Medical Research Archives

European Society of Medicine

OPEN ACCESS

Published: November 30, 2023

Citation: Taliaz D, Lilian RR, et al., 2023. Essential Regulatory Update for Implementation of Clinical Decision Support Software in the Psychiatric Field, Medical Research Archives, [online] 11(11). https://doi.org/10.18103/mra.v11i11.4658

DOI
https://doi.org/10.18103/mra.v11i11.4658

ISSN: 2375-1924

EDITORIAL

Essential Regulatory Update for Implementation of Clinical Decision Support Software in the Psychiatric Field

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ABSTRACT

Decision-making in the field of psychiatry, including diagnosis, is highly complex and is hindered by use of a dichotomous categorical classification system that is ill-suited to mental disorders which are multi-factorial behavioral conditions. In addition, traditional use of results from randomized controlled trials to guide medical device regulation in the field of psychiatry is also problematic, as marked heterogeneity exists within psychiatric patient groups, which precludes results from these trials being projected onto the general patient population. In the past 20 years, clinical decision support software (CDSS) has been found to improve decision-making abilities, but the traditional regulatory approach based on the categorical classification system and randomized controlled trials does not allow the necessary flexibility for CDSS-based decision-making in psychiatry. In this article, we will use Major Depressive Disorder as an example and will discuss regulatory considerations for CDSS, including artificial intelligence, in psychiatry. We will also provide an adjusted life-cycle framework for CDSS in psychiatry, given that the particular complexity of psychiatric disorders demands new and innovative decision support tools. We suggest that any new software would need to perform at least as well as the standard-of-care, which in psychiatry is an unfortunate trial-and-error process. This would be demonstrated during the pre-market validation stage using clinical data from back-end testing of the CDSS. We propose that pre-market evidence of CDSS efficacy should be based on parameters that are used to measure the software success rate, with evidence of safety including demonstration of the low risk of CDSS due to human involvement in the decision-making process. In the post-market stage, CDSS would be used by doctors to generate real-world data that would allow ongoing evaluation and improvement of the algorithms. Furthermore, CDSS would collect data beyond the initial intended-use patient population, allowing the CDSS to learn about related indications. These data would inform the pre-market phase, during which the CDSS could be updated with an expanded patient population. We anticipate that such changes would support effective use of CDSS in psychiatry and improved patient care, which is particularly important given the trial-and-process that comprises the current standard-of-care in the field.

Introduction

Decision-making in the medical field, including medical diagnosis, is a complex task[1]. Due to the particular complexity of psychiatry, this task is much more difficult and inconclusive[2,3]. The main cause of the inadequate diagnosis in psychiatry is the dichotomous categorical classification system of mental disorders, which can hold only one value per patient and is based on identifying symptoms[4]. The uniqueness of mental disorders as behavioral conditions does not necessarily fit the conditional categorical approach that suits other medical branches. The weakness of this approach, when applied to psychiatry, is evident in the prevalent comorbidities phenomenon[5–8]. An alternative classification method is the dimensional diagnosis system, which can keep a series of values for a single patient[9–14] and which allows different diagnostic criteria for various disorders, as opposed to the presence of specific symptoms. Other essential characteristics, such as behavioral or genetic patterns[9–14], also serve as vital parameters, as expressed in our previous article[15].

In terms of regulatory supervision, the traditional categorical diagnosis system is much easier to conform with. That is, it is easier to determine the intended patient population of a therapeutic product using the categorical method, much like randomized controlled trials (RCTs), where the categorical diagnosis system is especially suited to selecting patients who comply with a trial's inclusion criteria. In contrast, the dimensional diagnosis system challenges the current regulatory guidelines, as has already been recognized[9,16]. Despite these difficulties, the ideas that stand behind the dimensional approach should not be neglected. Since the current regulatory framework supports the traditional categorical system, which is limited in terms of the needs of the psychiatric field, it stands to reason that the regulatory framework may be a factor that has contributed to the lack of advancement in the field in the past 60 years. This lack of advancement is evident in the trial-and-error process that characterizes the standard-of-care in psychiatry[17,18].

