A Template for Class III Active Implantable Device Research in the UK

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Investigational research using class III active implantable devices require rigorous design, safety and ethics. Yet, these barriers can be broken down and addressed using a systematic approach. An ongoing trial in paediatric epilepsy illustrates this methodology and our lessons learned.

Background

The Children's Adaptive Deep Brain Stimulation for Epilepsy Trial (CADET) (NCT05437393) at Great Ormond Street Hospital (GOSH) is a University College London (UCL)-sponsored first-in-human clinical device study exploring the use of adaptive deep brain stimulation (DBS) to treat Lennox-Gastaut syndrome, a severe and treatment-resistant form of childhood epilepsy. This trial represents the first use of this advanced DBS technology in paediatric patients in the UK, making it a first-in-human application in this population. The pilot study aims to enrol four patients to assess the safety and feasibility of the therapy. Following this initial phase, the trial will expand to include 22 children, and to evaluate the efficacy of DBS in reducing seizure frequency and improving quality of life.

The motivation for the CADET is to deliver personalised neuromodulation for children whose seizures have not responded to conventional treatments such as anticonvulsants. The system and therapy are still under investigation and might not ultimately be successful in clinical translation, but the 'process of setting up the trial' can serve as a roadmap for others exploring higher risk device studies (Figure 1a).

Clinical investigations

The Medicines and Healthcare Products Regulatory Agency (MHRA) is an executive agency of the Department of Health and Social Care in the United Kingdom (UK). It is responsible for regulating and ensuring that medicines, medical devices and blood components are effective, acceptable and safe. There are two sets of regulations: the UK Medical Devices Regulations 2002 (UK MDR 2002) for Great Britain (GB)[1], and the

EU MDR 2017/745 for Northern Ireland under the Windsor Framework.[2] Where Northern Ireland (NI) is included, a single EU MDR application to MHRA covers both GB and NI sites.

The process for initiating a class III active implantable trial in the UK closely mirrors the Food and Drug Administration in the United States (US FDA) process. Applications are submitted via the IRAS portal to the MHRA, where they are validated for required documents. Invalid applications are returned for correction; valid ones start a 60-day 'no-objection' period (GB), whereas NI requires formal authorisation within 45 days (per EU MDR). Subject matter experts across various fields assess the submission and might raise queries that sponsors must resolve before MHRA raises no grounds for objection (GB) or issues authorisation (NI). The MHRA's clinical investigations team provides regulatory advice meetings for sponsors, with demand rising due to increasingly complex enquiries. These meetings often involve advanced technologies, including cardiac devices, glaucoma drug delivery systems, imaging, neurotechnology, ophthalmology, organ preservation, AI-based software, surgical robotics, and vascular implants. Lessons from these interactions are illustrated through the CADET trial example.

Step 1: Building a Multi-disciplinary Team with a Collaborative Approach

Developing and delivering a clinical device trial requires a multi-disciplinary approach. For example, the CADET Project has mobilised a team of engineers (including those from both the academic and industrial sectors), surgeons, physicians, and nurses. The CADET Project has two participating National Health Service (NHS) hospitals within the UK cluster and draws from the experience of an international Scientific Advisory Group. The cross-functional team provides insights and experience for the design of both the device and clinical trial(s) and ensures that children will transition to an appropriately skilled healthcare network that is able to support and life-long care.

Step 2: Integrating Patients and Carers Perspectives into the Trial and Design

The CADET Project, like any investigational trial, should prioritise the user needs, long-term care and well-being of the children and their families. During trial preparation, patient and carer inputs were integrated into the trial design and patient information sheets. A child- and family-focused approach is essential to the translation of the therapy[3]. One source of feedback was the Young Persons Advisory Group (YPAG) at Great Ormond Street Hospital. This group, composed of young individuals with lived experience of medical care, provided critical input on ethical considerations and the overall patient journey from a young person's perspective. Their insights ensured that the trial was sensitive to the unique needs of paediatric participants and their carers (Figure 1b); the patient information sheets and illustrations were modified based on their insightful feedback.

