Planning document for CounterACT experiments (version 1.04a)

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.

Research Question(s) (in PICO format [https://guides.nyu.edu/c.php?g=276561&p=1847897]) or Milestone Being Addressed (quote milestone text):

*In the TETS/SE model, is perampenal more effective than midazolam in reducing the duration of seizures or the associated mortality?*

*In the TETS/SE model, is perampenal more effective than diazepam in reducing the duration of seizures or the associated mortality?*

Experimental model:  *TETS/SE mouse model*

Outcome Table:

<table>
<thead>
<tr>
<th>Construct</th>
<th>Operationalization / reliability evidence level / blinded assessors</th>
<th>Timing</th>
<th>Distribution type</th>
<th>Anticipated model</th>
<th>Priority</th>
</tr>
</thead>
<tbody>
<tr>
<td>Seizure duration/mortality</td>
<td>Animals instrumented for EEG &amp; videotaped. Dorota scores for presence of [detail particular seizure feature(s) of interest]. Composite indicator for seizure/death is made for each minute. /Low evidence for reliability /Not blinded</td>
<td>Minute-by-minute, up to 180 minutes post-intoxication, with treatment typically administered at 10 or 40 minutes</td>
<td>Binary</td>
<td>Composite outcomes formed by partitioning follow-up time into three periods ([0, 45), [45, 90), and 90+ minutes) and summing the minute-to-minute counts for the period Mixed-effects Poisson</td>
<td>Primary</td>
</tr>
<tr>
<td>Convulsions/mortality</td>
<td>&quot;</td>
<td>&quot;</td>
<td>&quot;</td>
<td>&quot;</td>
<td>Secondary</td>
</tr>
</tbody>
</table>

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 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 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 Perampenal (x.xx dose, 40 minutes) (n = XX )

Vehicle control for Midazolam (x.xx dose, 40 minutes) (n = XX )

Midazolam (x.xx dose, 40 minutes) (n = XX )

Perampenal (x.xx dose, 40 minutes) (n = XX )

Historical comparison groups (including relevant dosing information), sample size

(Source files for historical controls: DZP_MDZ_cleaned_102915V5ExtraSurvivalData.csv & forStat DZP_MDZ_cleaned_102915V5.csv from folder H:\CounterAct\Project1\Seizure\Data\forStat)

Vehicle control for Diazepam (x.xx dose, 40 minutes) (n = XX )

Diazepam (x.xx dose, 40 minutes) (n = XX )

Vehicle control for Midazolam (x.xx dose, 40 minutes) (n = XX )

Midazolam (x.xx 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 incidence rate ratios of 0.50 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: mid-May, 2016

Anticipated turn-around time for Core C analysis (this would typically be at 4 to 6 weeks, given the three major analysis tasks [plan, implement, and review] and the many other commitments of Core C personnel): 4 weeks

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: