When is endpoint achieved in a mouse model of amyotrophic lateral sclerosis?

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**Background:** There is no consensus among research laboratories around the world on the criteria that define endpoint in studies involving animal models of amyotrophic lateral sclerosis (ALS). Examples of endpoints in the literature include paralysis in both hind legs (clinical score of 4; CS 4) in addition to 1) weight loss (wt. loss) of ≥ 20% vs. peak body weight (20%Peak), 2) wt. loss of ≥ 20% vs. body weight immediately prior to disease onset of CS 2 (20%CS2), 3) body condition < 2 (BC<2), or 4) righting reflex (identified as CS 5; different laboratories use different time periods ranging between 10-30 sec). **Rationale:** Increasingly strict standards set by research ethics boards stipulate the adoption of endpoints that minimize the suffering of research animals. **Objective:** To investigate which criteria should be used to establish a measure of endpoint that is valid and meets stringent research ethics standards. **Methods:** Data from 4 animal studies using 162 G93A mice, a model of ALS, were analyzed to determine if differences exist between the following endpoint criteria: CS 4, CS 5 (CS 4 plus righting reflex > 20 s), and CS 4+ which combines the presence of CS 4 in addition to the earliest of the following criteria: 1) 20%Peak, 2) 20%CS2, 3) BC<2, or 4) CS 5. The age (d; mean ± SD) at which mice reached endpoint was recorded as the unit of measurement. **Results:** On average, mice reached CS 4 at 124 ± 10 d, CS 4+ at 127 ± 10 d and CS 5 at 128 ± 10 d, all significantly different from each other (P < 0.01). There was a significant positive correlation between CS 4 and CS 5 (r = 0.95, P < 0.01), CS 4 and CS 4+ (r = 0.96, P < 0.01), and CS 4+ and CS 5 (r = 0.97, P < 0.01). Logrank tests revealed that mice reached CS 4 34% faster than CS 5 (HR = 1.34, P = 0.006), however no significant differences were observed between CS 4 and CS 4+ (P = 0.053), and between CS 4+ and CS 5 (P = 0.404). **Conclusion:** There is a strong correlation between the different endpoints, with mice reaching CS 4 four days sooner than CS 5, and minimum bias between CS 4 and CS 5 (mean ± SD bias = 2.9 ± 2.5%, lower limit = -2.1%, upper limit = 7.9%). An endpoint of CS 4 would spare a mouse an average of 4 days (P < 0.01) from further neuromuscular disability and poor quality of life compared to CS 5. Alternatively, the righting reflex (CS 5) provides information regarding proprioception and severe motor neuron death,
both could be important parameters in establishing the efficacy of specific treatments. Converging ethics and discovery, would adopting CS 4 as endpoint compromise the acquisition of insight about the effects of interventions in animal models of ALS?

*Supported by NSERC, HHSF and Faculty of Health - York University*