BACKGROUND: Diffuse midline glioma (DMG), particularly the subtype known as diffuse intrinsic pontine glioma (DIPG), poses a significant challenge due to its aggressive nature and low survival rates, especially in children. Despite ongoing research and clinical trials, the survival rate remains alarmingly low. The scarcity of cases and siloed nature of current registry efforts have hindered the establishment of a reliable natural disease history for benchmarking studies and led to the need for randomization in clinical trials. METHODS: xPedite [NCT06140719] is a fully virtual, patient-driven, nationwide, real-time observational study to collect, annotate, standardize, and report the critical data elements of DMG and DIPG in a regulatory-compliant framework. Patients of any age can join via electronic consent, with recruitment supported by provider referrals and patient advocacy organizations DDRFA and My DIPG Navigator. Medical records are accessed from institutions, sequencing vendors, and health information networks. Notably, data elements are annotated comprehensively and longitudinally in a 21 CFR Part 11-compliant clinical database by xCures remote study staff, eliminating the need for data entry by treating site staff or physicians. Data collected include anti-cancer interventions, non-cancer medications, biomarker results, radiological endpoints, steroid use, vitals, demographics, raw DICOM images, and genomics. In addition to clinical data, patient- and caregiver-reported outcome questionnaires (PROs) and video assessments of mobility and neurological status are collected for clinician review. The objective of the study is to collect these clinical, imaging, biomarker, and assessment data in a manner suitable to provide to health authorities to reduce randomization in future trials. In a commitment to scientific understanding and collaborative research, the data collected through the xPedite study is openly available to academic, government, and non-profit researchers. As of January 2024, 182 patients were enrolled in xPedite. Real-time enrollment and data statistics are available at https://xicures.com/dmgdashboard/.