

# Characterizing Hospitalization as an Outcome Measure in ALS Clinical Trials

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## BACKGROUND

- Composite endpoints that include time to first hospitalization and other clinical outcomes have potential for evaluation of long-term delay of disease progression and potentially cost-effectiveness
- This endpoint is commonly used in clinical trials of other life-threatening diseases, yet it has only recently been employed in amyotrophic lateral sclerosis (ALS) clinical trials
- Two approaches have been used thus far:
  - Including all hospitalizations, independent of their underlying cause, as used in the CENTAUR clinical trial<sup>1</sup>
  - Including only hospitalizations due to ALS progression (not otherwise defined), as used in the post-hoc analysis of MCI-186<sup>2</sup>

## OBJECTIVES

- To establish a method to characterize and analyze risk of hospitalization that will be implemented in COURAGE-ALS, a phase 3 clinical trial of *reldesemtiv* in ALS

## METHODS

### Review of hospitalizations from VITALITY-ALS and FORTITUDE-ALS

- To identify general scenarios leading to hospitalizations, we reviewed non-fatal serious adverse event narratives associated with first hospitalizations in two studies:
  - VITALITY-ALS: a 56-week phase 3 clinical trial of *tirasemtiv*<sup>3</sup>
  - FORTITUDE-ALS: a 16-week phase 2 clinical trial of *reldesemtiv*<sup>4</sup>
- Events were classified as related to ALS progression or underlying ALS, unrelated to ALS, or indeterminate (Table 1)

Table 1. Proposed classification of hospitalizations

	Proposed Definition
<b>Related to ALS progression (RP-ALS)</b>	Hospitalization occurred due to clear-cut worsening of the disease with documentation by serial measurements or scores on relevant ALSFRS-R items
<b>Related to underlying ALS (RU-ALS)</b>	The hospitalization was for something that most likely was related to their underlying ALS though the patient's ALS was clinically stable
<b>Unrelated to ALS (U-ALS)</b>	The event causing the hospitalization had no relationship to ALS – i.e., the patient would have developed the event independent of ALS and would have required hospitalization
<b>Indeterminate (IN)</b>	None of the above

