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Possible Consequences of Reclassification of Non-Invasive Brain Stimulating as Class III Medical Devices in Europe and Its Reflections on Our Country

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ABSTRACT

Neuromodulation techniques (NIBS) and devices that have emerged in the last thirty years continue to develop rapidly. NIBS, which initially appeared to be effective only for the treatment of some neurological diseases, have been found to be effective in increasing the capacities of normal people for education, sports, business life, and military fields over time. This has led to the production of home/individual-use versions of NIBS devices. On the one hand, individual use of these devices is increasing rapidly in many countries; on the other hand, many research studies on the effectiveness, safety, and new usage areas of the techniques continue. The production, placing on the market, and use of all these NIBS devices to be used for scientific research, treatment, or individual uses are directly or indirectly dependent on the rules and conditions in the Medical Devices Regulation (MDR) of the European Union (EU). Our country also complies with these rules. A new regulation numbered 2022/2347 has

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been published by the EU for the specification of non-medical product groups included in Annex XVI of Regulation No. 2017/745. NIBS devices, one of the product groups in question, have been subjected to a new classification due to this regulation, and this change has caused various objections from all stakeholders related to this field. Objections to the new classification stem from the fact that ethics committees will drastically change their approach to research in these areas and that these changes involve much more challenging conditions for researchers and device manufacturers than before. As a result of this situation, the main concern has emerged that the limitation of research will lead to the interruption of production and development activities in this field and even prevent patients from benefiting from these treatments.

In this study, the old and new regulations are analyzed together, and it is aimed to evaluate the appropriateness of the procedure and content of the regulation, its reflections on the field, and the criticisms brought to the regulation in the light of scientific data in the field. Based on this assessment, an attempt has been made to provide a perspective to the relevant stakeholders in Turkey, researchers, ethics committees that authorise/supervise research with these devices in line with the EU, and the competent authority that oversees the production, distribution, and conformity of medical devices, both on the current situation and what should be.

Keywords: European Union Medical Device Regulation, Non-invasive neuromodulation, MDR, Turkish Medicines and Medical Devices Agency (TİTCK)

INTRODUCTION

Today's world of technology is becoming a place where, on the one hand, mental power and capacity are becoming increasingly important in individual and social life, and on the other hand, a number of neurological disorders are rapidly spreading. Both of these situations have prompted researchers to further investigate the structure, functioning, possibilities, and limitations of the brain. In addition, newly developed technologies in the field of healthcare are now a candidate to change the classical provision of better but more expensive healthcare. For example, artificial intelligence-based follow-ups make it possible to reduce chronic and age-related diseases and contribute to the economy as well as health. In this sense, it can be said that neuromodulation techniques,

a groundbreaking approach that aims to improve the functions of the brain, which is the organ that controls every aspect of human thinking, perception, and behavior, in many ways, to increase its capacity and to correct it when damaged, have similar characteristics. With the simplest example, NIBS is a technology that has the potential to contribute to both health and the economy by reducing or even eliminating the use of medication in diseases such as depression and chronic pain, which are considered chronic and unsolvable today. Therefore, not only the use but also the production of these technologies are of strategic importance in the globalizing world.

These techniques are not only effective in the "clinical" field where they first appeared, such as the treatment of diseases, but also in many other fields such as education, sports, increasing productivity in business life, and military use, apart from clinical treatment (Da Silva et al., 2022; Wexler, 2017; Dündar-Coecke, 2021; Davis et al. 2019). In this context, household types of devices for individual use are produced and sold in many countries (Da Silva et al., 2022; Wexler, 2017). Proportionally, studies conducted both in our country and around the world to determine the effectiveness and safety in various fields of devices are rapidly replicating (Valiengo et al., 2020; Antal et al., 2017; Rossi et al., 2020). Our country, which has the ability to lead the world in terms of both research and production capacities in this field, regulates the decisions regarding devices in line with the EU accession process.

The legal regulations to be complied with these devices to be used for both scientific research and individual-purpose applications were regulated in many countries, including our country, and these legitim regulations are in accordance with the "Medical Devices Regulation (MDR)" published by the European Union (EU) in 2017 (EU, 2017/ 745). However, on December 1, 2022, a new regulation was made regarding the brain stimulation devices included in the non-medical products group in Annex XVI of this regulation, leading to a reclassification of these devices (EU, 2022/2347). With the new classification, these devices are included in the highest risk group, making the production and sale of these devices, and therefore scientific activities in this field, more difficult. The scientific community and device manufacturers, who conduct intensive research in this field in member countries, reacted strongly to this decision, which will affect all activities in the field, citing that it is not based

on scientific data (European Society for Brain Stimulation, 2023; Onarheim, 2023). Our country also implements these decisions in accordance with the EU membership process.

