Patient-Centric Trial Design (PaCTD) Rating Criteria

The PaCTD rating system was created by a group of patient and caregiver volunteers on the I AM ALS Clinical Trials Team. Their goal is to outline criteria for humane and efficient trial design. This rating system objectively evaluates trials based on select trial design elements in three key categories: optimizing access to investigational therapies, advancing scientific progress and if the trial is patient friendly.

What are PaCTD ratings?

The PaCTD rating system is a 5-star rating system. The I AM ALS Clinical Trials Team used nine elements to assess clinical trial design. For definitions of the nine elements, see the definition section below. These elements fell into three primary categories and were given percentage weighting for the overall rating as listed below:

- **Optimizing access to investigational therapies (60%).** This category addresses whether a trial includes the following elements:
    - Open-Label Extension
    - Minimizes placebo usage
    - An Expanded Access Program
- **Advancing 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 for interim efficacy check-ins if warranted
- **Being patient friendly (10%).** This category addresses whether a trial includes the following elements:
    - Use of run-in observation period
    - Reduce travel burden by use of novel methods

PaCTD ratings do *not* measure or evaluate the treatment's safety or efficacy. A high rating on this scale does not indicate promising science and a low rating on this scale does not mean the treatment is ineffective -- it purely measures the design of the trial from the patient and caregiver perspective across the criteria outlined.

Within the ALS Signal dashboard you can hover your mouse over an individual PaCTD rating to see the specific elements included in a particular trial. If you have any questions about this rating system, please contact community@iamals.org.

Helpful Definitions

The document referenced throughout this page as “FDA”is the FDA ALS Clinical Trial Guidance Document. It can be found here.

Open-Label Extension: The trial allows for trial participants to continue to access the treatment after the participation commitment in the trial has ended through Open-Label Extension (FDA p.5).

Minimize placebo usage: The clinical trial design seeks to minimize placebo administration to 1/3 of trial participants or less (FDA p.4 B1).

An Expanded Access Program: The drug sponsor provides access for patients who do not meet trial inclusion/exclusion requirements through an Expanded Access Program (FDA p.4).

Consideration of disease heterogeneity: The trial utilizes novel design features to sort out the effects of disease heterogeneity (e.g. crossover design; delayed start design; re-randomization of outlier disease progressors as part of a post-trial subset analysis) (referred throughout the FDA guidance). For more on ALS disease heterogeneity, click here.

Use of scientifically justified eligibility criteria: All trial inclusion/exclusion requirements are scientifically justified and do not reflect a cut and paste attempt to copy prior unsuccessful trials (FDA p.3).

Investigation of biomarker: The trial attempts to identify and substantiate novel disease-related biomarkers (FDA p. 3 and 7).

Independent Unblinded Review Panel: The trial utilizes an Independent Unblinded Review Panel. This panel has the ability to halt a trial due to patient safety concerns. It also has the ability to identify early indicators of success so that there can be an adjustment to the trial to speed consideration of review (FDA p.3).

Use of minimal run-in observation period: The trial utilizes a run-in period of one month or less. A run-in period is a period of time between when a patient is accepted into a clinical trial and undergoes initial tests/screening and when the investigational drug/treatment is administered to a patient (FDA p.6 #3).

Reduce travel burden by use of novel methods: The trial design utilizes telemedicine, wearable technologies, financial reimbursement and/or other novel methods to limit patient travel and the number of clinic visits throughout the trial (FDA p.7).

PaCTD Ratings for Individual Trials

Click below to view a PaCTD Rating for:

- Brainstorm (NurOwn)
- Orphazyme (Arimoclomol)
- Alexion (Ultomiris)
- Biogen (BIIB067 (SOD1))
- Platform Trial
    - Clene Nanomedicine (CNM-Au8)
    - Biohaven Pharmaceutical Holding Co (Verdiperstat)
    - Ra Pharmaceuticals (Zilucoplan)
- Theracurmin
- Pegcetacoplan (Apellis)

