# Neurofeedback in a regulated world: How national and international legislation influence medical research in Europe and in the United States

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## Abstract

Medical devices such as software applications for neurofeedback training are subject to national and international regulation when they are used to improve health-related outcomes. In the European Union the Medical Device Regulation (MDR; Regulation (EU) 2017/745 on Medical Devices) has been in force since 2021. In the USA, the Federal Drug Agency (FDA) recently increased regulatory requirements for clinical fMRI-based neurofeedback studies. The new regulations increase the required effort for clinical projects significantly, incurring imminent challenges to conduct neurofeedback research under the constraints of funding programs, limited intramural funds and limited availability of qualified staff and time. Concerns are growing over the effects that these developments may have on the neurofeedback field. In face of this situation, a plenary discussion was held on that topic at the real-time Functional Imaging and Neurofeedback (rtFIN) meeting (Heidelberg, Germany) on 6th November 2024. Five experts discussed how the historic changes in the regulatory landscape shape their research programs and how they affect university spin-offs. This article presents an edited transcript of the session. As opinion leaders in the field of real-time fMRI, the discussants provide their first-person perspective, drawing on their diverse backgrounds in academia, psychiatry, industry and international consortia. They are concerned about the impending hazards that regulations pose to the progress of the field, particularly with regard to the transition of real-time fMRI applications to medical treatment. Aspects are identified that are still a matter of discussion, such as classification, and require researchers to familiarize with this topic at a rather early stage. While medical software, including neurofeedback software, is heavily regulated, concerns were raised that other software that is not intended for a medical purpose is under-regulated. While broad similarities of the situation in the EU and the USA were identified, there are also major differences including constraints of the funding landscapes and the scope of regulations addressing commercialization and research. Despite all the challenges, the panel hoped that researchers will still embark on clinical applications of real-time fMRI in the future, and that the pressure of regulatory frameworks would at least improve efficiency and lead to even greater attention to quality of research. After all, the fact that the field is facing these problems reflects its maturity and indicates that regulatory agencies recognize it as a form of clinical intervention.

## List of abbreviations

AI: Artificial intelligence

BCI: Brain-Computer Interface

BOLD: Blood Oxygenation level Dependent

BrainTrain: International real-time fMRI consortium (2013-2018)

CEO: Chief Executive Officer

EEG: Electroencephalogram

EMG: Electromyogram

EU: European Union

FDA: Federal Drug Agency

fMRI: functional Magnetic Resonance Imaging

IRB: Institutional Review Board (i.e., Ethics committee)

MDR: Medical Device Regulation

NSR: Non-significant risk determination

rtFIN: real-time Functional Imaging and Neurofeedback meeting (bi-annual international scientific conference)

SOP: Standard Operating Procedure

## Main text

Christian Paret: Researchers in the real-time fMRI field are driven by their excitement for the method, their interest into the underlying mechanisms and psychological aspects, and their dedication to help patients. They rather not want to use their time to study law. Why should they be concerned, David Linden?

David Linden: Since the rtFIN conference 2022 I have seen major developments in at least three areas of neurofeedback research: Advanced analytical methods, large-scale data analyses including meta-analyses with existing data sets, and setup of clinical trials. All the areas are interconnected and, in fact, they are all connected to the topic of this plenary. Why? When you develop a new method, especially if ultimately it might be useful for patients, it makes sense to think about a medical device regulation situation of whatever legislation you work under, while you're developing it. How does the meta-analyses work relate to this? It is essential to provide aggregated evidence of efficacy and safety once you are going to seek approval for your trial from your regulatory authority.

Paret: How do regulations influence neurofeedback research in the EU?

Linden: We have been involved in clinical and neurofeedback studies for a considerable amount of time, particularly in collaboration with Rainer Goebel. About four years ago, the medical device regulation came into force for medical software. For any new clinical trial, we had to go through the process of medical device regulation and that has been a learning experience for us. We also realized that there are many aspects that are still open to discussion and interpretation, because they are not specifically addressed by law. In the end, we all need to become experts on the regulatory environment we are in.

Kymberly Young: I'll give you the perspective from the United States: The FDA decided that fMRI neurofeedback is a device based intervention in May 2024 (NIMH Workshop: Neurofeedback Intervention Development. 2024 May, Washington, DC). Since then, they started working out the details of classification, which is an ongoing process. One of the themes of my discussions with them has been "we don't know". In this unclear situation, it is difficult to launch new projects, which I find frustrating. As it stands now, your local IRB will request an NSR (non-significant risk determination), which means you have to go to full review, which in my case, in my university, it was expedited review[1]. Additionally, many IRBs have a policy that only an MD can obtain informed consent from device-based trial participants. As I am a PhD, I'm not allowed to consent my participant anymore. I have to find an MD who often does not know about neurofeedback and I instruct them and have them consent my patients. If your IRB makes a NSR, you can go on with your study. If your IRB makes a significant risk determination, you have to go to the FDA and apply for what's called an investigational device exemption, which costs money and takes time. Although the situation is frustrating for a researcher, there is a bright side to it: the fact that the FDA is now regulating us means they are taking us seriously as a clinical intervention, and they do see the potential for us to be offering our services to the general public and maybe being covered by insurance. On the one hand, it is kind of legitimizing our field and our research and acknowledging the important work we are doing. On the other hand, it is quite a regulatory burden, and it is delaying studies and grant submissions as well.

Paret: The lawmakers in the first instance did not think about researchers who want to find out about psychobiological mechanisms of patient treatment or psychopathology. Presumably, they rather were concerned with the safety and efficacy of products accessing the markets. Still, as a researcher

[1] Expedited review: A single person reviews the protocol on an ongoing basis, it does not have to wait to go to a scheduled full board meeting to be reviewed.

investigating health outcomes of neurofeedback, you must conduct your study within the MDR[2]. The MDR and national laws explain what companies have to do when they want to sell their medical products in the EU. How may the complicated national legislations influence neurofeedback companies, Talma Hendler?

Talma Hendler: Luckily, I am not responsible for that in the company. I think we should rely on the experts help as much as we can, although this costs money. There is no way I as a researcher would be able to understand the regulatory situation sufficiently. This is clearly not something I can see a lab doing. It's neither in the expertise nor in the capacity. I myself realized that my work was not properly ready for regulation. There is a gap between what we are doing in the lab and what is needed to be done in order to get regulation clearance. Nowadays, with hindsight, I might be a bit more aware of it. The spin-off company (GrayMatters Health Ltd., where I am de-facto a cofounder of and the chief medical officer) started everything 'from scratch'. I watched them and I know a little better now how to approach things. And I would still take an expert to help me because expertise is required to collect the data correctly, to document everything and, finally, to present it to the regulatory authorities in the right way. To answer the question: Everything is not simple, it's not just 'do it'. You need to understand why and what you are doing. I agree with Kymberly Young that, on the one hand, it is a burden, but on the other hand, this means that we can move forward and become more impactful in the medical world, which is rewarding and worthwhile.

Young: I just want to echo that. First, I tried working with the FDA, just as me, as a researcher and it was a disaster. Then, I found consultants who only spend their lives trying to get device-based interventions approved, and they can help you and take a lot of the burden off of you.

Paret: Many attendees of rtFIN want to use real-time fMRI to show feasibility, prove neuropsychological theories, or they have different aims unrelated to showing efficacy and safety of a neurofeedback application. As CEO of the first company providing real-time fMRI neurofeedback software solutions, can you provide first-person experience of how MDR regulations changed the business?