Furthermore, iterative feedback from the participants and their families was and is crucial in understanding the user needs and areas for device refinement. For example, the CADET Project has a 'Parents Advisory Group', that has offered points of refinement for both the device and the clinical trial delivery. A parent of a CADET participant provides their experience in the Q&A box in **Supplementary information**.

To support long-term device management, the investigational system includes surgical guide tubes that facilitate future DBS lead replacements or adjustments, reducing the need for invasive interventions. Additional long-term trial considerations include defining the transition from childhood to adult care – CADET has a protocolised clinical care pathway to that ensure the children transition from paediatric to partnering adult neuromodulation and epilepsy services. This pathway was carefully designed to provide continuity of care and address the evolving medical and psychological needs of patients as they age. Forward-thinking design underscores a trial's commitment to patient-centred care by considering immediate and long-term outcomes. By focusing on the durability of the device and the quality of the patient-caregiver experience, the CADET trial seeks to achieve a holistic approach to managing paediatric epilepsy.

Step 3: Aligning the Investigational Device Design with User Needs

Design inputs are then translated into unambiguous requirements for the investigational device (figure 1c). CADET modified the *Picostim-DyNeuMo system,* which is a cranially-mounted, rechargeable DBS device. The *Picostim-DyNeuMo* system incorporates several features that make it uniquely suited for paediatric epilepsy research[3,4]. Its cranial mounting design allows the device to be placed directly in the skull, reducing the risk of lead or wire damage that could occur as children grow. Additionally, its rechargeable system decreases the need for frequent surgical interventions to replace batteries, providing a less invasive and simplified daily procedure (approximately 30 minutes) as a sustainable treatment option for young patients. Finally, the *Picostim-DyNeuMo* system was also modified to deliver adaptive stimulation[5–7] through wireless updates, a feature that can personalize therapy by providing a unique combination of background stimulation to suppress seizure activity, responsive stimulation for breakthrough seizures, and synchronization of device operation to patient-specific symptom rhythms (for example, circadian). This enhanced adaptability might prove crucial for managing the variable symptoms of Lennox-Gastaut syndrome and optimizing therapeutic outcomes over time.

Step 4: Securing Research Ethics, Regulatory, and NHS Approval for the Study

Approval of the CADET a study requires substantial documentation and compliance with regulatory, ethical and safety standards. Class III devices require comprehensive preclinical data to demonstrate safety, performance and risk management, regardless of geography (**Supplementary Table 1**). In many paediatric trials, the design dossier often leverages considerable prior experience from adult trials, and supplemental work focuses on unique elements of the paediatric use case. A specific example in CADET was the design of the cranial recharge system, where patient-specific solutions were required to align with each child's individual needs. Cybersecurity and autonomy for the recording of neural activity data and automated algorithms, respectively; the YPAG group raised 'reading my mind' and 'being controlled' as concerns. Finally, the CADET study aligns with the NHS's economic constraints, and documents healthcare outcomes to demonstrate cost effectiveness.

Call to Action

Research studies investigating novel invasive devices in underserved populations such as children clearly involve substantial clinical, ethical and institutional risk. Nevertheless, there is a strong need to deliver improved care for these populations, and innovators should be encouraged to work in partnership with regulators to evaluate and deliver new technologies. We hope that sharing our experience can help others in this pursuit.

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Related links:

MHRA. The Medicines and Healthcare Products Regulatory Agency (MHRA). https://www.gov.uk/government/organisations/medicines-and-healthcare-products-regulatory-agency (2024).

GOSH Young Persons' Advisory Group (YPAG) for Research. https://www.gosh.nhs.uk/our-research/taking-part-research/get-involved-in-research-and-innovation-at-gosh/gosh-young-persons-advisory-group-for-research/

Competing Interests: Tim Denison is a Founder and Chief Engineer at Amber Therapeutics. His conflict of interest is managed by the Department of Engineering Science at the University of Oxford.

