Data Management 101

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NINDS Clinical Trials Methodology Course

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Why is data management important?

- GCP = how we need to do things
- Study design = how we plan to do things
- Trial operations = we do what was planned
- Data management = we record what was done
- Final analysis = we analyze and validate our analysis
- **A break down in any of these steps can lead to a failed trial!**

Types of data problems in clinical trials

- Data collection not done – missing data
- Data collection done incorrectly – intentional or unintentional
- Data not verified

How do we avoid these problems?

- Build robust data collection tools
- Keep it simple
- Only collect the data that you need for the analysis
- Don't ask the same question twice
- Test the system
- Think like a coordinator
- The EDC is your "nanny" … sort of!

Case Report Form Development

- In person meeting
- Start with standardized language
  - NINDS Common Data Elements (CDEs)
  - Federal Interagency Traumatic Brain Injury Research (FITBIR)
  - National Database for Autism Research (NDAR)
  - Clinical Data Interchange Standards Consortium (CDISC)

Case Report Form Development

- Make data questions clear and concise
- Create multiple choice questions with sound logic
- Use skip outs to reduce data errors
- Minimize open text fields
- Use real-time validation to prevent errors
- Use standardized CRFs to avoid errors

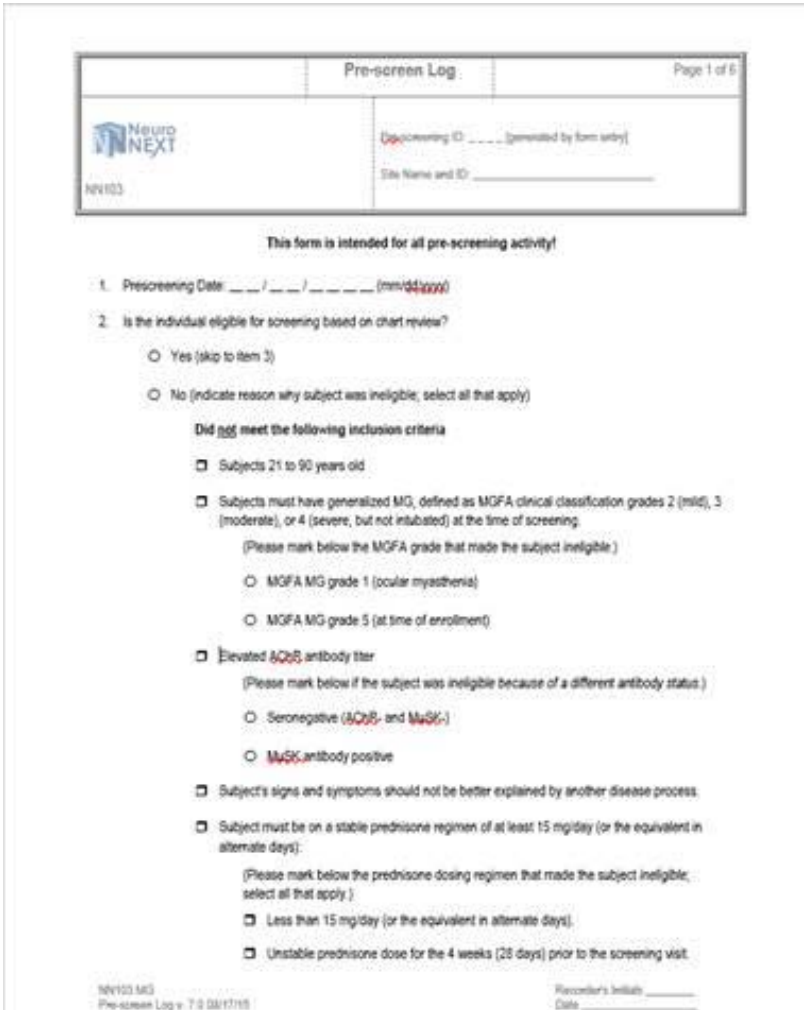
Ask good questions

- Q1: Baseline blood pressure <140/90?
  - What is the purpose of the question?
    - Eligibility? Safety?
  - What if BP is 138/90? Or 152/74?
- Better way to capture BP data would be:
  - Baseline blood pressure is ___/___mmHg

Defining Eligibility

- Original Criteria: Prednisone dose of at least 15 mg/day (or the equivalent in alternate days) and the subject must be on a stable dose of prednisone for 4 weeks prior to the screening visit.
  - Is 4 weeks a month?
    - Better to define time in days to avoid confusion
  - Patients are on other immunosuppressive therapy were not eligible
    - Did not anticipate major impact on overall study recruitment

Pre-Screening Log: Data Management Tool



Pre-screen Log

Page 1 of 6

NN103

Pre-screening ID: _____ [generated by form entry]

Site Name and ID: _____

This form is intended for all pre-screening activity!

