

Building a Natural History Study for Canavan Disease

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Canavan Disease

Who

What

When

Where

Why

Ultra rare leukodystrophy

1000 patients globally, 1:100,000 births

Autosomal recessive

Mutations in the *ASPA* gene, coding for the aspartoacylase enzyme

Defect prevents normal myelin from forming

Symptoms become most prominent in the first 3 to 5 months of life

Early symptoms: severe hypotonia, head lag & macrocephaly, seizures, etc

Severe neurologic deterioration leading to profound developmental delay

Why is a natural history study needed?

Paucity of published data

No established endpoints in Canavan

No scales / measures that are consistently used

Goal: to identify clinically meaningful changes that can be used to establish the necessary endpoint(s) for a treatment trial AND to use the data as a historical control

Commitment: Aspa will make data available to researchers

Challenges with NH Studies

If the study was too burdensome, families would not join

If the study was too burdensome, they would withdraw

Creative approach to making it as easy as possible

Family travel support to site visits

Inconsistency across medical records

Important to note that  and our future treatment trial, while connected by data, are not linked

a patient does not need to be enrolled in the natural history study to enroll in the treatment trial and vice versa



Unique Aspects of Our Study

Record retrieval

Data extraction

In home assessments (US only) for prospective visits

Efforts to Date: **CAN**inform

Retrospective
Prospective

Established strong relationships with KOLs / PIs to learn about current management of patients with Canavan disease



Patients Advocacy Groups input at all stages



Conducted Parent Focus Groups / Interviews to determine what they feel is most important when dealing with Canavan disease

Efforts to Date: **CAN**inform

Retrospective
Prospective

Contracted with several vendors



Consulted with several experts working on similar rare pediatric diseases



Retrospective Data: Record Collection

Challenges with record retrieval

Time consuming & costly

Most critical: first 3 years of life

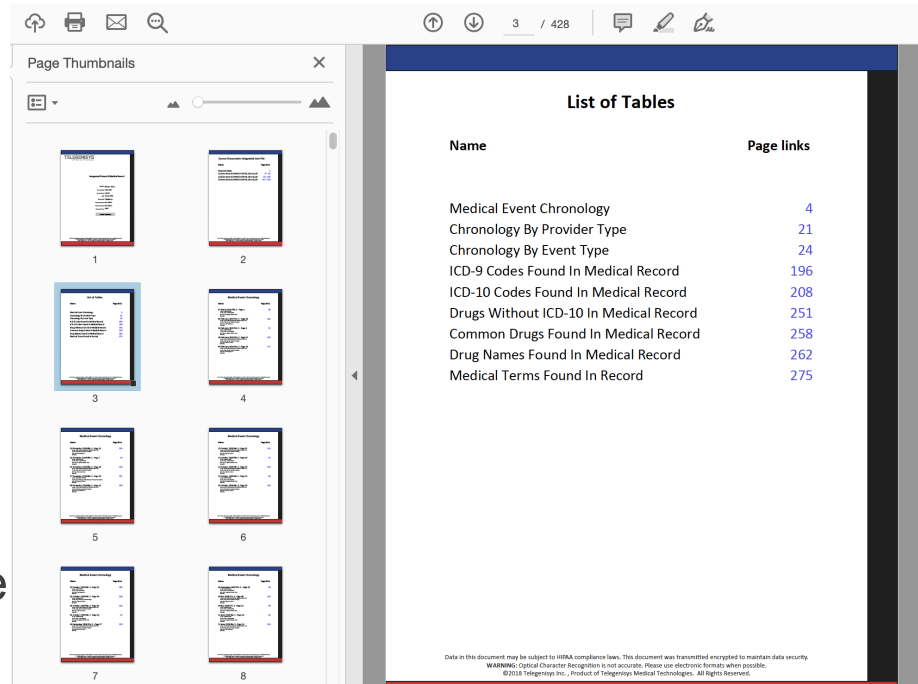
Identified Telegenisys & wrote protocol
Received IRB approved

Record: Hyperlinked, bookmarked

Once family receives record, they will be asked to enroll in NH study

Upon signing consent, record is transferred to site

To date, 15 families have signed up from US & outside EU



Data Extraction

Challenges with making sense of data across records

Link between sign and point on a scale

Data Extraction Plan (DEP): defines the steps for extracting data

Visit Number: □ Entry Visit □ Visit	Aspa Therapeutics, CVN-101											
	Rater Initials:			Subject Number:			Date:			D D M M Y Y Y Y		
	A	B	C									

SCREENING GET									
Item	Position	Test Procedure	Response	Score	Item Score	Behavioral State			
14	Head rotation side to side	Infant is held upright or in sitting, tipped back 30 degrees, with upper trunk and base of head lightly supported in midline by examiner's hands. Elbows should be positioned close to the trunk, but hands are not to be held. If the infant resists reclined position and can control head independently, test the infant in upright sitting with support at the	No response or unable to achieve state 4 during testing	0		□ State 1- deep sleep □ State 2- light sleep □ State 3- drowsy or semi-drowsy □ State 4- alert, with bright look □ State 5- eyes open, considerable activity			

