Regulatory Aspects

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Abbreviations

CE	Conformité Européene
CES	Cranial electrotherapy stimulation
FDA	Food and Drug Administration
HD-tDCS	High-definition transcranial direct current stimulation
IDE	Investigational device exemption
IRB	Institutional Review Board
NIBS	Noninvasive brain stimulation
NSR	Nonsignificant risk
PMA	Premarket approval
SR	Significant risk
tDCS	Transcranial direct current stimulation

40.1 Introduction

The field of noninvasive brain stimulation (NIBS) has undergone considerable advances in the last decade. The increased research on transcranial direct current stimulation (tDCS) around the world reflects its potential as a therapeutic tool through the modulation of cortical excitability, and its safety and efficacy have motivated scientists to increase its use in several conditions such as stroke [1–4], chronic pain [5, 6], cognitive impairment [7–9], and neuropsychiatric disorders [10–13].

Compared to other NIBS techniques, the relative ease of use, portability, and low cost of tDCS make it an attractive technique that can be easily accessed and used without any supervision, including for nonmedical reasons. Therefore, it is important to have regulatory guidelines regarding the use of tDCS in both research and clinical practice. Currently, there is no international consensus with well-defined regulations for the use and distribution of tDCS [14]. In this chapter, we provide an overview of the regulatory process, the current status of tDCS in the USA and other countries, tDCS devices, special considerations on patient selection, and the practical aspects involving the use of tDCS.

40.2 FDA Regulation of Medical Devices

The federal agency responsible for regulating medical devices in the USA is the Food and Drug Administration (FDA). This agency has defined a medical device as an "*instrument, apparatus, implement, machine, contrivance, implant,* in vitro *reagent or other similar or related article, including a component part, or accessory which is*:

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- *Recognized in the official National Formulary, or the United States Pharmacopoeia, or any supplement to them,*
- *Intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in man or other animals, or*
- *Intended to affect the structure or any function of the body of man or other animals, and which does not achieve any of its primary intended purposes through chemical action within or on the body of man or other animals and which is not dependent upon being metabolized for the achievement of any of its primary intended purposes*" [15].

Before receiving the permission by the FDA to be legally marketed, the medical device submission enters in a review process for premarket and postmarket approvals. In the first case, the FDA classifies the medical devices according to the risk they pose to the consumers. Class I Medical Devices include devices such as elastic bandages or examination gloves for which general controls provide sufficient evidence of safety and efficacy. Class II Medical Devices include devices posing moderate risk to the patients, such as infusion pumps for the treatment of pain. Finally, for Class III Medical Devices, there is insufficient information to assure their safety or efficacy. Examples that fall in this last category are heart replacement valves or deep brain stimulating electrodes [16, 17].

Additionally, this classification determines the regulatory requirements that the manufacturer must follow. A device classified as Class I is exempt from the premarket notification. In the case of moderate and high-risk devices, the clearance is carried out through a premarket approval (PMA) or Product Development Protocol Processes [16]. The PMA process is usually longer and consists of conducting clinical studies to provide evidence of safety and efficacy of the medical device; most Class III and novel devices pass through this process in order to receive the FDA approval.

Furthermore, the premarket submission of a 510 (k) notification must be done to demonstrate that the device is substantially equivalent to a device that is already in the market. This notification includes information regarding the design and characteristics of the device and its components, as well as the clinical or nonclinical studies that were done to support the performance of the device. This is required to assess the quality of the new device and thus, be able to compare to the currently available devices. Most Class I and II devices are exempt from this submission before their sale; they do however undergo further control requirements [18]. This 510 (k) notification is also required for already marketed devices when there have been changes in their technology or a new indication for their use is foreseen.

Once the FDA approves the medical device for marketing, the manufacturer must follow other postmarket requirements: labeling and advertising, manufacturing, postmarketing surveillance, device tracking, and adverse event reporting [16].