1. Prescreening Date: __ __ / __ __ / __ __ __ __ (mm/dd/yyyy)
2. Is the individual eligible for screening based on chart review?
   - ○ Yes (skip to item 3)
   - ○ No (indicate reason why subject was ineligible; select all that apply)

Did not meet the following inclusion criteria

- ☐ Subjects 21 to 90 years old
- ☐ Subjects must have generalized MG, defined as MGFA clinical classification grades 2 (mild), 3 (moderate), or 4 (severe, but not intubated) at the time of screening.
  (Please mark below the MGFA grade that made the subject ineligible.)
  - ○ MGFA MG grade 1 (ocular myasthenia)
  - ○ MGFA MG grade 5 (at time of enrollment)
- ☐ Elevated AChR antibody titer
  (Please mark below if the subject was ineligible because of a different antibody status.)
  - ○ Seronegative (AChR- and MuSK-)
  - ○ MuSK antibody positive
- ☐ Subject's signs and symptoms should not be better explained by another disease process.
- ☐ Subject must be on a stable prednisone regimen of at least 15 mg/day (or the equivalent in alternate days).
  (Please mark below the prednisone dosing regimen that made the subject ineligible; select all that apply.)
  - ☐ Less than 15 mg/day (or the equivalent in alternate days).
  - ☐ Unstable prednisone dose for the 4 weeks (28 days) prior to the screening visit.

NN103-MG
Pre-screen Log v. 7.0 09/17/15

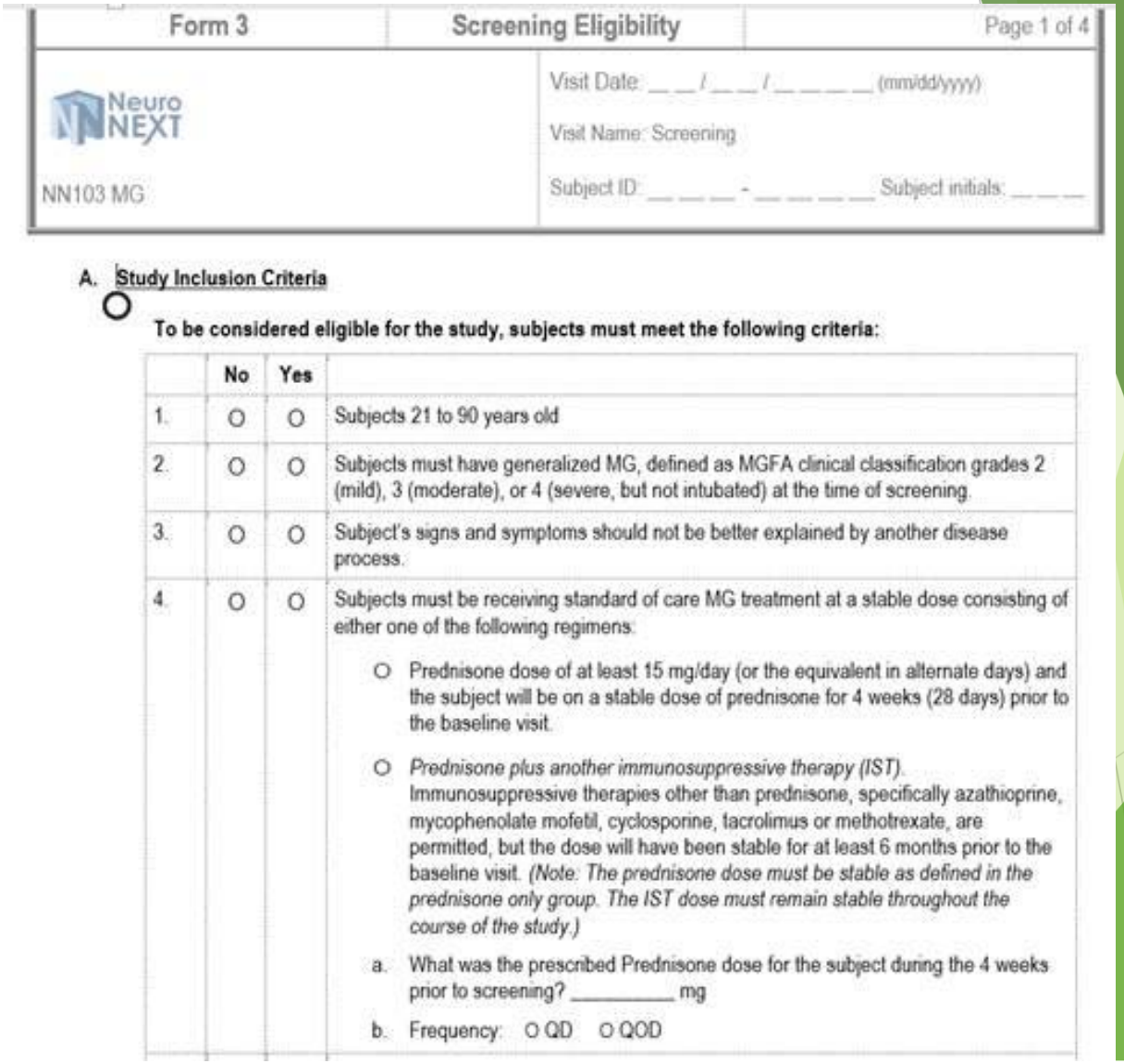
Recorder's Initials _____
Date _____

- Identified criteria for changes to improve recruitment – which required a major change to the protocol that required both IRB and DSMB review and approval and resulted in an additional sub-group analysis