In this study, it is aimed firstly to clarify what the new regulation means for the use of devices and scientific research, and then to examine the new regulation and the criticisms brought against it in light of scientific data and to inform the authorities and interested parties in Turkey in a comprehensive manner.

What are Neuromodulation Techniques?

Neuromodulation is defined as the modulation of the nervous system through electrical, electromagnetic, chemical, or optogenetic methodologies for the purpose of long-term activation, inhibition, modification, and/or regulation of neural activity. With its rapidly growing popularity, it is applied in a wide range of treatments for neurological and neuropsychiatric disorders in an invasive and non-invasive technology-based manner (Budak and Hanoğlu, 2018).

If we take a short look at the history, the modern era of neuromodulation began in the early 1960s, first with deep brain stimulation and invasive methods. Today, however, we have a large number of predominantly "non-invasive" neuromodulation methods (Polat and Hanoğlu, 2021). Among them, the most common non-invasive techniques used are transcranial magnetic (TMS) and direct current (tES) which affect brain activity based on electromagnetic principles (Demirci and Hanoğlu, 2014) and finally trigger or modulate neuronal activity. TMS creates an instantaneous magnetic field with a power of up to 2 tesla (T) units, which is rapidly generated in less than 1 millisecond. This temporary magnetic field is applied to the surface of the scalp by focusing it with a coil (Chou et al., 2019). It is a very safe stimulation technique when appropriate precautions are taken and applied within the framework of certain principles (Farzan et al., 2016; Rossi et al., 2021).

Many studies have been conducted on the use of the TMS device in the treatment of different neurological and psychiatric diseases. Studies have been published showing the potential effects in the treatment of many diseases such as Parkinson's, Alzheimer's, epilepsy, ALS, MS, and tinnitus (Lefaucheur et al., 2020; Dougall et al., 2015; Pereira et al. ., 2016;). There are studies showing

rTMS can be effective in many psychiatric diseases such as depression, anxiety disorder, panic attacks, obsessive-compulsive disorder (OCD), post-traumatic stress disorder, and addiction (Lefaucheur et al., 2014; Berlim et al., 2012; Li et al. et al., 2014, Fregni et al. 2021). Finally, TMS was approved by the FDA for the treatment of depression in 2008, migraine aches in 2013, and OCD in 2018 (FDA, 2018).

The tES method, on the other hand, is a non-invasive brain stimulation technique that is effective due to the electrical waves transmitted through the electrodes placed in the determined area and changes the membrane potentials of the neurons so that the excitability of depolarized neurons increases, and the excitability of repolarized neurons decreases. In other words, although the electrical current sent is well below the cut-off level to create an action potential, it can contribute to the formation of an action potential by slightly lowering the excitability threshold.

tES is also divided into three types according to the types of electric currents transmitted through the electrodes if using a) direct current in the transcranial direct current stimulation (tDCS) method; b) alternating current in transcranial alternating current stimulation (tACS) and c) transcranial random noise stimulation (tRNS). The difference between tRNS and tACS is defined as a variable but not constant frequency and amplitude of the applied current (Paulus, 2011, Antal et al., 2017).

There are studies showing that tES methods are an effective treatment method for depression (Brunoni et al., 2016; Mutz et al., 2019; Moffa et al., 2020). Although there are some studies supporting its curative effect on schizophrenia symptoms, its effectiveness is still unclear (Liu et al., 2021; Valiengo et al., 2020). Apart from these, its effectiveness in treating neurological and psychiatric diseases is still unclear. However, recent meta-analysis studies have provided level A and level B evidence of indications (Lefaucheur et al., 2014; Fregni et al., 2021). Furthermore, individualization and possible interventions in the course of the disease at an early stage in neurodegenerative diseases have been on the agenda thanks to their application with neuroimaging in recent years (Hanoğlu et al. 2021).