Currently, there is no regulation of tDCS devices for therapeutic uses. The FDA regulates cranial electrotherapy stimulation (CES) devices, but does not consider tDCS as a CES due to the use of direct current stimulation and the difference in electrode placement [19]. However, considering the FDA framework on medical devices as discussed above, tDCS could be contemplated and regulated as such, considering its intended use for the treatment of different medical conditions and its effects on brain function.

40.3 tDCS in Research

All clinical evaluations of investigational devices are under the Investigational Device Exemption (IDE) regulation [20, 21]. This exemption allows the new device to be used in clinical trials to provide information regarding its safety and effectiveness. Moreover, it distinguishes between significant and nonsignificant risk device studies and, based upon this, the process for the study

approval may vary. Clinical studies using devices classified as significant risk (SR) require both the FDA and the Institutional Review Board (IRB) approval before the initiation of the study, and in order to obtain the FDA approval, the investigator must submit the IDE application. Specific information including details about the sponsor, report of prior investigations, and the investigational plan is required to apply. Furthermore, the sponsor must demonstrate that the potential risks to which the subjects may be exposed are reasonable in relation to the anticipated benefits and generation of scientific knowledge.

For studies involving nonsignificant risk (NSR) devices, only the IRB approval is required, and the sponsors' submission of the IDE is made directly to the IRB. The sponsors should also provide the study proposal and an explanation of why the device study should be considered as a NSR. If the IRB agrees, the study can begin without submission of an IDE application to the FDA. However, if the IRB determines it is a SR device, the sponsor has to report this decision to the FDA within a week (CFR Part 812.150(b)) [22, 23].

Finally, the approval of the proposed research by the IRB is based on the same criteria involving any FDA-regulated product; where the decision takes into account the risks and benefits of the investigational device and the contribution to science [24].

In the case of tDCS, these devices have been considered of NSR by the IRBs, so an IDE submission to the FDA is not required. Furthermore, its use has also been considered of minimal risk by some IRBs, which allows tDCS studies to be approved through an expedited review procedure [14, 22]. However, this is not indicative of its approval or the clearance by the FDA for the use of tDCS in scenarios other than research.

To date, the only companies having an IDE for tDCS devices by the FDA are Soterix Medical Inc. (tDCS and high-definition transcranial direct current stimulation [HD-tDCS]) and neuroConn GmbH [14]. The regulation of these devices has been subject to the FDA Quality System guidelines.

40.4 tDCS in Clinical Practice

Besides research, health care professionals in the USA can prescribe tDCS as an off-label treatment. This term refers to the use of a therapy that has proved to be safe within established parameters, for a purpose that has not been approved by the FDA. Considering that it is performed under the physician's professional and ethical judgment, the FDA has developed Clinical Practical Guidelines intended to help them make decisions regarding individual patient care [25]. Off-label uses of tDCS include motor recovery in stroke, improvement of balance and gait in cerebral palsy, and pain improvement in fibromyalgia.

Since the FDA has no legal authority to regulate clinical practice, unsupervised application of tDCS needs to be carefully reviewed for ethical and safety considerations. Off-label treatment should be applied according to the conventional protocols, with the approved devices and by trained personnel to guarantee safety and efficacy of the tDCS.

It is also important to consider that there is insufficient information regarding the long-term effects of stimulation, so this practice should be conducted with caution.

Furthermore, people who are not eligible to participate in a clinical trial may be able to get tDCS outside of a clinical trial through a "compassionate treatment." According to the FDA, it can be considered as an option in patients with serious or life-threatening conditions that do not respond to currently approved treatments [26]. To date, this option has been accepted in most countries, considering the course of neuropsychiatric diseases and the limited treatment options [14].

The application of tDCS in either scenario must be ruled by ethical and legal considerations. Every medical research involving participation of human beings should be preceded by careful assessment of the benefit–risk ratio, an equitable selection of subjects, and the obtainment of informed consent [27]. Especially for the latter, it is important to use simple and clear language to describe the tDCS procedure, as well as its potential benefits and adverse events.