Revised Criteria:

- *Prednisone only:* Prednisone dose must be at least 15mg/day (or the equivalent on alternate days), and the dose of prednisone must have been stable for at least 4 weeks (28 days) prior to the baseline visit.
- *Prednisone plus another immunosuppressive therapy (IST).* Immunosuppressive therapies other than prednisone, such as azathioprine, mycophenolate mofetil, cyclosporine, tacrolimus or methotrexate, are permitted, but the dose must have been stable for at least 6 months prior to the baseline visit.
- *(Note: The prednisone dose must be stable as defined in the prednisone only group. The IST dose must remain stable throughout the course of the study).*

EDC validates eligibility



Form 3	Screening Eligibility	Page 1 of 4
Neuro NEXT NN103 MG	Visit Date: __ __ / __ __ / __ __ __ __ (mm/dd/yyyy) Visit Name: Screening Subject ID: __ __ __ - __ __ __ __ Subject initials: __ __ __	

A. Study Inclusion Criteria

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

	No	Yes	
1.	O	O	Subjects 21 to 90 years old
2.	O	O	Subjects must have generalized MG, defined as MGFA clinical classification grades 2 (mild), 3 (moderate), or 4 (severe, but not intubated) at the time of screening.
3.	O	O	Subject's signs and symptoms should not be better explained by another disease process.
4.	O	O	Subjects must be receiving standard of care MG treatment at a stable dose consisting of either one of the following regimens: O Prednisone dose of at least 15 mg/day (or the equivalent in alternate days) and the subject will be on a stable dose of prednisone for 4 weeks (28 days) prior to the baseline visit. O *Prednisone plus another immunosuppressive therapy (IST).* Immunosuppressive therapies other than prednisone, specifically azathioprine, mycophenolate mofetil, cyclosporine, tacrolimus or methotrexate, are permitted, but the dose will have been stable for at least 6 months prior to the baseline visit. *(Note: The prednisone dose must be stable as defined in the prednisone only group. The IST dose must remain stable throughout the course of the study.)* a. What was the prescribed Prednisone dose for the subject during the 4 weeks prior to screening? _____ mg b. Frequency: O QD O QOD

Ask the questions in a way that you will get usable data

- How many years of education?
  - 12…13…15…16….
- Highest level of education completed?
  - Grade school
  - High school
  - Associate’s degree
  - Bachelor’s degree
  - Master’s degree…

Enhancing Data Quality

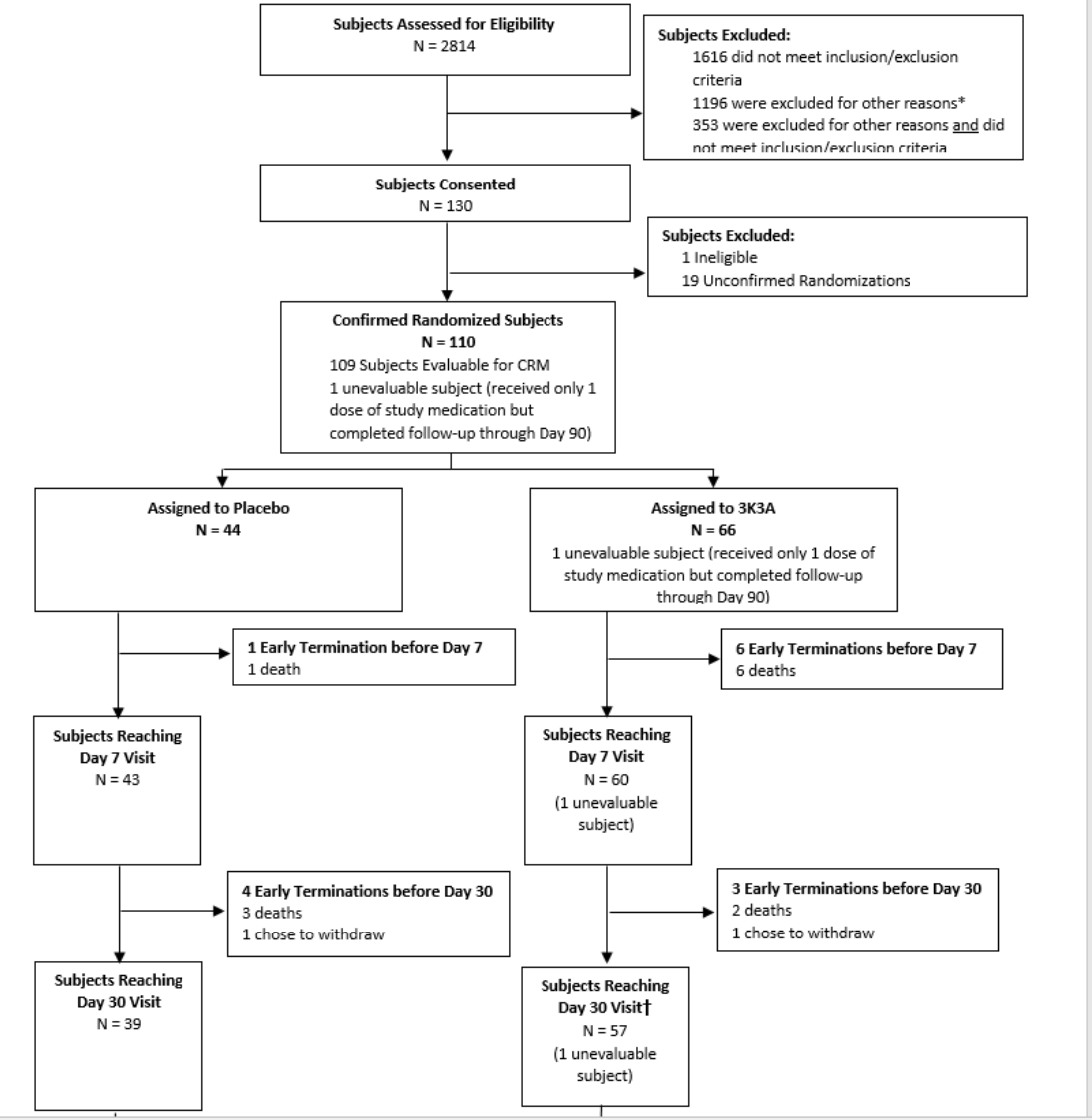
- Review protocol deviations and work to minimize
- Control protocol amendments and CRF changes
- Maximize the potential of the EDC and minimize the site work load
- Think about your CONSORT diagram from the beginning
  - CONsolidated Standards Of Reporting Trials – completeness of reporting of randomized controlled trials published in medical journals

Protocol amendments and CRF changes

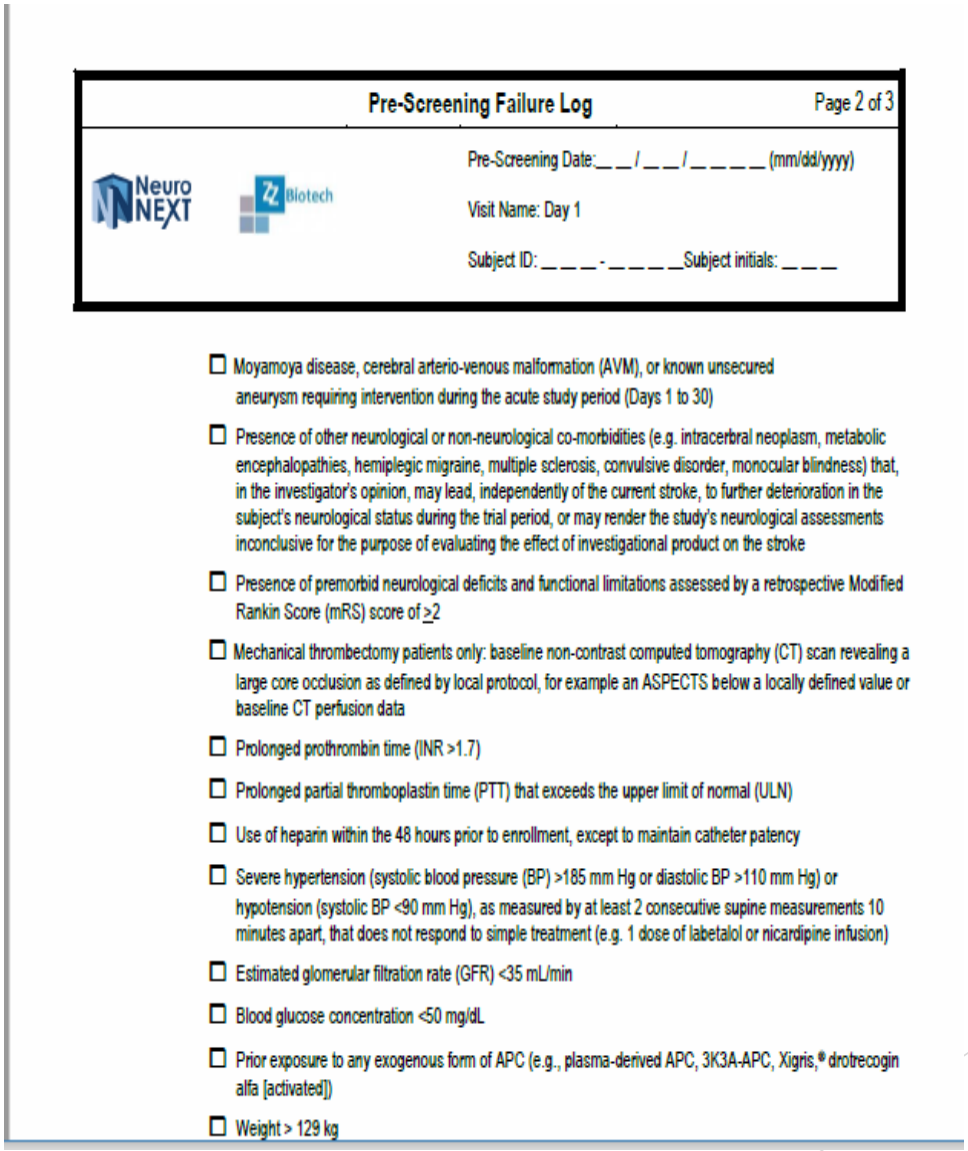
- Eligibility criteria may change
- Assessments and visit schedules may change
- Response options and/or validation rules may change

- General strategy
  - Consider cost/benefit ratio
  - If creating new data items, never delete old data
  - If options change, reassess previously collected data

Data management decisions that lead to the final consort diagram



Avoid excessive lists of long options



Pre-Screening Failure Log Page 2 of 3

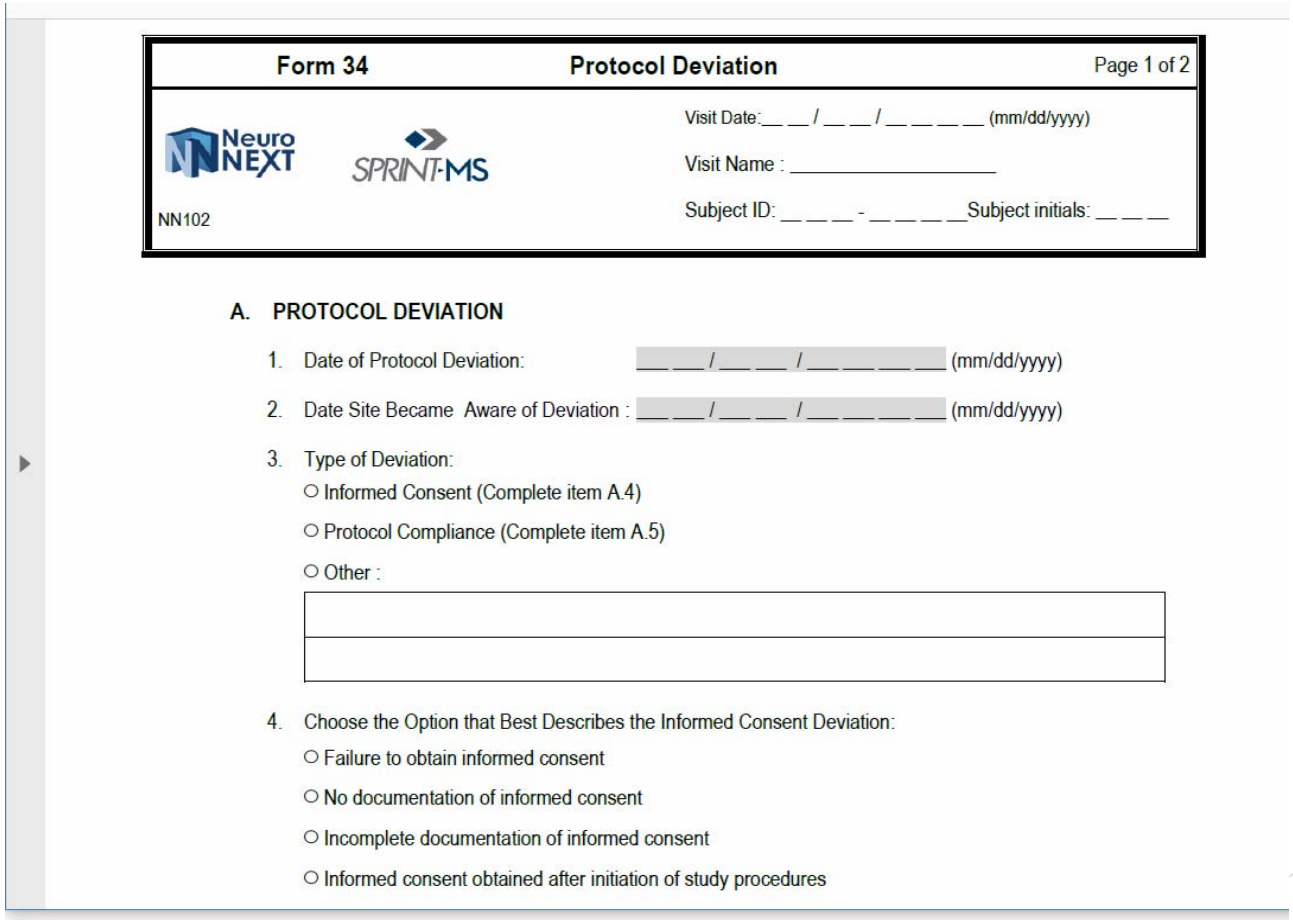
Pre-Screening Date:__ __ / __ __ / __ __ __ __ (mm/dd/yyyy)

Visit Name: Day 1

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

- ☐ Moyamoya disease, cerebral arterio-venous malformation (AVM), or known unsecured aneurysm requiring intervention during the acute study period (Days 1 to 30)
- ☐ Presence of other neurological or non-neurological co-morbidities (e.g. intracerbral neoplasm, metabolic encephalopathies, hemiplegic migraine, multiple sclerosis, convulsive disorder, monocular blindness) that, in the investigator's opinion, may lead, independently of the current stroke, to further deterioration in the subject's neurological status during the trial period, or may render the study's neurological assessments inconclusive for the purpose of evaluating the effect of investigational product on the stroke
- ☐ Presence of premorbid neurological deficits and functional limitations assessed by a retrospective Modified Rankin Score (mRS) score of ≥2
- ☐ Mechanical thrombectomy patients only: baseline non-contrast computed tomography (CT) scan revealing a large core occlusion as defined by local protocol, for example an ASPECTS below a locally defined value or baseline CT perfusion data
- ☐ Prolonged prothrombin time (INR >1.7)
- ☐ Prolonged partial thromboplastin time (PTT) that exceeds the upper limit of normal (ULN)
- ☐ Use of heparin within the 48 hours prior to enrollment, except to maintain catheter patency
- ☐ Severe hypertension (systolic blood pressure (BP) >185 mm Hg or diastolic BP >110 mm Hg) or hypotension (systolic BP <90 mm Hg), as measured by at least 2 consecutive supine measurements 10 minutes apart, that does not respond to simple treatment (e.g. 1 dose of labetalol or nicardipine infusion)
- ☐ Estimated glomerular filtration rate (GFR) <35 mL/min
- ☐ Blood glucose concentration <50 mg/dL
- ☐ Prior exposure to any exogenous form of APC (e.g., plasma-derived APC, 3K3A-APC, Xigris,® drotrecogin alfa [activated])
- ☐ Weight > 129 kg