In the wider medical field, decision making has been improved in the last 20 years by the utilization of clinical decision support software (CDSS). Many CDSSs have been implemented in hospitals, improving the performance of diagnostic procedures[19]. When addressing CDSSs, particular attention should be brought to artificial intelligence (AI)-based software. Clinical decision support software integrated with AI algorithms allows simulation of the human thinking process, analysis of accumulated data, and pertinent decision making[20–22]. Such sophisticated software detects features within big data and allows pattern recognition to support the complicated medical diagnosis process[23,24]. This ability provides AI-based CDSS a major advantage that was demonstrated in clinical studies, where AI-based software outpaced human diagnosis[20–22]. Evidence for the effectiveness of AI in clinical psychiatry has already been published[25–28]. As was previously mentioned by Fakhoury[29], AI has certain importance in psychiatry, as it allows learning of underlying patterns that cannot be recognized via questionnaire-based traditional techniques. Use of AI can thus support learning from the current trial-and-error process to ultimately improve patient care.

Medical device, including CDSS, regulation is based for the most part on approval of specific medical indications and patient populations[30,31], relying on results from RCTs. However, marked heterogeneity exists within psychiatric patient groups[5–7,32], and this does not allow results of RCTs to be projected onto a specified patient population. Furthermore, the inclusion criteria of psychiatric RCTs do not fit the general patient population, as is demonstrated by the very high placebo-response of psychiatric clinical trials[33,34]. As expressed previously, our perspective based on this evidence is that the challenges of RCTs in the field of psychiatry, together with the underlying complexity in this field, negatively impact clinical practice[35]. Therefore, our evidence-based perspective is that the traditional regulatory approach does not allow the flexibility that is needed to support CDSS-based decision-making for patients with mental health conditions.

In this article, we will use Major Depressive Disorder (MDD) as an example and will discuss regulatory considerations for CDSS and AI that are used in the field of psychiatry. We will then provide an adjusted regulatory framework for CDSS in psychiatry, which uses AI to learn from real-world data (RWD) instead of relying on data from RCTs.

Major Depressive Disorder

Major Depressive Disorder is one of the most disabling psychiatric conditions, with a significant impact on pubic health[36]. The lifetime prevalence of MDD ranges widely based on geography, from 2% in China to 21% in France, with little change over the past decades[36]. Diagnosis of MDD is challenging and provides little clinical utility, having very low inter-rater reliability and a lack of treatment specificity or precise diagnostic boundaries[37]. A study by Zimmerman et al. examined the diagnostic heterogeneity of MDD[38]. They found that one quarter of the 227 possible ways to meet the symptom criteria for MDD did not occur[38].

Using AI in the context of depression has been discussed in multiple studies[39–44]. A review by Barua et al.[44] found that AI could rapidly and accurately detect depression and/or anxiety in a cost-effective manner that could overcome the limitations of traditional diagnostic methods. The review also proposed extracting multiple components, including facial images, speech signals, and visual and clinical history features from deep models[44].

For AI-based systems to work accurately for diagnosis and management of MDD, RWD are required. The lack of valid real-world databases that are needed to feed data-intensive AI algorithms has been acknowledged as a challenge for real-world implementation of AI-based tools in mental health[45], and challenges associated with limited datasets used for developing algorithms for depressive disorders have been discussed[42]. A key recommendation to support implementation of AI-based tools in mental health is collection of large-scale representative datasets for training and validation of AI tools[45]. This may also support the provision of personalized treatment to patients suffering from MDD and mental health disorders, and allow ongoing learning and improvement of the unfortunate trial-and-error process which is the current standard-of-care in the field.

Regulatory guidelines for Clinical Decision Support Software and Artificial Intelligence

European Union (EU) Medical Device Regulation (MDR) 2017/745 provides guidance regarding the marketing of medical devices for human use, including clinical investigations concerning these devices[31]. The MDR guidelines also established a Medical Device Coordination Group (MDCG), composed of medical device experts from the EU Member States[31]. In 2019, the MDCG provided guidance on classification of software in medical device regulations[46], which further developed the Medical Devices Documents (MEDDEV) 2016 guidelines for stand-alone software[47]. In 2020 and 2022, the MDCG released guidelines pertaining to post-market clinical follow-up and periodic safety update reporting, wherein they describe the use of RWD in the post-market phase of a medical device[48,49]. Real-world data may be sourced from electronic health records or digital health-monitoring devices, and can form part of real-world evidence analyses[48,49].

