Welcome

47TH Annual Meeting

PHOENIX

May 17-20, 2026

SCT

SOCIETY FOR CLINICAL TRIALS

NN111 ExTINGUISH Trial: Lessons Learned in Trial Implementation, Recruitment, and Retention for a Rare Disease in an Acute Care Setting, International Trial

NIH National Institute of Neurological Disorders and Stroke

The University of Iowa

Massachusetts General Hospital
Founding Member, Mass General Brigham

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Introduction to the NeuroNEXT Network, Recruitment and Retention Challenges and Lessons Learned in the NN111 ExTINGUISH Trial

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Disclosures

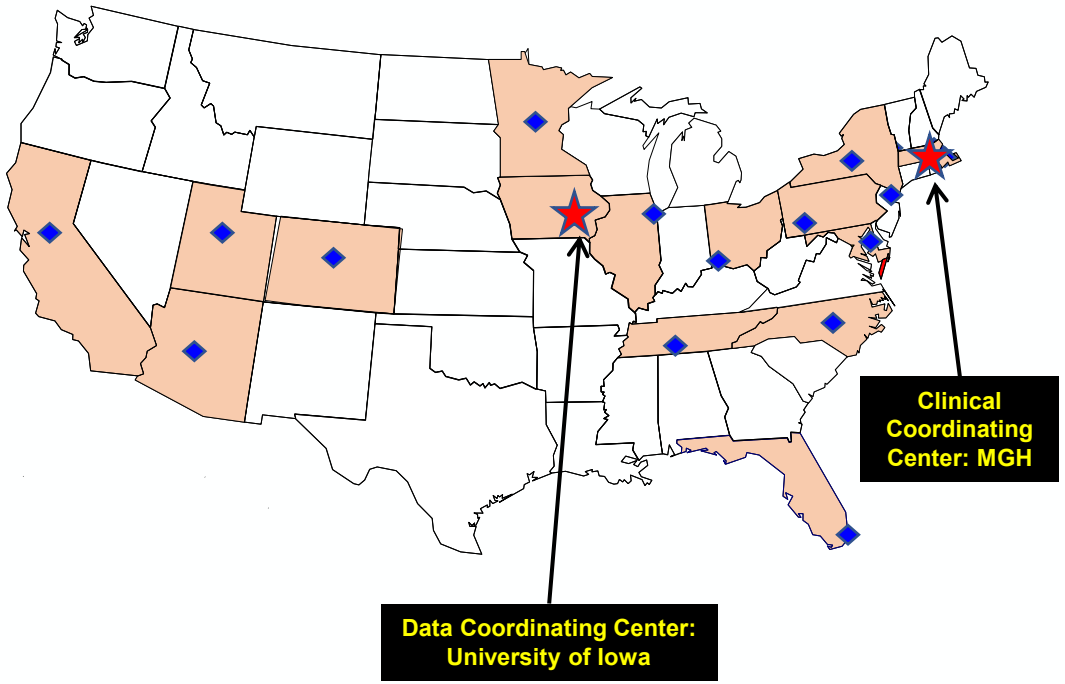
- I have no relevant disclosures

Neuro NEXT

The NEXT Generation of Neurologic Treatments

NIH-Network for Excellence in Neuroscience Clinical Trials

What is NeuroNEXT?



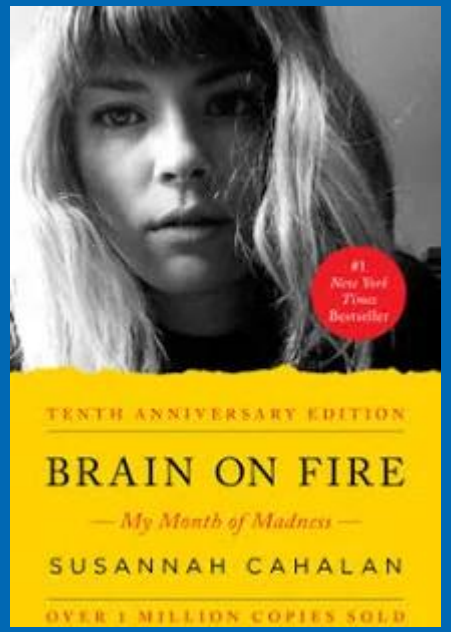
- National Institute of Neurological Disease and Stroke (NINDS) funded network consisting of:
  - Clinical Coordinating Center
    - Single IRB
    - Protocol Development
    - Project Management
  - Data Coordinating Center
    - EDC Development
    - Statistical Analysis
    - Monitoring
  - Funded Study Sites
    - Premier Academic Centers across the US
    - FTE Site Program Manager
    - Network Investigator
- Primarily a Phase II Trial Network

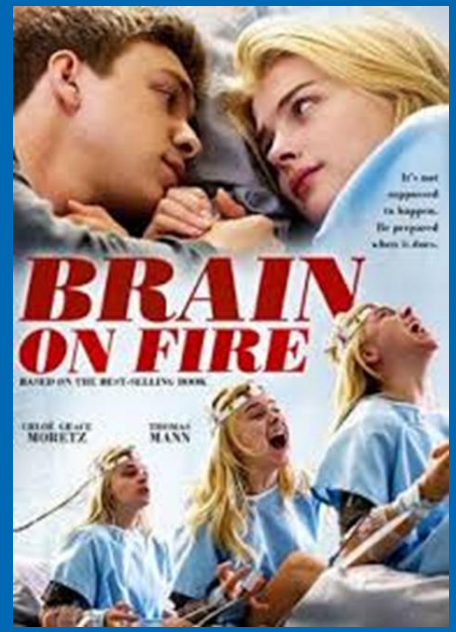
For additional information, visit:
www.neuronext.org

NN111 ExTINGUISH

Anti-NMDA receptor encephalitis

- Autoimmune encephalitis first named in 2007
- Diagnosed by:
  - A subacute change in mental status consistent with autoimmune encephalitis and,
  - Positive cell-based assay for NMDAR IgG Ab in the CSF
- Often presents with psychiatric symptoms/behavior changes
- Impacts approximately 1 in 1.5 million people annually
- Can require long-term immunosuppression to treat
- No currently approved treatments;



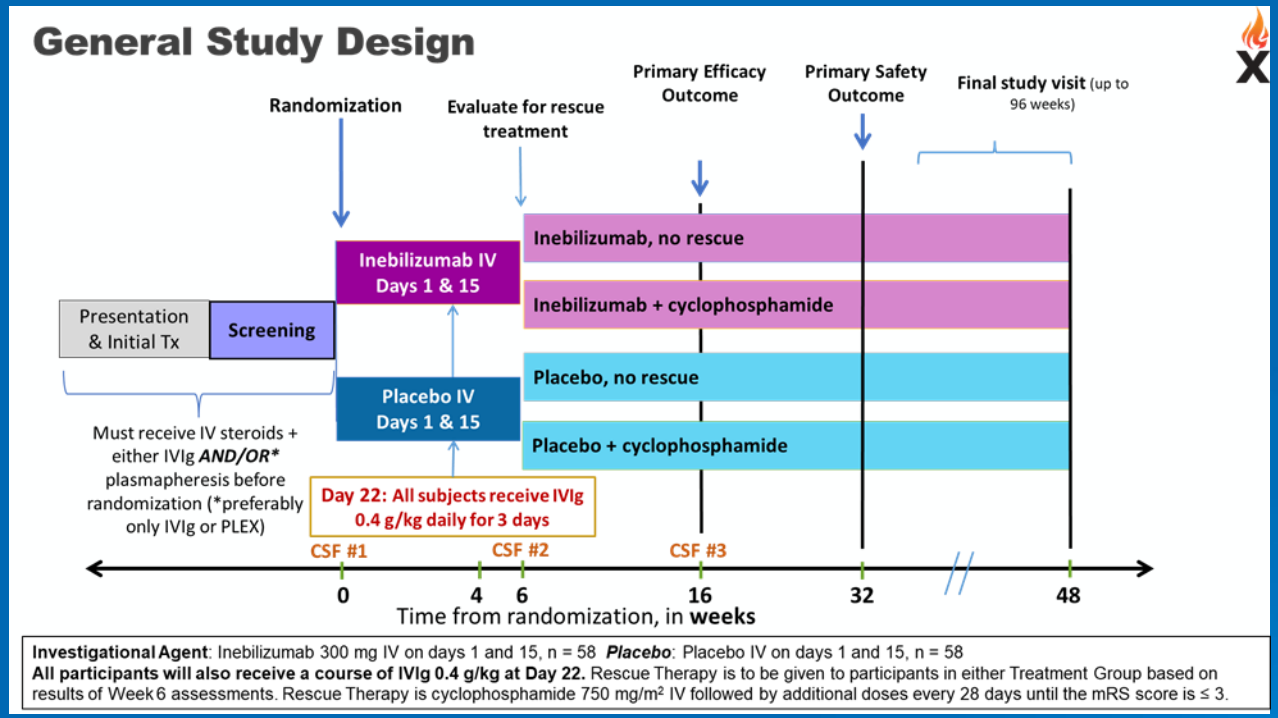


Described in the autobiographical account “Brain on Fire” by Susannah Cahalan and adapted into a film of the same name.

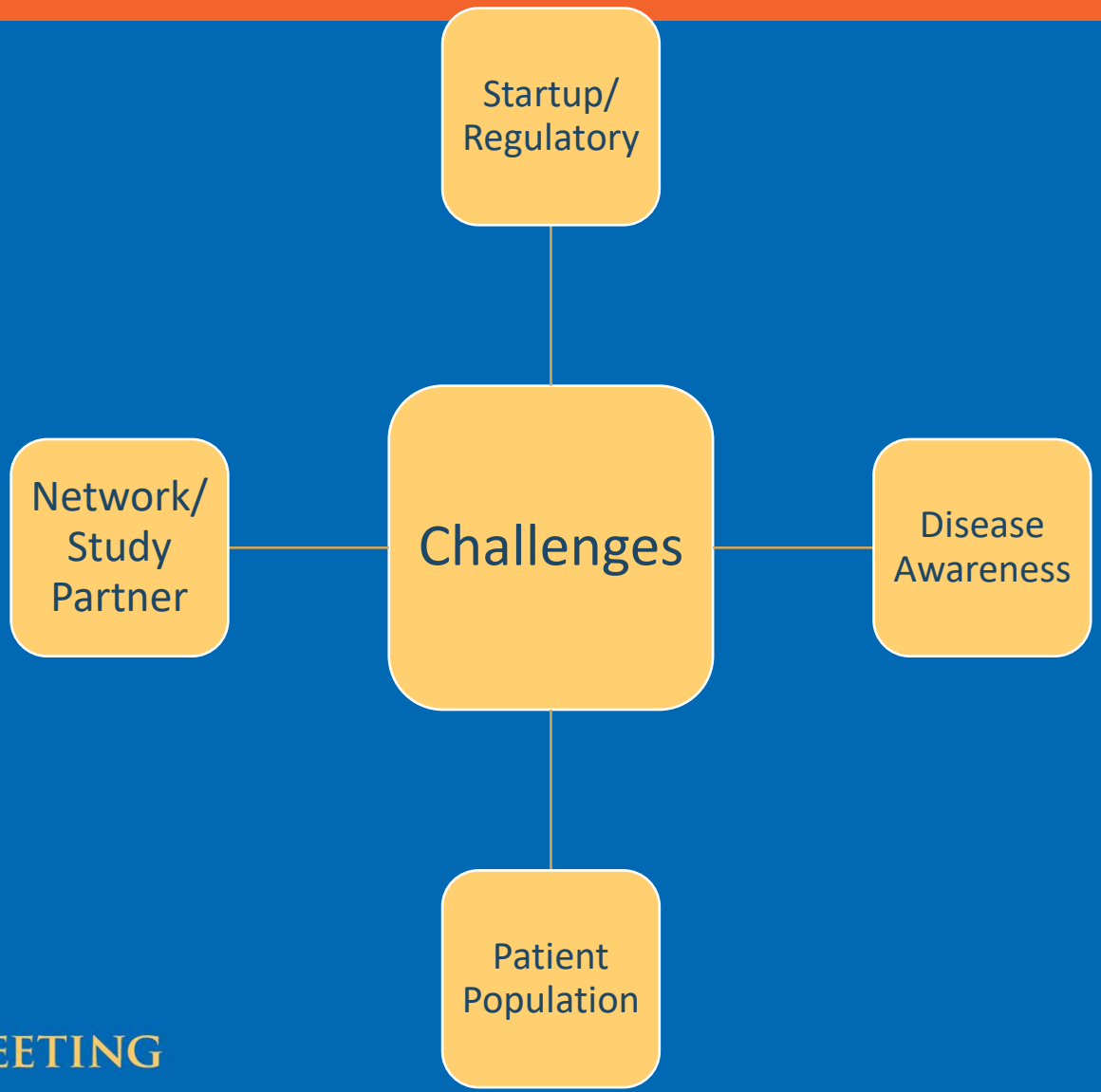
NN111 ExTINGUISH

What is the ExTINGUISH Trial?

