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1) Introduction:

For roughly forty years, implantable neurostimulation devices have been developing as an experimental treatment for those with drug-resistant epilepsy and several other drug-resistant neurological disorders including Parkinson's Disease.[i] These neurostimulator implants are implanted intracranially to provide electrical stimulation to neural tissue. Thus, this stimulation regulates specific neural regions that either are being overstimulated (i.e. epilepsy) or under stimulated (i.e. depression).[ii] Open looped deep brain stimulation (DBS) devices are U.S. Food and Drug Administration (FDA) approved for Parkinson's disease, dystonia, severe tremor, use as an investigational device (humanitarian exemption) for Obsessive Compulsive Disorder (OCD), Tourette's Syndrome, and Major Depressive Disorder. Closed-loop DBS looks to be the next stage in neurostimulation treatments.

In the early twenty-first century , the first generation of closed-loop DBS was tested as a potential therapeutic alternative for the treatment of drug-resistant epilepsy.[iii] These closed-loop devices provided the electrical stimulation of previous DBS models with the additional ability to regulate the amount and the frequency of stimulation given by recording the neural states of the patient. Said differently, these closed-loop DBS systems could record and utilize the neural states of a patient to influence the stimulatory behavior of the device. This change in stimulation pattern was an improvement over a traditionally constant stimulation patterns of open-loop DBS devices by providing the stimulation only when needed and simultaneously saving battery

power.[iv] If open-loop devices needed adjustment to their stimulation, then a healthcare provider or consult programmer would manually have to change it. Contrastingly, closed-loop DBS stimulation patterns were the result of a personalized algorithm within the device that interpreted the neural data and systematically determined when stimulation was needed.[v] Thus, with closed-loop DBS, an algorithm is in control of these, and its own, regulatory behaviors. These algorithms have become a unique component of the devices compared to other therapeutic neurotechnologies. However, despite this substantial difference, closed-loop DBS devices in the U.S. have not been federally examined any differently for safety.

This manuscript is concerned with how personalized algorithm-controlled devices present uniquely individualized risks and how these risks of severe iatrogenic harms might be unassessed in the traditional quantitative research method. This manuscript will argue that the inclusion of closed-loop in N-of-1 trials will more accurately address these risks than double blind-control trials. While the similarity of DBS treatment and personalized medicine has been described before [vi] and used to understand the logistical limitations of employing these devices [vii], this paper will explore what these physiological and psychological risks may entail and how the use of N-of-1 trials as a research method could be used for accounting for these risks. Our hypothesis is based on the understanding of N-of-1 trial methods as emphasizing an individual's characteristics above their statistical significance in a cohort, thus allowing each personalized device and personalized experience to be accounted for. This paper will not argue that closed-loop DBS devices are unsafe per se, nor that traditional quantitative research methods are ineffective for assessing the overall safety of closed-loop DBS. Nor will this paper follow previous remarks around the challenges of DBS research and how a comparison to personalized medicine provides insight into the modern regulatory hurdles of the device.[viii] The purpose of

your article is to emphasize that the grounds to certify neurotechnologies may benefit from N-of-1 inputs. Accordingly, this paper will demonstrate that due to the use of a personal algorithm in closed-loop DBS device, N-of-1 trials could provide a further beneficial way to research their treatment by collecting phenomenological data to properly inform its use.

2) N-of-1 trials:

To highlight the importance of the patient's individual characteristics with N-of-1 treatments it is helpful to analyze it analogously through the lens of personalized medicine where these trials has been used frequently. Precision medicine encompasses medical practices that emphasize the differences between patients, in particular via their genetic material or psychosocial characteristics, as determining factors in their treatment.[ix] It has grown favor over the past decade with the support of the former Obama Administration to mitigate traditional ineffective treatment standards.[x] This practice of precision medicine incorporates N-of-1 trials to assess clinical knowledge over conventional larger cohort studies. These trials include a single patient as the testing platform for a treatment ($n=1$). As an example, but not strictly an N-of-1 trial, comparative effectiveness research between patients has been demonstrated to assist in the treatment of cancers due to each tumor having a unique genetic make-up that may react differently to an array of pharmaceutical interventions.[xi] Overall, N-of-1 studies can be combined, if conducted with similar parameters, to include meta-analytic studies to assess the effectiveness of a treatment in a cost-effective manner.[xii] [1] While there has been a criticism of