In the United States (US), there have been parallel regulatory guidelines, including the 21st Century Cures Act, which was enacted in 2016[50], followed by various US Food and Drug Administration (FDA) medical device guidelines in 2017[51,52]. Like the European regulators, the FDA encouraged use of RWD evidence to support regulatory decision-making for medical devices, provided that the data are accurately and reliably captured at key points in the device lifecycle[51]. The FDA also acknowledged the pitfalls of traditional clinical trials, and the potential for RWD to fill this gap[51]. Real-world data is similarly discussed in the FDA's software as a medical device (SaMD) guidance document[52]. The on-going lifecycle process for SaMD includes, in the pre-market phase, generating evidence regarding the product's sensitivity, specificity, accuracy, reliability, limitations, and scope of use in the intended use environment, and in the post-market phase, collection of RWD to monitor the product's safety and performance in the real world[52]. Monitoring RWD may contribute to evolving functionality and intended use for the SaMD, which may ultimately support a change to the initial SaMD definition statement[52]. The FDA encouraged taking advantage of the ability of SaMD to capture real-world performance data to support future intended uses, and in this way, the collection of post-market information was seen as a form of "continuous learning"[52].

To further support the unique requirements of software-based devices, the FDA announced the Software Precertification Pilot Program in 2017[53]. This program was designed to investigate a new regulatory framework in which the FDA would first assess organizations to confirm that they performed high-quality software design, testing, and monitoring[53]. Such organizations would then qualify for a more streamlined pre-market review, while better leveraging post-market data collection[53]. The precertification program used a Total Product Lifecycle (TPLC) approach and included real-world performance as a key component, encompassing a real-world performance analytics framework with user experience analytics, real-world health analytics, and product performance analytics[53]. The final report on the precertification program pilot was released in 2022, and it was concluded that that this model could not practically be implemented under the current statutory and regulatory authority of the FDA[54]. Nevertheless, the pilot did demonstrate the value of a systems-based approach with a learning regulatory system and data-drive insights[54]. In 2022, the FDA also released draft guidance pertaining to computer software assurance for production and quality system software[55], with final guidance to be released in the future.

With regard to CDSS specifically, neither US nor EU guidelines have fully clarified all issues concerning the regulation of this software, as was previously claimed by Van Laere et al.[50]. In addition, it has been inherently challenging to develop a regulatory framework with the right balance between innovation and rapid market access, versus safety and quality[50]. The latest regulatory guidance for CDSS from the FDA was published in 2022 in order to clarify the types of CDSS that are not regulated as devices[56]. Clinical decision support software that is intended to support or provide recommendations about prevention, diagnosis or treatment to a healthcare professional may be excluded from the definition of a medical device provided that additional criteria are also met, including that the healthcare professional independently reviews the basis for the recommendations provided by the software[56]. In comparison, devices in the EU that are intended to provide information which is used to make diagnostic or therapeutic decisions would be considered class IIa medical devices, needing to be assessed by an EU-notified body as specified in the MDR[31,57]. Even though the FDA guidance has been met with mixed reviews, the EU legislation is seen to be lagging behind with regard to clarity[57].

Regulating AI in healthcare poses additional challenges, including the need for a regulatory process that spans the entire life-cycle of the application and a regulatory framework that reflects patient populations in whom the technology will ultimately be used[58]. In Europe, the European Commission presented its AI package in 2021, including a proposal for a regulation laying down harmonized rules on AI (the AI Act)[59]. In the US, the FDA published a discussion paper in 2019 with a proposed regulatory framework for AI/machine learning-based SaMD[60]. This paper recognized the patient population's adaptive potential in AI-based software[60]. The FDA addressed this issue by suggesting the establishment of a "software update" when there is favorable evidence that the software has gathered enough data to support a new intended patient population. In 2021, the FDA published an AI/machine learning-based SaMD action plan in response to stakeholder feedback wherein they acknowledged the importance of medical devices being well suited for a diverse intended patient population and the need for improved machine learning algorithms that identify and eliminate bias[61]. They further committed to working with stakeholders who are piloting RWD performance approaches to support this process [61].