The ill-fated “other” category



Form 34 **Protocol Deviation** Page 1 of 2

Neuro NEXT SPRINT-MS

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

Visit Name : _____

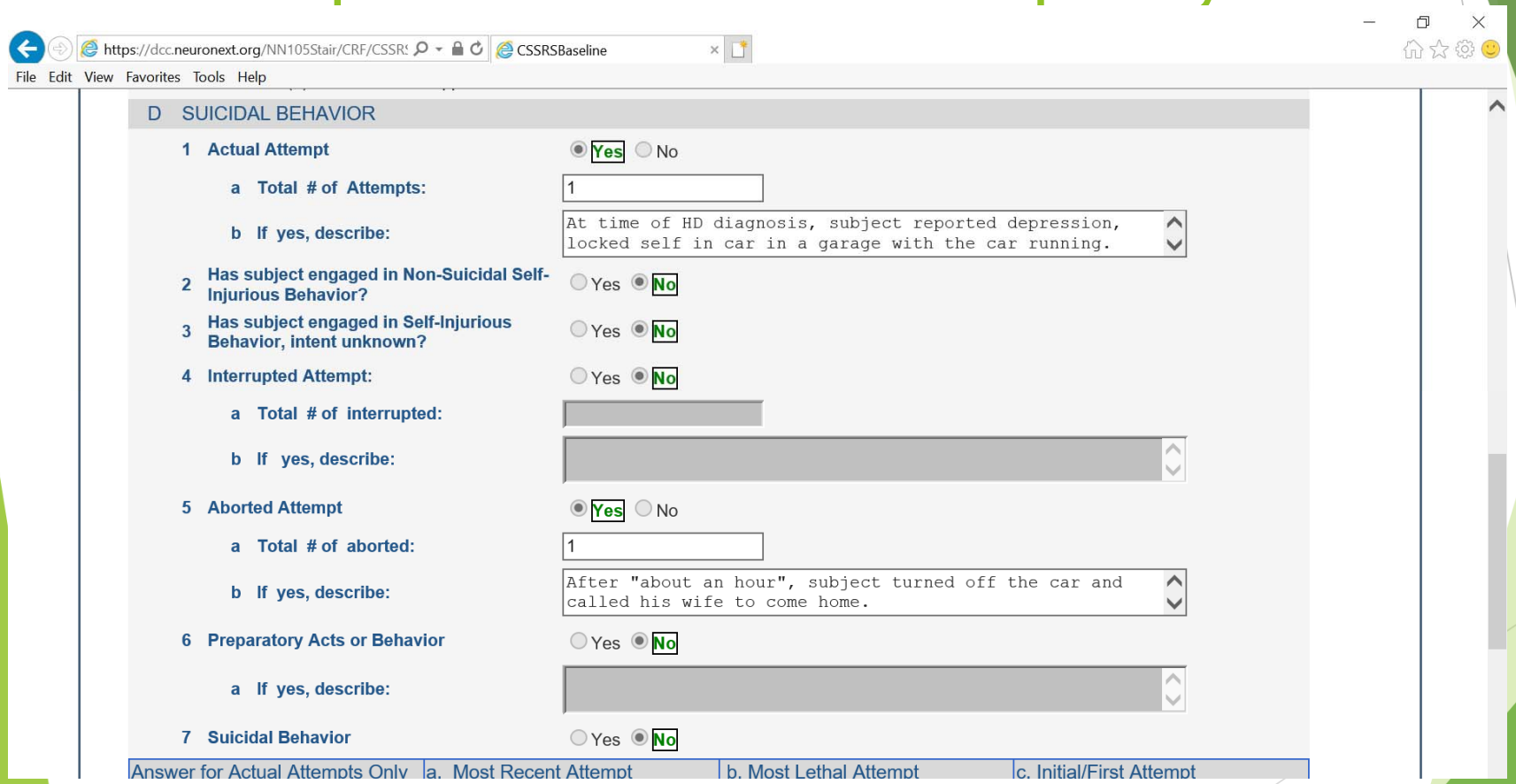
NN102

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

A. PROTOCOL DEVIATION

1. Date of Protocol Deviation: ___ ___ / ___ ___ / ___ ___ ___ ___ (mm/dd/yyyy)
2. Date Site Became Aware of Deviation : ___ ___ / ___ ___ / ___ ___ ___ ___ (mm/dd/yyyy)
3. Type of Deviation:
   - ○ Informed Consent (Complete item A.4)
   - ○ Protocol Compliance (Complete item A.5)
   - ○ Other :
4. Choose the Option that Best Describes the Informed Consent Deviation:
   - ○ Failure to obtain informed consent
   - ○ No documentation of informed consent
   - ○ Incomplete documentation of informed consent
   - ○ Informed consent obtained after initiation of study procedures

Use skip outs to assure data quality



Define data validation rules

- Edit rules
  - Logic checks (male and pregnant?)
  - Range values (lab values)
  - Date/time questions (study procedures before ICF)
- Intra form logic
- Inter form logic
- Query system

