

Limited output transcranial electrical stimulation (LOTES-2017): Engineering principles, regulatory statutes, and industry standards for wellness, over-the-counter, or prescription devices with low risk



Marom Bikson^{a,*}, Bhaskar Paneri^a, Andoni Mourdoukoutas^a, Zeinab Esmaeilpour^a, Bashar W. Badran^{m,n}, Robin Azzam^o, Devin Adair^a, Abhishek Datta^b, Xiao Hui Fang^a, Brett Wingeier^c, Daniel Chao^c, Miguel Alonso-Alonso^d, Kiwon Lee^e, Helena Knotkova^{f,g}, Adam J. Woods^h, David Hagedornⁱ, Doug Jeffery^j, James Giordano^k, William J. Tyler^l

^a The City College of New York, Department of Biomedical Engineering, New York, NY 10031, USA

^b Soterix Medical Inc., New York, NY 10001, USA

^c Halo Neuroscience Inc., San Francisco, CA 94103, USA

^d Harvard Medical School, Berenson-Allen Center for Noninvasive Brain Stimulation, Division of Cognitive Neurology, Boston, MA, USA

^e Ybrain Inc., Sampyeong-dong, Seongnam-si, South Korea

^f MJHS Institute for Innovation in Palliative Care, New York, NY, USA

^g Department of Family and Social Medicine, Albert Einstein College of Medicine, The Bronx, NY, USA

^h Center for Cognitive Aging and Memory, McKnight Brain Institute, Department of Clinical and Health Psychology, University of Florida, USA

ⁱ Evoke Neuroscience Inc., Jacksonville, NC, USA

^j Thync Inc., Los Gatos, CA 95030, USA

^k Department of Neurology and Neuroethics Studies Program, Pellegrino Center for Clinical Bioethics, Georgetown University Medical Center, Washington, DC, USA

^l Arizona State University, School of Biological and Health Systems Engineering, Tempe, AZ 85287, USA

^m U.S. Army Research Laboratory, Aberdeen Proving Ground, MD, USA

ⁿ Department of Psychology, University of New Mexico, Albuquerque, NM, USA

^o Caputron, New York, NY, USA

ARTICLE INFO

Article history:

Received 4 April 2017

Received in revised form

16 September 2017

Accepted 15 October 2017

Available online 17 October 2017

Keywords:

Limited output tES

FDA clearance

Over-the-counter device

Prescription medication

FDA product codes

Manufacturer guidance

Regulatory standards

ABSTRACT

We present device standards for low-power non-invasive electrical brain stimulation devices classified as limited output transcranial electrical stimulation (tES). Emerging applications of limited output tES to modulate brain function span techniques to stimulate brain or nerve structures, including transcranial direct current stimulation (tDCS), transcranial alternating current stimulation (tACS), and transcranial pulsed current stimulation (tPCS), have engendered discussion on how access to technology should be regulated. In regards to legal regulations and manufacturing standards for comparable technologies, a comprehensive framework already exists, including quality systems (QS), risk management, and (inter) national electrotechnical standards (IEC). In Part 1, relevant statutes are described for medical and wellness application. While agencies overseeing medical devices have broad jurisdiction, enforcement typically focuses on those devices with medical claims or posing significant risk. Consumer protections regarding responsible marketing and manufacture apply regardless. In Part 2 of this paper, we classify the electrical output performance of devices cleared by the United States Food and Drug Administration (FDA) including over-the-counter (OTC) and prescription electrostimulation devices, devices available for therapeutic or cosmetic purposes, and devices indicated for stimulation of the body or head. Examples include iontophoresis devices, powered muscle stimulators (PMS), cranial electrotherapy stimulation (CES), and transcutaneous electrical nerve stimulation (TENS) devices. Spanning over 13 FDA product codes, more than 1200 electrical stimulators have been cleared for marketing since 1977. The output characteristics of conventional tDCS, tACS, and tPCS techniques are well below those of most FDA cleared devices, including devices that are available OTC and those intended for stimulation on the head. This engineering analysis demonstrates that with regard to output performance and standing regulation, the availability of tDCS, tACS, or tPCS to the public would not introduce risk, provided such devices are

* Corresponding author.

E-mail address: bikson@ccny.cuny.edu (M. Bikson).

responsibly manufactured and legally marketed. In Part 3, we develop voluntary manufacturer guidance for limited output tES that is aligned with current regulatory standards. Based on established medical engineering and scientific principles, we outline a robust and transparent technical framework for ensuring limited output tES devices are designed to minimize risks, while also supporting access and innovation. Alongside applicable medical and government activities, this voluntary industry standard (LOTES-2017) further serves an important role in supporting informed decisions by the public.

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Part 1: definitions, regulations, and manufacturing practices relevant to limited output tES

Introduction and scope of part 1

Transcranial electrical stimulation (tES) has a rich and varied history, which predates that of modern pharmacotherapy. While a complete discussion of the history of tES is beyond the scope of the present paper, our prior detailed review of tES development and use provides salient features for the historical success of this approach [1]. Paramount among these was the “Qualification and Regulation” of the techniques and its use in practice. It is as misguided to qualitatively consider all tES methods the same as it is to consider all neuro- and psychotropic drugs to be the same; changing device output (for definition of tES dose, see Ref. [2]) and quality control is as crucial to the functional viability of tES as changing chemical formulation and consistency is to pharmaceuticals. At the same time, it is equally uninformed to discuss standards for new technologies (including types of limited output tES) and their applications, while ignoring rich experience gained to date with comparable devices. The ongoing debate over the potential uses and distribution of limited output tES devices, including use for the treatment of neuropsychiatric disorders by prescription/over-the-counter (OTC) or for general wellness purposes within a direct-to-consumer (DTC) market, must be informed by existing standards and regulations that establish definitions and distinct controls. In this light, consideration of the function and outputs of new technologies (in comparison to widely distributed existing technology) can and should be regarded as an engineering analysis.

For all the above reasons, one of the key contributions for this guidance is defining a scope for limited output tES devices (based on a voluntary industry guidance, in Part 3) because any engineering analysis and rational discussion on relevant regulations must be based around clearly delineated range of devices. The output of limitation output tES devices can then be contrasted with other low power non-invasive electrical stimulation techniques, as well as other types of electrical stimulation devices (Part 2). This document begins with the current regulatory context surrounding limited output tES devices (Part 1).

Recent articles have speculated on emerging ethical, legal, and social implications and issues fostered by possible clinical, occupational, and public uses of limited output tES [3–7]. Informed discussion of tES regulations is based on extant international standards and extensive regulatory frameworks [8] and should not imply that such laws are absent or do not apply. For example, the United States Food and Drug Administration (FDA) has well-established procedures for evaluating and obtaining approval of devices (including electrostimulation products) that are intended for use on the head, neck, and face – for various indications. Additionally, the International Electrotechnical Commission (IEC) has established exhaustive technical safety standards and engineering specifications for all electrical devices and accessories. These standards can be independently audited by governmentally

certified organizations, and are recognized and referenced by US and European Union regulatory agencies.

In Part 1, we review salient features of current regulation of medical devices, and attempt to clarify the scope of such regulation (e.g. what legally constitutes a medical device). We describe the established industry practices governing design, manufacture and distribution. In Part 2, to provide technical context relevant to the functional utility of conventional transcranial direct current stimulation tDCS, transcranial alternating current stimulation tACS, and transcranial pulsed current stimulation tPCS, we review output performance characteristics and regulatory class of existing OTC and prescription electrical stimulation devices, and summarize existing diversity and range in performance. In light of this diversity of current and proposed applications of tES, in Part 1, we consider the existing peer-reviewed scientific evidence, industry standards, and federal guidelines to support claims, direction, and governance of valid and viable use-in-practice. We explain established engineering and legal standards for the design and distribution of such devices, including federal regulations and international electrical, mechanical, and performance standards. The scope of the technical review provided in Part 1 is thus limited to summarizing existing law as applicable to conventional tDCS, tACS, and tPCS protocols; with any conclusions based solely on legal and engineering principles.

Risk management

Risk management serves as the cornerstone for guideline, regulation, and compliance development for any device that interacts with the body and should be performed continuously throughout the product lifecycle – spanning from the device prototype stage through the end of the device lifecycle (e.g. years after commercial product release). Risk management is defined as the application of various practices to analyze, evaluate, and control risk (of burden and/or harm that might be incurred). Specific best practices of risk management for medical devices are defined by the International Organization for Standardization (ISO) 14971 standard, and entail a multi-step process. First, a manufacturer should analyze the possible ways in which its device could bring harm to a user or patient, ideally casting a wide net to include causes such as human-factors issues or plausible interactions with other devices. Then, the manufacturer must determine the likelihood of each potential risk, using evidentiary data when and where possible, and supplemented by engineering and clinical best judgment. In this process, the gravity of any given risk is defined as the product of its severity (i.e. how great is the potential harm, on a spectrum from mild inconvenience to death) and its (actual) likelihood of occurrence.

Next, the manufacturer must identify safety measures, called mitigators, that act to reduce each identified unacceptable risk, so as to reduce (viz. mitigate) such risk to an acceptable range. The best mitigators are clear engineering requirements that can be designed and incorporated into a product – and, as importantly, can be empirically evaluated for their capacity to prevent or reduce

risk(s). For example, a neurostimulation device might include a feature that independently monitors output current and shuts off if and when excessive current is detected. In some cases, a manufacturer could adopt label mitigators (e.g. a warning label stating that a product should not be used under hazardous conditions). Ideally, these labeling mitigators are documented and verified to be salient, legible, and comprehensible before a product is released for clinical and/or market use. A complex device may have many (e.g. hundreds of) such risk mitigators.

The increased importance of risk management is a key development in the field of medical device regulation. IEC 60601-1, the primary standard governing medical device safety, has placed increasing emphasis on risk management from Edition 1 through Edition 3. Risk management has become fundamental to ensuring safety in a world where devices are controlled by complex software, and IEC cannot generate standards for every possible device function. Edition 3 was published in 2005 and became mandatory for new devices in the United States and Europe by 2013. The third edition has also become mandatory in additional regions (e.g. Korea in 2015). A manufacturer committed to the risk management process is far more likely to avoid last-minute compliance issues and unexpected problems in use, and even an OTC device manufacturer should approach execution and documentation of risk management activities according to these best practices.

Quality systems

As part of effective risk management processes, it is necessary to ensure that device design and testing are conducted in an orderly way, and that manufactured devices uniformly meet the requirements of the design. Best practices here, also known as current good manufacturing practices (CGMP), are similar to the principles of quality assurance used in many industries (for example, the ISO 9001 standards). These principles are codified by FDA in the Quality Systems Regulation (QSR, 21 CFR part 820) and internationally by the ISO 13485 standard. It is of note that these regulations apply to a variety of devices, and therefore rather than explicitly defining how a manufacturer must produce a specific device, they provide a template that manufacturers must follow to ensure orderly design, development, production, installation, and delivery. In practice, because CGMP regulations encompass a relatively wide array of devices, it remains partially up to a manufacturer to establish a quality system and design process within these templates (FDA's 21 CFR part 820 and/or ISO 13485), as well as establishing device requirements, that are sufficient to insure safety and effectiveness.

Labeling ethics, off-label use, and informed consent

In the United States, labeling of both medical and non-medical devices is directed by the Fair Packaging and Labeling Act (FPLA). The FDA administers the FPLA with respect to medical devices, while the Federal Trade Commission is responsible for execution of the FPLA for non-medical, consumer goods. Discussion of specific guidance for the labeling of tES devices is provided in Part 3. Here we consider ethico-legal issues germane to distinctions between clinical use (OTC or prescription), investigational uses, and more broad, consumer use of limited output tES products.

In the United States, current GMPs and requirements for devices are defined and prescribed in part 820 (21 CFR part 820), as originally authorized by section 520(f) of the Federal Food, Drug, and Cosmetic Act, which was issued as a final rule in the Federal Register of July 21, 1978 (43 FR 31 508), and which became effective on December 18, 1978. Manufacturers intending to market a device for a medical indication must first comply with relevant FDA requirements (see FDA regulatory class and degree of controls).

With regard to use and marketing by care-givers, the FDA (and comparable organizations that regulate device manufacturers outside of the United States) does not regulate the practice of medicine, which instead is subject to the direction of state and federal professional and licensing boards. Importantly, different regulations apply for off-label device use in medical practice vs research [9], and the “demarcation line” between the two is guided by the following definitions: The goal of medical practice is to “provide diagnosis, preventative treatment or therapy.” Research, on the other hand, is “designed to test a hypothesis, permit conclusions to be drawn, and thereby to develop or contribute to generalizable knowledge.” [10].

Regulations pertaining to off-label device use in medical practice: The FDA makes it clear that it does not regulate the practice of medicine and that the federal Food, Drug, and Cosmetic Act of 1938 will not play a role in creating physician liability for off-label device use. When not classified as tools involved in research, medical devices can be used in an off-label manner in medical practice without FDA regulatory oversight. Currently, the general legality and value of off-label uses is integral for medical practice [10]. Any ambiguity related to the matter was removed by the decision of the Supreme Court in *Buckman Co. v. Plaintiffs Legal Committee*, which states that “off-label use is generally accepted” in medicine, and under the law, “physicians may prescribe drugs and devices for off-label uses” (531 U.S. 341, 351 & n.5, 2001) [11]. It has been concluded that “the off-label use of a medical device is merely a matter of medical judgment and, as such, subjects a physician to professional liability for exercising professional medical judgment, but off-label use of a medical device is not barred by the U.S. Food and Drug Administration.” The limitation to this rule is that physicians may only prescribe off-label devices if the physicians are not employed by the medical or pharmaceutical companies in question. Further, manufacturers are limited as to what they may give to physicians as educational resources. Regarding whether informed consent must be obtained from the patient for off-label use of device in medical practice, no court decision to date has mandated that a physician must disclose, through an informed consent process, the off-label use of a drug (or device) [12].

Off-label device use for research purposes: For the application of the device in clinical research outside of or contrary to FDA approvals, the following requirements must be met:

- Approval by an institutional review board (IRB); and additionally, if the study involves a significant risk device (defined as one that presents a potential for serious risk to the health, safety, or welfare of a subject), approval of an investigational device exemption (IDE) by FDA
- Informed consent from all patients
- Labeling of the device for investigational use only
- Monitoring of the study and
- Required records and reports

Broadly any research involving human subjects, including that which involves limited output tES devices, must comply with the mandates for informed consent, and capacity for voluntary withdrawal from the experimental treatment as explicated by the Declaration of Helsinki, and as upheld in the United States by the Office of Research Integrity (ORI) and the Department of Health and Human Services Secretary's Advisory Council for Human Research Protection (SACHRP). In the United States, devices used in human trials are governed by the Investigational Device Exemptions (IDE) regulation, 21 CFR 812. Note that medical devices manufactured and employed under an IDE are not discharged from requirements set forth by 21 CFR 820.30 of the QS regulation. One path involves explicit FDA approval of an IDE application. However, the FDA

allows for various exceptions to explicit FDA review and approval of an IDE application: if a local IRB considers the trial to present minimal risk (i.e. non-significant risk, or NSR) then explicit FDA review is not required as long as the abbreviated IDE requirements (such as informed consent) of 21 CFR 812.2(b) are followed. The investigator provides the IRB with an initial assessment of the level of risk associated with their trial. The IRB may consult the FDA for a risk designation and/or guidance as defined in Part 3 of this document. As per the FDA definition, the denotation of non-significant risk is based on article 21 CFR 812.3 which states:

A non-significant risk device is one that does not meet a definition of a significant risk (SR) device:

Under 21 CFR 812.3(m), a significant risk device is defined as one that:

- Is intended as an implant and presents a potential risk to health, safety, or welfare of a subject;
- Is purported or represented to be for use supporting or sustaining life AND presents a potential risk to health, safety, or welfare of a subject;
- Is for a use of substantial importance in diagnosing, curing, mitigating, or treating disease, or otherwise preventing impairment of human health and life AND presents a potential risk to health, safety, or welfare of a subject;
- Otherwise presents a potential for serious risk to the health, safety, or welfare of a subject.

The IRB approval of a human trial is always specific to the subjects, conditions of use, and monitoring involved in the research, rather than simply being blanket approval of the use of a device. Nonetheless, the performance of a device features prominently in the review and approval process. An IRB may request information about both device operation (e.g. a manual) and the manufacturer, including documentation of compliance with standards (such as this industry guidance; Part 3). The requirement for IRB review is invoked by the intended use for research (see the definition of research above), irrespective of whether a device is marketed for clinical (i.e. a medical indication) or non-clinical (i.e. occupational or wellness) purposes. The majority of human research on limited output tES (e.g. tDCS), including those studies using clinical and healthy populations, have been, and continue to be conducted with a NSR designation and process (e.g. obtaining only local IRB approval).

As previously noted, labeling requirements for consumer devices, without a medical indication, are established under the FPLA, 16 CFR 550, 500–503, regulated by the United States Federal Trade Commission (FTC; and principally overseen by the Bureau of Consumer Protection). As well, the United States Department of Commerce, National Institutes of Standards and Technology Office of Weights and Measures executes additional oversight of labeling of consumer commodities, household goods, and resources. Per regulation, labeling must be conspicuous, clear, and explicate the contents, identity of the commodity, and name and address of the product's manufacturer, packer, and/or distributor. Device design and clear and definitive labeling are important to communicate particulars about the device and parameters for its responsible use, mitigate unintentional misuse, and in these ways uphold ethical aspects of trust-in-trade. Of course, despite attempts at stringency of labeling and directions for use, there will be instances of inappropriate use or overt abuse of any product that is made directly available to consumers. However, it is, and will be increasingly important to insure that the DTC market is not permeated by a *caveat emptor* mentality, in which consumers must be wary of risk

of injury because of a proliferation of poorly constructed, and/or inadequately labeled tES devices. Thus, we posit that developing and enforcing guidelines for labeling and use as we propose in Part 3 will be important to risk management by both fortifying industry standards and affording consumers access to design- and labeling-compliant tES devices.

Sub-vs extra-cranial targets

In this paper, we describe regulation of and recommendations for limited output tES devices. While in many cases these devices are intended to produce neuromodulation in sub-cranial targets, including cortical and deep brain regions enclosed by the skull, such devices may also be intended to modulate (or may modulate as an additional effect) extracranial neural tissue, such as peripheral nerves on the body or cranial nerves outside the skull. For the purpose of this paper, we define devices with either or both effects as tES devices, and we include in our discussion of stimulation types those waveforms intended to modulate any or both types of target (e.g., tPCS also includes pulsed stimulation applied to the head intended to activate cranial nerves).

We group these devices together for several reasons. First, it is likely that most tES interventions intended to stimulate the cerebrum by applying current through electrodes on the scalp in fact also stimulate cranial nerves, whether or not the effect is clinically or functionally meaningful. Research on “transcranial” stimulation has focused on direct electrical stimulation of the cortex to explain findings from behavioral, cognitive, neurophysiologic, and/or imaging studies [13–15]. However, the physics of tES dictate a much lower current density in the brain than in the skin and skull foramina (Fig. 2) - which means that a level of current that achieves meaningful cerebral neuromodulation may also potentially stimulate the cranial nerves that transverse the skin (e.g. forehead, neck) and foramina near the electrodes [16,17]. For example, transcranial direct current stimulation (tDCS) trials to treat major depressive disorder (MDD) intend to modulate the dorsolateral prefrontal cortex (DLPFC) by placing electrodes laterally across forehead [18,19] – but the forehead is innervated by upper branches of both the trigeminal (i.e.- fifth, nV) and facial (i.e.- seventh; nVII) cranial nerves. In healthy individuals it is also common to place tDCS electrodes on or across the forehead with the intention to modulate the frontal cortex to change cognition [20,21].