[1] N-of-1 Trials could provide the opportunity for other "smaller" trials to be conducted and meta-analyzed. That is, large companies like NeuroPace can afford lofty and rigorous randomized control clinical trials that inherently prioritize the objective risks described in Section Two. N-of-1 Trials could provide an opportunity for other companies and institutions to research the use of these devices. This process might increase the transparency of the research increasing the overall safety of patients enrolled in these trials.

these trials as being only anecdotal, some authors noted that this quality of patient-centered trials is analogous to the end goal of classical research methods; practical bedside patient care.[xiii]

Historically, some of the first open-loop DBS trials were N-of-1, for instance when targeting symptoms in the treatment of Tourette's syndrome.[xiv] Within this singular context, testing the technology involved more than targeting quantifiable endpoints, as it focused on examining the patient's intrinsic experiences. This sort of focus allowed data that would have otherwise been missed with randomized double-blind control trials to be collected.[xv] In one example of an N-of-1 Tourette's trial, clinicians were able to collect non-quantifiable data which is not the primary endpoint of controlled double-blind trial. For instance, the patient reported subjective experience with the technology: "before, I was oblivious, now I am lucid and can't stand being this way."[xvi] This subjective data are examples of further evidence contributing to assessment of the technology. Specifically, it is this ability to revolve around a patient's subjective characteristics that could make N-of-1 trials imperative for better understanding closed-loop DBS treatments. Quantitative research, such as randomized double-blind control trials on the other hand, does not allow per se for examination of these subjective characteristics.

Demonstrating the limitations and criticism of randomized control trials demonstrate areas were N-of-1 trials can be used as a methodological tool to assess personal and qualitative risks. To start, in analyzing the benefits of treatment options for patients from quantitative research, their individualities can drastically affect a treatment's benefits.[xvii] Even analyzing the benefits of treatments between subgroups of patient populations, such as age and gender, has been shown to have treatment limitations.[xviii] As Kent and Hayward emphasized: "it is not even known how often the summary results of a clinical trial apply to most of the patients in the trial. Counterintuitively, it does not take extreme assumptions to generate conditions where the

summary results of a trial do not even apply to the typical patient of the trial."[xix] While these critiques have proved the base for positions against the effective use of randomized trials and the insertion of other statistical alternatives, it is presented here to provide an example of the limitation of quantifiable methods for personalized characterizes.[xx] Thus as N-of-1 trials can be seen to be necessary over quantifiable techniques, it is important that the variables of interest are indeed personal in nature. That is, unless a key element of the analogy is met, namely how these devices are as personalized as our genome, the overall analogy is weak at best.

To draw an analogy from genetic research again to demonstrate the element of patient personalization, the multitude of facets associated with genetic material are leading to modifications in pharmacological treatments that effectively place the patient's unique genomic data at the forefront of medical analysis.[xxi] Thus, the collection and use of this information in the N-of-1 format has been crucial, because through nature and nurture genetic material and gene expression can vary from person to person.[xxii] However, closed-loop DBS devices, while complicated, may not seem completely analogous to our genome. This is because regardless of the change in biomarker, neurological disease, the stimulation type, and the kind of device implanted, the patients can still be grouped by their treatments. For example, a group of two-hundred neurological patients might be broken down into group of roughly six depending on these criteria, however, none of these patients would be considered receiving an entirely *personal* treatment. Thus, while the groups may be small there does not seem like a single factor, like a patient's genome, that is unique for each patient.

Closed-loop DBS with the development and implementation of the personalized algorithm pushes these devices into a class like genomic medicine where each patient is unique. This is because closed-loop DBS, to some degree is metaphorically similar to a patient's genome

adapting over time to the changing individual. It is important though to distinguish now that the personalization relation is specifically related to the programing itself and not the injury or physiology of the patient. This is due to the fact that in the former the closed-loop DBS system will adapt with the patient to optimize and create a treatment regimen tailored for them specifically. This has been stated elsewhere that due the complexities of the algorithm and the lack of commercial availability of these devices, these devices and associated algorithms "may need to be patient dependent."[xxiii] This allows us to postulate that there are issues about how these devices are being quantitatively measured from a cohort of subjects with a randomized control trial and the need for accounting for qualitative and personal characteristics with N-of-1 trials. However, there are specifically certain risks that can be analyzed by N-of-1 trials for closed-loop devices.