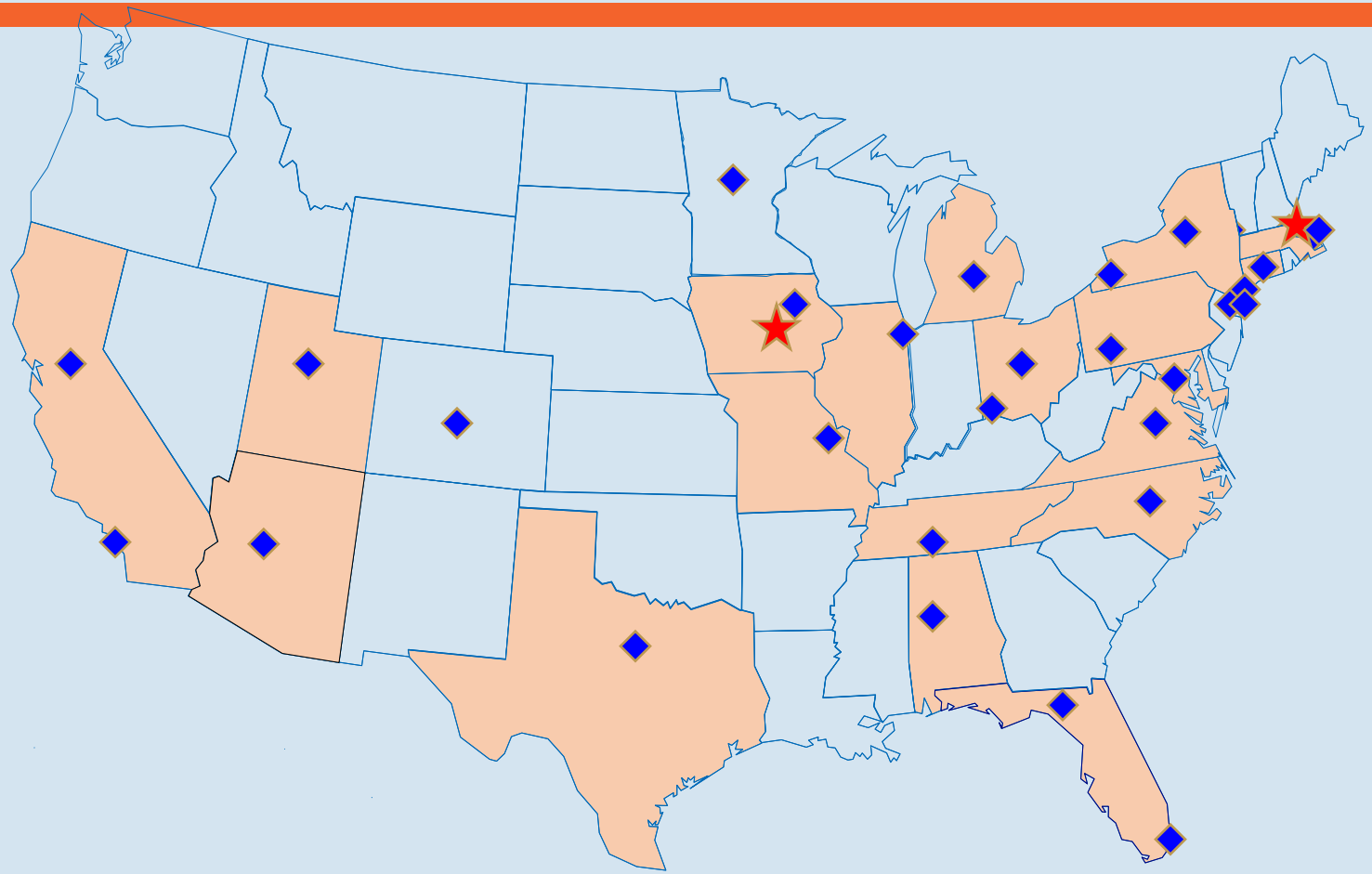
- Double-blind placebo-controlled trial on the safety and efficacy of inebilizumab
- Participants presenting as acutely ill (≤90 days from symptom onset)
- Identified through CSF testing
- Participants must be ≥ 12 years of age



Challenges for Operations, Recruitment, & Retention



Challenges - Network & Study Partner



NeuroNEXT Network Renewed in 2023

- # of Network sites dropped from 25 to 13
- New Network sites added
- ~ ½ of activated sites lost FTE Site Program Manager
- Resulted in some activated sites discontinuing in the study
- Primarily a Phase II trial network managing a registration trial

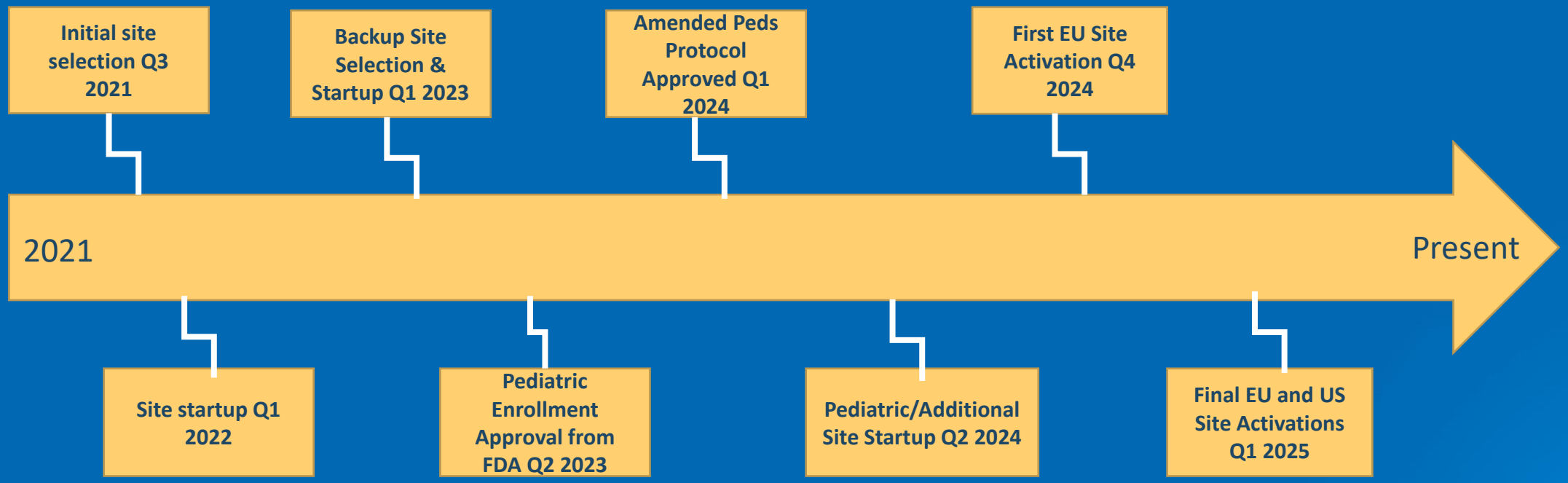
Challenges - Network and Study Partner

- Multiple acquisitions of industry partner
  - Support staff changed with each acquisition
  - Time spent bringing new staff up to speed
  - Challenges with delivery of study drug to EU sites

Challenges - Startup & Regulatory

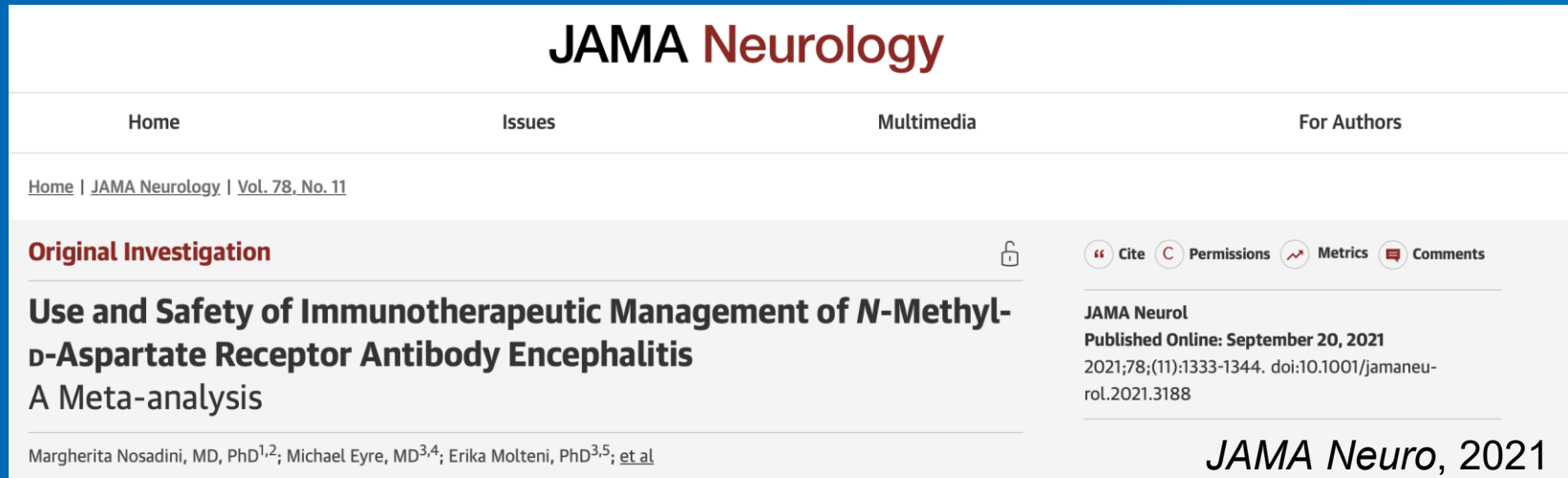
- Site startup initiated in 2021
- Last site activated in February 2025
  - Slow first year of enrollment led to study site expansion
  - Addition of non-NeuroNEXT sites
- FDA delayed approval for pediatric enrollment
  - Approval granted in 2024
  - Resulted in a need for pediatric sites
  - Required protocol amendment
- EU site challenges
  - Logistics with drug labeling and shipping to EU sites
  - Protocol & Monitoring Plan alignment

Study Timeline



Challenges - Disease Awareness

- Rareness of the disease
- Lack of standard processes in assessment and first-line treatments
  - Treatment approaches are informed by retrospective studies and guided by 'expert consensus': subject to a high degree of bias
- Reliance of physicians on another monoclonal antibody (Rituximab)



JAMA Neurology

Home | Issues | Multimedia | For Authors

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Original Investigation

Use and Safety of Immunotherapeutic Management of *N*-Methyl-D-Aspartate Receptor Antibody Encephalitis
A Meta-analysis

Margherita Nosadini, MD, PhD[1,2]; Michael Eyre, MD[3,4]; Erika Molteni, PhD[3,5]; et al

Cite | Permissions | Metrics | Comments

JAMA Neurol
Published Online: September 20, 2021
2021;78;(11):1333-1344. doi:10.1001/jamaneurol.2021.3188

JAMA Neuro, 2021

Challenges - Patient Population Recruitment & Retention

- Acute Trial Design
  - No pre-existing patient registry for recruitment
  - Finding participants at disease presentation/diagnosis
    - Need to reach patients before prohibited medications are administered
    - Patients may be misdiagnosed

- Long-term recovery
  - Logistical challenges to returning to study sites
  - Patients often uninsured or underinsured
  - Desire of patients to get back to "normal" life
    - Avoidance of returning to study site

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RESEARCH

Worldwide survey of neurologists on approach to autoimmune encephalitis

Aravind Ganesh, MD, DPhil, Luca Bartolini, MD, and Sarah F. Wesley, MD, MPH

Correspondence
Dr. Ganesh
aravindganeshy@yahoo.ca

Neurology: Clinical Practice Month 2019 vol. 10 no. 1 1-9 doi:10.1212/CPJ.0000000000000701

Anti-NMDA-receptor encephalitis: case series and analysis of the effects of antibodies

Josep Dalmau, *Amy J Gleichman, *Ethan G Hughes, Jeffrey E Rossi, Xiaoyu Peng, Meizan Lai, Scott K Dessain, Myrna R Rosenfeld, Rita Balice-Gordon, David R Lynch

Lancet Neurol, 2008

Neuro-inflammation

Review

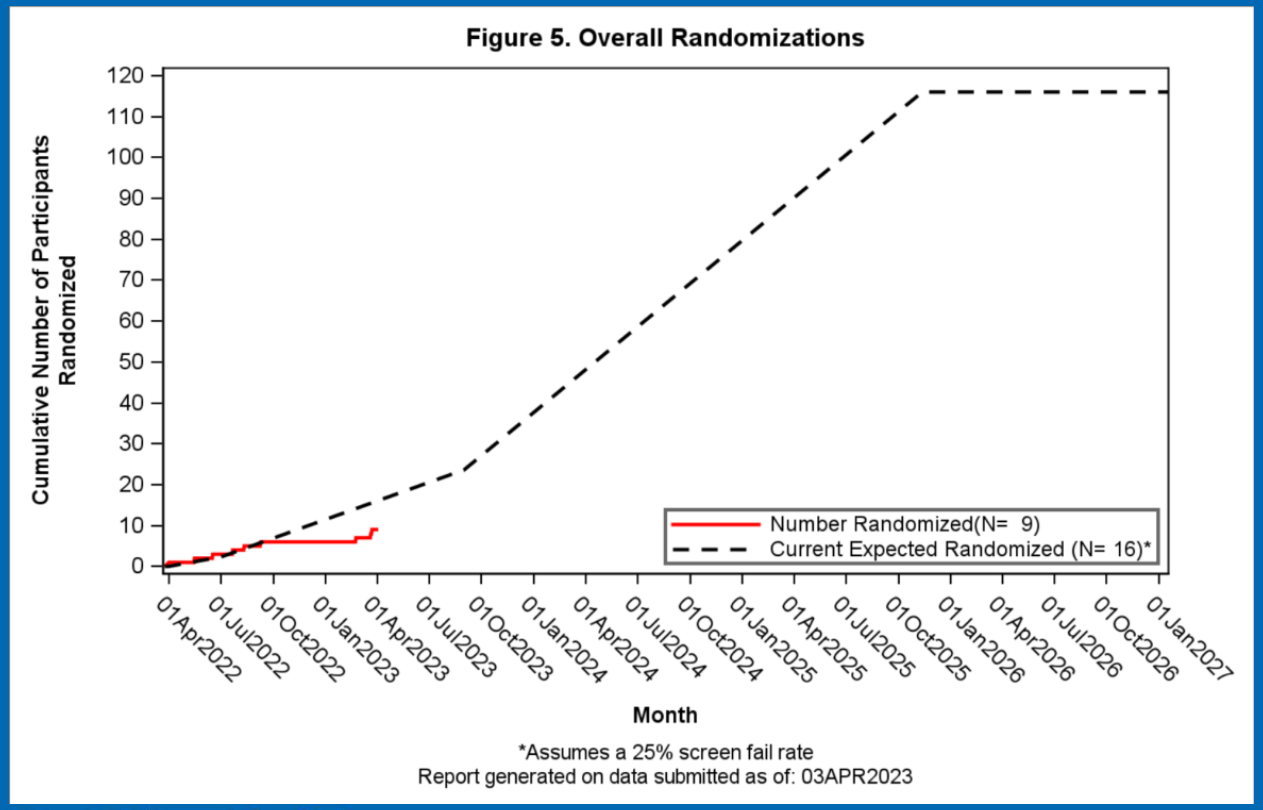
Autoimmune encephalitis: proposed recommendations for symptomatic and long-term management

Hesham Abboud [1,2] John Probasco,[3] Sarosh R Irani [4] Beau Ances,[5] David R Benavides,[6] Michael Bradshaw,[7,8] Paulo Pereira Christo,[9] Russell C Dale,[10] Mireya Fernandez-Fournier,[11] Eoin P Flanagan [12] Avi Gadoth,[13] Pravin George,[14] Elena Grebenciucova,[15] Adham Jammoul,[14] Soon-Tae Lee,[16] Yuebing Li,[14] Marcelo Matiello,[17,18] Anne Marie Morse,[19] Alexander Rae-Grant,[14] Galeno Rojas,[20,21] Ian Rossman,[22] Sarah Schmitt,[23] Arun Venkatesan,[3] Steven Vernino,[24] Sean J Pittock [12] Maarten Titulaer [25] Autoimmune Encephalitis Alliance Clinicians Network

JNNP, 2021

Impact on Enrollment

- After One Year of Enrollment 9 of 116 Randomized



- ~1/2 of anticipated enrollments in year 1
- EU sites not activated for enrollment
- Revisions to projected study timeline required

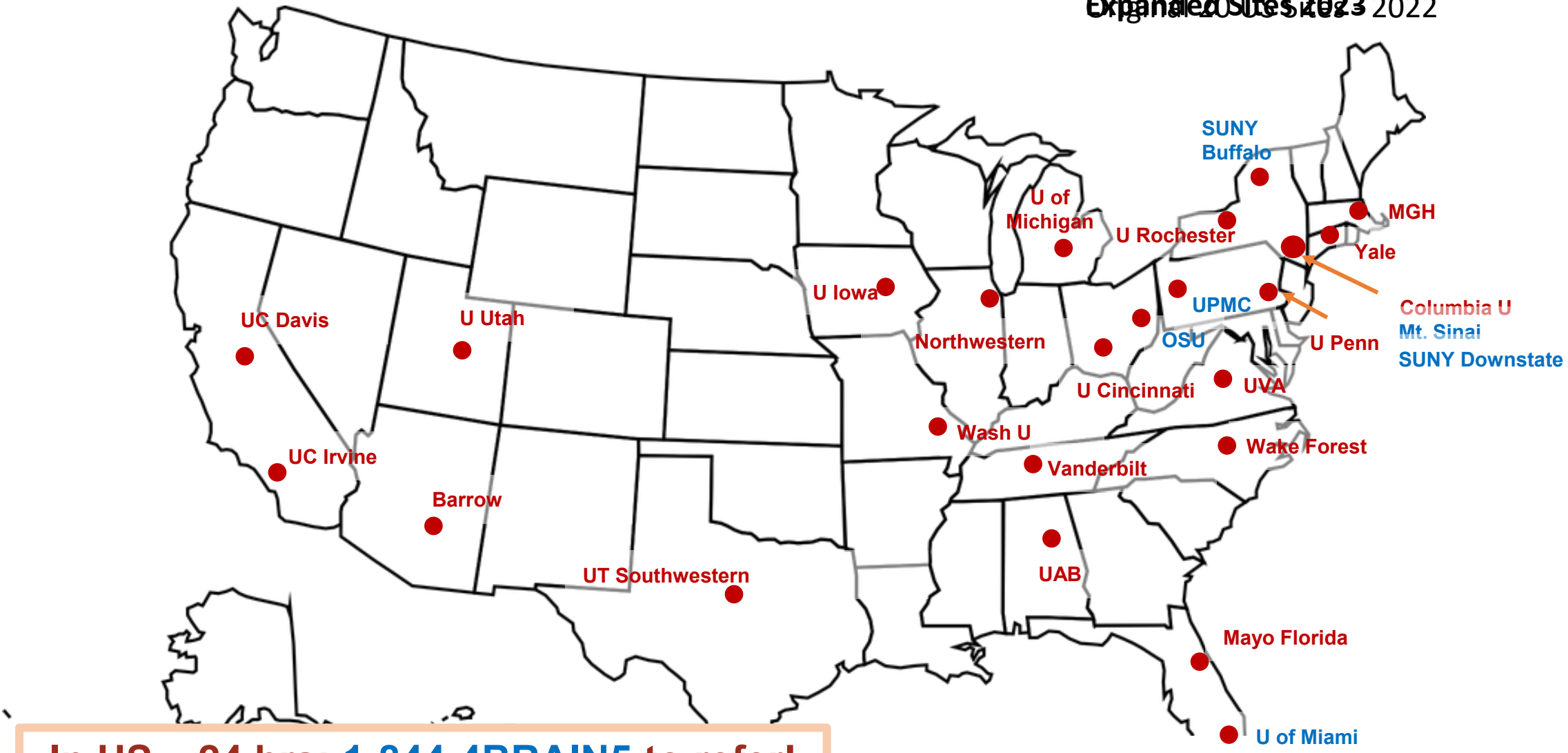
Site Expansion

- US Sites increased from 20 to 36
  - Two rounds of site expansion
  - Pediatric Sites added to target enrollment of 12-17 years of age
  - Strong push to finalize EU site startup

Trial Sites: Coast to Coast

THE EXTINGUISH
NMDAR ENCEPHALITIS TRIAL

Original 20 Sites 2022
Expanded Sites 2023

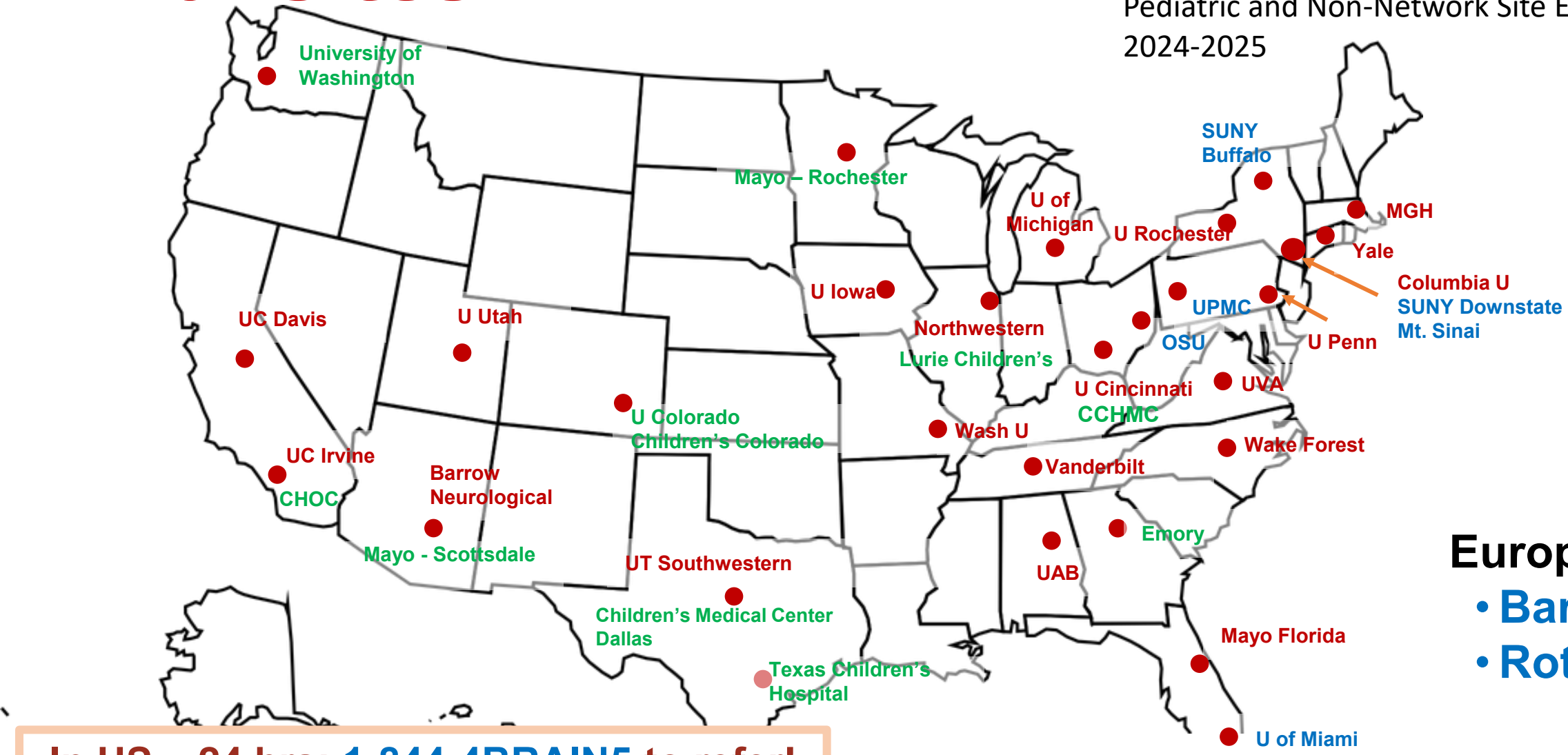


In US – 24 hrs: 1-844-4BRAIN5 to refer!

Trial Sites: Coast to Coast

THE EXTINGUISH
NMDAR ENCEPHALITIS TRIAL

Pediatric and Non-Network Site Expansion
2024-2025



Europe:

- **Barcelona**
- **Rotterdam**

In US – 24 hrs: 1-844-4BRAIN5 to refer!

Identifying Strategies for Improvement

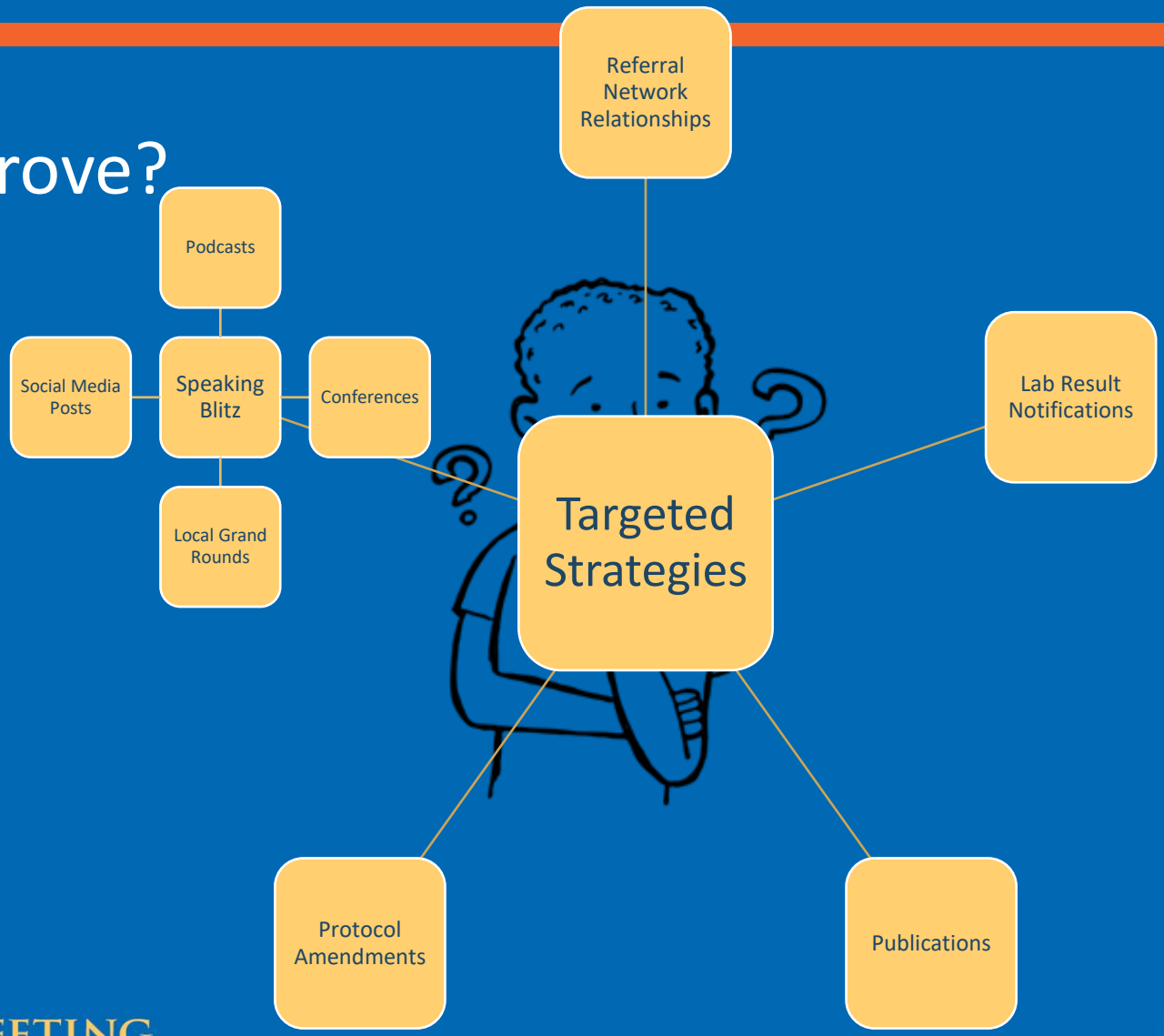
Site Expansion addressed some geographical issues, but we were still missing participants. Why?

Review of site submitted pre-screening logs for areas for intervention

- Education issues
- Trial awareness
- Existing practice
  - Administration of trial prohibited medications
- Concerns about placebo arm
- Length of trial enrollment/ability to attend all visits

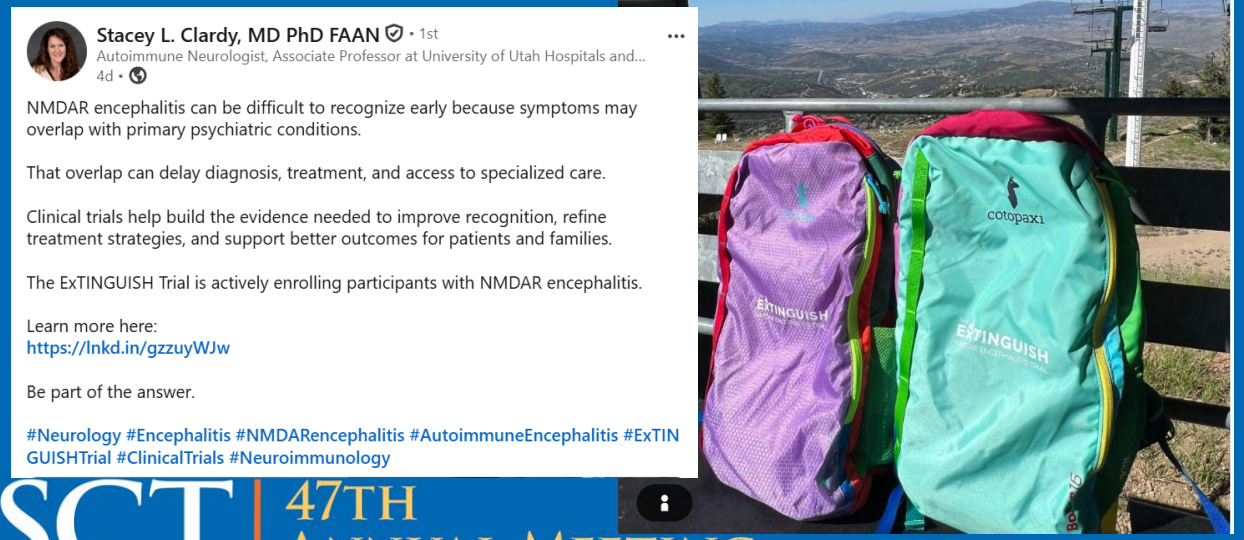
Meeting the Challenge

How do we improve?



Overcoming Challenges - Speaking Blitz

Neurology Podcast:
https://www.neurology.org/media/podcast/autoimmune-encephalitis-series-advancing-science



ASENT. American Society for Experimental Neurotherapeutics

American Academy of Neurology

ECTRIMS European Committee for Treatment and Research in Multiple Sclerosis

Autoimmune Encephalitis Alliance

Encephalitis International — The brain inflammation non-profit

AAN Autoimmune Neurology Conference

Over 150 speaking engagements for the Protocol PI Team including:

- 40+ Grand Rounds
- Lectures
- Invited Sessions
- Keynote Addresses
- Poster Presentations
- Webinars

- No opportunity too small!

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Overcoming Challenges - Education

- Engagement with referral networks
  - Site outreach to regional providers
  - Conversations after missed enrollments
  - Dedicated 24/7 study hotline
    - Available for all referral questions

- Study alerts on CSF Anti NMDA-R test result notifications from 4 major labs
  - Direct outreach from trial affiliated labs to referring providers
    - Phone calls and targeted emails

ARUP LABORATORIES

MAYO CLINIC LABORATORIES

- Publications from the study team

Meta-Analysis > J Neuroimmunol. 2025 Aug 15:405:578651.

doi: 10.1016/j.jneuroim.2025.578651. Epub 2025 May 27.