Rainer Goebel: When we founded the company Brain Innovation about 25 years ago, we had no clue that, one day, we may walk the full way to certification of software as medical device. When we discussed scenarios like this in the past, we always cancelled them and said: "We can't afford that. This is expensive, you need people you need a lot of money." And we are a small company. Before we embarked into this endeavor, the whole company was sitting together and, univocally, had to decide to do this step together or not. It changes a small company radically. You also have to invest in restructuring your company. You need a professional quality management system, you have to document the flow of documents, who has to sign it, who has responsibility for what. You establish SOPs (Standard Operating Procedures) to organize everything. There were two reasons for us to get involved: we had collaborated with David (Linden) for a long time and it was exciting to help to bring neurofeedback to patients. Second, David received an EU grant for the BrainTrain project to explore neurofeedback for clinical applications, and that grant gave us some financial support to try it out. Talma (Hendler) and others were also involved in this project.

Hendler: I remember how I was annoyed that you brought in the clinical trial people. And you forced us to constrict ourselves, otherwise we would have been much looser on many aspects. Even then, despite that, when the company (GrayMatterHealth, Ltd.) started, they did it all over again, although

[2] The MDR applies to clinical investigations of devices in the EU. Whether MDR applies is conditional on the 'intended purpose' of the software, i.e., whether the manufacturer intends it for diagnosis, treatment, alleviation of disease, or investigation/modification of a physiological or pathological process. Different criteria may apply in the US.

we were building on the previous work in my lab that has been funded and inspired by my competitive grants for the previous decade including the BrainTrain grant. I would like to respond to something that David said earlier: I was actually surprised you brought it from the perspective of researchers. I don't think we should think so far. Otherwise, you are frozen by that. I think it's really difficult to think broadly and dream, if you are constantly under the threat of regulation. So, you must allow yourself, especially in the beginning, to just try things and not think till the end, to the last step. Otherwise, it suffocates the freedom of thinking and limits innovations. Clearly, at some point, as evident when you run a company, you must freeze a configuration and accumulated experience and advance with this only without changing. It is a lesson for scientists in translational research to explore up to a point.

Goebel: Good point and I fully agree. No one of us started with that in mind and as a researcher, I am also at the university, we love to do our science and as a company, we love to develop and distribute scientific software tools. We did not think for a long time about medical device regulation. We now know that it requires a lot of effort, but I think it is worth doing it, because a certified medical product can be easier applied for helping patients. Because of the small number of clinical applications of our certified software, it is not yet anything you would do for money. Therefore, for a small company like ours, you think twice before you do it. At the end of the BrainTrain project, when we received approval under the old regulatory system, I said to Michael Lührs who led our regulatory efforts "We've done it! But we'll never do this again". And then the new regulations came, the MDR, and together with David we wanted to explore the possibility of some other clinical applications. We started a discussion in the company until we decided to bite in the apple and try a second time despite very different regulatory rules, and a different classification system. The new classification rules turned out to be a very critical point, because it is unclear to us in which class our medical product, software for fMRI neurofeedback, will be classified. If it falls in class 1, which we currently aim for, it may be financially possible for us to do it, but if it is classified as class 2a, the process becomes an order of magnitude more expensive for various reasons – too expensive for our small company.

Paret: According to European law, class 1 medical products are considered, in general, safe for patients and health care providers. With any risk of doing harm to patients, a product would fall in class 2 or higher. A higher risk class involves additional regulatory efforts, which also costs more money. Are we at the point to conclude that neurofeedback is safe from a regulatory viewpoint?

Linden: We looked at this in detail with academic and commercial partners and members of different European research consortia. Looking at the criteria for higher risk classification, I would say that fMRI-neurofeedback generally carries a low risk if it is done with proper patient selection criteria, precautions and psychological support mechanisms in place. However, in addition to the safety assessment, there are two general criteria applied by the MDR to support the classification (into a higher level than class 1), whether the software is intended to provide information 'which is used to take decisions with diagnosis or therapeutic purposes', or whether it is intended to monitor a physiological process[3]. From my perspective, and I share this view with many others, neither of those applies. The first step is relatively obvious: We are not applying real-time extraction of signals in order to support a therapeutic or diagnostic decision. It is a self-regulation tool. It is not intended for a clinician to make a therapeutic decision, and not to inform a decision-making process in the patient even. The other point may be less evident. The signal that we are extracting with real-time fMRI (the BOLD signal) is certainly reflecting a physiological process. Yet it is not used to monitor the physiological process in any common use of that word in the field of medicine. It is not something that anyone familiar with the medical world would consider a monitoring of a physiological process in the sense that an ambulatory monitoring device might monitor your glucose level or your blood pressure. I think these types of monitoring for deviations from a range of normative values are what is meant by

[3] According to Rule 11 of Annex VIII Chapter 3 Classification rules (6.3).