Second, many techniques that explicitly intend to electrically stimulate cranial nerves use a dose (produce outputs) that overlap with “transcranial” methods. Transcranial alternating current (tACS) over the occipital cortex is intended to modulate the visual cortex leading to subject perception of flashes of light known as phosphenes [13,22,23]. However, there is a long-standing debate over the origin of the phosphenes [24,25] and some studies conclude phosphenes are generated as a result of retinal electrical stimulation regardless of the placement of the stimulation electrodes [26,27]. Similarly, in the context of visuospatial attention, tES uses stimulating electrodes over the posterior parietal cortex in patients with visuospatial neglect [28]. But the vestibular system can be stimulated directly using galvanic vestibular stimulation (GVS) by placing electrodes near the mastoid, producing some overlapping behavioral effects [29]. Disambiguating which outcomes of tES (e.g. - tDCS, tACS, tPCS) reflect stimulation of cranial nerves is not within the scope of this document.

Distinctions between sub- and extra-cranial targets of limited output tES impact scientific investigation of mechanisms and engineering design, and may be considered in review by regulators. But as illustrated above, the engineering output, including

methods of application, of these devices – and so in ultimate actions on the body – can overlap. Even when action on one target is proven, it does not exclude (disprove) secondary action on other targets. So, unless otherwise indicated, for the purposes of this document we do not distinguish between the “intent” to stimulate sub-vs extra-cranial targets.

Regulatory definitions and general standards

As noted above, the FDA and comparable (trans)national agencies do not regulate the practice of medicine or general commerce. Rather, they prescribe quality and safety standards and regulations for the development and production of drugs and devices. As relates to specific issues and questions fostered by tES, it becomes important to clarify the definition of a “medical device”. Regulatory bodies and agencies of different countries have adopted varied positions and standards in defining a medical device. The United States has implemented what is recognized as perhaps the most conservative approach, which has served as a model for many international standards and codes. According to the FDA a medical device is:

“An instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including a component part, or accessory which is:

- 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.”

In addition, the FDA has established three different classifications for medical devices, designated as Class I, Class II, and Class III with distinct standards and controls that ensure safety and effectiveness depending on the risks imposed by device use. For example, dental floss, toothbrushes, and “band-aids” are Class I medical devices. Non-invasive blood pressure monitors, condoms, and OTC transcutaneous electrical nerve stimulation (TENS) devices for treatment of pain or for aesthetic purposes represent examples of Class II medical devices. Heart replacement valves or deep-brain stimulating electrodes, which are “life sustaining” or present a relatively large risk of injury, are examples of Class III medical devices. Based on the FDA definition of a medical device, and recognizing the spectrum of devices regulated, it is therefore the conservative position of this guidance document that tES technologies (i.e. tDCS, tACS, tPCS, etc.), whether indicated and/or employed for medical treatments, diagnostic purposes, wellness aids, recreational or entertainment devices, or any other purposes, may be classified as a medical device per the FDA – although others have argued contrarily [30]. Importantly, jurisdiction does not equate with targeted regulation or enforcement – for example, non-medical treadmills or heaters are intended (and marketed) to “affect the body” but are in practice not controlled by the FDA as medical devices. Regardless, whether the FDA does not have jurisdiction or elects to not regulate, Part 3 of this paper provides a necessary guidance for manufacturers.

Closely related to the FDA classification of medical devices is application of the provisions of General and Special Controls. The basic provisions of the 1976 Medical Device Amendments to the

Food, Drug, and Cosmetic Act provided the FDA with the means and authority to regulate devices in order to ensure their safety and effectiveness. Unless specifically exempted from regulation, all devices (Class I, II, and III) are subject to General Controls. Class I devices that pose a low to moderate risk are only subject to General Controls, which include provisions that relate to misbranding, device registration and listing, premarket notification, banned devices, notification and repair, replacement and refund, records and reports, restricted devices, and Good Manufacturing Practices. Class II devices, posing a moderate to high risk, are subject to both General and Special Controls; and Class III devices that pose a high risk are subject to General Controls and Premarket Approval (PMA). Special Controls are regulatory requirements imposed on Class II devices for which General Controls are insufficient, but for cases where there exists sufficient technical and clinical knowledge to confidently propose additional controls that will provide assurance of safety and effectiveness. These Special Controls are typically device-specific and include upholding performance standards, premarket data requirements, post-market surveillance, establishment of patient registries, special labeling requirements, and other guidelines. Premarket Approval applies to Class III devices that pose a high risk, are intended to be used in supporting or sustaining human life, and/or substantially preventing impairment of human health. The PMA process is reserved for devices that are designated such that General and Special Controls cannot sufficiently assure safety and efficacy. This category of devices is subject to the most stringent of all FDA regulations.

In countries other than the United States, the intended use of a tES device, whether to treat a disease or to provide neuro-modulation for consumer-oriented purposes, will determine if the device is regulated as a medical device or not. For example, a tES device indicated to treat depression will be regulated as a medical device in almost all countries. However, a tES device indicated to enhance cognitive abilities might not be uniformly regarded or regulated as a medical device. This does not imply, however, that consumer-oriented tES devices are not regulated by other safety standards, such as electrical and mechanical safety guidelines, or regulations regarding fair marketing of consumer products. For example, in the EU tES devices must at minimum receive a CE mark prior to being cleared for marketing and distribution.

A CE mark, in turn, will require compliance with applicable electro-mechanical design and production standards, which are often subject to independent (3rd party) verification and documentation. The IEC has established globally accepted guidelines to ensure the manufacture of safe electrical products. Medical devices are specifically subject to the IEC-60601 family of standards, most importantly the general safety controls in IEC-60601-1. This general standard is well harmonized between the international (IEC) and United States' (Underwriters' Laboratories-UL) versions. Collateral standards in the 60601 family cover topics such as equipment's alarm systems, equipment for home health care environment, electromagnetic immunity and emissions of the equipment, equipment's performance and usability, programmable electrical medical systems equipment, nerve and muscle stimulators, electroconvulsive therapy equipment [31]. Some types of devices are also subject to specific standards; for instance, TENS units must adhere to IEC-60601-2-10, “Particular requirements for the basic safety and essential performance of nerve and muscle stimulators.”

While allowing “member States to decide on a case-by-case basis whether or not a product falls within the scope of [medical device] regulation”, the EU has indicated that at least risk management should apply to tES regardless of medical or consumer indicated use [32]:

[Medical device] regulation shall also apply to the groups of products without an intended medical purpose that are listed in Annex XV ... taking into account the state of the art, and in particular existing standards for analogous devices with a medical purpose, based on a similar technology. The common specifications for a group of products listed in that annex shall address, at least, application of risk management ... and, where necessary, clinical evaluation regarding safety.

[Annex XV includes] 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.

Here the European Parliament and Council on Medical Devices distinguishes stimulation that is sub-cranial (vs *trans*-cranial) in intended use (see: Sub-vs Extra-Cranial Targets).

The aforementioned points illustrate that classification of tES devices as medical devices or other products can be complex and depend on country. Irrespective of definition and jurisdiction by agencies that govern medical devices, jurisdiction does not imply or mandate targeted regulations – in other words, a product might be considered a medical device and fall under the jurisdiction of a regulatory agency such as FDA according to the statutory definition, but the agency may choose not to explicitly examine the product, for example as described by FDA for “general wellness devices.” Further, there is recognition that even when devices are not strictly defined as medical, risk management is important. Thus, notwithstanding these differences, in most developed countries, any tES device, regardless of indication for use, would be regulated by rigorous design, production, and often distribution standards – notably the CE mark in Europe. As well, further legal restrictions may apply. For example, as previously noted, in the United States, marketing claims for tES devices fall under the purview of either the FDA, and/or the FTC, which serves to protect consumers against false labeling and advertisements. Thus, in most countries, including the United States, debating “if” tES devices should be regulated is a moot point, since regulations under international and regional laws already exist that specify engineering standards and rules for distribution. Part 3 of this paper thus provides guidance on best practices that align with existing rules.

FDA regulatory class and degree of controls

For any tES device intended for a purpose of providing therapeutic intervention against a disease or medical condition (i.e. a medical label), medical device regulation by the FDA is further subject to the particulars of regulatory class. There are several possible regulatory paths within the FDA by which a product can be approved for market. First, is that a device or product can be exempt from a clearance path, which is often referred to as a 510(k) exemption. Nearly all Class I Medical Devices are exempt from regulatory clearance paths, in the sense that formal submissions to the FDA for marketing are not required, assuming that a manufacturer meets relevant regulations and international guidelines (e.g. IEC-60601).

Most non-invasive electrostimulation devices that are in some way similar to tES in function and application, such as TENS, powered muscle stimulation (PMS), and iontophoresis devices are Class II medical devices and, as such, are regulated by a Premarket Notification 510(k) process. These devices may be cleared for prescription or OTC use. In the past, most electrostimulation products cleared through the 510(k) process have been designated as prescription-use devices, for example, TENS devices that were intended to treat pain. However, with increased confidence in the

safety of electrostimulation technologies and devices gained over the past four decades, many such products have now been approved for OTC use. Thus, TENS devices, whether used to treat pain or for aesthetic purposes, as well as PMS devices for muscle conditioning, can now be marketed for OTC use and purchased at many pharmacies and/or online.

Under the 510(k) path, the FDA can deem a new device intended to be marketed to be substantially equivalent to a “predicate” device that is already on the market for a specific indication. If cleared, the FDA will assign the product code of the predicate device for a specific intended use. When there is no clear predicate or path, a device manufacturer may seek clearance through the *de novo* 510(k) process, and a new FDA product code may be assigned. The *de novo* 510(k) process is often used for devices that are recognized as being safe and comparable to others already marketed, but where the closest comparable FDA-cleared device(s) are used for a different indication and intended use, and consequently cannot serve as predicate devices under the conventional 510(k) process. For example, the *Cefaly* device, a TENS unit indicated to relieve pain associated with headaches via the use of low level electrical current delivered through electrodes placed on the head, recently received clearance by the FDA through this *de novo* 510(k) process. The *Cefaly* device is approved for prescription use only, and is not sold OTC.

In 2008, the FDA approved the *Neuronetics (Neurostar)* device, which uses repetitive transcranial magnetic stimulation (rTMS), under *de novo* 510(k) with a Class II product code OBP. *Brainsway (Deep TMS)* rTMS followed in 2013. Other rTMS products have since been approved under the 510 k process. The use of high-intensity repetitive pulsing by these devices is associated with a low risk of seizures [33]. It is noteworthy that a broad range of energy output devices have been classified as Class II and/or cleared through the 510 k process. Also notable is that electroconvulsive therapy (ECT) devices, which by intent and design produce seizures, and utilize electrical currents having a magnitude on the order of hundreds of mA, while characteristically designated as Class III devices, have been granted “grandfathered” clearance (see below) under a 510(k) process by the FDA-despite incurring cognitive side effects (e.g. mild memory impairment). Furthermore, it has been proposed that these devices be re-classified to Class II, for at least some indications [34]. (Fig. 1).

Typically, the PMA pathway is designated for Class III medical devices that may pose significant safety risks and thus require extensive proof of safety and effectiveness prior to obtaining clearance. Cranial electrotherapy stimulation (CES) devices, which deliver pulsed current for therapeutic indications, are presently designated as Class III Medical Devices, but this reflects their pre-amendment (viz. - “grandfathered”) status rather than actual risk level. In 2016 the FDA issued new guidance for CES devices, including re-classification of certain indications to Class II. While the regulatory process for CES has been updated, clinical evidence supports that there are minimal risks associated with existing CES protocols [35–37]. At present, CES devices are intended to treat clinical conditions (e.g. depression, certain forms of anxiety) and can only be legally obtained through provision by a clinician.

In 2010, the FDA published Class II Special Controls Draft Guidance Documents for Industry and FDA staff, which if put into effect, would make certain OTC TENS and PMS devices with specific medical or aesthetic labels exempt from the premarket notification 510(k) regulatory process [38,39]. The premise of these documents is to establish Special Controls with Limited Output guidelines for several types of OTC electrostimulation products with medical indications that are designated as Class II devices. For example, TENS with limited outputs for aesthetic purposes, and PMS with limited outputs for muscle conditioning, are both intended for OTC consumer use and would therefore be exempt from a premarket

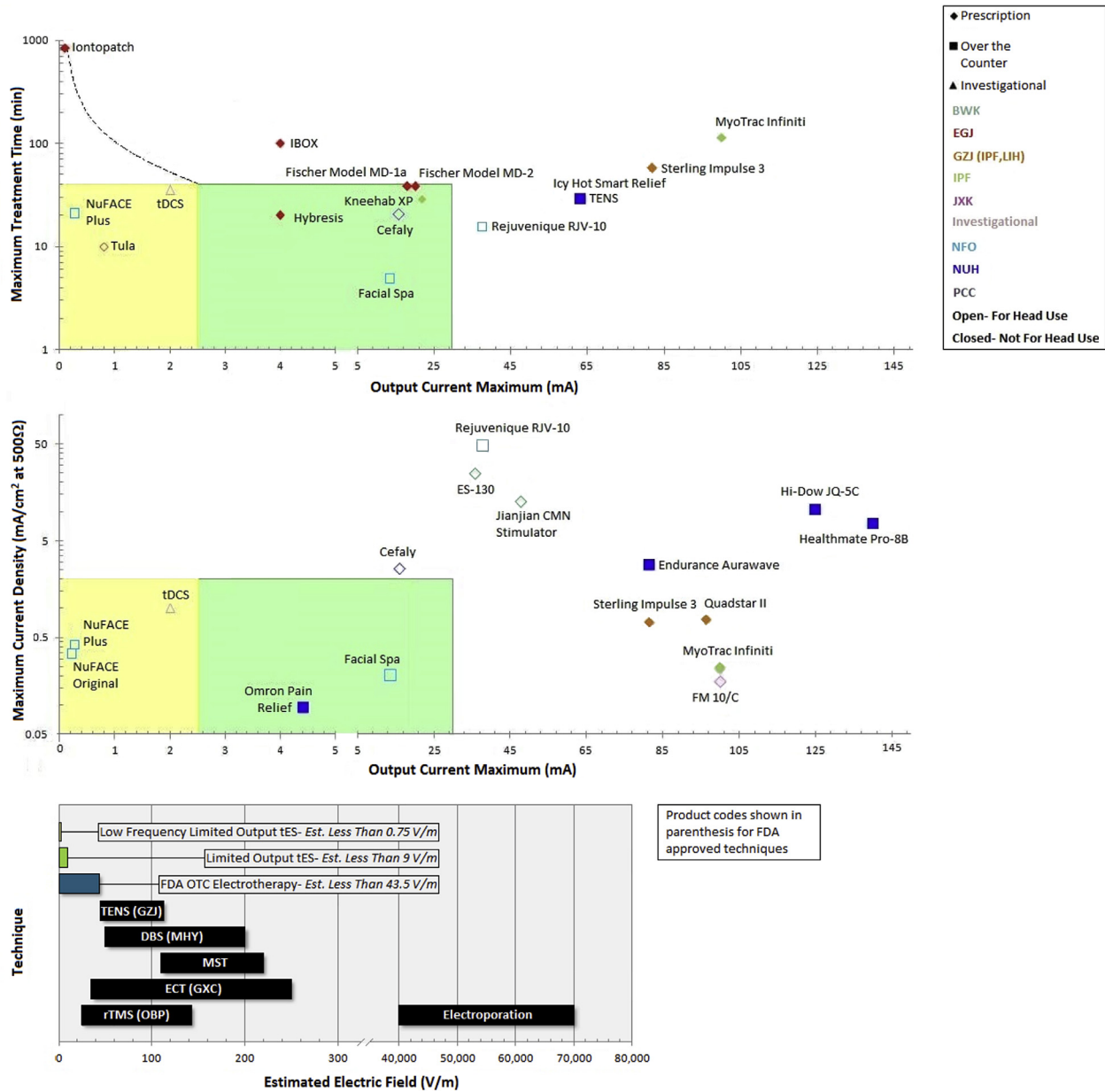


Fig. 1. Output comparisons of various electrostimulation and neurostimulation devices cleared or approved by the FDA in contrast to tES. The scatterplot (top) illustrates a wide range of maximum current outputs as a function of treatment time for tES approaches and FDA-cleared or approved electrical stimulation and neurostimulation devices. The devices selected are exemplary and a complete set would evidently cover at least as wide a range. As indicated by the legend, devices output markers have been color-coded according to FDA product codes, shapes represent device status (triangle = investigational device, square = over-the-counter, and diamond = prescription use), and fills illustrate whether a device has been intended for use on the head or not (closed symbols = not intended for use on the head, open symbols = device has been intended for use on the head). Conventional output limits for tPCS are indicated by the green highlighted region, including the yellow region. Conventional output limits for tDCS and tACS are indicated by the yellow region. The black dotted line traces points at which 6000 mC are delivered - the highest deliverable charge in the yellow area. The middle graph illustrates the range of maximum current outputs as a function of maximum current density under a 500 Ω load for FDA-cleared or approved electrical stimulation and neurostimulation devices. The bottom graph illustrates the range of predicted electric field strengths proposed for tDCS/tACS, tPCS, FDA cleared devices that are OTC (TENS), prescription use TENS devices cleared by the FDA [151], magnetic seizure therapy (MST) [152], FDA-approved DBS [153–155], rTMS [156,157], and electroconvulsive therapy (ECT [158,159]) devices, and electroporation devices [160,161]. Output characteristics and quantities were obtained from referenced sources [162–180] and as described in text. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

notification 510(k) clearance process. It is critical to note that these devices will still be Class II devices and required to verifiably uphold certain General and Special Controls, as well as international safety standards. The draft guidance documents establishing Special Controls and Limited Output concepts are important because they establish defined parameters with which to deem and insure the

safety of electrostimulation products of various types (regardless of indication for use), as based upon the bulk of evidence available to date. Therefore, the industry guidance we propose in Part 3 for limited output tES devices with medical (prescription or OTC) or wellness labeling is harmonized with this draft FDA guidance; while in Part 2 (*Engineering analysis of electrostimulation output*