40.5 tDCS Devices

The stimulation devices must meet safety requirements to be suitable for medical or scientific use. Generally, the use of battery-driven devices is preferred because it prevents the delivery of dangerous high voltages and/or currents to the patient in case of technical problems. The device must be designed to indicate and allow adjustment of the parameters by the operator, specifically the output current, voltage, and duration of the stimulation. Furthermore, the protection of the patient must be enhanced through the presence of a gradual increase or decrease ("ramp-up" and "ramp-down" phases) of the desired current over a defined time interval (e.g., 30 s) at the beginning and the end of the stimulation, respectively. Moreover, the devices should have an accessible stop button to abort the stimulation in case of any adverse events.

Finally, it is recommended that an impedance monitoring system is included in these tDCS devices. The optimization of the technique might rely as well on the quality of the electrode preparation and the voltage demands to maintain the direct current magnitude [28, 29].

FDA-approved iontophoresis devices have been used by clinicians and researchers for tDCS in the off-label program. Iontophoresis devices use direct current stimulation (approximately ≤4 mA) to introduce ions of soluble salts or other drugs through the skin. These devices lack many of the controlled elements mentioned previously, so their use as off-label treatment should be done with caution. In addition, they manage different doses and they were not designed to deliver current to the brain, and thus, they would not be ideal for performing tDCS [29].

Commercial devices claiming to have the same technology used for tDCS are already being sold to the public in the USA and other countries. Devices such as *foc.us* [30, 31] promoting the improvement of cognitive performance have raised concerns among health care professionals and researchers. In the first place, the company declares that as their product is not considered a medical device, no FDA regulation is required. In addition, these types of devices are usually designed with fixed stimulation parameters whose safety and/or efficacy have not been proved yet.

Indeed, a recent study on healthy volunteers assessed the effect of online and off-line foc.us tDCS applied over the prefrontal cortex on working memory. The authors showed that active stimulation (constant current of 1.5 mA during 20 min with a linear fade-in/fade-out of 15 s) with foc.us, compared to sham, significantly decreased the ability to monitor and update information in the working memory [31].

This device exemplifies that commercial devices may be sold without proper validation that may result in an inadequate use of the technique. In the case of foc.us, it has been presented as an alternative to "Conformité Européene" (CE)-marked tDCS devices that have shown positive results on the working memory in healthy subjects [9, 32].

Furthermore, the media has encouraged programs such as Do-It-Yourself (DIY), where step-by-step tutorials on how to build a tDCS device and its application are widely available for untrained individual users [33]. Enthusiastic benefits of these devices are promoted without taking into account the population, parameters of stimulation, and medical background of the users. This reflects the need of regulation on devices that are being advertised in the media as potential tDCS devices carrying the risk of negative neuroplastic effects and misuse.

40.6 Considerations on Patient Selection

A careful patient selection is the core for an adequate tDCS intervention, and they evolve as daily publications define and refine the specific parameters of stimulation that maximize the benefits of the tDCS therapy and reduce the adverse events. However, the patient population, the medical illness, and the interaction between concomitant treatments are factors that must be taken into account before the application of tDCS.

40.7 tDCS Candidates

The identification of subjects who are appropriate candidates either for a study or an off-label program must be conducted carefully. Although specific inclusion criteria may vary according to the specific study, certain considerations must be assessed in each patient to guarantee the safety and efficacy of tDCS:

- History of neurological and psychiatric conditions
- History of traumatic brain injury with loss of consciousness
- History of brain surgery or tumor
- History of seizures
- Presence of metallic plates in the head
- History of alcohol or substance abuse
- Use of psychopharmacological drugs
- Children
- Pregnancy

Ideally, tDCS should be adjusted in a patient-specific manner to select the best tDCS approach, reaching adequately the targeted region and avoiding safety concerns. As an example, skull defects or stroke-related lesions might need modification of tDCS dose montages [28].

General exclusion criteria include the presence of unstable medical conditions (i.e., heart disease), intracranial metallic implantation, or other conditions that may increase the risk of stimulation [28].