'physiological monitoring' when this term is used in the field of medicine. In our neurofeedback applications, we do not have normative or immediately clinically interpretable values. There can be different scenarios for real-time monitoring of brain activity: Extracting real-time EEG data to monitor epileptic activity, which may then have a therapeutic consequence, is something different, for example. In my view, it would thus go against the general use of the term 'monitoring of a physiological process' in medicine to consider fMRI-neurofeedback under this heading and thus make this point a criterion for class 2a classification. I appreciate that this classification question may need to be assessed yet by case because, for example, some clinical EEG-neurofeedback applications do reference individual patient data to normative data sets, so this may come closer to 'physiological monitoring'.
I do agree with Talma, you need experts to help you, but I think also we as researchers need to become experts. Because the argument that I am just making, a general medical technology officer will not be able to make, because they are less familiar with the content. This is what I meant when I said that we need to become experts in regulatory matters, but it does not replace the actual experts from companies or medical technology departments whom you will still need to guide you through this process, if you are interested in developing something that will ultimately need approval from the regulatory authorities.

Paret: The search for brain-based biomarkers is a trending theme in psychiatric neuroscience. In its usual meaning, a biomarker is suitable to inform, at least to some extent, diagnostic or treatment decisions. Some researchers are going to use – or claim that they are already using – biomarkers for neurofeedback.

Linden: As soon as you argue that you are using a biomarker that may support a diagnostic or therapeutic decision, it is a different story and requires separate discussion. If this is your intention, you have to seriously consider whether it would come under class 2a. We want to develop something that is clinically relevant, yes. And you may almost be forced to make claims of a biomarker by the funding landscape. But by the time you want to evaluate these claims in a clinical trial, you may come in the domain of medical software again and also in the higher risk classification. That probably may not apply yet if you are exploring a potential biomarker for proof-of-concept, but by the time you really want to look at the validation or any clinical application you may come into this domain.

Paret: Do this kind of risk classes exist for the FDA, Kymberly Young?

Young: It is not the same as in the EU. We do have classes of risk, and they have determined that fMRI neurofeedback is class 2, but that is not as bad as class 3, so it could be worse. The main problem we are facing right now is that the FDA is still in the process of deciding what they want to regulate. However, this is not for research but for commercialization, for clearance. They have told us that we do not fit in with EEG biofeedback, that we are not equivalent, and that we are 'de novo', and that we need to do additional work. If I was able to use Dr. Hendler as an example, and say fMRI neurofeedback is equivalent to EEG biofeedback I would do a '5 10 C' which costs about 30.000 $. However, when they are using the term 'de novo' it costs 170.000 $. So, right now in America it is really unclear how we fit in, and I need to submit something called a '5 13 G'. So I'm learning all sorts of letters and numbers, but again, the consultants have been critical for that.

Paret: Did I get it right, you are aiming for commercialization, or 'clearance', as it is called by the FDA? If you would just want to continue research, would the situation be different?

Young: If you just want to do research, you just need to follow the device regulations, which means you need a non-significant risk determination from your IRB. Or an investigational device exemption from the FDA. Your IRB should make that determination but if the FDA decides they do not like that determination their word rules. And I asked them under what circumstances they would come in and make that determination and they don't know. Just to continue your research it means a little delay,

you have to do a non-significant risk determination by your IRB or an investigational device exemption by the FDA and an MD must be consenting your patients. The commercialization is a whole different story.