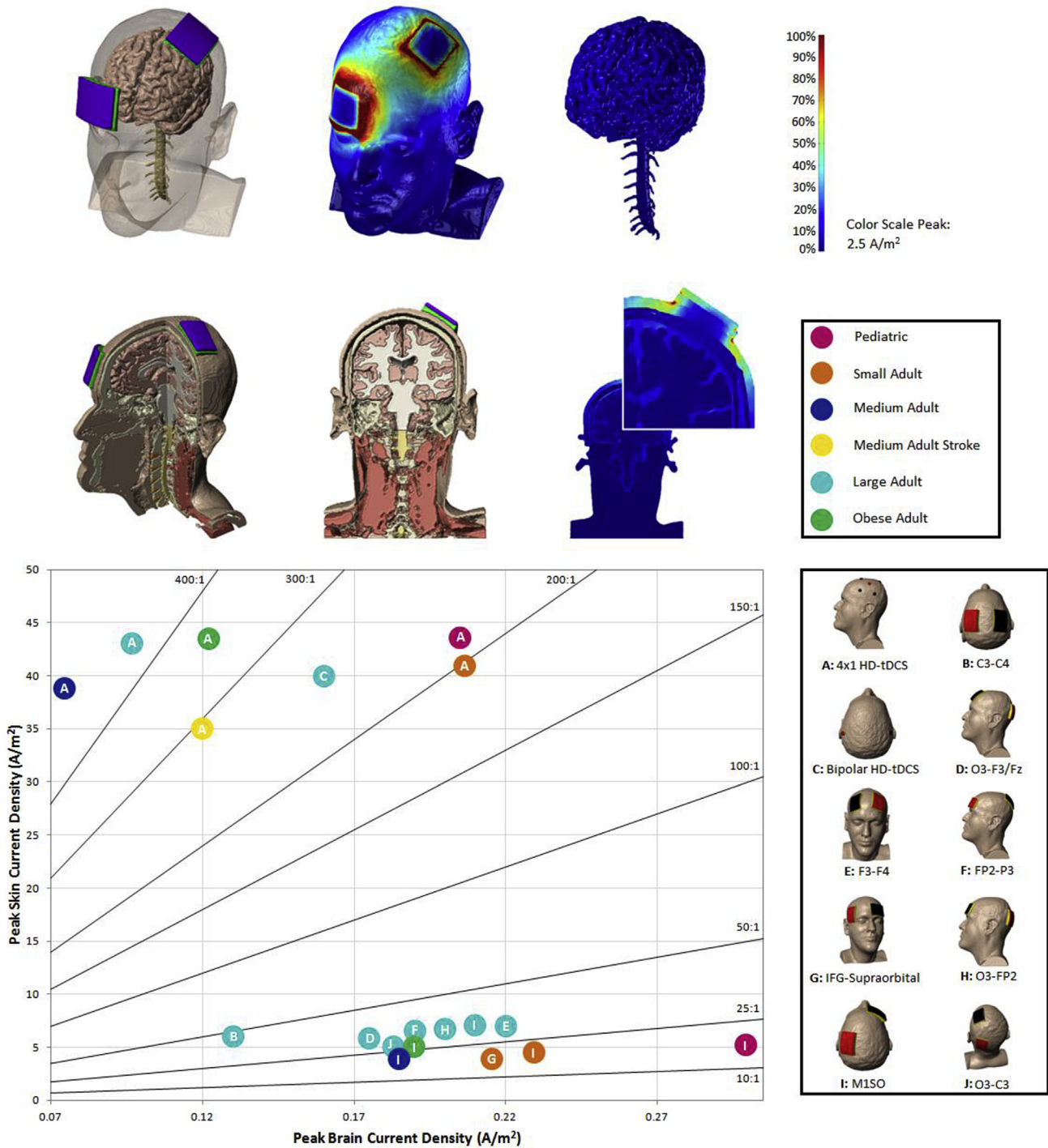


Fig. 2. Prediction of current flow through tissue layers highlights the ratio of current densities between the skin and brain. The most common side effect to tES and other FDA-cleared electrostimulation and neurostimulation devices is skin irritation, redness, itching, or mild burning sensations. We used computational modeling to illustrate the behavior of electrical current delivered by electrical currents as they pass through the scalp, skull, dura, CSF, and into the brain (top; values per mA current applied). Because electrodes are placed on the scalp during tES, and due to the conductivity and anatomy of the underlying tissue, the majority of the current does not reach the brain and the fraction that does reach the brain is diffuse and orders of magnitude below biologically damaging thresholds. Thus, the current density at skin is invariably higher than the current density in the brain. The skin provides a biological “protection” layer, since it receives the highest exposure levels. Conventional tDCS, tACS, and tPCS would have peak current density limit below the levels of many OTC TENS devices indicated for cosmetic purposes and intended for placement upon the head and face. As illustrated by the scatterplot (bottom) the ratio of current density at the skin versus the brain is variable and depends on several factors including the electrode montage, fat distribution on the head, age, and other tissue properties – but inherently independent of applied current. For a single head, the ratio is predicted for various conventional and High Definition (HD) montages used. The ratio of the estimated current density at the scalp to the current density in the brain varies from greater than 10:1 to 400:1. Computational methods used and some of the current estimates used were obtained from referenced sources [181–183].

parameters) we describe the range of waveform parameters produced by FDA cleared (OTC) devices, which constrains the scope of devices included in this industry guidance.

Table 1 depicts different electrostimulation devices for which FDA product codes presently exist, including five product codes for OTC electrostimulation devices with limited output. These devices encompass, and in many cases exceed, output characteristics of state-of-the-art tES methods that are currently being used. There is also overlap in use; for example, iontophoresis devices have been used off-label in numerous tDCS clinical trials (with IRB non-significant risk designation). Table 1 also indicates the Medical Device Class for each product code, the regulatory path for obtaining clearance, whether a device is indicated for OTC use, and whether a device is intended for use on the head. The specific output characteristics of these devices are discussed in further detail below.

The role of government and non-government agencies in public health standards related to limited output tES

The distinction between regulatory jurisdiction and a need to restrict manufacturer activities through explicitly targeted standards or enforcement is a significant source of confusion in discussions concerning the regulation of limited output tES. To reiterate, the position of this guidance document is that the FDA (and counterpart agencies in other countries) has jurisdiction over limited output tES devices regardless of intended use. However, the mandates of these agencies typically relate to both “protecting” public health with minimal/reasonable burden, and simultaneously “promoting” reasonable access to medical and wellness technology, as well as “innovation”. The decision to define, impose, and enforce standards targeted toward specific industries is therefore guided by overall consideration and dictates for public health. Thus, regardless of the definition of a medical device for the purpose of jurisdiction, the need to protect both personal liberty and public health informs government activity. In this sense, Part 3 of this document provides guidance for devices that pose minimal risk.

Indeed, the majority of technical standards applied to medical and consumer devices, as selectively adopted by the FDA, are developed externally by non-government organizations (e.g. the Institute of Electrical and Electronics Engineers [IEEE], UL, and the

IEC), thereby placing the burden of ongoing development and revision of these standards upon a coalition of industry veterans and standards professionals. As new technologies are introduced to the public, applicable standards are developed and refined in order to help ensure quality, safety, and effectiveness. The IEC and other organizations work by consensus to rationally establish standards and requirements, using engineering analysis and scientific data (e.g. results/outcomes of human trials; for example [40]) in contrast to engaging in mere speculation in the absence of specific data. This level of objectivity is essential, as speculation based on “slippery slope” arguments, subjective “calls for caution” in the absence of data, and/or “what if” propositions that do not reflect realistic circumstances may impede authentic deliberation and sound standards [41]. This is particularly important because industry standards serve a role in more than just regulation; alongside medical and government activities, industry standards also serve to support informed decisions by the public. It is in this light that this document seeks to draft such an industry standard for limited output tES.

Clarifying home-use in the context of consumer and medical limited output tES

For wellness indications, the possibility of a home use device is implicit. For medical indications, the FDA defines key aspects of a home-use medical device to be:

- “A medical device intended for users in any environment outside of a professional healthcare facility. This includes devices intended for use in both professional healthcare facilities and homes.
- A user is a patient (care recipient), caregiver, or family member that directly uses the device or provides assistance in using the device.
- A qualified healthcare professional is a licensed or non-licensed healthcare professional with proficient skill and experience with the use of the device so that they can aid or train care recipients and caregivers to use and maintain the device.”

Herein, we distinguish four basic categories of “at home” use, each of which poses different issues that must be considered in the

Table 1
FDA product codes for electrical stimulation and neurostimulation devices that are equivalent to tES devices as exhibited by off-label use in thousands of clinical investigations and basic research studies, as well as by the DIY community to achieve tES.

Product Code	Device	Class	Regulation	OTC	Cleared use on head
GZJ	Stimulator, Nerve, Transcutaneous, For Pain Relief	2	510(k)	No	No
JXK	Stimulator, Cranial Electrotherapy	3	510(k)	No	Yes
NFO	Stimulator, Transcutaneous Electrical, Aesthetic Purposes	2	510(k)	Yes	Yes
NUH	Stimulator, Nerve, Transcutaneous, Over-The-Counter	2	510(k)	No	No
NYN	Stimulator, Electrical, Transcutaneous, For Arthritis	2	510(k)	No	No
PCC	Stimulator, Nerve, Electrical, Transcutaneous, For Migraine	2	510(k)	No	Yes
BWK	Stimulator, Electro-Acupuncture	1	510(k)	No	Yes
IPF	Stimulator, Muscle, Powered	2	510(k)	No	No
NGX	Stimulator, Muscle, Powered, For Muscle Conditioning	2	510(k)	Yes	No
NUW	Stimulator, Muscle, Powered, Dental	2	510(k)	No	Yes
EGJ	Device, Iontophoresis, Other Uses	3	510(k)	No	Yes
KTB	Device, Iontophoresis, Specific Uses	2	510(k)	No	Yes
LIH	Interferential Current Therapy	2	510(k)	No	No
OCF	Stimulator, Nerve, Electrical, Transcutaneous, Limited Output, Arthritis Pain Relief	2	510(k)	Yes	No
NYY	Stimulator, Muscle, Powered, With Limited Output, For Rehabilitation	2	510(k)	Yes	No
NYZ	Stimulator, Muscle, Powered, With Limited Output, For Muscle Conditioning	2	510(k)	Yes	No
NYW	Stimulator, Nerve, Electrical, Transcutaneous, With Limited Output	2	510(k)	Yes	No
NYX	Stimulator, Electrical, Transcutaneous, With Limited Output, For Aesthetic Purposes	2	510(k)	Yes	Yes

The FDA product codes cover more than 1200 electrical stimulation devices that have been cleared for marketing since 1977. Each of the product codes are classified with short device description, the FDA Medical Device Class, the regulatory path for obtaining FDA clearance, whether the device is specified for OTC use and whether the device is designed to be used on the head. The grey shaded rows indicate product codes for OTC electrostimulation devices with limited output.

risk management process (Part 3). The first category is those devices that are used in the context of a home visit by a clinician. Second is those devices employed within a telemedicine approach, in which the use of a device is remotely supervised. Third is representative of use of a device by patients who are under medical care but for whom regular in-clinic treatment represents an intractable or unnecessary burden. Fourth is the use of devices for wellness purposes. Additional use cases would either fold into one of these categories or be outside the scope of this guidance. Effective risk management in each and all of these categories of use must consider the technology, indication for use (e.g. medical or wellness), and factors including the training and physical condition of person using the device, as well as the training and capability of any individuals providing assistance in administering the device. Table 2 illustrates the different categories (modes) for at-home uses of limited output tES that require distinct risk management. Risk management must incorporate features and mitigators that are specific to the nature of intended use (category).

For the first category of home-use, if a physician or caregiver certified in tES at home travels to a patient’s home with a device designed for in-clinic use (*local supervised and expert administered*), limited output tES can likely be applied in the home setting with well-defined and maintained benefit and minimal risk(s). In this case, even devices designed for in-clinic use may be directly applied in home-use, though additional mitigators may be incorporated.

The second category, remotely-supervised tES for telemedicine, has been developed with a detailed risk management structure that spans device design, operator training, patient clearance, and ongoing monitoring [42]. Qualified health-care professionals function as supervisors who are responsible for device selection and customization (programming, head-gear adjustment), training and certification of patients or proxies, and ongoing remote support and monitoring. Such considerations are typically indication- and patient-specific (e.g. multiple sclerosis [43]; including considerations of whether tES should be self-applied (*Remote-supervised self-administered*), or administered by a proxy (*Remote-supervised proxy-administered*), such as family member or caregiver. In contrast to availability by conventional prescription or OTC access (i.e.- the third category), remotely-supervised tES requires: (1) prescription of devices by a healthcare provider or inclusion of a patient in a clinical trial, (2) patient screening (typically in a clinic), (3) patient/proxy training and certification, and (4) ongoing monitoring (e.g. device recording, supervisor telemedicine) to insure compliance with prescribed use [42]. Devices and accessories designed or certified explicitly for remotely-supervised use must insure that all stimulation waveforms are pre-set and the

timing of application is limited (by either temporal parameters or use codes provided by the supervisor). For example, in the transition from in-clinic to remotely-supervised tDCS, device settings and protocols that are appropriate for use at a medical center (e.g. adjustable headgear, multi-step electrode preparation) may introduce burdens and/or risk if/when applied by patients or a proxy; these risks are mitigated through the integration of rational device design and procedural controls [42].

In the third category, prescription (*prescription and self-administered option*) or OTC (*over-the-counter and self-administered option*) medical use, the limited output tES device is provided for a medical indication for at-home use. Such medical devices can be administered either with the assistance of a caregiver (e.g. a medical aide, family member) or directly by the patient (self-application option). For the transition of medical use device from in-clinic to the home-use and then from prescription to OTC, the governing principle remains risk management, especially consideration of human factors specific to the intended user(s) and taking into account their medical status and/or disability if relevant. The patient must be able to self-diagnose, self-treat, and self-manage (as assessed by label comprehension studies and actual-use studies) in order to be viable for OTC access and use.

The fourth home-use category is specific to devices that are obtained by consumers for wellness purposes (i.e.- without a medical label or supervision), and are used in situations in which self-administration is expected. The presumption of self-use evidently does not obviate any of the requirements in this guidance.

In each of these modes of use, we advocate that manufacturers should apply the following two principles of risk management:

- Reduce as far as possible the risks related to the ergonomic features of the device and the environment in which the device is intended to be used (i.e.- design device for patient safety), and
- Consider the environment/context, and technical knowledge, experience, education, training, and physical and/or medical condition of intended user(s) as applicable to particular category/mode of use (i.e.- design device for professional, lay, disabled, and/or other users' safety).

Part 2: Engineering analysis performance characteristics of FDA cleared electrical stimulation devices compared to tDCS, tACS, and tPCS

Table 1 illustrates FDA product codes covering more than 1200 electrical stimulation devices that have been cleared for marketing since 1977. Supported by more than 40 years of commercially

Table 2
Categories of home-use and related considerations.

Intended Use (label)	Medical	Medical	Medical	Medical	Medical	Wellness*
Category (Mode of use)	(1) Local-supervised use and expert administered	(2) Remote-supervised use and proxy-administered	(2) Remote-supervised use and self-administered	(3) Prescription and self-administered option	(3) Over-the-counter (OTC) self-administered option	(4) Consumer self-administered
Monitoring	Local administered by on-site expert	Remote monitored -telemedicine	Remote monitored -telemedicine	Use not directly monitored	Use not directly monitored	Use not monitored
Device User	Traveling certified caregiver	Family member or local caregiver	Self (Patient)	Self (Patient) option	Self (Patient) option	Self (Consumer)
Device Customized from In-Clinic Technology	Not Needed.	Needed.	Needed.	Needed.	Needed.	N/A

The medical devices are divided up in three categories to differentiate how the devices can be monitored. The first category includes devices that are strictly administered by clinicians who visit the patient’s home. The second category uses the telemedicine approach in which the clinician remotely monitors patients while the device is administered either by family or by patients themselves. The third category of medical device is self administered and not directly monitored by clinicians. The fourth category, wellness, does not involve devices labeled for medical indication and is directed towards consumers who administer the device on their own. *Per this guidance document, medical grade design and manufacture standards apply for devices marketed for medical purposes.

regulated use to date, three of the product codes (NFO, NUH, and NGX) cover 98 cleared products indicated as OTC electrical stimulation devices, which can be purchased without a prescription. An additional five product codes (grey highlights in Table 1; OCF, NYX, NYZ, NYW, and NYX) have been established by the FDA under Class II Special Control draft guidance documents specifying limited output guidelines, but have yet to become legally adopted. The output parameters of both prescription and OTC electrostimulation devices span a large parameter space of waveform type, peak current output, maximum voltage, maximum average power, and current density.

There is a diversity of output parameters for prescription and OTC electrostimulation devices (Table 4) cleared by the FDA. To highlight this point, we compare two TENS products cleared by the FDA that are both intended for electrode placement on the head and face. The first, *Cefaly*, is a prescription device recently cleared through a *de novo* 510(k) process under the newly established product code PCC, which is a TENS device to be used for the treatment of migraine. As shown in Fig. 1, the *Cefaly* device has a maximum pulsed current output of 16 mA under a 500 Ω load and provides a maximum current density of 2.37 mA/cm² and an average power density of 0.17 mW/cm² at 500 Ω . In contrast, the *Rejuvenique* device is an OTC TENS unit indicated for cosmetic purposes, and cleared under product code NFO. As shown in Fig. 1, *Rejuvenique* has a maximum pulsed current output of 37.6 mA under a 500 Ω load and provides a maximum current density of 46.4 mA/cm² and an average power density of 2.31 mW/cm² at 500 Ω . These values illustrate an OTC TENS device indicated for cosmetic use that has a maximum current output that is more than twice that of a prescription TENS device indicated to relieve pain associated with headache. Further, the maximum current density of the OTC TENS device is more than 19 times higher than the prescription device. In any case, the FDA clearance is predicated on the confidence in device safety for these output parameters, which is buttressed by decades of post-market experience with limited output tES waveforms.

The electrode current density (i.e. the applied current divide by the electrode area) typically employed for tES in both research studies, investigational clinical studies deemed as non-significant risk by IRBs, and the FDA is ≤ 2 mA/cm² [44]. Additionally, there is an inherent biological safety mechanism built into tES devices. The skin surface is subjected to the highest current densities (Fig. 2). Skin irritation and, in extreme cases, burns are the first signs of adverse events. At standard tES doses, the brain is subject to current densities that are orders of magnitude lower than that of the skin (Fig. 2). Although, the damage threshold for the brain tissue is different from the scalp [45].

The electric field strength generated by TENS and other electrostimulation devices intended for placement on the head and face (Fig. 1) provides further indication of safety margins when compared to the relatively weak electric fields induced by techniques such as tDCS, tPCS, or tACS (Fig. 2). The high current density in the skin also prompts questions about putative mechanisms of action. Depending on electrode montages used, it is plausible that cranial nerves (e.g. CN V, VII, and X) are also activated by traditional tES methods. For example, tDCS electrodes positioned over the dorso-lateral prefrontal cortex are situated such that they could modulate the activity of trigeminal (CN V) nerve branches extending across the top of the forehead, while electrodes placed on the back of the head, neck and shoulders likely affect the activity of cervical spinal nerves (C2–5). At present, it is difficult to know what extent of effects from tDCS are generated by direct brain modulation versus modulation of cranial nerve afferents (which may then incur “bottom-up” effects via subsequent activation of brainstem and ascending pathways).

Conversely, for technologies intended (e.g. a hypothesis of mechanism) to modulate the cranial nerves (e.g. *Cefaly*) or to more generally apply current to the head (TENS for aesthetic purposes), weak currents generated within the brain may be comparable to those generated by tDCS/tPCS/tACS. While discussion of ancillary targets is beyond the scope of the present paper, from an engineering analysis it is rational to group technologies that apply comparable currents to the head regardless of intended use – the name of the device (nominal application) does not change its effects on the body. Thus, while we recognize that “tES” is typically used in a general sense to indicate a nominal intention for direct (sub-cranial) brain activation, evidence for safety of TENS to the head, including when nominally intended to stimulate cranial nerve pathways, is relevant, as summarized in the following section.

A large study was recently conducted to assess the safety of supraorbital trigeminal nerve stimulation for the treatment of headache using the *Cefaly* device at a peak current 16 mA and a maximum current density of 2.37 mA/cm² for 40-days (20 min/day). In a sample size of 2313 subjects, there was a 4.3% incidence rate of adverse events, the most common of which was skin irritation, and the most severe of which was a skin allergy [46]; most likely causes of the skin allergy are a result of contact dermatitis from the acrylates or glycerin used in the conductive adhesive, not as a result of the device output. Some devices fall into the category of TENS for cosmetic or aesthetic purposes, which have been cleared by the FDA through a 510(k) process for OTC marketing. One example is the Bio-medical Research (BMR) Face device, which is an OTC TENS device designed to target the trigeminal nerve and provide neuromuscular electrical stimulation (NMES) to encourage facial rejuvenation for aesthetic purposes. A recent study examined the safety and efficacy of this device at a peak current intensity of 35 mA when used five days per week for 20 min each day for 12 weeks [47]. There were 56 subjects in the active treatment group and 52 in the sham-control group. There were no significant adverse events in this study, and the only reported side effects were minor skin redness following stimulation, which disappeared within 10–20 min following use [47]. Additionally, there was one report of a subject who experienced eye fluttering, which was thought to be a result of stimulation, although this effect abated after a couple of days. Similar safety profiles have been reported for devices that stimulate the trigeminal nerve for the treatment of depression or epilepsy [48–51]. Collectively, these findings further attest to the safety of electrical stimulation applied to the head and face, even at peak currents that are substantially higher than what is typically used for tES.

Another cosmetic device, the *Facial Spa* marketed by Nu Skin Enterprises recently received 510(k) clearance for OTC distribution for stimulation of healthy facial skin. The *Facial Spa* provides 0.4 mA of Direct Current stimulation, applied through a hand-held device; stimulation sessions can be initiated *ad libitum*. In clinical trials, the number of sessions is typically limited to one per day (in some cases increased to two). And, while all electro-stimulation devices approved by the FDA are limited in session duration (and hence are also limited in total charge), there is not a standard limitation on the ability of a user to re-activate the device in order to deliver protracted stimulation. For repeated use, this industry guidance proposes an approach that is even more conservative than existing FDA Limited Output standards and guidelines for currently marketed prescription and OTC devices. Rational risk management should nonetheless allow a least-burdensome manufacture of well-tolerated medical grade tES devices.

Part 3: voluntary industry Guidance for tES with limited output

Introduction and scope of part 3

The adoption of voluntary industry standards is driven by an imperative to insure access to safe, limited output tES. These standards in no way reduce the need to comply with all relevant regulations. Notably, if the intended use includes the treatment of a medical condition, the device manufacturer must comply with relevant federal regulations (i.e., in the United States with applicable FDA statutes; see above). But industry standards may also inform design of devices for non-medical use. Based upon (1) experience with, and evidence gained from work with comparable devices (Part 2), and (2) existing regulations (Part 1), we herein propose rigorous engineering standards for tES technology with limited output (Part 3). We assert that voluntary industry adoption of these standards will improve consumer safety and confidence by differentiating those devices for which safety is not necessarily established from those technologies that have been subject to manufacturers' requirements for best practices for risk management and quality systems design.

Diverse applications and possible indications for tES

An important consideration for the regulation of tES devices is that there are numerous potential indications for use. At present, tES has been employed in the treatment of stroke [52–56], depression [57–59], obsessive-compulsive disorder [60], spinal cord injury [61–64], chronic, neuropathic, and/or acute post-operative pain [65–70], post-traumatic stress disorder [71], epilepsy [72,73], schizophrenia [74–77], attention-deficit disorders [78–80], coma [81,82], Parkinson's disease [83–86], and addiction [87–91]. Although further clinical trials are important to establish efficacy in many of these applications, the potential benefit (e.g. relief from pain, restoration of function) and minimal risk of limited output tES has attracted significant interest from both the medical community and patients.

With few exceptions, the progression to end-phase clinical trials for many of the abovementioned indications could take several years (if not decades), delaying FDA approval processes, and thereby preventing patient access to on-label tES. The range of possible indications means that even if FDA approval for one indication is granted, the use of tES in the treatment of numerous other disorders may remain unapproved. Moreover, clinical effectiveness trials typically adopt highly restrictive inclusion/exclusion criterion (for data integrity and statistical power reasons), meaning if/when approval is achieved for a given indication, most patients would not strictly qualify under the label (requiring off-label use by physician discretion [92]).

Challenges in defining therapeutic potential (and so obtaining regulatory approval) of tES are also due, at least in part, to the use of varied types of stimulation (e.g. tDCS, tACS, transcranial random noise), and electrode montages that are employed in and across studies. To date, patients and doctors do not have sufficient access to “off-label” tES devices that enable replication of therapies, such as tDCS, that are used in clinical trials. This can result in unfortunate substitutions, and/or modification of devices that may not be suitable or safe for a given indication. Thus, the uniform adoption of limited output standards and availability of medical-grade consumer tES devices would: 1) provide that clinicians and patients have access to tES devices engineered and manufactured in accordance with medical device quality and standards; and 2) support

the development and validation of tES therapy paradigms in a safe and responsible manner. Any medical claim that is part of the device labeling by the manufacturer would be subject to proper validation and certification through the appropriate regulatory bodies. Further physician oversight and prescription use may be required as a condition for providing such therapies.

With regard to the potential use of tES in healthy individuals (i.e. non-medical or “wellness” use), basic research and human trials have suggested that tES may (positively) modulate working memory [93–100], enhance memory consolidation [101–105], suppress fearful memories [101], increase vigilance or sustained attention [98,106,107], facilitate creative problem solving and insight [108–111], accelerate language acquisition and enhance its retention [112–116], improve reading efficiency [117], increase learning [105,118–121], improve mathematical abilities [122,123], increase self-awareness during lucid dreaming [124], increase physical endurance and reduce perceived physical exertion [125,126], and improve motor skill acquisition [127–131]. The practical “real world” impact of these results, which are often incremental, reflective of limited stimulation sessions, and determined under experimental laboratory conditions, remains to be established. The efficacy of tES for several indications remains under investigation and is not without debate – importantly tES is “not one thing” and so debate for any given indication and technology should not be conflated with a separate application [132–138]. Yet, the broad and increasing number of these potential non-medical applications justifies the need for industry guidance through standards for design and use of limited output tES as applicable to consumer electrical stimulation devices. Our proposed industry guidance is based on medical-grade (inter)national standards and limitations on output that are consistent with or more stringent than those used for currently FDA cleared devices. Many of the applications for use fall under the category of a lifestyle product, or of a product intended for general wellness. Just as consumers may purchase a treadmill, or work out with gym equipment for diverse reasons (e.g. improve golf swing; keeping up with grandchildren, etc.), they may make a personal choice regarding their use of limited output tES, with the intent to improve various aspects of their quality of life. The standards we propose here insure that no new risk to the consumer is introduced, by establishing that devices marketed to promote a healthy lifestyle (viz.- general wellness products) are developed with appropriate medical-grade practices and output controls. Through compliance with these standards, including indicated restrictions on claims, we believe that such devices can be confidently assessed as low-risk, as consistent with the FDA guidance policy for general wellness devices (version issued July 29, 2016).

The preponderance of evidence supports that limited output tES is a well-tolerated method of achieving noninvasive neuro-modulation when well-established protocols (e.g. output control, and appropriate placement of properly designed electrodes) are followed [40,139]. In the following section, we propose a guidance framework for limited output tES manufacturers, which parallels draft guidance for other medical-grade electrical stimulation devices (such as TENS for aesthetic purposes, OTC TENS for the treatment of pain, and PMS for muscle conditioning), but with additional caveats for use. Our emphasis is on defining engineering principles of limited output tES devices, and explaining how existing regulations apply to their design and distribution. By focusing on biomedical engineering analysis as applied to extant regulation(s) of limited output tES devices, we seek to avoid more diffuse ethical debates about the impact of these devices on medicine and society.

FDA guidance on limited output specifications

As previously stated, the 1976 Medical Device Amendment afforded the FDA authority to establish General and Special Controls for regulating devices. The FDA established draft guidance documents specifying Class II Special Controls and Limited Output guidelines for certain types of OTC TENS and PMS devices, after nearly 40 years of well-tolerated use of such devices [38,39]. TENS devices for the treatment of pain, and for aesthetic purposes, and PMS devices for muscle stimulation can be purchased OTC, but at present these devices must still obtain premarket notification clearance through a 510(k) process. If and when these draft documents are put into effect and incorporated to the FDA regulatory practices, such devices will no longer be required to gain premarket notification clearance through a 510(k) process. They will, however, continue to be subject to both General and Special Controls, and must adhere to international safety guidelines such as IEC-60601. According to the FDA Draft Guidance documents [38,39] Limited Output specifications are met when: the device utilizes a stimulus generator that delivers, into a resistive load the worst case of either 500 Ω or the typical load expected during normal conditions of use, the following:

- (i) A maximum charge per phase that does not exceed Q, where $Q = 20 + (28)(t) \mu\text{C}$ (and where t is the phase duration expressed in ms and measured at 50% of the phase amplitude);
- (ii) A maximum average current that does not exceed 10 mA (average absolute value);
- (iii) A maximum primary (depolarizing) phase duration that does not exceed 500 μs ;
- (iv) An average DC current that does not exceed 100 μA when no pulses are being applied, or if the device fails;
- (v) A maximum current density that does not exceed a root mean square (RMS) value of 2 mA/cm^2 of electrode conductive surface area; and
- (vi) A maximum average power density that does not exceed 0.25 W/cm^2 of electrode conductive surface area.

In order to assure device safety, the FDA has recommended additional guidelines; these include the following.

- The output of the stimulus generator should be controlled by appropriately marked knobs, dials, switches, indicators, etc., and these controls should modulate output intensity in a smooth, incremental, and predictable manner.
- The stimulus generator should not become unsafe if the output is switched on with open-circuited or short-circuited electrodes.
- Battery supply voltage fluctuations of $\pm 10\%$ should not affect the stimulus generator output amplitude, pulse duration, or pulse repetition frequency (rate) by more than $\pm 10\%$.
- The stimulus generator should be limited to use with a battery power source, should be isolated from earth ground, and should not be capable of use with an AC power source or use while connected to a battery charger.
- All skin-contacting materials should be biocompatible for their intended use. To determine the applicable device category and tests, it is recommended to consult ANSI/AAMI/ISO 10993–1:2003, “Biological evaluation of medical devices – Part 1: Evaluation and testing.” This FDA-recognized standard recommends evaluation and testing of medical devices based upon the duration and type of contact. For cutaneous electrodes with a limited contact duration (e.g., less than 24 h), the FDA recommends the following tests to establish material safety: dermal irritation, sensitization, and cytotoxicity.

These documents support the safe use of several products that use electrodes placed upon the head and face for a variety of differing intentions and purposes (e.g. TENS devices for cosmetic or aesthetic purposes). We posit that these draft Special Controls establishing limited output guidelines are an appropriate framework for regulating tES devices for lifestyle and general wellness use, and can also inform the regulation of prescription or OTC use tES devices to treat certain neuropsychiatric conditions.

An approach to establishing Special Controls and Limited Output Guidelines for tES devices

As discussed above, and elsewhere in the literature [40,140,141], tES has a substantive history of safe use when quality devices are aptly used in accordance with established protocols. Hence, both device design (e.g. waveform output, electrodes) and usability (e.g. headgear, accessory preparation) are important considerations for regulation. Based on extant FDA regulations and historical precedent(s), limited output tES intended for medical therapy would mostly likely be classified as a Class II device, and subjected to different clearance pathways dependent upon intended use. A necessary distinction must be made for tES products that are marketed for intended use in diagnosing or treating a medical condition or disease. Such devices would require instructions and close monitoring by a physician. Therefore, any tES device marketed by a manufacturer to treat a medical condition (e.g. depression, anxiety) would only be cleared for prescription use, unless explicitly exempted for OTC. Prior to clearance for marketing, devices intended for medical or diagnostic applications must meet the burden of proof to demonstrate efficacy through appropriate clinical trials.

On the other hand, DTC provision would be appropriate for limited output tES devices that are marketed to optimize certain cognitive abilities or to achieve certain wellness goals, such as stress reduction, and which are not intended for treatment of a medical condition. Restriction of output parameters as described herein (which are in accordance with the aforementioned Class II Special Controls) would provide adequate safety assurances. Additionally, marketing strategies and claims made by tES manufacturers of consumer-directed devices would be subject to United States FTC regulation (and/or procedures of regulatory bodies in other countries; see above).

Provided devices meet the criteria for limited output tES, existing standards would provide guidelines for device design and dissemination, as reflective of a history of safe use of similarly regulated low-intensity electrical stimulation devices. Importantly, recognition of existing laws illustrates the distinction between medical-grade technology and so-called do-it-yourself (“DIY”) brain stimulation devices. There is an active community of so-called “bio-hackers” and DIY enthusiasts that are devoted to “at-home” construction of tES devices, sharing open source plans for building tES devices. The *ad hoc* nature of the design (e.g. not following an exhaustive risk management protocol), manufacture (e.g. incomplete controls and documentation), usability (e.g. prone to misuse), testing (e.g. strict quality systems), marketing/distribution (including labeling), and monitoring (e.g. established protocols for documenting and responding to user reports) of DIY devices position them outside of the limited output tES guidelines and standards. Our guidance does not advocate restricting access, but rather providing consumers access to specifically defined and controlled quality devices.

We believe that regulated, available paths for the responsible commercialization of limited output tES devices make controlled products available to healthy users, and additionally can prevent injuries that may be incurred through the use of adulterated tES

products by the DIY community. It is important to emphasize that companies commercializing limited output tES devices, regardless of intended use, should adhere to Good Manufacturing Practices and any/all applicable international and regional standards. This industry guidance provides a framework for such compliance.

Treatment by a physician or therapist is also regulated by strict federal and state medical standards, and there is an ethical and legal imperative – and obligation – for health care providers to be well informed by current evidence demonstrating safety and effectiveness of therapeutic approaches employed, inclusive of neurotechnologies such as tES [92,142,143]. For limited output tES devices, we consider these standards to be necessary and sufficient for patient protection. Continued supervision by a physician allows for control of dose, monitoring of progress, and reporting of any adverse events. Indeed, off-label use of drugs is ubiquitous, and when done correctly serves humanitarian and ethical goals of medicine as a practice. Undue regulation that prevents a physician from prescribing a therapy he or she considers to be of genuine and evidence-based benefit in treating a particular patient violates the probity of medicine, and undermines the value of regulatory action to insure sound care [144]. Moreover, failure to make available certified tES devices to physicians/patients can also promote the use of untested and unsafe devices.

As appropriate, physicians and therapists may direct patients toward: 1) Direct-to-Consumer limited output tES devices which are otherwise available to healthy individuals and/or 2) Prescription/OTC tES devices marketed for the given indication or for off-label use. Prescription devices may not necessarily need to be held to restrictive limited outputs, but can be as governed by this guidance. As emphasized above, all tES devices, including those with limited output, are under the jurisdiction of FDA or other international regulatory agencies and consequently may be considered medical devices, and are therefore subject to extensive design and production standards. Thus, it will be increasingly important to define which tES devices are limited output and compliance controlled.

Voluntary industry standard for compliance controlled limited output tES devices

In this section, we specify performance characteristics and guidelines that have been adopted from the Class II Special Control Guidance Documents previously referenced. These guidelines are intended for limited output tES methods including pulsed waveforms, alternating currents, direct currents, and modified direct currents. While these standards apply regardless of device indication (including for consumer products) they are uniformly considered to be “medical grade” as based on, and in many cases exceeding FDA guidance.

Risk management process

We recommend that manufacturers develop a robust risk management process that is based on relevant basic components of ISO 14971 for identifying and reducing risk to acceptable levels, including design, testing, and compliance activities. In particular, the process should include well-documented testing of any device features identified as risk mitigators, and continued analysis of production and post-production data to ensure low risk through the entire device life cycle. Principles from FDA QSR (21 CFR 820) and/or ISO 13485, the quality systems regulations, should be applied as necessary to ensure integrity of risk management in design, testing, production, and monitoring. Senior management as well as engineering and clinical personnel should be involved in this risk management process, so as to ensure that all reasonable risks are considered. The manufacturer’s risk analysis should

include human factors analysis based on the intended and likely user population(s).

In cases where the manufacturer posits that one or more of the performance and safety recommendations (below) is/are inapplicable, any such exclusion should be justified by complete address and elucidation through the risk management process (e.g. as provided for by ISO 14971).

Quality systems and design controls

We recommend that manufacturers implement, document, and follow a disciplined design process based on 21 CFR 820.30 (“design controls”) or its equivalent in ISO 13485 (section 7, “product realization”). These practices include advance planning of how a product will be developed; collection of product requirements; documentation of design outputs; review of product design; testing (verification) to ensure the product meets requirements; validation to ensure the product meets user needs; rigorous transfer to production; careful review, tracking, and testing of design changes; and thorough documentation. These principles are essential to the integrity of the risk management process, as well as to ensuring that finished products are both safe and effective.

Performance characteristics

Output waveforms. For each output mode defined in Section C, below, we recommend that manufacturers maintain records, such as oscilloscope tracings, time-series data, or accurate diagrams, to describe the device’s electrical output waveform, and to clearly illustrate both individual pulse and pulse-burst characteristics. These tracings should use time and voltage scales that are sufficient to graphically represent the amplitude (i.e., voltage) and temporal characteristics of both individual pulses and pulse-burst duration. Where useful, separate oscilloscope tracings using different time scales should be maintained. For example, the graphical representation of a repeating burst of pulses may consist of one tracing with a shorter time scale and a second tracing with a long (er) time scale that depicts burst characteristics. Documentation should include three tracings to describe the individual pulse output waveform under loads of 500, 2 k, and 10 k ohms, and one tracing to illustrate a series of pulses (i.e., pulse burst or pulse train) under a load of 500 Ω . Each tracing should include the following:

- The name of the output mode
- Clearly labeled amplitude and time traces, with appropriate scales (i.e., volts per division and time per division)
- Identification of the amplitude baseline
- A list of all output parameter settings, e.g., amplitude, pulse duration, frequency
- A load resistance, in ohms

Basic unit characteristics. We recommend that manufacturers maintain records describing a device’s basic unit characteristics. The parameters listed in this section are assumed to be independent of the selected output mode. If this is not the case, or if any of the listed parameters are not applicable to the manufactured device, we recommend that an explanation of such variation be included; a tabular format would be desirable, as shown in Table 3.

Output specifications. For the purpose of this document, an output mode is defined as a version of a waveform produced by the unit. For example, we consider biphasic symmetrical, biphasic asymmetrical, and monophasic to be separate output modes. We also consider each unique pre-set combination of stimulation parameters (sometimes referred to as a “program”) to constitute a distinct output mode. For example, if a device offers the user the ability to

Table 3
Sample of data to detail device information and specification.

Parameter	Response
Device Name and Model	
Manufacturer	
Power Source(s)	
- Method of Line Current Isolation	
- Patient Leakage Current	
▪ Normal Condition (µA)	
▪ Single Fault Condition (µA)	
Current R.M.S. through electrodes when device is on but no stimulation is being applied (µA)	
Number of Output Modes	
Number of Output Channels	Synchronous or Alternating? Method of Channel Isolation
Regulated Current or Regulated Voltage?	
Software/Firmware/Microprocessor Control?	Yes / No
Automatic Overload Trip?	Yes / No
Automatic No-Load Trip?	Yes / No
Automatic Shut Off?	Yes / No
User Override Control?	Yes / No
Indicator Display:	On/Off Status? Low Battery? Voltage/Current Level?
Timer Range (minutes)	
Compliance with Voluntary Standards?	If yes, specify
Compliance with 21 CFR 898?	Yes / No
Weight (lb., oz.)	
Dimensions (in.)[W x H x D]	
Housing Materials and Construction	

choose between “Program 1,” consisting of a monophasic waveform with a specific range of output voltages, pulse durations, frequencies, etc.; “Program 2,” consisting of a monophasic waveform with a different range of output voltages, pulse durations, frequencies, etc.; and “Program 3,” consisting of a biphasic waveform, this device would be considered to have three output modes. Devices sometimes have unique indications for use/intended uses associated with each output mode. We recommend that the following information (Sections D and E) be separately documented for each output mode. We also recommend that any parameters that are not applicable to the specific device be identified. Here too, a tabular format, in which each output mode is separately presented, would be desirable; as shown in Table 4.