An updated, comprehensive meta-analysis of the treatment of anti-NMDAR encephalitis: Analysis, equipoise, and the urgent need for evidence over anecdote

Yoji Hoshina [1], Tammy L Smith [2], Alen Delic Mstat [1], Ka-Ho Wong [1], Lisa K Peterson [3], Anastasia Zekeridou [4], Albert Aboseif [4], Christopher Coffey [5], Melissa A Wright [6], Brenda Banwell [7], Annalisa Dialino-Felix [8], Susan Flavin [8], Lisa Dill [8], Maarten J Titulaer [9], Gregory S Day [10], Stacey L Clardy [11]

A Phase-2B Double-Blind Randomized International Prospective Trial of Inebilizumab in NMDAR Encephalitis: The ExTINGUISH Trial

Ka-Ho Wong [1,2,*], Gregory Scott Day [3], James C Torner [4], Merit Cudkowicz [5], Christopher S Coffey [4], Hyun Joo Sophie Cho [6], Ursula Utz [6], David B Clifford [7], Eliezer Katz [8], John Ratchford [8], Susan Flavin [9], Annalisa Dialino-Felix [9], Lisa M Dill [9], Cornelia Kamp [10], Eric C Klawiter [5], John Robinson Singleton [1,2], Janel Fedler [4], Elizabeth A Klingner [4], Dixie Ecklund [4], David Klements [5], Michele Costigan [4], Erin Steinhart [5], Brenda Pearson [4], Christina Desir [5], Josep O Dalmau [11], Maarten J Titulaer [12], Stacey L Clardy [1,2,*]

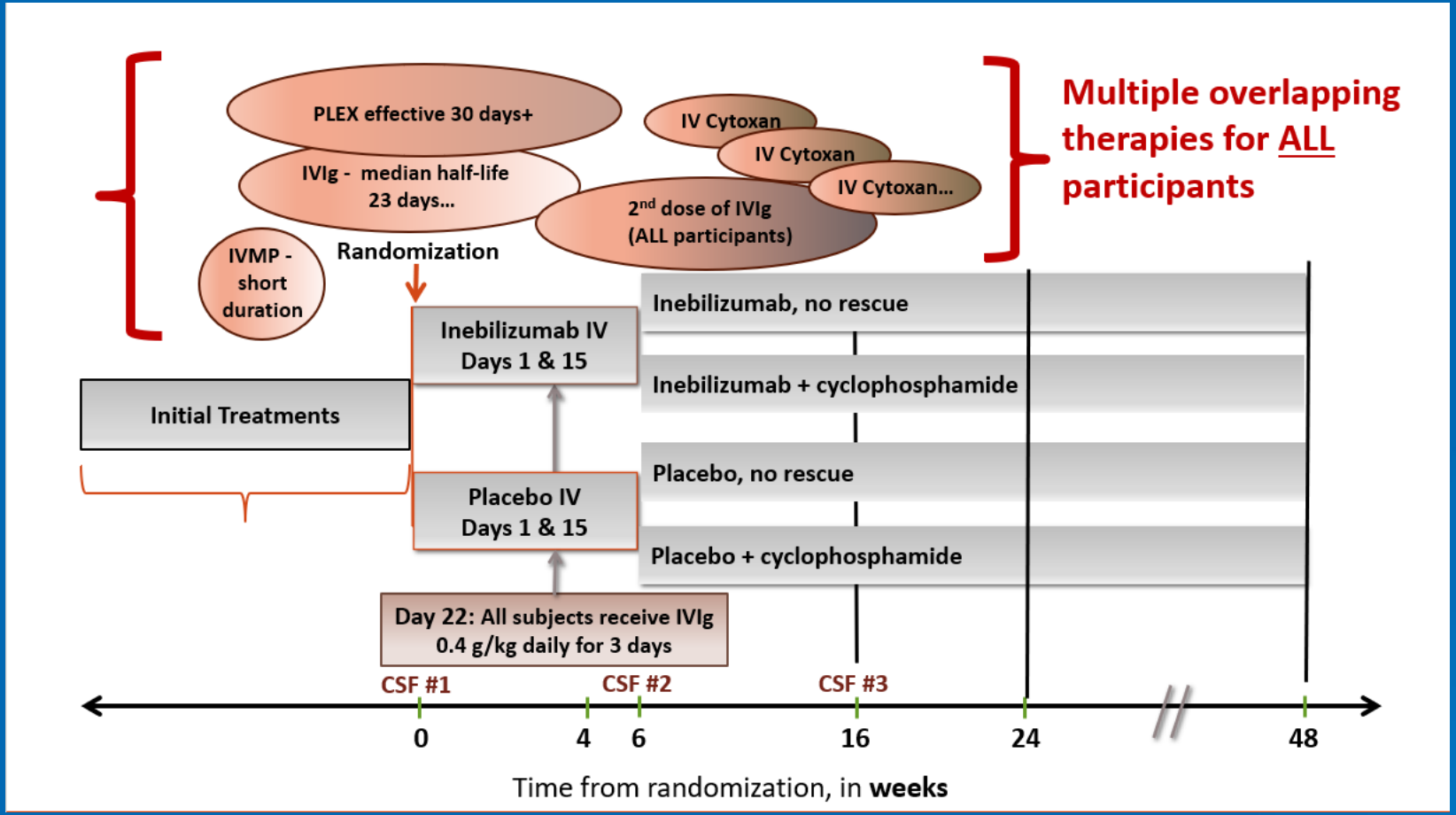
Author information · Article notes · Copyright and License information

PMCID: PMC12233123 NIHMSID: NIHMS2087188 PMID: 40625668

Hoshina et al. 2025 – Neuroimmunology
Wong et al. 2025 – Neurology Open Access

Overcoming the Challenge – Provider & Participant Concerns

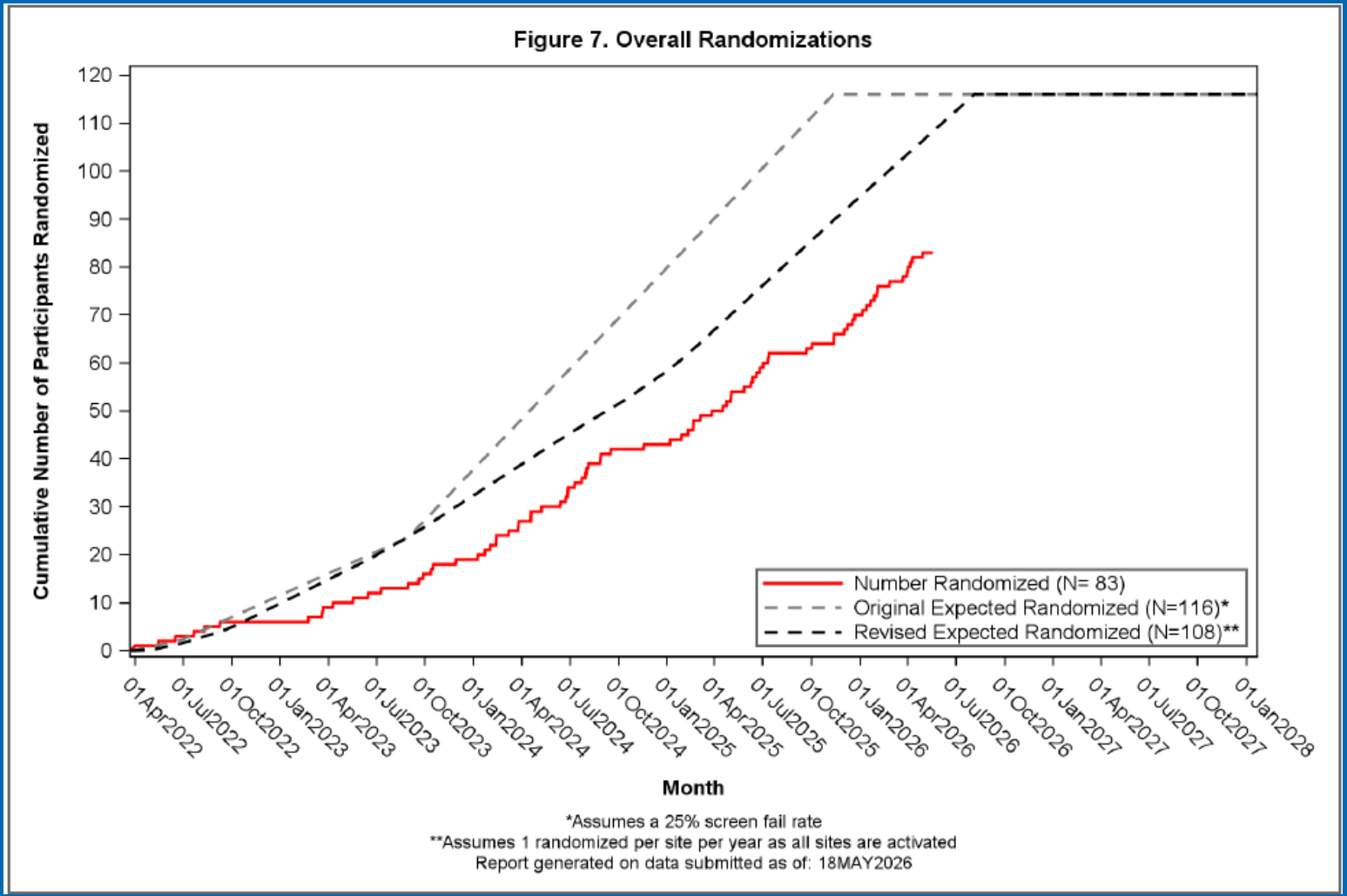
Addressing placebo concerns

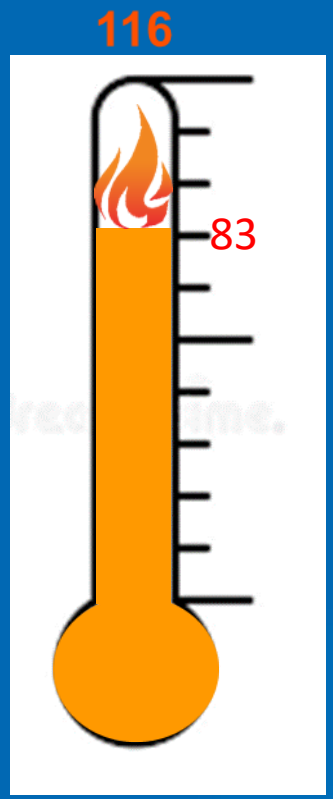


Overcoming the Challenge – Participant Concerns

- Protocol amendments to allow flexibility in timing of study visits and where they take place

Where are we now?





Lessons Learned

- Early recruitment challenges kept us under the enrollment curve
- Trial awareness and education in the rare disease space needs to be addressed early and often
  - Sometimes necessitates outside the box thinking

Acknowledgments

- We’d like to acknowledge and thank the NN111 central study team, NN111 study sites, and our participants for their contributions.

Data Collection Mid-Study Modifications in the NN111 ExTINGUISH Trial

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Disclosures

- No Disclosures

Overview

- Standard Network data collection forms
- Updates for data integrity
  - Con Meds
  - RBANS
  - Modified Rankin Scale
- Updates for Adding EU sites
  - Central and Local Labs
  - Central Pharmacy System
- Updates for added Cohort
  - Demographics/Stratification

Standard Network Data Collection Forms

- CDEs
- Demographics
- Con Meds
- Adverse Events
- Protocol Deviations

Updates for Data Integrity

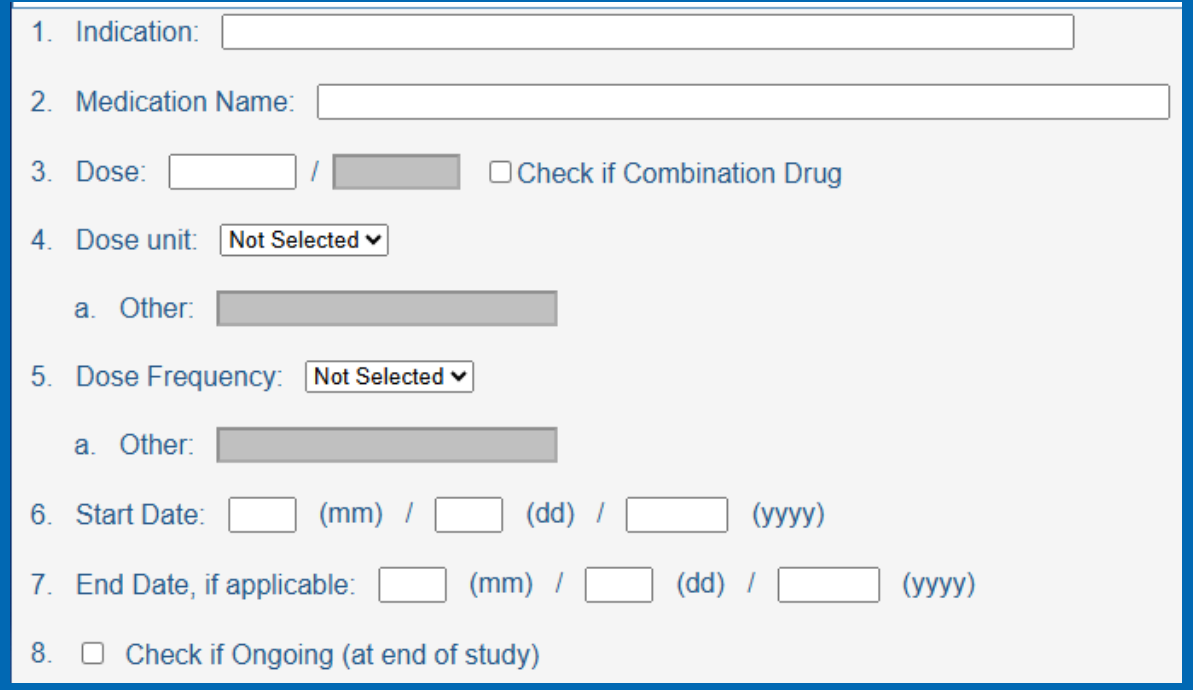
Con Meds

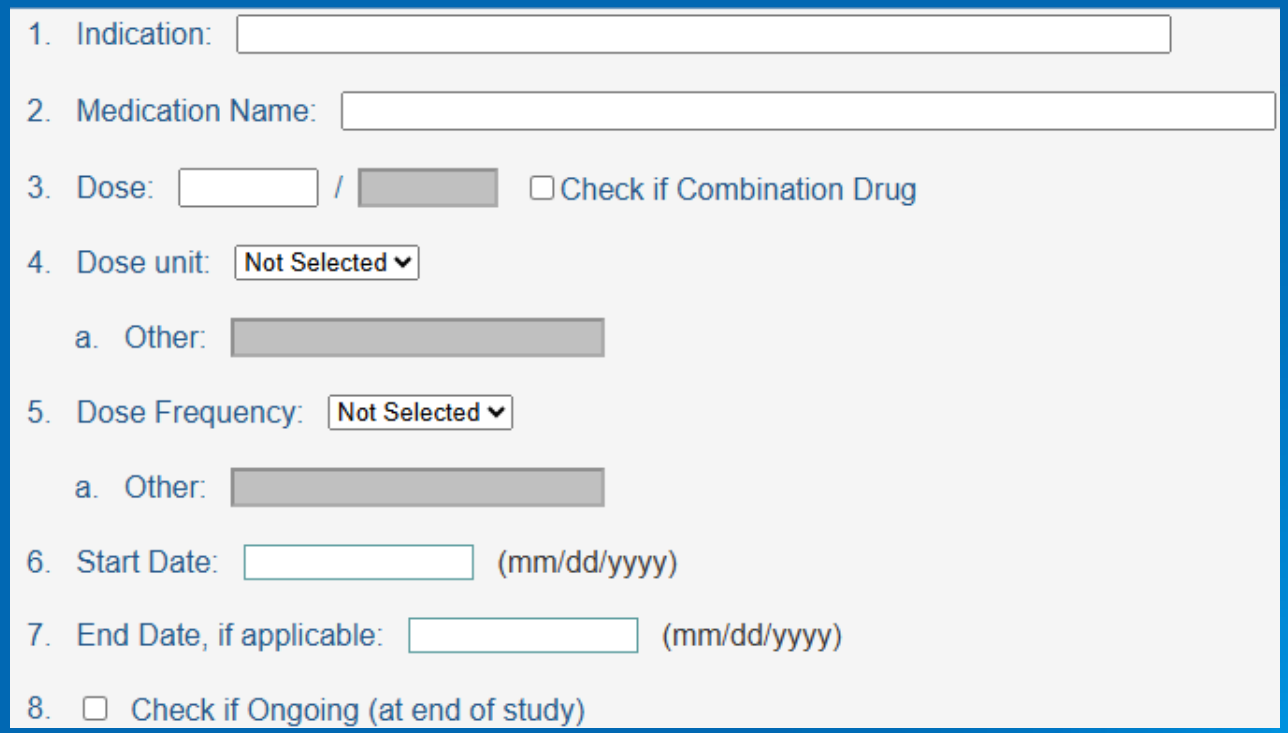
- Initially broken into 3 collection phases
  - Prior to Hospitalization
    - 3 part dates
  - Hospitalization
  - Post Hospitalization

