



ICMRA

Informal Innovation Network

Horizon Scanning Assessment Report – Artificial Intelligence

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Disclaimer: This report reflects the outcome of an exercise based on hypothetical technology, and none of the content of the report should be taken as the regulatory thinking or position of any of the ICMRA members

EXECUTIVE SUMMARY

Background

New technologies are increasingly challenging regulatory frameworks. In response to this, the International Coalition of Medicines Regulatory Authorities (ICMRA) has set up an Informal Network for Innovation. This network seeks to adapt regulatory frameworks to facilitate safe and timely access to innovative medicines. As part of this, horizon scanning is being used to identify challenging topics and develop hypothetical case studies to stress-test existing regulatory frameworks and develop recommendations to adapt them. To date, ICMRA members have identified three such topics: 3D printing,¹ gene editing and artificial intelligence.

This report details the results of the horizon scanning exercise in Artificial Intelligence (AI), with relevance for regulators and stakeholders across the medicines development landscape. The Informal Network for Innovation working group members in this report were the Italian Medicines Agency (AIFA), the Danish Medicines Agency (DKMA), the European Medicines Agency (EMA) as working group lead, the USA's Food and Drug Administration (FDA) as an observer, Health Canada (HC), the Irish Health Products Regulatory Authority (HPRA), Swissmedic and the World Health Organisation (WHO).

AI in medicines development

AI technologies are increasingly applied in medicines development.² Opportunities to apply AI occur across all stages of a medicine's lifecycle: from target validation and identification of biomarkers, to annotation and analysis of clinical data in trials, pharmacovigilance and clinical use optimisation. This range of applications brings with it regulatory challenges, including the transparency of the algorithms themselves and their meaning, as well as the risks of AI failures and the wider impact these would have on its uptake in pharmaceutical development and ultimately on patients' health. To elucidate some of the challenges AI use poses for global medicines regulation, two hypothetical case studies were developed by ICMRA members. These examples were then used to 'stress test' the regulatory systems of ICMRA members to discover the areas where change may be needed. This report details the methods used and the findings, as summarised below.

Hypothetical case study 1: AI in clinical medicine development and use - A 'Central Nervous System App'

The CNS App's intended uses include the recording and analysis of baseline disease status and diagnosis (for selection of patients to be included in clinical trials), the monitoring of changes in disease status (as endpoints), adherence and response to therapies in both clinical trial settings and post-approval (for efficacy / effectiveness). It also provides personalised posology advice post-approval.

The role of regulators is linked to the context of use of the AI system and its software and algorithm(s). For many regulators this system could be regulated as a medical device in one of the higher risk classes. As with other medical devices, the input from medicinal product regulators would focus on the elements of the app that impact the benefit/risk of the medicinal product to be authorised and that impact the safety of subjects in clinical trials.

Due to the complexity and novelty of this case study, regulators would strongly encourage such products' developers to come for early advice. This advice would encompass the legal, regulatory, scientific and ethical aspects of the app and would involve collaboration with other stakeholders such as medical device regulators and academia.

¹ http://www.icmra.info/drupal/sites/default/files/2019-10/ICMRA_Innovation_WS3_3D_Bio-printing.pdf

² <https://doi.org/10.1038/s41573-019-0024-5>; <https://doi.org/10.21276/ijprhs.2018.02.01>

Clinical validation of the app, as part of its conformity assessment, would be needed for its uses, as described, which impact the benefit/risk of a medicinal product. This validation would require some level of understandability or explainability and may require access to the underlying algorithm and datasets by regulators. However, it may not be possible to fully validate the App with conventional approaches; more sophisticated approaches may be needed such as investigating machine behaviour (Rahwan et al. 2019).

Updates to the AI software or hardware would need re-testing or bridging studies to ensure reproducibility/validation. Any changes which affect the benefit/risk of the medicinal product may then require regulatory resubmission e.g. for a variation to the marketing authorisation. Testing is the responsibility of the developer to carry out. Ideally, the developer should have strengthened governance structures to oversee and understand the evolving algorithm and ensure continued data management, security and privacy.

Hypothetical case study: AI in pharmacovigilance

In principle, AI systems appear suitable for the detection of safety signals. The current signal detection and management tools have a heavy manual component that may be hard to sustain in the future, partly due to the growing data from increased ADR reporting worldwide. In implementing AI solutions, the challenge will lie in getting the balance right between AI and human oversight of signal detection and management, which may vary according to the risk of the medicinal product(s).

There is also potential for such AI use to discover safety signals that are more difficult to detect with current methods, such as drug-drug interactions, drug-disease interactions, medication errors, secondary malignancies, changes in frequency and severity of known events, patterns of use in medications, and misuse.

In applying this software, as per the case study, the marketing authorisation holder company would require specialist expertise in AI, data quality and pharmacovigilance signal detection to govern its use. If the AI is operated by a third party, there would need to be assurances that this third party doesn't renege on any of the responsibilities of the sponsor and that the tool could be inspected by regulators.

Software updates that affect the data will need to be communicated to regulators. The company would be responsible to assess the effectiveness of updates: such as new methods, new algorithms, new tools for signal detection. This would be subject to internal audits and regulatory inspections.

Key Recommendations

- Consider a permanent ICMRA working group, or a standing ICMRA agenda item on AI to share experiences of regulating AI use by developers, and best practices for its use within the Agencies themselves.
- Regulators may need to elaborate a risk-based approach to assessing and regulating AI, and this could be informed through exchange and collaboration in ICMRA. The scientific or clinical validation of AI use would require a sufficient level of understandability and regulatory access to the employed algorithms and underlying datasets. Legal and regulatory frameworks may need to be adapted to ensure such access options. In addition, limits to validation and predictability may have to be identified and tolerated when, for example, the AI is to learn, adapt or evolve autonomously (on each user's device, as in hypothetical case 1); such deployments would also be considered higher-risk AI uses.
- Regulators should bring together or engage with existing ethics committees' networks and AI expert groups, to collaborate on ethical issues of AI in medicines development, use and regulation.

- Sponsors, developers and pharmaceutical companies should establish strengthened governance structures to oversee algorithm(s) and AI deployments that are closely linked to the benefit/risk of a medicinal product, such as trial conduct automation or product use depending on individual data-based algorithms. A multi-disciplinary oversight committee should be in place during product development to understand and manage the implications of higher-risk AI. Health professionals should be involved early and be fully informed about how AI and algorithm(s) are monitoring patients and influencing their medicine use.
- Regulators should consider establishing the concept of a Qualified Person responsible for AI/algorithm(s) oversight compliance (similar to legally accountable natural persons for medical devices or pharmacovigilance).
- Regulatory guidelines for AI development and use with medicinal products should be developed in a number of areas, including data provenance, reliability, transparency and understandability, validity (construct, content, external etc.), development and use for pharmacovigilance purposes, real-world performance and monitoring.
- Regulators should support the international development and standardisation of good machine learning practices in the biomedical domain.
- In the EU, to address the rapid, unpredictable and potentially opaque nature of AI updates, the post-authorisation management of medicines, including the Variation framework, may need to be adapted to accommodate updates to AI software linked to a medicinal product. There may be an advantage to defining major vs minor updates, in a risk-based approach, for all digital tools that impact the quality, safety or efficacy of a medicinal product and thus linked to its benefits and risks.

Next steps

ICMRA hopes this report is useful for stakeholders across the medicines' development landscape. The implementation of recommendations will be discussed at the ICMRA. The ICMRA member regulatory authorities will be responsible for their approach to implementation.

1. INTRODUCTION

1.1 Network Background

New technologies are increasingly challenging regulatory frameworks. In response to this, the International Coalition of Medicines Regulatory Authorities (ICMRA) has set up an Informal Network for Innovation. This network seeks to adapt regulatory frameworks to facilitate safe and timely access to innovative medicines. As part of this, horizon scanning is being used to identify challenging topics and develop hypothetical case studies to stress-test existing regulatory frameworks and develop recommendations to adapt them. To date, ICMRA members have identified three such topics: 3D printing,¹ gene editing, and artificial intelligence (AI).

1.2 Topic choice rationale

The development and post-authorisation safety monitoring of medicines is subject to oversight by medicines regulators. The growing use of AI in medicines development and use, therefore, requires regulatory understanding at a minimum, and regulatory oversight where it is used in a regulated process. This requirement is made more challenging, as with any fast-developing field, by its changing shape and growing complexity. AI was therefore chosen by several ICMRA members as a topic for horizon scanning. This report uses two case studies to challenge member's regulatory systems and identify gaps in preparedness and recommendations for a future of greater AI use. The breadth of this topic should ensure a relevance beyond regulators, to stakeholders across the medicines' development landscape.