Device safety. We recommend that limited output tES should meet all applicable general device controls (including relevant medical IEC statutes), as well as the following special controls:

- (i) A maximum charge per phase that does not exceed Q, where $Q = 20 + (28)t \mu\text{C}$ (and where t is the phase duration expressed in ms and measured at 50% of the phase amplitude);
- (ii) A maximum average current that does not exceed 10 mA;
- (iii) A maximum primary (depolarizing) phase duration that does not exceed 500 µs except as specified in vii;

Table 4
Sample of device output performance characteristics to document.

Parameter	Response
Mode or Program Name	
Waveform (e.g., pulse monophasic, biphasic)	
Shape (e.g., rectangular, spike, rectified sinusoidal)	
Maximum Output Voltage [volts]	@ 500 Ω
(± _____ %)	@ 2 kΩ
	@ 10k Ω
Maximum Output Current [specify units] (± _____ %)	@ 500 Ω
	@ 2 kΩ
	@ 10k Ω
Duration of primary (depolarizing) phase [µsec]	
Pulse Duration [µsec]	
Frequency [Hz](or Rate [pps])	
For multiphasic waveforms only:	Symmetrical phases? Yes/No
	Phase Duration(include units) (state range, if applicable) (both phases, if asymmetrical)
Net Charge (microcoulombs [µC] per pulse) (If zero, state method of achieving zero net charge)	____ @ 500 Ω
Maximum Phase Charge [µC]	@ 500 Ω
Maximum Current Density [mA/cm ² , r.m.s.]	@ 500 Ω
Maximum Average Current [average absolute value, mA]	@ 500 Ω
Maximum Average Power Density, [W/cm ²], (using smallest electrodes conductive surface area)	____ @ 500 Ω
Burst Mode:	(a) Pulses per burst
	(b) Bursts per second
	(c) Burst duration (seconds)
	(d) Duty Cycle [Line(b) x Line(c)]
ON Time [seconds]	
OFF Time [seconds]	
Additional Features (specify, if applicable)	
Maximum time per session	
Maximum current density (calculated as maximum current divided by electrolyte-skin contact area)	
Uses direct current or continuous sustained current passage greater than 1 second, or square wave, or rectified or bias sinusoidal, or pulses with >25% duty cycle including all phases.	Yes/No
Maximum average current	
Battery supply during stimulation	Yes/No

- (iv) An average DC current that does not exceed 100 μA when no pulses are being applied, except as specified in vii, and does not exceed 100 μA when the device is inactive or when the device fails;
- (v) A maximum current density that does not exceed an RMS of 2 mA/cm^2 of electrode conductive surface area; and
- (vi) A maximum average power density that does not exceed 0.25 W/cm^2 of electrode conductive surface area;
- (vii) For devices using direct current or continuous sustained current passage greater than 1 s, or square wave, or rectified or bias sinusoidal, or pulses with >25% duty cycle including all phases, if the maximum average current does not exceed 4 mA (average absolute value) then criteria (i), (iii), and (iv) are waived;
- (viii) A maximum peak output current that does not exceed 30 ma;
- (ix) A maximum current density that does not exceed 2 mA/cm^2 of electrolyte-skin contact area;
- (x) A maximum time per session that does not exceed 60 min;
- (xi) A maximum total charge per session that does not exceed 6000 mC
- (xii) Electrode labeling: conditions for disposal or re-use specified.
- (xiii) Skin tolerability testing conducted under electrode labeling conditions xiii;
- (xiv) Electrode testing consistent with draft guidance document Class II Special Controls Guidance Document: Cutaneous Electrode [145] or sufficient component-material documentation or usability testing;
- (xv) Electrolyte testing consistent with draft guidance document Class II Special Controls Guidance Document: Electroconductive Media [146] or sufficient component-material documentation or usability testing;
- (xvi) Battery supply is exclusively used during stimulation. Should batteries be re-charged within the device, the device cannot stimulate during connection with an AC source (charging). During connection to an AC source, patient leakage current, including at the device outputs, should be at an acceptable level. In such cases, measurements of patient leakage current under both normal and single fault conditions should be recorded based on the FDA-recognized standard, IEC 60601–1, “Medical Electrical Equipment – Part 1: General Requirements for Safety” or an equivalent method to show that the measured levels of patient leakage current are acceptable;
- (xvii) Any electronic equipment physically connected to the device, for example for the purpose of data collection or triggering, is considered part of the device for the purpose of these special controls;
- (xviii) At least one electrode must be positioned on the head; if one or more electrodes are positioned below the neck, a risk analysis is required and waveform limits (i to xii above) should be further limited if necessary as determined by the outcome of this analysis.

In order to assure device safety, these additional recommendations (which are adapted from FDA guidance on transcutaneous electrical stimulators with limited output for aesthetic purposes) are also advocated.

- If the output of the stimulus generator should be controlled by appropriately marked knobs, dials, switches, indicators, etc., then these controls should modulate output in a predictable manner.

- The stimulus generator should not become unsafe if the output is switched on with open-circuit or short-circuit electrodes.
- Battery supply voltage fluctuations of $\pm 5\%$ should not affect the stimulus generator output amplitude, pulse duration, or pulse repetition frequency (rate) by more than $\pm 5\%$.
- The stimulus generator should be limited to use with a battery power source, should be isolated from earth ground, and should not be capable of use with an AC power source or use while connected to a battery charger.
- All skin-contacting materials should be biocompatible for their intended use. To determine the applicable device category and tests, you should consult ANSI/AAMI/ISO 10993–1:2003, “Biological evaluation of medical devices – Part 1: Evaluation and testing.” This FDA-recognized standard recommends evaluation and testing of medical devices based upon the duration and type of contact. Based on intended use and risk management, for cutaneous electrodes with limited contact duration (e.g., less than 24 h), the following tests may be used to establish material safety: dermal irritation, sensitization, and cytotoxicity or appropriate usability testing.

These safety recommendations supplement the safety information communicated by labeling, as described below.

Device effectiveness. If claims of effectiveness are made, in order to provide reasonable assurance of device effectiveness, evidence that is sufficient to demonstrate that the device is as effective as other legally marketed devices for its described intended uses, indications for use, and marketing claims should be maintained. This should include data and analysis that correlate the intended use and the device output parameters with objective outcome measures (i.e. physiologic changes) and/or subject outcome measures (e.g. self-reported) that are appropriate to support the intended uses, indications, and claims.

Accessories. For each device accessory, manufacturer should maintain records that list and describe all relevant technological characteristics. For any accessory that has received prior marketing clearance, we recommend that the name of the manufacturer of the accessory and, if applicable, the 510(k) number be identified. We also advocate that the recommendations described for accessories, as presented below, should also be followed:

Electrodes. Cutaneous electrodes used with transcutaneous stimulation devices with limited output are regulated as Class II devices under 21 CFR 882.1320. The FDA has proposed to designate Special Controls and exempt these cutaneous electrodes from premarket notification requirements under section 510(k) of the act in the proposed rule issued with draft guidance of limited output devices. In addition, the draft guidance entitled Class II Special Controls Guidance Document: Cutaneous Electrode [145] defines the specific recommendations for this accessory. The guidance document recommended (specified) the materials, construction, type, and size of the electrodes. For assurance of device performance, the following parameters should be evaluated and documented: electrodes’ biocompatibility, electrical performance, adhesive performance, stability, and, if applicable, suitability for reuse. Lot information and date of manufacture (DOM) should be clearly labeled to track potential lot issues.

Electrode conductive medium (gel). Electroconductive media used in transcranial electrical stimulators with limited output are regulated as Class II devices under 21 CFR 882.1275. The FDA has proposed to designate Special Controls and exempt these electroconductive media from premarket notification requirements under section 510(k) of the act in the proposed rule issued with draft guidance of limited output devices. In addition, the draft guidance

entitled Class II Special Controls Guidance Document: Electroconductive Media [146] defines the specific recommendations for this accessory. For assurance of device performance, we recommend that parameters of the electroconductive medium's biocompatibility, electrical performance, and stability should all be evaluated (either directly or by appropriate component-material documentation or usability testing) and documented in device records.

Electrode connections. We recommend that the length(s), construction, materials, and connections between the stimulator device and the electrodes be described and documented. If used, electrode lead wires and patient cables intended for use with a medical device are subject to the mandatory performance standard set forth in 21 CFR Part 898, as well as clause 8.5.2.3 of IEC 60601-1:2005. We note that an increasing number of tES devices may be constructed without conventional lead wires and/or cables; for instance, wearable headsets having snap-in electrodes, which are not specifically covered by the existing standards such as 21 CFR Part 898. In such designs, a risk management process shall be conducted and documented to assess and, if necessary, mitigate any risk associated with the electrode connection.

Batteries. The number, size, and type of batteries used with the device, as well as any special cases such as replacing or recharging batteries should be identified.

Battery charger. If the device is intended for use with internal rechargeable batteries, we recommend that an appropriate method of current isolation be identified, and that IEC 60601-1, "Medical Electrical Equipment – Part 1: General Requirements for Safety" be followed in order to demonstrate that the levels of patient leakage current, measured under both normal and single fault conditions, are acceptable.

Software/firmware/microprocessor control. For tES devices with limited output that is controlled by software (or firmware, or a microprocessor), we recommend that the appropriate information, based on the level of concern and recommendations described in the guidance documents entitled, *Guidance for the Content of Premarket Submissions for Software Contained in Medical Devices* [147], *General Principles of Software Validation; Final Guidance for Industry and FDA Staff* [148] and *Medical Mobile Applications Guidance for Industry and Food and Drug Administration Staff* [149] be documented in the design history file and device master records.

Electromagnetic compatibility (EMC). If performance characteristics related to EMC are described in labeling, we recommend that the valid scientific evidence that supports these performance characteristics, as well as any documentation of adherence to any international standards (for instance *IEC 60601-1-2: Medical Electrical Equipment- Part 1–2: General Requirements for Basic Safety and Essential Performance- Collateral Standard: Electromagnetic Compatibility-Requirements and Tests*) be maintained in device records.

Usability study. The manufacturer or company must conduct appropriate usability studies (including as relevant, focus group studies or compliance trials) such as those described in the guidance document entitled *Applying Human Factors and Usability Engineering to Medical Devices* [150]. Usability studies are designed to address:

- Whether operators can identify if they are appropriate candidates for use of the devices; and
- Whether users can operate the device in a safe and effective manner based on their reading and following the directions for use contained in the device labeling (e.g., applying electrodes

properly, choosing appropriate output modes, adjusting stimulation parameters properly).

Manufacturers should document these usability studies, including:

- A description of the usability study protocol;
- A discussion of the usability study results and conclusions to support safe and effective use of the device, as labeled, in the intended population;
- A discussion of any device features or labeling statements specifically developed to address the usability study results;
- A discussion of and justification for any differences between the device used in the usability study and the final marketing version of the device; and
- A discussion of and justification for any differences between the labeling (including directions for use) used in the usability study and the final labeling included with the final marketing version of the device.

We recommend adherence to relevant standards, for instance *IEC 60601-1-6: Medical Electrical Equipment-Part 1–6: General Requirements for Basic Safety AndEssential Performance-Collateral standard: Usability* and *IEC 62366: Medical Devices-Application of Usability Engineering to Medical Devices*.

Labeling. The following suggestions are provided to assist in preparation of labeling in supplement to applicable requirements for General Device Labeling- 21 CFR Part 801.

Device user manual

A user manual must be provided with the device. The manual should include clear and complete descriptions of:

- The device and all accessories
- How the device interconnects with other components or accessories
- All features, functions, output modalities, and specifications
- All user-accessible controls
- Indicators, markings, and labels on the device, which provide information about the function or meaning of each control, display, output jack, etc.
- The size and type of electrodes used with the devices, including whether electrodes are interchangeable, single-use, multi-use or replaceable.

The user manual should also contain the following:

- A list of all available output modes or programs and a summary of the specific indications for use associated with each mode or program;
- Illustrations of the device and accessories;
- Instructions for storage, cleaning, and maintenance of the device and accessories as applicable.

For a medical indication, the device labeling must include adequate directions for use in accordance with all applicable statutes in 21 CFR 801.5. Under this rule, labeling (e.g., package insert) must describe the intended use of the device, and include a listing of indications, contraindications, warnings, precautions, and adverse reactions, relevant to the device (21 CFR 801.5(a)). This information must be prominently placed on the labeling of both prescription and OTC devices (21 CFR 801.15, 801.61). For non-medical indications, labeling should include consideration of fair marketing and risk management.

The additional labeling recommendations as described below are not intended to represent all possible limitations or strict instructions for tES devices with limited output. Therefore, when developing adequate directions for use, it may be necessary to include additional limitations (e.g., contraindications, warnings, precautions, adverse reactions), and other instructions that are appropriate for the device, depending both upon its specific design, features, and performance characteristics, and the results and conclusions drawn from usability studies.

Intended use for OTC/non-medical applications

For prescription or OTC medical use, labeling is regulated per relevant FDA classification of the device. Non-medical tES devices with limited output characteristics are intended for OTC neuro-modulation for lifestyle or wellness applications. Any further marketing claims relating to optimizing users' cognitive abilities or to achieving certain wellness goals should be validated through appropriate studies, and supported by evidence from human trials. Some devices may contain multiple operating modes, with each mode having a unique indication for use. In this case, the device master record and labeling should specify the particular indication for use that corresponds to each mode of operation.

Our proposal is aligned with the FDA “General Wellness”: Policy for Low Risk Devices Guidance (July 29, 2016), wherein a general wellness device is defined as having “... (1) an intended use that relates to maintaining or encouraging a general state of health or a healthy activity, or (2) an intended use that relates the role of healthy lifestyle with helping to reduce the risk or impact of certain chronic diseases or conditions and where it is well understood and accepted that healthy lifestyle choices may play an important role in health outcomes for the disease or condition.” This reinforces that device regulation by the FDA is predicated on intended use (as indicated by the label; see also: *Part 1: Regulatory definitions and standards*; of the present document.)

Moreover, the FDA General Wellness guidance notes “... [Center for Devices and Radiological Health] CDRH's general wellness policy applies only to general wellness products that are low risk” and indicates that “in assessing whether a product is low risk ... consider whether CDRH actively regulates products of the same type as the product in question” (NB: see also *Part 1 Engineering analysis of electrostimulation output parameters* and the performance standards outlined to manage risk).

If and only if references to a specific condition or disease are not made, the FDA General Wellness guidance further defines general wellness claims to include:

- “Claims to promote relaxation or manage stress;
- Claims to increase, improve, or enhance the flow of qi “energy”;
- Claims to improve mental acuity, instruction following, concentration, problem solving, multitasking, resource management, decision-making, logic, pattern recognition or eye-hand coordination;
- Claims to enhance learning capacity;
- Claims to promote physical fitness ... develop or improve endurance, strength or coordination, or improve energy;
- Claims to promote sleep management;
- Claims to promote self-esteem, such as to boost self-esteem;
- Claims that address a specific body structure or function, such as to increase or improve muscle size or body tone, tone or firm the body or muscle, or enhance or improve sexual performance;
- Claims to improve general mobility or to assist individuals who are mobility impaired in a recreational activity (e.g., sport wheelchairs, beach access wheelchairs)”

The labeling must avoid the use of text, pictures, and/or figurative signs that may mislead the user or the patient with regard to the device's intended purpose and performance by:

- (a) Ascribing functions and properties to the product which the product does not have;
- (b) Creating a false impression regarding medical treatment or diagnosis, functions or properties which the product does not have – and for OTC consumer devices, avoiding any impression the device is intended to treat or diagnose a disease;
- (c) Suggesting uses of the product other than those declared in the intended purpose when the risk management was executed.

Warnings

We recommend that the user manual provide the following caveats:

- If you are under the active care of a physician, consult with your physician before using this device;
- Do not use without consulting your physician if you have a history of seizures;
- Do not use if you have a pre-existing neurological or neuropsychiatric condition, without consulting your physician;
- Do not use without consulting with your physician if you have an active implanted medical device, such as a cardiac pacemaker or neurostimulation device, such as a spinal cord stimulator, vagal nerve stimulator, auricular stimulator, or deep-brain stimulating electrodes;
- Apply stimulation electrodes to locations only as directed, avoid applying stimulation across the chest;
- Apply stimulation only to normal, intact, clean, healthy skin;
- Do not apply stimulation over open wounds or rashes, or swollen, red, irritated, infected, or inflamed areas or skin eruptions;
- Do not use when in the bath or shower;
- Do not apply stimulation while driving, operating machinery, or during any activity in which you are otherwise at significant risk of injury.
- At home, unsupervised use in children is not recommended.
- Do not use this device while intoxicated or incapacitated.
- If you are pregnant or may be pregnant, you should follow precautions recommended by your physician.
- If you have a defect in your neurocranium, have an implant inside your skull, cochlear implant, or implanted hearing aid consult your physician prior to using this device.
- As relevant, follow any instructions on the preparation of the skin include concerns about hair products, make up, and other topical skin products.

Precaution

We recommend that the user manual also should afford the following precautions:

- Unless directed by a physician, do not use the device on children.
- The safety of electrical stimulation during pregnancy has not been established;
- You may experience skin irritation or hypersensitivity due to the electrical stimulation or electrical conductive medium (gel);

- If you have suspected or diagnosed heart disease, you should follow precautions recommended by your physician; and
- If you have suspected or diagnosed epilepsy, you should follow precautions recommended by your physician.
- Consult with your physician prior to using the device after a recent surgical procedure;
- Consult with your physician prior to using the device if you have a cardiac pacemaker, implanted defibrillator, or other implanted metallic or electronic device;
- Use caution if stimulation is applied over areas of skin that lack normal sensations.
- Keep this device out of the reach of children; and
- Use this device only with the leads, electrodes, and accessories recommended by the manufacturer.

Adverse reactions

We recommend that the user manual include information about known adverse reactions, for example:

- Some skin redness under the electrode or near the electrode sites is due to increased local blood flow and is normal and should subside within approximately an hour of end of use;
- Do not apply electrodes over broken or damaged skin. Variation of impedance due to such skin damage may undesirably focus current and create further irritation and/or skin damage.
- You may experience skin irritation beneath the stimulation electrodes applied to your skin, do not apply stimulation over irritated skin;
- You should stop using the device and should consult with your physicians if you experience adverse reactions from the device.
- Some subjects may experience mild tingling, itching, or burning sensations under or near the electrode region. If these sensations become severe or uncomfortable, please discontinue.

