Advisory Panel on Rare Disease Fall 2015 Meeting

Washington, DC

October 30, 2015

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Welcome and Plans for the Day

Hal Sox, MD

Chief Science Officer, PCORI

Vincent Del Gaizo

Co-Chair, Advisory Panel on Rare Disease, PCORI

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Housekeeping

- Today's webinar is open to the public and is being recorded.
- Members of the public are invited to listen to this teleconference and view the webinar.
- Anyone may submit a comment through the webinar chat function or by emailing advisorypanels@pcori.org.
- Visit www.pcori.org/events for more information.
- Chair Statement on COI and Confidentiality

Today's Agenda

Start Time	Item	Speaker
8:30 a.m.	Welcome and Plans for the Day	H. Sox V. Del Gaizo
8:45 a.m.	Final PCORI Guidance on PCOR for Rare Diseases	D. Whicher
9:00 a.m.	A Randomized Controlled Trial of Anterior Versus Posterior Entry Site for Cerebrospinal Fluid Shunt Insertion: Current Progress and Lessons Learned	W. Whitehead
9:45 a.m.	Follow up Guidance to the Rare Disease Landscape Review	D. Whicher
10:15 a.m.	Break	
10:30 a.m.	Guidance for Rare Disease Research Breakout Groups • Human Subjects • Research Prioritization • Challenges with Producing Reliable Evidence for Rare Diseases	P. Furlong M. Bull N. Aronson

Today's Agenda (cont.)

Start Time	Item	Speaker
12:15 p.m.	Lunch	
1:15 p.m.	Reports from Breakout Groups	P. Furlong M. Bull N. Aronson
2:15 p.m.	Update on PCORI's Rare Disease Portfolio	H. Edwards M. K. Margolis V. Gershteyn
3:30 p.m.	Recap and Next Steps	V. Del Gaizo D. Whicher P. Aggarwal
3:45 p.m.	Adjourn	

Final PCORI Guidance on PCOR for Rare Diseases

Danielle Whicher, PhD, MHS

Program Officer, Clinical Effectiveness Research, PCORI

Purpose: PCORI's Guidance on Research in Rare Diseases

- Background
  - Developed based on structured meetings of PCORI science staff
  - Discussion topics were informed by questions PCORI staff received from applicants wishing to propose research studies in rare diseases

- Purpose
  - To provide guidance to applicants planning to propose research studies in rare diseases for PCORI funding
  - To provide guidance to staff responsible for reviewing LOIs and applications

Revisions Incorporated since Last Discussion on May 27

- Efforts were made to simplify the language and decrease the reading level
- A table comparing the requirements for CER in common conditions to CER in rare conditions was added
- The document now links to the list of PCORI funded rare disease projects

Table Comparing the Requirements for CER in Common Conditions to CER in Rare Conditions

Comparison of PCORI Requirements for Patient-centered CER in Common versus Rare Clinical Conditions		
	Common Diseases	**Rare diseases**
Commonly used	The intervention(s) should be used by physicians and/or health care systems across the United States for treatment of individuals with the condition being studied.	The intervention(s) should be considered a realistic clinical choice for individuals with a given rare disease even if the intervention is not widely offered in health care systems across the country.
Evidence based	The intervention(s) should have been previously studied in at least one adequately powered efficacy study.	The intervention(s) should have been previously studied. PCORI may consider applications that involve interventions with limited evidence if they meet the other criterion described above.
Comparators	PCORI prefers comparisons of two interventions. If this is not possible, applicants should specifically describe what the control group will receive and how this will be measured over the course of the study in each patient.	
Outcome Measures	PCORI encourages investigators to use validated outcome measures, including patient reported outcomes.	

Final Guidance Terms

- **Commonly Used =** Make the case that the intervention(s) you plan to compare represent a ***realistic clinical choice*** for individuals with a given rare disease even if those interventions are not widely offered in health care systems across the country.

- **Efficacious =** The intervention(s) should have been previously studied. PCORI may consider applications that involve interventions with limited evidence if they meet the other criterion described above.

Final Guidance Dissemination

- Blog post: "New PCORI Guidelines for Research on Rare Diseases" (Posted on October 20, 2015)
- Incorporation into FAQs for applicants
- PDF on PCORI's website:
  - On blog post webpage
  - On "Research We Support" webpage

A Randomized Controlled Trial of Anterior Versus Posterior Entry Site for Cerebrospinal Fluid Shunt Insertion: Current Progress and Lessons Learned

William E. Whitehead, MD, MPH

Division of Pediatric Neurosurgery, Texas Children's Hospital, Baylor College of Medicine

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A RCT of Anterior v. Posterior Entry Site for CSF Shunt Insertion:

The HCRN, Study Progress, and Lessons Learned

William Whitehead

Texas Children's Hospital

PCORI Advisory Panel on Rare Diseases

Fall Meeting

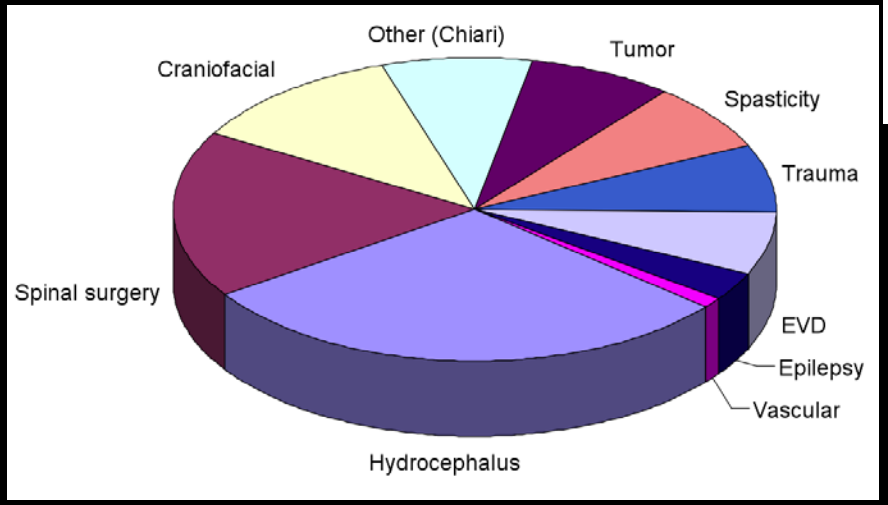
October 30, 2015

Overview

- HCRN Network
- Rationale and Methodology of the Entry Site Trial
  - Identification of Evidence Gap
  - Study Protocol
- Study Progress

Why Pediatric Hydrocephalus?

- Each year:
  - 37,500-39,250 admissions
  - 380 - 420,000 hospital days
  - $1.20-1.95 billion charges

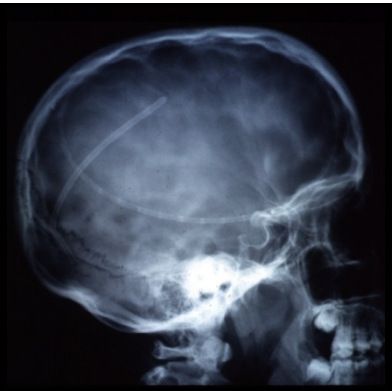


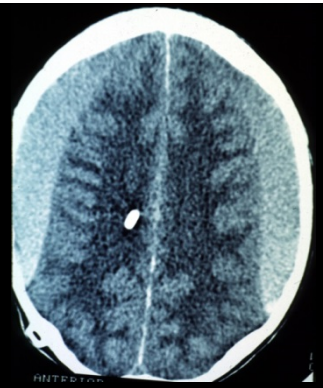
J Neurosurg Pediatrics 1:131–137, 2008

Hospital care for children with hydrocephalus in the United States: utilization, charges, comorbidities, and deaths

TAMARA D. SIMON, M.D., M.S.P.H.,[1] JAY RIVA-CAMBRIN, M.D., M.SC.,[2] RAJ SRIVASTAVA, M.D., M.P.H.,[1] SUSAN L. BRATTON, M.D., M.P.H.,[3] J. MICHAEL DEAN, M.D., M.B.A.,[3] AND JOHN R. W. KESTLE, M.D.,[2] FOR THE HYDROCEPHALUS CLINICAL RESEARCH NETWORK

Department of Pediatrics, Divisions of [1]Inpatient Medicine and [3]Critical Care; and [2]Department of Neurosurgery, Division of Pediatric Neurosurgery, University of Utah, Salt Lake City, Utah





- most studies are single center, retrospective series
- prospective or multicenter work uncommon
- RCTs rare (and negative)
- discussions repetitive
- “no progress since the introduction of silicone shunts 50 years ago”

Shunt Design Trial

Children (< 18 yrs)
First shunt

R

Delta

Standard

Sigma

10 centers from Canada, US, Europe

Pediatric Neurosurgery

Original Paper

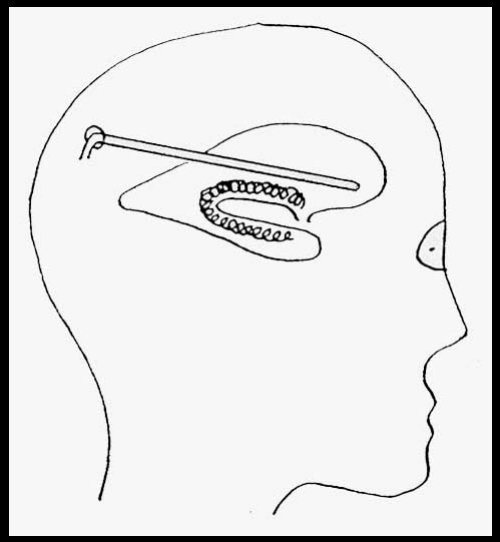
Pediatr Neurosurg 2000;33:230–236

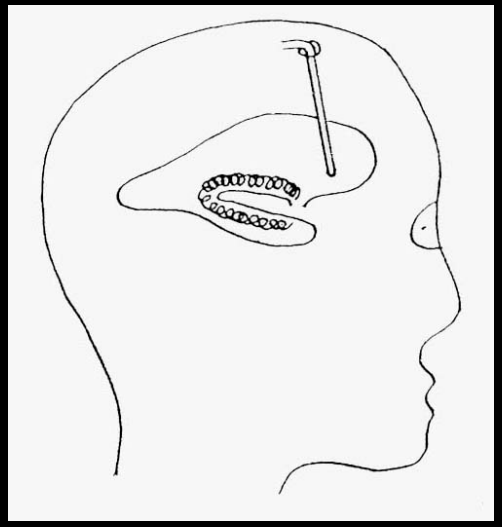
Received: July 31, 2000
Accepted: September 13, 2000

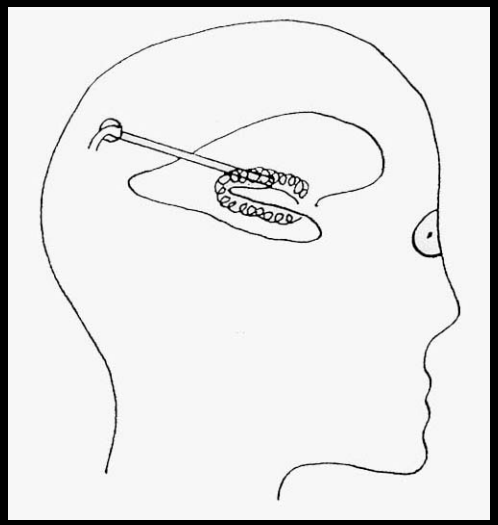
Long-Term Follow-Up Data from the Shunt Design Trial

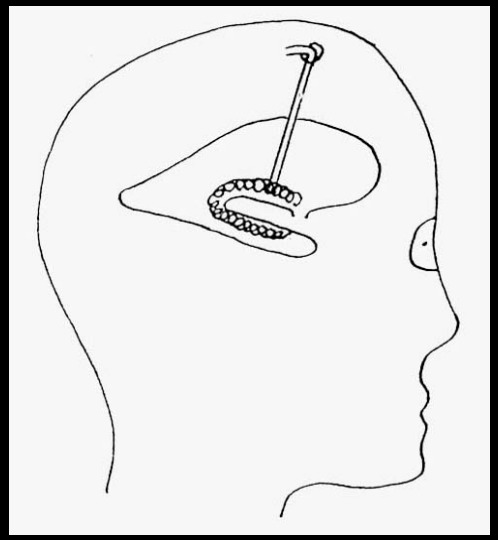
J. Kestle[a] J. Drake[b] R. Milner[h] C. Sainte-Rose[c] G. Cinalli[c] F. Boop[d] J. Piatt[e] S. Haines[f] S. Schiff[g] D. Cochrane[h] P. Steinbok[h] N. MacNeil[h] for the collaborators

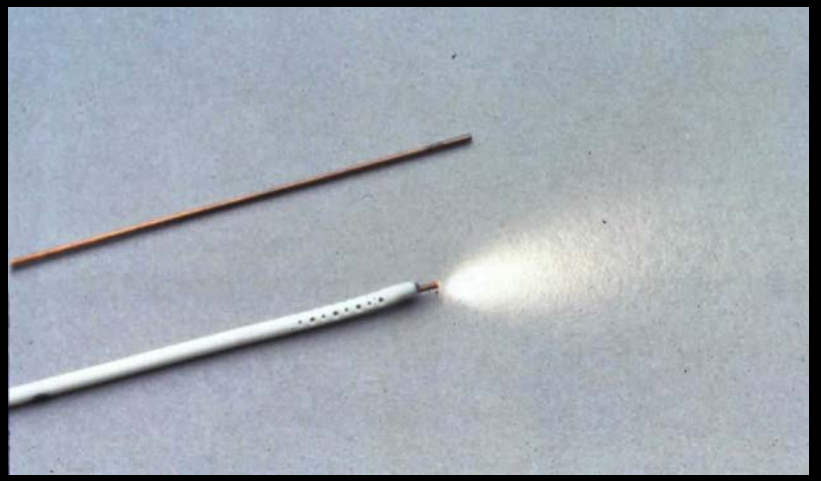
Endoscopic Shunt Insertion Trial











Endoscopic Shunt Insertion Trial

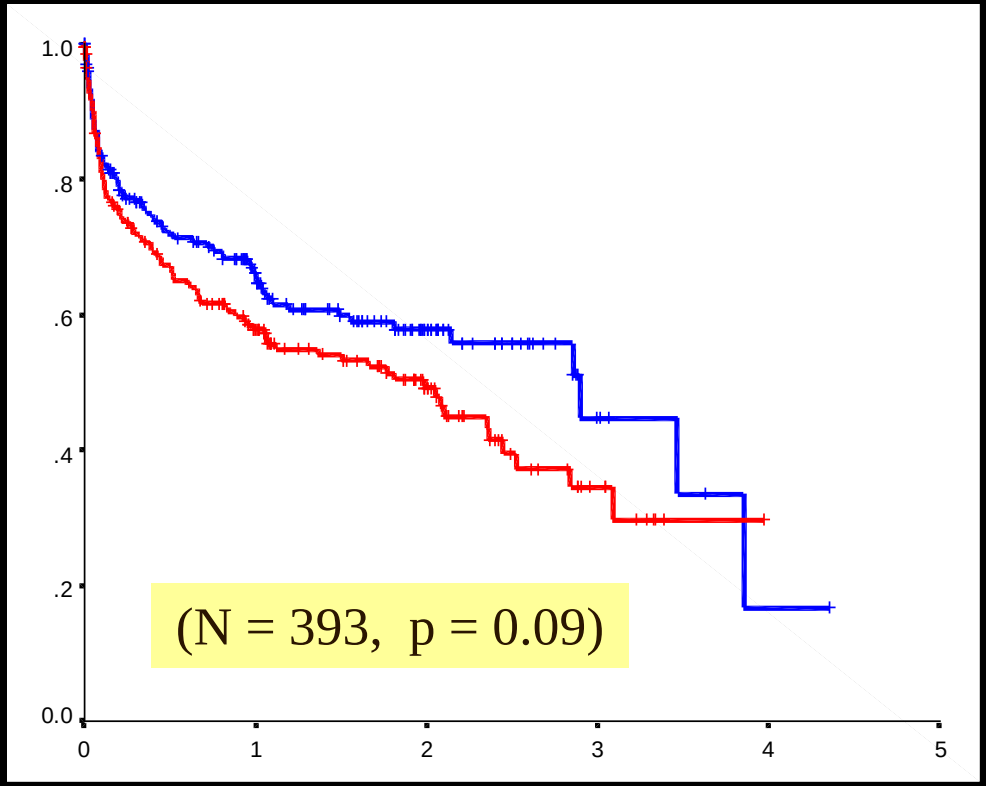
393 children
Hydrocephalus
First shunt

R

Endoscope No Endoscope

Shunt failure?

Shunt survival in endoscope and non endoscope groups



Frustrations

- one active study at each center
- accrual is slow
- can’t justify a full-time research assistants
- data collection – surgeon/clinical nurse
- delayed data acquisition - missing data
- funding study specific trial (paid per patient)

Frustrations

- one active study at each center
- accrual is slow (even in hydrocephalus!!!!)
- can’t justify a full-time research assistants
- data collection – surgeon/clinical nurse
- delayed data acquisition - missing data

Network

- multiple simultaneous projects
- high volume centers
- support personnel in each center
- clinical research expertise
- history of cooperation in clinical trials
- pediatric neurosurgical expertise

Critical mass of trained investigators

Common problem

Clinical trials experience

Hydrocephalus Association NIH Consensus Conference 2005

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Goals

Monitor/improve quality

Standardize care

Collaborative research

"Every child on a protocol"

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Founding Principles

Clinical epidemiology training

Large centers

A study idea

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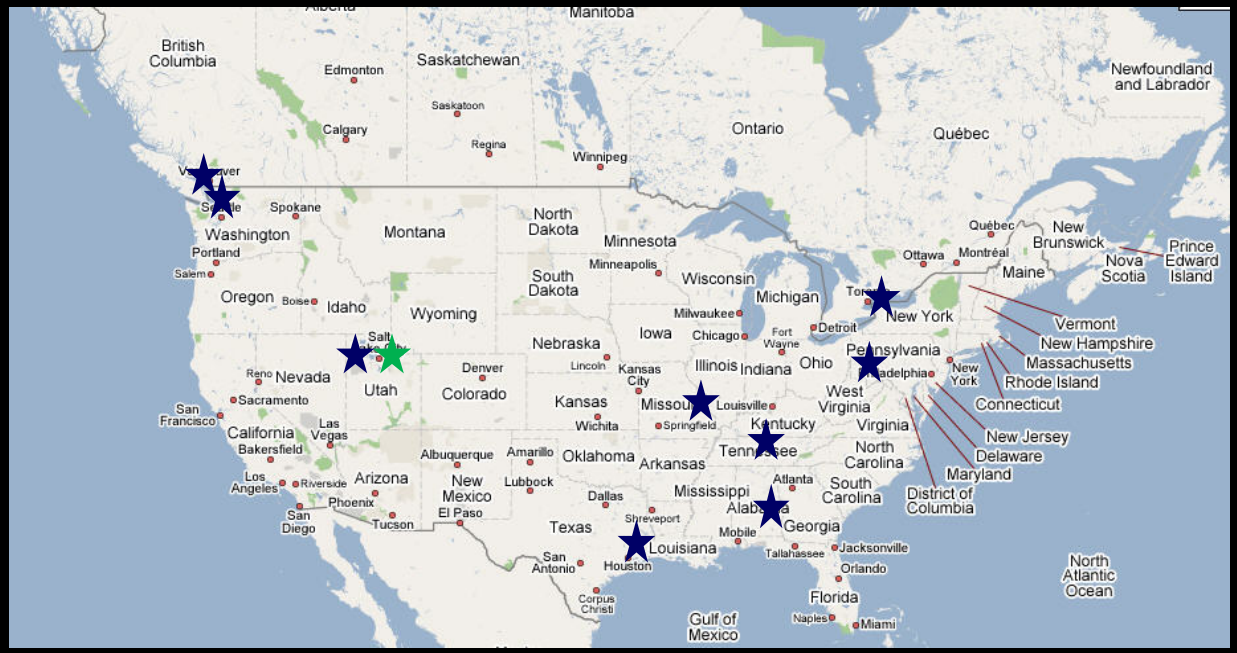
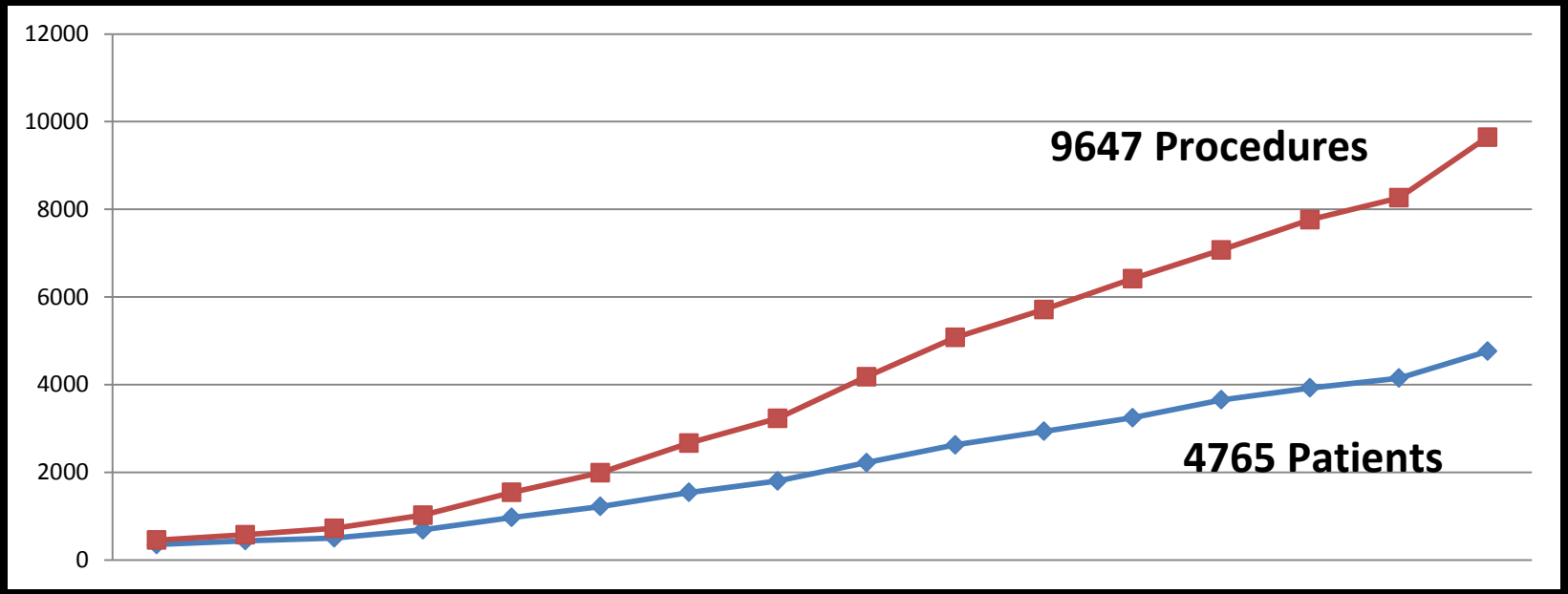
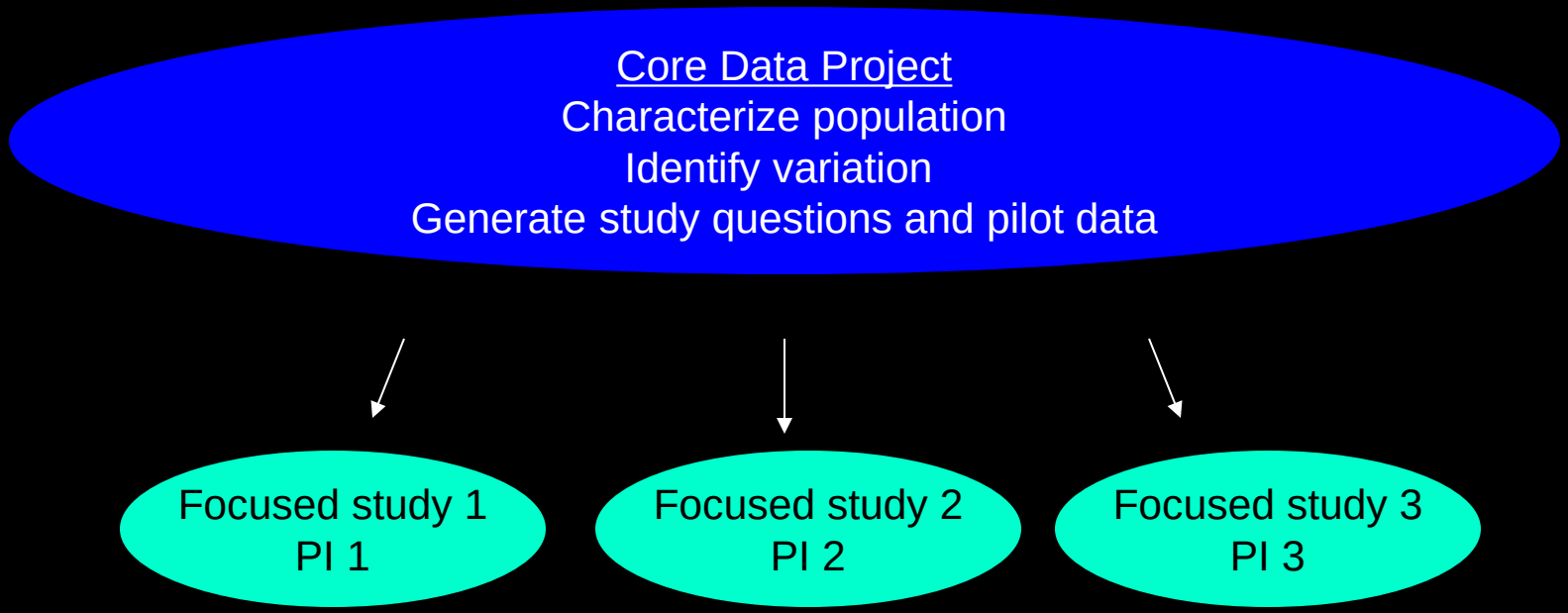
University of Utah, Salt Lake City,
University of Toronto, Toronto
U of Alabama at Birmingham
Baylor College of Medicine/TCH
University of Pittsburgh
University of Washington, Seattle
Washington University, St. Louis
Vanderbilt, Nashville
Uof British Columbia, Vancouver





Scientific Strategy



hydrocephalus
clinical research network

Study lines

QI to reduce infection — Kestle, Utah

Mx of IVH — Wellons, Vanderbilt

Shunt insertion — Whitehead, TCH

ETV/CPC — Kulkarni, HSC

Core Data Project

- Shunt surgery — Riva-Cambrin, SLC
- Third ventric — Kulkarni, HSC
- Shunt infection — Simon, SLC

Biomarkers in PHH — Limbrick, St Louis

Neuropsych — Riva-Cambrin, Utah

Implementation — Tamber, Pittsburgh

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First meeting	August 2006
First study began	June 2007
First presentation	December 2007

Shunt Failure

Core Data Project

Hydrocephalus Clinical Research Network

- 1036 first shunts
- April 2008 – Dec 2011
- 334 shunt failures (32%)
- age < 6m, cardiac condition
- valve type had no impact on shunt survival
- endoscopic insertion decreased shunt survival

hydrocephalus clinical research network

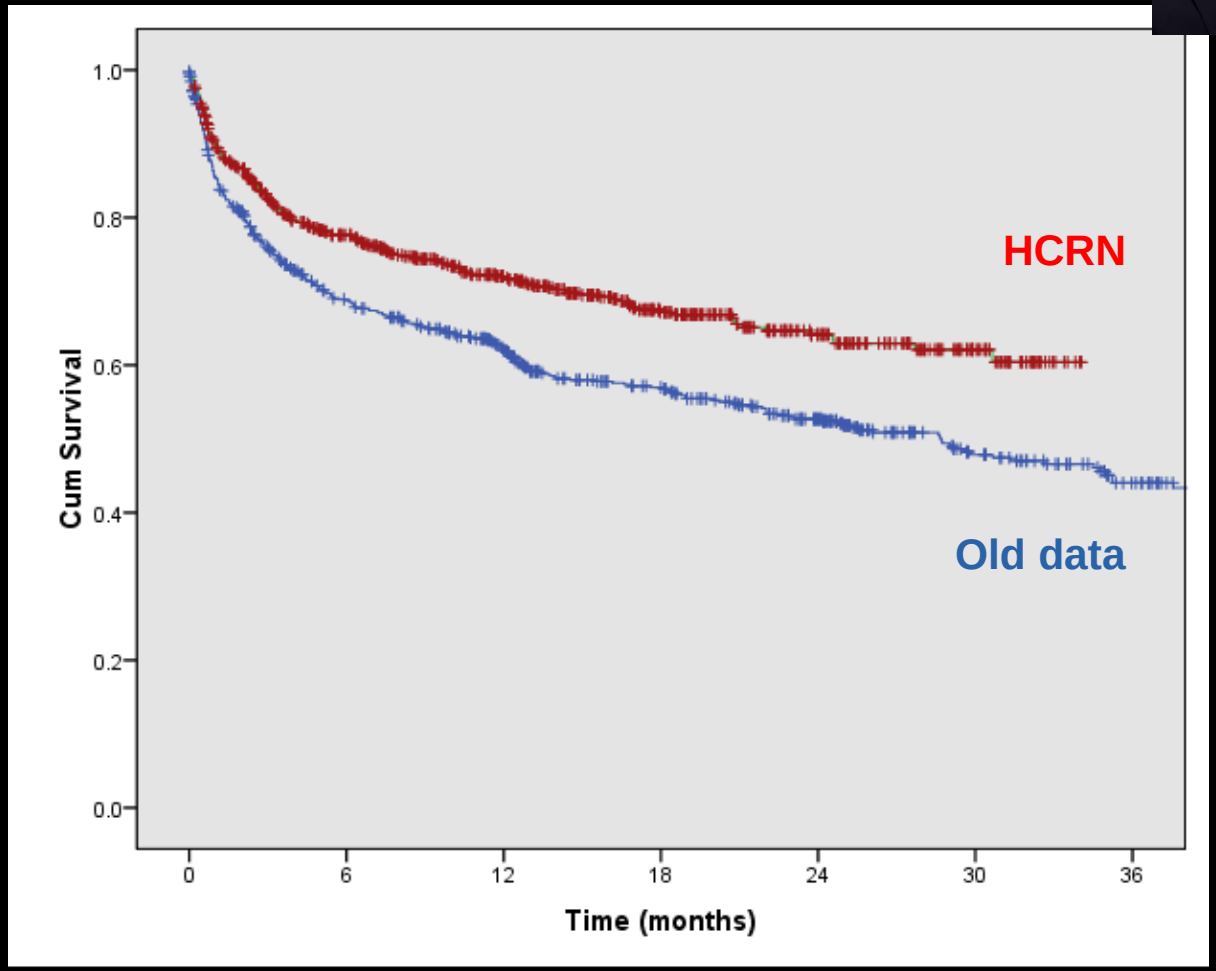
Riva-Cambrin et al, submitted

Shunt Failure

Cox model adjusted for age/etiology

- curves sig different
- all first time shunts
- reduced infection?
- different shunts?
- better guidance?