3) Closed-loop deep brain stimulation and risk of iatrogenic harms:

As seen in the introduction, closed-loop DBS devices are a modified form of open-loop DBS that incorporates feedback from a patient's neural activity to create a personalized neurostimulatory treatment. Neuropace devices were the first commercially available devices and predicted epileptic seizures to provide therapeutic responses accordingly.[xxiv] This allowed the technology to close the loop between brain and machine since the order of causal events goes from the brain to the device then back to the brain. This causal circle starts at the neurological biomarkers called Local Field Potentials (LFPs) that have been identified and implemented via ECoGs and electroencephalograms (EEGs).[xxv] The placement and type of these biomarkers determine the accuracy as each presents a different level of sensitivity for separate pathological factors and neural markers.[xxvi] Similarly, the associated stimulation parameters can vary to regulate the neural desynchronized or pathologic states.[xxvii] These regulatory and stimulatory

parameters are coordinated and personalized by the control algorithms of each device to allow the neural states that are constantly changing to be monitored in real time.[xxviii] This ability for an algorithm to gain feedback from the brain also allows the devices to receive inputs about the most effective waveform in which to use.[xxix] For example, an algorithm specifically developed for the countering of contrary neural stimulation has been developed.[xxx] This contrary stimulation is an associated problem and technological challenge with closed-loop DBS since the site being recorded for neural desynchrony may be near and affected by the stimulation of the device itself, thus causing false probe stimulation.

The risks associated with the uses of closed-loop DBS can fall into a similar spectrum of physiological and psychological harms. The complications from surgery include intracerebral hemorrhage, edema, and post-operation infections.[xxxi] With the treatment, patients have been reported having headaches, site pain, and dysesthesias.[xxxii] These more physiological complications are accompanied by psychological complications including hypomania, mania, hypersexuality, and gambling.[xxxiii] Aligning with open-loop DBS, patients have been reported to have an increased rate of suicide as high as a 15-fold increase.[xxxiv] Other phenomenological harms are described as affecting the patient's personality after the treatment has been successful, or during the treatment.[xxxv] There is still currently a discussion in the fields of neuroethics and the neurosciences trying to elucidate putative DBS postoperative phenomena on the psychology of patients. Whether they are purely a reactive response to stimulation,[xxxvi] modification of drug intakes,[xxxvii] successful alleviation of symptoms,[xxxviii] lesioning of devices,[xxxix] or natural evolution of disease,[xl] is actively being debated.[xli] Such discussions call for ethical attention to potentially unwanted psychological adverse effects resulting from novel invasive neurotechnologies.

These potential phenomenal harms raised in the above paragraph are not encompassed, for instance within NeuroPace's clinical trials of closed-loop DBS.[xlii] While this clinical trial examined cognitive flexibility, visual-spatial abilities, measures of language, and validated mood inventories, the phenomenological data has been collected secondarily by researchers.[xliii] Motivated by the notion that randomized control trial research methods do not include accounting for the fundamental differences these devices have with their personalized algorithms on a patient's individualized phenomenal experiences, the importance of utilizing N-of-1 trial methods can be seen. Similarly, such N-of-1 research can be produced as N-of-1 trials of closed-loop DBS devices can practically be added to current research techniques being used in the current policy approval processes of the United States.