Generic Medication Name	Indication	Dose	Dose Unit	Dose Frequency	Start Date (mm/dd/yyyy)	End Date (mm/dd/yyyy) *If applicable*	Check if Ongoing (at end of study)
					__/__/____ (mm/dd/yyyy)	__/__/____ (mm/dd/yyyy)	☐
					__/__/____ (mm/dd/yyyy)	__/__/____ (mm/dd/yyyy)	☐
					__/__/____ (mm/dd/yyyy)	__/__/____ (mm/dd/yyyy)	☐

Con Meds

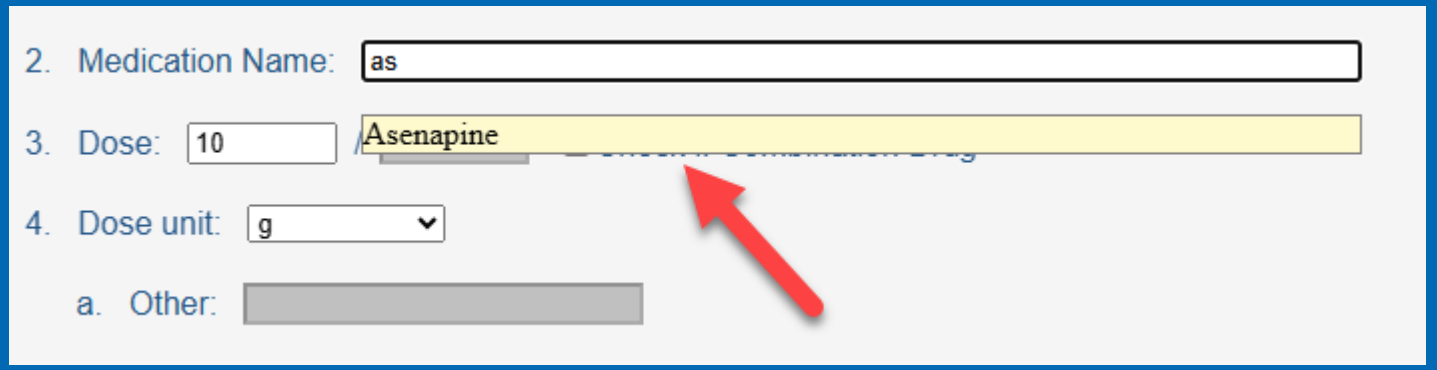
- Reason for change
  - Site and monitoring burden
- Changes made
  - Prior to Hospitalization
    - none
  - Post Hospitalization
    - Combined with Hospitalization





Con Meds

- Reason for change
  - Site and monitoring burden

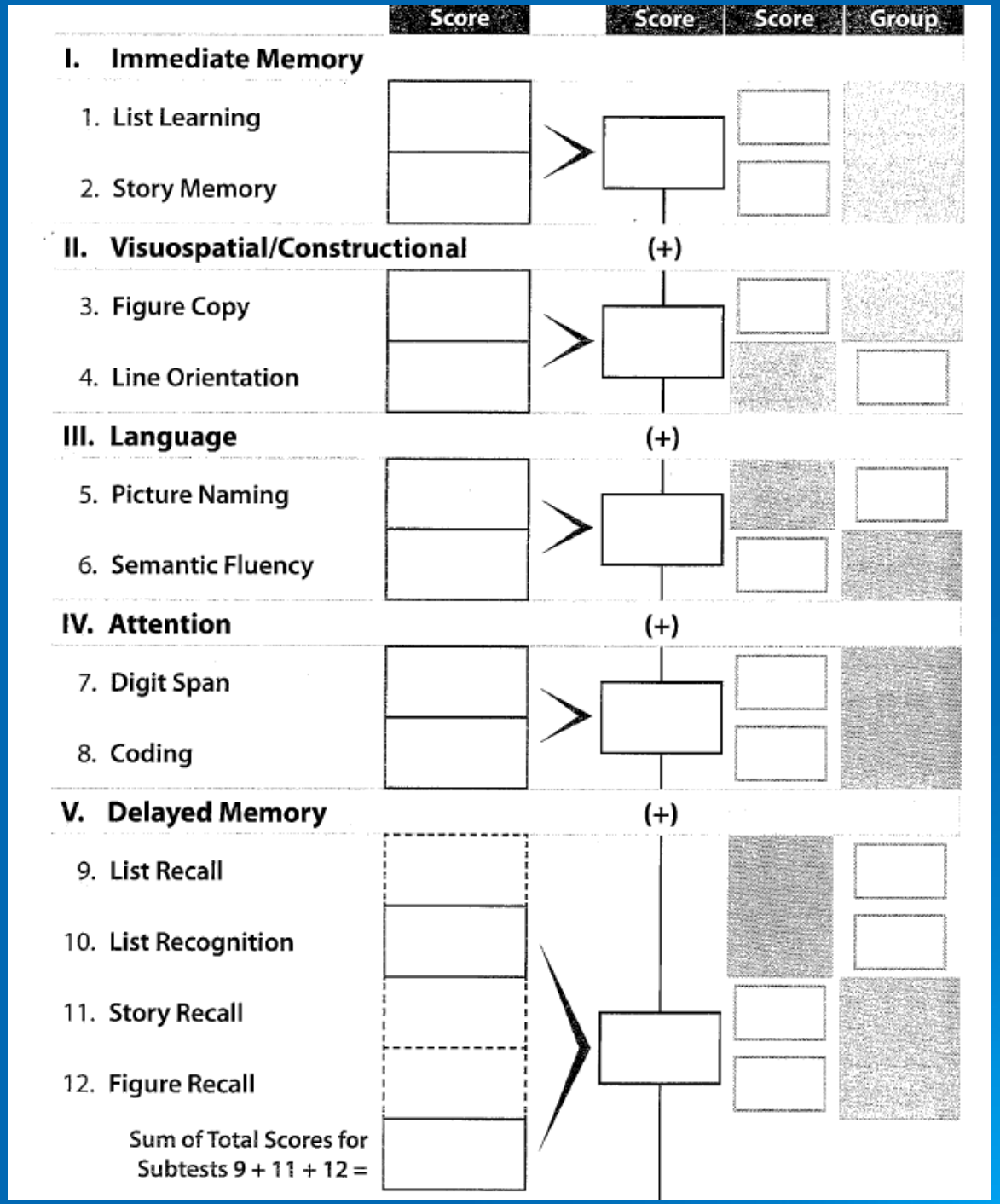


- Changes made
  - Hospitalization
    - Added autofill
    - Added "Update Dose"
    - Removed Dose
    - Removed Frequency

Generic·Medication·Name¤	Indication¤	Start·Date·(mm/dd/yyyy)¤	End·Date·(mm/dd/yyyy)·*If·applicable*¤	Check·if·Ongoing·(at·end·of·study)¤
¤	¤	__·__·/__·__·/__·__·__·__·(mm/dd/yyyy)¤	__·__·/__·__·/__·__·__·__·(mm/dd/yyyy)¤	☐¤
¤	¤	__·__·/__·__·/__·__·__·__·(mm/dd/yyyy)¤	__·__·/__·__·/__·__·__·__·(mm/dd/yyyy)¤	☐¤
¤	¤	__·__·/__·__·/__·__·__·__·(mm/dd/yyyy)¤	__·__·/__·__·/__·__·__·__·(mm/dd/yyyy)¤	☐¤

R-Bans

- Collected at a single time point
- Adjudication process added
  - Central expert rater
  - 100% of R-Bans checked
  - Central module auto filled



Modified Rankin Scale

- Initial Development
  - Use in Anti-NMDAR Encephalitis
  - Capture Cognitive Symptoms
  - Capture Psychiatric Symptoms

1. Select the description below that best describes the participant's condition. Write the number on the line provided.

   - ○ 0-No symptoms at all
   - ○ 1-No significant disability despite symptoms, Able to carry out all usual duties and activities
   - ○ 2-Slight disability: Unable to carry out all previous activities but able to look after own affairs without assistance
   - ○ 3-Moderate Disability: Requiring some help, but able to walk without assistance
   - ○ 4-Moderately severe disability: Unable to walk without assistance, and unable to attend to own bodily needs without assistance
   - ○ 5-Severe disability: Bedridden, incontinent, and requiring constant nursing care and attention
   - ○ 6-Death

1. Constant Care

	i. Now		ii. Before Encephalitis	
a. Does the person require constant care?	○ Yes	○ No	○ Yes	○ No

2. Assistance to attend to bodily needs/for walking

	i. Now		ii. Before Encephalitis	
a. Is assistance essential for eating?	○ Yes	○ No	○ Yes	○ No
b. Is assistance essential for using the toilet?	○ Yes	○ No	○ Yes	○ No
c. Is assistance essential for routine daily hygiene?	○ Yes	○ No	○ Yes	○ No
d. Is assistance essential for walking?	○ Yes	○ No	○ Yes	○ No

3. Assistance to look after own affairs

	i. Now		ii. Before Encephalitis	
a. Is assistance essential for preparing a simple meal?	○ Yes	○ No	○ Yes	○ No
b. Is assistance essential for basic household chores?	○ Yes	○ No	○ Yes	○ No
c. Is assistance essential for looking after household expenses?	○ Yes	○ No	○ Yes	○ No
d. Is assistance essential for local travel?	○ Yes	○ No	○ Yes	○ No
e. Is assistance essential for local shopping?	○ Yes	○ No	○ Yes	○ No

Modified Rankin Scale Revisions

- Reason for Modification
  - Data accuracy

1. Constant Care

	i. Now	ii. Before Encephalitis
a. Is the person bedridden, incontinent, and requiring constant care?	○ Yes ○No	○ Yes ○No

2. Assistance or supervision to attend to bodily needs/for walking **over a 24 hour period**

	i. Now	ii. Before Encephalitis
a. Is assistance or supervision essential for eating?	○ Yes ○No	○ Yes ○No
b. Is assistance or supervision essential for using the toilet?	○ Yes ○No	○ Yes ○No
c. Is assistance or supervision essential for routine daily hygiene?	○ Yes ○No	○ Yes ○No
d. Is assistance or supervision essential for walking?	○ Yes ○No	○ Yes ○No

3. Assistance or supervision to look after own affairs **over a 24 hour period**

	i. Now	ii. Before Encephalitis
a. Is assistance or supervision essential for preparing a simple meal?	○ Yes ○No	○ Yes ○No
b. Is assistance or supervision essential for basic household chores?	○ Yes ○No	○ Yes ○No
c. Is assistance or supervision essential for looking after household expenses?	○ Yes ○No	○ Yes ○No
d. Is assistance or supervision essential for local travel?	○ Yes ○No	○ Yes ○No
e. Is assistance or supervision essential for local shopping?	○ Yes ○No	○ Yes ○No

4. Usual Duties and activities

4.1 Work

a. Before encephalitis, was the person working or seeking work (or studying as a student), or able to if desired?		○ Yes ○No
b. Since the encephalitis, has there been a change in the person's ability to work or study?		○ Yes ○No
c. If yes, how restricted are they?	○ Reduced level of work	○ Currently unable to work

4.2 Family responsibility

a. Before encephalitis, was the person looking after family at home, or able to if desired?		○ Yes ○No
b. Since the encephalitis, has there been a change in their ability to look after family at home?		○ Yes ○No
c. If yes, how restricted are they?	○ Reduced responsibility for looking after family	○ Currently unable to look after family

4.3 Social and leisure activities

a. Before encephalitis, did the person have regular free-time activities, or were they able to have them if desired?	○ Yes ○No
b. Since encephalitis, has there been a change in their ability to participate in these activities?	○ Yes ○No
c. If yes, how restricted are they?	○ Participate a bit less: at least half as often as before the encephalitis.
	○ Participate much less: less than half as often.
	○ Unable to participate: rarely, if ever, take part.

Modified Rankin Scale Revisions

1. Constant Care

	i. Now	ii. Before Encephalitis
a. Is the person bedridden, incontinent, and requiring constant care?	○ Yes ○No	○ Yes ○No / Unknown

2. Assistance or supervision to attend to bodily needs/for walking **over a 24 hour period**

	i. Now	ii. Before Encephalitis
a. Is assistance or supervision essential for eating?	○ Yes ○No	○ Yes ○No / Unknown
b. Is assistance or supervision essential for using the toilet?	○ Yes ○No	○ Yes ○No / Unknown
c. Is assistance or supervision essential for routine daily hygiene?	○ Yes ○No	○ Yes ○No / Unknown
d. Is assistance or supervision essential for walking?	○ Yes ○No	○ Yes ○No / Unknown

3. Assistance or supervision to look after own affairs **over a 24 hour period**

	i. Now	ii. Before Encephalitis
a. Is assistance or supervision essential for preparing a simple meal?	○ Yes ○No	○ Yes ○No / Unknown
b. Is assistance or supervision essential for basic household chores?	○ Yes ○No	○ Yes ○No / Unknown
c. Is assistance or supervision essential for looking after household expenses?	○ Yes ○No	○ Yes ○No / Unknown
d. Is assistance or supervision essential for local travel?	○ Yes ○No	○ Yes ○No / Unknown
e. Is assistance or supervision essential for local shopping?	○ Yes ○No	○ Yes ○No / Unknown

4.4 Family and Friendships

a. Before encephalitis was the patient able to maintain social relationships and friendships?	○ Yes / Unknown	○No
b. Since the encephalitis, has there been a reduction in the patient's ability to maintain social relationships and friendships?	○ Yes	○No
c. If yes, what is the extent of disruption/strain?	○ Occasional- less than weekly	
	○ Frequent- once a week or more, but tolerable	
	○ Constant- daily & intolerable	

5. Symptoms as a result of the encephalitis

a. Does the patient have **any new or worsening** symptoms resulting from encephalitis?		○ Yes ○No
Symptom Checklist	i. Now	ii. Before Encephalitis
b. Does the person have difficulty reading or writing?	○ Yes ○No	○ Yes ○No / Unknown
c. Does the person have difficulty speaking or finding the right word?	○ Yes ○No	○ Yes ○No / Unknown
d. Does the person have problems with balance or coordination?	○ Yes ○No	○ Yes ○No / Unknown
e. Does the person have visual problems?	○ Yes ○No	○ Yes ○No / Unknown
f. Does the person have numbness (face, arms, legs, hands, feet)?	○ Yes ○No	○ Yes ○No / Unknown
g. Has the person experienced loss of movement (face, arms, legs, hands, feet)?	○ Yes ○No	○ Yes ○No / Unknown
h. Does the person have difficulty with swallowing?	○ Yes ○No	○ Yes ○No / Unknown
i. Any other symptoms? (Please record:)	○ Yes ○No	○ Yes ○No / Unknown

C.