Core Data Project



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Shunt Infection

Core Data Project

- 1036 patients with first shunt
- revisions strongest predictor of infection
  - one revision 4X infection risk
  - two or more revisions 13X infection risk

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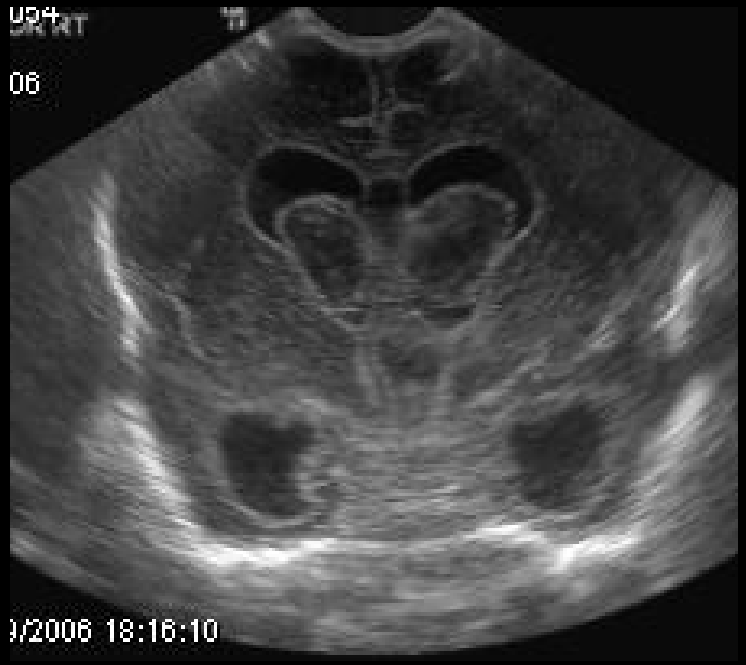
Simon et al, J Pediatr 2014

Management of IVH

Premie IVH



IVH: HCRN 4 centers, 5 yr review

- 109 premie IVH, grade ¾
  RES better than SGS

Who needs surgery?

CENTER

(JNS:Peds 2009, 2012)

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Quality improvement

Protocol

Reduce Variation

Improve outcome

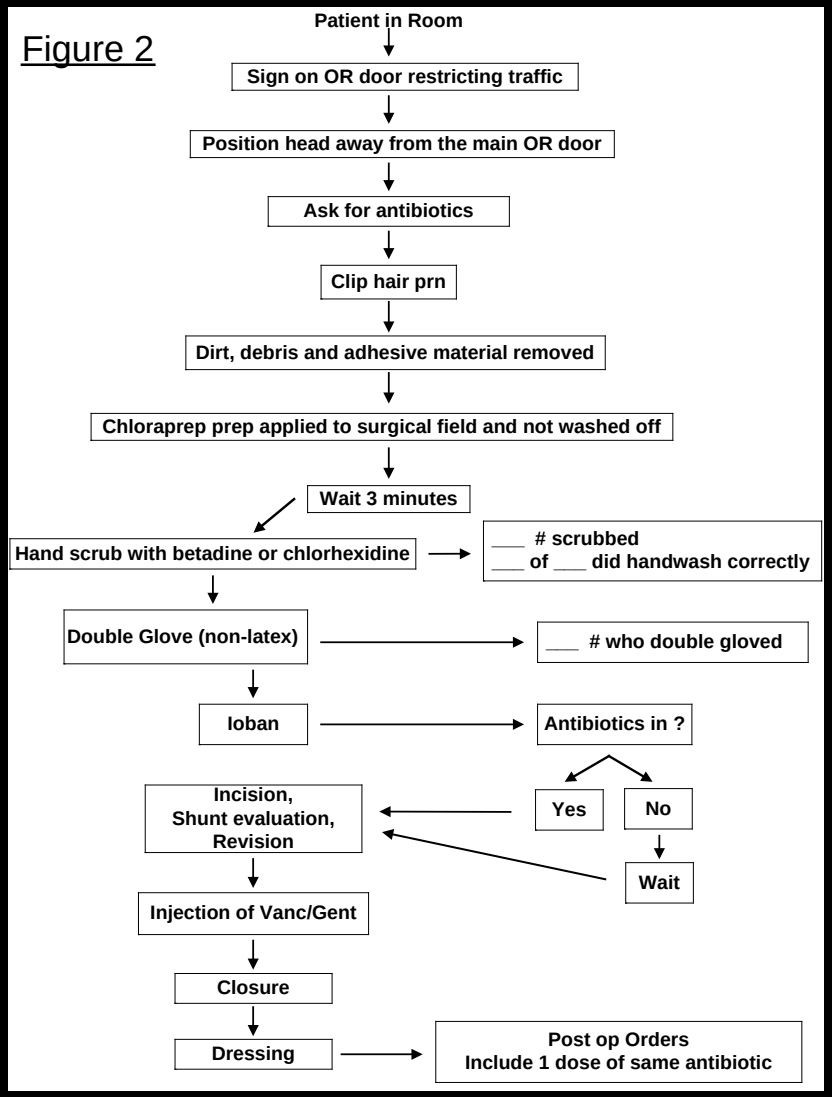
QI: shunt infection

Compliance recorded
(overall 74.5%)

Infections:

- before protocol (n = 896) 8.8%
- on protocol (n = 1571) 5.7%

(p = 0.0027)



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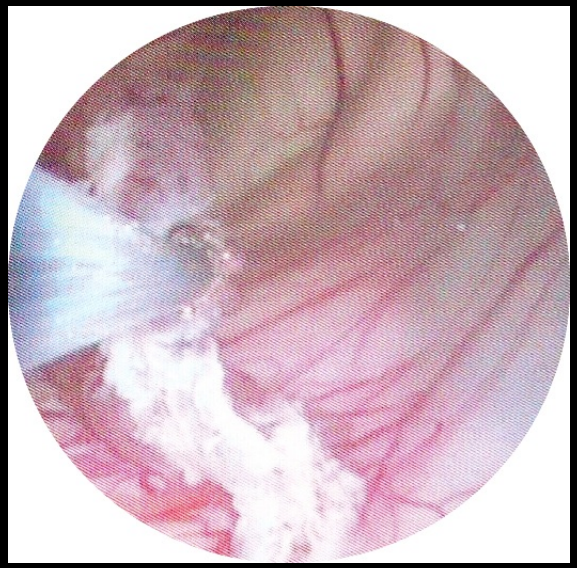
Surgical technique – ETV/CPC



36 unselected ETV/CPC

Better results with more CPC

Better results with more experience

Implications for learning

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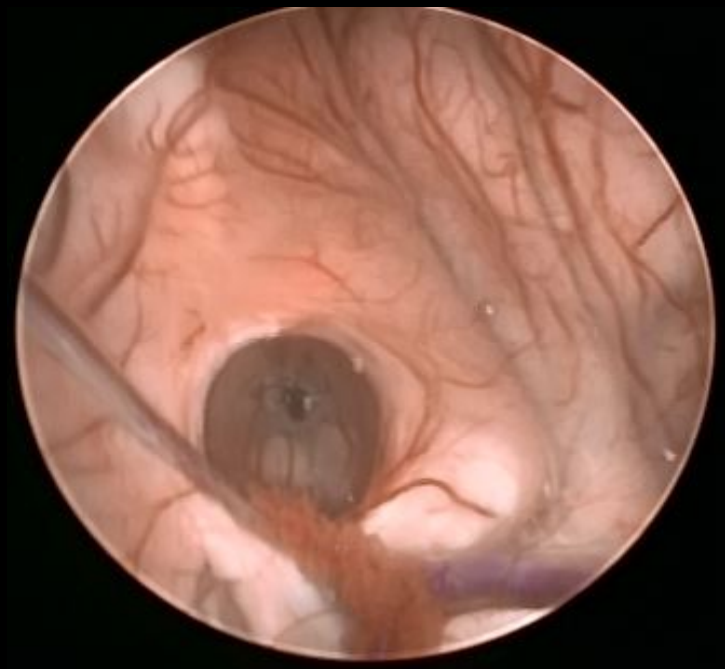
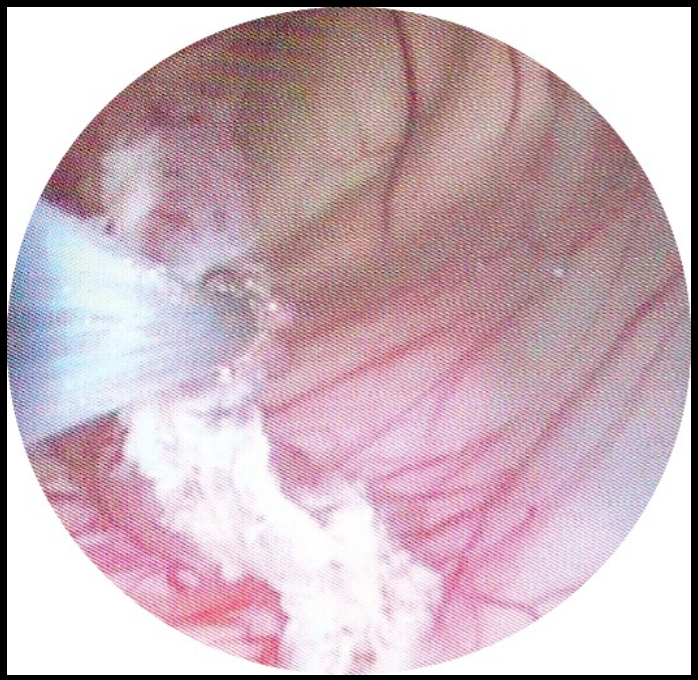
Surgical technique – ETV/CPC





Retro → Prospective obs → RCT

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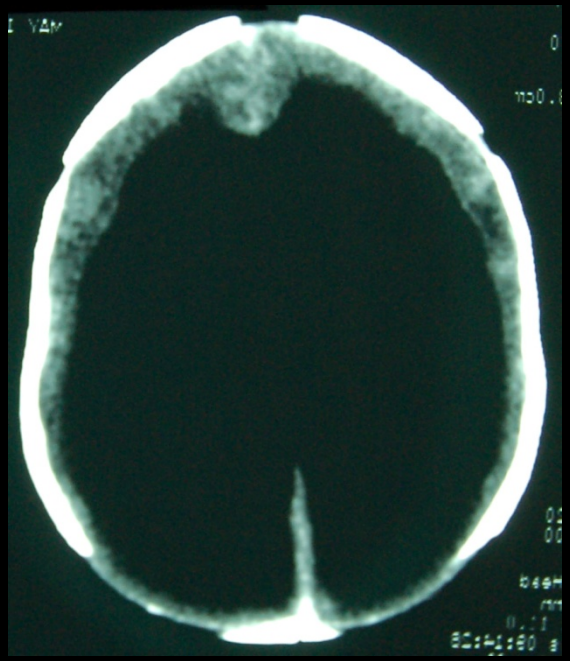
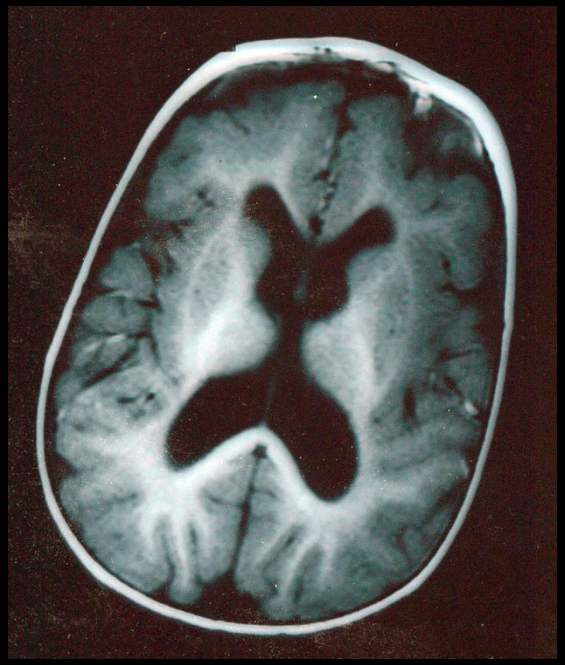
VINOH Ventricle Size Involvement in Neuropsychological Outcomes in Pediatric Hydrocephalus

Ventricle size vs outcome





New hydro
Over 5 y old

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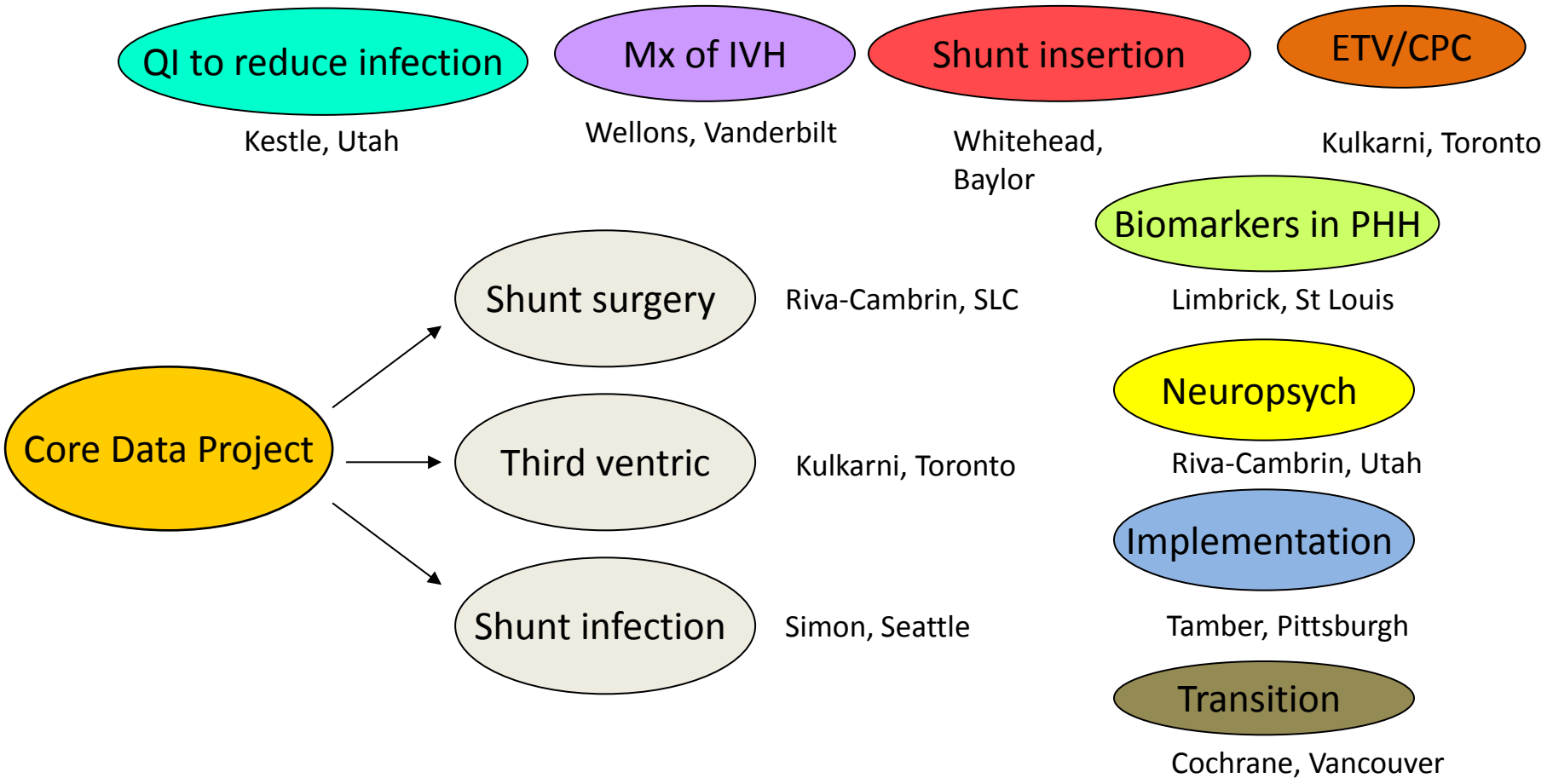
Challenges

Collaboration

- pilot data
- ability to work together
- follow a study protocol
- publish together

Maintaining interest

Broad participation: a study is being run by a PI from 8 different centers



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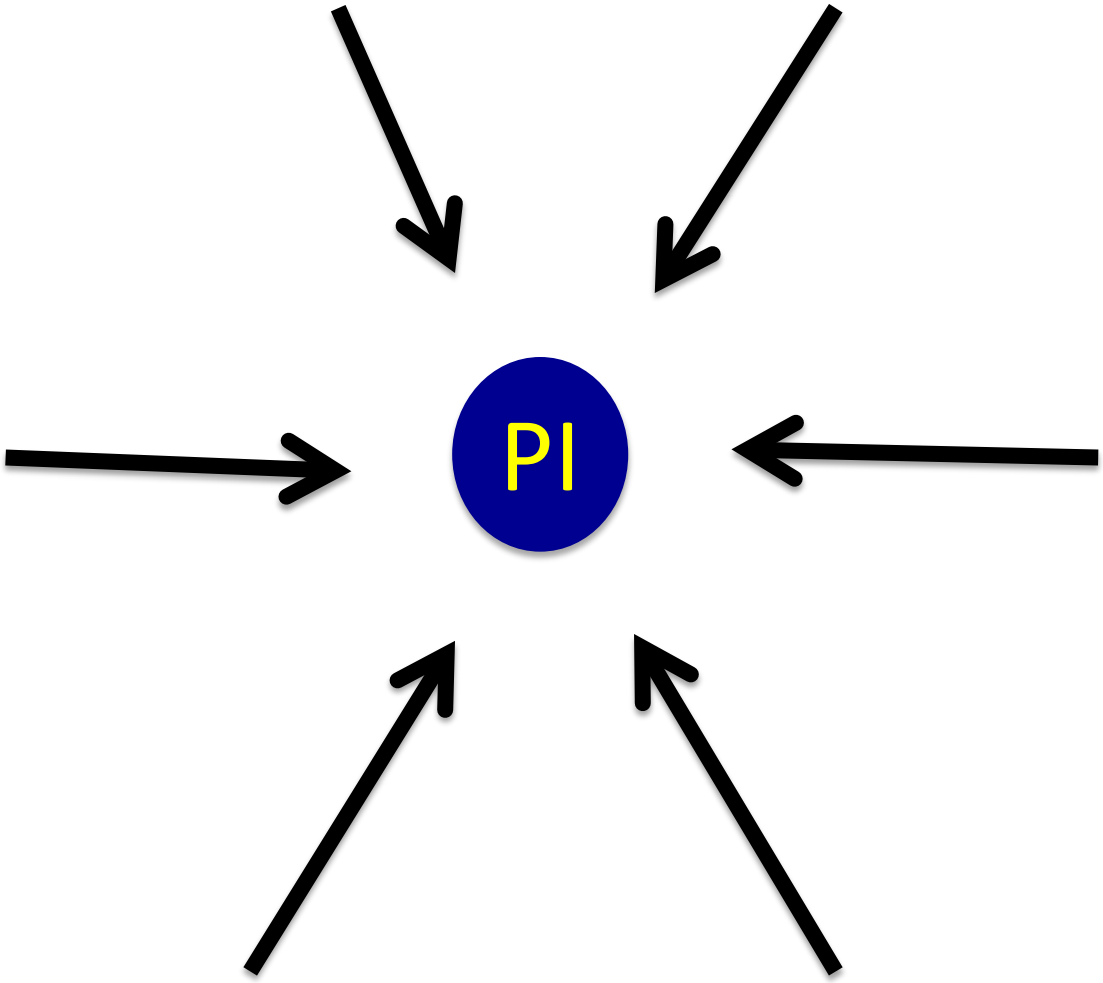
Academic credit



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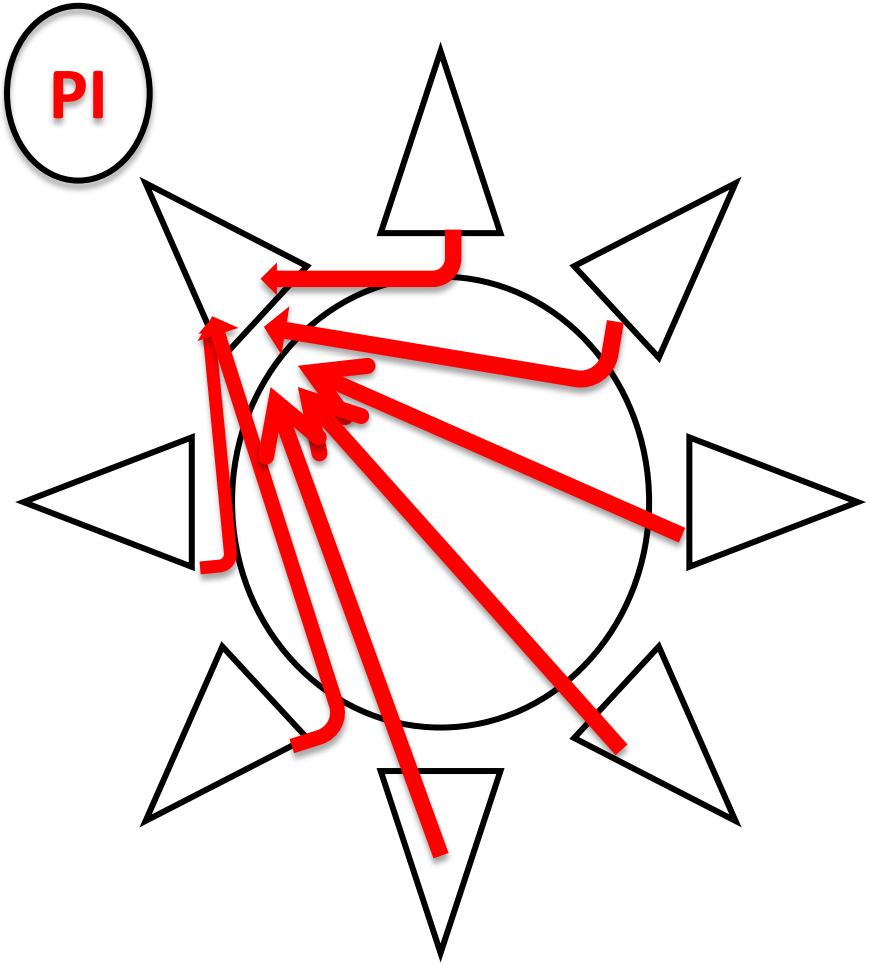

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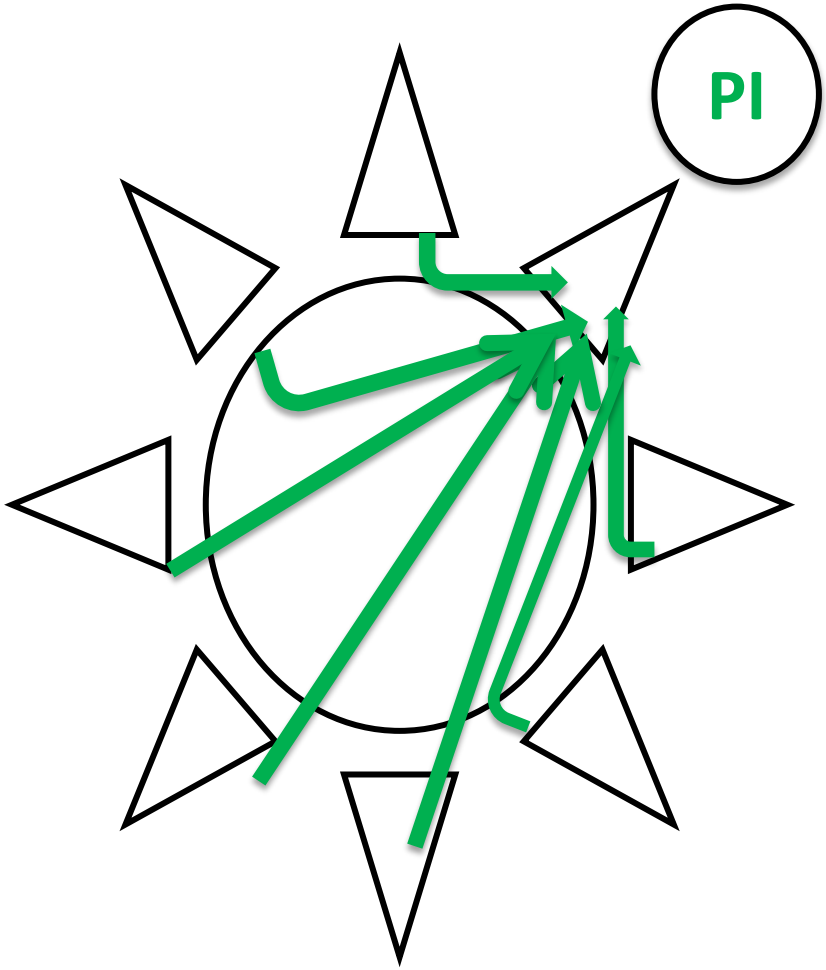

Collaboration

Advantages

Variation

Collaboration allows you to

1) identify it

2) manage it – in study plans
- in data analysis

3) learn from it

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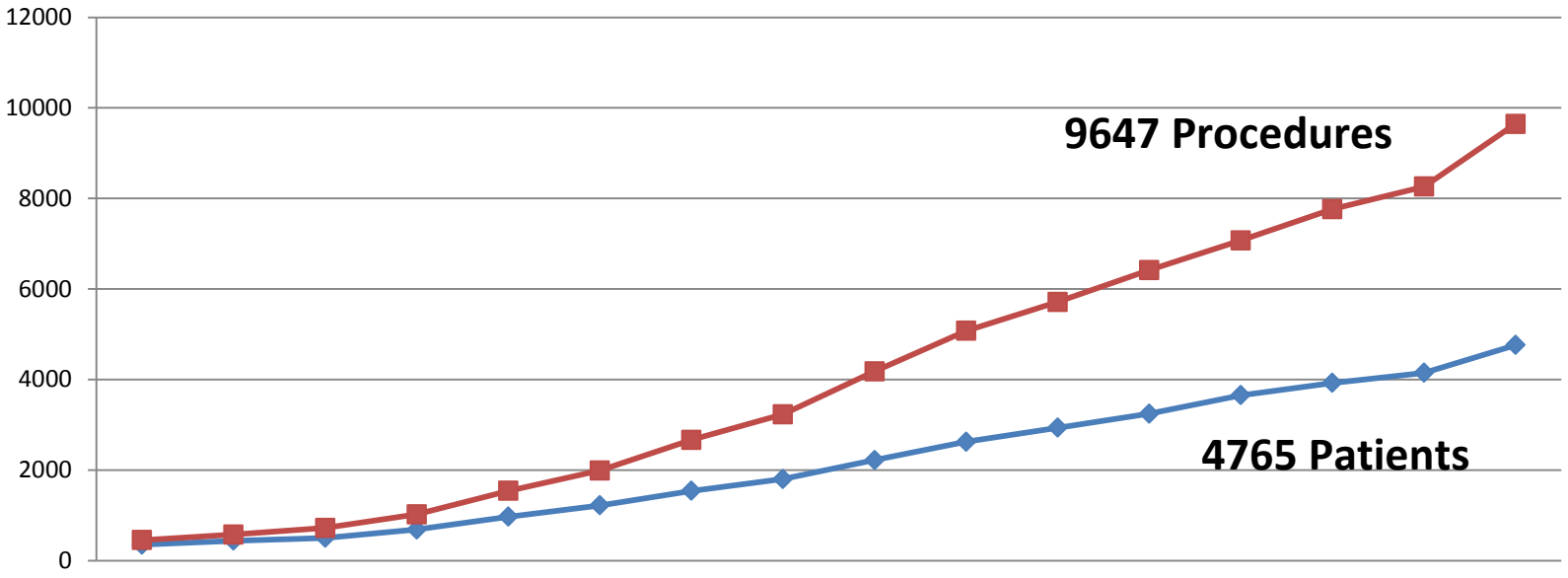
Volume

First look

Accrual, sample size

Power



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Learning

Frequent discussions

- conf call q 2 weeks
- network meeting q 6 months

Learn from each other

- study question
- study design
- data forms
- data analysis
- manuscript prep

9 clin epi trained
2 PhD stats
8 experienced peds neurosurg researchers
10 expert coordinators

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Rationale and Methodology of the Entry Site Trial

William Whitehead, MD
Principal Investigator
Texas Children's Hospital

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Hydrocephalus Association

Shunt Survival Curve in Pediatric Patients

Shunt Failure is a major problem for pediatric patients with hydrocephalus

-Drake, Kestle, et.al., Neurosurgery, Vol.43,No.2, August 1998

Hydrocephalus Association Survey Results

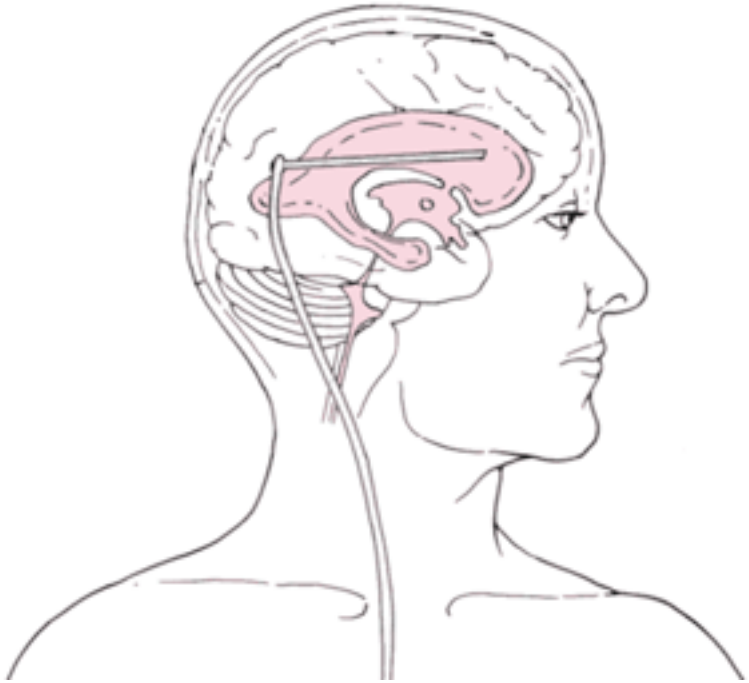
How important is this research topic to you? Please rank each one using the scale provided.