1.3 Artificial Intelligence

Artificial intelligence is a broad term to encompass iterative, 'learning' algorithms that utilise (big) data and high computing power to make interpretations, predictions or decisions in an autonomous or semi-autonomous fashion that could be seen to imitate intelligent behaviour. In general, it is the Artificial General Intelligence that captures the imagination (e.g. a robot with human-like intellectual abilities) but current real-life applications tend to be of Artificial Narrow Intelligence, with utility limited to specific tasks (e.g. self-driving cars, chatbots). AI systems can exist in software only (e.g. image analysis software, search engines, subject recognition systems) or can be embedded in hardware devices and interact with the physical world (e.g. robots, machines, sensor application). The diversity of methods and applications of AI means there is no single agreed standard and definition of AI at this time.³

Some of the prevalent methods used for AI systems are as follows:

- *Machine learning*: the computing method to 'learn' or derive rules or patterns without the latter being explicitly programmed. This can be supervised machine learning (ML) if it learns from data which includes correct answers, or unsupervised ML if it finds clusters of similar things, and reinforcement learning where the system learns through trial and error. An example is predictive text in a phone: the phone comes pre-programmed with a set of rules but learns new ones as the user writes the same words repeatedly over time.
- *Deep learning*: considered a subset of machine learning where algorithms tend to transform data over a series of steps (aka layers). For instance, in computer vision an initial transformation of a picture is often edge detection (using matrix convolutions) to find boundaries of different brightness within a picture to facilitate the subsequent identification of shapes.

³ The High-Level Expert Group on AI of the EC recognised that a specific definition for AI should be agreed in order to offer certainty in relation to what is considered within the scope of policymaking and monitoring. Moreover, ISO/IEC JTC 1/SC 42, the technical sub-committee responsible of standardization in the area of AI, is currently working on the standard ISO/IEC 22989 'Artificial intelligence - Concepts and terminology'.

- *Natural language processing*: applications to analyse, represent or generate human language. Computational techniques include rule-based or symbolic approaches (i.e. exact string search) or statistical methods (i.e. machine learning models).
- *Robotic Process Automation (RPA)*: these are software tools that automate a specific procedure and are used to reduce human intervention in purely rule-based processes e.g. issuing receipts at the end of each month and archiving them. RPAs can be unassisted or assisted. Assisted RPAs are the traditional systems where a specific set of rules is set. Unassisted RPAs use AI to go beyond the setting of rules.

1.3.1 AI in medicines development and use

In medicines development, the application of artificial intelligence features occurs throughout the development ecosystem, across stakeholders and along the entire lifecycle of a medicine (Vamathevan et al. 2019):

- *Target profile identification and validation*: using AI to associate genotypes with disease, predicting chemical interactions and therefore 'drugability' of targets (such as for COVID-19).
- *Compound screening and lead identification*: Compound design to achieve desirable properties and its synthesis reaction plans.
- *Preclinical development*: Biomarker identification, response biosignatures.
- *Clinical development*: Digital endpoints, determination of cellular microenvironment and response through cellular phenotyping and analysis of digital pathology and even clinical data in clinical trials to providing decision support systems to investigators.
- *Regulatory application*: Regulatory intelligence and dossier preparation – extracting data and pre-filling forms.
- *Post marketing requirements*: AI to extract and process adverse event reports (Schmider et al. 2019).

The variety of use cases for AI in the public and private sector is growing quickly (e.g., Broadband Commission Working Group on Digital and AI in Health - Reimagining Global Health through Artificial Intelligence 2020). New advisory, consultancy and ethical groups on AI are being established, and AI is already being considered more for its implementation than as a hypothetical tool (High-level expert group on artificial intelligence set up by the European Commission 2020a).

However, important limitations for AI in health have emerged such as algorithmic social bias leading to discrimination and misguided learning using incorrect features or inappropriate datasets (Zech 2018, Agniel, Kohane, and Weber 2018). These pose serious risks for patients when using AI in health scenarios. In addition, the unpredictable "self-learning" of AI systems results in uncertainty about the outputs and prevents their comprehensive description. To address ethical considerations, the WHO issued the first global report on Artificial Intelligence (AI) in health and six guiding principles for its design and use.⁴

Artificial intelligence is slowly arriving in home-use, industrial as well as medical devices, and autonomous AI systems (that is, those not connecting to central computing servers over networks) are to be expected. One of the case studies therefore addressed the additional regulatory challenges of person-specific AI.

⁴ <https://www.who.int/publications/i/item/9789240029200>

1.4 Member agency activities for AI

In this section, some of the ICMRA member agencies in the working group outlined their plans and activities that concern AI.

1.4.1 Health Canada

Ongoing regulatory science initiatives for AI include:

- Established a Digital Health Division in 2018 to add additional technical capacity in the safety assessments of software as a medical device including AI/ML medical devices
- Extensive engagement campaigns across Canada with various academic and industry stakeholders
- Active member of the WHO/ITU AI4HEALTH Focus Group
- Collaboration with other federal partners within the Government of Canada
- Active members on the IMDRF AI Medical Device Working Group and
- Convened a Scientific Advisory Committee in Digital Health

Health Canada is also developing its first guidance to industry on 'locked' AI/ML-enabled medical devices. In addition, given their unique regulatory challenges, AI/ML enabled medical devices are being considered as a candidate for Canada's Advanced Therapeutic Product Pathway⁵

Health Canada recognizes the potential benefits of AI in increasing efficiency of signal detection and is aware that Marketed Authorisation Holders (MAHs) are exploring how to do this. Launched initiatives include:

- Conducting a survey to all MHAs on the current and potential use of AI within their pharmacovigilance system with the objective of developing a guidance document for Good Pharmacovigilance Practices (GVP)
- Using the AI tool for the detection of health products making false and/or misleading advertising claims online

Initiatives under consideration include:

- Developing a data training set for use to train machine-learning algorithms
- Exploring and establishing data governance
- Innovation project to explore annotation of scientific literature for pharmacovigilance and environmental and radiation health sciences, pending approval
- Seeking collaborations with international partners on future AI tool development and beta-testing of AI tools

1.4.2 Japan MHLW/PMDA

Ongoing regulatory science initiatives for AI regarding medical devices include:

- Published a recommendation to summarize the challenges of diagnostic systems and medical devices which utilise AI⁶
- Active member of the WHO/ITU AI4HEALTH Focus Group
- Active member of the IMDRF AI Medical Device Working Group and
- Considering a future regulatory review of software as a medical device, which include those utilizing AI.

⁵ <https://www.canada.ca/en/health-canada/corporate/about-health-canada/legislation-guidelines/acts-regulations/targeted-regulatory-reviews/health-biosciences-sector-regulatory-review/policy-program-initiatives-novel-regulatory-approaches.html>

⁶ https://www.jstage.jst.go.jp/article/abe/7/0/7_7_118/_pdf/-char/en

1.4.3 EU

Over the last five years, European Union institutions have become increasingly active on AI and Big Data. The European Parliament is in the process of advancing legislative initiatives on ethical aspects of artificial intelligence.⁷

The EMA's Regulatory Science Strategy to 2025⁸ and Big Data Task Force⁹ have a number of relevant recommendations, including the following.

Regulatory Science Strategy to 2025:

- Establish a digital innovation lab to explore, pilot and develop solutions and processes, across the drug regulation spectrum, that leverage novel digital technology and artificial intelligence to support an increase in efficiency and regulatory decision-making;
- Develop capacity and expertise across the regulatory network through curriculum development and knowledge-sharing initiatives on data science, digital technologies and artificial intelligence- related solutions, products and endpoints, and their applications in the regulatory system;
- Create and maintain a Health Data Science and AI forum to engage with a diverse set of stakeholders in novel digital technologies and artificial intelligence. This will include the technical, ethical, legal, regulatory and scientific perspectives of the use of digital technologies, and AI-powered applications;
- Establish a dedicated framework for the development of guidelines and recommendations. The framework should address which guidelines are a priority, how the guidelines should be developed, and which areas might be impacted, as well as the acceptability metrics or success factors;
- Engage in efforts (e.g. via standardisation activities) for achieving greater global alignment with other regulators (e.g. FDA) on these topics;

The EU Heads of Medicines Agencies (HMA)/EMA Big Data Task Force:

- Develop a Big Data training curriculum and strategy based on a skills analysis across the Network, collaborate with external experts including academia, and target recruitment of data scientists, omics specialists, biostatisticians, epidemiologists, and experts in advanced analytics and AI;
- Strengthen the Network ability to validate AI algorithms;

In 2020, the EMA conducted workshops to learn about and address AI in the context of clinical trials¹⁰ and data exchange in the context of the EU's General Data Protection Regulation (GDPR). These are part of the EMA and HMA Big Data Steering Group workplan¹¹

The European medicines agencies network strategy to 2025¹² will underpin these recommendations, and EMA itself recently underwent a restructuring, including the creation of two task forces to enhance its capability in digital technologies and data analytics, including AI¹³.

⁷ [https://oeil.secure.europarl.europa.eu/oeil/popups/ficheprocedure.do?reference=2020/2012\(INL\)&l=en.\]](https://oeil.secure.europarl.europa.eu/oeil/popups/ficheprocedure.do?reference=2020/2012(INL)&l=en.)

