## eMethods

*Clinical Trial Design, Protocol Approvals, Registrations, and Consents*

Informed consent was obtained in person from all participants directly. Participants had one or two microelectrode arrays placed in the precentral gyrus (and, in one case, the middle frontal gyrus) of the motor-dominant hemisphere; each array connects to a percutaneous pedestal affixed to the skull; the pedestal is connected to a cable or wireless transmitter that sends neural activity to the signal decoding system. After a brief hospitalization, participants returned to their primary place of residence. Safety data were obtained and documented in structured case report forms (CRFs) by clinical investigators at regularly scheduled and as-needed visits at the participant's residence and, when necessary, during any inpatient hospitalizations. The primary outcome is safety of the BrainGate system; the safety endpoint is achieved if the sensors are not explanted for safety reasons during the one-year post-implant evaluation period and there are no device-related serious adverse events (SAEs) that result in death or permanently increased disability during the one-year post-implant evaluation period. Secondary safety outcomes include the type and frequency of other adverse events. Additional secondary outcomes regard feasibility for use with assistive technology and are reported elsewhere.[1–6] Up to 22 participants will be enrolled in this ongoing trial; sample size was selected to obtain preliminary safety data and develop experience with efficacy metrics that will inform a subsequent pivotal study. Although this clinical trial is ongoing, we are reporting preliminary safety data at this time due to the study's long duration, substantial experience accrued, and the growing public awareness of BCIs. A summary of the clinical trial protocol is included at the end of this **Supplement.**

From June 2004 – May 2009, two IDEs (and thus formally two separate but concurrently administered clinical trials) existed, one that enrolled individuals with spinal cord injury or

brainstem stroke, the other that enrolled individuals with motor neuron disease. In 2009, trial sponsorship transitioned from private industry (Cyberkinetics, Inc.) to an academic consortium supported by federally funded and philanthropic grants. Those two trials were closed, and a second-generation trial ("BrainGate2") was initiated that was inclusive of all diagnoses. For reporting purposes, except where otherwise specified, these three administrative entities are collectively referred to as the singular "BrainGate clinical trial". Regarding prospective registration, the first two IDEs were started in 2004 and 2005, prior to clinicaltrials.gov requirements. In 2009, the first two IDEs were closed, and the third (and ongoing) IDE was initiated. This trial was registered with clinicaltrials.gov (NCT00912041) when the IDE was granted in 2009 and before any additional participants were enrolled.

*Data Review Process*

All clinical, demographic, and adverse event data were documented and recorded per applicable regulations. Findings are reported here in accordance with the CONSORT Extension for Pilot and Feasibility Trials.[7,8] We reviewed annual reports submitted to the FDA from 2004-2021, all documentation, presentations, and minutes submitted for biannual meetings of the BrainGate Clinical Oversight Committee (COC), and all databases of adverse and other clinical events maintained by the coordinating center at Massachusetts General Hospital (MGH). For adverse events documented as either serious adverse events or device-related adverse events of any severity, we reviewed the original adverse event case report forms and any supporting data (e.g., pathology reports, imaging reports, contemporaneous correspondence to study investigators and/or IRBs). Similarly, for non-serious adverse events that were not classified by site investigators as device-related but for which device involvement could be considered (e.g., new neurologic symptoms), supporting data were reviewed by a clinician-scientist not involved in the original determination.

*Data availability*

All reasonable requests for collaboration involving de-identifiable materials will be fulfilled provided that a written agreement is executed in advance between authors and the requester (and their affiliated institution). Proposals may be directed to the corresponding author.

*Role of the funding source*

Study sponsors (i.e., funding agencies) had no role in the collection, analysis, and interpretation of data; in the writing of the report; or in the decision to submit the paper for publication.

*eMethods References*

1. Hochberg LR, Serruya MD, Friehs GM, et al. Neuronal ensemble control of prosthetic devices by a human with tetraplegia. Nature. 2006;442:164–171.
2. Hochberg LR, Bacher D, Jarosiewicz B, et al. Reach and grasp by people with tetraplegia using a neurally controlled robotic arm. Nature. 2012;485:372–375.
3. Nuyujukian P, Albites Sanabria J, Saab J, et al. Cortical control of a tablet computer by people with paralysis. PLoS One. 2018;13:1–16.
4. Pandarinath C, Nuyujukian P, Blabe CH, et al. High performance communication by people with paralysis using an intracortical brain-computer interface. Elife. 2017;6:1–27.
5. Bacher D, Jarosiewicz B, Masse NY, et al. Neural point-and-click communication by a person with incomplete locked-in syndrome. Neurorehabil Neural Repair. 2015;29:462–471.
6. Willett FR, Avansino DT, Hochberg LR, Henderson JM, Shenoy K V. High-performance brain-to-text communication via handwriting. Nature. Nature Research; 2021;593:249–254.
7. Eldridge SM, Chan CL, Campbell MJ, et al. CONSORT 2010 statement: Extension to randomised pilot and feasibility trials. BMJ. 2016;355.
8. Lancaster GA, Thabane L. Guidelines for reporting non-randomised pilot and feasibility studies. Pilot Feasibility Stud. Pilot and Feasibility Studies; 2019;5:1–6.