4) The use of N-of-1 trials in the evaluation of closed-loop deep brain stimulation devices:

In 1967, the Medical Device Amendments to the Federal Food, Drug, and Cosmetic Act was passed allowing the FDA to begin regulating and evaluating therapeutic neurotechnological devices.[xliv] This regulatory body placed objective measures on the safety and effectiveness standards of medical devices. In the years since, the trend in clinical studies of neurotechnologies has been conducted with: a large number of participants numbered, randomized treatment groups, and double-blind standards to demonstrate effectiveness and safety. While this classical research model has provided grounds for the collective safety and effectiveness of closed-loop DBS, it has not allowed for and analysis of how the unique psychology of each patient interacts with the device and its effects on their phenomenal experiences, and the risks associated with having a personalized algorithm running therapeutic treatments. To provide a cautionary quote from an FDA approval meeting on open-loop DBS in the evaluation of a stimulatory device for

Parkinson's disease "unless that side effect [from DBS] slaps you in the face or is quite profound, you may not find subtle effects like the neurological changes."[xlv] This comment reflects the risk of having subtle effects undetected via quantitative measurement. These effects might be unnoticed especially if they are subtly interfering or disrupting the unique psychological continuity of each patient and are resulting from interactions with the device and its entanglement with the phenomenal experiences.[xlvi]

As neurotechnologies are examined, they are reviewed by organizations such as the Center for Devices and Radiological Health (CDRH) and the Division of Neurological and Physical Medicine Devices (DNPMD). Due to their high-risk, closed-loop DBS devices are considered a Class III device per the CDRH's standards. There are also several pathways to certify neurotechnologies such as the Premarket Approval Submission (PMA), De Novo Submission, Premarket Notification 510(k), or Humanitarian Device Exemption. These paths all change in comparison to the length of time required until certification for market place use with the PMA pathway taking the longest and required for new devices. The device taking any of these pathways largely relates to if there is another device on the market for similar safety and efficacy comparison. If another similar device can be found, the device will flow through the De Novo Submission pathway.[xlvii] In the early 2010's it was reported that 99% of medical devices were reported as taking this quicker certification pathway.[xlviii] However not all pathways are equal for it has been argued that DBS devices, in the treatment of Obsessive-compulsive disorder, should follow the PMA pathway over the Humanitarian Device Exemption. [xlix, 2]

[2] It's important to note that the technology rather than the pathology itself may dictate which pathways to follow. This is crucial with closed-loop components which are not yet fully understood. For instance, closed-loop autonomous ability of the algorithm to control the signal will likely push regulation into the realm of Artificial Intelligence (AI). It is still unclear what aspects of these regulations may change if closed-loop devices are to be considered a form of AI. However, within the "Future of Artificial Intelligence Act of 2017" bill, the US

It is specifically through the PMA track that an area of N-of-1 incorporation can be found. Through the PMA track the FDA will report an assessment of the device that will weigh the probable benefit from the risk of clinical side effects with its use. As can be seen in the evaluative criteria of NeuroPace, the first closed-loop DBS device was measured using this safety and effectiveness for these devices using data from randomized control trials.[1] A, presumably smaller, measurement of the device was also taken from patient feedback. This feedback included the trade-offs they might be willing to accommodate or live with for access to these devices.[li] However, we are unaware of how weighted or rigorous these assessments are in the approval process of the devices. If these assessments are the patient impact statements of these treatments, which consists of a bleak summary of a patient's experience with their DBS treatment, then there is likely room for improvement.[lii] It is here that the utilization of N-of-1 trials may be included to provide further insight into the patient's experiences of the devices. This may include phenomenal experiences from the patients or personal narratives. Similarly, the number of subjects that could be examined could vary.

5) Articulating potential risks of harm in informed consent:

Overall, our article illustrates the challenges encountered by traditional double-blind quantitative trials concerning the phenomenological dimensions of a patient's postoperative experiences after implantation with DBS. In our article, we present the idea that N-of-1 trials may be a better regulatory fit for evaluating safety of neurotechnologies such as closed-loop

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government specifically defined AI as the lack of human oversight on the regulation of stimulation. (John Delaney, "Text - H.R.4625 - 115th Congress (2017-2018): FUTURE of Artificial Intelligence Act of 2017," webpage, May 22, 2018, https://www.congress.gov/bill/115th-congress/house-bill/4625/text.) This policy is but one aspect of the growing regulation and ethical assessment concerns of AI. We draw from this that closed-loop DBS devices should be understood as having an AI component and may fall under the risks associated with usage of AI, however, may not meet all the ethical and legal concerns that arise with AI technologies.