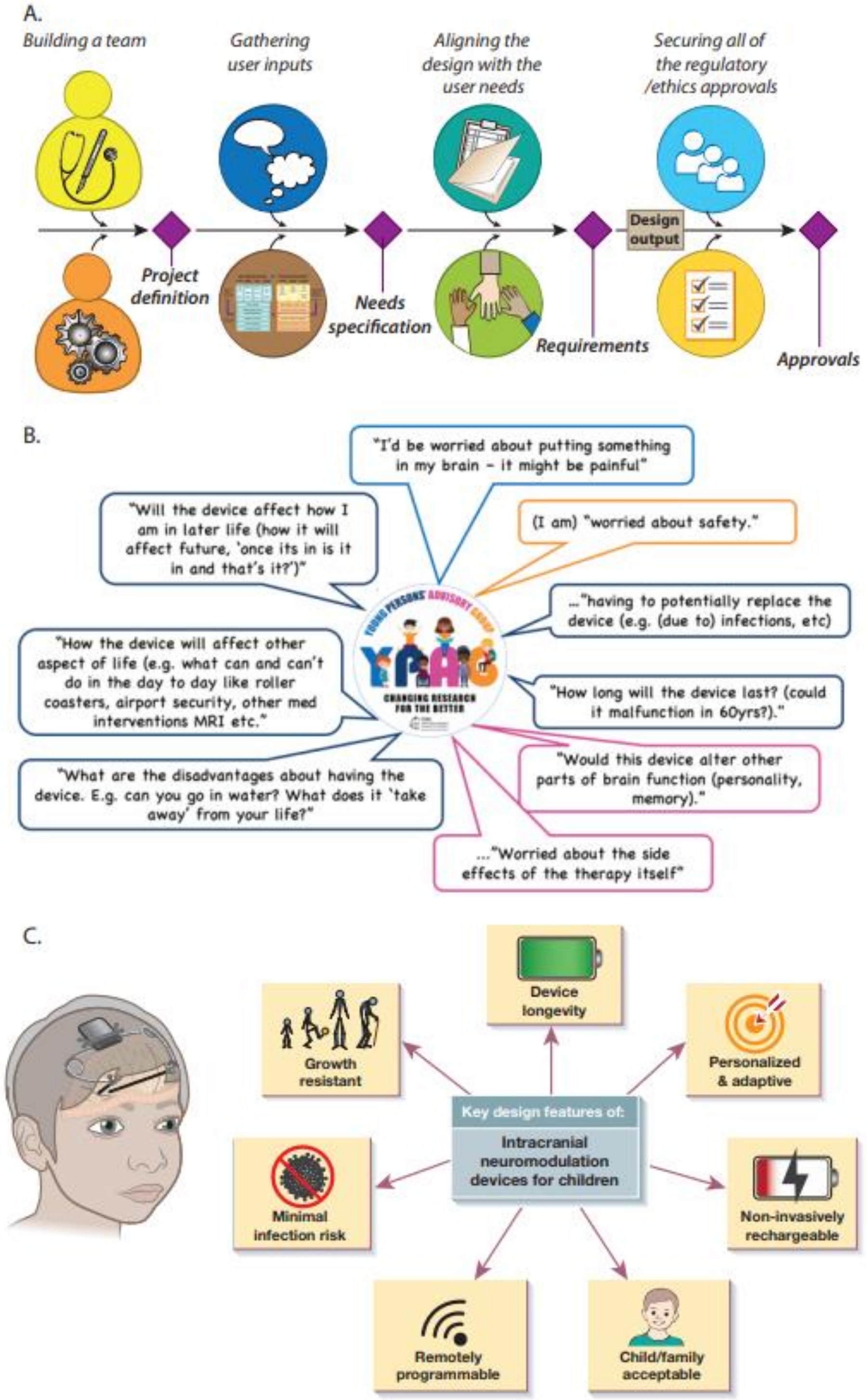

Figure 1: A) the process steps for researchers to engage in an investigational trial set-up. B) examples of questions posed from the Young Person's Advisory Group at Great Ormond Street Hospital. C) mapping of high-level user needs to requirements and design outputs for the final design history file.