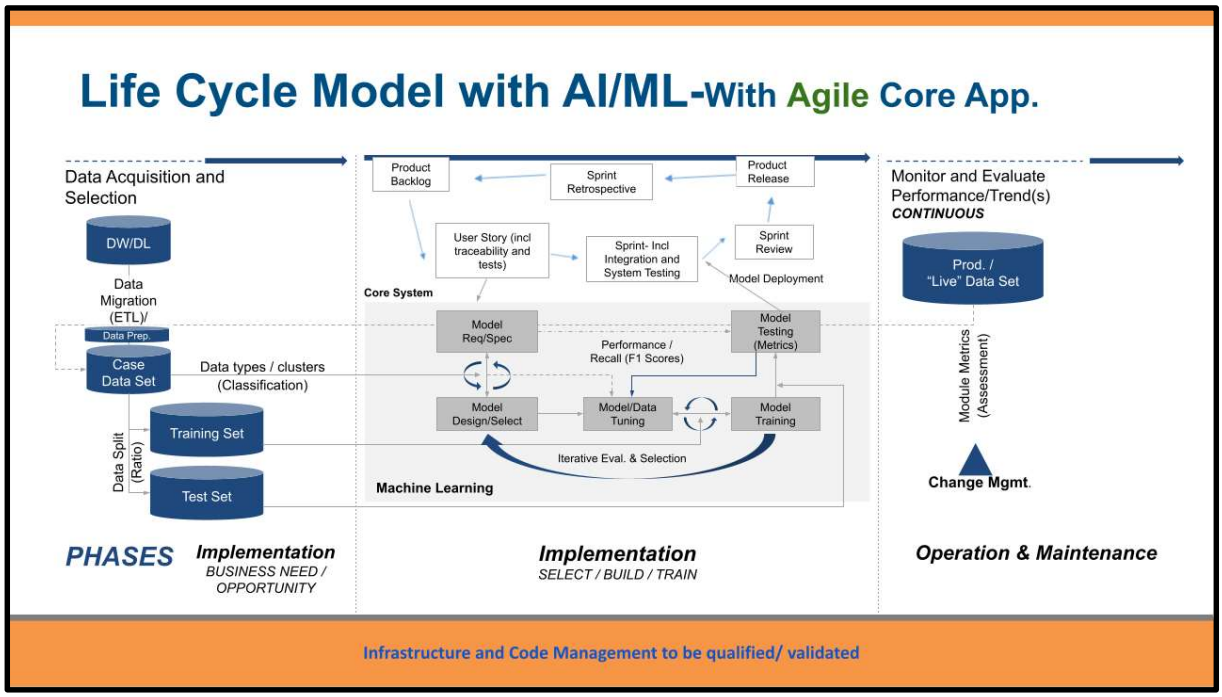

Figure 2: AI Validation Agile Model

4.1 Data Acquisition and Selection (Implementation Phase)

Unlike rules-based systems, the quality of outputs of AI models are largely based on the quality of the data used for ground truth development, model training and validation. Therefore, a Data Acquisition and Selection Strategy should be put in place for each AI Algorithm model.

Data Source(s) & Repository Identification (Data Warehouse (DW) and Data Lakes (DL)) / Extract, Transfer Load (ETL)
The sources of data and any associated qualifications should be adequately described. The infrastructure used for data collection, curation, storage and its level of qualification should be defined.

Data Selection

- Principles used for data identification and selection should be clearly documented.
- Sources of potential biases in the data should be identified and documented. Bias prevention steps should be implemented when possible.

Data Migration/Ingestion

- Data generation procedures should be described or referenced to demonstrate that the data was acquired in a consistent, clinically relevant and generalizable manner that aligns with the algorithm's intended use and modification plans.

Data Preparation - Labelling & Annotation (Characterization)

- The processes used to characterize, label or annotate data in preparation for Case Data Set creation should be described.

Case Data Set Preparation

- In order to validate the AI model two case data sets are required to be prepared:
  1. Training Data Set (Training and Tuning Test Sets).
  2. Test Data Set (Independent Test/ Validation Set for Performance Testing).
- Rationale for selection of the test sets used for validation should be documented.
- Appropriate separation between training and test datasets should be maintained.