ALSFRS-R, ALS Functional Rating Scale-Revised

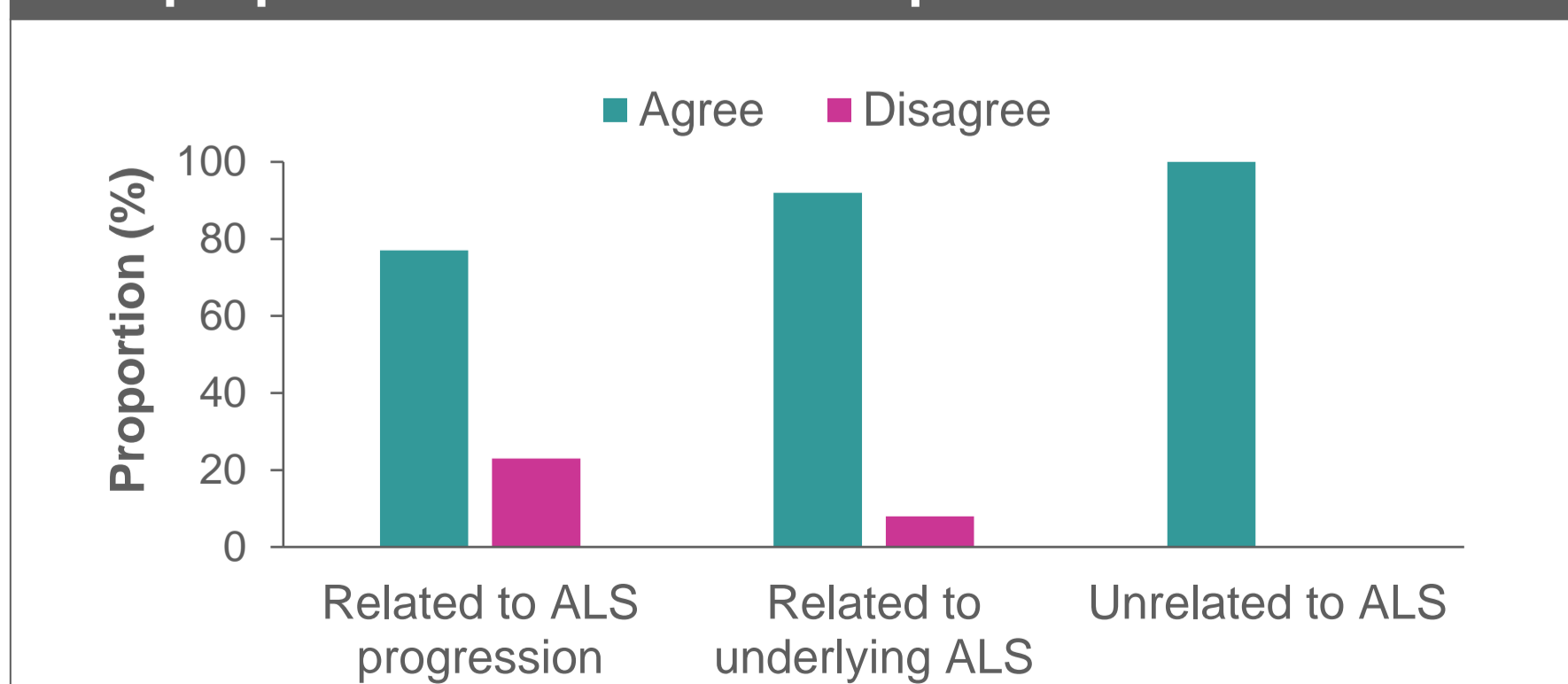
### Survey

- Members of the COURAGE-ALS Steering and Executive Committees participated in a survey to determine the degree of agreement in defining terminology and classifying events
  - The survey described clinical scenarios based upon results of the review; the experts classified each scenario as RP-ALS, RU-ALS, U-ALS, or IN

## RESULTS

- First hospitalization occurred in 6% of patients in FORTITUDE-ALS and 12% in VITALITY-ALS (Table 2); the difference is likely due to the different study durations
- Respiratory events were the most common cause of hospitalization in both clinical trials (Table 3)
- Although there was 77–100% agreement with proposed classification definitions (Figure 1), no clinical scenarios were classified in the same manner by all experts (Figure 2)

Figure 1. Proportion of survey respondents in agreement with proposed definitions of hospitalizations