In addition to the appropriate patient selection, it is important to assess and report adverse events/safety during and after tDCS. The following items are included in the proposed questionnaire by Brunoni et al. to survey tDCS adverse effects: headache, neck pain, scalp pain, tingling, itching, burning sensation, skin redness, sleepiness, trouble concentrating, acute mood changes, and others. The subject should enter a value from 1 to 4 (1, absent; 2, mild; 3, moderate; 4, severe) to each item and, if present, assess if it is related to the tDCS [28, 34] (also see Chap. 23 of this book for a discussion regarding safety).

40.8 tDCS in Pediatrics

There are limited reports on the use of tDCS in the pediatric population, mainly due to safety concerns that rise when studies on adults with tDCS are extrapolated to children. To date, the optimal dose of tDCS for safety and efficacy in the pediatric population has not been well established. Studies reporting the use of tDCS in children have considered the following stimulation parameters: duration of stimulation up to 20 min, current intensities from 1 to 2 mA, and bilateral (anodal and cathodal) or cathodal montages [26, 35, 36] in conditions such as refractory epilepsy, schizophrenia, and autism. Serious adverse events have not been reported yet, and the most common adverse events are tingling and itching at the electrode site [26]. Although published data suggest that the use of tDCS in children is well tolerated, special considerations have to be taken into account.

Previous modeling studies have shown that the potential variability in the tDCS efficacy between these populations may result from differences in brain size, neuroplasticity, development, and age-dependent anatomical features (i.e., skull thickness, and white and gray matter volumes) [37–40]. For example, the scalp brain distance increases with age due to increases in extra-axial cerebrospinal fluid (CSF) space and skull thickness. Considering that the bone conductivity is low and that the skull thickness in children is decreased compared to an adult, the transmission of the current would be higher. Furthermore, the decreased amount of extra-axial CSF would provide less shunting of the current and more focal stimulation [37, 40, 41].

In the case of the white and gray matter proportion, it is important to consider that after reaching the maximum brain volume by age 5, the gray matter volume decreases approximately 1.1% per year and there is an estimated increase of 1.5% in the white matter volume until 18 years of age [39, 42–44]. The differences in this proportion, reflecting maturation in the brain structure, influence the depth of the current penetration being higher in a pediatric patient.

Another important anatomical feature dependent on age and sex is the head circumference [37]. Approximately, 98% of the total head circumference growth occurs before the age of 18 years. After the greatest gains in head growth during the first year of life, the head circumference increases at a slower pace until adulthood. At the age of 8 years, the mean head circumference for boys is 52 cm and for girls 51 cm. Once they reach the age of 18 years, the mean head circumferences are 56 and 55 cm for boys and girls, respectively [45]. This anatomical factor, as well as the size of the conventional tDCS electrodes, affects the focality of the stimulation. As the conventional tDCS protocol uses 5 cm by 5–7 cm sponge-wrapped rubber electrodes, their use in a small head circumference would end up covering the majority of the scalp, thus losing focality [37].

Based on the empirical experience with tDCS in children and the considerations mentioned previously, tDCS given within the standard parameters is well tolerated. However, due to the limited safety studies and the lack of information about the neurophysiological effects with different parameters of stimulation, caution is warranted for pediatric populations. In fact, the benefits of tDCS must be clear before designing clinical trials, especially in children with very young age (≤7 years), taking into account the phases of brain development, tDCS potential of neuroplastic changes, and the risk of inducing maladaptive plasticity in these patients.

40.9 tDCS in Pregnancy

To our knowledge, few studies have been performed on tDCS in pregnant patients. In healthy subjects, a recent study showed that tDCS does not induce any significant changes in the autonomic function, ventilation rate, or core body temperature [46–48]. These results, in addition to the localized nature of tDCS [49] and the low risk of seizures, suggest that tDCS is unlikely to cause any significant risk to the fetus. To date, a case report showed successful application of tDCS in a pregnant woman with schizophrenia, with no adverse events reported on the fetus [50]. Furthermore, a pilot study using tDCS for the treatment of major depression during pregnancy [51] provided a basis for the development of future larger multicenter studies including this population.