	Not Important	Somewhat Important	Important	More Important	Very Important	Total	Average Rating
Reduce shunt infection rates.	**1.35%** 9	**3.76%** 25	**20.00%** 133	**18.35%** 122	**56.54%** 376	665	4.25
Reduce shunt failure rates.	**0.90%** 6	**0.60%** 4	**6.63%** 44	**13.25%** 88	**78.61%** 522	664	4.68
Improve the identification and treatment of slit ventricles (occurs when the ventricles become small and slit-like, usually due to too much fluid drainage over time).	**2.72%** 18	**9.83%** 65	**28.29%** 187	**22.69%** 150	**36.46%** 241	661	3.80
Treat hydrocephalus without a surgically implanted device (example: moving from the shunt to an Endoscopic Third Ventriculostomy (ETV) as the most common treatment).	**1.80%** 12	**5.71%** 38	**17.89%** 119	**19.10%** 127	**55.49%** 369	665	4.21
Conduct lab-based research, possibly using animal models, to understand the brain with hydrocephalus and how it works.	**8.17%** 54	**14.22%** 94	**23.75%** 157	**18.31%** 121	**35.55%** 235	661	3.59
Prevent the development of hydrocephalus.	**2.40%** 16	**5.24%** 35	**14.22%** 95	**14.22%** 95	**63.92%** 427	668	4.32

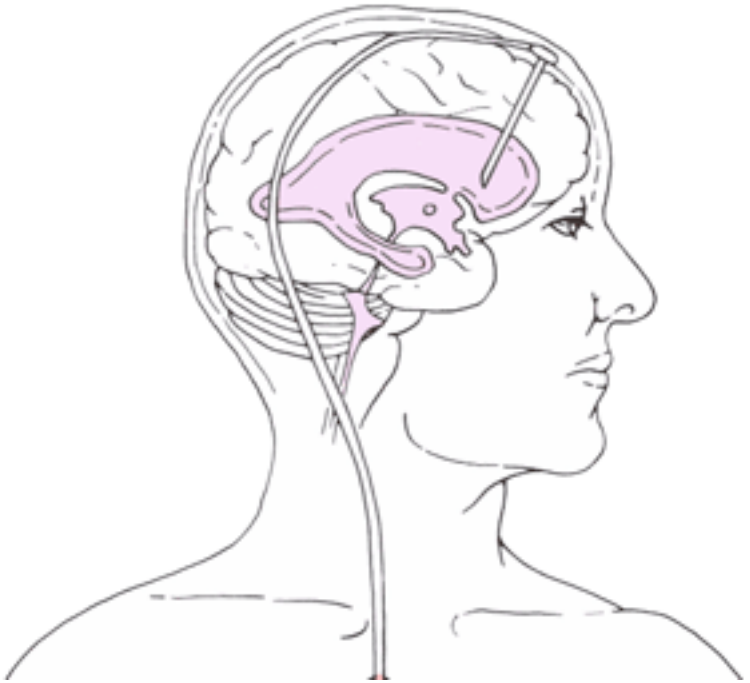
HA Members: Amanda Garzon (Dir Comm and Marketing), Aisha Heath (Dir of Development), Karima Roumila (Dir of Support and Education), Amy Weist (Business Manager), Laurel Fleming, Paul Gross

Entry Site

Background

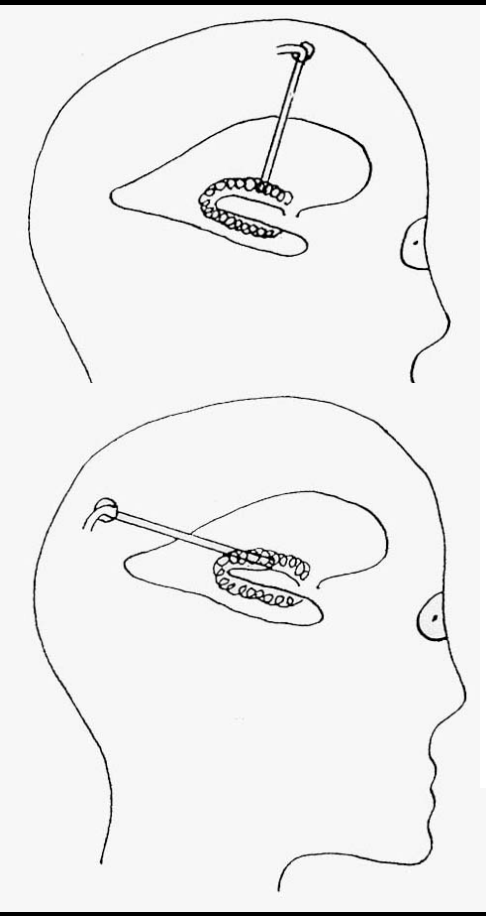


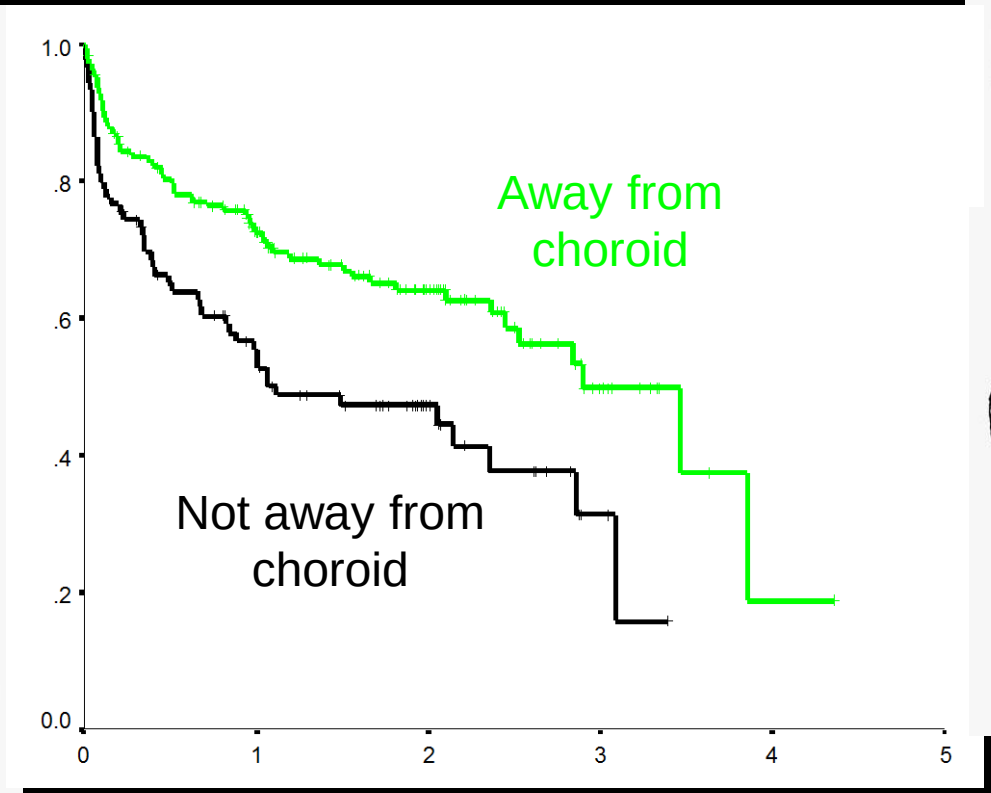
Posterior

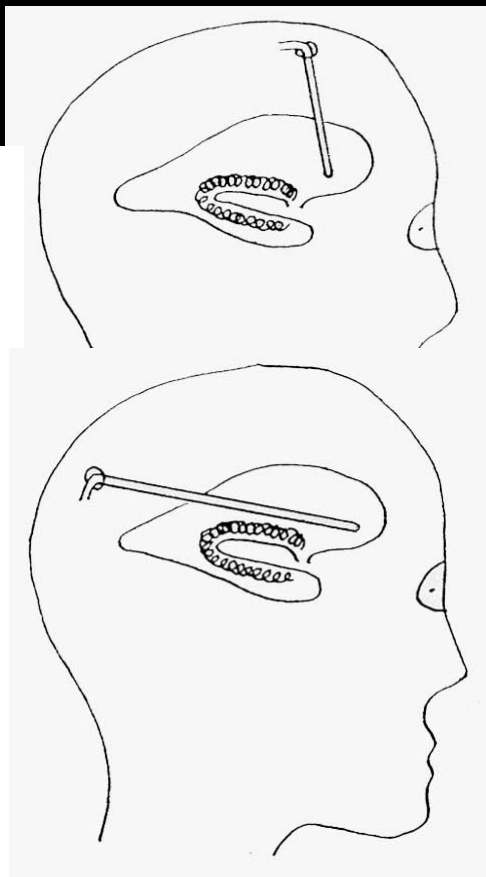


Anterior

Endoscopic Shunt Insertion Trial







Study Question

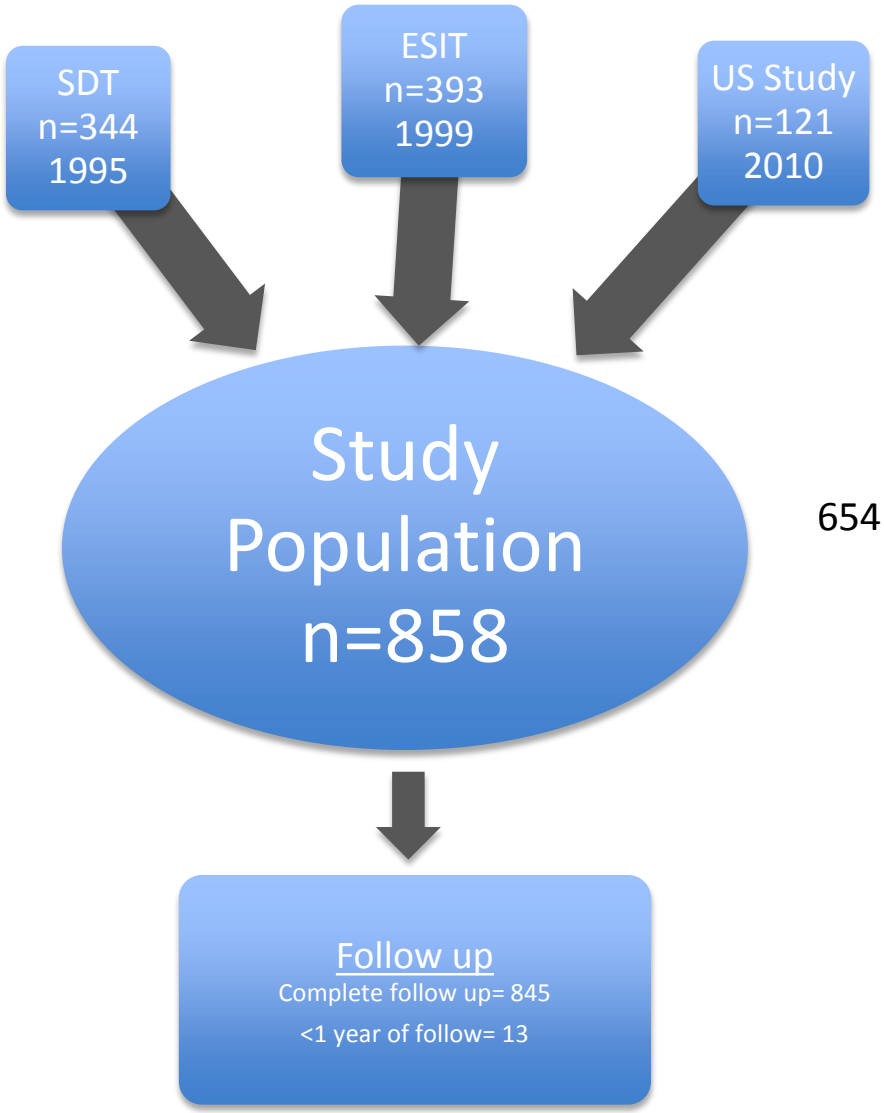
Using shunt survival as the outcome, what is the best target for CSF shunt ventricular catheters in pediatric patients undergoing first time shunt insertion?

HCRN Study on Ventricular Catheter Location

RECRUITMENT

ELIGIBILITY

F/U

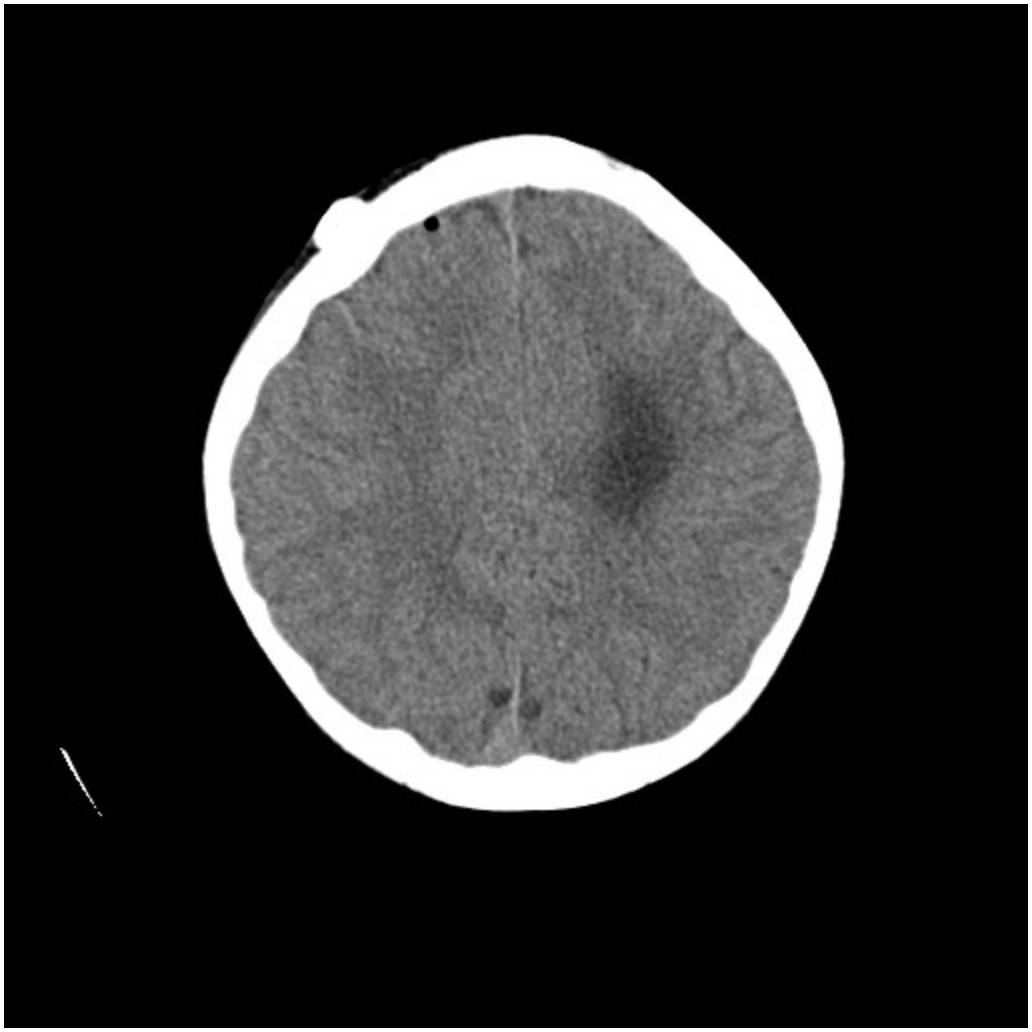


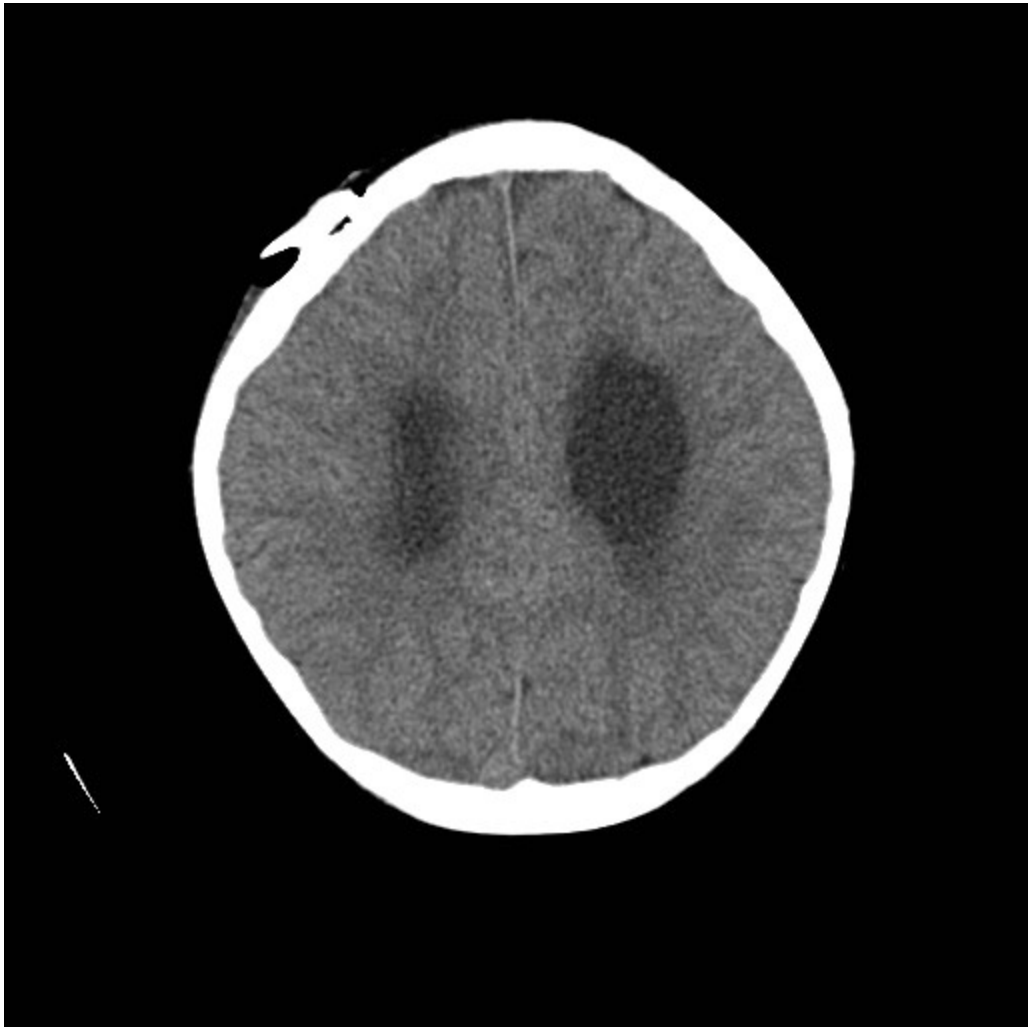
654 subjects with reviewable scans

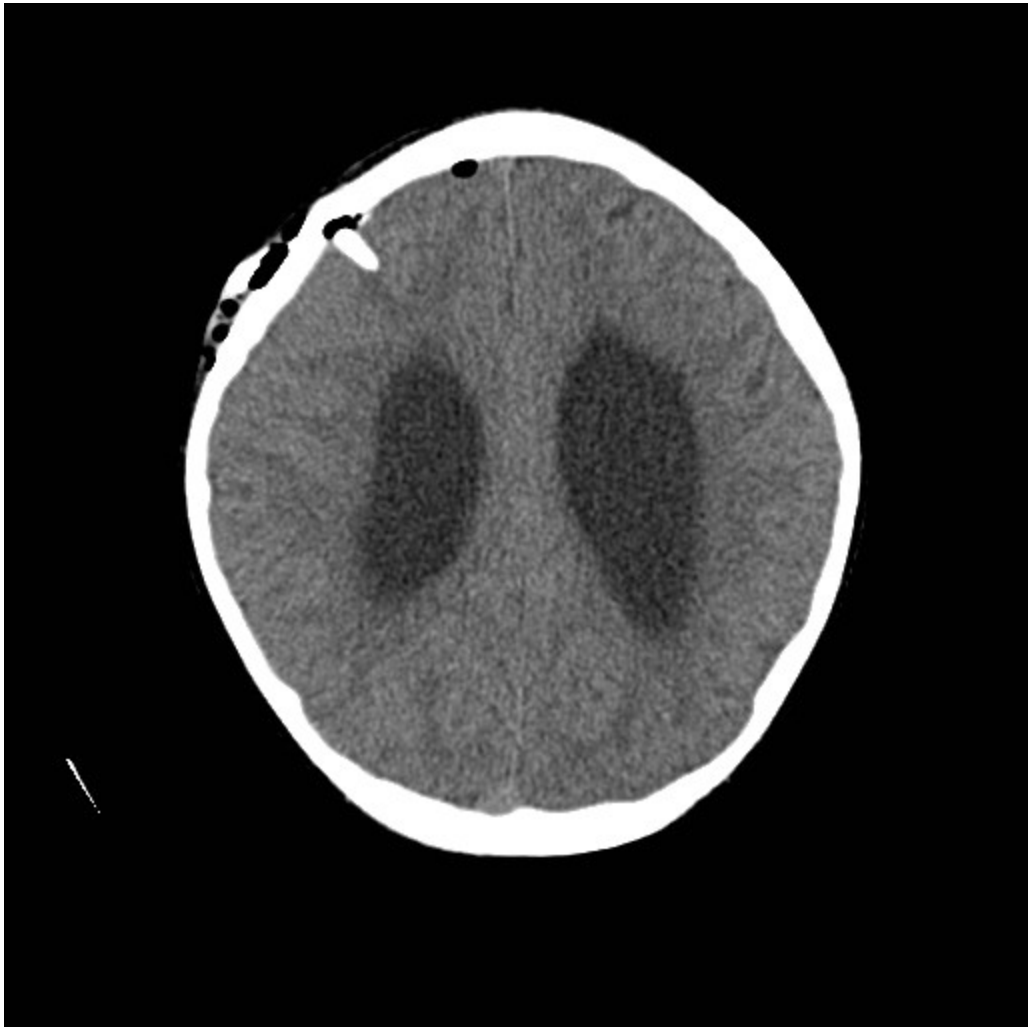
Variables

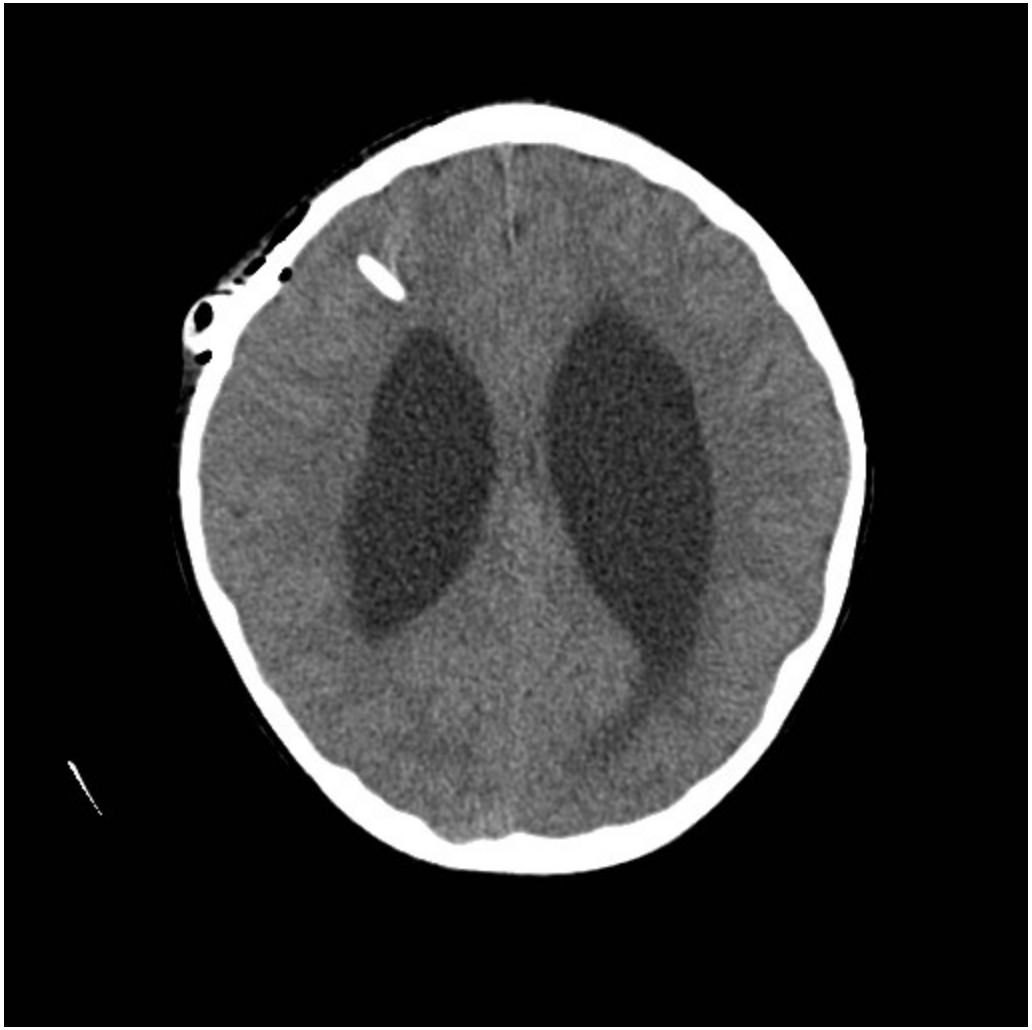
- Ventricular Catheter Location (target)
  - Frontal Horn
  - Trigone
  - Body
  - Third
  - Temporal Horn
  - Brain
  - Cistern
- Other Variables:
  - Age (<1 m; 1-6m; 6-12m; 1 to 10y; >10y)
  - Surgeon (>10 cases)
  - Etiology of hydrocephalus
  - Decade of Surgery (1990s; 2000s)
  - Entry Site (anterior; posterior)