⁸ https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/ema-regulatory-science-2025-strategic-reflection_en.pdf

⁹ https://www.ema.europa.eu/en/documents/other/hma-ema-joint-big-data-taskforce-phase-ii-report-evolving-data-driven-regulation_en.pdf

¹⁰ EMA- GCP IWG virtual meeting "Artificial intelligence in clinical trials – ensuring it is fit for purpose" held on 22 Sep 2020

¹¹ https://www.ema.europa.eu/en/documents/work-programme/workplan-hma/ema-joint-big-data-steering-group_en.pdf

¹² https://www.ema.europa.eu/documents/report/european-union-medicines-agencies-network-strategy-2025-protecting-public-health-time-rapid-change_en.pdf

¹³ <https://www.ema.europa.eu/en/about-us/who-we-are/task-forces>

At the European level, the Commission has recently introduced a legislative proposal for a Regulation on Artificial Intelligence (Artificial Intelligence Act) with harmonised rules for the development, placement on the market and use of AI systems in the Union following a proportionate risk-based approach.¹⁴

A High-level expert group (HLEG) on AI has been established by the European Commission to provide advice including on ethical aspects (High-level expert group on artificial intelligence set up by the European Commission 2019). Their ethics guideline aims at trustworthy AI, with human oversight as a constituent element (European Commission 2020b). However, human oversight may not always be realistic for a variety of reasons: knowledge in AI is lacking, AI would become inefficient or "slowed down" by humans, or AI systems could outpace human experience. Additionally, human oversight may not always address the root causes of concern e.g. unfairness through inherent bias re-enforcement (see below). In fact, the guideline already concedes that proper human oversight may be impossible and that the alternative "*can include the decision not to use an AI system in a particular situation, to establish levels of human discretion during the use of the system, or to ensure the ability to override a decision made by a system*". Accordingly, in certain situations, regulators must consider the question of necessity and alternatives to AI systems. Concerns about AI noted by the European Commission are that "*the use of AI can affect the values on which the EU is founded and lead to breaches of fundamental rights, including the rights to freedom of expression, freedom of assembly, human dignity, non-discrimination based on sex, racial or ethnic origin, religion or belief, disability, age or sexual orientation, as applicable in certain domains, protection of personal data and private life, or the right to an effective judicial remedy and a fair trial, as well as consumer protection. These risks might result from flaws in the overall design of AI systems (including as regards human oversight) or from the use of data without correcting possible bias (e.g. the system is trained using only or mainly data from men leading to suboptimal results in relation to women)*." (European Commission 2020b).

Regulators will need to address these concerns to be able to require and evaluate any evolving mitigation strategies.

1.4.4 Swissmedic

Swissmedic has launched the digital initiative, 'Swissmedic 4.0', to explore the possibilities of the digital transformation in depth and as a priority. It is an agile, well-resourced and independent unit within Swissmedic. The initiative will ensure that Swissmedic has the resources to tackle the challenges of digital transformation in a comprehensive and sustainable approach, regardless of the limitations imposed by daily business. Technical and process questions arising from other areas of the organisation will be received, analysed and processed and the resulting solutions fed back into the organisation. The initiative will learn from these solutions and improve. This will allow Swissmedic to actively engage with the digital transformation as an opportunity rather than allowing it to pass by.

AI to detect safety signals

Yearly, about 200 clinical trials are approved by Swissmedic. There are over one million new biomedical scientific publications per year. To better accomplish the mission to monitor the safety of investigative clinical products, Swissmedic was looking for new methods to support this task. To this end, Swissmedic started a pilot project using machine learning and natural language processing techniques to verify their suitability. Several open-source publications were screened using five investigational medicinal substances on a retrospective basis. Different cloud tags were built: 1) investigational medicinal substance, 2) indication and 3) adverse events. The information

¹⁴ <https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX%3A52021PC0206>

obtained by checking the publications was filtered and ranked by relevance so that an appropriate number of results were finally communicated to the human reviewer.

To assess the suitability of the system, the results obtained from the machine search were compared to a manual search by a human reviewer. All the hits identified manually were also identified by the machine. Out of 24 relevant hits identified by the machine, the human reviewer only identified seven of them through active search, and one through passive monitoring. In three cases out of the five, the human reviewer could not find the relevant machine-detected hits through active search. The results obtained by the machine, were evaluated by the human reviewer in terms of relevance. 100% of the hits identified by the machine were considered relevant. The human reviewer needed approximately 2.5h to perform the active monitoring whereas the machine needed 10 min to detect and review relevant hits.

In conclusion, in our pilot project, it was shown that machine learning techniques are very likely appropriate in terms of time saving and reliability to detect safety signals in investigational medicinal products. Swissmedic 4.0 developed such a literature search application first for the needs of one department, with the long-term goal of making the application available across multiple departments. The project served as a reference for the hypothetical case study 'AI and pharmacovigilance' in this report.

Furthermore, Swissmedic is pursuing three additional objectives with this project. Firstly, the potential of artificial intelligence can be demonstrated on a relevant use case and the opportunities and risks of AI can be explored. Secondly, the know-how for designing, implementing and maintaining AI solutions will be built up in the responsible departments such as Swissmedic 4.0 and IT. In addition, first experiences with relevant algorithms (i.e. BioBERT), concepts (i.e. containerization), services and infrastructure (i.e. AWS) will be gathered.

Further initiatives

This experience is directly incorporated into further AI implementation currently under investigation by the Swissmedic 4.0 team, such as automated request-response. With an automated Q&A tool for classifying emails and a chat function, Swissmedic hopes to gain valuable knowledge and experience with regard to neurolinguistics programming (NLP) methods on the one hand, and to relieve our communications department by filtering and channelling audience enquiries on the other.

The Swissmedic 4.0 team is convinced that Swissmedic's various organisational units can benefit enormously from the opportunities offered by AI. Further use cases lie, for example, in the processing of applications or in the preparation and consolidation of assessment reports. For this reason, Swissmedic 4.0 continually conducts ideation workshops in order to identify further potential within the organisation. The aim is not to become more efficient at any price. Instead, the aim is to delegate standardised and repetitive processes to machines, so that the specialists can focus on knowledge work.

1.4.5 Therapeutic Goods Administration (TGA), Australia

The Therapeutic Goods Administration's initiatives for AI include:

- Active members on the IMDRF AI Medical Device Working Group
- Active representation on the Standards Australia AI Committee (IT-043) and
- Established a specialized unit in the TGA to increase capacity in assessing and monitoring software-based medical devices, including those that utilize AI.

The TGA has also recently implemented reforms to the regulation of software-based medical devices, including software that functions as a medical device in its own right. Australia's regulation of software-based medical devices is based on the approach of the IMDRF and broadly aligned with other international regulators.

2. METHODS

The ICMRA AI working group members were asked to design hypothetical case studies for AI, which would challenge their regulatory system. The working group members were the Italian Medicines Agency (AIFA), the Danish Medicines Agency (DKMA), the European Medicines Agency as working group lead (EMA), the USA's Food and Drug Administration (FDA) as an observer, Health Canada (HC), the Irish Health Products Regulatory Authority (HPRA), Swissmedic and the World Health Organisation (WHO). These case studies were then reviewed and amended by the group and two were chosen for this report: a 'Central Nervous System App' and 'Pharmacovigilance Signal Management' which both utilise AI (see below).

Four regulators conducted one of the hypothetical case studies that are covered in this report (AIFA, EMA, HPRA and Swissmedic). These regulators held internal discussions to explore challenges and elucidate the regulatory considerations that each case study posed. These case studies were kept broad for the purpose of this exploration. This approach was guided by the discussion template (see Annex B), which were also used to summarize the findings. These findings were then shared with the working group and summarised in a draft report. This draft report was then peer-reviewed amongst all working group members to produce this report. Where required, the information in this report was supplemented with literature (grey and academic).

2.1 Case study: AI in clinical medicine development and use - A 'Central Nervous System App'

Indication: Neurodegenerative disorder e.g. Parkinson's or Alzheimer's

Medical need: Apps could have an advantage over occasional Healthcare professional (HCP) monitoring by offering an insight on subtle changes in prodromal patients, allowing either recruitment of pre-symptomatic patients or monitoring of effect of disease-modifying medicines.

Description: A Central Nervous System (CNS) smart phone App which measures a variety of neurological variables to replicate and build upon existing gold-standard diagnostic tools e.g. speed, movement, memory etc. It is also linked to electronic health records. Using this data, it applies artificial intelligence and Bayesian statistics, to look for associations between the variables, disease progression and treatment.

A hypothetical company wishes to use it in clinical trials to select patients with prodromal symptoms and to monitor their progression. Post-approval, the company wishes to use it over the long-term to constantly monitor effectiveness, adherence and response. They hope this will allow dose adjustments and the demonstration of effectiveness (and therefore value). The App will regularly update, suggesting improved dosing regimes, improved testing methods and more robust measures of benefit/risk.