I AM ALS Patient Centric Trial Design (PaCTD)	Brainstorm NurOwn[1]	
Open Label Extension	No	0
Minimize placebo usage - 33% or less	No (50%)	0
A side by side Expanded Access Program	No	0
Part 1 Total		**0**
Part 1 Rating-Seats at the Table		**0**
Consideration of disease heterogeneity: e.g., Cross-Over Design or Delayed Start Design	Yes	1
Use of scientifically supportable inclusion criteria, pre-defined subset analysis, re-randomization at trial conclusion to equalize outlier progressors between trial arms, or alternative controls (historical, algorithmic etc.)	24 months from onset, no older than 60 years of age. Some were scientifically justified.	0.5
Investigation of biomarker	Yes	1
Independent Unblinded Review Panel that can communicate with FDA where substantial proof of "efficacy" emerges before end of trial	No	0
Part 2 Total		**2.5**
Part 2 Rating-Advancing Science Quickly		**0.1875**
Use of Run-In Observation Period - 3 months not acceptable -1 month ideally	Yes (3 months)	0
Use of novel methods: wearables, telemedicine visits, financial burden	Telemedicine visits through COVID-19.	0.5
Part 3 Total		**0.5**
Part 3 Rating-Patient-Friendly		**0**
Total Rating		**0.1875**
x5		**1.0625**
I AM ALS PaCTD 5-Star Rating:		**1-Star**

[1] Brainstorm's clinical trial design was created before the FDA updated its ALS clinical trial guidance in the Amyotrophic Lateral Sclerosis: Developing Drugs for Treatment Guidance for Industry in September 2019.

I AM ALS Patient Centric Trial Design (PaCTD)	Orphazyme Arimoclomol[2]	
Open Label Extension	Yes-18 months	1
Minimize placebo usage - 33% or less	Yes (33%)	1
A side by side Expanded Access Program	No	0
Part 1 Total		**2**
Part 1 Rating-Seats at the Table		**0.4**
Consideration of disease heterogeneity: e.g., Cross-Over Design or Delayed Start Design	Yes	1
Use of scientifically supportable inclusion criteria, pre-defined subset analysis, re-randomization at trial conclusion to equalize outlier progressors between trial arms, or alternative controls (historical, algorithmic etc.)		1
Investigation of biomarker	Yes	1
Independent Unblinded Review Panel that can communicate with FDA where substantial proof of "efficacy" emerges before end of trial	No	0
Part 2 Total		**3**
Part 2 Rating-Advancing Science Quickly		**0.225**
Use of Run-In Observation Period - 3 months not acceptable -1 month ideally	No	1
Use of novel methods: wearables, telemedicine visits, financial burden	telemedicine visits, travel reimbursement, drug shipped to home, home nursing visits	1
Part 3 Total		**2**
Part 3 Rating-Patient-Friendly		**0.1**
Total Rating		**0.725**
x5		**3.625**
I AM ALS PaCTD 5-Star Rating:		**4-Star**

[2] Orphazyme's clinical trial design was created before the FDA updated its ALS clinical trial guidance in the Amyotrophic Lateral Sclerosis: Developing Drugs for Treatment Guidance for Industry in September 2019.

I AM ALS Patient Centric Trial Design (PaCTD)	Alexion Ultomiris	
Open Label Extension	Yes - 2 years	1
Minimize placebo usage - 33% or less	Yes (33%)	1
A side by side Expanded Access Program	No	0
Part 1 Total		**2**
Part 1 Rating-Seats at the Table		**0.4**
Consideration of disease heterogeneity: e.g., Cross-Over Design or Delayed Start Design	Subset Analysis & NFL	1
Use of scientifically supportable inclusion criteria, pre-defined subset analysis, re-randomization at trial conclusion to equalize outlier progressors between trial arms, or alternative controls (historical, algorithmic etc.)	No age restriction, symptom onset 36 months, Riluzole and Radicava fine	1
Investigation of biomarker	Yes	1
Independent Unblinded Review Panel that can communicate with FDA where substantial proof of “efficacy” emerges before end of trial	No	0
Part 2 Total		**3**
Part 2 Rating-Advancing Science Quickly		**0.225**
Use of Run-In Observation Period - 3 months not acceptable -1 month ideally	No	1
Use of novel methods: wearables, telemedicine visits, financial burden	telemedicine visits, travel reimbursement	1
Part 3 Total		**2**
Part 3 Rating-Patient-Friendly		**0.1**
Total Rating		**0.725**
x5		**3.625**
I AM ALS PaCTD 5-Star Rating:		**4-Star**