1. Rankin Grade= _____

Modified Rankin Scale Training

- Revised training
- Certification
  - Requires score of 80% or better for approval
  - 1 chance to re-test
- Adjudication available

The participant has been discharged from inpatient hospital and continues their recovery at an inpatient rehabilitation facility. They are able to verbalize their needs and are working on managing their activities of daily living with occupational therapy but are unable to manage personal hygiene independently. They are able to walk without physical assistance but cannot navigate around obstacles without assistance.

The participant has been discharged from the hospital and is residing with a caregiver. They are able to ambulate unassisted and toilet and bathe independently. They are able to feed themselves but require supervision to ensure they do not put too much food into their mouth. They require reminders to eat and drink and if they were left alone would not be able to prepare their own food.

Updates for EU Sites

Local and Central Labs

- Original development
  - EU and US sites would use same local and central lab forms
- Reason for Modification
  - Change of process for EU sites prior to activation
  - New EU Specific forms created
    - Expanded local labs
    - Reduced central labs
- Unit updates
  - Units at EU sites changed

Local and Central Labs

1. Was whole blood drawn for Flow cytometry (B cell count and cell subsets)? (all) ○ Yes ○ No
   a. Date of Collection: __ __/__ __/ __ __ __ __ (mm/dd/yyyy)
   b. Time of Collection: __ __ : __ __ (24 hour clock)
2. Was blood drawn for Inebilizumab concentration PK pre dose? (v2, v3) ○ Yes ○ No
   a. Date of Collection: __ __/__ __/ __ __ __ __ (mm/dd/yyyy)
   b. Time of Collection: __ __ : __ __ (24 hour clock)
3. Was blood drawn for Inebilizumab concentration PK 15 minutes post dose? (v2, v3) ○ Yes ○ No
   a. Date of Collection: __ __/__ __/ __ __ __ __ (mm/dd/yyyy)
   b. Time of Collection: __ __ : __ __ (24 hour clock)
4. Was blood drawn for Inebilizumab concentration PK? (v5-v11) ○ Yes ○ No
   a. Date of Collection: __ __/__ __/ __ __ __ __ (mm/dd/yyyy)
   b. Time of Collection: __ __ : __ __ (24 hour clock)
5. Was blood drawn for Inebilizumab ADA? (v1, v6, v9, v11, v14-v16) ○ Yes ○ No
   a. Date of Collection: __ __/__ __/ __ __ __ __ (mm/dd/yyyy)
   b. Time of Collection: __ __ : __ __ (24 hour clock)

1. Was blood drawn for Hematology to be sent to the central lab? (v3, v5-v11) ○ Yes ○ No
   a. Date of Collection: __ __/__ __/ __ __ __ __ (mm/dd/yyyy)
   b. Time of Collection: __ __ : __ __ (24 hour clock)
2. Was blood drawn for Chemistry to be sent to the central lab? (v3, v5-v11) ○ Yes ○ No
   a. Date of Collection: __ __/__ __/ __ __ __ __ (mm/dd/yyyy)
   b. Time of Collection: __ __ : __ __ (24 hour clock)
3. Was blood drawn for HbA1c? (v2, v3, v5-v11) ○ Yes ○ No
   a. Date of Collection: __ __/__ __/ __ __ __ __ (mm/dd/yyyy)
   b. Time of Collection: __ __ : __ __ (24 hour clock)
4. Was blood drawn for IgM, IgG, IgA, IgE? (v1, v9, v11, v14-v16) ○ Yes ○ No
   a. Date of Collection: __ __/__ __/ __ __ __ __ (mm/dd/yyyy)
   b. Time of Collection: __ __ : __ __ (24 hour clock)
5. Was whole blood drawn for Flow cytometry (B cell count and cell subsets)? (all) ○ Yes ○ No
   a. Date of Collection: __ __/__ __/ __ __ __ __ (mm/dd/yyyy)
   b. Time of Collection: __ __ : __ __ (24 hour clock)
6. Was blood drawn for Serum Pregnancy to be sent to the central lab? (v1, v5) ○ Yes ○ No
   a. Date of Collection: __ __/__ __/ __ __ __ __ (mm/dd/yyyy)
   b. Time of Collection: __ __ : __ __ (24 hour clock)
7. Was blood drawn for Hep B Surface Antigen, Hep B Core Antigen, HCV, HIV 1/2? (v1) ○ Yes ○ No
   a. Date of Collection: __ __/__ __/ __ __ __ __ (mm/dd/yyyy)
   b. Time of Collection: __ __ : __ __ (24 hour clock)
8. Was blood drawn for CD4? (v1) ○ Yes ○ No
   a. Date of Collection: __ __/__ __/ __ __ __ __ (mm/dd/yyyy)
   b. Time of Collection: __ __ : __ __ (24 hour clock)
9. Was blood drawn for Inebilizumab concentration PK pre dose? (v2, v3) ○ Yes ○ No
   a. Date of Collection: __ __/__ __/ __ __ __ __ (mm/dd/yyyy)
   b. Time of Collection: __ __ : __ __ (24 hour clock)
10. Was blood drawn for Inebilizumab concentration PK 15 minutes post dose? (v2, v3) ○ Yes ○ No
    a. Date of Collection: __ __/__ __/ __ __ __ __ (mm/dd/yyyy)
    b. Time of Collection: __ __ : __ __ (24 hour clock)
11. Was blood drawn for Inebilizumab concentration PK? (v5-v11) ○ Yes ○ No
    a. Date of Collection: __ __/__ __/ __ __ __ __ (mm/dd/yyyy)
    b. Time of Collection: __ __ : __ __ (24 hour clock)
12. Was blood drawn for Inebilizumab ADA? (v1, v6, v9, v11, v14-v16) ○ Yes ○ No
    a. Date of Collection: __ __/__ __/ __ __ __ __ (mm/dd/yyyy)
    b. Time of Collection: __ __ : __ __ (24 hour clock)
13. Was blood drawn for Serum for anti-NMDA receptor antibody titers? (v1, v6, v9, v11) ○ Yes ○ No
    a. Date of Collection: __ __/__ __/ __ __ __ __ (mm/dd/yyyy)
    b. Time of Collection: __ __ : __ __ (24 hour clock)
14. Was blood drawn for Whole blood gene expression? (v1, v5, v7, v11, v13-v16) ○ Yes ○ No
    a. Date of Collection: __ __/__ __/ __ __ __ __ (mm/dd/yyyy)
    b. Time of Collection: __ __ : __ __ (24 hour clock)
15. Was blood drawn for Serum for exploratory biomarkers? (v1, v3, v5-v11) ○ Yes ○ No
    a. Date of Collection: __ __/__ __/ __ __ __ __ (mm/dd/yyyy)
    b. Time of Collection: __ __ : __ __ (24 hour clock)
16. Was blood drawn for Serum for oligoclonal bands? (v1, v6, v9) ○ Yes ○ No
    a. Date of Collection: __ __/__ __/ __ __ __ __ (mm/dd/yyyy)
    b. Time of Collection: __ __ : __ __ (24 hour clock)

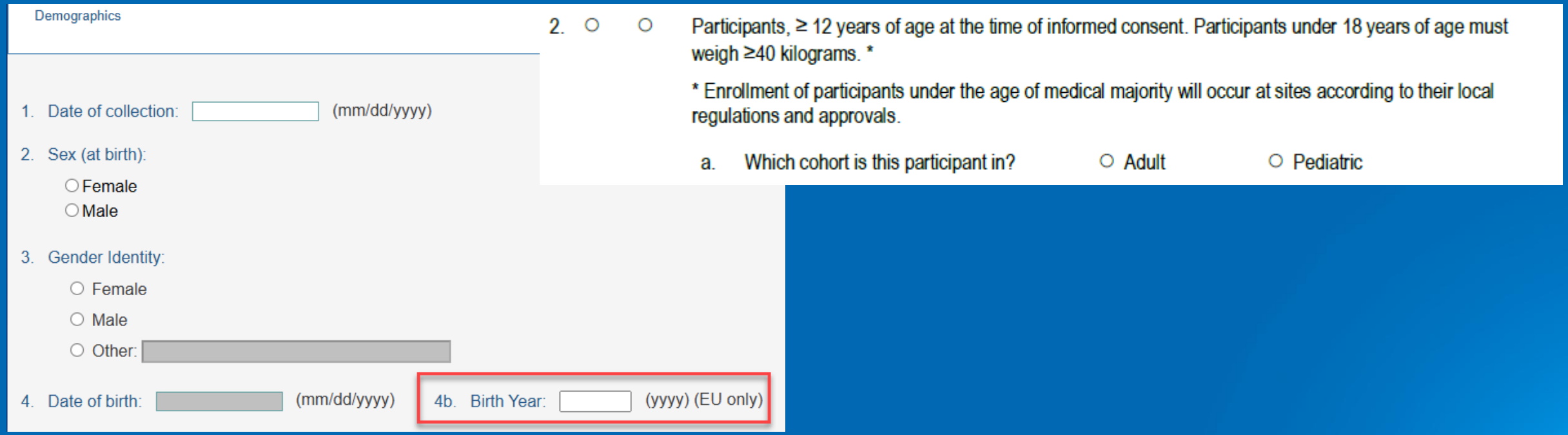
Central Pharmacy module

- Modification to drug dispensing system
  - Originally built to match NN Central Pharmacy processes
  - Accommodate 2 groups of central users that service different study sites
    - Separate IP Codes
    - Isolated access by region
    - Separate automated reminders

Updates for Added Pediatric Cohort

Pediatric Cohort added to protocol

- Demographics updated to capture Birth year for EU sites
- Added Stratification for pediatric participants



Demographics

1. Date of collection: (mm/dd/yyyy)
2. Sex (at birth):
   - Female
   - Male
3. Gender Identity:
   - Female
   - Male
   - Other:
4. Date of birth: (mm/dd/yyyy)

4b. Birth Year: (yyyy) (EU only)

2. Participants, ≥ 12 years of age at the time of informed consent. Participants under 18 years of age must weigh ≥40 kilograms. *

* Enrollment of participants under the age of medical majority will occur at sites according to their local regulations and approvals.

a. Which cohort is this participant in? Adult Pediatric

Acknowledgments

- NINDS
- NN111 Study Team

Monitoring and Safety Challenges in an International Anti-NMDA Receptor Encephalitis Trial

SCT | 47TH ANNUAL MEETING

Disclosures

- I have no disclosures

Why Safety Oversight was Uniquely Complex

🧠 **Acute, Rapidly Evolving Neurologic Illness**
- Clinical status and safety signals could change within hours

🏥 **Critically Ill, Often Incapacitated Participants**
- Limited ability for symptom reporting and real-time assessments

🧩 **Rare Disease with Heterogeneous Presentation**
- Wide variability in severity and manifestations complicated signal attribution

🌎 **International, Multi-Regulatory Environment**
- Required coordination across global health authorities and reporting standards

🛡️ **Immunosuppressive Investigational Therapy**
- Elevated infection risk with overlap between drug- and disease-related effects

Monitoring in Acute Care Setting

- ICU and inpatient neurology enrollment
- Rapid clinical deterioration or improvement
- Frequent desire for off-protocol rescue therapies required continuous site education
- Sedation and limited off-hour staffing obscuring neurologic change and protocol execution
- Unpredictable deterioration or improvement complicating timing and assessments

Safety & Monitoring Challenges: 4 High Risk Areas

- Encephalitis trials present unique monitoring and safety complexities due to acute neurologic illness and rapid clinical changes.
    1. Eligibility Review: real time eligibility checklist
    2. AE and SAE identification and reporting
    3. Administration of second dose of study drug in setting of intercurrent infection
    4. Relapse Adjudication

Role of the Medical Safety Monitor (MSM)

- Independent encephalitis clinical expert providing unbiased safety oversight
  - Evaluation of eligibility per protocol
  - Real-time review of SAEs and Grade 3 AEs to support timely clinical decision-making
  - Contextual clinical interpretation distinguishing disease activity from safety signals
  - Relapse Adjudication

Eligibility Worksheet for Clinical Sites

Eligibility Worksheet (Optional) Page 1 of 6

Neuro NEXT

Visit Date: __ __ / __ __ / __ __ __ __ (mm/dd/yyyy)

Visit Name : _____

NN111

Subject ID: __ __ __ - __ __ __ __ Subject initials: __ __ __

1. Date of Collection: __ __ / __ __ / __ __ __ __ (mm/dd/yyyy)

A. Study Inclusion Criteria

To be considered eligible for the study, participants must meet the following criteria:

	No	Yes	Unknown	
1.	○	○	○	Diagnosis of NMDAR encephalitis, defined by both a and b: a. A subacute onset of change in mental status consistent with autoimmune encephalitis, b. A positive cell-based assay for anti-NMDA receptor IgG antibody in the CSF confirmed in study-specified laboratories.
2.	○	○	○	Participants, ≥ 12 years of age at the time of informed consent. Participants under 18 years of age must weigh ≥40 kilograms. * * Enrollment of participants under the age of medical majority will occur at sites according to their local regulations and approvals.
3.	○	○	○	Written informed consent and any locally required authorization (e.g., Health Insurance Portability and Accountability Act [HIPAA] in the United States of America [USA], European Union [EU] Data Privacy Directive in the EU) obtained from the participant/legal representative prior to performing any protocol-related procedures, including screening evaluations.
4.	○	○	○	Non-sterilized participants who are sexually active with a partner capable of becoming pregnant must

Eligibility Worksheet (Optional) Page 2 of 6

Neuro NEXT

Visit Date: __ __ / __ __ / __ __ __ __ (mm/dd/yyyy)

Visit Name : _____

NN111

Subject ID: __ __ __ - __ __ __ __ Subject initials: __ __ __

contraception for study purposes. Acceptable methods of contraception are listed in the table below:

Physical Methods	Hormonal Methods [e]
• Intrauterine device (IUD) • Intrauterine hormone-releasing system, also known as drug-eluting IUD [a] • Bilateral tubal occlusion • Vasectomized partner [b] • Sexual abstinence [c]	• Combined (estrogen and progestogen-containing hormonal contraception) • Oral (combined pill) • Injectable • Transdermal (patch) • Progestogen-only hormonal contraception associated with inhibition of ovulation [d] • Implantable • Intravaginal

a This is also considered to be a hormonal method.
b With appropriate post-vasectomy documentation of surgical success (absence of sperm in ejaculate).
c Sexual abstinence is considered to be a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of the study and if it is the preferred and usual lifestyle of the participant.
d Progestogen-only hormonal contraception, where inhibition of ovulation is not the primary mode of action (minipill) is not accepted as a highly effective method.
e. These methods are only considered highly effective and therefore acceptable when used in conjunction with a barrier method (i.e., diaphragm with spermicide, sponge with spermicide, cervical cap with spermicide, condoms, spermicide alone.)