Use validated assessments

- NIHSS
- SF-36
- mRS
- CSSR
- NeuroQOL

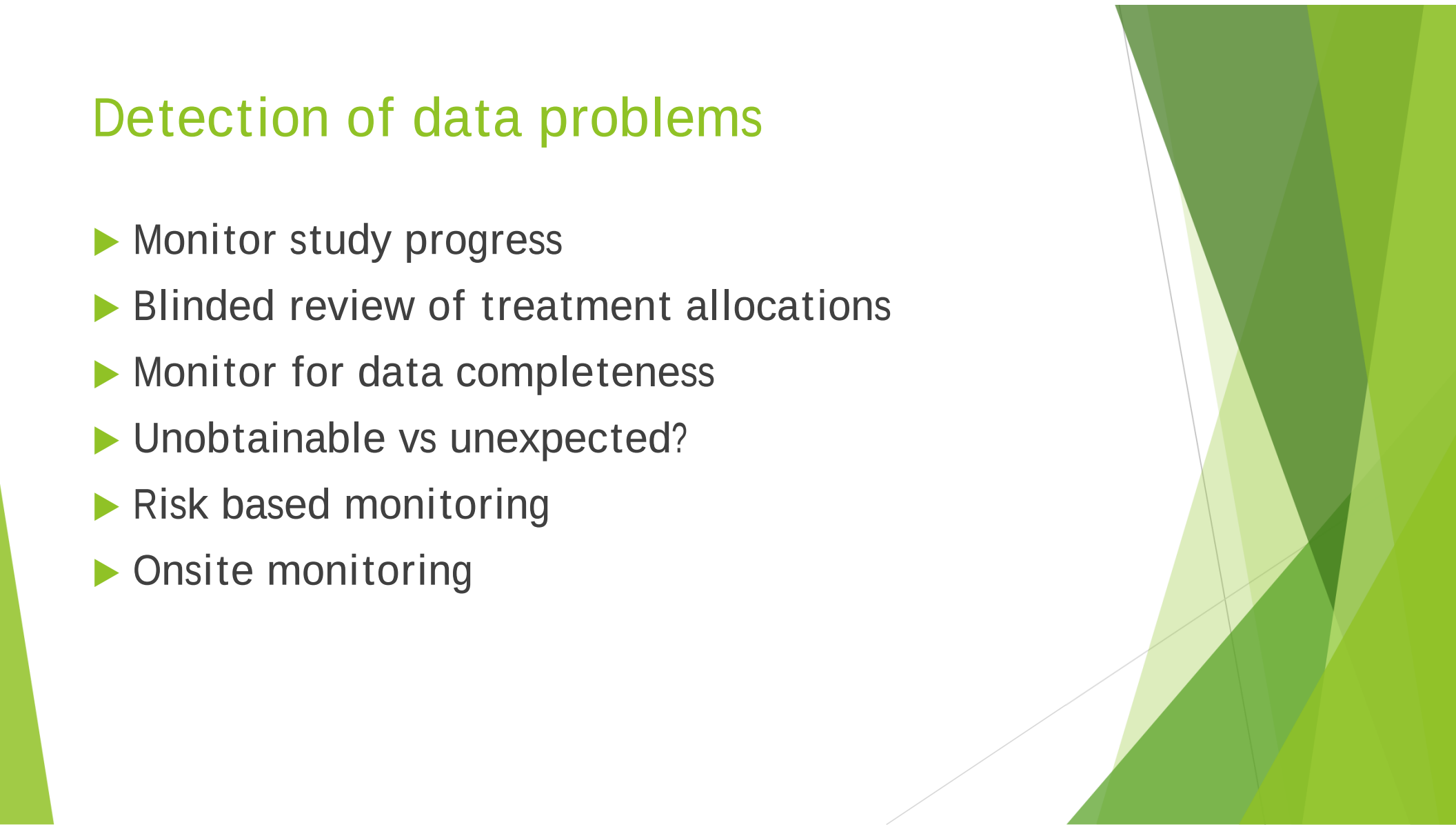
Consider workload distribution

- Reduce work load for the boots on the ground folks

- Maximize the work load of the computer system

Detection of data problems

- Monitor study progress
- Blinded review of treatment allocations
- Monitor for data completeness
- Unobtainable vs unexpected?
- Risk based monitoring
- Onsite monitoring



Risk based monitoring

- Target data that affects trial results
  - Eligibility CRF
  - Randomization CRF
  - Study treatment CRF
  - Adverse Event CRFs
  - Primary and secondary outcome CRFs
  - Protocol violation CRFs (per protocol analysis)
  - Termination/early termination CRFs

Keep track of missing data

Screening	Baseline	Week 4	Week 8	Week 12	Week 24	Week 36	Week 48	Week 60	Week 72	Week 84	Week 96	Week 100	Termination Visit	Relapse Visit	
Status	Status	Status	Status	Status	Status	Status	Status	Status	Status	Status	Status	Status	Status	Status	Termination Date
Complete	Complete	Complete	Complete	Unobtainable	Terminated	Terminated	Terminated	Terminated	Terminated	Terminated	Terminated	Terminated	Overdue	Not Started	13OCT2014
Complete	Complete	Complete	Complete	Complete	Complete	Complete	Complete	Complete	Incomplete	Complete	09JUN2016	07JUL2016	Not Started	Not Started	.
Complete	Complete	Complete	Complete	Complete	Complete	Complete	Complete	Complete	Complete	Complete	07JUN2016	05JUL2016	Not Started	Incomplete	.
Complete	Complete	Complete	Complete	Complete	Complete	Complete	Complete	Complete	Incomplete	10MAY2016	02AUG2016	30AUG2016	Not Started	Not Started	.
Complete	Complete	Complete	Complete	Complete	Complete	Complete	Complete	Complete	Overdue	23JUN2016	15SEP2016	13OCT2016	Not Started	Not Started	.
Complete	Complete	Complete	Complete	Complete	Complete	Complete	Overdue	23JUN2016	15SEP2016	08DEC2016	02MAR2017	30MAR2017	Not Started	Not Started	.

Keep an eye on study close out from the beginning

						Active Queries		
Site	Pending Study Term.	Incomplete eCRFs	Overdue eCRFs	Continuing AEs	Unreviewed PD	Queries Released to Site	Queries on Hold, Realease to DCC or New	Pending PI Sign off
	1	1	1	0	0	0	6	3
	3	3	4	3	1	1	3	10
	0	0	0	0	0	0	0	2
	0	0	0	0	0	0	0	4
	1	0	0	0	1	0	0	8
	1	0	0	1	0	0	1	4
	1	0	0	0	0	0	3	2
	0	0	0	0	0	0	0	4
	0	0	0	0	0	0	0	2
	1	1	15	1	1	0	1	8
Total	***14***	***9***	***23***	***6***	***3***	***5***	***18***	***101***

Top 3 points to consider

- Avoid missing data at all costs
- Design data collection tools to ensure data is collected accurately
- Monitor/verify all data to produce accurate results

Congratulations!

- You are an official Data Management 101 graduate!
  - Build case report forms smartly
  - Ask good questions/not so good questions
  - Think about your consort diagram from the beginning