## RESULTS continued

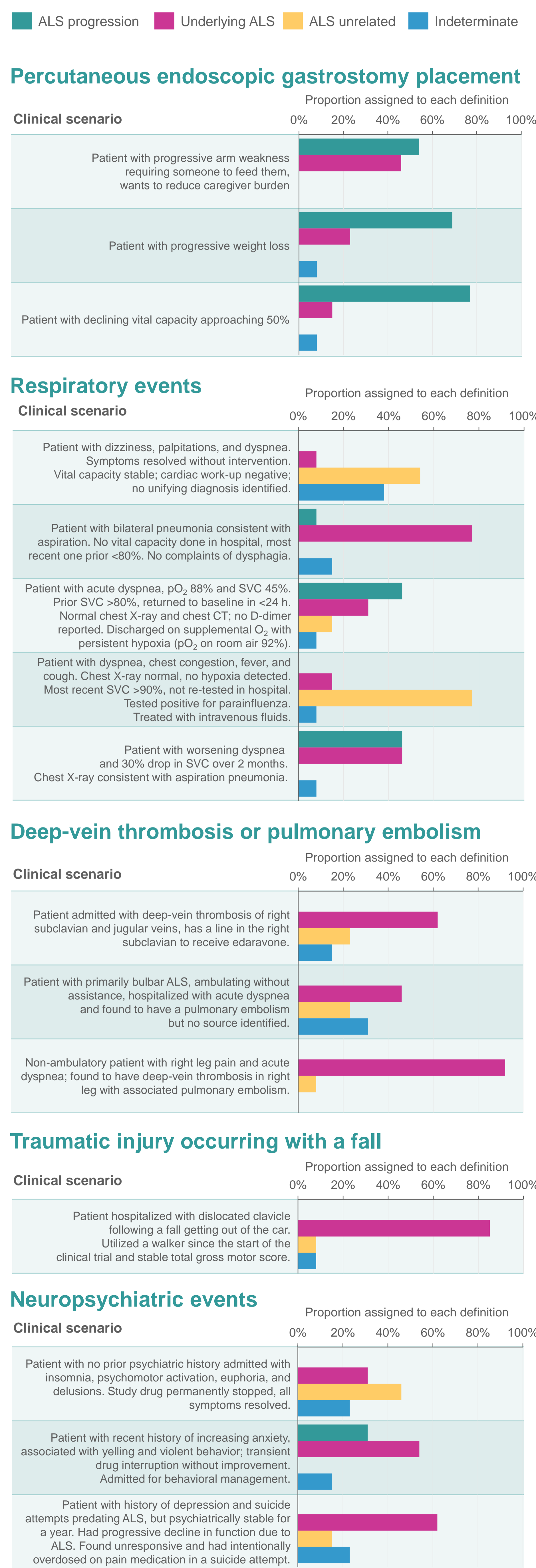
Table 2. Classifications of events

First hospitalization, n (%)	FORTITUDE-ALS N=457	VITALITY-ALS N=566
<b>Total*</b>	27 (6%)	67 (12%)
<b>RP-ALS†</b>	7 (26%)	26 (39%)
<b>RU-ALS†</b>	6 (22%)	14 (21%)
<b>RP-ALS + RU-ALS†</b>	13 (48%)	40 (60%)
<b>U-ALS†</b>	10 (37%)	18 (27%)
<b>IN†</b>	4 (15%)	9 (13%)

\*Number of first hospitalizations (percentage of patients at risk).

†Number of first hospitalizations (percentage of first hospitalizations).

Figure 2. Classifying hospitalization for clinical scenarios



CT, computed tomography; pO<sub>2</sub>, partial pressure of oxygen; SVC, slow vital capacity

## RESULTS continued

Table 3. Reasons for hospitalization

	FORTITUDE-ALS N=457	VITALITY-ALS N=566
<b>Respiratory*</b>	7 (26%)	20 (30%)
<b>Hospitalization for PEG</b>	3 (11%)	13 (19%)
<b>Dysphagia</b>	2	6
<b>Weight loss</b>	1	2
<b>Worsening respiratory function</b>	0	4
<b>Both dysphagia and weight loss</b>	0	1
<b>Urological†</b>	4 (15%)	1 (1%)
<b>DVT and / or PE</b>	2 (7%)	4 (6%)
<b>Fall leading to broken bone / head trauma</b>	2 (7%)	3 (4%)

\*Respiratory includes increased dyspnea, acute respiratory distress, bronchitis, initiating non-invasive ventilation and pneumonia; excludes worsening respiratory function as cause for PEG.

†Urological includes urinary tract infection, urosepsis, and urinary retention.

DVT, deep-vein thrombosis; PE, pulmonary embolism; PEG, percutaneous endoscopic gastrostomy

## CHALLENGES

- As part of the survey, experts were asked if they preferred hospitalizations related to ALS to be separately categorized as RP-ALS and RU-ALS
  - The majority (69%) preferred separate categories in theory; however, after the survey results showed the diversity of scenario classification, all experts preferred collapsing RP-ALS and RU-ALS into the single option of "related to ALS"
- The following issues were identified as most likely to be problematic with classifying hospitalizations:
  - Different thresholds for hospitalization among various physicians and hospitals
  - Variations in resources in the home and the family's willingness and/or ability to provide care
  - Differences in patient's wishes, including advanced care planning

## CONCLUSIONS

- In our review of two prior ALS clinical trials, approximately a quarter to a third of hospitalizations were classified as unrelated to ALS
  - Consequently, distinguishing between hospitalizations that are related or unrelated to ALS is worthwhile
- However, when classifying hospitalizations that could be related to ALS progression or to underlying ALS, there were diverse opinions even among ALS experts
  - Therefore, a simplified approach may lead to consistent classification, giving results that are more meaningful to patients, clinicians, and payers

## References

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