I AM ALS Patient Centric Trial Design (PaCTD)	Biogen BIIB067 (SOD1)[3]	
Open Label Extension	Yes	1
Minimize placebo usage - 33% or less	Yes (33%)	1
A side by side Expanded Access Program	No	0
Part 1 Total		**2**
Part 1 Rating-Seats at the Table		**0.4**
Consideration of disease heterogeneity: e.g., Cross-Over design or Delayed Start Design	SOD1	1
Use of scientifically supportable inclusion criteria, pre-defined subset analysis, re-randomization at trial conclusion to equalize outlier progressors between trial arms, or alternative controls (historical, algorithmic etc.)		1
Investigation of biomarker	Yes	1
Independent Unblinded Review Panel that can communicate with FDA where substantial proof of "efficacy" emerges before end of trial	No	0
Part 2 Total		**3**
Part 2 Rating-Advancing Science Quickly		**0.225**
Use of Run-In Observation Period - 3 months not acceptable -1 month ideally	No	1
Use of novel methods: wearables, telemedicine visits, financial burden	telemedicine visits, state travel reimbursement	1
Part 3 Total		**2**
Part 3 Rating-Patient-Friendly		**0.1**
Total Rating		**0.725**
x5		**3.625**
I AM ALS PaCTD 5-Star Rating:		**4-Star**

[3] Biogen's clinical trial design was created before the FDA updated its ALS clinical trial guidance in the Amyotrophic Lateral Sclerosis: Developing Drugs for Treatment Guidance for Industry in September 2019.

I AM ALS Patient Centric Trial Design (PaCTD) The HEALEY ALS Platform Trial tests multiple treatments in one trial. This listing will be updated if additional drugs are added to the trial.	**Platform Trial** **Clene Nanomedicine** **CNM-Au8** **Biohaven Pharmaceutical Holding Co** **Verdiperstat** **Ra Pharmaceuticals** **Zilucoplan**	
Open Label Extension	Yes - up to 1 year +	1
Minimize placebo usage - 33% or less	Yes (25%)	1
A side by side Expanded Access Program	CNM-Au8 - Yes Verdiperstat - Yes Zilucoplan - Pending[4]	1[5]
Part 1 Total	**3**	**3[6]**
Part 1 Rating-Seats at the Table	**0.6**	**0.6[7]**
Consideration of disease heterogeneity: e.g., Cross-Over Design or Delayed Start Design	Yes	1
Use of scientifically supportable inclusion criteria, pre-defined subset analysis, re-randomization at trial conclusion to equalize outlier progressors between trial arms, or alternative controls (historical, algorithmic etc.)	Yes (36 months from symptoms). No upper age limit.	1
Investigation of biomarker	Yes	1
Independent Unblinded Review Panel that can communicate with FDA where substantial proof of “efficacy” emerges before end of trial	No	0
Part 2 Total	**3**	**3**
Part 2 Rating-Advancing Science Quickly	**0.225**	**0.225**
Use of Run-In Observation Period - 3 months not	No	1

[4] Ra Pharmaceuticals’ Zilucoplan Expanded Access Program is pending.
[5] Ra Pharmaceuticals’ Zilucoplan rating is 0 until the Expanded Access Program begins.
[6] Ra Pharmaceuticals’ Zilucoplan receives a 2 until the Expanded Access Program begins.
[7] Ra Pharmaceuticals’ Zilucoplan receives a 0.4 until the Expanded Access Program begins.

acceptable -1 month ideally		
Use of novel methods: wearables, telemedicine visits, financial reimbursement	Yes	1
Part 3 Total		**2**
Part 3 Rating-Patient-Friendly		**0.1**
Total Rating		**0.925**[8]
x 5		**4.625**[9]
I AM ALS PaCTD 5-Star Rating:		**5-Star**[10]

[8] Ra Pharmaceuticals' Zilucoplan receives a 0.725 until the Expanded Access Program begins.
[9] Ra Pharmaceuticals' Zilucoplan receives a 3.625 until the Expanded Access Program begins.
[10] Ra Pharmaceuticals' Zilucoplan receives a 4-Star rating until the Expanded Access Program begins. A 5-Star rating is an average of the three drugs in the trial.