5.	○	○	○	Willing to forgo other immunomodulatory therapies (investigational or otherwise) for NMDAR encephalitis during the study.
6.	○	○	○	Participant must have received at least 3 days of methylprednisolone 1000 mg IV or equivalent

Eligibility Worksheet for Sites

NeuroNEXT

NN111

Visit Date:__ __ / __ __ / __ __ __ __ (mm/dd/yyyy)

Visit Name : _____

Subject ID: __ __ __ - __ __ __ __Subject initials: __ __ __

recurrent or severe infections in the preceding 6 months and have normal tetanus or haemophilus influenzae titers. Final adjudication of this eligibility criteria will be made by the central study team with input from the MSM.

14. ○ ○ ○ Active hepatitis B or C established with positive hepatitis B serology (hepatitis B surface antigen **and** core antibody) and/or positive hepatitis C PCR testing and confirmed by the MSM

15. ○ ○ ○ Any live or attenuated vaccine within 4 weeks prior to Day 1 (administration of killed vaccines is acceptable).

16. ○ ○ ○ Bacillus of Calmette and Guérin (BCG) vaccine within 1 year of enrollment.

17. ○ ○ ○ History of alcohol or drug abuse that, in the opinion of the Investigator, might affect participant safety or compliance with visits or interfere with safety or other study assessments.

18. ○ ○ ○ Recurrence of previously treated NMDAR encephalitis within the last 5 years, or suspicion of symptomatic untreated NMDAR encephalitis of greater than 3 months duration at the time of screening.

19. ○ ○ ○ Evidence of active tuberculosis* (TB) or being at high risk for TB based on:

   a. History of active TB or untreated/incompletely treated latent TB. Participants with a history of active or latent TB who have documentation of completion of treatment according to local guidelines may be enrolled.

   b. History of recent (≤ 12 weeks of screening) close contact with someone with active TB (close contact is defined as ≥ 4 hours/week OR living in the same household OR in a house where a person with active TB is a frequent visitor).

   c. Signs or symptoms that could represent active TB by medical history or physical examination.

   d. Positive, indeterminate, or invalid interferon-gamma release assay test result at screening, unless previously treated for TB. Participants with an indeterminate test result must have their clinical history, including any relevant imaging, reviewed by the MSM to confirm there are no concerns of active or latent TB that would preclude enrollment.

   e. Chest radiograph, chest computed tomography or MRI scan that suggests a possible diagnosis of TB or suggests that a work-up for TB should be considered; all participants must have had lung imaging with an acceptable reading within 6 months prior to consent, or during screening.

20. ○ ○ ○ Active, clinically significant (CS) infection at the time of randomization (IP administration may be

NeuroNEXT

NN111

Visit Date:__ __ / __ __ / __ __ __ __ (mm/dd/yyyy)

Visit Name : _____

Subject ID: __ __ __ - __ __ __ __Subject initials: __ __ __

C. Eligibility Status

	No	Yes	
1.	○	○	Is it expected that the subject may meet inclusion/exclusion criteria in the next 7 days?

a. Please explain: _____

_____

_____

_____ _____

Investigator's Signature **Date of Signature** (mm/dd/yyyy)

The following criteria are not necessarily exclusionary but require review from the MSM to determine if a participant should be excluded due to safety concerns:

1. At screening (out of range lab values may be reviewed with the MSM to determine whether a potential participant should be excluded for safety reasons; repeat testing may be conducted to confirm results within the same screening period, prior to randomization), any of the following:

   a. Aspartate transaminase (AST) > 2.5 × age-based upper limit of normal (ULN)

   b. Alanine transaminase (ALT) > 2.5 × age-based ULN

   c. Total bilirubin > 1.5 × age-based ULN (unless due to Gilbert's syndrome)

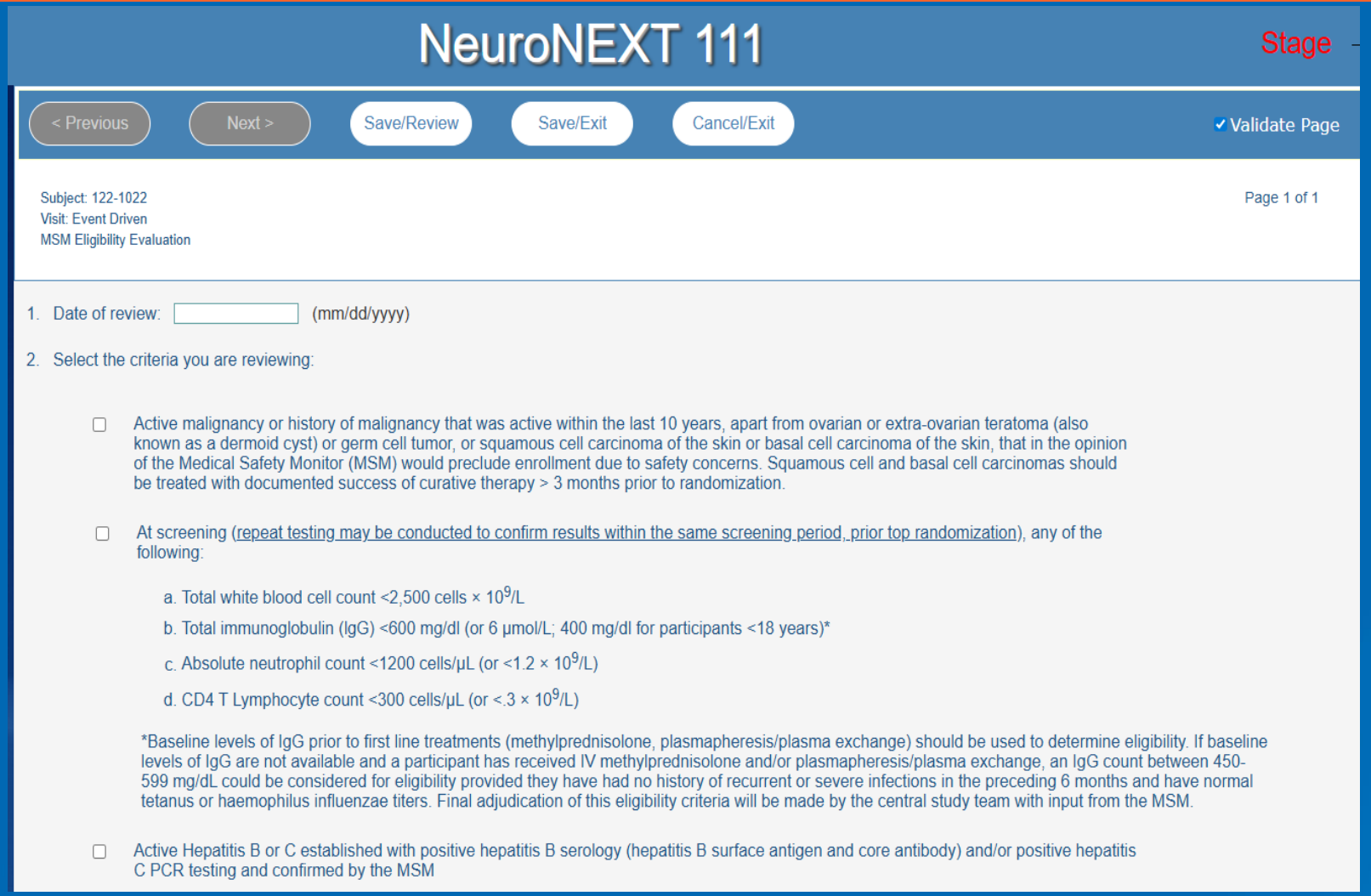
   d. Platelet count < 75,000/μL (or < 75 × 10^9/L)

   e. Hemoglobin < 8 g/dL (or < 80 g/L or 5 mmol/L)

2. History of untreated hepatitis C infection. Participants who are considered cured following antiviral therapy with an HCV load below the limit of detection may be enrolled pending confirmation from the MSM that there are no safety concerns for inclusion.

3. Patients with coexistent autoantibodies should not immediately be excluded but should be reviewed with the MSM

MSM Eligibility Review



NeuroNEXT 111

Stage –

< Previous | Next > | Save/Review | Save/Exit | Cancel/Exit | ☑ Validate Page

Subject: 122-1022
Visit: Event Driven
MSM Eligibility Evaluation

Page 1 of 1

1. Date of review: _____ (mm/dd/yyyy)

2. Select the criteria you are reviewing:

☐ Active malignancy or history of malignancy that was active within the last 10 years, apart from ovarian or extra-ovarian teratoma (also known as a dermoid cyst) or germ cell tumor, or squamous cell carcinoma of the skin or basal cell carcinoma of the skin, that in the opinion of the Medical Safety Monitor (MSM) would preclude enrollment due to safety concerns. Squamous cell and basal cell carcinomas should be treated with documented success of curative therapy > 3 months prior to randomization.

☐ At screening (repeat testing may be conducted to confirm results within the same screening period, prior top randomization), any of the following:

a. Total white blood cell count <2,500 cells × 10^9/L
b. Total immunoglobulin (IgG) <600 mg/dl (or 6 µmol/L; 400 mg/dl for participants <18 years)*
c. Absolute neutrophil count <1200 cells/µL (or <1.2 × 10^9/L)
d. CD4 T Lymphocyte count <300 cells/µL (or <.3 × 10^9/L)

*Baseline levels of IgG prior to first line treatments (methylprednisolone, plasmapheresis/plasma exchange) should be used to determine eligibility. If baseline levels of IgG are not available and a participant has received IV methylprednisolone and/or plasmapheresis/plasma exchange, an IgG count between 450-599 mg/dL could be considered for eligibility provided they have had no history of recurrent or severe infections in the preceding 6 months and have normal tetanus or haemophilus influenzae titers. Final adjudication of this eligibility criteria will be made by the central study team with input from the MSM.

☐ Active Hepatitis B or C established with positive hepatitis B serology (hepatitis B surface antigen and core antibody) and/or positive hepatitis C PCR testing and confirmed by the MSM

MSM Eligibility Review

☐ Evidence of active tuberculosis* (TB) or being at high risk for TB based on:

a. History of active TB or untreated/incompletely treated latent TB. Participants with a history of active or latent TB who have documentation of completion of treatment according to local guidelines may be enrolled.

b. History of recent (≤ 12 weeks of screening) close contact with someone with active TB (close contact is defined as ≥ 4 hours/week OR living in the same household OR in a house where a person with active TB is a frequent visitor).

c. Signs or symptoms that could represent active TB by medical history or physical examination.

d. Positive, indeterminate, or invalid interferon-gamma release assay test result at screening, unless previously treated for TB. Participants with an indeterminate test result must have their clinical history, including any relevant imaging, reviewed by the MSM to confirm there are no concerns of active or latent TB that would preclude enrollment

e. Chest radiograph, chest computed tomography or MRI scan that suggests a possible diagnosis of TB or suggests that a work-up for TB should be considered; all participants must have had lung imaging with an acceptable reading within 6 months prior to consent, or during screening.

The following criteria are not necessarily exclusionary but require review from the Medical Safety Monitor (MSM) to determine if a participant should be excluded due to safety concerns:

☐ At screening (out of range lab values may be reviewed with the MSM to determine whether a potential participant should be excluded for safety reasons; repeat testing may be conducted to confirm results within the same screening period, prior to randomization), any of the following:

a. Aspartate transaminase (AST) > 2.5 x age-based upper limit of normal (ULN)

b. Alanine transaminase (ALT) > 2.5 x age-based ULN

c. Total bilirubin > 1.5 x age-based ULN (unless due to Gilbert's syndrome)

d. Platelet count < 75,000/μL (or < 75 x 10^9/L)

e. Hemoglobin < 8 g/dL (or < 80 g/L or 5 mmol/L)

☐ History of untreated hepatitis C infection. Participants who are considered cured following antiviral therapy with an HCV load below the limit of detection may be enrolled pending confirmation from the MSM that there are no safety concerns for inclusion.

☐ Patients with coexistent autoantibodies should not immediately be excluded but should be reviewed with the MSM to determine eligibility