Public health relevance and summary

Over the past several years, there has been ongoing discourse, if not debate, about the ethical probity of both medical and non-medical use of tES. On one hand, discussion centers on the validity of results achieved in well-conducted studies, and the value of tES in treating certain neuro-psychiatric conditions, and even facilitating particular aspects of cognitive and motor performance. At the core of such discussion is the presumption that failure to continue such research and translate viable outcomes to protocols for clinical practice represents relative harms of omission. On the other hand are conversations about lack of complete understanding of mechanisms, variability in outcomes as a consequence of differing device outputs, electrode placements, and individual and environmental circumstances and contexts. Here issues center upon potential harms of commission. We acknowledge and respect these concerns, and assert that any ethical address must begin with, be based upon, and proceed from facts. Like any intervention, tES will vary in effect and effectiveness, based upon a host of factors, inclusive of technical capabilities of the device employed, parameters of current delivered, electrode montage, and contexts of brain state and environments of use. The goal is to optimize technical factors so as to maximize benefits in defined domains of applications in practice.

To be sure, there is a public health mandate and ethical obligation to study, develop and deploy technologies and techniques that can lessen the burden of disease, injury and illness. Yet, there is an equal ethical obligation to establish how such approaches can and should be used, so as to insure safety and effectiveness in each

domain of use. The framework that we have developed and presented here seeks to achieve these goals. Within the confines of clinical practice, responsibility for the safe and effective use of tES rests upon the clinician. However, tES is increasingly employed outside the clinical encounter, for use in occupational settings and for goals of personal wellness (and/or performance enablement). Guidelines and regulations should be aimed at maximizing benefits, and reducing identified theoretical risks from tES, irrespective of settings of application and/or use.

This is important in that such guidelines can exert three-fold influence. First, they provide a framework for use in clinical practice, affording clinicians defined parameters for how such devices can and should be operated. Second these guidelines define bases and limitations for occupational and (at home) consumer use. Third, such guidelines undergird device manufacturers' responsibility to develop and produce technologies that are effective and safe, when operated in accordance with specified settings and directions for use. In the first case, these afford security for clinicians to administer tES with confidence in the specifications and capabilities of the devices used. In the second, guidelines enable manufacturers to inform consumers (e.g. precautions via labeling and manuals) on correct use, and thereby promote consumer protection. And in the last case, these guidelines afford manufacturers clear and uniform standards for design, risk management, and labeling.

We summarized how off-label and investigational use of electrotherapy devices has been safely implemented for neuro-modulation in numerous research studies and clinical trials of tES. Such trials have shown tES (including tDCS, tACS, and tPCS) to be safe and well tolerated when medical-grade devices are used and strict protocols for application are followed [40]. Consumers have safely used OTC electrical stimulation devices for various indications for more than four decades. For example, many cosmetic TENS devices that are indicated for placement on the head and are marketed and sold for OTC use, have output specifications exceeding limited output tES. We have explained medical device regulations as applicable to limited output tES devices. Based on existing (inter)national standards, decades of experience with comparable devices, and biomedical engineering analysis, we are confident that LOTES17 guidelines will ensure the well-controlled manufacture and responsible distribution of OTC tES devices. Identification of devices compliant with this guidance will support informed decisions by the public. Thus, we posit that adoption of the industry guidelines defined in this report will, alongside relevant medical and government activities, ensure that OTC limited output tES devices safely provide a net benefit to the public.

Financial conflict of interest disclosure

A. Datta, M. Bikson, K. Lee, B. Wingeier, D. Chao, D. Hagedorn, and W.J. Tyler, R. Azzam, B.W. Badran are inventors on issued and pending patents related to the transcranial modulation of brain function. M. Bikson has equity in Soterix Medical Inc. and serves on the Boston Scientific Inc. scientific advisory board. A. Datta has equity in Soterix Medical. D. Hagedorn has equity in Evoke Neuroscience. B. Wingeier and D. Chao have equity in Halo Neuroscience. R. Azzam has equity in Caputron.

References

- [1] Guleyupoglu B, Schestatsky P, Edwards D, Fregni F, Bikson M. Classification of methods in transcranial electrical stimulation (tES) and evolving strategy from historical approaches to contemporary innovations. *J Neurosci Methods* 2013;219(2):297–311. <https://doi.org/10.1016/j.jneumeth.2013.07.016>.
- [2] Peterchev AV, Wagner TA, Miranda PC, Nitsche MA, Paulus W, Lisanby SH, et al. Fundamentals of transcranial electric and magnetic stimulation dose:

- definition, selection, and reporting practices. *Brain Stimul* 2012;5(4): 435–53. <https://doi.org/10.1016/j.brs.2011.10.001>.
- [3] Hamilton R, Messing S, Chatterjee A. Rethinking the thinking cap: ethics of neural enhancement using noninvasive brain stimulation. *Neurology* 2011;76(2):187–93. <https://doi.org/10.1212/WNL.0b013e318205d50d>. Epub 2011/01/12.
- [4] Cohen Kadosh R, Levy N, O'Shea J, Shea N, Savulescu J. The neuroethics of non-invasive brain stimulation. *Curr Biol* 2012;22(4):R108–11. <https://doi.org/10.1016/j.cub.2012.01.013>. Epub 2012/03/01.
- [5] Dubljevic V, Saigle V, Racine E. The rising tide of tDCS in the media and academic literature. *Neuron* 2014;82(4):731–6. <https://doi.org/10.1016/j.neuron.2014.05.003>. Epub 2014/05/24.
- [6] Fitz NS, Reiner PB. The challenge of crafting policy for do-it-yourself brain stimulation. *J Med Ethics* 2013;41(5):410–2. <https://doi.org/10.1136/medethics-2013-101458>. Epub 2013/06/05.
- [7] Maslen H, Savulescu J, Douglas T, Levy N, Cohen Kadosh R. Regulation of devices for cognitive enhancement. *Lancet* 2013;382(9896):938–9. [https://doi.org/10.1016/s0140-6736\(13\)61931-5](https://doi.org/10.1016/s0140-6736(13)61931-5). Epub 2013/09/17.
- [8] Fregni F, Nitsche MA, Loo CK, Brunoni AR, Marangolo P, Leite J, et al. Regulatory considerations for the clinical and research use of transcranial direct current stimulation (tDCS): review and recommendations from an expert panel. *Clin Res Regul Aff* 2015;32(1):22–35. <https://doi.org/10.3109/10601333.2015.980944>.
- [9] Wittich CM, Burkle CM, Lanier WL. Ten common questions (and their answers) about off-label drug use. *Mayo Clin Proc* 2012;87(10):982–90. <https://doi.org/10.1016/j.mayocp.2012.04.017>. Epub 2012/08/11.
- [10] Riley Jr JB, Basilius PA. Physicians' liability for off-label prescriptions. *Hematol Oncol News Issues* 2007;6(5):24–37.
- [11] *Bax Global Inc v Brenneeman*, (Ohio Ct App 2007).
- [12] Wilkes M, Johns M. Informed Consent and Shared Decision-Making: A requirement to disclose to patients off-label prescriptions. *PLoS medicine* 2008;5(11):1553–1556. Epub November 11, 2008. doi: 10.1371/journal.pmed.0050223.
- [13] Kanai R, Chaieb I, Antal A, Walsh V, Paulus W. Frequency-dependent electrical stimulation of the visual cortex. *Curr Biol* 2008;18(23):1839–43. <https://doi.org/10.1016/j.cub.2008.11.027>. Epub 2008/11/26.
- [14] Boggio PS, Ferrucci R, Rigonatti SP, Covre P, Nitsche M, Pascual-Leone A, et al. Effects of transcranial direct current stimulation on working memory in patients with Parkinson's disease. *J Neurol Sci* 2006;249(1):31–8. <https://doi.org/10.1016/j.jns.2006.05.062>. Epub 2006/07/18.
- [15] Weber MJ, Messing SB, Rao H, Detre JA, Thompson-Schill SL. Prefrontal transcranial direct current stimulation alters activation and connectivity in cortical and subcortical reward systems: a tDCS-fMRI study. *Hum Brain Mapp* 2014;35(8):3673–86. <https://doi.org/10.1002/hbm.22429>. Epub 2014/01/24.
- [16] Rush S, Driscoll DA. Current distribution in the brain from surface electrodes. *Anesth Analg* 1968;47(6):717–23. Epub 1968/11/01.
- [17] Datta A, Bansal V, Diaz J, Patel J, Reato D, Bikson M. Gyri-precise head model of transcranial direct current stimulation: improved spatial focality using a ring electrode versus conventional rectangular pad. *Brain Stimul* 2009;2(4): 201–7. <https://doi.org/10.1016/j.brs.2009.03.005>. 7.e1. Epub 2010/07/23.
- [18] Brunoni AR, Nitsche MA, Bolognini N, Bikson M, Wagner T, Merabet L, et al. Clinical research with transcranial direct current stimulation (tDCS): challenges and future directions. *Brain Stimul* 2012;5(3):175–95. <https://doi.org/10.1016/j.brs.2011.03.002>. Epub 2011/11/01.
- [19] Seibt O, Brunoni AR, Huang Y, Bikson M. The pursuit of DLPFC: non-neuronavigated methods to target the left dorsolateral pre-frontal cortex with symmetric bicephalic transcranial direct current stimulation (tDCS). *Brain Stimul* 2015;8(3):590–602. <https://doi.org/10.1016/j.brs.2015.01.401>.
- [20] Kincses TZ, Antal A, Nitsche MA, Bartfai O, Paulus W. Facilitation of probabilistic classification learning by transcranial direct current stimulation of the prefrontal cortex in the human. *Neuropsychologia* 2004;42(1):113–7. Epub 2003/11/15.
- [21] Iyer MB, Mattu U, Grafman J, Lomarev M, Sato S, Wassermann EM. Safety and cognitive effect of frontal DC brain polarization in healthy individuals. *Neurology* 2005;64(5):872–5. <https://doi.org/10.1212/01.wnl.0000152986.07469.e9>. Epub 2005/03/09.
- [22] Antal A, Kincses TZ, Nitsche MA, Paulus W. Manipulation of phosphene thresholds by transcranial direct current stimulation in man. *Exp Brain Res* 2003;150(3):375–8. <https://doi.org/10.1007/s00221-003-1459-8>. Epub 2003/04/17.
- [23] Schwiedrzik CM. Retina or visual Cortex? The site of phosphene induction by transcranial alternating current stimulation. *Front Integr Neurosci* 2009;3:6. <https://doi.org/10.3389/fnins.2009.07.006>. Epub 2009/07/06.
- [24] Rohracher H. Über subjektive Lichterscheinungen bei Reizung mit Wechselstromen. *Z für Sinnesphysiol* 1935;66:164–81.
- [25] Brindley GS. The site of electrical excitation of the human eye. *J Physiol* 1955;127(1):189–200.
- [26] Schutter DJ, Hortensius R. Retinal origin of phosphenes to transcranial alternating current stimulation. *Clin Neurophysiol* 2010;121(7):1080–4. <https://doi.org/10.1016/j.clinph.2009.10.038>. Epub 2010/03/02.
- [27] Kar K, Krekelberg B. Transcranial electrical stimulation over visual cortex evokes phosphenes with a retinal origin. *J Neurophysiol*. 1082012. p. 2173–2178.
- [28] Sparing R, Thimm M, Hesse MD, Kust J, Karbe H, Fink GR. Bidirectional alterations of interhemispheric parietal balance by non-invasive cortical stimulation. *Brain* 2009;132(Pt 11):3011–20. <https://doi.org/10.1093/brain/awp154>. Epub 2009/06/17.
- [29] Rorsman I, Magnusson M, Johansson BB. Reduction of visuo-spatial neglect with vestibular galvanic stimulation. *Scand J Rehabil Med* 1999;31(2): 117–24. Epub 1999/06/25.
- [30] Wexler A. A pragmatic analysis of the regulation of consumer transcranial direct current stimulation (tDCS) devices in the United States. *J Law Biosci* 2015;2(3):669–96. <https://doi.org/10.1093/jlb/lsv039>. Epub 2016/10/25.
- [31] List of IEC 60601 Standards 2017 [August 28, 2017]. Available from: http://www.601help.com/Other_601_Standards/other_601_standards.html.
- [32] Proposal for a REGULATION OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL on medical devices, and amending Directive 2001/83/EC, Regulation (EC) No 178/2002 and Regulation (EC) No 1223/2009 EUR-Lex Access to European Union law: EUROPA; 2012 [cited 2017 02/09/17]. Available from: <http://eur-lex.europa.eu/legal-content/EN/TXT/?uri=celex:52012PC0542>.
- [33] Rossi S, Hallett M, Rossini PM, Pascual-Leone A. Safety, ethical considerations, and application guidelines for the use of transcranial magnetic stimulation in clinical practice and research. *Clin Neurophysiol* 2009;120(12):2008–39. <https://doi.org/10.1016/j.clinph.2009.08.016>. Epub 2009/10/17.
- [34] Donnell A, DN T, Lawrence M, Gupta V, Zieba T, Truong DQ, et al. High-definition and non-invasive brain modulation of pain and motor dysfunction in chronic TMD. *Brain Stimul* 2015;8(6):1085–92. <https://doi.org/10.1016/j.brs.2015.06.008>.
- [35] Kirsch DL, Nichols F. Cranial electrotherapy stimulation for treatment of anxiety, depression, and insomnia. *Psychiatr Clin North Am* 2013;36(1): 169–76. <https://doi.org/10.1016/j.psc.2013.01.006>.
- [36] Taylor AG, Anderson JG, Riedel SL, Lewis JE, Kinser PA, Bourguignon C. Cranial electrical stimulation improves symptoms and functional status in individuals with fibromyalgia. *Pain Manag Nurs* 2013;14(4):327–35. <https://doi.org/10.1016/j.pmn.2011.07.002>. Epub 2013/12/10.
- [37] Lee SH, Kim WY, Lee CH, Min TJ, Lee YS, Kim JH, et al. Effects of cranial electrotherapy stimulation on preoperative anxiety, pain and endocrine response. *J Int Med Res* 2013;41(6):1788–95. <https://doi.org/10.1177/0300060513500749>. Epub 2013/11/23.
- [38] U.S. Food and Drug Administration Center for Devices and Radiological Health. Draft guidance for industry and FDA staff: class II special controls guidance document: transcutaneous electrical nerve stimulator with limited output for pain relief. U.S. Department of Health and Human Services Food and Drug Administration, Center for Devices and Radiological Health; 2010.
- [39] U.S. Food and Drug Administration Center for Devices and Radiological Health. Draft guidance for industry and FDA staff: class II special controls guidance document: transcutaneous electrical stimulator with limited output for aesthetic purposes. U.S. Department of Health and Human Services Food and Drug Administration, Center for Devices and Radiological Health; 2010.
- [40] Bikson M, Grossman P, Thomas C, Zannou AL, Jiang J, Adnan T, et al. Safety of transcranial direct current stimulation: evidence based update 2016. *Brain Stimul* 2016;9(5):641–61. <https://doi.org/10.1016/j.brs.2016.06.004>.
- [41] Giordano J. Toward an operational neuroethical risk analysis and mitigation paradigm for emerging neuroscience and technology (neuroST). *Exp Neurol* 2016;287(Pt 4):492–5. <https://doi.org/10.1016/j.expneurol.2016.07.016>. Epub 2016/10/25.
- [42] Charvet LE, Kasschau M, Datta A, Knotkova H, Stevens MC, Alonzo A, et al. Remotely-supervised transcranial direct current stimulation (tDCS) for clinical trials: guidelines for technology and protocols. *Front Syst Neurosci* 2015;9:26. <https://doi.org/10.3389/fnins.2015.00026>.
- [43] Kasschau M, Sherman K, Haider L, Frontario A, Shaw M, Datta A, et al. A protocol for the use of remotely-supervised transcranial direct current stimulation (tDCS) in multiple sclerosis (MS). *J Vis Exp* 2015;106:e53542. <https://doi.org/10.3791/53542>.
- [44] Food and Drug Administration H. Class II Special Controls Guidance Document: Transcutaneous Electrical Nerve Stimulator with Limited Output for Pain Relief - Draft Guidance for Industry and FDA Staff. In: Services USDo-HaH, editor. Food and Drug Administration.
- [45] Bikson M, Datta A, Elwassif M. Establishing safety limits for transcranial direct current stimulation. *Clin Neurophysiol* 2009;120(6):1033–4. <https://doi.org/10.1016/j.clinph.2009.03.018>.
- [46] Magis D, Sava S, d'Elia TS, Baschi R, Schoenen J. Safety and patients' satisfaction of transcutaneous supraorbital neurostimulation (tSNS) with the Cefaly(R) device in headache treatment: a survey of 2,313 headache sufferers in the general population. *J Headache Pain* 2013;14:95. <https://doi.org/10.1186/1129-2377-14-95>.
- [47] Kavanagh S, Newell J, Hennessy M, Sadick N. Use of a neuromuscular electrical stimulation device for facial muscle toning: a randomized, controlled trial. *J Cosmet Dermatol* 2012;11:261–6.
- [48] DeGiorgio CM, Murray D, Markovic D, Whitehurst T. Trigeminal nerve stimulation for epilepsy: long-term feasibility and efficacy. *Neurology* 2009;72(10):936–8. <https://doi.org/10.1212/01.wnl.0000344181.97126.b4>.
- [49] DeGiorgio CM, Fanselow EE, Schrader LM, Cook IA. Trigeminal nerve stimulation: seminal animal and human studies for epilepsy and depression. *Neurosurg Clin N Am* 2011;22(4):449–56. <https://doi.org/10.1016/j.nec.2011.07.001>.