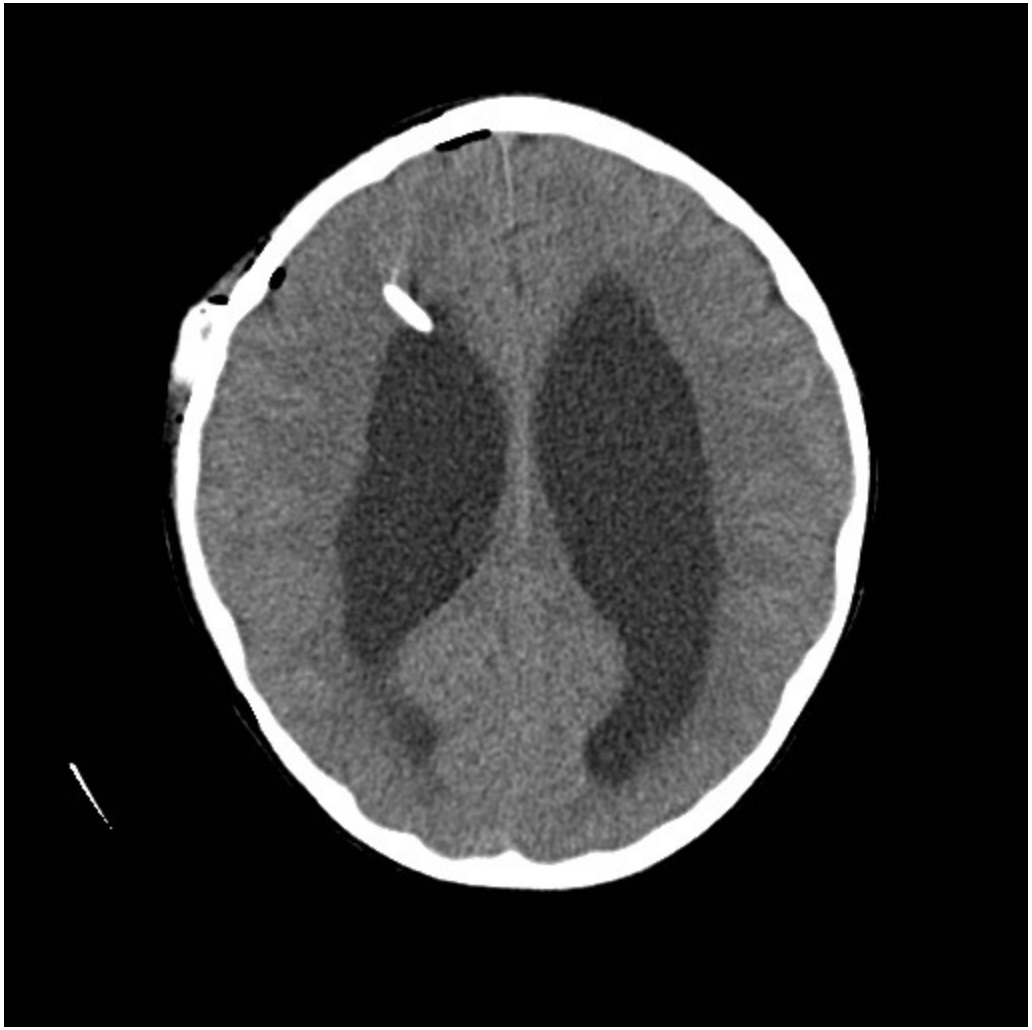
Frontal Horn

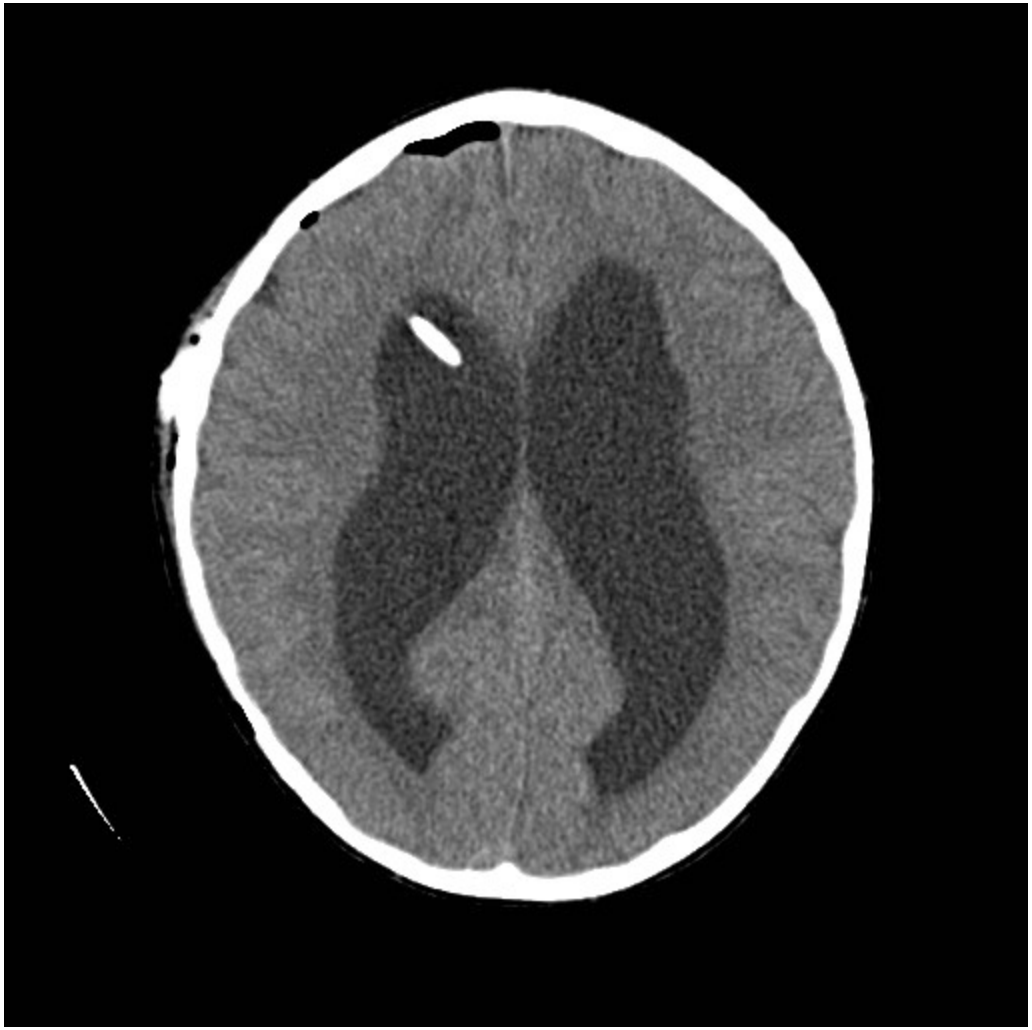


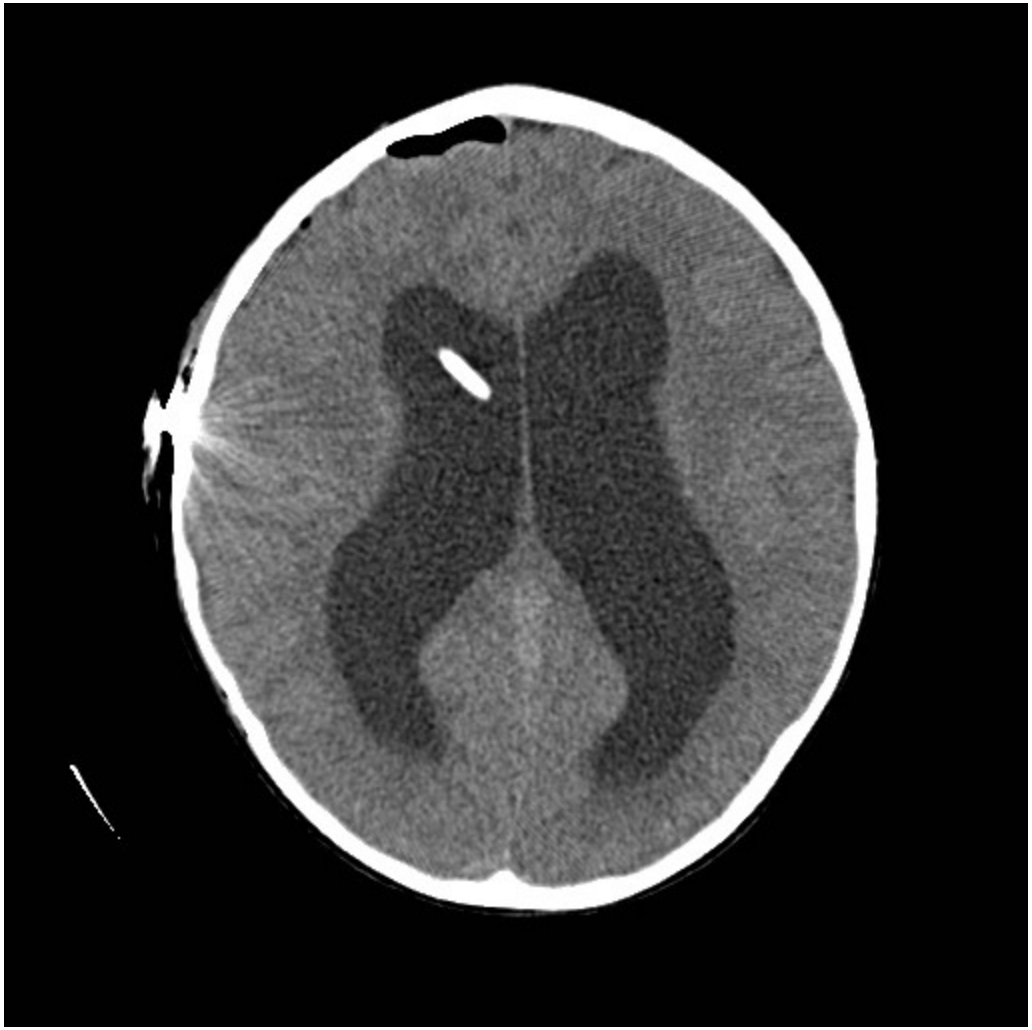


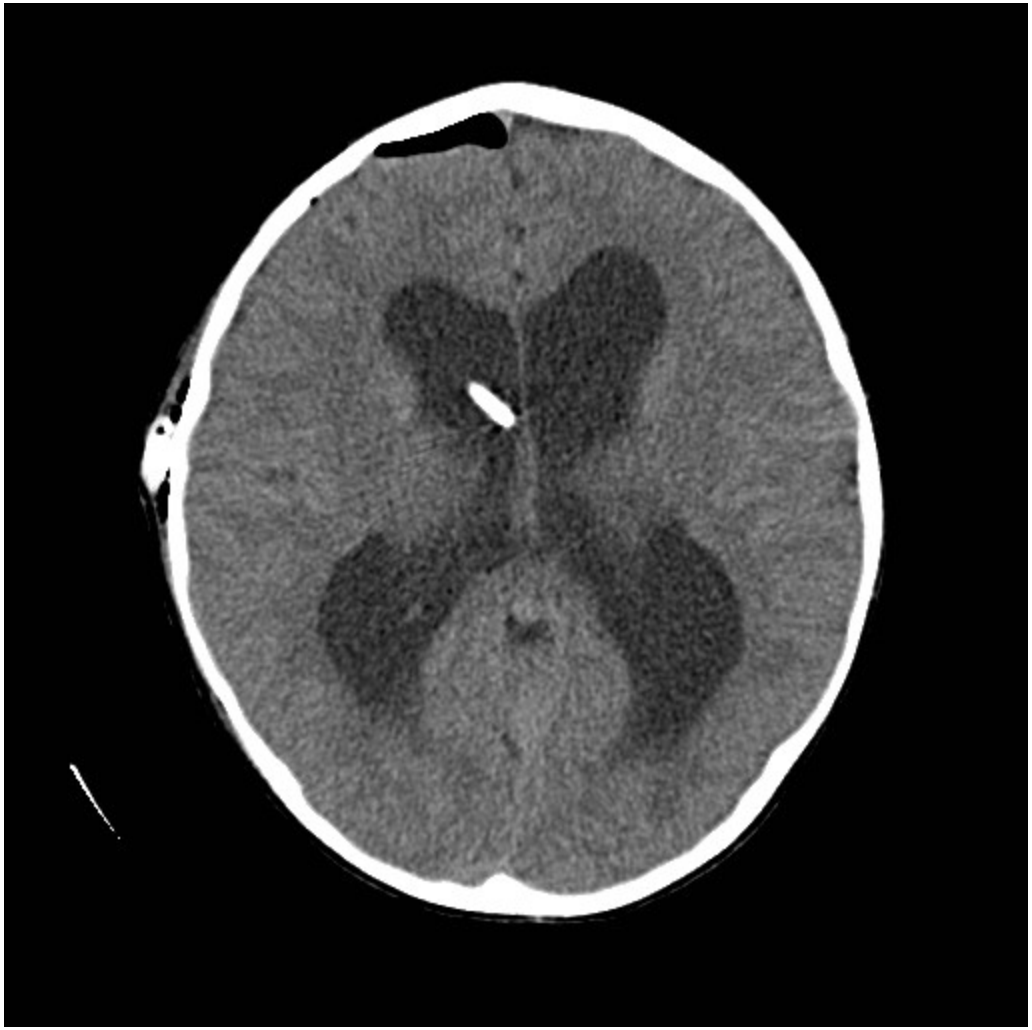


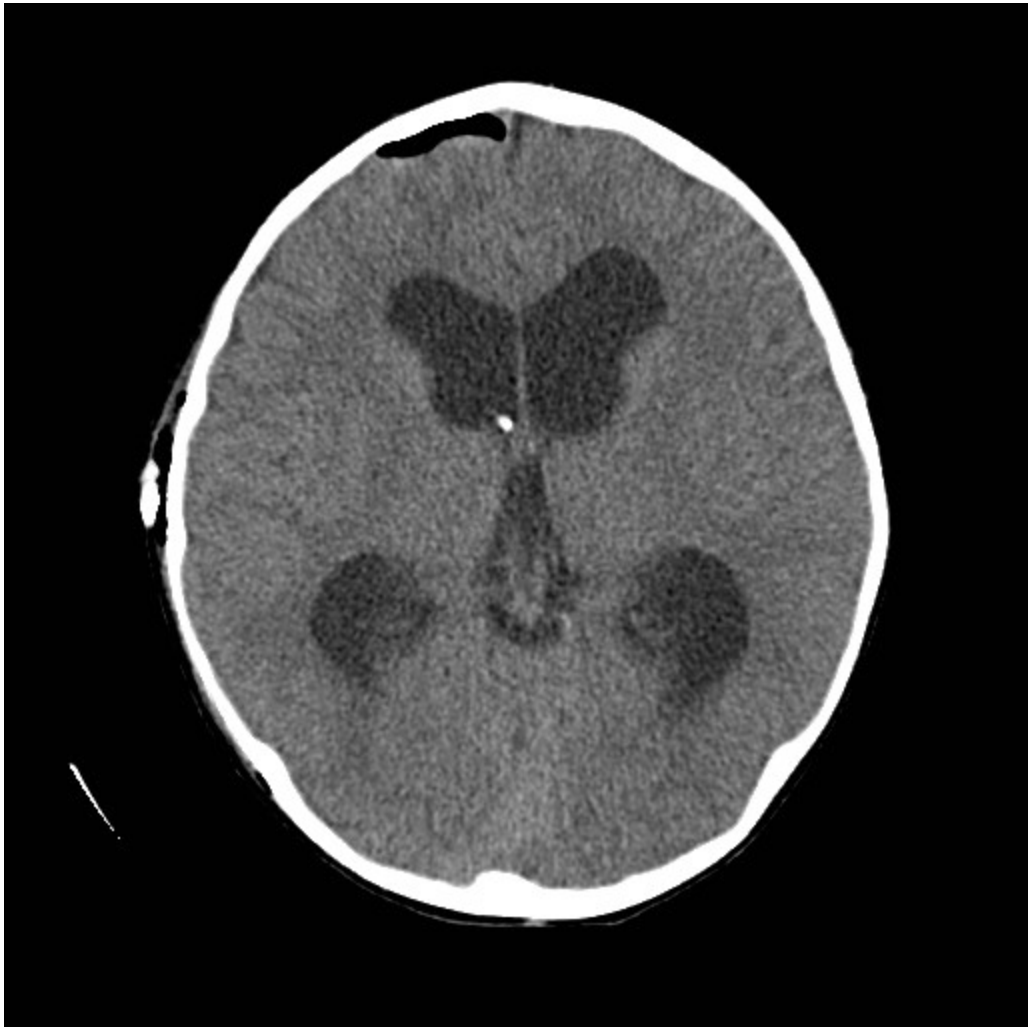


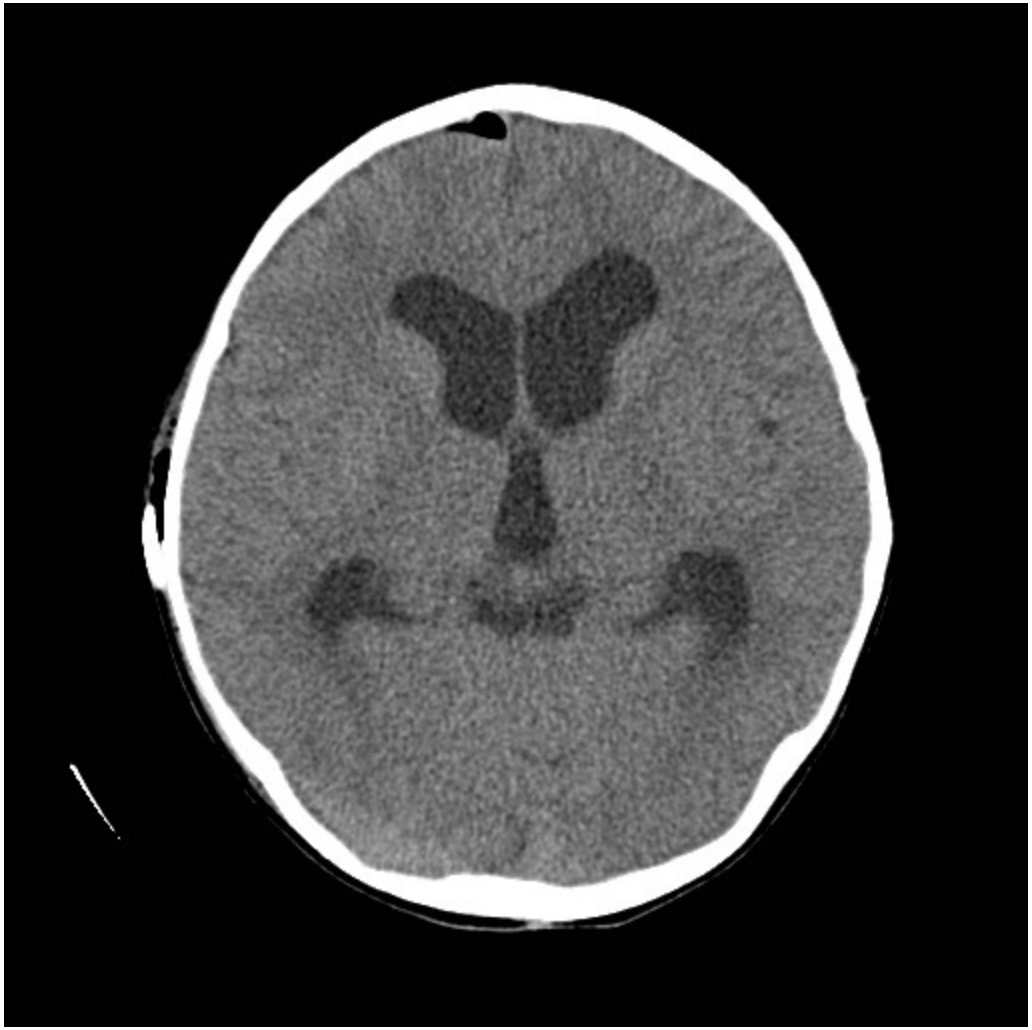




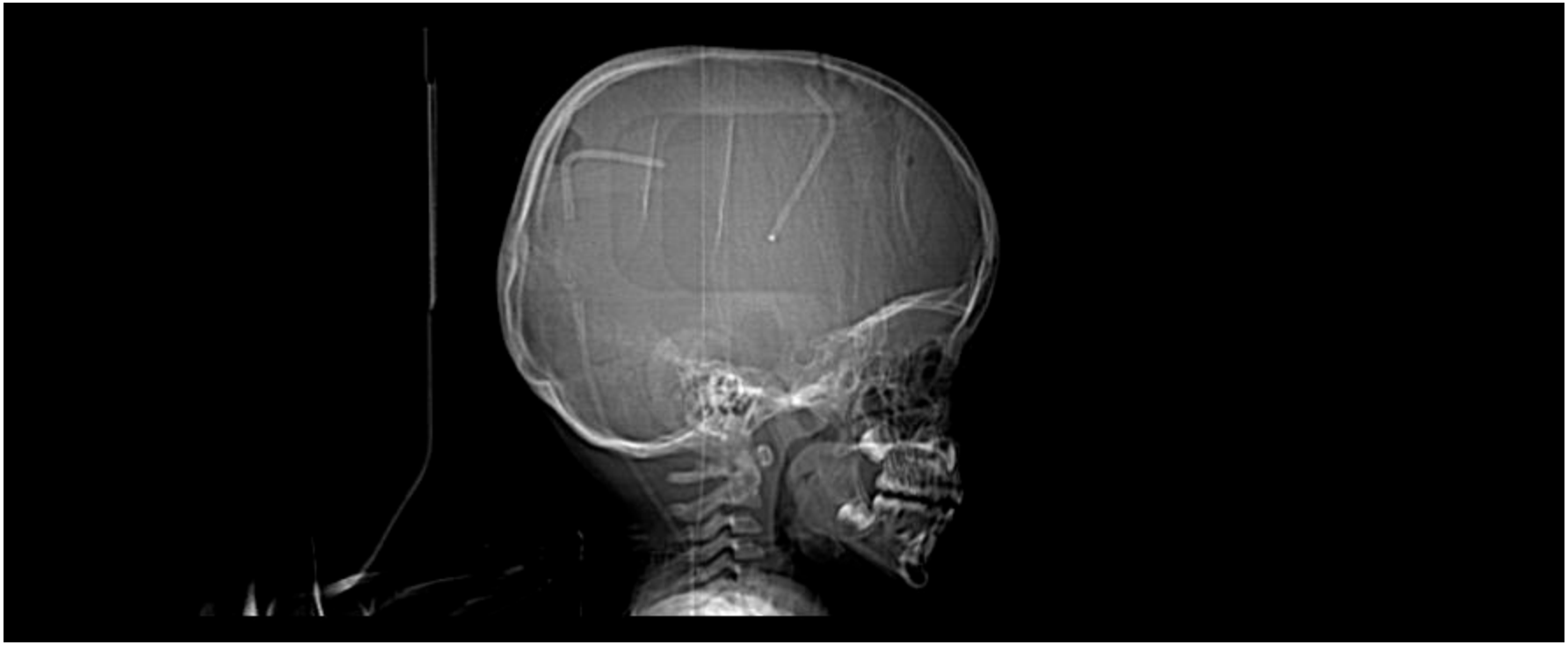


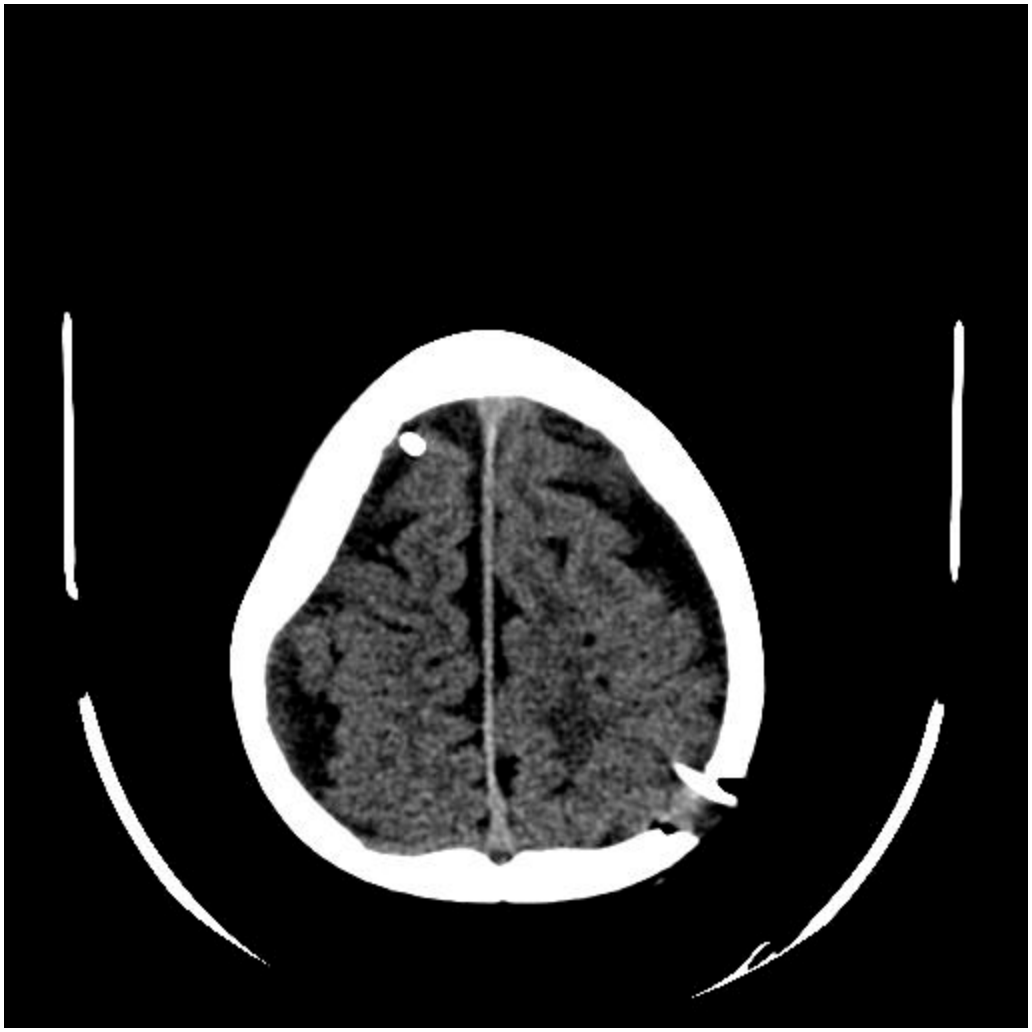


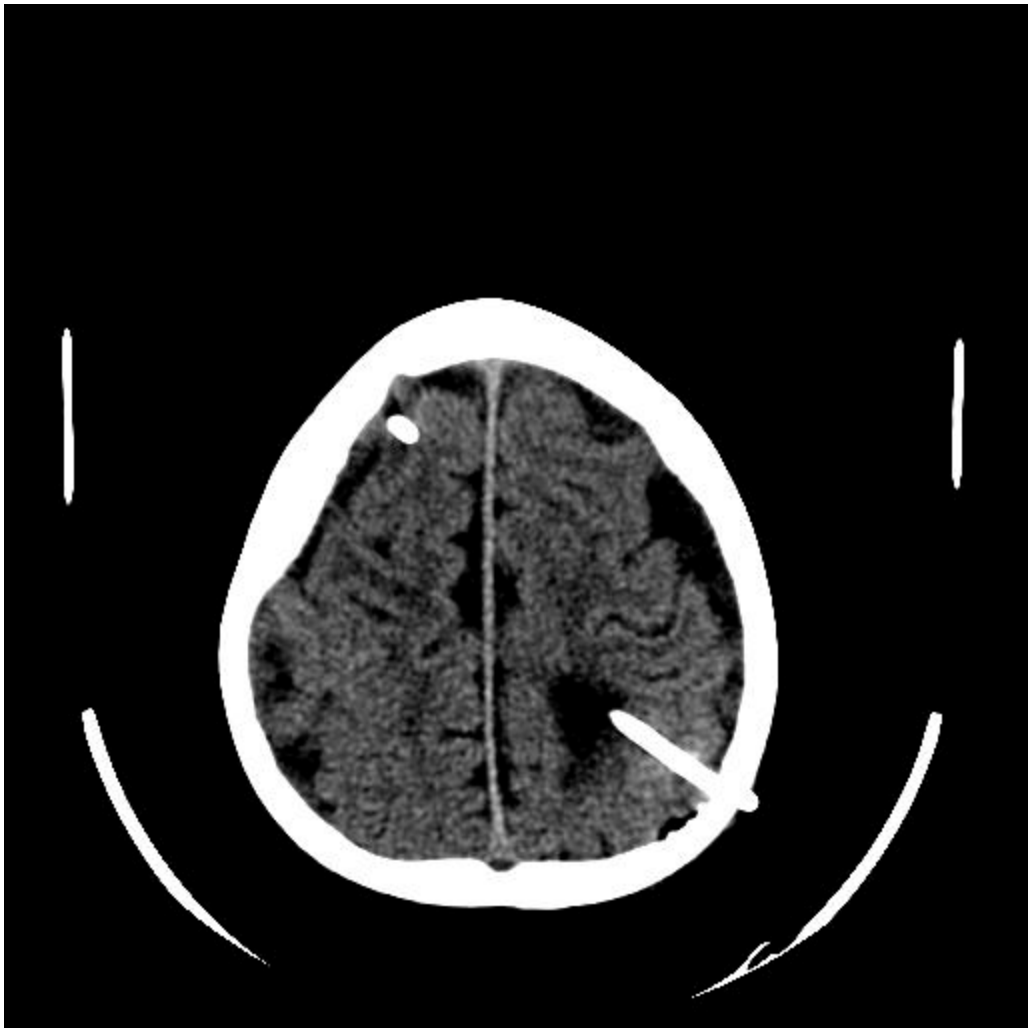


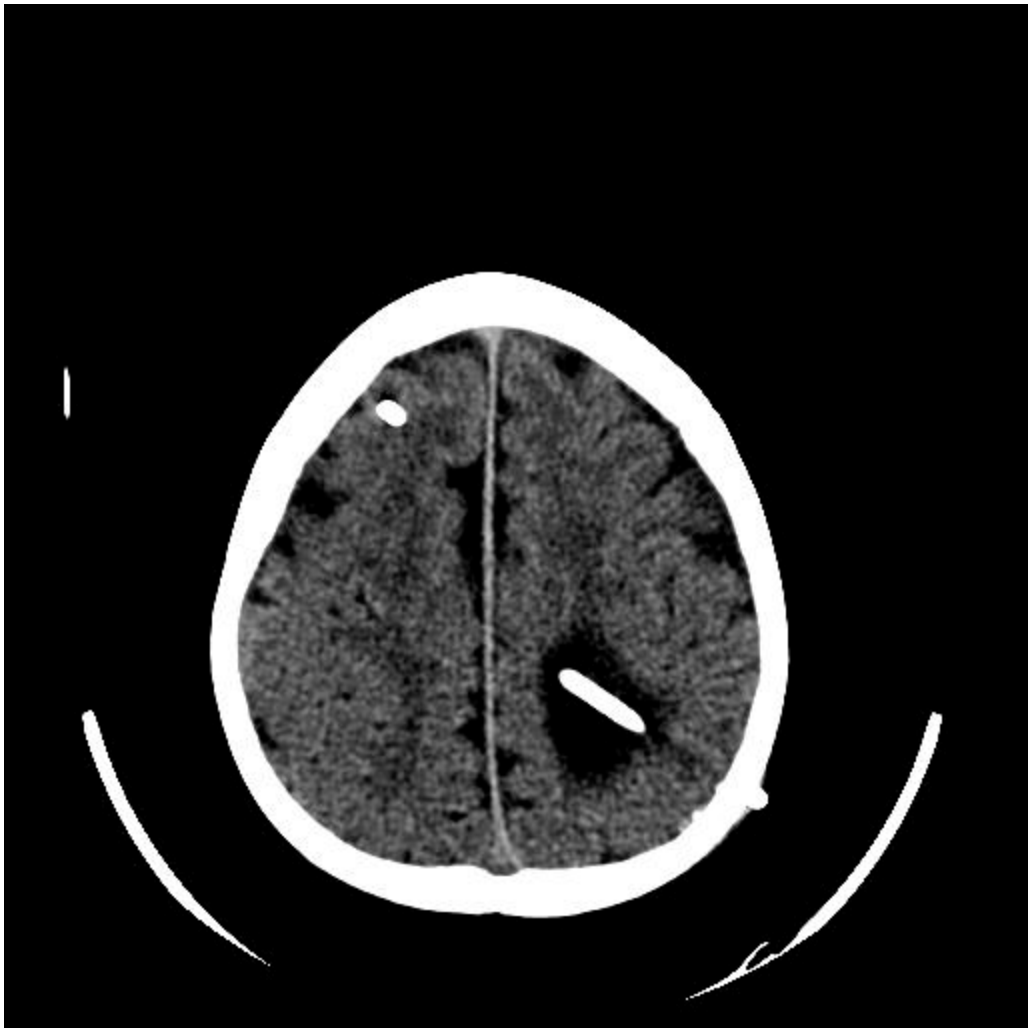


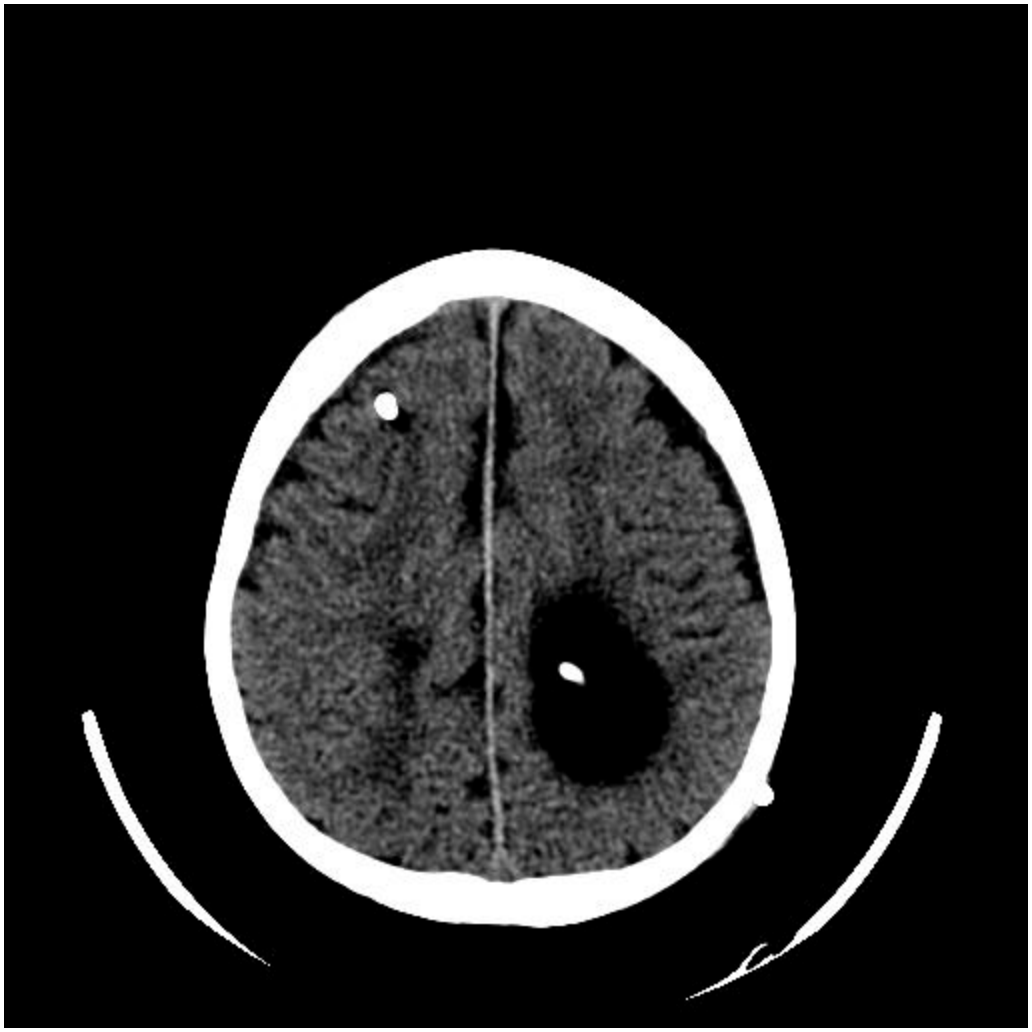
Trigone



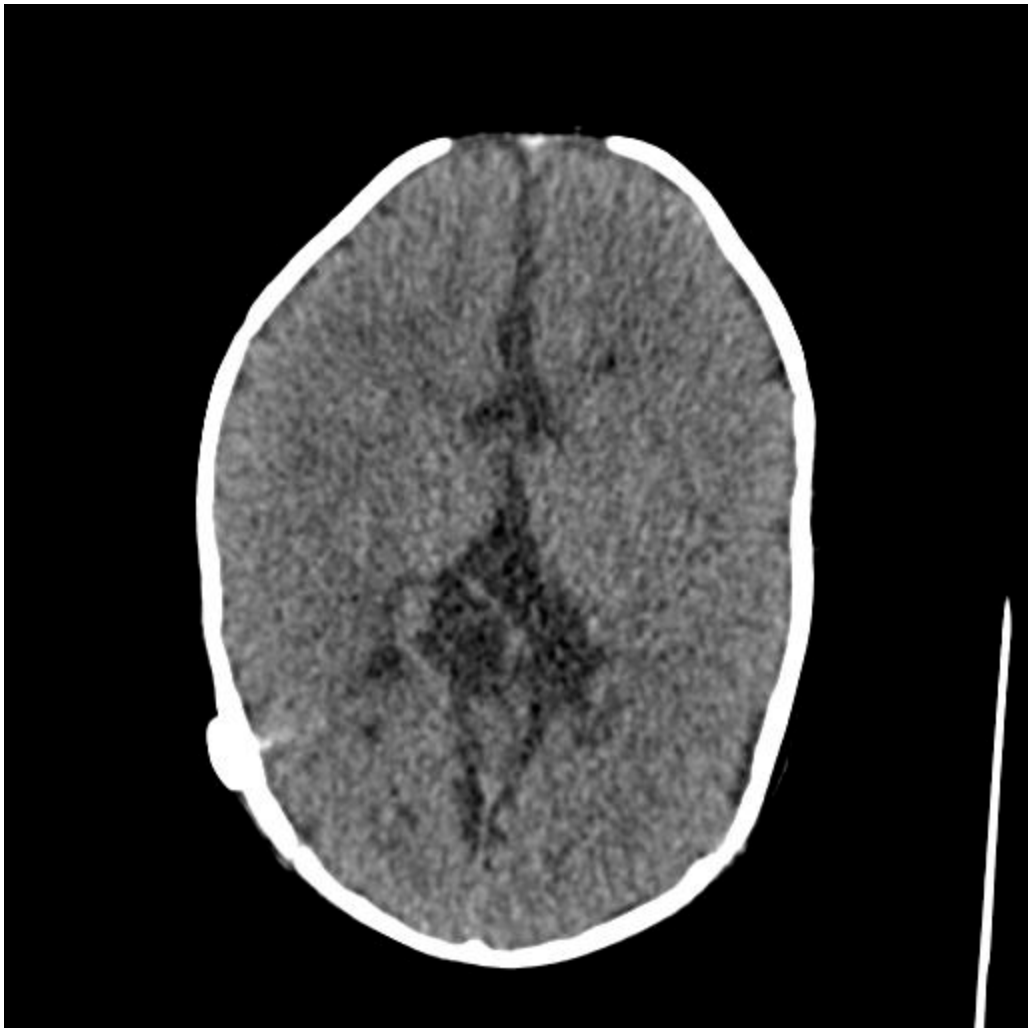


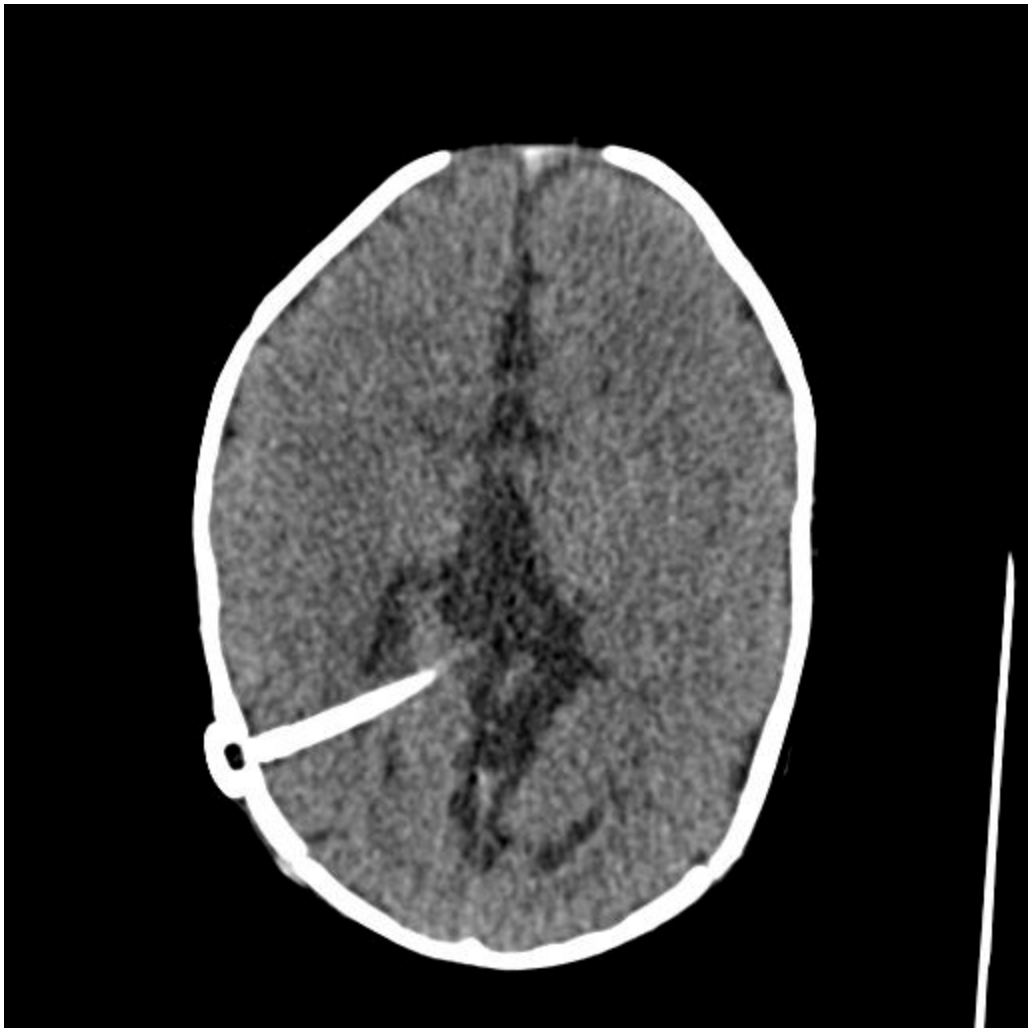