Michelle Hampson: I just wanted to follow up on that a little bit. In terms of doing research, not so much with the focus of trying to appease the FDA, but just the structure of the funding in the US, the regulatory structure of the funding with everything being clinical trials has forced us to use late-stage clinical trial methods in early-stage research. As Talma was eluding to earlier, it is super important in early-stage research to explore, not just to think that everything you look at you have to look at in a well-powered trial. Then you can only look at three things in a decade. Whereas if you can search around in a broad way without everything being well powered you can discover a lot more - that is important for healthy early-stage research. Unfortunately, right now this is very problematic in the US because of the clinical trial framework. So we have been advocating to try to get funding mechanisms that really support exploration, which involves having less of an emphasis on being well-powered at a very early stage. I also want to mention that my main interest in regulatory issues is not related to getting medical devices to the market but related to the fact that non-medical neuro-tech is not at all regulated in the US, and I think in most countries it is not well regulated. So, if Facebook markets you a headset that reads your brain patterns and gives you feedback to virtual reality goggles, supposedly to optimize your consumer experience, that is not regulated at all. They could be programming you to like a certain person's face without you knowing it if they have the tech to do that. That is completely legal, currently. That kind of thing is something that we all as researchers should have some sense of ethical responsibility for.

Young: To add to that, you cannot submit a grant without the non-significant risk determination. But the advice I was given when I first started to do this was: "Stop saying you are helping depression. Just say you are improving memory recall. Just say you are improving emotion. If you don't use the word depression, if you don't use that diagnosis, then they won't be in your business and you can go on as usual." What Michelle says is absolutely true and that is the advice I have been given, but I do not think that is the right way to go.

Hampson: It would be great if, as an international community, we would come up with some sort of recommendations for what kind of cautions should be taken for non-medically regulated devices. Because that is the Wild West. Medical applications are generally highly regulated, actually to a point that is probably stifling in many cases. But the non-medical applications are often completely unregulated and the resulting potential for abuse is concerning and deserves attention.

Linden: I think what Michelle alluded to will come now under the AI regulations in the EU[4]. Hence, the EU may be stricter on this issue than the US, but exactly what this means for cognitive neuroscience and neuroscience research is a matter for debate. And there is an active debate on this particularly in the BCI community about the implication of the AI regulations.

Goebel: It is especially related to emotions: emotion recognition, detection and modification. The AI regulations are very strict if BCI applications aim to read a person's emotions. This is a problem because enhancing emotion regulation is one of the core application of clinical fMRI neurofeedback.

Paret: Do you believe that, in the end, this will affect some of the neurofeedback work?

[4] The Regulation (EU) 2024/1689 on artificial intelligence came into force in July 2024. Also called the 'AI act', it classifies software according to four risk-categories, where medical software would typically classify high-risk. Depending on risk assessment, non-medical software can be regulated similarly as medical software (i.e., if high-risk) or could go largely unregulated (e.g., if minimal risk).

Goebel: I think so because I already receive requests from the government-level in the Netherlands with questions such as “Do you use AI? Do you do something with emotions?” and so on. These new AI regulations start already to influence regulatory-related decisions in our company.

Paret: If there are any questions from the audience, this is the opportunity to direct them to the people sitting here.

Audience member: Many of our studies, even though they have some clinical relevance, they are all one by one different in one or the other aspect. It seems almost impossible to go through such regulation for each of these studies. My practical question is, do you think we have any hope that these studies could argue that sort of one core piece of software in the middle, say that takes the data from the scanner and delivers brain data out, could be certified? Otherwise, I really do not see how it is ever feasible when every single kind of different study has to go through the regulatory process[5].

Goebel: Creating one certified neurofeedback software that then could be applied to many disorders was what we had hoped for when we decided to go through this process. The first thing we learned is that as a medical product, software in our case, we have to demonstrate effectiveness for each specific application. There need to be existing clinical trials with clinical populations and proper controls to show, that the treatment benefits patients. It is relatively simple to generalize our neurofeedback software from depression treatment to another disorder. The challenging problem is that applying fMRI neurofeedback to another disease, or even when to a slightly different neurofeedback approach for the same disease, you have to start again to prove effectiveness of your new treatment.