DBS. N-of-1 trials may simply be a better option to observe qualitative variations such as potential unwanted psychiatric adverse effects than double-blind trials.[3] To further support this argument from an ethical perspective, one major area of focus is obtaining adequate informed consent as it should articulate the limits and risks of novel invasive neurotechnologies. In particular, decisions to enroll in these trials should account for long-term psychological effects experienced by patients who are also experiencing improvement in their illness's core symptoms.[liii] Identifying these potential postoperative issues can provide support to patients experiencing unexpected post-implantation neuropsychiatric effects,[liv] prepare caregivers to deal with potential neuropsychiatric consequences,[lv] educate family members about potential sudden behavioral changes, and generate knowledge that could guide prospective patients and their families through the decision-making process prior to implantation. Importantly, involving family in decision-making may implicitly and unrecognizably undermine autonomous consent of participants. As such, participant voice should ultimately prevail. Informed consent process leading to N-of-1 trials should account for these realities.

The use of N-of-1 trials for closed-loop DBS should translate into solutions for three potential ethical issues.[lvi] (A) Patients knowing of the potential qualitative variations such as unwanted psychiatric adverse effects might prefer not to be implanted with closed-loop DBS knowing that these changes could occur postoperatively. However, should the risk be deemed acceptable by the patient, then (B) there may be a way to design a better decision-making process, involving the patient's family/caregiver's, in order to prepare those relevant parties for possible neuropsychiatric effects. Should this process lead to a fair negotiation between the

[3] However, it should be noted that even if our argument is current, it would not mean that closed-loop DBS devices are free of ethical issues when tested in an N-of-1 fashion.

patient and their family, then (C) all of them must consent to accepting the potential long-term unanticipated phenomenological consequences (Burden to Normality: from the patient perspective “I am symptom-free but I may become an unexpected “new” person”; from the family/caregivers’ perspective “We are living with a treated but unanticipated “new” person”).

The first issue (A) appears to be a sole and ultimate decision made by the patient that aims to preserve patient sovereignty within their entourage. It engages with the patient capacities for self-determination and autonomy. The second issue (B) involves an acceptance of the potential risk from at least two parties, which includes preparatory phases to help the patient and their family/caregivers manage possible unwanted outcomes. In some open-loop trials, some patients experienced postoperative drastic socioenvironmental ruptures, requiring restructuration of family and environmental dynamics. For instance, up to 65% of patients who were married (who lived with a partner) before neuro-intervention experienced a conjugal crisis after the operation and up to 64% of patients who were working before surgery wanted to step after.[lvii] The third issue (C) addresses the possibility of adverse outcomes experienced by the patient that are incompatible with their family/caregivers’ values and expectations. This raises the issues of the patient’s autonomy as a new person, but as well as the family as an autonomous entity, where the new person is not welcomed. It highlights the importance of not just resolving the conditions which afflict the patient but to also address non-symptoms that might impact the family dynamic potentially arising from the treatment. These three possible ethical issues reflect the need for patients and families/caregivers to face phenomenological adversities (including potential psychiatric side effects) that may accompany the alleviation of the patient’s symptoms.

6) Conclusion:

In this paper, it has been argued that N-of-1 trials should be incorporated into the safety assessment of closed-loop DBS devices to accommodate for the risks that develop through use of a personalized algorithm. It has done so by describing closed-loop DBS devices as providing a unique and personalized treatment to patients due to their algorithms that N-of-1 trial will be able to assess because of their emphasis on personal characteristics. It then described the weakness of current quantitative methods to assess these characteristics and that as a result the risks of documented psychological and phenomenal harms that patients experience from the use of closed-loop DBS devices were not being adequately incorporated. This showed the importance of N-of-1 trials, and subsequent sections provided further support by describing that N-of-1 trials could possibly be utilized as patient feedback has been used in the current PMA procedures. Lastly, it touched one areas of ethical concern that having such N-of-1 data could impact and shape. This paper has, however, not answered the associated questions of to what degree N-of-1 trials should be considered in the risk assessment of closed-loop DBS. These concerns about the practical use of N-of-1 studies are the topic of further research. Ultimately, this paper has argued for contrastingly both a wider scope in which to assess closed-loop DBS safety standards by incorporating other measurement standards, and at the same time a more focused scope to the what the patients afflicted with serious neurological diseases are experiencing with this treatment.

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