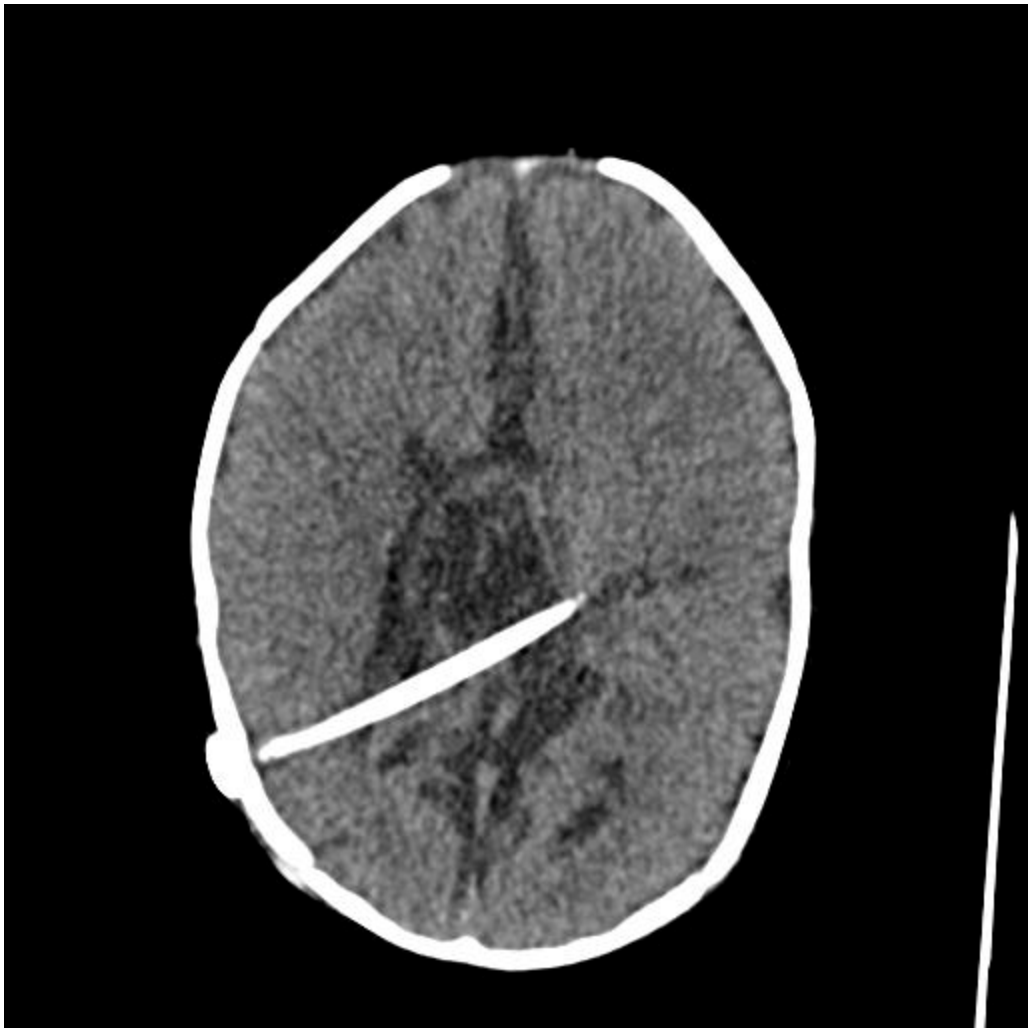


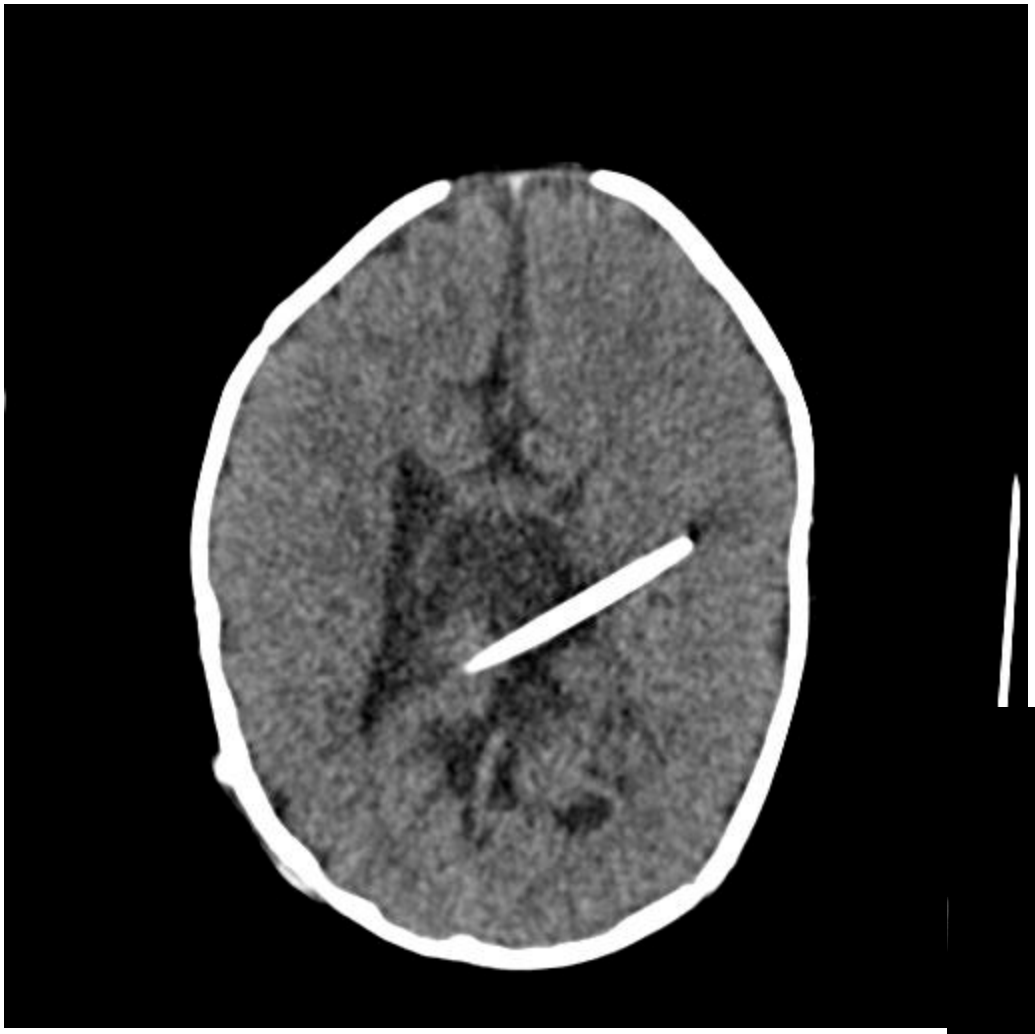


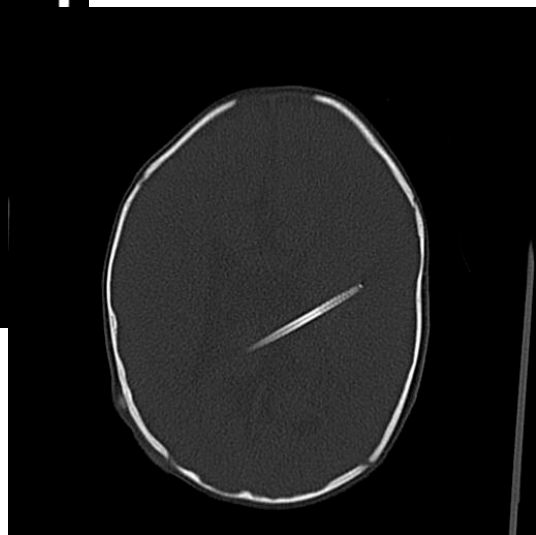
Brain

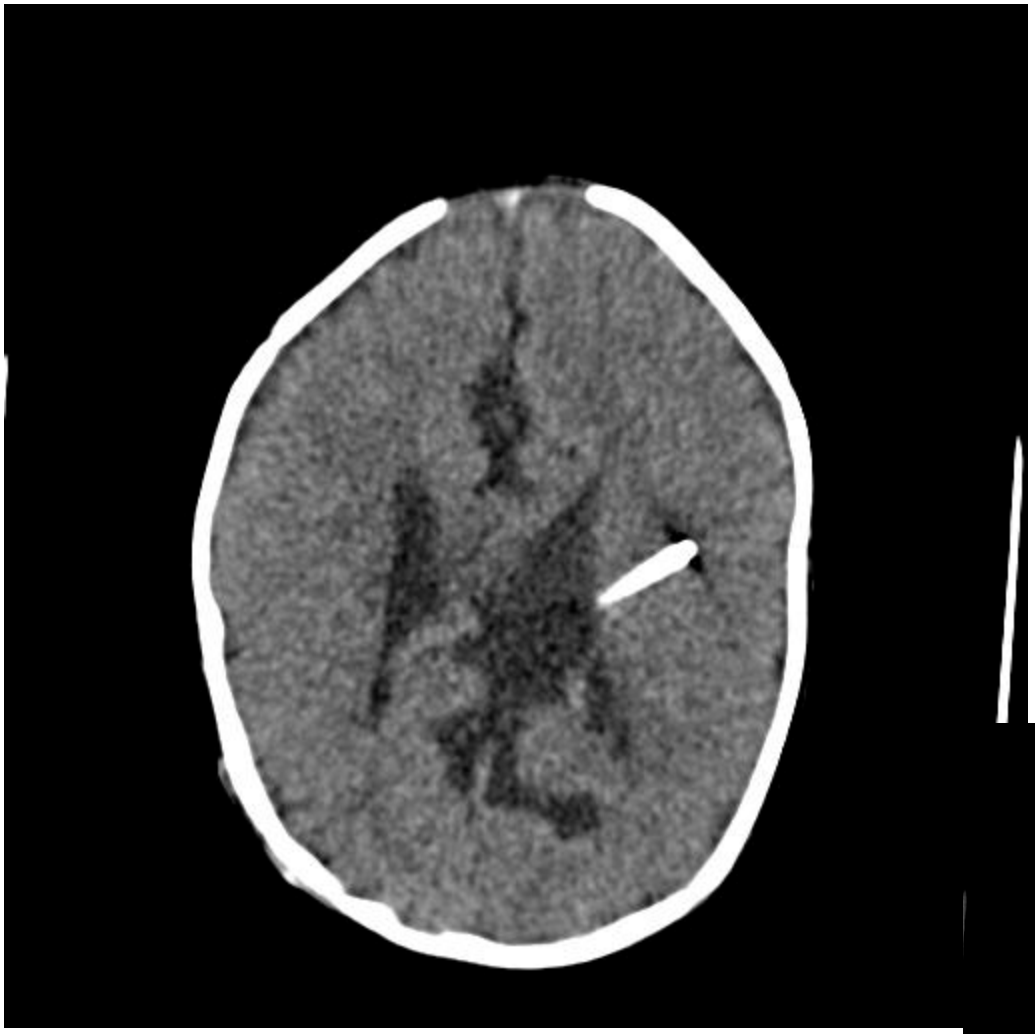


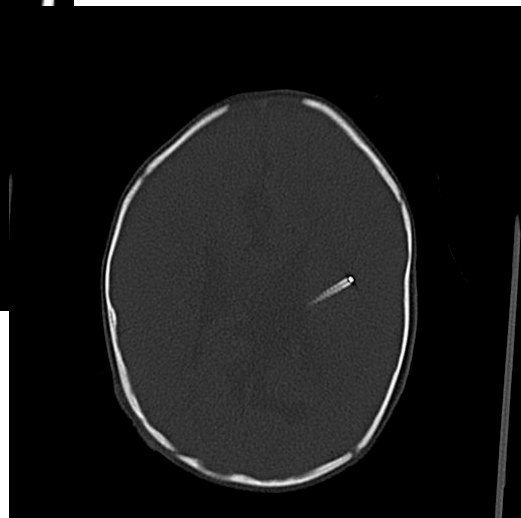


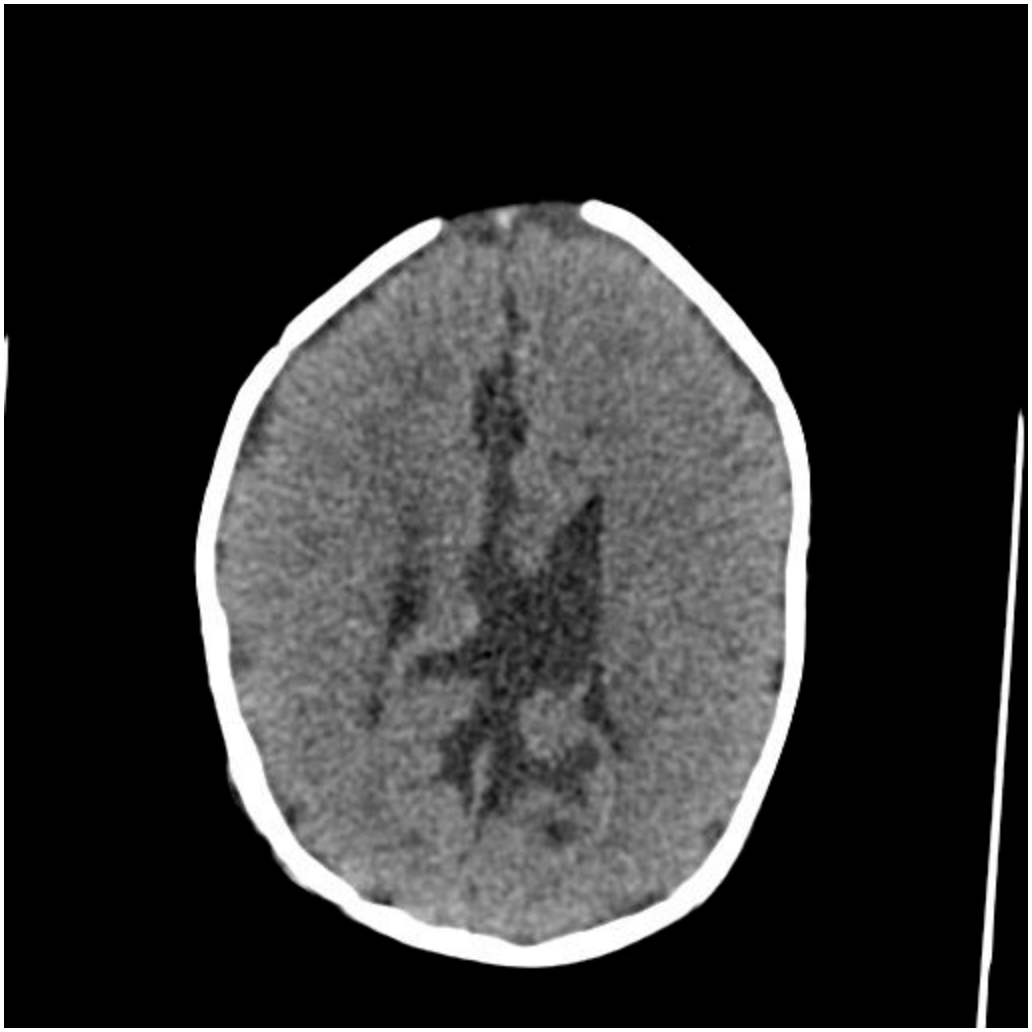


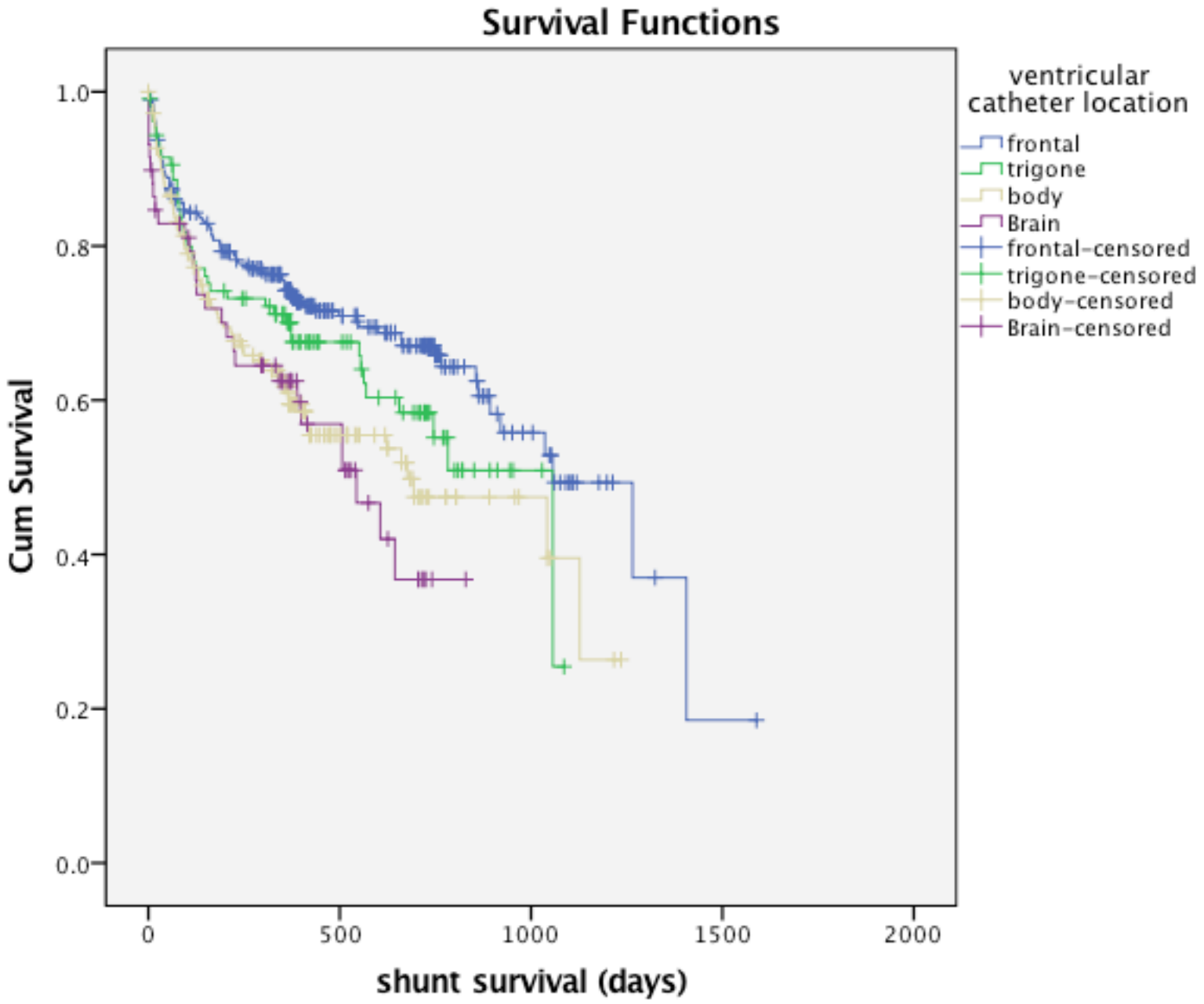




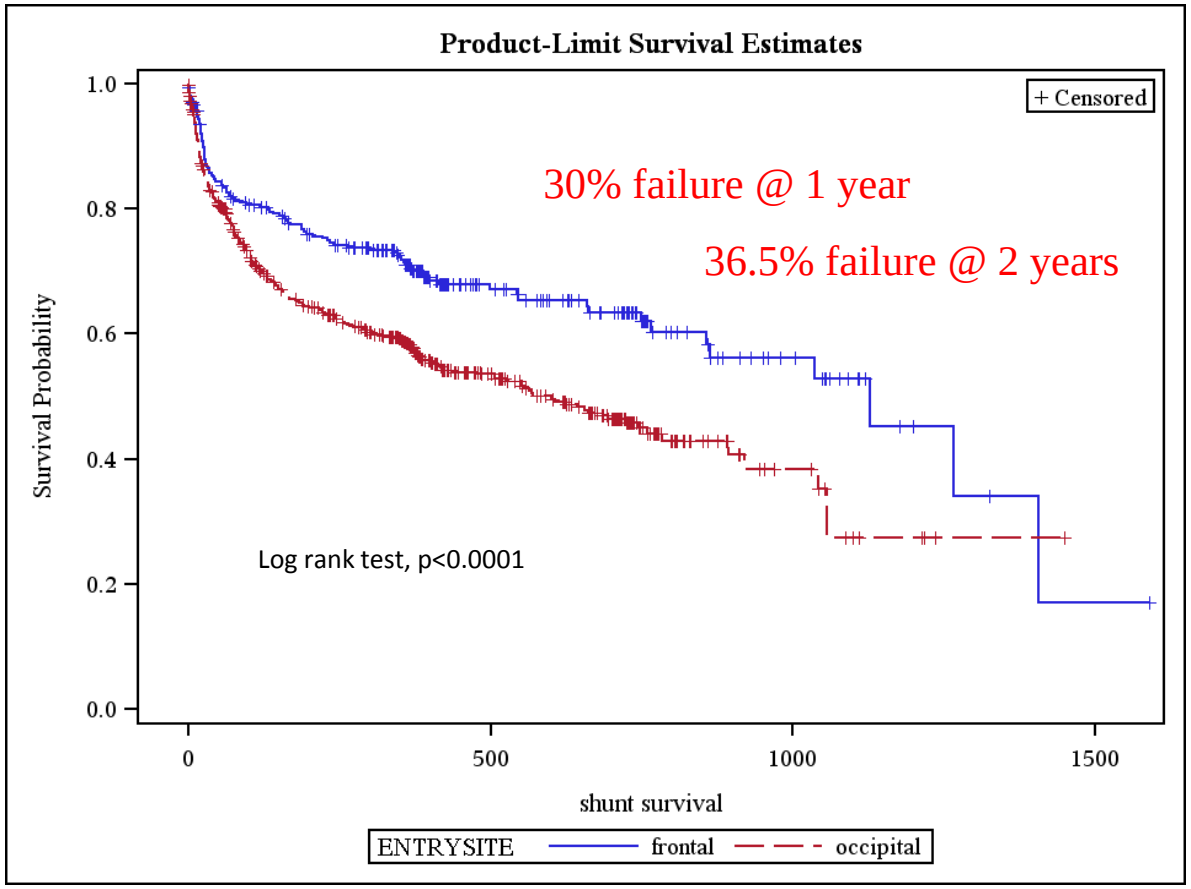







Survival Functions
Cum Survival
1.0
0.8
0.6
0.4
0.2
0.0
0
500
1000
1500
2000
shunt survival (days)
ventricular catheter location
frontal
trigone
body
Brain
frontal-censored
trigone-censored
body-censored
Brain-censored