- [50] Schrader LM, Cook IA, Miller PR, Maremont ER, DeGiorgio CM. Trigeminal nerve stimulation in major depressive disorder: first proof of concept in an open pilot trial. *Epilepsy Behav* 2011;22(3):475–8. <https://doi.org/10.1016/j.yebeh.2011.06.026>.
- [51] DeGiorgio CM, Soss J, Cook IA, Markovic D, Gornbein J, Murray D, et al. Randomized controlled trial of trigeminal nerve stimulation for drug-resistant epilepsy. *Neurology* 2013;80(9):786–91. <https://doi.org/10.1212/WNL.0b013e318285c11a>.
- [52] Adeyemo BO, Simis M, Macea DD, Fregni F. Systematic review of parameters of stimulation, clinical trial design characteristics, and motor outcomes in non-invasive brain stimulation in stroke. *Front Psychiatry* 2012;3:88. <https://doi.org/10.3389/fpsy.2012.00088>. Epub 2012/11/20.
- [53] Dmochowski JP, Datta A, Huang Y, Richardson JD, Bikson M, Fridriksson J, et al. Targeted transcranial direct current stimulation for rehabilitation after stroke. *Neuroimage* 2013;75:12–9. <https://doi.org/10.1016/j.neuroimage.2013.02.049>.
- [54] Hummel F, Celnik P, Giraux P, Floel A, Wu WH, Gerloff C, et al. Effects of non-invasive cortical stimulation on skilled motor function in chronic stroke. *Brain* 2005;128(Pt 3):490–9. <https://doi.org/10.1093/brain/awh369>. Epub 2005/01/07.
- [55] Hummel FC, Voller B, Celnik P, Floel A, Giraux P, Gerloff C, et al. Effects of brain polarization on reaction times and pinch force in chronic stroke. *BMC Neurosci* 2006;7:73. <https://doi.org/10.1186/1471-2202-7-73>. Epub 2006/11/07.
- [56] Shah PP, Szaflarski JP, Allendorfer J, Hamilton RH. Induction of neuroplasticity and recovery in post-stroke aphasia by non-invasive brain stimulation. *Front Hum Neurosci* 2013;7:888. <https://doi.org/10.3389/fnhum.2013.00888>. Epub 2014/01/09.
- [57] Loo CK, Alonzo A, Martin D, Mitchell PB, Galvez V, Sachdev P. Transcranial direct current stimulation for depression: 3-week, randomised, sham-controlled trial. *Br J Psychiatry* 2012;200(1):52–9. <https://doi.org/10.1192/bjp.bp.111.097634>. Epub 2012/01/05.
- [58] Brunoni AR, Valiengo L, Baccaro A, Zanao TA, de Oliveira JF, Goulart A, et al. The sertraline vs. electrical current therapy for treating depression clinical study: results from a factorial, randomized, controlled trial. *JAMA Psychiatry* 2013;70(4):383–91. <https://doi.org/10.1001/2013.jamapsychiatry.32>. Epub 2013/02/08.
- [59] Kuo MF, Paulus W, Nitsche MA. Therapeutic effects of non-invasive brain stimulation with direct currents (tDCS) in neuropsychiatric diseases. *Neuroimage* 2014;85(Pt 3):948–60. <https://doi.org/10.1016/j.neuroimage.2013.05.117>. Epub 2013/06/12.
- [60] Volpato C, Piccione F, Cavinato M, Duzzi D, Schiff S, Foscolo L, et al. Modulation of affective symptoms and resting state activity by brain stimulation in a treatment-resistant case of obsessive-compulsive disorder. *Neurocase* 2013;19(4):360–70. <https://doi.org/10.1080/13554794.2012.667131>. Epub 2012/05/05.
- [61] Fregni F, Boggio PS, Lima MC, Ferreira MJ, Wagner T, Rigonatti SP, et al. A sham-controlled, phase II trial of transcranial direct current stimulation for the treatment of central pain in traumatic spinal cord injury. *Pain* 2006;122(1–2):197–209. <https://doi.org/10.1016/j.pain.2006.02.023>. Epub 2006/03/28.
- [62] Ngernyam N, Jensen MP, Arayawichanon P, Auvichayapat N, Tiamkao S, Janjarasjitt S, et al. The effects of transcranial direct current stimulation in patients with neuropathic pain from spinal cord injury. *Clin Neurophysiol* 2014;126(2):382–90. <https://doi.org/10.1016/j.clinph.2014.05.034>. Epub 2014/07/17.
- [63] Wrigley PJ, Gustin SM, McIndoe LN, Chakiath RJ, Henderson IA, Siddall PJ. Longstanding neuropathic pain after spinal cord injury is refractory to transcranial direct current stimulation: a randomized controlled trial. *Pain* 2013;154(10):2178–84. <https://doi.org/10.1016/j.pain.2013.06.045>. Epub 2013/07/09.
- [64] Yoon EJ, Kim YK, Kim HR, Kim SE, Lee Y, Shin HI. Transcranial direct current stimulation to lessen neuropathic pain after spinal cord injury: a mechanistic PET study. *Neurorehabil Neural Repair* 2014;28(3):250–9. <https://doi.org/10.1177/1545968313507632>. Epub 2013/11/12.
- [65] Boggio PS, Amancio EJ, Correa CF, Cecilio S, Valasek C, Bajwa Z, et al. Transcranial DC stimulation coupled with TENS for the treatment of chronic pain: a preliminary study. *Clin J Pain* 2009;25(8):691–5. <https://doi.org/10.1097/AJP.0b013e3181af1414>. Epub 2009/11/19.
- [66] Dasilva AF, Mendonca ME, Zaghi S, Lopes M, Dossantos MF, Spierings EL, et al. tDCS-induced analgesia and electrical fields in pain-related neural networks in chronic migraine. *Headache* 2012;52(8):1283–95. <https://doi.org/10.1111/j.1526-4610.2012.02141.x>.
- [67] DosSantos MF, Love TM, Martikainen IK, Nascimento TD, Fregni F, Cumiford C, et al. Immediate effects of tDCS on the mu-opioid system of a chronic pain patient. *Front Psychiatry* 2012;3:93. <https://doi.org/10.3389/fpsy.2012.00093>. Epub 2012/11/07.
- [68] DosSantos MF, Martikainen IK, Nascimento TD, Love TM, DeBoer MD, Schambra HM, et al. Building up analgesia in humans via the endogenous mu-opioid system by combining placebo and active tDCS: a preliminary report. *PLoS One* 2014;9(7):e102350. <https://doi.org/10.1371/journal.pone.0102350>.
- [69] Mylius V, Borckardt JJ, Lefaucher JP. Noninvasive cortical modulation of experimental pain. *Pain* 2012;153(7):1350–63. <https://doi.org/10.1016/j.pain.2012.04.009>. Epub 2012/05/29.
- [70] Naylor JC, Borckardt JJ, Marx CE, Hamer RM, Fredrich S, Reeves ST, et al. Cathodal and anodal left prefrontal tDCS and the perception of control over pain. *Clin J Pain* 2014;30(8):693–700. <https://doi.org/10.1097/ajp.0000000000000025>. Epub 2013/11/28.
- [71] Saunders N, Downham R, Turman B, Kropotov J, Clark R, Yumash R, et al. Working memory training with tDCS improves behavioral and neurophysiological symptoms in pilot group with post-traumatic stress disorder (PTSD) and with poor working memory. *Neurocase* 2014. <https://doi.org/10.1080/13554794.2014.890727>. Epub 2014/03/04.
- [72] Faria P, Fregni F, Sebastiao F, Dias AI, Leal A. Feasibility of focal transcranial DC polarization with simultaneous EEG recording: preliminary assessment in healthy subjects and human epilepsy. *Epilepsy Behav* 2012;25(3):417–25. <https://doi.org/10.1016/j.yebeh.2012.06.027>. Epub 2012/11/06.
- [73] Yook SW, Park SH, Seo JH, Kim SJ, Ko MH. Suppression of seizure by cathodal transcranial direct current stimulation in an epileptic patient – a case report. *Ann Rehabil Med* 2011;35(4):579–82. <https://doi.org/10.5535/arm.2011.35.4.579>. Epub 2012/04/17.
- [74] Brunoni AR, Shiozawa P, Truong D, Javitt DC, Elkis H, Fregni F, et al. Understanding tDCS effects in schizophrenia: a systematic review of clinical data and an integrated computation modeling analysis. *Expert Rev Med Devices* 2014;11(4):383–94. <https://doi.org/10.1586/17434440.2014.911082>.
- [75] Hoy KE, Arnold SL, Emonson MR, Daskalakis ZJ, Fitzgerald PB. An investigation into the effects of tDCS dose on cognitive performance over time in patients with schizophrenia. *Schizophr Res* 2014;155(1–3):96–100. <https://doi.org/10.1016/j.schres.2014.03.006>. Epub 2014/04/08.
- [76] Narayanaswamy JC, Shivakumar V, Bose A, Agarwal SM, Venkatasubramanian G, Gangadhar BN. Sustained improvement of negative symptoms in schizophrenia with add-on tDCS. *Clin Schizophr Relat Psychoses* 2014;1–7. <https://doi.org/10.3371/csrp.jnvs.061314>. Epub 2014/06/22.
- [77] Shiozawa P, da Silva ME, Cordeiro Q, Fregni F, Brunoni AR. Transcranial direct current stimulation (tDCS) for the treatment of persistent visual and auditory hallucinations in schizophrenia: a case study. *Brain Stimul* 2013;6(5):831–3. <https://doi.org/10.1016/j.brs.2013.03.003>. Epub 2013/04/23.
- [78] Jacobson L, Ezra A, Berger U, Lavidor M. Modulating oscillatory brain activity correlates of behavioral inhibition using transcranial direct current stimulation. *Clin Neurophysiol* 2012;123(5):979–84. <https://doi.org/10.1016/j.clinph.2011.09.016>. Epub 2011/10/15.
- [79] Hsu TY, Tseng LY, Yu JX, Kuo WJ, Hung DL, Tzeng OJ, et al. Modulating inhibitory control with direct current stimulation of the superior medial frontal cortex. *Neuroimage* 2011;56(4):2249–57. <https://doi.org/10.1016/j.neuroimage.2011.03.059>. Epub 2011/04/05.
- [80] Kang EK, Baek MJ, Kim S, Paik NJ. Non-invasive cortical stimulation improves post-stroke attention decline. *Restor Neurol Neurosci* 2009;27(6):645–50. <https://doi.org/10.3233/rnn-2009-0514>. Epub 2010/01/01.
- [81] Angelakis E, Liouta E, Andreadis N, Korfiatis S, Ktonas P, Stranjalis G, et al. Transcranial direct current stimulation effects in disorders of consciousness. *Arch Phys Med Rehabil* 2014;95(2):283–9. <https://doi.org/10.1016/j.apmr.2013.09.002>. Epub 2013/09/17.
- [82] Thibaut A, Bruno MA, Ledoux D, Demertzi A, Laureys S. tDCS in patients with disorders of consciousness: sham-controlled randomized double-blind study. *Neurology* 2014;82(13):1112–8. <https://doi.org/10.1212/wnl.0000000000000260>. Epub 2014/02/28.
- [83] Benninger DH, Lomarev M, Lopez G, Wassermann EM, Li X, Considine E, et al. Transcranial direct current stimulation for the treatment of Parkinson's disease. *J Neurol Neurosurg Psychiatry* 2010;81(10):1105–11. <https://doi.org/10.1136/jnnp.2009.202556>. Epub 2010/09/28.
- [84] Floel A. tDCS-enhanced motor and cognitive function in neurological diseases. *Neuroimage* 2014;85(Pt 3):934–47. <https://doi.org/10.1016/j.neuroimage.2013.05.098>. Epub 2013/06/04.
- [85] Fregni F, Boggio PS, Santos MC, Lima M, Vieira AL, Rigonatti SP, et al. Noninvasive cortical stimulation with transcranial direct current stimulation in Parkinson's disease. *Mov Disord* 2006;21(10):1693–702. <https://doi.org/10.1002/mds.21012>. Epub 2006/07/04.
- [86] Pereira JB, Junque C, Bartres-Faz D, Marti MJ, Sala-Llonch R, Compta Y, et al. Modulation of verbal fluency networks by transcranial direct current stimulation (tDCS) in Parkinson's disease. *Brain Stimul* 2013;6(1):16–24. <https://doi.org/10.1016/j.brs.2012.01.006>. Epub 2012/03/14.
- [87] Shahbabaie A, Golesorkhi M, Zamanian B, Ebrahimipour M, Keshvari F, Nejati V, et al. State dependent effect of transcranial direct current stimulation (tDCS) on methamphetamine craving. *Int J Neuropsychopharmacol* 2014;1–8. <https://doi.org/10.1017/s1461145714000686>. Epub 2014/05/16.
- [88] Fecteau S, Knoch D, Fregni F, Sultani N, Boggio P, Pascual-Leone A. Diminishing risk-taking behavior by modulating activity in the prefrontal cortex: a direct current stimulation study. *J Neurosci* 2007;27(46):12500–5. <https://doi.org/10.1523/jneurosci.3283-07.2007>. Epub 2007/11/16.
- [89] da Silva MC, Conti CL, Klaus J, Alves LG, do Nascimento Cavalcante HM, Fregni F, et al. Behavioral effects of transcranial direct current stimulation (tDCS) induced dorsolateral prefrontal cortex plasticity in alcohol dependence. *J Physiol Paris* 2013;107(6):493–502. <https://doi.org/10.1016/j.jphysparis.2013.07.003>. Epub 2013/07/31.
- [90] Klaus J, Penido Pinheiro LC, Silva Merlo BL, Correia Santos GD, Fregni F, Nitsche MA, et al. A randomized controlled trial of targeted prefrontal cortex modulation with tDCS in patients with alcohol dependence. *Int J*

- Neuropsychopharmacol 2014;17(11):1793–803. <https://doi.org/10.1017/s1461145714000984>. Epub 2014/07/11.
- [91] Pedron S, Monnin J, Haffen E, Sechter D, Van Waes V. Repeated transcranial direct current stimulation prevents abnormal behaviors associated with abstinence from chronic nicotine consumption. *Neuropsychopharmacology* 2014;39(4):981–8. <https://doi.org/10.1038/npp.2013.298>. Epub 2013/10/25.
- [92] Bikson M, Paneri B, Giordano J. The off-label use, utility and potential value of tDCS in the clinical care of particular neuropsychiatric conditions. *J Law Biosci* 2016;3(3):642–6. <https://doi.org/10.1093/jlb/lsw044>.
- [93] Berryhill ME, Jones KT. tDCS selectively improves working memory in older adults with more education. *Neurosci Lett* 2012;521(2):148–51. <https://doi.org/10.1016/j.neulet.2012.05.074>. Epub 2012/06/12.
- [94] Hoy KE, Emonson MR, Arnold SL, Thomson RH, Daskalakis ZJ, Fitzgerald PB. Testing the limits: investigating the effect of tDCS dose on working memory enhancement in healthy controls. *Neuropsychologia* 2013;51(9):1777–84. <https://doi.org/10.1016/j.neuropsychologia.2013.05.018>. Epub 2013/06/12.
- [95] Javadi AH, Walsh V. Transcranial direct current stimulation (tDCS) of the left dorsolateral prefrontal cortex modulates declarative memory. *Brain Stimul* 2012;5(3):231–41. <https://doi.org/10.1016/j.brs.2011.06.007>. Epub 2011/08/16.
- [96] Mulquiney PG, Hoy KE, Daskalakis ZJ, Fitzgerald PB. Improving working memory: exploring the effect of transcranial random noise stimulation and transcranial direct current stimulation on the dorsolateral prefrontal cortex. *Clin Neurophysiol* 2011;122(12):2384–9. <https://doi.org/10.1016/j.clinph.2011.05.009>. Epub 2011/06/15.
- [97] Richmond L, Wolk D, Chain J, Olson IR. Transcranial direct current stimulation enhances verbal working memory training performance over time and near-transfer outcomes. *J Cogn Neurosci* 2014;26(11):2443–54. https://doi.org/10.1162/jocn_a.00657. Epub 2014/04/20.
- [98] Tseng P, Hsu TY, Chang CF, Tzeng OJ, Hung DL, Muggleton NG, et al. Unleashing potential: transcranial direct current stimulation over the right posterior parietal cortex improves change detection in low-performing individuals. *J Neurosci* 2012;32(31):10554–61. <https://doi.org/10.1523/jneurosci.0362-12.2012>. Epub 2012/08/03.
- [99] Zaehle T, Sandmann P, Thorne JD, Jancke L, Herrmann CS. Transcranial direct current stimulation of the prefrontal cortex modulates working memory performance: combined behavioural and electrophysiological evidence. *BMC Neurosci* 2011;12:2. <https://doi.org/10.1186/1471-2202-12-2>. Epub 2011/01/08.
- [100] Jausovec N, Jausovec K. Increasing working memory capacity with theta transcranial alternating current stimulation (tACS). *Biol Psychol* 2014;96:42–7. <https://doi.org/10.1016/j.biopsycho.2013.11.006>. Epub 2013/12/03.
- [101] Asthana M, Nueckel K, Muhlberger A, Neueder D, Polak T, Domschke K, et al. Effects of transcranial direct current stimulation on consolidation of fear memory. *Front Psychiatry* 2013;4:107. <https://doi.org/10.3389/fpsy.2013.00107>. Epub 2013/09/27.
- [102] Javadi AH, Cheng P. Transcranial direct current stimulation (tDCS) enhances reconsolidation of long-term memory. *Brain Stimul* 2013;6(4):668–74. <https://doi.org/10.1016/j.brs.2012.10.007>. Epub 2012/11/10.
- [103] Marshall L, Kirov R, Brade J, Mollle M, Born J. Transcranial electrical currents to probe EEG brain rhythms and memory consolidation during sleep in humans. *PLoS One* 2011;6(2):e16905. <https://doi.org/10.1371/journal.pone.0016905>. Epub 2011/02/23.
- [104] Marshall L, Mollle M, Hallschmid M, Born J. Transcranial direct current stimulation during sleep improves declarative memory. *J Neurosci* 2004;24(44):9985–92. <https://doi.org/10.1523/jneurosci.2725-04.2004>. Epub 2004/11/05.
- [105] Martin DM, Liu R, Alonzo A, Green M, Loo CK. Use of transcranial direct current stimulation (tDCS) to enhance cognitive training: effect of timing of stimulation. *Exp Brain Res* 2014;232(10):3345–51. <https://doi.org/10.1007/s00221-014-4022-x>. Epub 2014/07/06.
- [106] McIntire LK, McKinley RA, Goodyear C, Nelson J. A comparison of the effects of transcranial direct current stimulation and caffeine on vigilance and cognitive performance during extended wakefulness. *Brain Stimul* 2014;7(4):499–507. <https://doi.org/10.1016/j.brs.2014.04.008>. Epub 2014/07/23.
- [107] Nelson JT, McKinley RA, Golob EJ, Warm JS, Parasuraman R. Enhancing vigilance in operators with prefrontal cortex transcranial direct current stimulation (tDCS). *Neuroimage* 2014;85(Pt 3):909–17. <https://doi.org/10.1016/j.neuroimage.2012.11.061>. Epub 2012/12/14.
- [108] Chi RP, Snyder AW. Facilitate insight by non-invasive brain stimulation. *PLoS One* 2011;6(2):e16655. <https://doi.org/10.1371/journal.pone.0016655>. Epub 2011/02/12.
- [109] Chi RP, Snyder AW. Brain stimulation enables the solution of an inherently difficult problem. *Neurosci Lett* 2012;515(2):121–4. <https://doi.org/10.1016/j.neulet.2012.03.012>. Epub 2012/03/24.
- [110] Chrysikou EG, Hamilton RH, Coslett HB, Datta A, Bikson M, Thompson-Schill SL. Noninvasive transcranial direct current stimulation over the left prefrontal cortex facilitates cognitive flexibility in tool use. *Cogn Neurosci* 2013;4(2):81–9. <https://doi.org/10.1080/17588928.2013.768221>.
- [111] Woods AJ, Hamilton RH, Kranjec A, Minhaus P, Bikson M, Yu J, et al. Space, time, and causality in the human brain. *Neuroimage* 2014;92:285–97. <https://doi.org/10.1016/j.neuroimage.2014.02.015>.
- [112] Cattaneo Z, Pisoni A, Papagno C. Transcranial direct current stimulation over Broca's region improves phonemic and semantic fluency in healthy individuals. *Neuroscience* 2011;183:64–70. <https://doi.org/10.1016/j.neuroscience.2011.03.058>. Epub 2011/04/12.
- [113] De Vries MH, Barth AC, Maiworm S, Knecht S, Zwitserlood P, Floel A. Electrical stimulation of Broca's area enhances implicit learning of an artificial grammar. *J Cogn Neurosci* 2010;22(11):2427–36. <https://doi.org/10.1162/jocn.2009.21385>. Epub 2009/11/21.
- [114] Fiori V, Coccia M, Marinelli CV, Vecchi V, Bonifazi S, Ceravolo MG, et al. Transcranial direct current stimulation improves word retrieval in healthy and nonfluent aphasic subjects. *J Cogn Neurosci* 2011;23(9):2309–23. <https://doi.org/10.1162/jocn.2010.21579>. Epub 2010/10/16.
- [115] Javadi AH, Cheng P, Walsh V. Short duration transcranial direct current stimulation (tDCS) modulates verbal memory. *Brain Stimul* 2012;5(4):468–74. <https://doi.org/10.1016/j.brs.2011.08.003>. Epub 2011/10/04.
- [116] Meinzer M, Jahnigen S, Copland DA, Darkow R, Grittner U, Avirame K, et al. Transcranial direct current stimulation over multiple days improves learning and maintenance of a novel vocabulary. *Cortex* 2014;50:137–47. <https://doi.org/10.1016/j.cortex.2013.07.013>. Epub 2013/08/31.
- [117] Turkeltaub PE, Benson J, Hamilton RH, Datta A, Bikson M, Coslett HB. Left lateralizing transcranial direct current stimulation improves reading efficiency. *Brain Stimul* 2012;5(3):201–7. <https://doi.org/10.1016/j.brs.2011.04.002>.
- [118] Bullard LM, Browning ES, Clark VP, Coffman BA, Garcia CM, Jung RE, et al. Transcranial direct current stimulation's effect on novice versus experienced learning. *Exp Brain Res* 2011;213(1):9–14. <https://doi.org/10.1007/s00221-011-2764-2>. Epub 2011/06/28.
- [119] Fertonani A, Pirulli C, Miniussi C. Random noise stimulation improves neuroplasticity in perceptual learning. *J Neurosci* 2011;31(43):15416–23. <https://doi.org/10.1523/jneurosci.2002-11.2011>. Epub 2011/10/28.
- [120] Parasuraman R, McKinley RA. Using noninvasive brain stimulation to accelerate learning and enhance human performance. *Hum Factors* 2014;56(5):816–24. Epub 2014/08/22.
- [121] Vollmann H, Conde V, Sewerin S, Taubert M, Sehm B, Witte OW, et al. Anodal transcranial direct current stimulation (tDCS) over supplementary motor area (SMA) but not pre-SMA promotes short-term visuomotor learning. *Brain Stimul* 2013;6(2):101–7. <https://doi.org/10.1016/j.brs.2012.03.018>. Epub 2012/06/05.
- [122] Hauser TU, Rotzer S, Grabner RH, Merillat S, Jancke L. Enhancing performance in numerical magnitude processing and mental arithmetic using transcranial Direct Current Stimulation (tDCS). *Front Hum Neurosci* 2013;7:244. <https://doi.org/10.3389/fnhum.2013.00244>. Epub 2013/06/14.
- [123] Iuculano T, Cohen Kadosh R. Preliminary evidence for performance enhancement following parietal lobe stimulation in Developmental Dyscalculia. *Front Hum Neurosci* 2014;8:38. <https://doi.org/10.3389/fnhum.2014.00038>. Epub 2014/02/27.
- [124] Voss U, Holzmann R, Hobson A, Paulus W, Kopphele-Gossel J, Klimke A, et al. Induction of self awareness in dreams through frontal low current stimulation of gamma activity. *Nat Neurosci* 2014;17(6):810–2. <https://doi.org/10.1038/nn.3719>. Epub 2014/05/13.
- [125] Cogiamanian F, Marceglia S, Ardolino G, Barbieri S, Priori A. Improved isometric force endurance after transcranial direct current stimulation over the human motor cortical areas. *Eur J Neurosci* 2007;26(1):242–9. <https://doi.org/10.1111/j.1460-9568.2007.05633.x>. Epub 2007/07/07.
- [126] Okano AH, Fontes EB, Montenegro RA, Farinatti PD, Cyrino ES, Li LM, et al. Brain stimulation modulates the autonomic nervous system, rating of perceived exertion and performance during maximal exercise. *Br J Sports Med* 2013;49(18):1213–8. <https://doi.org/10.1136/bjsports-2012-091658>. Epub 2013/03/01.
- [127] Galea JM, Celnik P. Brain polarization enhances the formation and retention of motor memories. *J Neurophysiol* 2009;102(1):294–301. <https://doi.org/10.1152/jn.00184.2009>. Epub 2009/04/24.
- [128] Reis J, Fischer JT, Prichard G, Weiller C, Cohen LG, Fritsch B. Time- but not sleep-dependent consolidation of tDCS-enhanced visuomotor skills. *Cereb Cortex* 2013;25(1):109–17. <https://doi.org/10.1093/cercor/bht208>. Epub 2013/08/21.
- [129] Reis J, Schambra HM, Cohen LG, Buch ER, Fritsch B, Zarahn E, et al. Noninvasive cortical stimulation enhances motor skill acquisition over multiple days through an effect on consolidation. *Proc Natl Acad Sci U. S. A* 2009;106(5):1590–5. <https://doi.org/10.1073/pnas.0805413106>. Epub 2009/01/24.
- [130] Sriraman A, Oishi T, Madhavan S. Timing-dependent priming effects of tDCS on ankle motor skill learning. *Brain Res* 2014;1581:23–9. <https://doi.org/10.1016/j.brainres.2014.07.021>. Epub 2014/07/27.
- [131] Tecchio F, Zappasodi F, Assenza G, Tombini M, Vollaro S, Barbati G, et al. Anodal transcranial direct current stimulation enhances procedural consolidation. *J Neurophysiol* 2010;104(2):1134–40. <https://doi.org/10.1152/jn.00661.2009>. Epub 2010/06/12.
- [132] Horvath JC, Forte JD, Carter O. Quantitative review finds No evidence of cognitive effects in healthy populations from single-session transcranial direct current stimulation (tDCS). Epub 02/24 *Brain Stimul* 2015;8(3):535–50. <https://doi.org/10.1016/j.brs.2015.01.040>. Epub 2015 Jan 16.
- [133] Tremblay S, Lepage JF, Latulipe-Loiselle A, Fregni F, Pascual-Leone A, Théoret H. The uncertain outcome of prefrontal tDCS. *Brain Stimul* 2014;7(6):773–83. <https://doi.org/10.1016/j.brs.2014.10.003>.
- [134] Horvath JC, Forte JD, Carter O. Evidence that transcranial direct current stimulation (tDCS) generates little-to-no reliable neurophysiologic effect