Hendler: I will follow that, it is really frustrating as a researcher when I approach the company with any new idea, even something very small in the user interface that I want to change. They say ‘no’, we would have to go through a new regulation. It really is a huge burden and it translates to a lot of money for sure. Clearly, you would expect that situation e.g. when you claim a new medical effect. But even a change in the device or the software might be very meaningful. Because you need to proof safety and effectiveness; and that translates to money, a lot of money. And that is a big deal and it is the reason why I am saying, as researchers you should run your experiments as good as you can and do all the controls, but don’t expect this will take you through to FDA or European regulation. Don’t expect that, because it might not happen.

Goebel: Of course, Talma is right. Also, software changes, interface changes or method changes are important because you violate what you have certified for and you have to run through it again. But I think the task to prove effectiveness of the treatment is the more challenging one. This includes literature search, reviewing relevant articles whether they are showing the required effectiveness but it might also be necessary to run relevant studies yourself if the literature does not cover what you want to do.

Audience member: You could theoretically say we have one medical product that is doing the preprocessing and the second medical product that is the patient interface. And then, you would do the changes only in the latter, while the former remains the same. Which would reduce the effort a bit to do all the reporting and so on because you are just changing a display. We might say that we have a standardized format of preprocessing in the pipeline established, this is now handled in a medical product, and then from there you do your own work that you can maybe even vary easily from your institute. But unfortunately, we don’t have that standard yet. Only for certain applications maybe. In

[5] Although the MDR governs clinical investigations with medical devices, the requirements depend on whether the study involves an investigational device, a CE-marked device, post-market clinical follow-up or an in-house health-institution device. Thus, although the MDR may apply, the effort to prepare and conduct a clinical trial can differ to a great extent between projects.

a few years it could be one solution to partially package it and then use the certified product for preprocessing and continue from there.

Paret: I would like to comment on that. The situation is frustrating and this was the feeling I had when I first learned how this is going to go. Meanwhile, I still think it is a massive challenge. Yet, I can also see it from a different angle. It is of course challenging, but it also means that you need to think very well what kind of experiments you are doing. You need to decide very carefully on your protocol and in the end, it will probably lead to very well thought-through, standardized protocols in research. And simply because it is impractical to do a new protocol and change a design feature for every new study, it means that we will go more systematically over testing and reach a higher standardization in the end. Because it costs more money and much more effort. Amidst all the disadvantages, it may also bring some improvements.

Linden: I agree with you. Initially, the whole MDR process came as an added tier of administration. Essentially as a university researcher, our main purpose is not to develop a product, we want to do research, and the medical device regulations were made with industry in mind. But it is not our choice. I think it may be slightly different in the USA where you can go for different funding frameworks. Here the ethics committee generally, whether you come with a device developed by a company or with your own in-house developed device, will ask you these regulatory questions at some point and, certainly, at the point of a randomized trial with a clinical outcome measure. So, we have no choice, we have to embrace it at some point and then either work with a company or, if it is in-house developed software, with your medical technology department, and in either case it has to be done early on because it requires a lot of preparatory time. On the other side, it is now 12 years after the first rtFIN conference in Zurich, Switzerland, and I think the field has matured to move towards multi-center trials with standardized protocols. This is of course aligned with what the MDR are forcing us to do. We may also be able to use this framework positively, as Kymberly Young was saying, it also shows the recognition of the regulatory agencies that take us seriously as a field developing medical devices and new therapeutic applications. Eventually the standardization and harmonization enforced upon the community by the MDR may have a positive side, certainly when it comes to translation to clinical practice.

## Disclaimer

This article reflects the authors' opinions. The authors cannot guarantee the accuracy of their statements regarding the legal situation and applicable regulations. The text reflects the authors' understanding of the subject matter at the time of submission. No legal review was conducted prior to submission.

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