3. In your opinion should this participant be allowed to randomize?

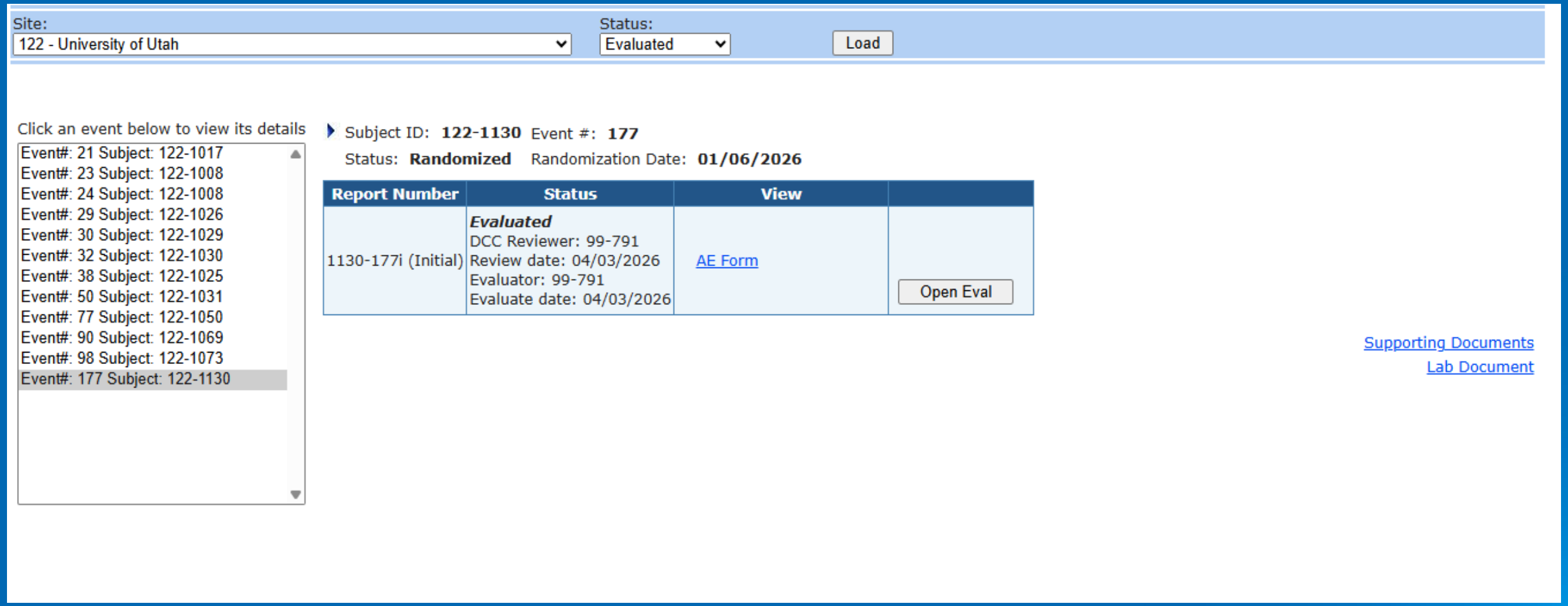
○ Yes
○ No

4. Please explain:

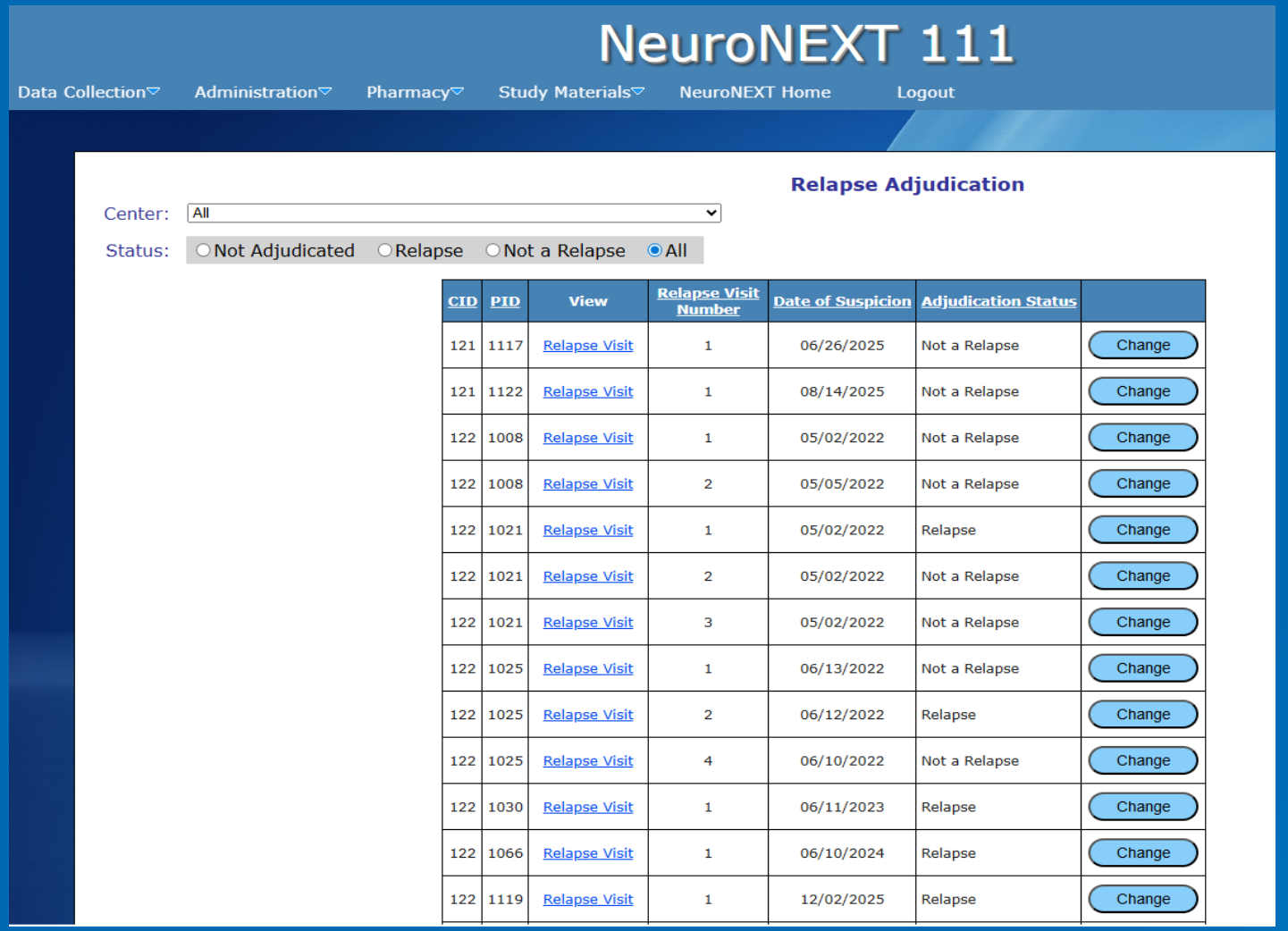
Defining “Expected” vs “Unexpected”

- Attribution Challenges in Acute Neurologic Trials
- Disease manifestations mimic adverse events, complicating causality assessment
- High baseline rates of seizures, dysautonomia, and infection obscure treatment signals
- ICU-related complications overlap with reportable safety events
- Neuropsychiatric symptoms intersect with protocol AE definitions

MSM Adverse Event Review System (AERS)



Relapse Adjudication



CID	PID	View	Relapse Visit Number	Date of Suspicion	Adjudication Status	
121	1117	Relapse Visit	1	06/26/2025	Not a Relapse	Change
121	1122	Relapse Visit	1	08/14/2025	Not a Relapse	Change
122	1008	Relapse Visit	1	05/02/2022	Not a Relapse	Change
122	1008	Relapse Visit	2	05/05/2022	Not a Relapse	Change
122	1021	Relapse Visit	1	05/02/2022	Relapse	Change
122	1021	Relapse Visit	2	05/02/2022	Not a Relapse	Change
122	1021	Relapse Visit	3	05/02/2022	Not a Relapse	Change
122	1025	Relapse Visit	1	06/13/2022	Not a Relapse	Change
122	1025	Relapse Visit	2	06/12/2022	Relapse	Change
122	1025	Relapse Visit	4	06/10/2022	Not a Relapse	Change
122	1030	Relapse Visit	1	06/11/2023	Relapse	Change
122	1066	Relapse Visit	1	06/10/2024	Relapse	Change
122	1119	Relapse Visit	1	12/02/2025	Relapse	Change

Safety Monitoring Challenges: 4 High Risk Areas

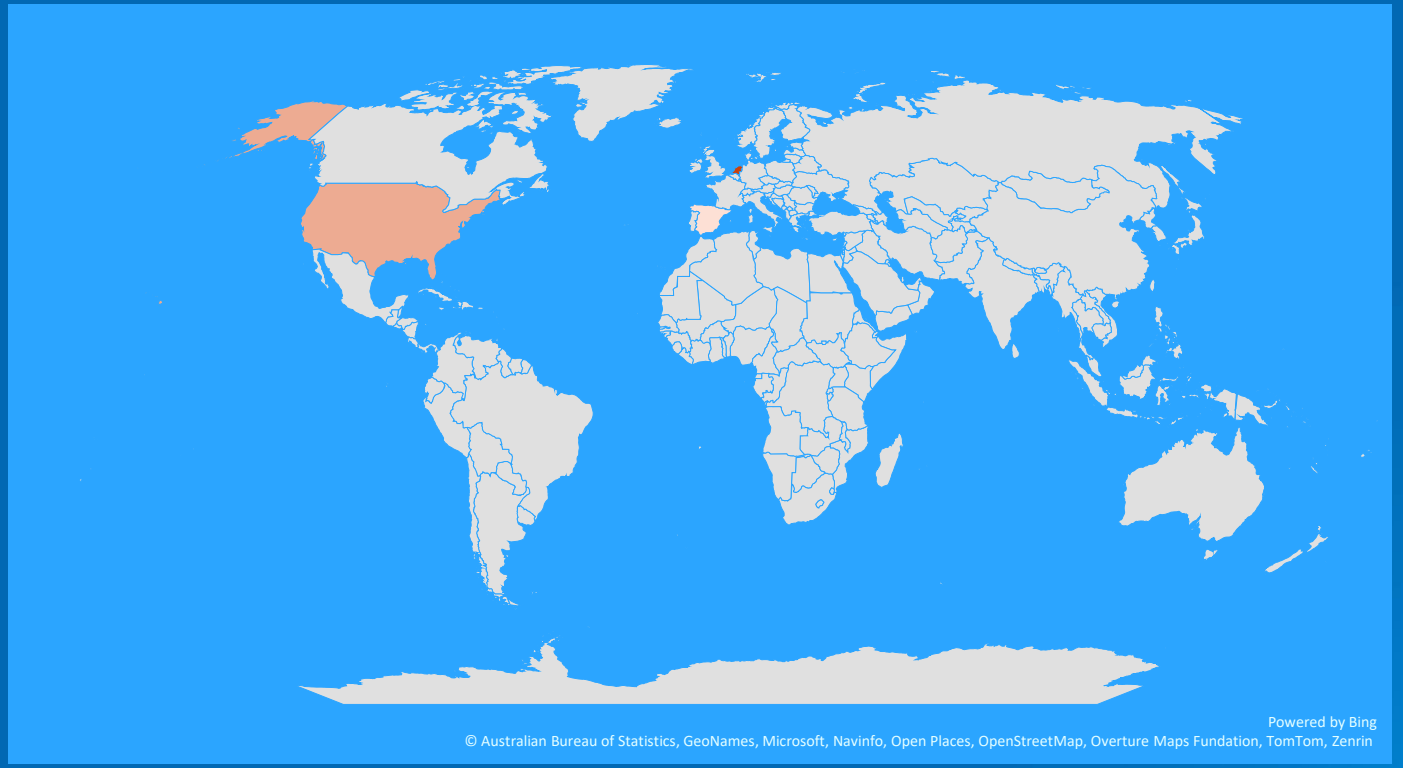
- Encephalitis trials present unique monitoring complexities due to acute neurologic illness and rapid clinical changes.
    1. Eligibility Review: real time eligibility checklist
    2. AE and SAE identification and reporting
    3. Relapse Adjudication
    4. Administration of second dose of study drug in setting of intercurrent infection

From Infrastructure to Implementation

- From Safety Infrastructure to Monitoring in Practice
  - Embedding safety expectations into site workflows
  - Reinforcing interpretation via Monitoring + MSM oversight
  - Detecting gaps between data entry and clinical reality
  - Aligning global sites with consistent safety reporting behavior

Monitoring Plans

- Three Plans Three Countries
  - U.S. Sites
  - Rotterdam Netherlands
  - Barcelona Spain



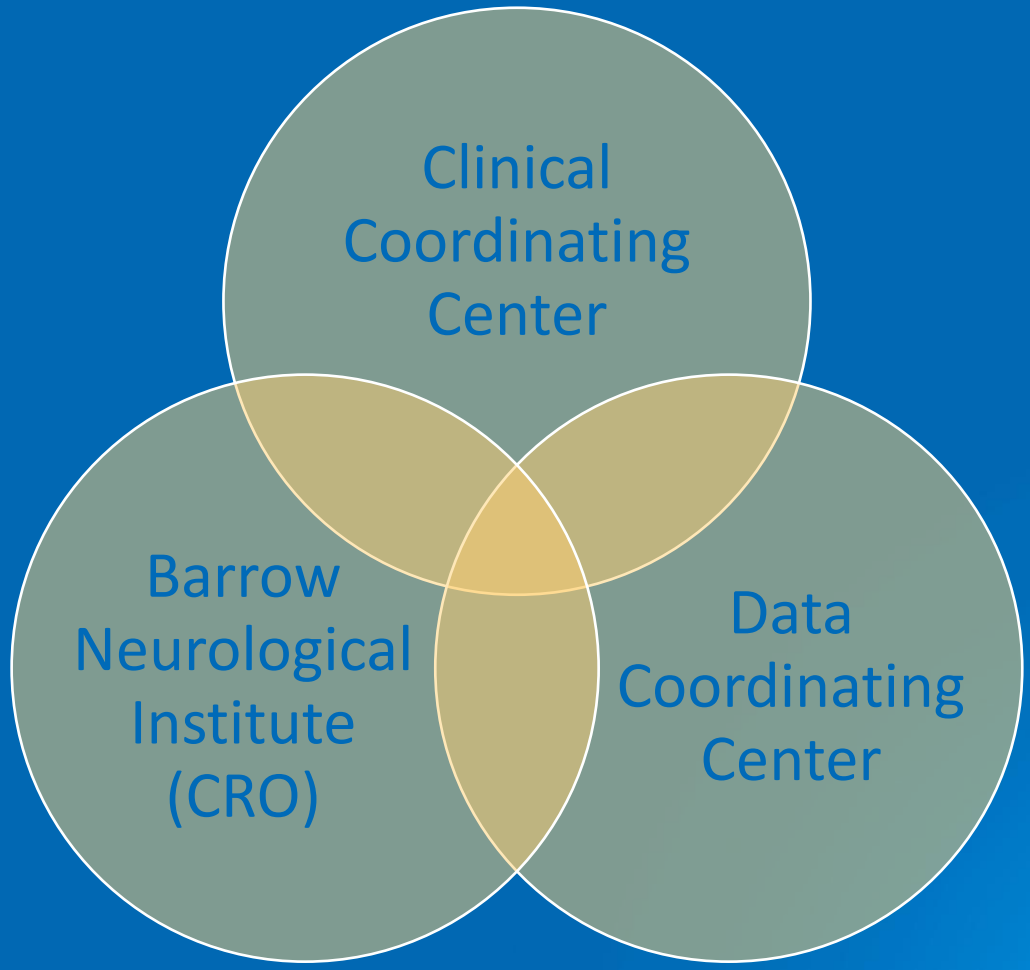
Similarities and Differences

- Plans Aligned Scientifically
- Common Monitoring activities
- Structured Visits
- Track Findings

- Monitoring Plan
  - Comprehensive
  - Site Level
- Organization Context
  - Split across 3 entities
  - Clinical Trial Unit
- Site Design
  - Multi Center
  - Single Center
- Frequency
  - 12-18 months
  - At least 2/year

Clinical Trial Monitoring

- Regulatory Document Compliance
- On-Site Monitoring
- Unblinded Monitoring
  - Investigational/Pharmacy monitoring
- Central/Remote Monitoring



Regulatory Document Monitoring

- Human Subjects Protection and Good Clinical Practice Training
- Licensure (Medical, Pharmacy)
- Curriculum Vitae
- Training Certifications and Attestations
- Protocol Signature Pages
- FDA Form 1572
- Conflict of Interest Forms and Financial Disclosures
- Delegation Logs

Clinical Data Monitoring Adaptations

- Risk-based, event driven monitoring
- Emphasis on safety-critical data
- Increased central review
- Near real-time data surveillance
- Local and Central Lab case report forms
- Language and documentation differences
- Time-zone differences

Key Takeaways

🧠 **Safety monitoring is uniquely complex**
Acute neurologic illness, ICU care, and overlapping disease vs. treatment signals demand constant vigilance

⚠️ **Four critical risk areas**
Eligibility review, AE/SAE detection, relapse adjudication, and dosing during intercurrent illness

👩‍⚕️ **Medical Safety Monitor (MSM) is essential**
Real-time expert review ensures consistent, accurate safety decisions across sites

🔗 **Success depends on integration**
Embedding safety into workflows + combining site monitoring with centralized oversight

🌎 **International trials add complexity—but are manageable**
Alignment across regulatory frameworks and reporting standards is achievable

Acknowledgments and Thank You

- Participants and Caregivers
- Clinical Study Sites and our NN111 Study Team
- Colleagues at the DCC, CCC, BNI
- NINDS