Aspa Therapeutics, CVN-101											
Cohort/Visit: □ Cohort 1 □ Cohort 2 □ Cohort 3 □ Cohort 4			Entry Visit □ Visit 1 □ Visit 2 □ Visit 3 □ Visit 4 □ Visit 5 □ Visit 6 □ Visit 7 □ Visit 8 □ Visit 9			Rater Initials:			Site Number:		
A B C			A B C			Date:			D D M M Y Y Y Y		
Subject Initials:			Subject Number:			Age:			DAYS MONTHS YEARS		
X Y Z						Start Time:			H H : M M		
						End Time:			H H : M M		

GROSS MOTOR FUNCTION MEASURE (GMFM) SCOPE SHEET (GMFM-88 scoring)

Record Form



Aspa Therapeutics, CVN-101											
Cohort/Visit: □ Cohort 1 □ Cohort 2 □ Cohort 3 □ Cohort 4			Entry Visit □ Visit 1 □ Visit 2 □ Visit 3 □ Visit 4 □ Visit 5 □ Visit 6 □ Visit 7 □ Visit 8 □ Visit 9			Rater Initials:			Site Number:		
A B C			A B C			Date:			D D M M Y Y Y Y		
Subject Initials:			Subject Number:			Age:			DAYS MONTHS YEARS		
X Y Z						Start Time:			H H : M M		
						End Time:			H H : M M		

Sex: ☐ Male ☐ Female

Subtest Summary Scores

Subtest	Total Raw Score	Scaled Score	Composite Score	Percentile Rank	Conf. Interval (%)
Cognitive (Cog)					

Calculate Age

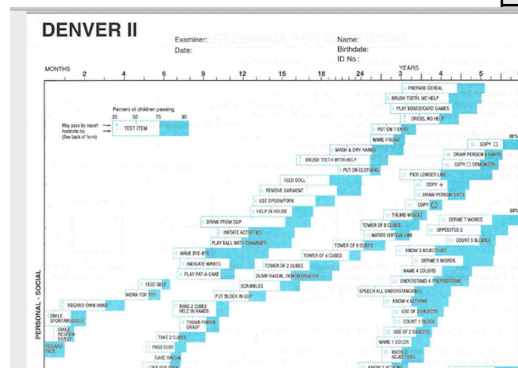
Years
Date Tested

Aspa Therapeutics, CVN-101											
Cohort/Visit: □ Cohort 1 □ Cohort 2 □ Cohort 3 □ Cohort 4			Entry Visit □ Visit 1 □ Visit 2 □ Visit 3 □ Visit 4 □ Visit 5 □ Visit 6 □ Visit 7 □ Visit 8 □ Visit 9			Rater Initials:			Site Number:		
A B C			A B C			Date:			D D M M Y Y Y Y		
Subject Initials:			Subject Number:			Age:			DAYS MONTHS YEARS		
X Y Z						Start Time:			H H : M M		
						End Time:			H H : M M		

HAMSMITH INFANT NEUROLOGICAL EXAMINATION SECTION 2: MOTOR MILESTONES (HINE-2)

Following examination, please record the correct Milestone Progression Score for each item.

MOTOR FUNCTION	MILESTONE PROGRESSION SCORE					Score	From which test was the item observed?
	0	1	2	3	4		
control	Unable to maintain head upright	Wobbles	Maintained upright all the time				1 This HINE-2 2 TAMPSI 3 GMFM-88 4 Bayley-II
ing	Cannot sit	With support at hips	Props	Stable sit	Pivots (rotates)		1 This HINE-2 2 TAMPSI 3 GMFM-88 4 Bayley-II



In Home Assessments / Rater Training

Extensive Rater training across US and GER raters

In person and & on line training modules

No Rater will perform an assessment until they have been certified by all qualified trainers

US – identified 3 highly qualified Physical Therapists to perform in home assessments (TIMPSI, GMFM, Bayley, HINE2)

Extensive support for US Raters as they travel to family homes has been put in place

Rater Relatability Testing

All Raters begin at the required level

Ongoing QC to ensure across prospective data, we maintain high level of quality & consistency

Conclusions

Don't under-estimate the effort required to build a natural history study

Be prepared for gaps in data – anticipate how you will work through

If retrospective, establish not only a solid record retrieval plan but also a plan for how to integrate this with prospective data collection

Develop robust plans to collect data in a rigorous way

A natural history study is a clinical study – treat it as such

Thank You

Key Opinion Leaders / PIs



Patient Advocates



Vendors



Consultants



MASSACHUSETTS
GENERAL HOSPITAL



Children's Hospital
of Philadelphia



JOHNS HOPKINS
UNIVERSITY



THE OHIO STATE UNIVERSITY
WEXNER MEDICAL CENTER

Holland Bloorview
Kids Rehabilitation Hospital



Northwestern
University



Future Families