Anterior v. posterior entry site shunt survival curves



Anterior entry Site has better shunt survival curve

Entry Site	Total cases	# of events	# censored	Shunt Survival 1 year	Shunt Survival 2 years
Anterior	300	102	198 (66%)	70.6%	63.5%
Posterior	550	256	294 (53.5%)	58.2%	45.7%

Multivariate Cox Model

- Age
- Surgeon
- Etiology of Hydrocephalus
- Decade of Surgery
- Entry Site
- Ventricular Catheter Location

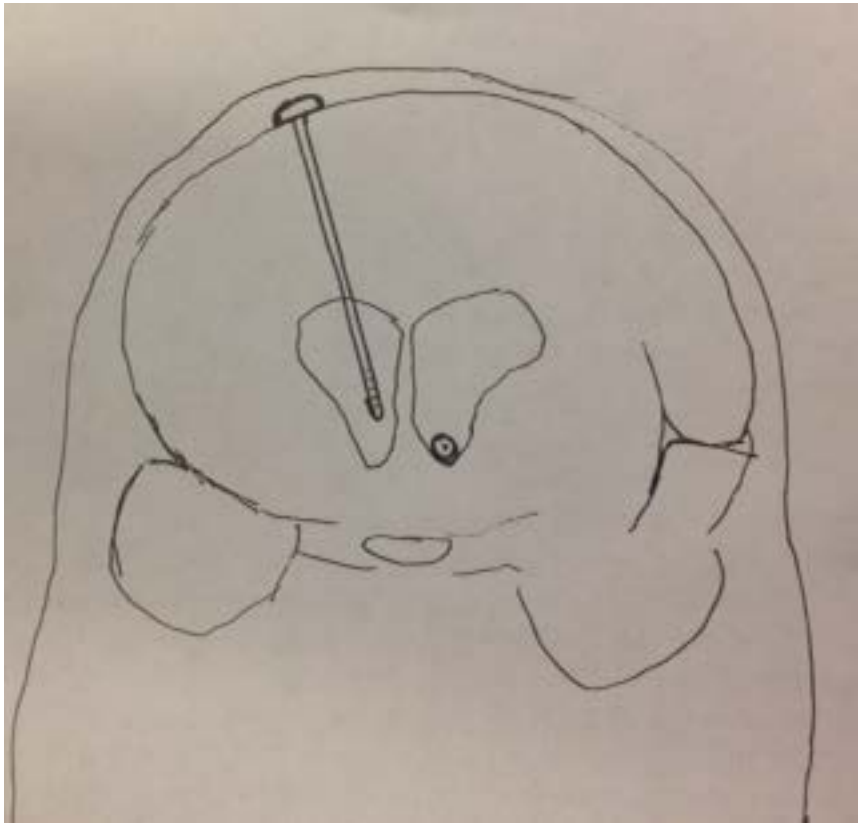
Results of Cox Proportional Hazard Model Analysis

Variable	Significance [p-value]	Hazard Ratio [Exp(B)]	95% CI Lower	95% CI Upper
Entry Site	0.016			
Posterior		Reference		
Anterior		**0.646**	0.453	0.922
Age	<0.001			
Etiology	0.103			
Surgeon	0.003			
Time period of Surgery	0.483 (NS)			
Ventricular Catheter Location	0.709 (NS)			

Background

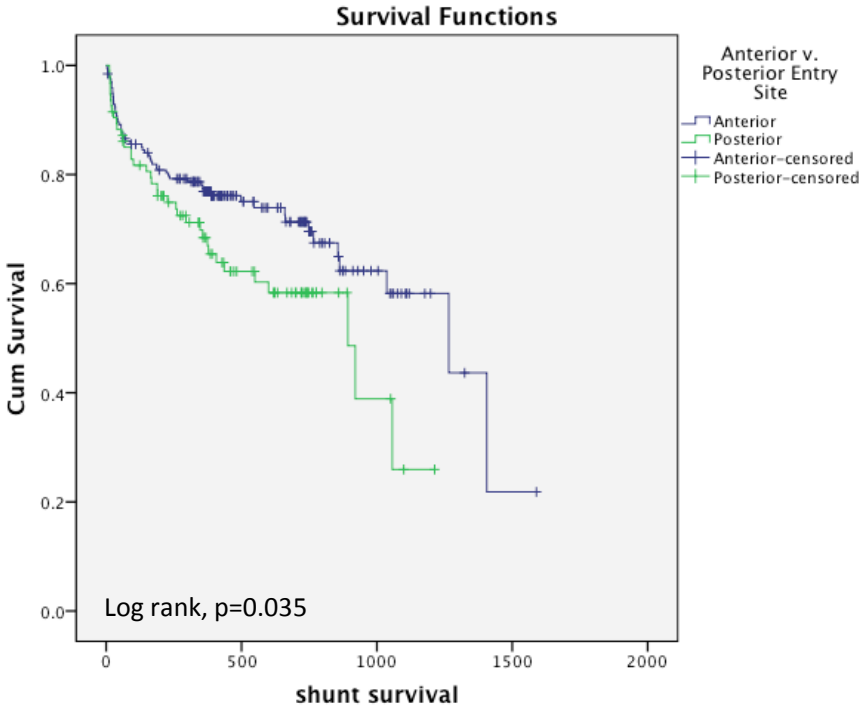
Entry Site

Anterior



Posterior

Anterior v. posterior entry site survival curves for catheters in frontal horn (n=289)



Entry Site & Ventricular catheter location	N	# of events	# censored	Shunt Survival 1 year	Shunt Survival 2 years
Anterior-Frontal horn	195	56	139 (71.3%)	76.9%	71.3%
Posterior- Frontal horn	94	37	57 (60.6%)	68.4%	58.4%

Comparison of shunt failure by sub-types

Type of Shunt Failure	Anterior Entry	Posterior Entry	Significance
Obstruction	**19.0%**	**32.9%**	Chi square=21.967; p<0.001
Overdrainage	2.7%	3.5%	
Loculation	2.3%	0.9%	
Infection	10.0%	9.3%	
Censored	66%	53.5%	

A decreased rate of catheter obstruction appears to be
The reason for better shunt survival

Entry Site Selection

Literature review

Study	Year	Anterior	Posterior
Albright (n=114)	1988	54.4%	45.6%
SDT (n=343)	1998	16%	84%
ESIT (n=386)	2003	44%	56%
HCRN US study (n=121)	2010	62.0%	38.0%
Australian/Asian Neurosurgical Society Survey (n=111, 57%)	2008	9%	90%

Medical literature suggests that both entry sites are used commonly.

Entry Site Selection by HCRN Surgeons in the US Study

	n	Anterior	Posterior
Surgeon			
1	18	100%	0%
2	15	100%	0%
3	10	100%	0%
4	7	100%	0%
5	5	100%	0%
6	2	100%	0%
7	1	100%	0%
8	1	100%	0%
9	7	0	100%
10	5	0	100%
11	4	0	100%
12	2	0	100%
13	1	0	100%
14	22	31.8%	68.2%
15	15	33.3%	66.6%
16	4	75%	25%
17	2	50%	50%

Entry site is usually determined by surgeon preference and not patient factors

	Advantages	Disadvantages
Anterior	- less chance of obstruction due to lower chance of contact with the CP[1, 2] -has more consistent anatomical landmarks and placement of the proximal catheter anterior to the choroid plexus is easier[3, 4]	-shaving the scalp frontally is psychologically damaging for the child[1] -requires additional bridging incision to pass to abdomen which increases chances of infection[5] -frontal cortex is a locus for post shunt epilepsy[6]; but this is disputed by others[7, 8] - catheters placed via this route in an infant migrate superiorly with growth into the cortical mantle
Posterior	-fewer incisions (no bridging incision for tunneling) - posterior horn is large and easier to hit[3] -the atrium is often the most dilated part of the lateral ventricle and potentially the last chamber to collapse[2]	- catheters placed via this route in an infant into the frontal horn migrate posteriorly with growth onto the choroid plexus[9, 10] -if target is the frontal horn the margin for error with regard to trajectory is narrowest[11]

Both groups argue that their shunts last longer and are easier to put in.

J Neurosurg 69:883–886, 1988

Function of parietal and frontal shunts in childhood hydrocephalus

A. Leland Albright, M.D., Stephen J. Haines, M.D., and Floyd H. Taylor, Sc.D.

Departments of Neurological Surgery and Community Medicine, University of Pittsburgh, Pittsburgh, Pennsylvania and Department of Neurosurgery, University of Minnesota, Minneapolis, Minnesota

✓ This study was performed to determine if cerebrospinal fluid (CSF) shunts inserted via the frontal and parietal regions function for similar lengths of time. The medical records of 114 children with CSF shunts were reviewed. In 83 of these cases computerized tomography scans were also available. Ninety percent of the operations were to insert the child's first shunt. The site of insertion, cause of hydrocephalus, patient's age, surgeon, duration of function (time from insertion to malfunction or to latest follow-up evaluation), presence of infection, catheter location within the ventricle, and duration of function of the subsequent shunt were recorded. Data were analyzed by the chi-square, logistic regression, and life-table methods. Shunts had been inserted via the frontal route in 62 children and via the parietal route in 52. The children's ages, causes of hydrocephalus, and infection rates were similar in both groups. Duration of shunt function was predicted by the site of shunt insertion and the catheter position within the ventricles: shunts inserted via the frontal region functioned significantly longer than parietally inserted shunts, both as the initial shunt (Wilcoxon, $p = 0.0008$) and after a malfunction, and catheters positioned within the ipsilateral frontal horn functioned significantly longer than those in other ventricular locations (Wilcoxon, $p = 0.03$).

Key Words • **hydrocephalus** • **ventriculoperitoneal shunt** • **frontal region** • **parietal region**

The treatment of childhood hydrocephalus is hindered by the two common complications of cerebrospinal fluid (CSF) shunts: obstruction and infection. The most common site of shunt obstruction is the ventricular catheter.[4,5] Catheters are usually inserted into the ventricular system either frontally, along the coronal suture at the pupillary line, or posteriorly, in the parietal region. Neurosurgeons have strong opinions as to which of the sites is preferable.

At the Children's Hospital of Pittsburgh, the years 1978 to 1981 were a period of transition from inserting shunts parietally to frontally, and children treated during that transition time have been followed long enough to be compared. This study was performed to determine

reviewed. Eighty-six children were excluded: those whose hydrocephalus was associated with tumors (because of uncertainty that persisted after tumor removal); those with hydrocephalus associated with cysts, if the shunt was inserted into the cysts; and those lost to follow-up study.

The study group comprised 114 children undergoing their first shunt in our hospitals; 90% were undergoing placement of their first shunt in any hospital. Four shunts were ventriculoatrial and 110 were ventriculoperitoneal. Ventricular catheters were not inserted with radiographic or ultrasound guidance, and none of the catheters had flanges. Postoperative computerized tomography (CT) scans were available for 83 of these

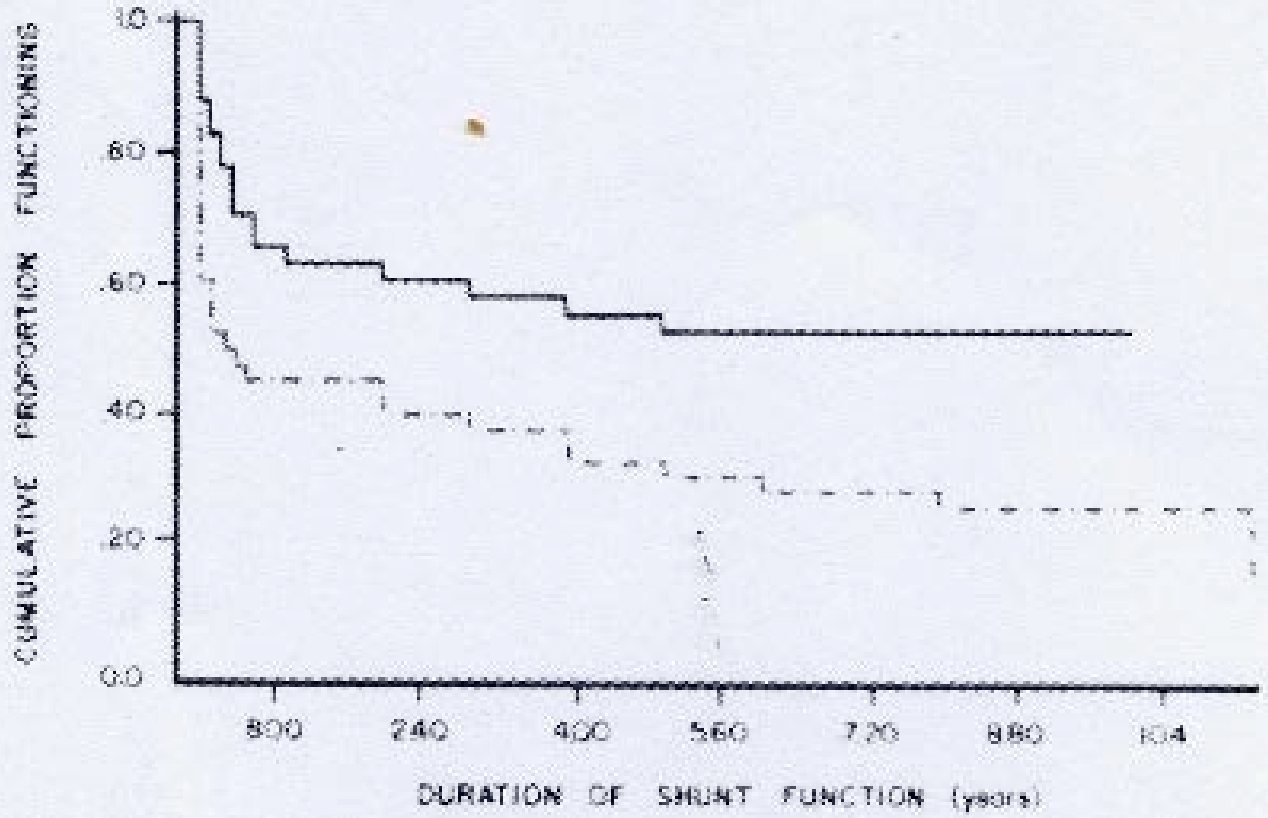


FIG. 1. Life-table analysis of duration of shunt function for children with shunts inserted in the frontal *(solid line)* and parietal *(broken line)* regions. The curves are significantly different (Wilcoxon, p = 0.0008; Savage, p = 0.0015).

Pediatr Neurosurg 1990–91;16:287–291

1016–2291/90–91/0166–0287 $ 2.75/0

A Prospective, Randomized Study of Shunt Function and Infections as a Function of Shunt Placement

Karin S. Bierbrauer[a], *Bruce B. Storrs*[b], *David G. McLone*[a], *Tadanori Tomita*[a], *Robert Dauser*[c]

[a]Division of Pediatric Neurosurgery, Children's Memorial Hospital, Chicago, Ill.; [b]Division of Pediatric Neurosurgery, Medical University of South Carolina, Charleston, S.C., and [c]Division of Pediatric Neurosurgery, University of Michigan, Ann Arbor, Mich., USA

Key Words. Hydrocephalus · Shunt · Shunt infection · Shunt malformation · Shunt insertion · Choroid plexus · Ventricular catheter

Abstract. Much controversy still exists about the relative advantages and disadvantages of anteriorly vs. posteriorly placed shunts in terms of infection rate and duration of function. During a 27-month period, all 121 patients seen requiring new shunt insertions were prospectively randomized to anterior or posterior placement. The mean duration of follow-up was 15 months. 70% of the shunts in the posteriorly placed group vs. 59% of the shunts in the anteriorly placed group did not require further surgery during the study period. In a life-table analysis of shunt survival as a function of placement, the shunts in the posteriorly placed group 'survived' slightly longer without malfunctioning or becoming infected than the anteriorly placed shunts. Therefore, the authors conclude that anteriorly placed shunts offer no advantage over posteriorly placed shunts in terms of shunt malfunction or infection.

Much controversy exists as to the proper placement of a new shunt in the pediatric patient with hydrocephalus. Some surgeons prefer an anterior insertion point just in front of the coronal suture, whereas others prefer a parieto-occipital location for the insertion of the ventricular catheter. The common goal is placement of the tip of the

undergo their initial shunt insertion procedure was an even or an odd month of the year, they were randomized into one of two groups: insertion via a frontal approach anterior to the coronal suture, or insertion via a posterior approach in the parieto-occipital region.

Seven pediatric neurosurgeons at this institution participated in the study. The majority (94%) of the distal systems used were medium pressure Pudenz-Schulte medical flow-control valves with integral distal

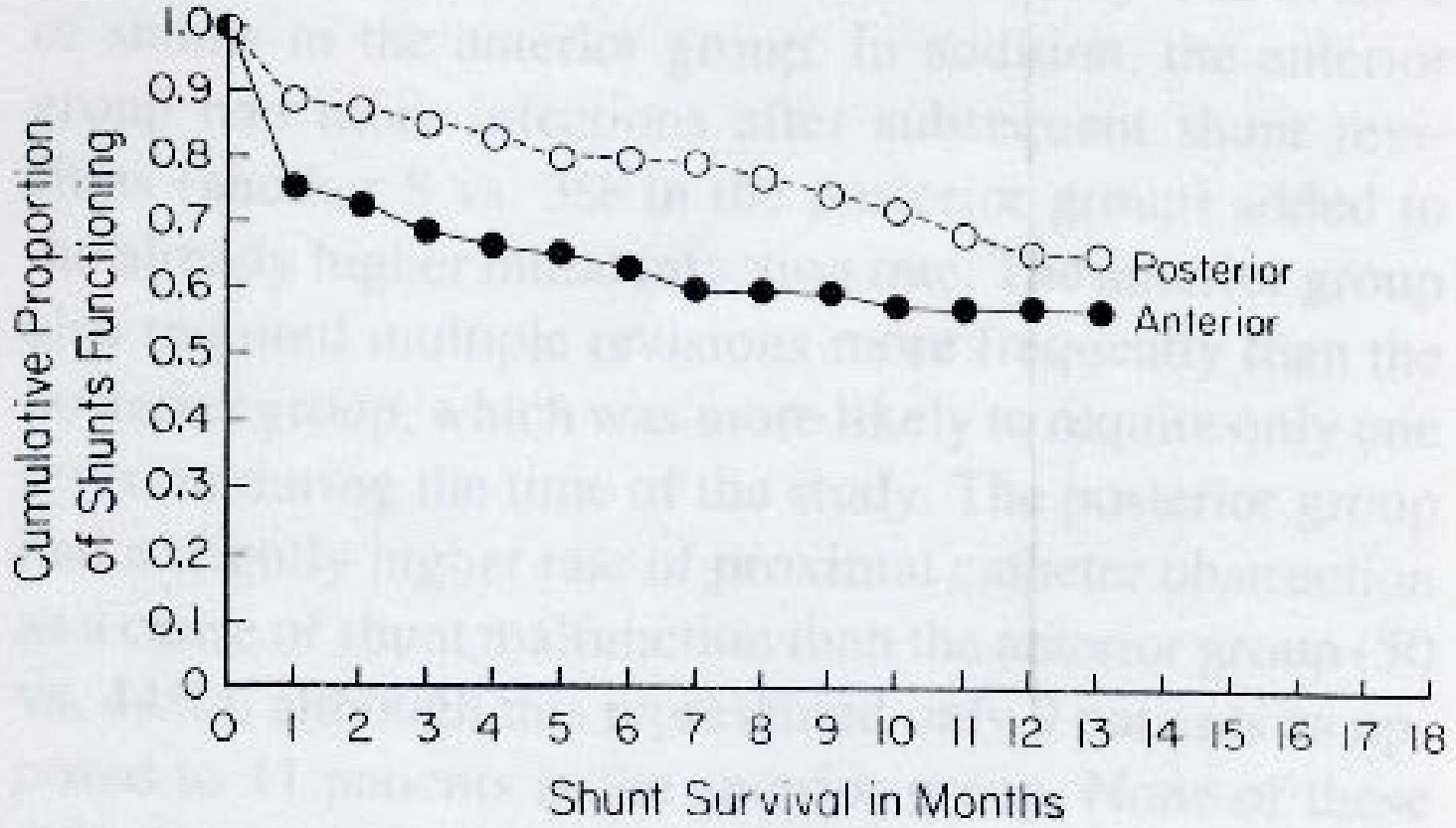
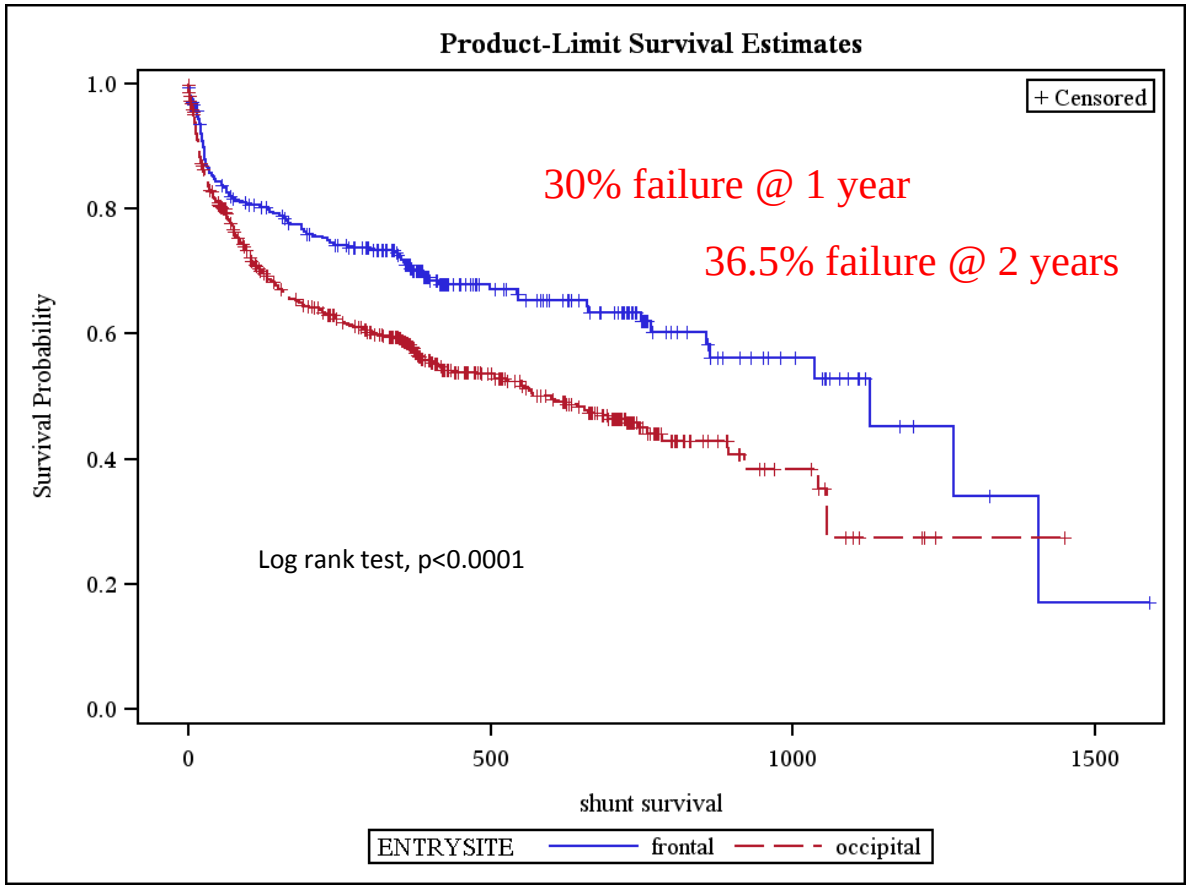


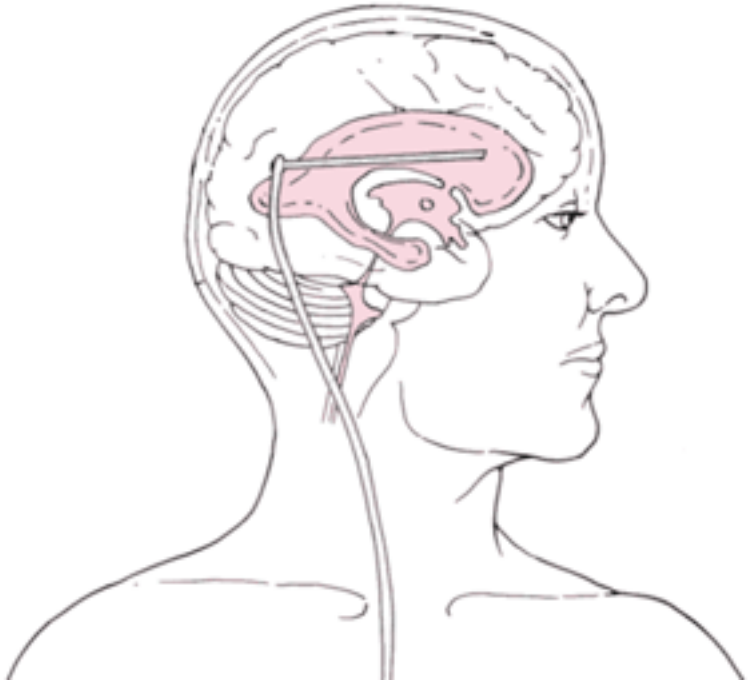
Fig. 1. Life-table analysis of shunt survival as a function of shunt placement. Survival = Shunt functioning without requiring revision or becoming infected.

Is this enough evidence to recommend anterior entry for patients?

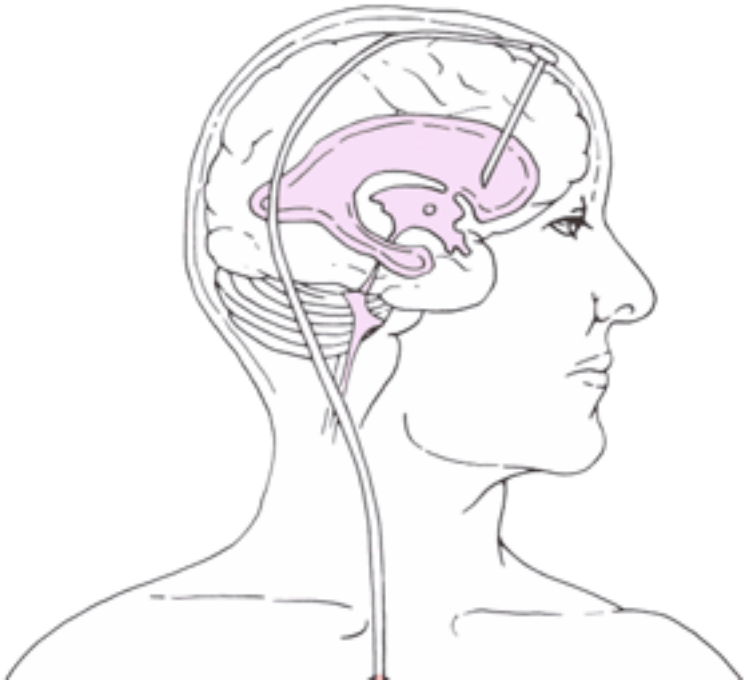


Entry Site	Total cases	# of events	# censored	Shunt Survival 1 year	Shunt Survival 2 years
Anterior	300	102	198 (66%)	70.6%	63.5%
Posterior	550	256	294 (53.5%)	58.2%	45.7%

Entry Site



Posterior



Anterior

Study Question

- In pediatric hydrocephalus patients who require a VP shunt, does the choice of shunt entry site (anterior or posterior) reduce the rate of shunt failure by 10% or more at 1 year?

Hypothesis: Shunt entry site has a significant effect on the subsequent rate of shunt failure.

The Entry Site Trial

study protocol

Primary Objective

- The primary objective of the Entry Site Trial is to determine in children with hydrocephalus requiring VP shunt, if:
  - shunt entry site significantly affects the risk of shunt failure

at major pediatric centers in North America.

Primary Endpoint

The primary endpoint of the study is the occurrence of shunt failure and the time to shunt failure measured from the day of shunt insertion surgery.

Secondary Objective

- The secondary objective of the study is to determine if:
  - Patient quality of life (acutely and chronically)
  - Total number of shunt revisions
  - Complication rates (e.g. infections)
  - Length of surgery and hospital stay
  - Number of catheter passes to enter ventricle
  - Location of ventricular catheter

  Is significantly different between the two treatment groups.