Use of artificial intelligence: It will use neural networks to build correlations between a range of neurological measures, treatments, patient characteristics and health records. This should serve to improve its diagnostic, prognostic and treatment advice.

2.2 Case study: Pharmacovigilance Signal Management

Indication: N/A

Medical need: N/A

Description: Industry and regulators are planning on using AI to deliver and process regulatory data. One area is pharmacovigilance, where certain regulators and companies are trialling AI to process pharmacovigilance data from literature and signals (see 'Member agency activities for AI')

for Swissmedic's pilot use of AI). Other areas include using real-world data on drug-drug or drug-disease interactions, post-approval efficacy etc.

A hypothetical pharmaceutical company has requested that it fulfils its pharmacovigilance obligations via an AI system, screening both literature and signals. The company has said that if it isn't allowed to use this system, they will have to withdraw the product from the market due to cost considerations.

Use of artificial intelligence: The machine learning methods (including natural language processing) in the hypothetical AI are trained by pharmacovigilance specialists using a large existing bibliographic and signal training dataset.

A dictionary of signal search terms was built from tag clouds for 1) investigational medicinal substances, 2) indications and 3) adverse events. The information is obtained by the software through checking publications and signals, which were filtered and ranked by relevance. A series of comparison studies were done between the results obtained through manual vs machine search. The machine had 100% sensitivity and routinely identified >4 times the number of relevant signals.

The machine learning algorithms have been tested with several further datasets exhibiting a similar sensitivity and specificity, beyond what the company, and literature, suggests human screening results in.

3. RESULTS

The results of elucidating the regulatory challenges and use classifications with the hypothetical case studies are separated into sections according to the region or regulator which they apply to or derive from.

3.1 Case study: AI in clinical medicine development and use - 'Central Nervous System App'

3.1.1 Product classification

Health Canada

Classification would likely be determined by the Guidance Document: 'Software as a Medical Device (SaMD): Definition and Classification'¹⁵ and may be as high as class III or IV in Canada, depending on whether it provides closed-loop dosing information.

Japan MHLW/PMDA

Classification would be based on Global Harmonization Task Force classification rules¹⁶ and would currently be class II or III in Japan. In addition, the Japanese Medical Device Nomenclature (JMDN) will be applied for the purpose of classification of the device.¹⁷

EU

In the EU based on its intended use, this App would be classified as a medical device and fall under rule 11 of the Annexes to the recent EU regulation (EU) No 745/2017¹⁸ on Medical Devices. It would be classified into one of the higher risk classes (class IIa or higher). However, rule 11 ("Software intended to provide information which is used to take decisions with diagnosis or therapeutic purposes") may not fully capture features and uses of AI, for example, when deployed onto a patient's device to direct the patient to change their medication or behaviour, without any healthcare professional interaction. This example shows how blurred the distinction between providing information and influencing decisions can become. In fact, a patient's autonomy could be compromised in this situation because of the continual exposure to a device that records and instantaneously reacts, and that becomes a fixed part of the patient's decision-making. Patients with impaired cognitive function may be particularly susceptible to such signals and could also be particularly unpredictable in their reactions; this may be difficult to anticipate when designing the App and may "confuse" the AI. Furthermore, it is possible that the AI in this case example would be classified as a class III device because it could lead to the situation that "*such decisions have an impact that may cause: — death or an irreversible deterioration of a person's state of health*" given the progressive nature of the neurological disease, or class IIb if it may cause a serious deterioration.

The case example also shows the limitations of the definitions in rule 11 with AI outputs to the patient that are not merely information but instructions, and the potential consequences of reinforcing an erroneous signal detrimental to the patient such as promoting exhausting physical or mental activity.

AI, particularly that which is permitted to continually evolve in situ, is also not predictable and cannot be fully described once a self-learning process has started (in contrast to "closed systems")

¹⁵ <https://www.canada.ca/en/health-canada/services/drugs-health-products/medical-devices/application-information/guidance-documents/software-medical-device-guidance-document.html>

¹⁶ <http://www.imdrf.org/docs/ghtf/final/sg1/technical-docs/ghtf-sg1-n77-2012-principles-medical-devices-classification-121102.pdf>

¹⁷ https://www.std.pmda.go.jp/stdDB/Data_en/InfData/Infetc/JMDN_en.pdf

¹⁸ <https://eur-lex.europa.eu/eli/reg/2017/745/oj>

as referenced in some guidance). This is because self-learning involves processing a continual stream of unique input data leading to iterative and incremental changes to the AI. In certain situations, this phenomenon is described with reference to the ‘butterfly effect’, where minuscule inputs can have a huge impact. Research to improve the understandability of AI is developing toward investigating and documenting behaviours of such systems (Rahwan et al. 2019).

For these reasons, the classification of software needs to be further evolved. The EC Classification and Borderline Expert and New & Emerging Technologies Group¹⁹ gives support in this classification process, and guidance on qualification and classification of software is available from the Medical Device Coordination Group (MDCG);²⁰ however, this does not yet cover AI.²¹ Further guidance has been published by the MDCG on cybersecurity and clinical evaluation, covering Medical Device Software (MDSW) yet not specifically AI or machine learning.²² This guidance refers, in turn, to the International Medical Device Regulators Forum (IDMRF) which covers personalised medical devices but has not yet introduced guidance on AI as in this case study.²³

Under the existing EU Medical Devices Directive, many software applications are Class I. Under Regulation (EU) No 2017/745 (MDR), the majority will undergo classification as indicated above and as such will require medical device authority oversight and notified body assessment prior to CE marking and placing on the market.

Medical device authorities are responsible for the clinical investigation and post-marketing surveillance, and notified bodies are responsible for pre-marketing assessment. Medical devices that are not used in association with medicinal products fall outside the remit of some medicinal product regulators, e.g. AIFA and EMA. However, as this software would impact the benefit/risk of a medicinal product, there would be a shared responsibility between medicinal product regulators, medical device authorities and notified bodies.

Therapeutic Goods Administration (TGA) - Australia

This product would meet the definition of a medical device under the *Therapeutic Goods Act 1989*. The risk classification would be determined as per the classification rules specified in the Therapeutic Goods (Medical Devices) Regulations 2002, and would currently be classified as IIa or higher, depending on the intended users of the device, and the nature of the diagnostic or treatment information provided.

Health Sciences Authority (HAS) – Singapore

This product would be classified as a Class B or C medical device, the risk class would be C if the app is used for a critical or very serious condition.

3.1.2 Early advice

The CNS App’s intended uses include the recording and analysis of baseline disease status and diagnosis for selection of patients to be included in clinical trials, the monitoring of changes in disease status for use as a clinical endpoint, and adherence and response to therapies in both the clinical trial settings and post-marketing (effectiveness), as well as personalised posology adjustments. In order to serve all these uses, the CNS App should be able to reliably and reproducibly record and monitor disease status independently of the user, device, disease stage, and treatment.

¹⁹

<https://ec.europa.eu/transparency/regexpert/index.cfm?do=groupDetail.groupDetail&groupID=1306&news=1>

²⁰ <https://ec.europa.eu/docsroom/documents/37581>

²¹ https://ec.europa.eu/health/sites/health/files/md_topics-interest/docs/md_mdq_2019_11_guidance_en.pdf

²² https://ec.europa.eu/health/md_sector/new_regulations/guidance_en#sec6

²³ <http://www.imdrf.org/documents/documents.asp>

Due to the complexity and novelty of this case study, medicinal product regulators strongly encourage such products to come for early advice. This advice would encompass the legal, regulatory and scientific aspects of the App and could involve collaboration with medical device regulators and academia. Regulators may also encourage early interactions by proactively reaching out to such developers when they are made aware of them through horizon scanning or pipeline activities.

EU

At EMA, early dialogue and procedural advice is mainly provided by the Innovation Task Force (ITF) and the SME office. In this case study, these would likely provide an initial orientation and then advocate for further Scientific Advice by the Scientific Advice Working Party (SAWP), and to validate the App for use as a diagnostic and endpoint through Qualification Advice by SAWP. Due to the data-heavy development, EMA may suggest that the developer seeks a collaborative development with other stakeholders to ensure the data are fully utilised.

National competent authorities can provide early stage advice via their innovation offices, and those that also have medical devices within their remit may offer specific advice related to medical devices, particularly in relation to the expectations for the clinical evaluation of medical device software.

The App developer would need to ensure that the software adheres to data and data protection regulations i.e. GDPR²⁴ (Regulation (EU) No 2016/679) and national data protection laws (Coravos et al. 2020).

3.1.3 Clinical development

There is a need to distinguish between clinical studies for medical device conformity assessment of the App and regulatory validation, and the clinical trials required for the development of a medicinal product with which the App is to be used. In the former case, such a study would be for validating the app's performance as a diagnostic, as a trial endpoint, as a measure of individual efficacy and for posology adjustment, respectively; for example, if the App were validated for posology adjustment, it could then be used in the safety and efficacy clinical trial of the medicinal product.

