Planning Document for CounterACT Experiments

Preamble: This document is intended to provide a brief, structured means for assessing the goals of an experiment and whether the study design, study variables, sample size, planned statistical analysis, randomization scheme and study timeline are well-aligned with the goals. It should be completed by the Core C statistical consultant in collaboration with Project personnel. Example entries are shown in italicized font. Note: Turn around by Core C can take 4 to 6 weeks given the 3 major analysis tasks of planning, implementing, and reviewing as well as the many other commitments of Core C personnel.

Research question(s) or milestone being addressed:

For research question, write in PICO (Patient, Population or Problem; Intervention or Exposure; Comparison; Outcome) or an appropriately analogous format: *In the DFP SE rat model, is the therapeutic candidate (TC) more effective than standard of care (SOC) in decreasing the frequency of spontaneous recurrent seizures?*

For a milestone, quote the milestone text: *Milestone 1: Establish the natural history of spontaneous recurrent seizures (SRS) and cognitive impairment in the rat model of acute intoxication with diisopropylfluorophosphate (DFP).*

Experimental model: *DFP SE rat model*

Outcome table:

Construct	**Operationalization / Reliability evidence level / Blinded assessors**	**Timing**	**Distribution type**	**Anticipated model**	**Priority**
Onset of SRS	*Animals instrumented for continuous EEG monitoring. Seizures will be defined using the same criteria used by the NINDS Epilepsy Therapy Screening Program (electrical spike train of at least 5 Hz lasting at least 10 sec with a distinct beginning, middle and end) /Medium evidence for reliability /Not blinded*	*Minute-by-minute, up to 21 d s post-intoxication , which will be reduced to the time when SRS initiated for each animal*	*Time-to-event*	*Survival analysis will be conducted to compare onset of SRS between DFP and VEH, males and females, and the interaction*	*Primary*

Cognitive behavior	*Fill in as appropriate*	*Fill in as appropriate*	*Fill in as appropriate*	*Fill in as appropriate*	*Primary*

Notes: Reliability evidence level should be scored as follows:
High: Operationalization is (i) purely objective measurements from laboratory instruments not prone to significant operator or batch effects or (ii) involves a subjective component but one where relevant evidence for reliability is available from studies in multiple labs
Medium: Operationalization is (i) purely objective measurements from laboratory instruments prone to operator or batch effects or (ii) involves a subjective component but one where relevant evidence for reliability is available from single-lab studies
Low: Operationalization involves a subjective component and no formal evidence for reliability is available. (Formal evidence could include reliability studies undertake in our own lab that aim to estimate the between-rater reliability of the measurement process.)

Concurrent comparison groups (including relevant dosing information) and sample size:

Vehicle control for therapeutic candidate (x dose, 40 minutes) (n = XX)

Historical comparison groups (including relevant dosing information), sample size, if being used:

Can be based on historic data (include source files) or lit search

Vehicle control for therapeutic candidate (x dose, 40 minutes) (n = XX)

Sample size justification:

Using results from previous studies, we applied the exemplary dataset method to determine that the given sample sizes would provide 80% power (two-sided alpha=5%) to detect hazard ratios of 1.50 or greater.

Randomization plan (brief mention of scheme and personnel who will ensure valid randomization):

Anticipated date when final study data will become available to Core C for analysis:

Anticipated turn-around time for Core C analysis:

Date experiment plan was initiated:

List (with dates) of all major changes, including changes to experimental design, choice of comparators, sample size, or study endpoints:

Date of last revision: