BrainChild-03 Protocol Version History

Document	Document Version/Version Date (vN.N/YYYY.MM.DD)	SC IRB Approval Date (YYYY.MM.DD)	Key Changes
Original Protocol submitted to FDA	V0.1/2019.04.24	N/A	N/A - Original
Original Protocol submitted to SRC	V0.2/2019.06.21 V0.3/2019.06.28	NA	Minor edits and corrections, addition of IND number, and clarification of data quality assurance procedures.
Original IRB Approved Protocol	V1.0/2019.08.20	2019.10.24	Minor edits and corrections, addition of language to exclude subjects who are pregnant or breastfeeding at time of initial CAR T cell infusions, update in requirements for initial and subsequent CAR T cell infusion to exclude pregnant or breastfeeding subjects, clarification of pre-medication requirements and prohibited medication, and disease response criteria updated to include Immune-related Progressive Disease (irPD).
Amendment 1	V2.0/2020.03.04	2020.03.27	Administrative/general updates to language for clarity and consistency. Updated study committee. Clarified enrollment inclusion criteria and requirements for infusion. Clarified prohibited and allowed con meds. Removed requirement for CSF catheter collection if not feasible. Removed requirement for disease evaluations if subject has already progressed. Modified the statistical design. Added pre-CAR T cell RCL testing.
Amendment 2	V3.0/2020.09.28	2020.11.10	Administrative/general updates for clarity & consistency. Updated study committee. Clarified inclusion criteria for subjects with existing apheresis product. Clarified delays due to subject preference or surgical recovery are allowed. Clarified levetiracetam is recommended but any anti-seizure medication is allowed. Standardized language regarding post-treatment long-term follow up. Added a 30 day follow up AE/Conmed review. Clarified timing of EOT visit. Clarified CRS and Neurologic grading scale criteria.
Amendment 3	V4.0/2021.05.05	2021.05.20	Protocol revised to remove 6 course treatment limit. Clarified dysphagia exclusion 4 only applies to Arm C subjects. Removed exclusion 7 criterion, inclusion criterion 7 already specifies that anti-cancer and chemotherapy agents must be discontinued if subject does not

			already have apheresis product available for use in manufacturing. Fatigue added as an adverse event observed in Clinical Trials with CAR-T cells. Revised radiation therapy washout period from ≥ 12 to ≥ 6 weeks. Clarified persistence testing will be discontinued after subject has 2 negative successive tests after their final infusion. Revised 4 week (1 course) observation period to a 7 day observation period between subjects within each DR on each arm after DR1. Clarified it is acceptable to use results from standard of care assessments for screening assessments. Clarified Arm C week 2 evaluations may be used for week 3 pre-infusion evaluations if performed within 2 days of the week 3 infusion. Clarified medical history is required yearly during the 15 year follow-up. Physical exam required yearly for the first 5 years of long term follow up, and beyond year 5 if subject has ongoing persistence or a prior positive RCL test. This was already required per section 7.19.1 but was inadvertently not represented in the schedule of procedures.
Amendment 4	V4.1/2021.06.08	2021.06.16	Dose Regimen figures 5-2, 5-3, 5-4, 5-6, and 5-7 corrected to reflect the dose level for courses 3 and beyond as per the narrative. Protocol V4.0 05-May-2021 figures contained errors, it was never intended for the dose level for course 3 and beyond to be revised from previous versions of the protocol except to allow treatment beyond course 6.
Amendment 5	V5.0/2021.07.21	N/A	This was submitted to the FDA but never to the IRB as the FDA immediately required changes. The 5.1 summary includes all changes from V4.1 to V5.1.
Amendment 6	V5.1/2021.08.18	2021.08.26	Sponsor name has changed to Seattle Children's Therapeutics. The term "gender" was revised to "sex". Absolute Lymphocyte inclusion criteria lowered from greater than 500cells/uL to greater than 100 cells/uL. This is in line with our liquid tumor trials and is being changed in the Solid/Brain tumor trials as we have had no issues with manufacturing CAR T cell products. Bleeding in or from the tumor, confusion, hiccups, and malaise added as risks of CAR T cell therapy to align with observed toxicities, added reference to the Investigator's Brochure. Clarified dexamethasone dose must be decrease

			for a week but only must be down to 2.5mg/m2/day on the date of infusion. Clarified disease responses assessments occur during all even courses, not just course 2, 4, 6. This was an oversight when we moved to protocol v4.0. Standardized language for persistence and clonality research tests. Revised treatment stagger requirement for subjects in DR2 and beyond from 7 days to 14 days per FDA request. Add that abnormal laboratory values or tests that are not clinically significant or do not require therapy are not considered AE.
Amendment 7	V6.0/2022.01.07	2022.02.10	Amended to add Expansion Cohort and clarify treatment plan delays & RCL testing.
Amendment 8	V7.0/2022.08.19	2022.10.06	Updated to reference current IB for safety information, add symptom management guidelines, update specifications for neurologic exam and CSF collection, update requirement for disease response assessment to as clinically indicated after study therapy, and clarify limits to treatment delays.
Amendment 9	V8.0/2022.12.01	N/A	This amendment was submitted to the FDA, but not to the IRB as further revision occurred prior to submission. All changes below to be reviewed by the IRB under next protocol version (V8.1). Amended to update Rebecca Gardner as Sponsor responsible medical officer, to add updated information regarding CNS catheter use, to allow Arm C subjects to receive a higher DL than assigned in Courses 3 and beyond if a subsequent DR had been cleared for escalation or for selection as MTDR, to clarify allowable treatment delays and corresponding pre-/post-infusion visit requirements, to allow subjects to undergo repeat apheresis after having initiated CAR T cell study therapy in order to manufacture additional product, to add PT and PTT as required CRS labs, to include additional suggested interventions for symptoms related to non-CRS toxicity, and to update the 30 day follow-up visit to 28 day follow-up visit.
Amendment 10	V8.1/2023.02.10	2023.04.26	Amended to remove post-infusion study visits as a protocol required procedure in Course 3 and beyond, and to remove Week 2 study visits as a protocol required procedure for Arm C subjects in Course 3 and beyond.
Amendment 11	V9.0/2023.10.10	2023-12-01	Addition of tumor inflammation-associated neurotoxicity (TIAN) definition, the timing of

			on study disease evaluation MRIs was updated to as clinically indicated, and the administered dose of CAR T-cell therapy may be within +/- 10% of the protocol prescribed dose. Update to Sponsor medical officer and minor other administrative changes.
Amendment 12	V9.1/2023.12.18		Amended to transition the role of Study Chair from Nick Vitanza to Rebecca Ronsley and to update the SCTx Sponsor representative to Colleen Annesley.