The positive and promising results obtained in the studies without any significant serious side effects make both TMS and tES methods suitable and ef-

fective tools for the treatment of Alzheimer's disease, Parkinson's disease, etc., for which there is no effective neuroprotective treatment today. Also, current gaps in neuroprotective treatment approaches in the neuropsychiatry discipline make these techniques a serious treatment alternative for psychiatric diseases such as chronic pain, depression, and anxiety (Rossi et al., 2021; Fregni et al., 2021; Antal et al., 2017; Lefaucheur et al., 2017; Velioğlu et al. et al., 2021; Hanoğlu et al. 2022; Sarıcaoğlu et al. 2022). Especially attractive for many neuroscientists is also the pro-cognitive and positive effects on general physical capacity of these techniques, which have led to a widespread study activity in the field of non-clinical uses on issues suggested in many articles (Coffman et al., 2014; Dedoncker et al., 2016; Young et al., 2010; Aktürk et al. 2022). Hence, it was not surprising that the scope of the research carried out within the framework of these techniques has expanded to also include the improvement of performance in education as well as the use for military purposes (Dündar-Coecke, 2021; Davis et al. 2019) including persons from different disciplines, such as firefighters, police, surgeons, etc. There are even discussions suggesting that community service workers increase their skills by using these devices (Santoni de Sio et al., 2014) leading to scientific studies that aim to determine the effectiveness and reliability of all these areas. Finally, any legal regulation to be undertaken regarding these devices will cover a wide spectrum of uses and users and, hence, will have a significant impact on the field.

Classification of Medical Devices

According to MDR, *"devices shall be divided into classes I, IIa, IIb, and III, taking into account the intended purpose of the devices and their inherent risks"* (EU, 2017). Class I devices (stethoscopes, goggles, non-invasive electrodes, etc.) are low-risk devices subject to general controls, while class IIa (needles, syringes, electrical acupuncture, etc.) and class IIb devices (hemodialysis devices, urethral stents, dental implants, etc.) are moderate-risk devices. Class III devices (spinal needles, cardiovascular catheters, implantable active devices such as cochlear implants, etc.) are devices with a high risk of disease and injury (Wexler, 2015; EU Medical Device Coordination Group, 2021).

For each device to be put on the market legally, it is dependent on fulfilling a number of safety and performance requirements, namely conformity assessment procedures, determined according to the class it belongs to. In this

context, the conformity assessment procedure for class I devices is carried out only under the responsibility of the manufacturers due to the low sensitivity and risk of the devices in this group, while for class IIa, IIb, and III devices, the involvement of an authorized organization at certain levels is required (EU, 2017). Therefore, as the grade level increases, medical device manufacturers are subject to some special controls such as performance standards, private labeling, and post-market surveillance (Wexler, 2015).

Herein, classification rules are determined according to device types (non-invasive, invasive, and active) specified in Annex VIII of the relevant regulation. In addition, for devices that can be evaluated in more than one class due to some of their features, it is obligatory to be subject to the requirements of the highest class they belong to (EU, 2017).

Neuromodulation devices are active therapeutic devices defined in Annex VIII of the regulation as *"any active device used, whether alone or in combination with other devices, to support, modify, replace, or restore biological functions or structures with a view to treatment or alleviation of an illness, injury, or disability"* have been treated as class IIa devices since 2017 (EU, 2017). In addition, since these devices have non-medical uses, neuromodulation devices were also included in the last item of the "List of Products for Non-Medical Use" in Annex XVI of the regulation, but no regulation was made regarding the status of the devices on this list.

The new regulation numbered 2022/2347, approved on December 1, 2022, has been prepared in order to make the necessary specifications for these devices listed in Annex XVI of the Regulation (EU, 2022/2347). Article (7) of the new regulation on neuromodulation devices states: *"According to available scientific evidence on equipment intended for brain stimulation that apply electrical currents or magnetic or electromagnetic fields that penetrate the cranium to modify neuronal activity in the brain as referred to in Section 6 of Annex XVI to Regulation (EU) 2017/745, such as those for transcranial magnetic stimulation or transcranial electric stimulation, the use of such products may cause side effects, for example, atypical brain development, abnormal patterns of brain activity, increase metabolic consumption, fatigue, anxiety, irritability, headaches, muscle twitches, tics, seizures, vertigo and skin irritation at the electrode site. While such equipment is not surgically invasive,*

the electrical currents or magnetic or electromagnetic fields do penetrate the cranium to modify neuronal activity in the brain. Such modifications can have long-lasting effects, and any unintended effects may be difficult to reverse. ***Such products should therefore be classified as Class III****"* (EU, 2022/2347).