Recruitment

- HCRN Centers (9)
  - Primary Children's Medical Center, Salt Lake City
  - Toronto
  - Birmingham
  - Houston
  - Seattle
  - Pittsburgh
  - St Louis
  - Vancouver
  - Nashville
- Informed consent by:
  - Surgeons at HCRN centers (n=36)
  - Study coordinators

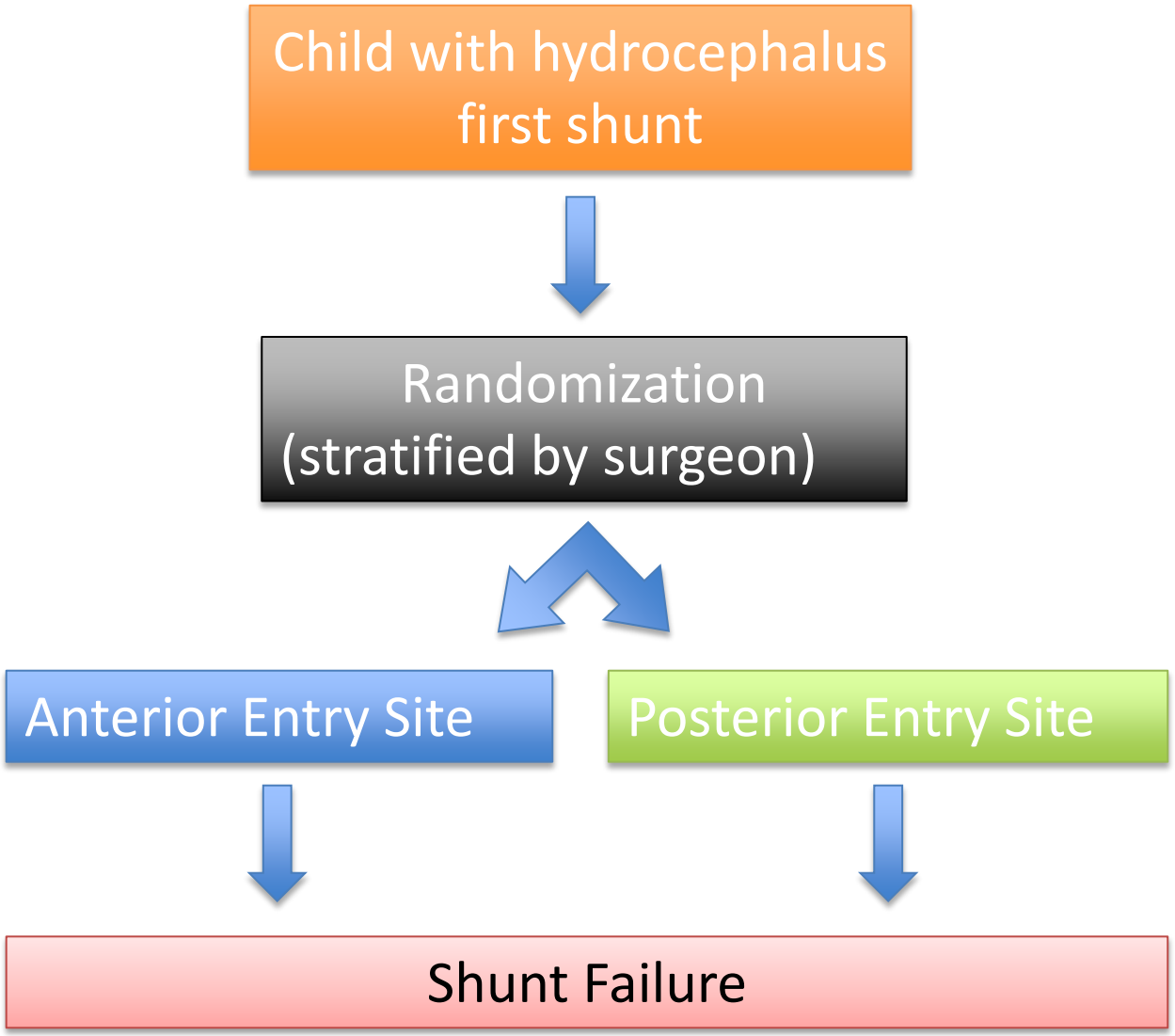
Inclusion Criteria

- <18 years of age at the time of shunt insertion
- Clinical evidence of hydrocephalus that requires a simple VP shunt as determined by a pediatric neurosurgeon
- No prior history of shunt insertion, but a history of the following are permissible:
  - external ventricular drain (EVD)
  - ventricular reservoir
  - subgaleal shunt
  - ETV with or without CPC
- Ventriculomegaly on imaging

Exclusion Criteria

- Active CSF or abdominal infection
- CSF leak without hydrocephalus
- Pseudotumor cerebri
- Hydranencephaly
- Loculations within the ventricular system
- Other difficulties that would preclude follow-up for 18 months
- Bilateral scalp, bone, or ventricular lesion that makes placement of either an anterior or a posterior shunt impracticable
- Bilateral slit-like frontal horns or trigones (<3mm)
- Require endoscopic procedure prior to shunt placement/ possible shunt placement

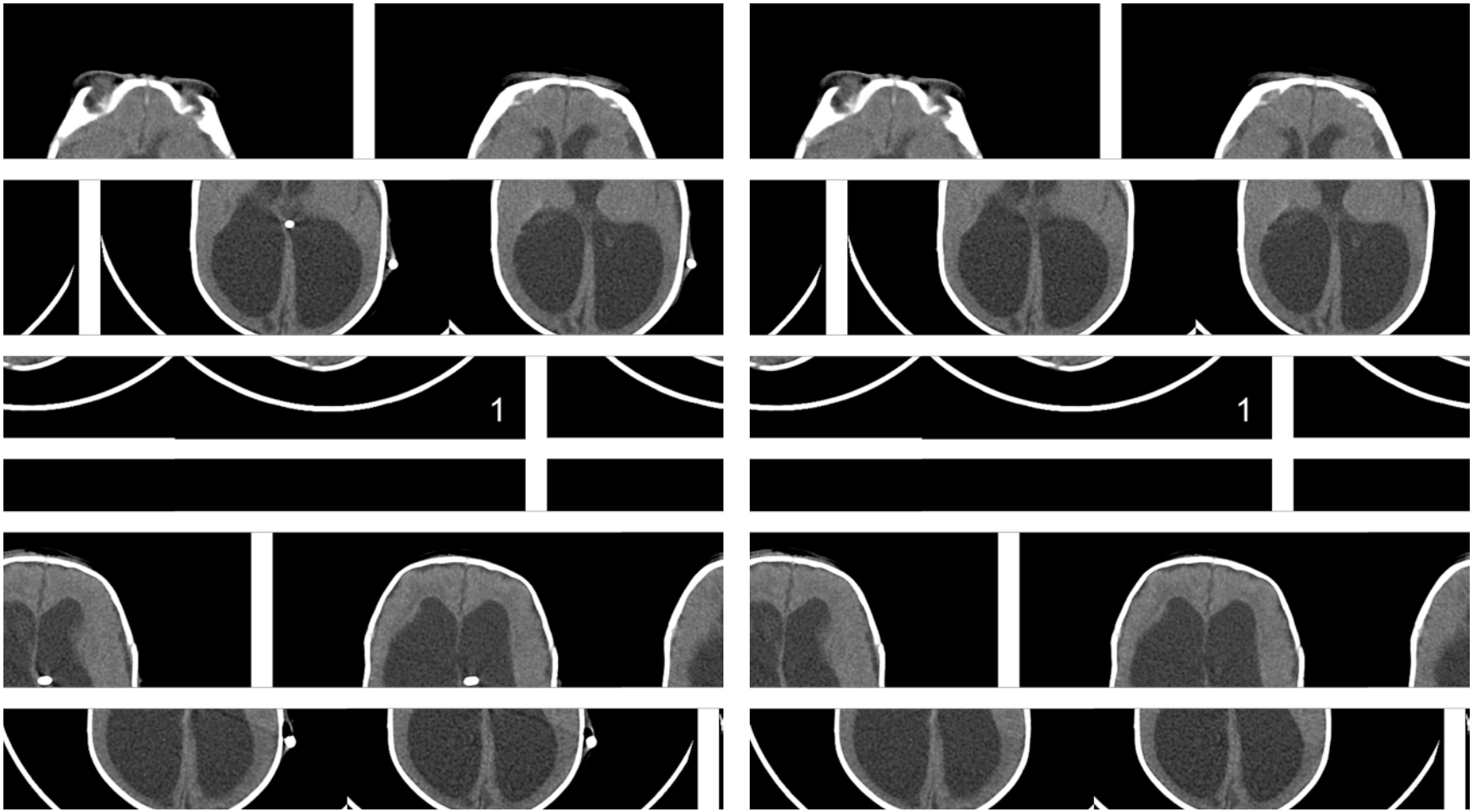
Study Design



Primary Outcome: Shunt Failure determined by Adjudication Committee

- There are four different classifications for shunt failure defined by clinical and imaging criteria. They are:
  - Obstruction
  - Overdrainage
  - Loculated compartments
  - Shunt infection
- If a subject meets the criteria for any of the above classifications, shunt failure is said to have occurred.
- A blinded adjudication committee will determine if subjects meet criteria for shunt failure by review of:
  - Clinical notes
  - Data collection forms
  - Radiographic images

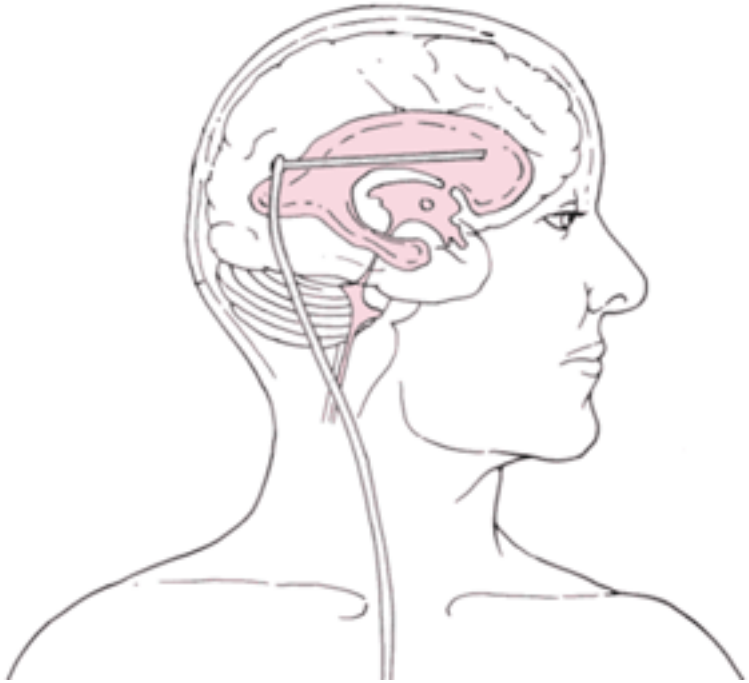
Example of blinding adjudication scans



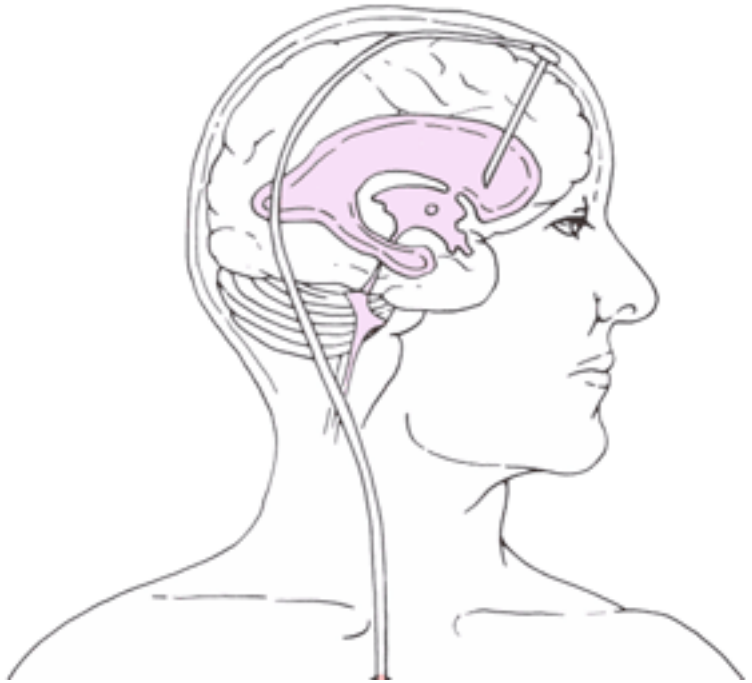
Adjudication Committee

- Independent group (no participation in the design/ implementation/ or conduct of the trial; no COI) which determines subject eligibility and the primary outcome after blinded review of subject data.
- Committee
  - 2 pediatric neurosurgeons
  - 1 pediatric neuroradiologist

Intervention



Posterior



Anterior

Surgery

- Any valve
- Any surgical adjunct technique
  - US
  - stereotaxy
- HCRN infection protocol
- Other peri-operative care left to surgeon and recorded

Follow up

- First visit within 12 weeks
- Annual visits
- Any other necessary visits
- Telephone follow-up at 6, 18, 30, and 42 months
- Minimum follow up is 18 months

Statistical Analysis

- Intention-to-treat analysis
- Primary outcome determined by adjudication committee

Sample Size Estimation

- Total sample size of 448
  - Alpha 0.05
  - Beta < 0.2 (power >80%)
  - Baseline shunt failure rate at one year: 30-40%
  - Clinically significant difference in shunt failure rate between the 2 treatment groups: >10%@ 1 year
- Adjustment for withdrawals/loss to follow-up: 3-5%.

Data Safety Monitoring Board

- 3 members completely independent of the study and study personnel
  - 2 clinicians
  - 1 biostatistician
- The primary responsibilities of the DSMB will be to periodically review and evaluate the accumulated study data for subject safety, study conduct and progress, and efficacy
- The board will make recommendations to the Investigators committee regarding continuation, modification, or termination of the trial

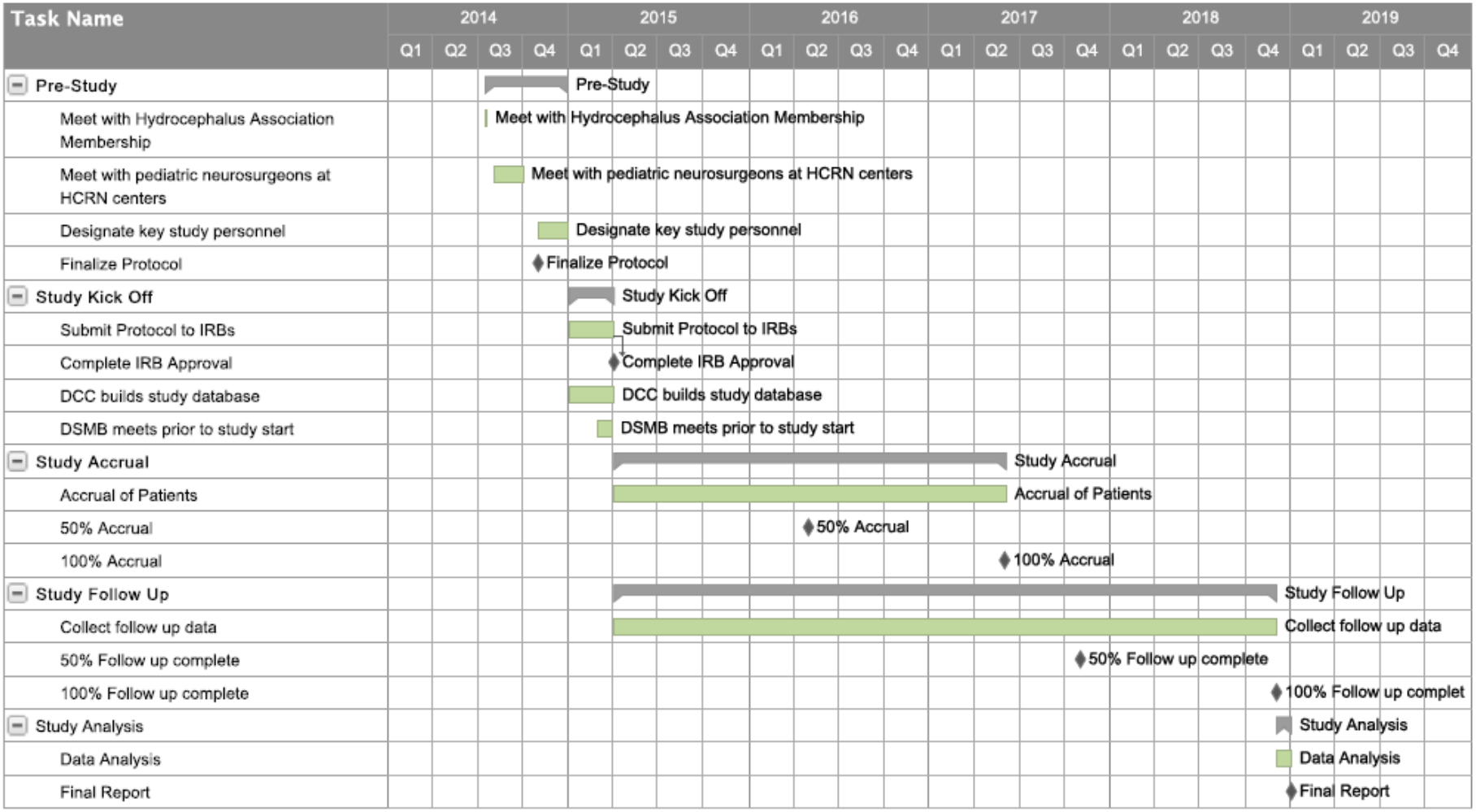
Steering Committee

- Responsible for the day-to-day running of the trial
- This committee will also provide information to:
  - the Adjudicating Committee
  - the Data Safety Monitoring Committee
  - the Investigators Committee
  - PCORI
- The committee will consist of:
  - a member of Hydrocephalus Association
  - the study PI
  - the HCRN Chair
  - the lead statistician
  - the lead clinical research coordinator from the Data Coordinating Center

Investigator Committee

- This group is responsible for:
  - overall planning
  - conduct of the study
  - distribution of the study results
- IC will oversee the activities throughout the study and have regular meetings to review study progress. All recommendations from the DSMB will come to this committee.
- An investigators committee will consist of:
  - the HCRN chairman
  - all site PIs
  - the lead statistician
  - two members of the Hydrocephalus Association (to represent the interests of patients and parents) will govern the trial.

Entry Site Trial Timeline



Sample size = 448

Entry Site Trial

Study Progress

hydrocephalus
clinical research network

Study Roll Out

- Protocol v 1.02
- Lead Study Manager Hired: Jason Clawson
- Coordinator Training (March 2015)
- Database Built in Open Clinica (April 2015)
- Manual of Operations (June 2, 2015)
- Accrual opened April 1, 2015
- All site enrolling patients as of September 2015

Hospital	PI	Coordinator	Participating Neurosurgeons	Study Opened
Primary Children's	John Kestle, Jay Riva-Cambrin	Nicole Tattersall	Douglas Brockmeyer Robert Bollo	May 19, 2015
Hospital for Sick Children	Abhaya Kulkarni	Homa Ashrafpour	James Drake James Rutka Michael Taylor Peter Dirks	May 19, 2015
Children's Hospital of Alabama	Curtis Rozzelle	Anastasia Arynchyna	Jerry Oakes Jeffrey Blount James Johnston Brandon Rocque	May 21, 2015
Texas Children's	Willliam Whitehead	Sheila Ryan	Sandi Lam Andrew Jea Robert Dauser Daniel Curry Thomas Luerssen	April 1, 2015
Seattle Children's	Sam Browd	Amy Anderson	Jeff Ojemann Amy Lee Rich Ellenbogen	July 10, 2015
St. Louis Children's	David Limbrick	Deanna Mercer	Matthew Smyth T.S. Park	April 30, 2015
Children's Hospital of Pittsburgh	Mandeep Tamber	Kimberly Diamond	Ian Pollack Elizabeth Tyler-Kabara Stephanie Greene	April 20, 2015
BC Children's	Douglas Cochrane	Alex Cheong	Paul Steinbok Ash Singhal	May 14, 2015
Monroe Carell	John C. Wellons, III	Stephen Gannon	Robert Naftel Chris Bonfield	September 11, 2015

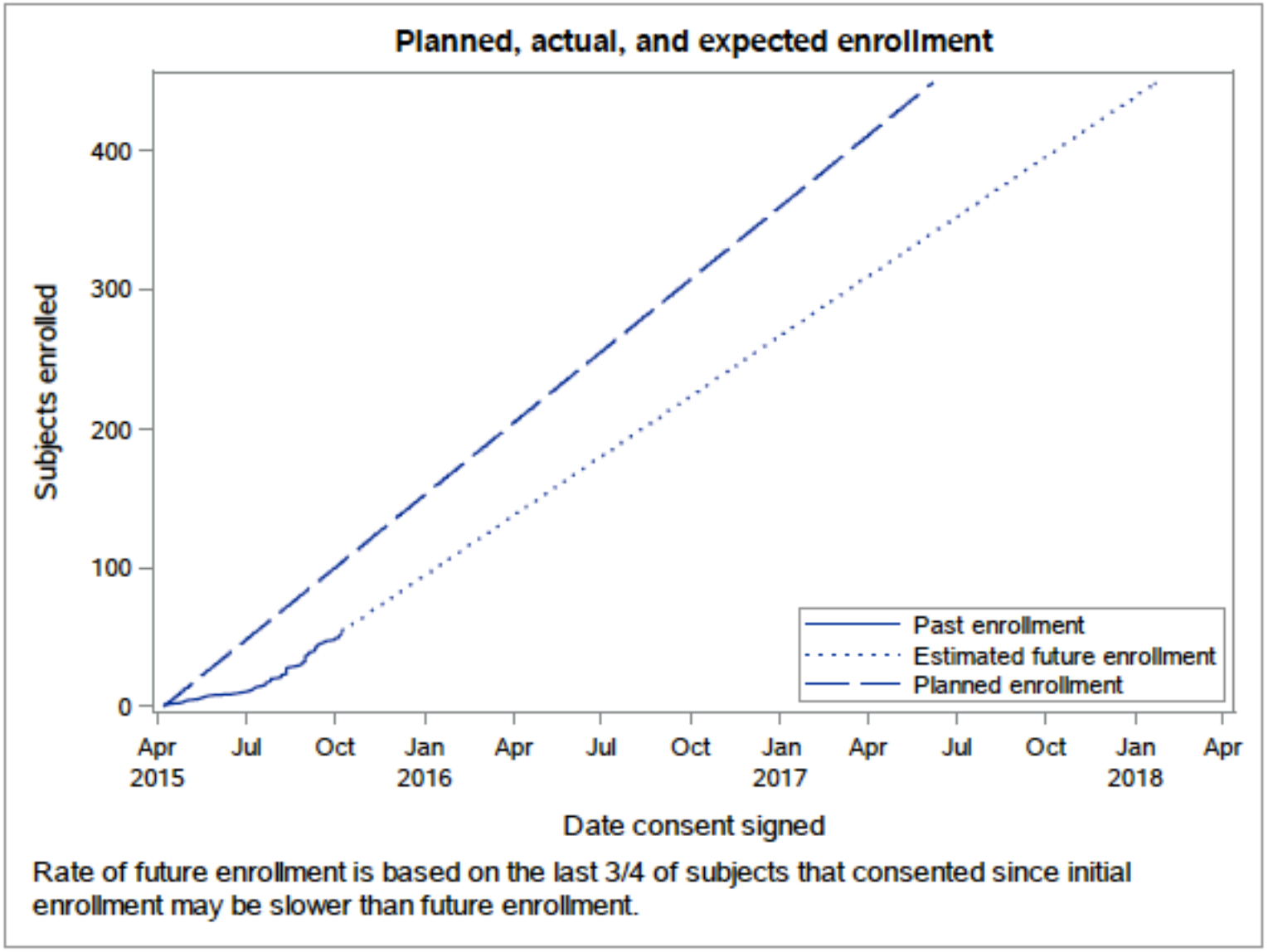
Committee Members

- Data and Safety Monitoring Board
  - Connor Mallucci, MB BS; Alder Hey Children's Hospital, Liverpool
  - Douglas Barnhart, MD; Primary Children's Medical Center, Salt Lake City
  - Kenneth Boucher, Ph D; University of Utah
- Adjudication Committee
  - Hugh Garton, MD; University of Michigan
  - Tina Sayama, MD; University of Oregon
  - Jeremy Jones, MD; Baylor College of Medicine

Hydrocephalus Association

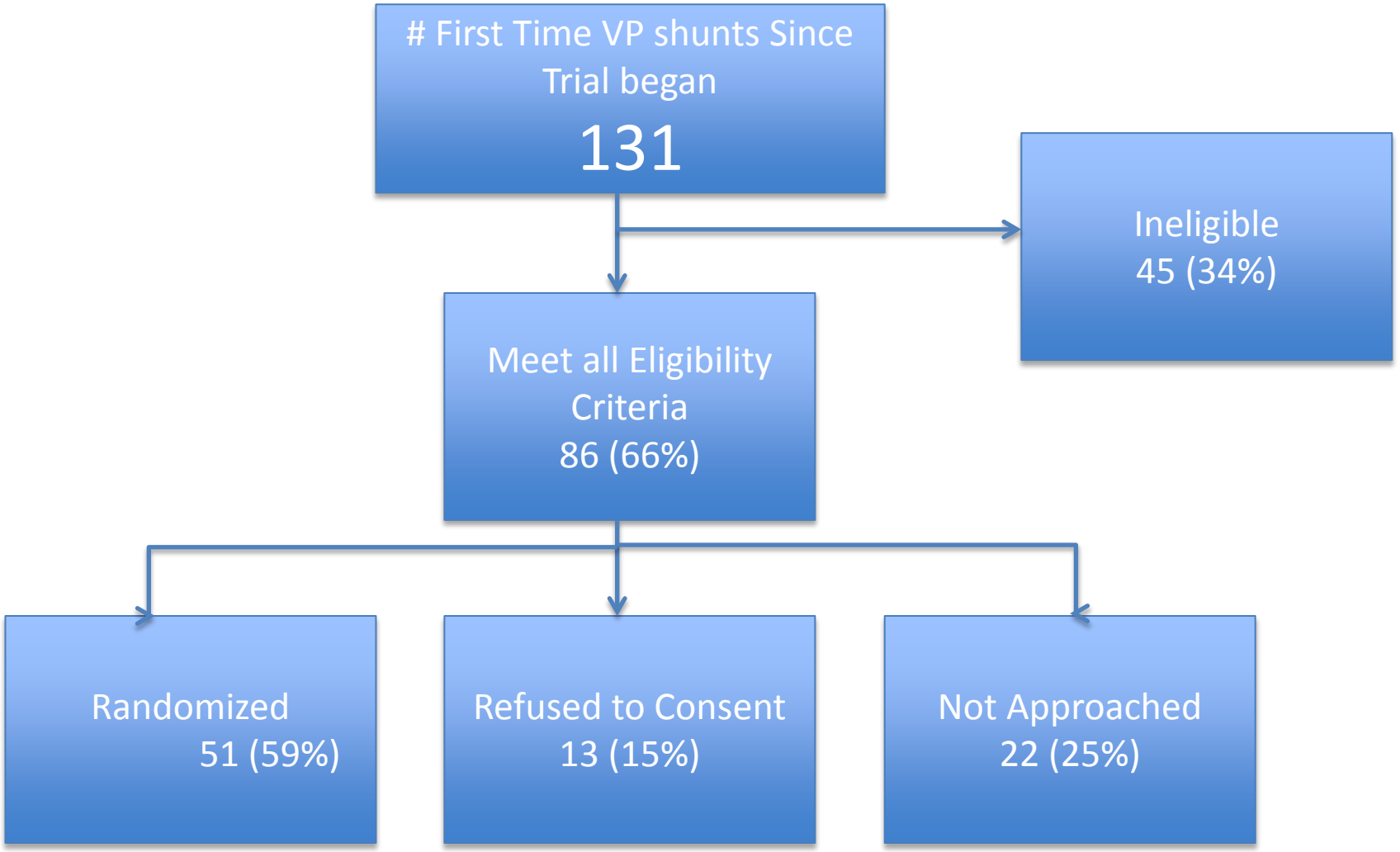
- Study Committee Members
  - Jenna Koschnitzky
  - Paul Gross
- Patient Partner Committee
  - Katie Cook Chicago, IL Parent
  - Brenda Bell Ennis Denver, CO Parent
  - Laurel Fleming Boston, MD Parent
  - Paul Gross Seattle, WA Parent
  - Mia Padron Long Island, NY Parent
  - Matt Pope Los Angeles, CA Parent
  - Jennifer Pope Los Angeles, CA Parent
  - David Browdy Salt Lake City, Utah Parent
  - Amanda Garzon Bethesda, MD Parent/Staff
  - Michael Schwab Portland, OR Parent
  - Robin Ennis Denver, CO Patient
  - Jennifer Johnston Detroit, MI Patient/Staff
  - Jamie Wright, Houston, TX Patient
  - SarahAnn Whitbeck Salt Lake City, Utah Patient
  - Karima Roumila San Fransisco, CA Staff

Hydrocephalus Association



Rate of future enrollment is based on the last 3/4 of subjects that consented since initial enrollment may be slower than future enrollment.