Artificial intelligence technology challenges the pre-approved intended use scheme, since AI algorithms constantly adapt. As AI software achieves new insights when new data are introduced, the software output changes in real time[62]. Hwang et al.[63] addressed this regulatory question by suggesting to pre-determine, in the pre-approval phase, a "safe harbor" with all the acceptable modifications of the software. Beyond this limit, the software could not operate. Recently, the FDA released draft guidance regarding submission of a pre-determined change control plan for AI/machine learning-enabled software at the marketing stage[64]. Such a plan would describe planned modifications to the machine learning-enabled device, together with validation and assessment methods, to preclude the need for additional marketing submissions for the specified modifications[64]. The regulatory guidelines are thus evolving to address the ever-changing landscape of AI-based technologies.

Revised regulatory framework for implementing Artificial Intelligence-based Clinical Decision Support Software for Major Depressive Disorder and other psychiatric conditions

As there are currently no regulatory specifications for an AI-based CDSS which supports clinical decision-making for MDD and other psychiatric conditions, we propose an updated regulatory framework for this area (**Figure 1**). Firstly, it is important to ensure that the design of the software does not contradict current clinical guidelines. For MDD and other psychiatric disorders, these guidelines are primarily the Diagnostic and Statistical Manual of Mental Disorders (DSM-5®)[4]. It is also essential to evaluate the current standard-of-care and the risk associated with this care, for example, rates of suicide, hospitalization or co-morbidities, as any new software will need to perform at least as well as the standard-of-care. For MDD, the current standard-of-care is based on a trial-and-error process, with a recent study demonstrating that patients with a lifetime history of MDD only succeed in attaining helpful treatment after seeing up to nine professionals for unhelpful treatments[17]. This demonstrates the experimental nature of MDD care, which is also prevalent in other psychiatric conditions[18]. New software for MDD or psychiatry would need to be at least as safe and effective as this existing trial-and-error process.

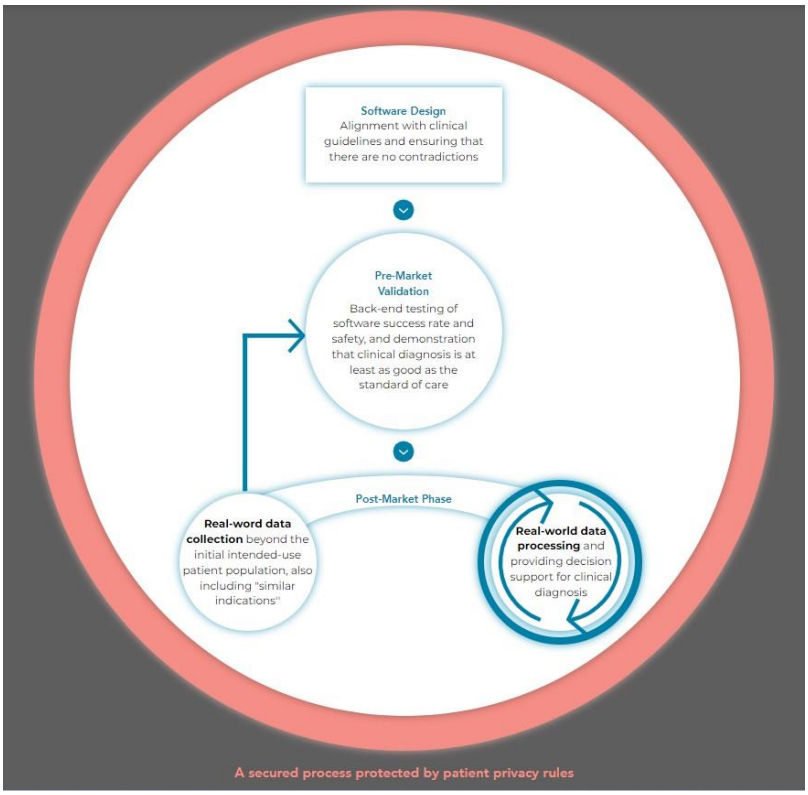

Figure 1. Applied regulatory framework for AI-based CDSS in the field of psychiatry.