Effects of Reclassification in the Field

The latest regulation includes neuromodulation devices in class III and imposes much stricter requirements on the production and sale of devices and the ethics committee requirements for research in the field. This situation will cause various disruptions and limitations in many countries that regulate medical device regulations in the light of EU decisions, such as in our country and the 28 EU member states. In addition, the fact that the devices in question are used for different purposes will primarily limit the access of many patients who benefit from neuromodulation techniques who will benefit from this treatment modality and will make it difficult to conduct scientific studies in the field of neuroscience, preventing the development of these techniques and methods. An important change for manufacturers will be to increase the production cost of the devices (Onarheim, ty). Indeed, the European Society for Brain Stimulation (ESBS), which describes itself as a professional association of participants interested in neurostimulation/neuromodulation, including representatives of national brain stimulation associations in Europe, medical doctors, psychologists, and neuroscientists, published a manifesto against these decisions a few months ago and sent a protest to the EU. The manifesto was published in the journal Brain Stimulation under the title "European reclassification of non-invasive brain stimulation as class III medical devices: A call to action" (Beaken, 2023).

Criticism of the Reclassification

It is seen that the criticisms of the people and institutions that are stakeholders in the production or use of neuromodulation techniques and devices are basically grouped under two headings. The first of these is about the preparation of the relevant article and the process of making this decision, while the second is criticism about the content of the article.

Criticisms of the Preparation Process of the Regulation

In the "Better Regulation Guide", which describes the criteria that will enable reaching the desired target in laws and policies in the most accurate way,

created by the EU, seven basic principles that should be in all stages of a legal regulation process such as design, preparation, acceptance, implementation and (if necessary) revision are mentioned. These principles are listed as an approach that is comprehensive, consistent, proportional, participatory, evidence-based, transparent and learning from experience (European Commission, 2021). However, it was stated that the "participatory approach" requirement, which is one of the seven principles for the relevant regulation, was violated, and it was criticized by claiming that the stakeholders were not included in the process. Because, this situation prevented first-hand access to reliable data to be obtained through the scientific community and the parties directly affected by the regulation, and thus opened the debate on the reliability of the reasons for the decision to debate (Beaken 2023, Onarheim, 2023).

Criticism of the Content of Article 7

Basically, three problematic points have been highlighted in the content of the reclassification item. The first of these is the fact that no differentiation of risk is taken into account for medical and non-medical use, and the devices have been increased from class IIa to class III, which is a high risk group, for all kinds of use (Onarheim, 2023). As a matter of fact, according to MDR, it was stated that the classification of devices depends on their intended use and the risks they carry due to their structure (EU, 2017/745). However, in the new regulation, it is evident that neuromodulation devices are classified without adhering this general rule, regardless of the purpose of use by only considering the risks due to their structure.

The risks claimed to be carried due to the nature of neuromodulation devices, which is expressed as the main and only reason for reclassification, is another problematic issue regarding the regulation. Because it is stated that the statements in Article 7 regarding the side effects of the devices such as *"atypical brain development, abnormal patterns of brain activity, increase metabolic consumption, fatigue, anxiety, irritability, headaches, muscle twitches, tics, seizures, vertigo and skin irritation at the electrode site"* and *" such modifications can have long-lasting effects"* are inconsistent with the existing scientific literature and that this decision was taken based on an erroneous assessment of the scientific literature on the safety of neuromodulation devices (Onarheim, 2023). As a matter of fact, no permanent or serious damage has

been reported in the studies conducted with neuromodulation techniques in the literature and in the meta-analysis of these studies (Antal et al., 2017; Rossi et al., 2020; Brunoni et al., 2011; Davis and Smith, 2019). This shows that the reclassification was made on grounds that clearly contradicted the scientific data, thus violating the "evidence-based approach" principle, which is one of the basic principles of Better Regulation (Beaken 2023, Onarheim, 2023).

The fact that the side effects or risks expressed in the regulation are expressed in a way that covers all brain stimulation devices without any discrimination is the third point that shows that the decision is quite problematic for devices that have different techniques and applications and therefore contain different risks and side effects. For example, skin irritation at the electrode site is a side effect that can be seen with brain stimulation devices (eg tDCS) that only use electrodes. Similarly, the claim to cause seizures is only available for TMS and rTMS among neuromodulation techniques, and this risk is too low to be supported by scientific evidence (Rossi et al., 2020; European Society for Brain Stimulation, 2023). In fact, the risk of seizures caused by rTMS (0.003%) is much lower than the risk of seizure formation (0.1-1.5%) of the drugs most commonly used in antidepressant treatment (European Society for Brain Stimulation, 2023). Moreover, this risk is absent in other neuromodulation devices such as low-density tDCS, tACS and tRNS (Pereire et al., 2016; European Society for Brain Stimulation, 2023). However, it is understood from the text of the decision that it is not paid attention to the fact that the devices in question contain different technologies and therefore have different risks and side effects, and that the risks listed in the examples are conveyed as if they apply to all devices. This again shows that the technological and scientific data on the devices are ignored, and the professionals and the scientific community are not included in the decision-making process (European Society for Brain Stimulation, 2023).