I AM ALS Patient-Centric Trial Design (PaCTD)	Duke University Theracurmin	
Open Label Extension	Yes - the whole trial is OLE	1
Minimize placebo usage - 33% or less	No placebo	1
A side by side Expanded Access Program		1
Part 1 Total		**3**
Part 1 Rating-Seats at the Table		**0.6**
Consideration of disease heterogeneity: e.g., Cross-Over Design or Delayed Start Design	Yes	1
Use of scientifically supportable inclusion criteria, pre-defined subset analysis, re-randomization at trial conclusion to equalize outlier progressors between trial arms, or alternative controls (historical, algorithmic etc.)	Yes	1
Investigation of biomarker	Yes - microbiome compared to healthy controls	1
Independent Unblinded Review Panel that can communicate with FDA where substantial proof of “efficacy” emerges before end of trial		1
Part 2 Total		**4**
Part 2 Rating-Advancing Science Quickly		**0.3**
Use of Run-In Observation Period - 3 months not acceptable -1 month ideally	No	1
Use of novel methods: wearables, telemedicine visits, financial burden	Yes	1
Part 3 Total		**2**
Part 3 Rating-Patient-Friendly		**0.1**
Total Rating		**1**
x5		**5**
I AM ALS PaCTD 5-Star Rating:		**5-Star**

I AM ALS Patient-Centric Trial Design (PaCTD)	Apellis Pegcetacoplan	
Open Label Extension	Yes	1
Minimize placebo usage - 33% or less	33% placebo	1
A side by side Expanded Access Program	No	0
Part 1 Total		**2**
Part 1 Rating-Seats at the Table		**0.4**
Consideration of disease heterogeneity: e.g., Cross-Over Design or Delayed Start Design	Yes	1
Use of scientifically supportable inclusion criteria, pre-defined subset analysis, re-randomization at trial conclusion to equalize outlier progressors between trial arms, or alternative controls (historical, algorithmic etc.)	Yes	1
Investigation of biomarker	Yes	1
Independent Unblinded Review Panel that can communicate with FDA where substantial proof of “efficacy” emerges before end of trial	No	0
Part 2 Total		**3**
Part 2 Rating-Advancing Science Quickly		**0.225**
Use of Run-In Observation Period - 3 months not acceptable -1 month ideally	No	1
Use of novel methods: wearables, telemedicine visits, financial burden	Yes	1
Part 3 Total		**2**
Part 3 Rating-Patient-Friendly		**0.1**
Total Rating		**0.725**
x5		**3.625**
I AM ALS PaCTD 5-Star Rating:		**4-Star**

I AM ALS Patient-Centric Trial Design (PaCTD)	Cytokinetics Courage Reldesemtiv	
Open Label Extension	Yes	1
Minimize placebo usage - 33% or less	33% placebo	1
A side by side Expanded Access Program	Enrolling 550 in COURAGE. All eligible for OLE + EAP participants in prior trials	1
Part 1 Total		**3**
Part 1 Rating-Seats at the Table		**0.6**
Consideration of disease heterogeneity: e.g., Cross-Over Design or Delayed Start Design	Yes; cross over	1
Use of scientifically supportable inclusion criteria, pre-defined subset analysis, re-randomization at trial conclusion to equalize outlier progressors between trial arms, or alternative controls (historical, algorithmic etc.)	Yes; Two years from symptom onset. Vital capacity of 65%. ALS-FRS-R of 44 or less. Riluzole and Radicava are allowed	1
Investigation of biomarker	Yes; serum (blood), DNA, DME, muscle strength, PROs	1
Independent Unblinded Review Panel that can communicate with FDA where substantial proof of “efficacy” emerges before end of trial	Yes; In the second interim analysis	1
Part 2 Total		**4**
Part 2 Rating-Advancing Science Quickly		**0.3**
Use of Run-In Observation Period - 3 months not acceptable -1 month ideally	No	1
Use of novel methods: wearables, telemedicine visits, financial burden	Yes; Novel methods; telemedicine visits, mobile phone apps, home nursing visit: remote labs, spirometry	1
Part 3 Total		**2**
Part 3 Rating-Patient-Friendly		**0.1**
Total Rating		**1**

x5		**5**
I AM ALS PaCTD 5-Star Rating:		**5-Star**