Comparison with the current standard-of-care should be performed during the pre-market validation stage using clinical data from back-end testing of the CDSS (**Figure 1**). We propose that in the pre-market stage, evidence for the efficacy of the CDSS should be based on parameters that are used to measure the success rate of the software, such as sensitivity and specificity. Evidence of safety should include demonstrating the low risk of the CDSS due to human involvement in the decision-making process, and commitment to perform post-market monitoring using RWD.

Following the pre-market phase, CDSS can be used by doctors treating MDD in the real world, allowing ongoing evaluation and improvement of the algorithms in the post-market phase (**Figure 1**). We suggest relying on RWD for post-market surveillance (PMS) instead of using data from traditional RCTs, as RCTs do not accurately reflect the psychiatric population in general, or the MDD population specifically, owing to the poor diagnostic classification system and the ensuing heterogeneity of the predefined patient populations[35]. Real-world data processing will provide support for clinical decision-making, which should ultimately contribute to improved patient care. The more RWD that is collected, the more the AI algorithms can learn, which can further improve patient care.

Furthermore, during the PMS phase, CDSS should collect data beyond their currently approved range of medical indications, thereby allowing the CDSS to learn about related indications (**Figure 1**). This approach will allow assessment of the software's indications in order to determine if the indications can be updated and expanded beyond MDD or another indication, in line with FDA guidance that expanding the intended patient population is one of the possible modifications related to a SaMD's intended use[60]. That is, data regarding related indications can inform the pre-market phase, during which the CDSS can be updated with an expanded patient population where applicable. By adopting this approach, the software's intended patient population should cover a range of mental disorders, instead of an intended patient population that is limited to dichotomous disorders which do not reflect the true patient landscape. This concept would not be considered extreme in the psychiatric world, since utilizing the same treatments for different disorders is common in this field[4], as is off-label prescribing[65–68]. To add an additional safety margin, routine safety events should be monitored in the real-world throughout the PMS phase.

The proposed framework harnesses the benefits of RWD and AI-based learning throughout the pre-market and post-market phases of CDSS implementation. This framework represents an avenue to improve the standard-of-care for MDD specifically, and psychiatry in general, which is hindered by an unmet need for improved treatment and classification systems[9]. It is important to note that this whole process would be implemented in strict compliance with all data protection and privacy requirements, thus ensuring that patient rights are protected at all times, while clinical decision-making is improved.

Conclusion

In conclusion, the particular complexity of psychiatric disorders such as MDD demand new and innovative decision support tools. Clinical decision support software, including AI-based software, have great potential in this field, with evidence for their success in psychiatry already being demonstrated. The regulatory authorities have published designated guidelines for medical software and AI in particular. However, the psychiatric branch has unique characteristics compared to other medical branches. Psychiatric disorders are behavioral conditions that involve different factors that are not necessarily physiological. In addition, there is solid evidence regarding the great heterogeneity within groups of patients with the same diagnosis. Therefore, special adaptations for the psychiatric world need to be established in regulatory guidelines.

We suggest the following:

A. Real-world data use instead of traditional RCTs:
   - Pre-market evidence about safety of the software by demonstrating the low risk due to human involvement in the decision-making process, and commitment to perform post-market monitoring using RWD.
   - Pre-market evidence about software efficacy via software success rate parameters, demonstrating that the efficacy of the software is at least as good as the efficacy of the doctor.

B. Post-market surveillance that includes data collection about both the current approved medical indications and other similar indications, thereby allowing the CDSS to learn about related indications.

C. A range of mental health disorders should be used as the CDSS's intended patient population instead of an intended patient population limited to dichotomous medical disorders.

We anticipate that the proposed steps will pave the way toward effective use of AI-based software in the psychiatric world and ultimately to better patient care.

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