What should be done?

This decision taken by the EU regarding the reclassification of neuromodulation devices has been met with reaction from the scientific community and manufacturers due to the reasons stated above. The European Brain Stimulation Society (ESBS), on the other hand, criticizes the decision and made some recommendations to engage the relevant stakeholders in response to this

decision. Accordingly, stakeholders have been asked to contact their national institutions or authorized bodies in the EU and inform them about the implications of the amendment and its objectionable points. In addition, it was stated that academic publications should be produced to address the problems and propose solutions related to the decision, including the scientific facts in the literature about the risks listed in the decision (European Society for Brain Stimulation, 2023).

It is stated that this effort, which will be put forward collectively, can be effective in halting or withdrawing the decision made by the EU. Thus, it is reasonable to expect? that a new regulatory environment based on scientific evidence can be created in which all stakeholders are included in the process in accordance with the principles of "Better Regulation" (European Society for Brain Stimulation, 2023).

CONCLUSION AND IMPACTS ON OUR COUNTRY

In this study, the effects and justifications of the amendment made in 2022 regarding the classification of neuromodulation devices as medical devices by the EU, which are described in the light of the data in the literature, their types and areas of use, are tried to be evaluated through the criticisms and scientific data on the decision. Accordingly, first of all, it can be said that the regulation was not made in accordance with the EU's own standards. Such as decision which will severely limit the future of neuromodulation devices and the scientific studies conducted in this field, as well as access to the current treatment provided with these devices, has been made without a basic level of care and attention. Another handicap is that devices with different risks and side effects due to different techniques and applications are considered as a single device without any discrimination, while also not considering the latest meta-analyses regarding the safety of the devices suggesting that their rationale are not based on scientific data a indicating that it should at least be reconsidered.

From the point of view of our country, the direct implementation of these decisions of the EU, will impose unnecessary heavy ethical committee burdens of researchers from domestic research activities, which are already weak but have serious development potential. This is also suggested in the ESBS manifesto that these decisions will undermine the role of European researchers as world leaders in the field of NIBS (Beaken, 2023).

Likewise, other consequence for our country is that will cause serious damage to our national production and development capacity of the devices and equipment in question, which is still in its infancy, and will condemn our country to foreign-production devices. However, development in this field emerges as a result of the collaborative efforts of researchers and device manufacturers and is extremely fast. Another consequence of the implementation of these decisions is that we will always be dependent on technologies produced outside our country, and we will never be able to become a leading country developing new technologies in this field, which is entirely feasible and within our reach. For the end-user patients, it will be the emergence of restrictions on the development and use of much more effective innovative non-drug neuromodulation therapies in our country in chronic diseases that require the use of large amounts of medication such as chronic pain, depression, and in diseases such as neurodegenerative diseases and dementias that do not have effective treatments today.

This evaluation is especially directed to the Turkish Medicines and Medical Devices Agency, which is the authority responsible for the legal regulations related to NIBS devices in our country, and the relevant legislators, at the point of implementing the changes made in EU practices on the subject in our country. For this reason, there are some limitations in the article and areas that need to be developed in subsequent articles. It is of strategic importance for our country to produce NIBS devices in our country and to carry out effective and globally effective research in this field through researcher/producer platforms. However, this important part of the subject has not been sufficiently explained and processed. Similarly, a detailed review of the scientific background of the EU amendment decision and its problematic aspects were left out of the subject as they may be too technical. The possible effects of the new regulation in our country and especially the burdens it will bring to device manufacturers could be addressed in a relatively limited way.

Finally, it is recommended that the aforementioned regulation be evaluated together with the deficiencies and errors mentioned in the regulation, taking into account national and international criticism. This assessment should be conducted by Turkish Medicines and Medical Devices Agency, which is responsible for the legal regulations regarding NIBS devices in our country.

Ethical Approval: Ethical approval was not required as the study was a scientific review.

Authors' Contributions: All authors analyzed the legal regulations and amendments subject to the study in the light of scientific data in the literature and contributed to the evaluation of the effects of the decision in the field and in the scientific community.

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