Harmonisation of clinical trial requirements across countries and regions for such challenging technologies would be promoted through the International Medical Device Regulators Forum.

EU

As the App would be a medical device, any clinical performance studies for the App's conformity assessment are subject to oversight by device authorities. Their assessment of all conformity requirements of the app would confer a CE mark for the specific context of use, without the involvement of medicines regulators.

Authorisation of clinical trials for an investigational medicinal product is given by the medicines regulators and ethics committees within the EU Member States in which the sponsor wishes to conduct the trial. To coordinate authorisation across Member States, the Clinical Trial Facilitation and Coordination Group (CTFG)²⁵ operates. Advice on the requirements for clinical trials can be provided for the medicinal product and the device (as far as its use for the development or monitoring of the medicinal product is concerned) through national or EU-level (EMA) scientific

²⁴ https://edps.europa.eu/press-publications/press-news/blog/artificial-intelligence-data-and-our-values-path-eus-digital_en,

https://edps.europa.eu/data-protection/our-work/publications/opinions/edps-opinion-european-commissions-white-paper_en

²⁵ <https://www.hma.eu/ctfg.html>

advice²⁶ (see next section) prior to seeking clinical trial authorisation. Where there is a co-development of a medicinal product and medical device, experts responsible for medicinal products and medical devices can be involved in the advice.

If the App is not CE marked at the time of the medicine's clinical trial application, device authorities would also be involved in the clinical trial application review and would typically request supporting evidence. The regulatory authorities approving the clinical trials would also need to see validation data for the App, and regulatory scientific or qualification advice would be advised to clarify minimum requirements. This would be best done in coordination with medical device authorities and if applicable, notified bodies, though their involvement in the regulatory qualification and advice is not mandatory. Meeting the requirements for both CE marking and regulatory qualification could run in parallel. If the App was already CE marked for the specific context of use, then regulatory qualification may require less input from device regulators.

If developers brought the medicinal product *and* medical device for joint scientific advice on the clinical development plan for the combined use, EMA and NCAs responsible for medicinal products and medical devices may provide input into the clinical development across several areas relevant to its use of AI:

- the feasibility of traditional clinical trials or the necessity to apply new trial design
- the case for the App's added value vs standard diagnostic and endpoint measures
- the definition of outcomes, endpoints, comparator, defined exposure (dose) and relationships between exposure and response
- AI-driven adaptations to posology across patient sub-populations within the trial, and to the diagnostic measures. These adaptions would require pre-specification of start and stop signals/parameters/statistics, as well as methodological considerations with respect to generating and confirming hypotheses linked to the adaptations
- ensuring the trial design and conduct is following GCP and that data capture, management, monitoring and ownership are clarified
- an additional multi-disciplinary oversight committee may be requested to understand the evolving algorithm and the complex clinical trial (CT) development – adding expertise to the Data and Safety Monitoring Board where one is set up
- CNS diseases also affect the paediatric population, and the development and assessment of the CNS App targeting this population deserves special attention.

3.1.4 Scientific advice

EU and Health Canada

Scientific advice (SA) can be sought from regulators. To advise on the utility of the AI approach and the validity of AI-generated data for the development of a medicinal product, elements such as the following would need to be evaluated by the regulators: the algorithm(s) with its inputs (data), its parameters, outputs and counterfactuals (what could have happened had inputs been changed in a particular way).

If there were a trade-off between increasing the understandability of the algorithm and increasing its effectiveness, regulators in the EU and Health Canada would make this trade-off on a case by case basis. For example, a highly complex and non-transparent algorithm may seem more effective than a simpler, more transparent one, but may also have certain unacceptable bias with it. A request may therefore be made to the developer to systematically consider the effects of bias

²⁶ https://www.ema.europa.eu/en/documents/other/questions-answers-qualification-digital-technology-based-methodologies-support-approval-medicinal_en.pdf

within the algorithm and to make them transparent. As the algorithm evolves, regulators may wish to see updated explanations of the new algorithm.

EU

During Scientific advice (SA) from regulators, applicants may also invite notified bodies to accompany them through this procedure. Currently, there is no EMA scientific guideline that covers specific AI issues such as those flagged in this case study and this is not on any work plan of any EMA scientific committee. Scientific publications by regulators address relevant topics such as on data models and quality (Cave, Kurz, and Arlett 2019) and general methodological approaches (Eichler et al. 2019).

In general, novel endpoints are encouraged to come for SA qualification and new diagnostics can be CE marked and/or qualified by EMA. During this qualification, EMA would likely request the algorithm for scrutiny and EMA would apply a risk-based approach to the level of understandability required of the algorithm. In this case study, a high level of understandability of the algorithm would be required, and the key assumptions and operating characteristics of the algorithm would need to be transparent.

Validity: the above understandability would be required in order to assess the construct and content validity. Patient and HCP input would also be required to define 'best practice' methods for the app's use.

Parameters or margins are to be established for maintaining validity and reliability which, if compromised by updates during development and post-approval, would require reporting and could lead to a resubmission request. This is akin to quality by design in manufacturing, and at the beginning, as experience is limited, these parameters/margins may have to be very tight. Other changes to the app would likely be viewed under this risk-based approach: impact on the data capture and processing capability, changes to the app ownership and the context of use.

In the development phase, changes to the pivotal or supportive nature of the data are important in evaluating the degree of risk and need to be evaluated appropriately. Information on the data management, performance management, evaluation protocols and update procedures may be required (Cerreta et al. 2020). An expansion or a change of data inputs with additional variables e.g. through new Electronic Health Records would require (re)qualification of the data for the software.

Qualification could include considerations on patient usability, minimising patient burden and increasing adherence. The advice may also suggest the inclusion of quality of life, patient-reported outcomes and physician-reported outcomes.

Seeking informed consent by users of this app in the context of a clinical trial (and seeking agreement of users of the app in medical care) may be challenging due to the complexities in its operations, in data ownership, in data sharing and in impact on patient management. In any case, data collected and used in the app should be proportionate and relevant. The app development must also safeguard data confidentiality. Planned uses of the data need to be made clear to the patient for a valid informed consent process.

In addition to EMA SA, or national SA, the product developer could request 'Simultaneous National Scientific Advice'²⁷ which is a pilot project of EMA-HMA European Union Innovation Network (EU-IN). This may be of interest, for example, for questions that concern national measures under the

²⁷ <https://www.ema.europa.eu/en/human-regulatory/research-development/innovation-medicines#eu-innovation-network-section>

GDPR (noting regulators cannot provide legal advice) or that concern the inter-operation of the CNS App with the national health care systems and their data.

Parallel consultations of EMA SA and Health Technology Assessment (HTA) bodies should also be encouraged so that the app addresses the evidence needs of the HTA bodies.

AIFA

Scientific advice should ensure clear data provenance, ensuring data sources are authenticated to contribute or receive data and associated metadata. Moreover, attention should be dedicated to the external validation process.

To ensure reliability, quality assurance is needed for how the system manages missing data and error detection. Particular attention should be given to integrity of the data and to the process of data acquisition. The system should guarantee the lineage and flow of data, chain of custody, tracking of any modification, ability to detect any anomalies in the data and access to summary data and analysis (Adamo et al. 2020).

3.1.5 Assessment for marketing authorisation

EU

In the EU, it is expected that hardware, firmware and software of this medical device used closely with a medicinal product would fall within the oversight of both EMA and medical device authorities/notified bodies, and so dialogue between authorities will be necessary.

Hardware

The hardware running the software may come under regulatory remit depending on the intended use specified by the manufacturer. General purpose equipment, such as laptops etc., do not fall under medical devices legislation. However, there is a requirement that software as a medical device, which is intended to be operated with other products, must be designed in such a way that the interoperability and compatibility with other hardware is reliable and safe (MDR, Annex I). Similarly, regulators would like to keep the hardware as non-proprietary.

In the context of the validation of the CNS app, the hardware capabilities (e.g. sensors such as accelerometers and GPS) and the operating system (e.g. how the APIs are exposing data) will also need to be assessed, for example with respect to the frequency and precision of their measurements in the data streams. In this example, where a general-purpose smartphone is being used, the medicine's label may indicate which smartphone or specifications this device has been approved for use with. Should the developer wish to change hardware, bridging evidence may be required across hardware (smartphones) but this assessment will be risk-based.

Firmware

EMA

Changes in firmware may need to be included into hardware bridging studies (as above). Performance parameters for the acceptability of firmware changes may have to be pre-agreed. If these parameters are breached, it may require revalidation. Firmware updates may need a revalidation regardless.

Software

EMA

As the App would be included in the label associated with the benefit/risk of a medicinal product(s), the software considerations would be the same as addressed in regulatory validation (qualification) during scientific advice. Where possible, regulators would like to keep the software as non-proprietary and open. Guaranteed access to the underlying, anonymised datasets for both

raw data and processed data, may be requested on a risk-based approach to allow the regulator to better understand the algorithm.