- beyond MEP amplitude modulation in healthy human subjects: a systematic review. *Epub 12/03 Neurophysiology* 2014;66:213–36. <https://doi.org/10.1016/j.neurophysiology.2014.11.021>. Epub 2014 Nov 20.
- [135] Sarkar A, Dowker A, Cohen Kadosh R. Cognitive enhancement or cognitive cost: trait-specific outcomes of brain stimulation in the case of mathematics anxiety. *J Neurosci* 2014;34(50):16605–10. <https://doi.org/10.1523/JNEUROSCI.3129-14.2014>. Epub 12/17.
- [136] Antal A, Keeser D, Priori A, Padberg F, Nitsche MA. Conceptual and procedural shortcomings of the systematic review “evidence that transcranial direct current stimulation (tDCS) generates little-to-no reliable neurophysiologic effect beyond MEP amplitude modulation in healthy human subjects: a systematic review” by horvath and Co-workers. *Epub 07/06 Brain Stimul* 2015;8(4):846–9. <https://doi.org/10.1016/j.brs.2015.05.010>. Epub 2015 Jun 5.
- [137] Lefaucheur JP, Antal A, Ayache SS, Benninger DH, Brunelin J, Cogiamanian F, et al. Evidence-based guidelines on the therapeutic use of transcranial direct current stimulation (tDCS). *Epub 11/21 Clin Neurophysiol* 2016;128(1):56–92. <https://doi.org/10.1016/j.clinph.2016.10.087>. Epub 2016 Oct 29.
- [138] Jamil A, Batsikadze G, Kuo HI, Labruna L, Hasan A, Paulus W, et al. Systematic evaluation of the impact of stimulation intensity on neuroplastic after-effects induced by transcranial direct current stimulation. *Epub 10/11 J Physiol* 2016;595(4):1273–88. <https://doi.org/10.1113/jp272738>. Epub 2016 Nov 8.
- [139] Woods AJ, Antal A, Bikson M, Boggio PS, Brunoni AR, Celnik P, et al. A technical guide to tDCS, and related non-invasive brain stimulation tools. *Clin Neurophysiol* 2016;127(2):1031–48. <https://doi.org/10.1016/j.clinph.2015.11.012>.
- [140] Paneri B, Adair D, Thomas C, Khadka N, Patel V, Tyler WJ, et al. Tolerability of repeated application of transcranial electrical stimulation with limited outputs to healthy subjects. *Brain Stimul* 2016;9(5):740–54. <https://doi.org/10.1016/j.brs.2016.05.008>.
- [141] Brunoni AR, Amadera J, Berbel B, Volz MS, Rizzerio BG, Fregni F. A systematic review on reporting and assessment of adverse effects associated with transcranial direct current stimulation. *Int J Neuropsychopharmacol* 2011;14(8):1133–45. <https://doi.org/10.1017/s1461145710001690>. Epub 2011/02/16.
- [142] Giordano J. Conditions for consent to the use of neurotechnology: a preparatory neuroethical approach to risk assessment and reduction: *AJOB Neuroscience: Vol 6, No 4. AJOB-Neurosci* 2015;6(4):12–14. Epub 11/30/2015. doi: <https://doi.org/10.1080/21507740.2015.1094557>.
- [143] Giordano JD, Donald. Toward right and good use of brain-machine interfacing neurotechnologies: ethical issues and implications for guidelines and policy. *Cogn Tech J* 2011;15(2):5–10.
- [144] Giordano J. Neurotechnology, Evidence, and Ethics: on stewardship and the good in research and practice. *Pract Pain Manag* 2010;10(2):63–9.
- [145] U.S. Food and Drug Administration Center for Devices and Radiological Health. Draft guidance for industry and FDA staff: class II special controls guidance document: cutaneous electrode. FDA: U.S. Department of Health and Human Services Food and Drug Administration, Center for Devices and Radiological Health; 2010.
- [146] U.S. Food and Drug Administration Center for Devices and Radiological Health. Draft guidance for industry and FDA staff: class II special controls guidance document: electroconductive media. U.S. Department of Health and Human Services Food and Drug Administration, Center for Devices and Radiological Health; 2010.
- [147] U.S. Food and Drug Administration Center for Devices and Radiological Health. Guidance for the content of premarket submissions for software contained in medical devices. 2010. <http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm089543.htm>.
- [148] U.S. Department of Health and Human Services Food and Drug Administration. In: Research CfDaRHACfBEa, editor. *General principles of software validation*; 2002.
- [149] U.S. Food and Drug Administration Center for Devices and Radiological Health. Mobile medical applications guidance for industry and Food and Drug Administration staff. 2013. <http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM263366.pdf>.
- [150] U.S. Department of Health and Human Services Food and Drug Administration. In: Center for Devices and Radiological Health, editor. *Applying human factors and usability engineering to medical devices*; 2016.
- [151] Thakral G, LaFontaine J, Najafi B, Talal TK, Kim P, Lavery LA. Electrical stimulation to accelerate wound healing. *Diabet Foot Ankle* 2013;4(1):22081. <https://doi.org/10.3402/dfa.v4i0.22081>.
- [152] Deng ZD, Lisanby SH, Peterchev AV. Electric field strength and focality in electroconvulsive therapy and magnetic seizure therapy: a finite element simulation study. *Epub 01/21 J Neural Eng* 2011;8(1):016007. <https://doi.org/10.1088/1741-2560/8/1/016007>. Epub 2011 Jan 19.
- [153] Kent AR, Grill WM. Neural origin of evoked potentials during thalamic deep brain stimulation. *J Neurophysiol* 2013;110(4):826–43. <https://doi.org/10.1152/jn.00074.2013>.
- [154] McIntyre CC, Mori S, Sherman DL, Thakor NV, Vitek JL. Electric field and stimulating influence generated by deep brain stimulation of the subthalamic nucleus. *Clin Neurophysiol* 2004;115(3):589–95. <https://doi.org/10.1016/j.clinph.2003.10.033>.
- [155] McIntyre CC, Savasta M, Kerkerian-Le Goff L, Vitek JL. Uncovering the mechanism(s) of action of deep brain stimulation: activation, inhibition, or both. *Clin Neurophysiol* 2004;115(6):1239–48. <https://doi.org/10.1016/j.clinph.2003.12.024>.
- [156] Sahlsten H, Isohanni J, Haapaniemi J, Salonen J, Paavola J, Loytyniemi E, et al. Electric field navigated transcranial magnetic stimulation for chronic tinnitus: a pilot study. *Epub 06/19 Int J Audiol* 2015;54(12):899–909. <https://doi.org/10.3109/14992027.2015.1054041>. Epub 2015 Jun 18.
- [157] Sahlsten H, Virtanen J, Joutsa J, Niinivirta-Joutsa K, Loytyniemi E, Johansson R, et al. Electric field-navigated transcranial magnetic stimulation for chronic tinnitus: a randomized, placebo-controlled study. *Epub 04/19 Int J Audiol* 2017;56(9):692–700. <https://doi.org/10.1080/14992027.2017.1313461>. Epub 2017 Apr 18.
- [158] Lee WH, Lisanby SH, Laine AF, Peterchev AV. Stimulation strength and focality of electroconvulsive therapy with individualized current amplitude: a preclinical study. *Conf Proc IEEE Eng Med Biol Soc* 2012;2012:6430–3. <https://doi.org/10.1109/EMBC.2012.6347466>.
- [159] Lee WH, Lisanby SH, Laine AF, Peterchev AV. Electric field characteristics of electroconvulsive therapy with individualized current amplitude: a pre-clinical study. *Conf Proc IEEE Eng Med Biol Soc* 2013;2013:3082–5. <https://doi.org/10.1109/EMBC.2013.6610192>.
- [160] De Marco Garcia NV, Fishell G. Subtype-selective electroporation of cortical interneurons. *J Vis Exp* 2014;90:e51518. <https://doi.org/10.3791/51518>.
- [161] Kim NH, Kim S, Hong JS, Jeon SH, Huh SO. Application of in utero electroporation of G-protein coupled receptor (GPCR) genes, for subcellular localization of hardly identifiable GPCR in mouse cerebral cortex. *Mol Cells* 2014;37(7):554–61. <https://doi.org/10.14348/molcells.2014.0159>.
- [162] U.S. Food and Drug Administration Center for Devices and Radiological Health. De Novo 510(k) Summary for Cefaly Device (K122566) 2012 [December 30, 2014]. Available from: http://www.accessdata.fda.gov/cdrh_docs/reviews/K122566.pdf.
- [163] U.S. Food and Drug Administration Center for Devices and Radiological Health. Premarket Notification 510(k) Summary for Myotrac Infinity (K053434) 2006 [December 30, 2014]. Available from: http://www.accessdata.fda.gov/cdrh_docs/pdf5/K053434.pdf.
- [164] U.S. Food and Drug Administration Center for Devices and Radiological Health. Premarket Notification 510(k) Summary for Sterling Medical Impulse 3 Stimulator (K121305) 2012 [December 30, 2014]. Available from: http://www.accessdata.fda.gov/cdrh_docs/pdf12/K121305.pdf.
- [165] U.S. Food and Drug Administration Center for Devices and Radiological Health. Premarket Notification 510(k) Summary for FM 10/C Cranial Electrical Nerve Stimulator (K090052) 2009 [December 30, 2014]. Available from: http://www.accessdata.fda.gov/cdrh_docs/pdf9/K090052.pdf.
- [166] U.S. Food and Drug Administration Center for Devices and Radiological Health. Premarket Notification 510(k) Summary for HealthMate Forever Pro-8AB (K121757) 2012 [December 30, 2014]. Available from: http://www.accessdata.fda.gov/cdrh_docs/pdf12/K121757.pdf.
- [167] U.S. Food and Drug Administration Center for Devices and Radiological Health. Premarket Notification 510(k) Summary for Tanyx (K123866) 2013 [December 30, 2014]. Available from: http://www.accessdata.fda.gov/cdrh_docs/pdf12/K123866.pdf.
- [168] U.S. Food and Drug Administration Center for Devices and Radiological Health. Premarket Notification 510(k) Summary for PM3030 (K110068) 2011 [December 30, 2014]. Available from: http://www.accessdata.fda.gov/cdrh_docs/pdf11/K110068.pdf.
- [169] U.S. Food and Drug Administration Center for Devices and Radiological Health. Premarket Notification 510(k) Summary for Hi-Dow JQ-5C (K102598) 2011 [December 30, 2014]. Available from: http://www.accessdata.fda.gov/cdrh_docs/pdf10/K102598.pdf.
- [170] U.S. Food and Drug Administration Center for Devices and Radiological Health. Premarket Notification 510(k) Summary for Rejuvenique (K011935) 2001 [December 30, 2014]. Available from: http://www.accessdata.fda.gov/cdrh_docs/pdf/k011935.pdf.
- [171] U.S. Food and Drug Administration Center for Devices and Radiological Health. Premarket Notification 510(k) Summary for Nu Skin Facial Spa (K122711) 2013 [December 30, 2014]. Available from: http://www.accessdata.fda.gov/cdrh_docs/pdf12/K122711.pdf.
- [172] U.S. Food and Drug Administration Center for Devices and Radiological Health. Premarket Notification 510(k) Summary for Jiajian CMN Stimulator (K130768) 2013 [December 30, 2014]. Available from: http://www.accessdata.fda.gov/cdrh_docs/pdf13/K130768.pdf.
- [173] U.S. Food and Drug Administration Center for Devices and Radiological Health. Premarket Notification 510(k) Summary for Jiajian Electra-acupuncture Stimulators (K122812) 2013 [December 30, 2014]. Available from: http://www.accessdata.fda.gov/cdrh_docs/pdf12/K122812.pdf.
- [174] U.S. Food and Drug Administration Center for Devices and Radiological Health. Premarket Notification 510(k) Summary for NuFace Plus Device (K103472) 2010. Available from: http://www.accessdata.fda.gov/cdrh_docs/pdf10/K103472.pdf.
- [175] Empi I. Hybrysis Patch Instructions for Use 2007 [Document Downloaded on December 30, 2014]. Available from: <http://www.djoglobal.com/sites/default/files/360353.pdf>.
- [176] Medical T. Iontopatch Overview 2013 [December 30, 2014]. Available from: <http://www.iontopatch.com/index.html>.
- [177] Company RAF. Fischer Model MD-2 Galvanic Unit Instruction Manual 2012 [Document Downloaded on December 30, 2014]. Available from: <http://www.rafischer.com/share/md2-manual-web.pdf>.

- [178] Company RAF. Fischer Model MD-1a Galvanic Unit Instruction Manual 2013 [Document Downloaded on December 30, 2014]. Available from: <http://www.rafischer.com/share/md1a-manual.pdf>.
- [179] Chattem I. IcyHot Smart Relief User Manual 2014 [December 30, 2014]. Available from: http://www.smartrelief.com/wp-content/uploads/2014/02/IH_SmartRelief_Inst_Manual.pdf.
- [180] Ltd B-MR. Neurotech KneeHab XP Instructions for Use 2012 [December 30, 2014]. Available from: http://www.neurotechgroup.com/library/us/downloads/Kneehab_and_Tens/US%20Kneehab+%20Controller%20IM%20Rev%202.pdf.
- [181] Russell M, Goodman T, Wang Q, Groshong B, Lyeth BG. Gender differences in current received during transcranial electrical stimulation. *Front Psychiatry* 2014;5:104. <https://doi.org/10.3389/fpsy.2014.00104>.
- [182] Javadi AH, Brunec IK, Walsh V, Penny WD, Spiers HJ. Transcranial electrical brain stimulation modulates neuronal tuning curves in perception of numerosity and duration. *Neuroimage* 2014;102(Pt 2):451–7. <https://doi.org/10.1016/j.neuroimage.2014.08.016>.
- [183] Truong DQ, Magerowski G, Blackburn GL, Bikson M, Alonso-Alonso M. Computational modeling of transcranial direct current stimulation (tDCS) in obesity: impact of head fat and dose guidelines. *Neuroimage Clin* 2013;2:759–66. <https://doi.org/10.1016/j.nicl.2013.05.011>.