Although further studies are required to have solid evidence of the safety profile of tDCS in pregnancy, a conservative therapeutic approach for future clinical trials and also potential off-label use appears to be justified in the case where a clear benefit for the patient is present.

40.10 Considerations on Application of tDCS

As clinical practice and research on tDCS advance, several practical aspects such as the setting and the person who should apply this technique turn relevant. For tDCS research studies, the IRBs usually do not require the principal investigator to be a licensed physician but an expert in the tDCS technique, its principles, neurophysiological changes, and the potential side effects. Besides this, safety must be guaranteed when defining a protocol for emergency response within the study protocols in case the subject has any unexpected adverse effect.

Even though there is no consensus regarding the training and the accreditation requirements for performing tDCS, it is important that the principal investigator guarantees proper training including basic knowledge of brain physiology, mechanisms of tDCS, potential risks, and the different protocols. Trained professionals may include MDs, technicians, psychologists, physiotherapists, and engineers, as in other techniques such as transcranial magnetic stimulation [52]. In our Neuromodulation Center at Spaulding Rehabilitation Hospital in Boston, the program includes 20 hours of theoretical and training sessions given by experts in the field, followed by the corresponding assessments and certification.

In the clinical practice, a licensed physician is responsible for prescribing tDCS as an off-label or compassionate treatment. During these sessions, the trained personnel must have full access to

emergency and life-support equipment to manage any potential acute complication of the treatment.

40.11 tDCS Experience in Other Countries

For other countries leading tDCS research such as Brazil and Germany, the regulations regarding the use of tDCS in research and the clinical practice depend on the local/governmental regulations. In addition, we include the example of South Korea where the experience with tDCS has been limited.

In Brazil, the regulatory considerations for tDCS are very similar to those in the USA. Clinical trials using tDCS require the approval by the local ethics committee (Comitê de Ética em Pesquisa, CEP). As the IRBs in the USA, the CEP bases the final decision on the statement of ethical principles from the World Medical Association-Declaration of Helsinki [24]. In addition, the National Ethics Committee (CONEP) may also be involved in the statutory regulation of basic and clinical tDCS research, especially in the situation of international multicenter trials. Further regulatory assessment is the responsibility of the National Health Surveillance Agency (ANVISA) that is in charge of the supervision and administration of medical devices such as tDCS. Currently, the only device that has been registered by the ANVISA for the use of tDCS is provided by the company "neuroConn GmbH." Although the tDCS device has not been approved for clinical use, the off-label and compassionate tDCS use is considered in specific situations [14].

In the case of Germany, clinical trials, which may be initiated by the producer of the device, require the approval of the local ethics committee and the Federal Institute for pharmaceutical and medical products (BfARM), which is the corresponding federal entity. In the case of nonclinical trials, the local ethics committee is free to assess the risk–benefit ratio of the study and its decision is sufficient to approve or not the study [14]. Besides research, off-label and compassionate tDCS are provided in the context.

Finally, the South Korean regulation on tDCS has been shown to be very strict. To date, no tDCS device has been approved by the Korean Ministry of Food and Drug Safety (MFDS). tDCS has been considered to have a class II risk profile and thus, its approval requires preexistent evidence either from research studies performed in South Korea or abroad.

The application and regulation for the device approval are variable; some study protocols require approval just from the local IRB and others from the MFDS. In either case, this process is repeated for every single trial and the tDCS devices should be destroyed after the study [14]. Further uses of tDCS have not been reported.

40.12 Conclusion

We provide an overview of the regulatory aspects and special considerations for the use of tDCS in the USA. In the case of other countries leading tDCS research, the requirements for its use vary according to their local/federal laws. We consider that the involvement of the international community is crucial for the establishment of consistent tDCS regulatory aspects and the development of guidelines for its use in research and clinical practice. The active participation of the scientific community in this process of tDCS will be helpful to mitigate the potential risks of misuse and the uncertainty of long-term effects on the brain, which are not fully known.

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