4.2 AI Model (Implementation Phase)

Implementation steps include:

- Model requirements must be prospectively defined and documented in an approved specification prior to formal validation testing.
- Model training, tuning and design go through several Iterative Evaluation and Selection Cycles.
- The Testing process for the AI Algorithm should be prospectively documented in a Model Test Plan. A Model Testing Process should include Model Metrics of test results against pre-specified performance requirements:
- The Testing process results for the AI Algorithm should be documented in a Model Test Report.
- When the model has passed the Model Testing step, the Model is Deployed into the Production Environment of the Core Computer System.

4.3 Monitor and Evaluate Trends (Operations and Maintenance)

Operations and maintenance steps include:

- Once the model has been released for use, it is subject to Change Management processes in the same manner as any other validated system. A GxP compliance Change Management process must be followed for any changes or updates to the system.
- However, in addition, an appropriate set of key Model Metrics must be put in place to ensure that the model continues to perform as expected and does not drift out of its specification for use. These Model Metrics must be defined prior to release of the model.
- AI models must be continuously Monitored and Evaluated for Performance Trends. If any issues are identified, then appropriate action like raising a Deviation and / or Change Control must be taken as per local procedures.

4.4 Additional considerations

Data Protection
Data privacy and confidentiality principles must be applied to data control, processing and access, and must be based on the system and data risks identified during the project's risk management process.

Explainability
To the extent possible, it should be transparent how the model works and makes decisions, and this must be able to be understood by humans. An appropriate level of transparency should be in place to enable users to understand the software's output and use it appropriately. This may include disclosure of model limitations, where appropriate.

Human Oversight
Depending on the Intended use and risk profile of the AI application. An appropriate involvement by human beings must be ensured (e.g., "human in the loop" technical or procedural risk mitigations).

Options for human in the loop can take various forms, including:

- AI provides proposed output and human must review/edit/approve output.
- AI is autonomous but human can intervene.

Fully autonomous AI is not appropriate for high risk applications.

4.5 Risk analysis and data protection

In 2022, the UK Information Commissioner's Office (ICO) published a toolkit related to AI and data protection risk, which is based on the guidance on AI and data protection. The Toolkit is designed to provide practical support to organisations using AI systems which may involve the processing of personal data [48], and to identify and mitigate potential issues related to AI systems that are in line with privacy requirements. The Toolkit a good step towards compliance with the anticipated AI regulation of the EC, as well as the FDA action plan on *Artificial Intelligence/Machine Learning (AI)-Based Software as a Medical Device (SaMD)* [49].

The ICO Toolkit include potential risks in each of the AI Lifecycle Stages, which are:

- Business Requirements and Design
- Data acquisition and preparation
- Training and testing the AI system
- Deploying and monitoring the AI system
- Procurement

In each of the AI lifecycle stages the Toolkit presents several risk domain areas, each mapped with a risk statement. The Toolkit suggests steps for each risk statement and suggests organizations implementing AI systems identify the measures and actions taken to address each risk.

ICO emphasizes that the compliance based on the Toolkit does not replace the requirement to carry out a Data Protection Impact Assessment (DPIA).

5 Positions of this Task Force and Future Work

In this paper we presented the state-of-play in clinical research in terms of regulatory framework and use cases, as well as approaches for clinical evaluation of AI systems to mitigate risks related to patients' safety

and non-compliance of solutions. The concluding remarks and positions of the AI Task Force are summarized below:

- AI in clinical research can offer significant value, as systems can assist researchers or healthcare professionals to better diagnose and treat diseases, for sponsors and CRO's to better manage clinical research, or patients to follow digital clinical pathways that outperform the existing ones.
- The rise of the AI technologies and software as a medical device (SaMD) in the past years are significant for improving health outcomes, but also introduce new risks. This makes it necessary to clarify the regulatory framework, where patients' privacy, safety and performance are of great importance. Today, there are significant efforts underway worldwide to develop the appropriate regulatory framework with guidelines and toolkits. Regulators are actively soliciting input from industry and other stakeholders.
- Researchers and solution providers of AI systems are facing significant challenges and responsibility to ensure that their solutions are approved and certified by regulators. This report makes an attempt to provide initial advice for approaches to clinical evaluation and AI validation, however, these need to be elaborated as technology, applications and regulations evolve.

The Task Force will continue to monitor the adoption of AI in clinical research and healthcare industries and follow the regulatory framework evolution across the globe. Furthermore, the identified use cases will be compiled into a report that will assist the industry to better understand and deploy AI solutions.

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