I AM ALS presents the Patient-Centric Trial Design (PaCTD) Rating System: A clinical trial rating system to promote more humane and efficient ALS clinical trials.

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Background:
Patient recruitment for ALS drug studies has been a challenge for the ALS community, both sponsors and patients. The PaCTD Rating System was born out of a need to have more humane clinical trials in ALS. We believe this will fill ALS trials faster, allowing quicker trial completion and delivery of effective treatments and cures into people who need them. This starts with collaboration between trial sponsors and ALS patients to develop patient-centric clinical trials. Through collaboration, we believe the impact will be far greater than it is today. If we harness the patient voice, we share the following outcomes/impact:

- More humane trial design
- Faster enrollment
- More efficient trials
- Shorter drug development timeline
- Alignment with the FDA's 2019 *Amyotrophic Lateral Sclerosis: Developing Drugs for Treatment Guidance for Industry*

In 2019, Ipsos surveyed 551 ALS patients on behalf of I AM ALS. This survey found that patients were more likely to enroll in phase 3 clinical trials with open label access, reimbursed travel expenses and a lower likelihood of receiving a placebo by 91%, 83%, and 74% respectively (1).

The I AM ALS Clinical Trials Team consists of patient and caregiver volunteers.

Methods:
The I AM ALS Clinical Trials Team created a five-star rating system to assess clinical trial design. This rating is based on nine design elements, which were grouped into three categories and weighted differently for the overall rating:

1. Optimizes access to investigational therapies (60% weighting). This category addresses whether a trial includes:
    - ○ Open-Label Extension
    - ○ Minimal placebo usage
    - ○ Expanded Access Program

2. Advances scientific progress (30%). This category addresses whether a trial includes the following elements:
    - ○ Consideration of disease heterogeneity
    - ○ Use of scientifically-justified eligibility criteria
    - ○ Investigation of one or multiple biomarkers
    - ○ Independent unblinded review panel

3. Is patient friendly (10%). This category addresses whether a trial includes the following elements:
    - ○ Use of run-in observation period
    - ○ Reduced travel burden with financial reimbursements and utilization of novel methods

The Clinical Trials Team employed a prioritization matrix to determine which criteria were the most important to the group as a whole. Twelve members participated in the exercise to determine the importance of the nine criteria using the prioritization matrix.

Criteria #1 was compared to Criteria #2, asking the question, "Is Open-Label Extension of more, equal or lesser value than the Expanded Access Program criteria?" A score of "10" was given if the evaluator thought that Open-label Extension was "much more value" than Expanded Access Program. A score of "5" was given for "more value" and a score of "1" for "equal value." If the criteria was deemed "less value" a score "0.2" was given and for "much less value" a score "0.1" was given. This process continued by comparing Criteria #1 to each subsequent criteria items 2-9 on the clinical trial ratings priority list. Similarly, Criteria #2 was compared and scored against the subsequent criteria 3-9 on the priority list. This process was replicated for each subsequent criteria element down the list. The results from all twelve evaluators were aggregated into the final priority list based on score. The final scores not only provided the list order, but also informed how much weight should be allocated to each criteria.

Results:
As of November 2020, six ALS clinical trials were evaluated using the PaCTD criterion:

- Alexion (Ultomiris)
- Biogen (BIIB067 (SOD1)
- Brainstorm (NurOwn)
- HEALEY ALS Platform Trial
- Orion Pharma (Oral Levosimendan)
- Orphazyme (Ariclomol)

Ratings were discussed in meetings and presented to therapy sponsors for comment before publication. The PaCTD Rating System can be found at https://iamals.org/patient-centric-trial-design-pactd-rating-criteria/

Since September 2020, drug sponsors have begun to actively consult with the I AM ALS Clinical Trials Team and PaCTD Rating System when designing their trials.

PaCTD Rating*	Drug/ Treatment	Sponsor	Country	Recruitment Status
★★★★★	Zilucoplan (...	MGH	USA	Recruiting
★★★★★	Verdiperstat ...	MGH	USA	Recruiting
★★★★★	CNM-Au8 (H...	MGH	USA	Recruiting
★★★★	BIIB067 (Tof...	Biogen	USA, Australi...	Recruiting
★★★★	Arimoclomol	Orphazyme	USA, Belgiu...	Not Recruiting
★★★★	Ravulizumab...	Alexion Ph...	USA, Canada...	Recruiting
★	NurOwn	Brainstorm ...	USA	Not Recruiting

Figure 1: The PaCTD Rating System within ALS Signal

The PaCTD Rating is not indicative of treatment safety or efficacy. The rating is based on nine criteria that evaluate humane trial design.

Conclusion:
The PaCTD Rating System is an invaluable tool that helps researchers build and patients find clinical trials that are efficient and humane. The team's next steps are to continue to rate clinical trials and promote awareness and utilization of this tool.

Acknowledgements:
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References:
1. Ispos, Clinical Trials Survey, 2019.