AIFA

Accessibility should be ensured for the API, data storage, and app integration into provider portals and clinical data warehouses, so that the entire data set can be utilized for patients' personalized therapy and for clinical research and development (Chung 2019). Moreover, security of log in procedures into the app should be ensured.

Governance

EMA

The governance of the AI development process should be based on a quality system which guarantees, as for medicines, Machine Learning quality standards across the whole lifecycle of the product, from clinical studies to the post approval phase. This could include a multi-disciplinary oversight committee to understand the evolving algorithm.

AIFA

Quality systems and Good Machine Learning Practices (GMLP) should apply.²⁸

Data security and privacy

EU

The app would have to adhere to GDPR, Good Clinical Practice (GCP) and other applicable data protection legislation, such as national data protection laws. It would also have to meet standards of cybersecurity e.g. as per the European Commission's Medical Device Coordination Group (MDCG) Guidance²⁹ or the International Medical Device Regulators Forum. Here, a risk-based approach would be taken, which would require stricter cybersecurity measures, reporting and updates for higher risk software. It may even require organisation inspection/evaluation such as the US Food and Drug Administration (FDA) Precertification Program, which evaluates the quality of the organisation overall and then provides a "streamlined" review pathway for pre-certified organisations (Coravos et al. 2020). The rights of the user should not change even in case of change of ownership.

AIFA

The system should guarantee the timeline and flow of data, the chain of custody, the tracking of any modification (e.g., through blockchain), the ability to detect any anomalies in the data and access to summary data and analysis. Data provenance should ensure that data sources are authenticated to contribute (or receive) data and associated metadata (Adamo et al. 2020).

Data management of new and old data

EMA

A data management plan would be required prior to initial marketing authorisation. Feeding ('teaching') the algorithm with new (real-world) training data sets, whether originating from the device of the user or based on Electronic Health Record datasets, would require an agreed risk-based process and oversight. This would include plans for the company to acquire, prepare and use training data sets to improve the AI.

²⁸ Proposed Regulatory Framework for Modifications to Artificial Intelligence/Machine Learning (AI/ML) Based Software as a Medical Device (SaMD). Available at:

<https://www.fda.gov/files/medical%20devices/published/US-FDA-ArtificialIntelligence-and-Machine-Learning-Discussion-Paper.pdf>

²⁹ <https://ec.europa.eu/docsroom/documents/41863>

3.1.6 Post-approval

Change management plan

EMA

In the EU, as above, any input from EMA depends on the context of use of the App in relation to medicinal products. In this case, as the device is included in the label of the medicinal product as a diagnostic and used to adjust posology, the below post-marketing requirements would be considered.

Reproducibility will need to be established for each App version through re-testing. Equally, new data linkages, e.g. the integration of new Electronic Health Records, would require reproducibility tests. This is the responsibility for the company to carry out. Verifying the algorithm performance and reliability when it is applied in a real-world setting may also be required in the post-marketing phase. Ideally, the App should be unchanging between the initial MAA and HTA assessment.

Hardware and Firmware

EMA

As it is a medical device, the usual post-marketing surveillance requirements apply. Bridging studies may also be required if new hardware alters effectiveness/risk, and this decision will be risk-based.

Software

EMA

At approval of the medicinal product, there may be a need to agree thresholds/parameters to initiate updates and updating methods. This is to prevent any validity, reliability, reproducibility drift. Updates may be required to be reported to regulators (medicines and device) and users (HCP's/patients). Any change to the AI algorithm family would require reassessment e.g. change from neural networks to a decision tree structure. Updates to the underlying software of the smartphone would have to be assessed by the developer for its impact on performance of the app.

Governance and auditing of data sets

EMA

The notified bodies and/or EMA may need to oversee governance matters. Ideally the company should have an additional multi-disciplinary oversight committee to understand an evolving algorithm. Standard auditing requirements would be applicable, as under GCP.

Updates

EU

A plan for updates would be required for those that impact the performance and intended use of the device, not for minor updates which would not. All updates would need testing and audit from the provider. If the company changes provider or contracts out this AI service, then it would have to inform the EMA. In the EU, after a company has completed verification and validation of a major update, a change in the terms of a marketing authorisation – a variation - would only be needed if the update impacts the benefit/risk of a medicinal product(s).

EMA

To roll out an update, therefore, EMA may require that formal approval is requested in a post-authorisation procedure for the medicinal product. This may include reanalyses using historical data to see the update's affects. In this case, the trigger for verification and validation could be if certain pre-agreed performance thresholds/parameters were breached in an update. The relevant aspects of the MDCG 'Guidance on clinical evaluation (MDR) / Performance evaluation (IVDR) of medical device software' should be applied.

Considerations of when and how to roll out an update are the same for whether they apply for personalised or global updates. Communication and transparency on major updates would require label change (electronic) via a variation procedure; transparency is especially important for patients and HCPs. Any changes to the Summary of Product Characteristics (SmPC) would require oversight as usual.

The quality management system of medical device manufacturers would be relevant to any updates and is generally aligned with the requirements of ISO 13485. Additional Quality systems and Good Machine Learning Practices (GMLP) for AI should also apply.

Post marketing risk surveillance and vigilance

EMA

EMA would expect reporting for any changes to the effectiveness or risks of the medicinal product on the market, as measured through the app. A detailed description of the process used by the algorithm to link serious ADR data with the other data resources should be provided.

3.2 Case study: AI and Pharmacovigilance

3.2.1 Product classification

EU

With its intended use, this software could potentially be classified as a medical device.

EMA

If the software meets the definition of a medical device and is CE-marked for the specific intended use, oversight of the software is within the remit of Notified Bodies and medical device authorities and EMA's remit would be limited.

3.2.2 Early advice and scientific advice

Early advice would be encouraged, and the following points would likely be included in this advice:

- Validity of the system and testing it on a wide number of molecules
- Data sources
- Data preparation
- Technology used
- Training of the system
- Further development of the system, including adaptation based on new data

Scientific advice may include collaboration with academia, other EU regulators, and experts on AI.

EMA

Early advice would be provided (e.g. in the context of an ITF Briefing meeting for orientation on legal, regulatory, scientific and ethical aspects), and the stringency of this advice would scale according to the risk of the product. In addition to above, it could include the following considerations:

- Ensure the database/literature screening includes all published information, including toxicology studies and information on other molecules in the same pharmacological class.
- Ensure the software can screen publications in different languages.
- Ensure the software adheres to data and data protection regulations (e.g. GDPR, EUDPR (Regulation (EU) No 2018/1725) and national data protection laws). This should be considered across the whole process e.g. copyright infringement from sharing published data (Coravos et al. 2020).

Early advice would likely result in the invitation to come for a formal, more in-depth Scientific Advice, and this would further help build understanding for both parties. This could include qualification (validation) advice. If it did come for qualification, annotated raw data used to train the machine would be required. EMA may also request to see the annotated results and the validation procedure. Furthermore, there would need to be a determination as to when human interventions are needed within the machine learning/AI processes. EMA would seek collaboration with academia, other EU regulators, and experts on AI.

While the scientific advice qualification is the preferable route, the AI tool's use could be submitted as a type two variation relating to the linked medicinal product. Here, assessment by the Pharmacovigilance Risk Assessment Committee would occur on the AI's use as part of the medicinal products' Risk Management System. The assessment would likely take a risk-based approach.

3.2.3 Assessment for marketing

If the software were CE marked as a Medical Device for this context of use, EMA would have limited remit for oversight, beyond a request for regulatory validation prior to use.

The wording in Good Pharmacovigilance Practices (GVP) is broad and describes the minimum requirements for pharmacovigilance, for example searching of the global literature at least weekly, as well as the recommended databases e.g. Medline or Embase, and considerations for precision and recall. This provides a considerable level of regulatory flexibility; however, it may also contribute to difficulties in ensuring compliance and citing findings where required.

Current guidelines do not outline requirements of such software in detail, however, per I.B.8 of GVP module I, IT systems used in pharmacovigilance should be fit for purpose, and "subject to appropriate checks, qualification and/or validation activities to prove their suitability".³⁰

Governance

Specialist expertise would be required by the company in this case: including in AI, data quality and pharmacovigilance signal detection. The need for external specialist expertise may increase the risk for conflicts of interest between the different participants and external companies. This would entail clarity on the owners of the data and how the data can be shared (copyrights etc.). If the AI is operated by a third party, there would need to be assurances that this third party doesn't renege on any of the responsibilities of the sponsor and that the tool could be inspected by regulators.

Data security and privacy

Pharmacovigilance data is very sensitive from a data protection perspective as there are patient identifiers within the data. The system would need access credentials and users' access control as a minimum. The sharing of information must also protect against the identification of individuals. It would need to adhere to all applicable EU and national data protection legislation.

Hardware

EU

Software systems will require appropriate hardware and firmware solutions, per I.B.8 of GVP Module I.

3.2.4 Post-approval

Software Updates

Software updates that affect the training data, algorithms or performance data will need to be communicated to regulators; transparency is especially important for patients and HCPs.

The company would be responsible to assess the consequences and to document the effectiveness of updates, in particular for new methods, new algorithms and new tools for signal detection. This would be subject to internal audits and regulatory inspections. Equally, if the company changes their service provider or contracts out this AI service then it would have to inform the EMA.

3.3 Expertise Gaps and Stakeholder Engagement

3.3.1 Central Nervous System App using AI

The complexity of the CNS case study highlights that regulators will require expertise from several disciplines including computer scientists, engineers, biostatistics, data analysts and hardware and software developers. Consideration would also need to be given to the patient's role in the development and the assessment stages.

³⁰ https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-good-pharmacovigilance-practices-module-i-pharmacovigilance-systems-their-quality-systems_en.pdf

EU

EU Regulators may lack the necessary in-depth expertise in AI, Bayesian adaptive statistics, medical devices, (bio)mathematics, cybersecurity, GDPR, ethics in the field of AI and hardware and software expertise. This may hamper their ability to provide advice, and timely regulation in the case of fast-moving AI development and adaptive clinical trials.

3.3.2 AI in pharmacovigilance

A multidisciplinary approach is needed in regulating such a case study, including internal and external experts.

EMA

There is a need for EMA to identify external experts in AI (e.g., data scientists, data quality, data engineering), and also EU pharmacovigilance inspectors will need to be trained on the AI tools.

4. RECOMMENDATIONS

Below are recommendations for implementation by ICMRA and its member authorities.

4.1 General Recommendations for AI

- Consider a permanent ICMRA working group, or a standing ICMRA agenda item on AI to share experiences of regulating AI use by medicine developers, and best practices for its use within the Agencies themselves.
- Consider the need for international guidance on AI from the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH). This could include AI development and use in the context of developing and using medicinal products for treatment and / or diagnosis. This could start with regulatory concerns that cut across areas of medicines regulation and the medicine life cycle.
- Regulators may need to elaborate a risk-based approach to assessing and regulating AI, and this could be informed through exchange and collaboration in ICMRA. The scientific or clinical validation of AI use would require a sufficient level of understandability and regulatory access to the employed algorithms and underlying datasets. Legal and regulatory frameworks may need to be adapted to ensure such access options. In addition, limits to validation and predictability may have to be identified and tolerated when, for example, the AI is to learn, adapt or evolve autonomously (on each user's device, as in hypothetical case 1); such deployments would also be considered higher-risk AI uses.
- Regulators should bring together or engage with existing ethics committees' networks and AI expert groups, to collaborate on ethical issues of AI in medicines development, use and regulation.
- Promote collaboration among Medicines and Medical Devices Regulatory authorities in early interactions with developers in order to harmonize opinions, needs and requirements.

4.2 Recommendations related to case study AI in Medicine Development, Clinical Trials and Use - Central Nervous System App using AI

- Sponsors, developers and pharmaceutical companies should establish strengthened governance structures to oversee algorithm(s) and AI deployments that are closely linked to the benefit/risk of a medicinal product, such as trial conduct automation or use depending on individual data-based algorithms. A multi-disciplinary oversight committee should be in place during product development to understand and manage the implications of higher-risk AI. Health professionals should be involved early and fully informed about how AI and algorithm(s) are monitoring patients and influencing their medicine use
- Regulators should consider establishing the concept of a Qualified Person responsible for AI / algorithm(s) oversight compliance (similar to legally accountable natural persons for medical devices or pharmacovigilance).
- Regulatory guidelines for AI development and Apps should be agreed:
 - Guidelines should aim at defining data provenance, ensuring that data are standardised, sources are authenticated to contribute or receive data and associated metadata. Moreover, attention should be dedicated to the external validation process.
 - Guidelines should describe the process for ensuring reliability, including quality assurance. These should include how the system manages missing data and error detection. Particular attention should be given to integrity of the data and to the process of data acquisition. The system should guarantee the lineage and flow of data, chain of custody, tracking of any modification, ability to detect any anomalies in the data and access to summary data and analysis (Adamo et al. 2020).

- Software as Medical Device guidelines could be further developed to include AI aspects related to algorithm transparency and understandability, validity (construct, content, external etc.) and reliability.
- Consider whether such Apps should be adherent to the principles of necessity (only collect the data needed for the questions at hand), proportionality (only collect as much data as needed) and subsidiarity (use least sensitive data where possible) (Adamo et al. 2020).
- Guidelines are necessary for developing a system to monitor real world performance of AI based software.
- Regulators should support the international development and standardisation of good machine learning practices in the biomedical domain.

Recommendations for the EU

- EMA would welcome a clear legal definition of AI use in medicines development vs a simple software, as well as a risk-categorisation for its use.
- There is a need to establish clear mechanisms for regulatory cooperation between medicines and medical device competent authorities and notified bodies to facilitate the oversight of AI-based software intended for use in conjunction with medicinal products. This is particularly true for cases where, unlike the CNS app example, software is marketed separately to the medicinal product and not specifically considered as part of the marketing authorisation for the medicinal product but could affect the benefit / risk of the medicinal product.
- Ideally, the medical device classification rules should be more specific to the type of technologies used, and in the case of AI would ensure how it is used guides the classification e.g. whether there is human oversight, safeguards, self-learning or device autonomy.
- The national clinical trial authorisation authorities could, through the CTFG, systematically exchange information about clinical trials involving AI use to the National Competent Authorities (NCAs) and the EMA. This would provide early awareness and feedback. It would also enable regulators to ask the developers to come for early advice.
- Regulatory agencies may choose to offer themselves as a trusted party and regulatory data custodian: as a hub for sensitive data underpinning marketing authorisation applications that cannot be shared within consortia. This would allow Agencies to accrue knowledge in these emerging areas. Where Apps interact with existing or official health data infrastructures, data custody could be linked to the European Health Data Space (EHDS).
- In the post-marketing use of such products, there may be a need for notification or occasional reassessment of data/cyber security and privacy measures. Define whether the regulator or the notified body would be responsible, this question is not answered by our existing legal framework.
- Due to the rapid, unpredictable and potentially opaque nature of AI updates, the post-authorisation management of medicines, including the Variation framework, may need to be adapted to accommodate updates to AI software linked to a medicinal product. There may be an advantage to defining major vs minor updates, in a risk-based approach, for all digital tools that impact the quality, safety or efficacy of a medicinal product and thus linked to its B/R.
- Consider requirements/parameters for when the EMA's Committee for Medicinal Products for Human Use would reassess the benefit/risk balance based on continual data from AI software linked to a medicine, such as the app.

4.3 Recommendations related to case study AI in pharmacovigilance

- Regulatory guidelines for algorithm development and use in pharmacovigilance should be defined.
- Conduct outreach to learn from:
 - Other regulators and MAHs who use AI to populate adverse drug reactions (ADRs) into safety databases;

- Other industries that have been using algorithms in critical services for a long time could be useful e.g. aviation/nuclear;
- Tech companies, or other government agencies using AI.

Recommendations for the EU

- Consider legislation for AI which impacts a medicinal product's use and/or benefit/risk. The new EU regulations on In vitro diagnostics (IVD) medical devices (Reg. (EU) 746/2017) give more stringent requirements for companion diagnostics to be used with medicinal products. A similar approach could be discussed for digital technologies, when their use impacts the medicinal product's use and/or its benefit/risk; for example when the technology is used for the selection of patients eligible to the treatment, as was also the case in the CNS case study, or when it is used as add-on, substitution, co-administration therapy). Similarly, consensus should be reached on the remit of NCAs to assess Clinical Decision Support Software which may impact the benefit/risk of a medicinal product.
- There is a need for the EMRN to perform a general risk-analysis of AI use in pharmacovigilance: for example, what are the specific risks, what happens if the algorithm fails etc.? In advance of guidelines, a living (guidance) document may help.
- Ensure adequate AI expertise and training within the inspections working party.
- For both of these case studies, clarity is needed regarding the compliance with the current EU legislation on conflict of interests and data protection.

4.4 Next steps

The implementation of recommendations will be discussed at the ICMRA and the outputs of which will be published. The ICMRA member regulatory authorities will be responsible for their approach to implementing them.

5. ABBREVIATIONS

ADR	Adverse Drug Reaction
AI	Artificial Intelligence
AIFA	Italian Medicines Agency
API	Application Programming Interface
CE	Certification for products sold in the EEA that have been assessed to meet high safety, health, and environmental protection requirements
CNS	Central Nervous System
CT	Clinical Trial
CTFG	Clinical Trials Facilitation and Coordination Group
DKMA	Danish Medicines Agency
EC	European Commission
EMA	European Medicines Agency
EMRN	European Medicines Regulatory Network
FDA	Food and Drug Administration (USA)
GCP	Good Clinical Practice
GDPR	EU General Data Protection Regulation
GVP	Good Pharmacovigilance Practices
HCP	Healthcare Professionals
HLEG	High-Level Expert Group
HMA	Heads of Medicine Agencies
HPRA	Health Products Regulatory Authority
HTA	Health Technology Assessment
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
ICMRA	International Coalition of Medicines Regulatory Authorities
IEC	International Electrotechnical Commission
IMDRF	International Medical Device Regulators Forum
ISO	International Organization for Standardization
ITF	Innovation Task Force
IVD	In Vitro Diagnostic
IVDR	In Vitro Diagnostic Regulation ((EU) 2017/746)
MAA	Marketing Authorisation Application
MAH	Marketing Authorisation Holder
MD	Medical Device
MDCG	Medical Device Coordination Group
MDR	Medical Devices Regulation ((EU) 2017/745)
ML	Machine Learning
NCA	National Competent Authority
SA	Scientific Advice
SME	Small and Medium-sized Enterprises
WHO	World Health Organisation

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Annex A – Case Study Discussion Guide

Case Study –Input/Discussion Guide

Please navigate this product/technology through your currently available regulatory system/pathways. Based on the given product information, identify the regulatory gaps and suggest possible regulatory methods to fill these gaps.

Life Cycle	Activity of Regulators	Existing Tools and Challenges	Desired Tools/Promising Solutions
1. Pre-clinical Development	Early Advice	<ul style="list-style-type: none"> What are the novel pathways, regulations, policy, guidance, standards you currently have to regulate this product? Are there any gaps/lack of flexibilities associated with your legal authorities and requirements for safety, efficacy and quality? 	<ul style="list-style-type: none"> What are the known best practices, regulations, policy, standards, and regulatory methods that you would need to regulate this product? What are the other promising tailored measures that would help you regulate this product, e.g. new legal authorities, regulatory sandbox, work sharing etc.?
2. Clinical Trials (CT)	CT Assessment (including acceptable CT design)		
	Scientific advice		
3. Market Authorization / Assessment	Classification (Drug, medical devices, other), How would product classification be determined? If you use defined factors, would certain product characteristics be more important than others?		
	Remit (When is it within remit? Is it when it appears in certain parts of the product information, or if the use of those technologies is expected to affect areas that will eventually impact benefit-risk assessments?)		
	Areas for regulatory oversight		
	Hardware (e.g. does this work across different hardware?)		
	Firmware		
	Software: <ul style="list-style-type: none"> Algorithm transparency Validity (construct, content, external etc.) Reliability Sensitivity to change in disease 		
	Governance		
	Reproducibility (if transparency is insufficient or the software high-risk, do you consider access to the underlying datasets and the algorithm to allow further understanding and analysis of the algorithm.)		
	Data security and privacy e.g. data protection issues and cybersecurity requirements		
4. Post- Market	Areas for regulation/surveillance/enforcement		

Life Cycle	Activity of Regulators	Existing Tools and Challenges	Desired Tools/Promising Solutions
	Change management plan Hardware Firmware Software, e.g. <ul style="list-style-type: none">• retraining objectives• methods (change in ML architecture)• criteria to initiative performance evaluation Governance		
	Data management of new and old data		
	Training		
	Security		
	Auditing of data sets		
	Performance Evaluation		
	Assessment metrics		
	Analysis plan		
	Update procedures		
	Update verification and validation		
	Roll-out (global vs personalised updates)		
	Communication and transparency on updates		
5. Health Technology Assessment + Healthcare system			
6. Expertise gaps			

Annex B - Applicable laws, guidelines and standards to CNS App using AI

This list is non-exhaustive.

- A Focus Group on artificial intelligence for health ([FG-AI4H](#)) has been established at The World Health Organisation and the ITU (the United Nations specialized agency for information and communication technologies). This includes subgroups on specific topics: Documentation & Transparency, Risk Management & Lifecycle Approach, Data Quality, Intended Use & Analytical and Clinical Validation, Data Protection & Information Privacy, Engagement & Collaboration.
- The European Commission's Medical Device Coordination Group (MDCG) has an [Expert Group](#) on New & Emerging Technologies, dealing with AI

Pre-clinical

- ISO/UNI/IEC/EN (e.g. IEC 62304:2006: 'Medical device software - Software life cycle processes'; and relevant updates; EC 80002-1:2009 Medical Device Software - Part1: guidance on the application of ISO 14971:2007 with reference to IEC 62304; IEC 80001-1 Risk management aspects; EC 82304-1:2016 Health software – Part1: General requirements for product safety; etc.)
(Of note: a new standard ISO/AWI TS 82304-2. Health software - Part 2: Health and wellness apps—Quality and reliability is under development)
- International Medical Device Regulators Forum guidelines on software, e.g.:
 - IMDRF/SaMD WG/N41FINAL:2017 Software as a Medical Device (SaMD): Clinical Evaluation (ref.: IEC 62304)
 - IMDRF/SaMD WG/N23 FINAL:2015 Software as a Medical Device (SaMD): Application of Quality Management System (ref.: IEC 62304)
 - IMDRF/SaMD WG/N12 FINAL:2014 Software as a Medical Device: Possible Framework for Risk Categorization and Corresponding Considerations (ref.: IEC 62304),
- International Conference on Harmonization (ICH) E6 guideline (Good Clinical Practice)

EU

- Regulation (EU) 2017/745 of the European Parliament and of the Council of 5 April 2017 on medical devices <https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX%3A32017R0745>
- MDCG Guidances, e.g. 2019-11 Guidance on Qualification and Classification of Software in Regulation (EU) 2017/745 – MDR and Regulation (EU) 2017/746 – IVDR, https://ec.europa.eu/health/md_sector/new_regulations/guidance_en
- MEDDEV Guidances: <https://ec.europa.eu/growth/sectors/medical-devices/current-directives/guidance>, e.g.
- MEDDEV 2.1/6 on Qualification and Classification of standalone software; Meddev 2.7/2 (2015) on validation and assessment of a clinical investigation application – annex 5.
- GDPR (EU-General Data Protection Regulation)
- BfArM has produced some guidance on Medical Apps https://www.bfarm.de/EN/MedicalDevices/Differentiation/MedicalApps/_node.html

Clinical

IMDRF guidelines on software development, e.g. IMDRF/SaMD WG/N41FINAL:2017 – Guidance on Software as a Medical Device (SaMD): Clinical Evaluation

EU

- MEDDEV 2.1.7 rev 4 'Clinical Evaluation: A Guide for Manufacturers and Notified Bodies Under Directives 93/42/EEC and 90/385/EEC'
- MDCG 2020-1 Guidance on Clinical Evaluation (MDR)/ Performance Evaluation (IVDR) of Medical Device Software March 2020.
- HMA-EMA Joint Big Data Taskforce Phase II report "Evolving Data-driven Regulation"

Software

- Harmonised standard IEC 62304 covers medical device software requirements in relation to design, development, verification, testing and release.

EU

Under the MDR, software design requirements are covered under Annex I, part 17.

Data security and privacy

EU

- Annex I of the MDR requires that medical device software be designed such that there is sufficient protection against unauthorised access. The Medical Devices Coordination Group has published a document with further details, 'Guidance on cybersecurity for medical devices', which would be applicable.
- REGULATION (EU) 2016/679

Annex C - Applicable regulations, guidelines and standards: AI Pharmacovigilance Signal Management

This list is non-exhaustive.

EU

Overarching legislation:

- Regulation (EC) No 726/2004 as amended
- Directive 2001/83/EC as amended
- Implementing Regulation (EU) No 520/2012

Guidance specific to Literature searching:

- In the case of medicinal products containing the active substances referred to in the list of publications monitored by the Agency pursuant to Article 27 of Regulation (EC) No. 726/2004, the holder of the relevant authorisation or registration shall not be required to report to the Eudravigilance database the suspected adverse reactions recorded in the listed medical literature for that medicinal product, but he or she shall monitor all other medical literature and report any suspected adverse reactions.
- For the identification of individual case study reports, VI.B.1.1.2, VI.App.2 of GVP Module VI.
- VIII.B.5.11 of GVP Module VII.
- For signal detection purposes, IX.B.1 of GVP Module IX.

Signals

- Regulation (EC) No 726/2004, Directive 2001/83/EC and Commission Implementing Regulation (EU) No 520/2012 include provisions for signal management in the European Union (EU) [DIR Art 107h, REG Art 28a, IR Chapter III].
- IX.B.2 of GVP Module IX, describes methodology for signal detection activities, with Addendum I providing guidance on statistical aspects.

Additional guidance is provided in

- Report of the Council for International Organizations of Medical Sciences (CIOMS) Working Group VIII on Practical Aspects of Signal Detection in Pharmacovigilance
- The Strengthening Collaboration for Operating Pharmacovigilance in Europe (SCOPE) Joint Action Work Package 5 – Signal Management - Best Practice Guide
- EMA Questions & Answers on Signal Management
- Screening for Adverse Reactions in EudraVigilance

There is no single fixed method for signal detection, and the guidance reflects this. It is noteworthy that an element of clinical judgement should always be applied (IX.B.2 of GVP Module IX), and this would pose difficulties in moving to a purely AI based system.