# EXECUTIVE PROTOCOL SUMMARY

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| **Protocol Title:** | BrainGate2: Feasibility Study of an Intracortical Neural Interface System for Persons with Tetraplegia |
| **Protocol Number:** | MGH-BG2-TP-001 Rev 10.3 |
| **Indication for Use:** | For the detection and transmission of neural signals from motor-related areas of cortex to externally powered communication systems, environmental control systems, and assistive devices by persons unable to use their hands due to physical impairment |
| **Study Objectives:** | Obtain preliminary device safety information and demonstrate proof of principle (feasibility of efficacy) of the ability of people with tetraplegia to control a computer cursor and other assistive devices with their thoughts. |
| **Study Design:** | Prospective, open-label, feasibility study |
| **Primary Endpoint:** | Safety: Sensor(s) successfully implanted, not explanted for safety reasons during the one year post-implant evaluation, and there are no device-related Serious Adverse Events which result in death or permanently increased disability during the one year post-implant evaluation period. |
| **Secondary Endpoints:** | Feasibility: Investigate the potential utility of the BrainGate2 Neural Interface System and establish the parameters for a larger clinical study, such as appropriate neural decoding algorithms, sample size, indices of measurement, success criteria, and endpoints. Contributing secondary endpoints include:<br><br>Signal Measurement: Ability of the system to measure adequate neural signals to develop a patient-controlled intracortical neural interface system.<br><br>Cursor Task Performance: Ability of the system to create a neural decoder for cursor control that can be used to perform tasks.<br><br>Neural decoder creation for speech/language decoding: Ability of the system to record neural signals related to speech / language generation and then decode them to produce either a synthetically produced vocalization or text.<br><br>Other Task Performance: Ability of the system to permit a patient to use the neural signals to perform other (non-cursor-requiring) tasks. |

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| **Number of Patients:** | Up to 22 patients will receive the investigational device, inclusive of one additional patient from a previous IDE; up to 6 of the 22 patients may have a diagnosis of cerebral palsy. |
| **Number of Sites:** | Up to 6 total study sites (including enrolling and surgical implantation sites) |
| **Study Duration:** | Up to 4 month baseline, 12 month evaluation after implant, extendable to 72 months evaluation after implant |
| **Baseline Evaluations:** | Up to 4 months after enrollment (consent), prior to implant |
| **Implantation:** | Expected to be ~4-8 hour surgical procedure and 1-5 days hospitalization |
| **Evaluation:** | Safety and proof of principle (feasibility) will be determined during a 12-month post-implant evaluation. |

## OVERALL STUDY FLOWCHART

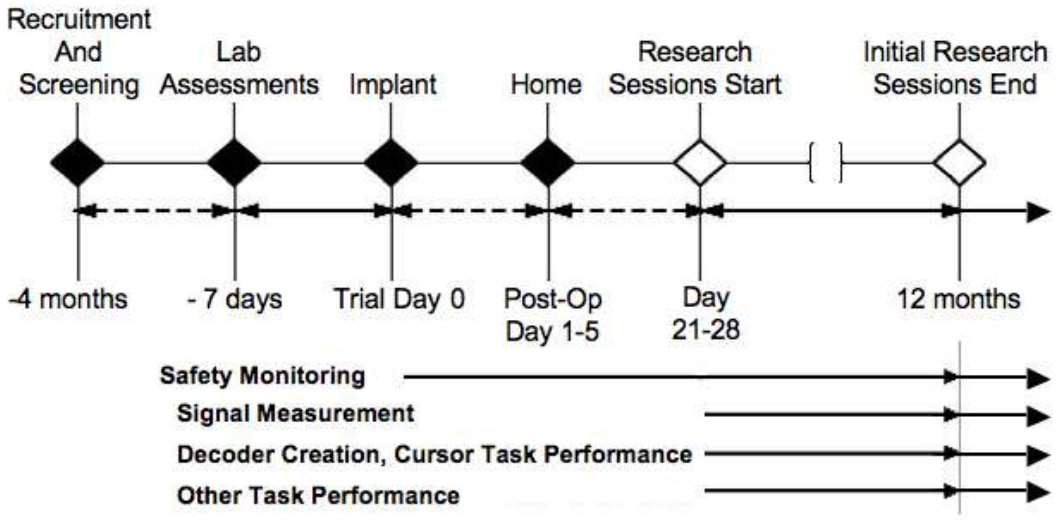


**Figure 1: Overall Study Flowchart**