Accrual Flow Sheet



Reasons not approached

Emergent case, no time	4 (18.2%)
No one available to consent subject	**2 (9.1%)**
Forgot to evaluate	**2 (9.1%)**
Patient determined to be not eligible by surgeon due to a competing medical or surgical reason	9 (40.9%)
Other	5 (22.7%)

Medical/Surgical reasons for not seeking consent

Surgeon wants to use previous entry site of a RES/SGS/EVD/ETV for the insertion of the new VP shunt	2
Previous anterior ETV site had CSF leak 1 week prior and required revision; concerned about infection if anterior site used	1
Anterior location was not ideal for shunt due to previous incision for temporization/ETV procedure	1

Medical/Surgical reasons for not seeking consent

Patient had a recent occipital cervical fusion and positioning for a posterior shunt would jeopardize fusion	1
Subject will need bilateral anterior hardware placement for craniofacial surgery making anterior approach for shunt undesirable	2
Thin cortical mantle occipitally puts subject at high risk for CSF leak with posterior shunt	2

Other reasons for not seeking consent

Patient is ward of the state	1
Mom recovering from C-section at another hospital, unavailable for consent	1
Waiting for IRB approval of Spanish consent; family is Spanish speaking only	1
Subject excluded for anatomic reasons	2 (there is an exclusion criteria for this; specify)

Subject Characteristics (n=51)

Characteristic	
Age (mean)	2.1 y (3.87)
Age (median)	6 months
Gender (female)	21 (40.4%)
Ethnicity	
Hispanic or Latino	10 (19.2%)
Not Hispanic	37 (71.2%)
Unknown or Not Reported	5 (9.6%)
Race	
American Indian or Alaska Native	2 (3.8%)
Black or African American	10 (19.2%)
White	33 (63.5%)
Multiracial	2 (3.8%)
Unknown or Not Reported	5 (9.8%)

Subject Characteristics (n=51)

Etiology	
Myelomeningocele	11 (21.2%)
Post IVH secondary to prematurity	9 (17.3%)
Aqueductal Stenosis	6 (11.5%)
Spontaneous ICH/IVH/SAH	4 (7.7%)
Post-infectious	4 (7.7%)
Supratentorial tumor	4 (7.7%)
Communicating congenital hydro.	3 (5.8%)
Posterior fossa cyst	2 (3.8%)
Encephalocele	2 (3.8%)
Posterior fossa tumor	1 (1.9%)
Post-head injury	1 (1.9%)
Other intracranial cyst	1 (1.9%)
Other congenital	1 (1.9%)

Subject Follow-Up and Data Entry

Summary of subject study events and compliance

Event	completed	expected
Enrollment	51	52
Surgery	50	52
Discharge	51	52
12 week follow-up	33	52

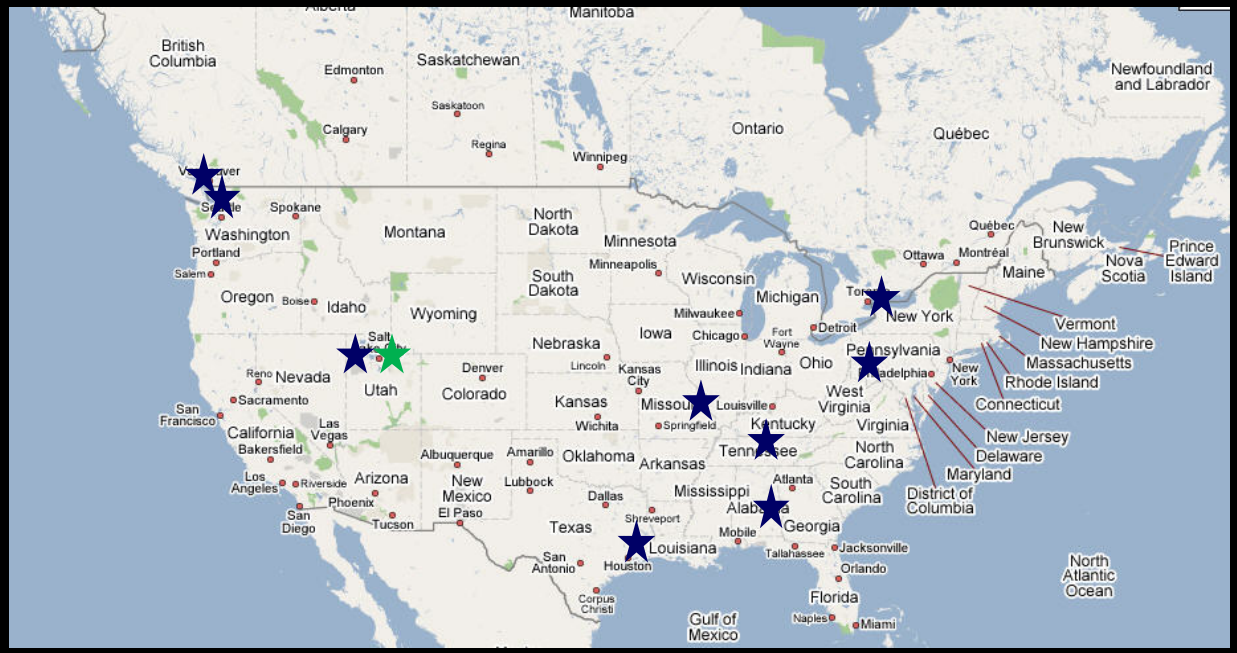
Table generated on 20OCT2015.
Expect number is the number of subjects randomized via randomize.net.
Enrollment is considered complete if the enrollment and PreOpImage forms are marked complete.
Surgery is considered complete if the surgery form is marked complete.
Discharge is considered complete as long as at least one PrimComplication form is marked complete.
12 week follow-up is considered complete as long as at least one ShuntFunctionEval form has been marked complete and has a date within 4 months (121 days or less) of consent.

Upcoming events

- Adjudication Meeting (November 2015)
- DSMB Meeting (December 2015)
- Meeting with the PPC (November/December 2015)
- Project update to PCORI (December 2015)
  - Accrual
  - Possible addition of new sites

hydrocephalus
clinical research network

University of Utah, Salt Lake City,
University of Toronto, Toronto
U of Alabama at Birmingham
Baylor College of Medicine, Houston
University of Pittsburgh
University of Washington, Seattle
Washington University, St. Louis
Vanderbilt, Nashville
Uof British Columbia, Vancouver



HCRN

Founders
Dr. John Kestle, HCRN Chair
Paul Gross

University of Utah
Dr. Jay Riva-Cambrin
Nicole Tattersall, Clinical Site Coordinator
University of Alabama, Birmingham
Dr. J Oakes
Dr C Rozelle
Anastasia Arynchyna, Clinical Site Coordinator
University of Toronto
Dr. J Drake
Dr. Abhaya Kulkarni
Homa Ashrafpour, Clinical Site Coordinator
University of British Columbia
Dr. D Cochrane
Ross Hengel, Clinical Site Coordinator

Baylor College of Medicine
Dr. Tom Luerssen
Dr. William Whitehead
Sheila Ryan, Clinical Site Coordinator
University of Washington
Dr. Samuel Browd
Dr. Tamara Simon
Amy Anderson, Clinical Site Coordinator
University of Pittsburgh
Dr. Mandeep Tamber
Arlene Luther, Clinical Site Coordinator
Vanderbilt University
Dr. Jay Wellons
Chevis Shannon, PhD
Dr. Rob Naftel
Angela Davis, Clinical Site Coordinator
Washington University
Dr. David Limbrick
Deanna Mercer, Clinical Site Coordinator

Neurosurgical Colleagues

Data Coordinating Center (SLC)
Marcie Langley, DCC Coordinator
Jeff Yearley, Data Management
Rich Holubkov (Statistical PI)

Coordinators

Follow up Guidance to the Rare Disease Landscape Review

Parag Aggarwal, PhD

Senior Program Officer, Addressing Disparities, PCORI

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Background

- During RDAP Spring meeting topics missing in the landscape review were identified to be addressed in a follow up document
- PCORI staff called for volunteers for each topic; 4 topics were covered by volunteers:
  - Human Subjects
  - Incorporating PROs into Registries
  - Registry Purposes
  - Evidence Grading
- PCORI staff/RDAP leadership proposed a reframing of the priority topics

Proposed Reframing of Priority Topics for Further Guidance

- Human subject issues specific to rare diseases
- The importance of and best practices for research prioritization
- Considerations related to the challenges with producing reliable evidence for rare diseases

Breakouts and Participants

- **Human Subjects**
  - Patricia Furlong (chair)
  - Kate Lorig
  - Jacqueline Alikhaani
  - Sindy Escobar-Alvarez
  - Philip Ruff
- **Research Prioritization**
  - Marilyn Bull (chair)
  - Vincent Del Gaizo
  - Mardi Gomberg-Maitland
  - Lisa Heral
  - William Whitehead
- **Challenges with Producing Reliable Evidence for Rare Diseases**
  - Naomi Aronson (chair)
  - Yaffa Rubinstein
  - James Wu
  - Marshall Summar (remote attendance)
  - Mark Skinner (remote attendance)

Breakout 1: Human Subjects – Key Questions

- What are the most important considerations when developing consent forms for registries enrolling adults with rare diseases?
- What are the most important considerations when developing consent forms for registries enrolling children with rare diseases?
- What measures can be implemented to protect the privacy of individuals who are enrolling in a rare disease registry?
- What are some best practices for developing consent forms and privacy protection measures for a rare disease registry?
- What are some best practices to engage patients, families, and/or caregivers in the development of consent forms and privacy protections measures for a rare disease registry?

Breakout 2: Research Prioritization – Key Questions

- What are some good examples of a cohesive rare disease research community that was able to come to consensus regarding the research priorities for a given rare condition?
- What are some best practices to engage the patient and stakeholder community in setting a research agenda?
- What are some best practices to form strong partnerships between the rare disease patient/caregiver communities and the research communities, to ensure that the priorities established are implemented?

Breakout 3: Challenges with Producing Reliable Evidence for Rare Diseases – Key Questions

- What features of a rare disease impact the ability to generate reliable evidence about treatment options for that condition?
- How do each of those features impact evidence generation? How do those features impact which study designs are feasible to implement?
- Is it possible and would it be useful to organize those features into a framework or typology to help decision makers and researchers understand what type of study designs can be implemented and why level of evidence can be produced in different situations?
- How can we capture considerations of both strength of evidence and the degree of uncertainty and risk that is acceptable in various contexts?

Breakouts Session Structure

- **10:30 – 11:15 am:** Discuss the questions posed by breakout memo
- **11:15 – 11:45 am:** Define a preliminary set of objectives for the workgroup
- **11:45 – 12:15 am:** Develop a set of next steps and consider what information and resources you need to achieve the objectives you have outlined. Specifically, consider the following:
  - Are there specific types of expertise that should be represented on this workgroup that are currently missing? If so, can you recommend someone with that expertise?
  - In order to inform future discussions, would a synthesis of the existing literature on this topic be useful? If so, what key words/MeSH terms should be included in the search?
  - Are there other resources that you need to carry out this work?

Project Timeline

- **November 2015 – January 2016:** Refine the workgroup objectives and deliverables and develop an outline for the workgroup document. At the January 2016 RDAP meeting, time will be reserved for workgroups to meet and review their document outlines.
- **January 2016 – April 2016:** Draft a document that provides guidance to the rare disease community based on the outline discussed at the January 2016 RDAP meeting. At the April 2016 RDAP meeting, time will be reserved for the workgroups to discuss the complete draft documents.
- **April 2016 – July 2016:** Revise and finalize the draft document. Time will be reserved at the July 2016 RDAP meeting for presentations of the final guidance documents. The goal is to publish the documents produced by each group on the PCORI website and in a special issue of a peer-reviewed medical journal

Break

10:15 – 10:30 a.m.

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Guidance for Rare Disease Research Breakout Groups

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Audio Access for Breakout Sessions

- **Breakout #1 – Human Subjects**
  - Dial 1 (866) 640-4044 – Enter 621762# when prompted
- **Breakout #2 – Research Prioritization**
  - Dial 1 (866) 640-4044 – Enter 851836# when prompted
- **Breakout #3 – Challenges with Producing Reliable Evidence for Rare Diseases**
  - Dial 1 (866) 640-4044 – Enter 746521# when prompted

Reports from Breakout Groups

Patricia Furlong
Member, Advisory Panel on Rare Disease, PCORI
Marilyn Bull, MD, FAAP
Member, Advisory Panel on Rare Disease, PCORI
Naomi Aronson, PhD
Member, Methodology Committee, PCORI

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Human Subjects Breakout Group

Are there specific types of expertise that should be represented on this workgroup that are currently missing? If so, can you recommend someone with that expertise?

- Additional expertise/consultants who have experience in bioethics and government regulations should talk to the panel
- We need insight to inform us to address the issues of privacy, informed consent for children/adults
- Recommended experts to consult:
  - Yaffa Rubenstein, NIH (Government)
  - Donald Patrick, U. Wash (Bioethics)
  - Art Caplan, NYU (Bioethics)
  - CTTI, Duke (Clinical Trials)
  - Recommendation to survey rare disease groups in 3 areas:
    - People who have participated in a registry and signed a consent form
    - People who have been asked to participate and refused
    - People who have no experience with informed consent

In order to inform future discussions, would a synthesis of the existing literature on this topic be useful? If so, what keywords/MeSH terms should be included in the search?

- There is limited (if any) information on rare diseases, so we want to use keywords to look at issues of consent with children.
  - CTTI has a work project on informed consent in the context of clinical trials

Are there other resources that you need to carry out this work?

- We are recommending that PCORI considers working with this group to create, deploy, and analyze the survey data from this exercise

Research Prioritization Breakout Group

Breakout 2: Research Prioritization – Key Questions

- What are some good examples of a cohesive rare disease research community that was able to come to consensus regarding the research priorities for a given rare condition?
- What are some best practices to engage the patient and stakeholder community in setting a research agenda?
- What are some best practices to form strong partnerships between the rare disease patient/caregiver communities and the research communities, to ensure that the priorities established are implemented?

Research Prioritization – Question 1

- **Q: What are some good examples of a cohesive rare disease research community that was able to come to consensus regarding the research priorities for a given rare condition?**
  - The Hydrocephalus Clinical Research Network (HCRN)
  - Was founded by a parent and a neurosurgeon. The parent was involved in broad outreach efforts to the patient and caregiver community.
  - Cystic Fibrosis community is well versed in connecting patients to research efforts
  - Down Syndrome Community
  - Spinal Muscular Atrophy Community

Research Prioritization – Question 2

- **Q: What are some best practices to engage the patient and stakeholder community in setting a research agenda?**
  - Strategic planning is a key best practice
  - An example of a strategy:
  - Reach out to advocacy groups that can contact patients and survey them on their concerns. Patient concerns are collated and used to build a CER question. These questions are revised by the advocacy groups for further input and prioritization. They are then presented to the oversight board for final approval.

Research Prioritization – Question 2 (cont.)

- Patients should be queried on specific outcomes that are important to them when making a treatment choice. This will help validate the research. Patients should not be asked questions related to study design.
- The study design can be changed based on the patient's (desired) reported outcomes.
- Advocacy organizations and scientific agenda meetings are critical to proving information on patient reported outcomes (PROs).
- A best practice is to educate patients that attend the scientific agenda meetings on the value and impact of their input.
- The information they gain at these meetings are to be taken back to their communities.

Research Prioritization – Question 3

- **Q: What are some best practices to form strong partnerships between the rare disease patient/caregiver communities and the research communities, to ensure that the priorities established are implemented?**
  - Survey patients for their perspective on prioritization
  - Allocate research leader and patient leader in research efforts.
  - Grassroots outreach methods to ensure inclusion of diverse and disparate populations.
  - To support funding of initial rare disease research, identify other funding channels (other than PCORI) that might better support such efforts.
  - Developing an effective process for data collection and data ownership.
  - Developing effective plans for outcome dissemination.

Research Prioritization – Next Steps

- Identify diverse outreach and collaboration strategies/methods
- Define variables for registries and research efforts to support quality data
- Include and engage clinical epidemiologists; individuals from data coordination centers (i.e., statisticians); and information technologists in this dialogue.
- Develop and implement better data collection toolkits (i.e., EPIC, survey monkey, etc.) to determine the evidence-base.
- Develop a roadmap for interested parties that would include tools for strategic prioritization.
- Identifying funding resources for research (other than PCORI).
- Gather data from those who are at different levels in their research (i.e., in their infancy, intermediate, well defined).

Challenges with Producing Reliable Evidence for Rare Diseases Breakout Group

Breakout #3: Challenges with Producing Reliable Evidence for Rare Diseases

- **Objectives**

  1. Delineate characteristics that present barriers and opportunities for creating an evidence base for rare diseases: ceiling and floor of the evidence that can be produced

  2. Create a typology relating the characteristics to study considerations and design

  3. Outline implications of the typology for practice/implementation/regulation

Breakout #3: Challenges with Producing Reliable Evidence for Rare Diseases

- **Disease Characteristics**
  - Prevalence
  - Lethality
  - Homogeneous/heterogeneity
  - Progressive/relapsing/remitting or combos
  - Pediatric/Adult
  - Non disease characteristics of the population, e.g.:
    - Patterns of care
    - SES
    - Psychological effects
  - Genetic/non-genetic/suspicions in between
  - Temporality
  - Cross-cutting targets and pathways/relatedness of different diseases

Breakout #3: Challenges with Producing Reliable Evidence for Rare Diseases

- **Infrastructure Characteristics**
  - Existing networks or registries
    - Governance
  - Ethical/legal issues
  - Variations in regulations
  - Availability of specialists and/or centers of excellence: medical and methodological
  - Patient support network
    - Level of funding
    - Focus on research agenda
    - Level of organization
  - Patterns of care

Breakout #3: Challenges with Producing Reliable Evidence for Rare Diseases

- **Next Steps**
  - **Additional expertise:**
    - 2 or more trialists
    - individual(s) with expertise in observational study design and analysis
    - individual(s) with expertise in creating data networks
    - individual(s) with expertise in transforming siloed groups into collaborative communities
  - **Other resources:**
    - Expert writer
    - Literature/web search for other typologies and definitions of disease characteristics
  - **PCORI staff to draft outline and work plan for circulation to the workgroup**

Update on PCORI's Rare Disease Portfolio

Heather Edwards, PhD, MPH, MBA
Program Officer, Strategic Portfolio Analysis, PCORI
Mary Kay Margolis, MPH, MHA
Senior Program Officer, Evaluation and Analysis, PCORI
Vadim Y. Gershteyn, MPH
Program Associate, Evaluation and Analysis, PCORI

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Today's Presentation

- Update on overall Rare Disease (RD) portfolio since last presentation
- Summary of eight RD projects funded in Fall 2014 and Spring 2015
- Aggregate data on recent awards compared to RD portfolio
- Aggregate data on RD portfolio compared to overall portfolio

Funded Projects on Rare Disease

- Through October 2015, PCORI has 52 awards on Rare Diseases

Funding Mechanism	# of Projects	% of Funding Mechanism Portfolio
Broad Funding Announcements	20	6%
Pragmatic Clinical Studies	1	6%
Pilot Projects	3	6%
Infrastructure	20	100% of Clinical Data Research Networks; 50% of Patient Powered Research Networks
Pipeline to Proposal	5	6%
Engagement Awards	3	8%

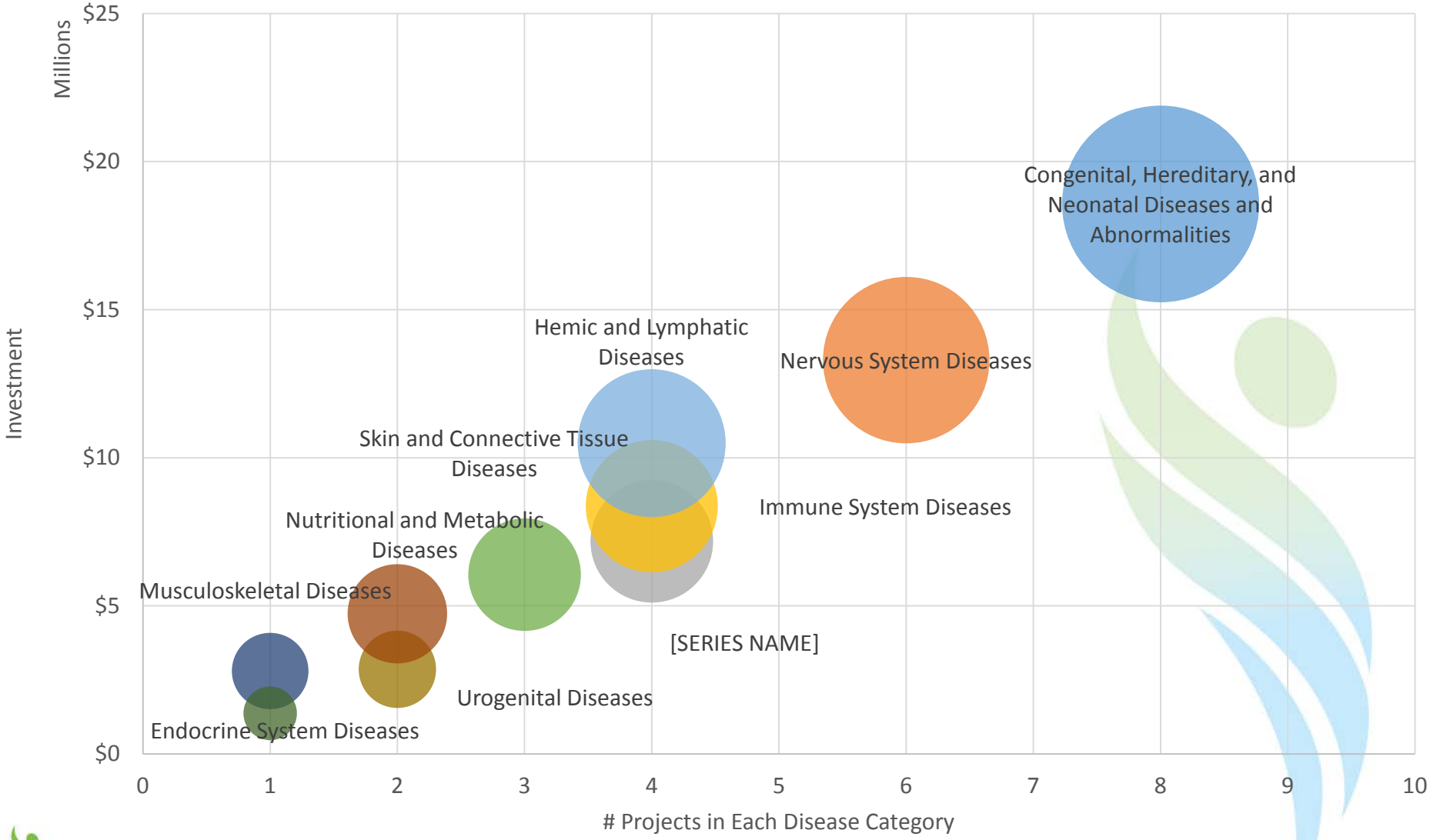
Rare Disease Projects Funded in 2015

PI	Title	Condition(s) Studied
Richard Aplenc, MD, PhD	Home or Away from Home: Comparing Clinician and Patient/Family-Centered Outcomes Relevant to the Care of Pediatric Acute Myeloid Leukemia during Periods of Neutropenia	Pediatric Acute Myeloid Leukemia
Judith Fridovich-Kiel, PhD	Intervention and Outcomes in Duarte Galactosemia	Duarte Galactosemia
Alexander Gelbard, MD	Treatment Alternatives in Adult Rare Disease; Assessment of Options in Idiopathic Subglottic Stenosis	Idiopathic Subglottic Stenosis
Michael Kappelman, MD, MPH	Anti-TNF Monotherapy versus Combination Therapy with Low Dose Methotrexate in Pediatric Crohn's Disease	Pediatric Crohn's Disease

Rare Disease Projects Funded in 2015 *(cont'd)*

PI	Title	Condition(s) Studied
Yukiko Kimura, MD	Comparative Effectiveness of CARRA Treatment Strategies for Polyarticular Juvenile Idiopathic Arthritis	Polyarticular Juvenile Idiopathic Arthritis
David Limbrick, MD, MS, PhD	Posterior Fossa Decompression with or without Duraplasty for Chiari type I Malformation with Syringomyelia	Chiari Type I Malformation (CM) and Syringomyelia (SM)
Mendel Tuchman, MD	Comparative Effectiveness of Therapy in Rare Diseases: Liver Transplantation vs. Conservative Management of Urea Cycle Disorders	Urea Cycle Disorders
Kevin Winthrop, MD, MPH	Comparative Effectiveness and Safety of Inhaled Corticosteroids and Antimicrobial Compounds for Non-CF Bronchiectasis	Non-CF Bronchiectasis

Disease Categories Represented in RD Portfolio*



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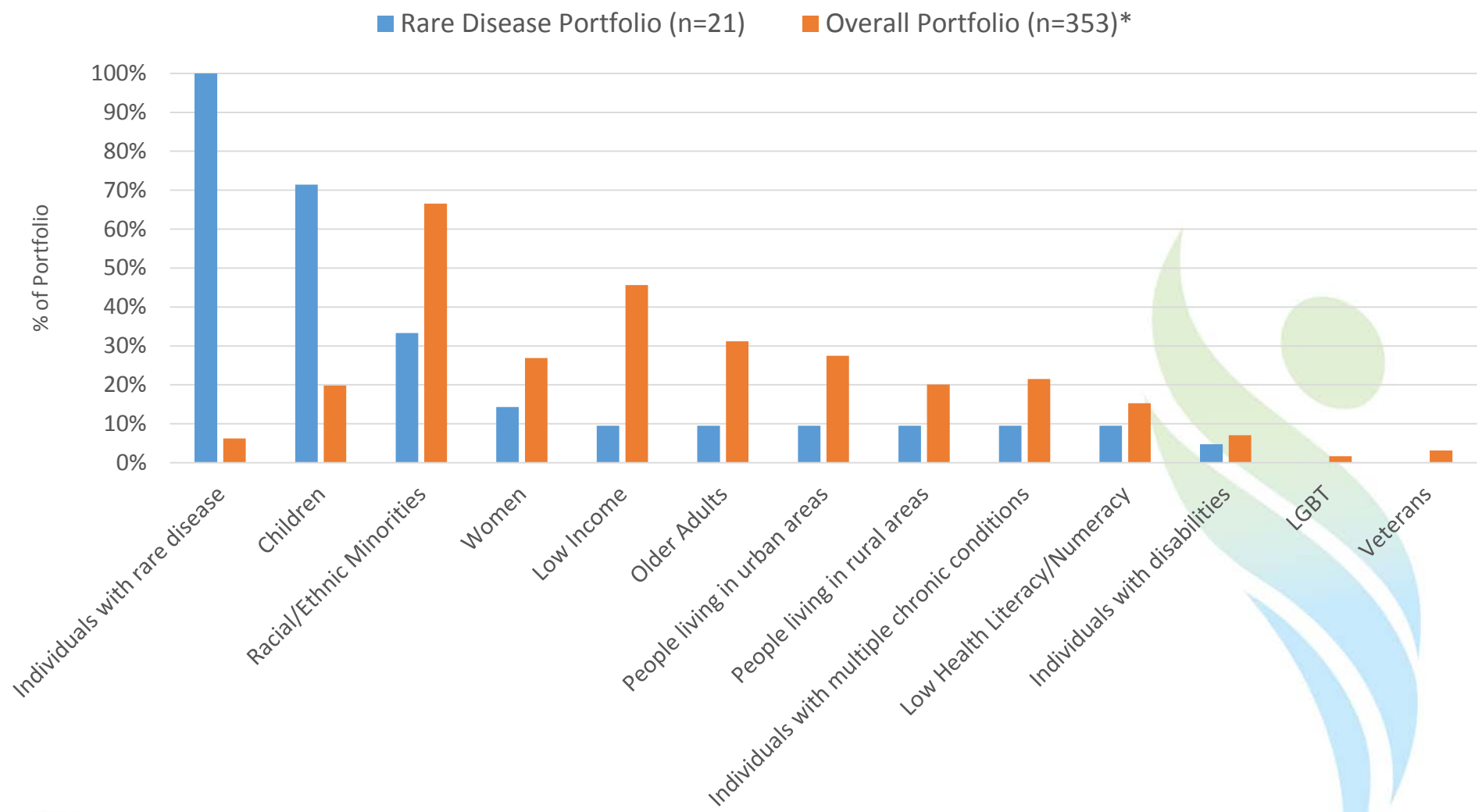
*n=21, disease categories not mutually exclusive

Populations of Interest Represented in Rare Disease Portfolio vs. Overall Portfolio



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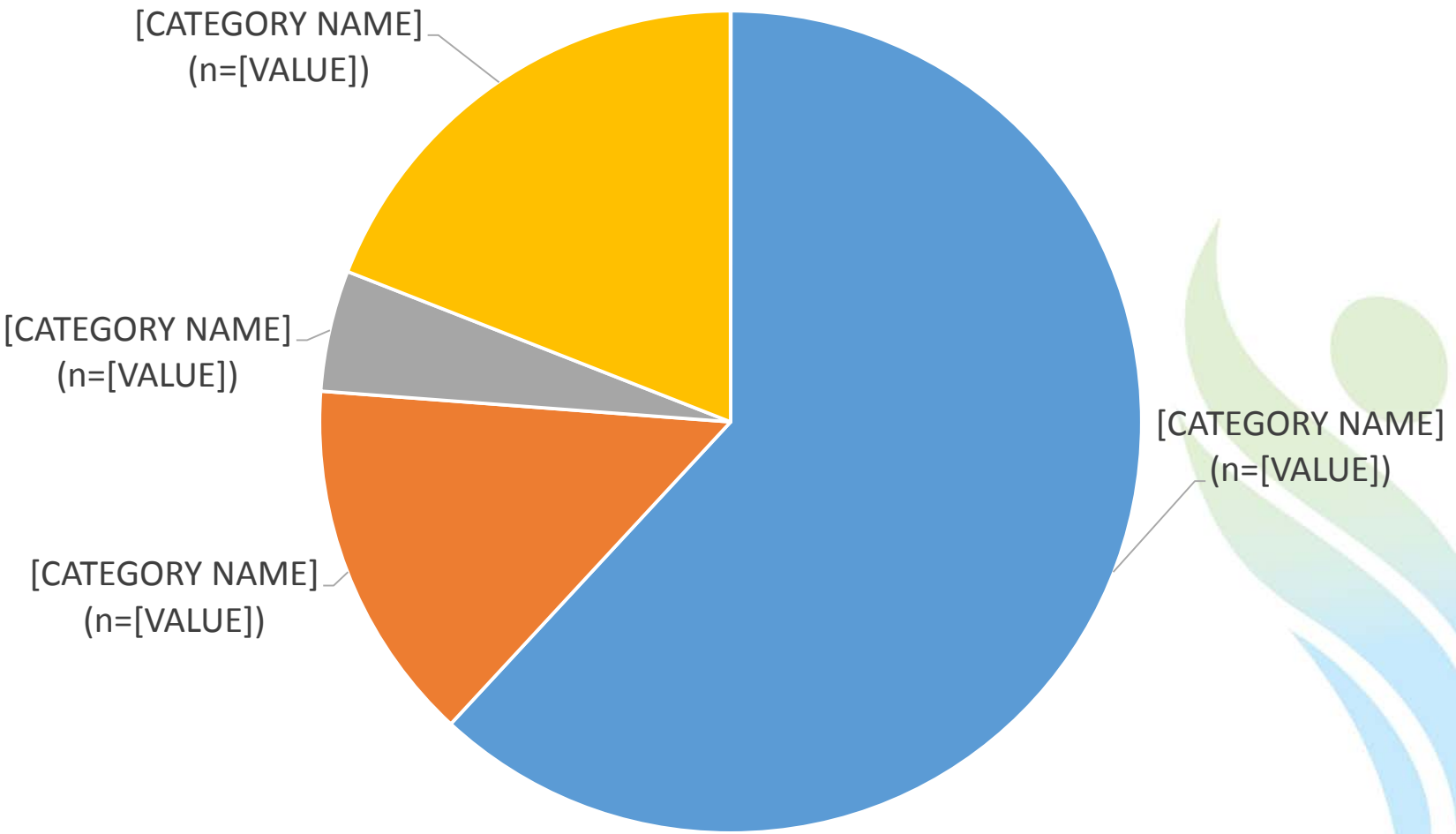
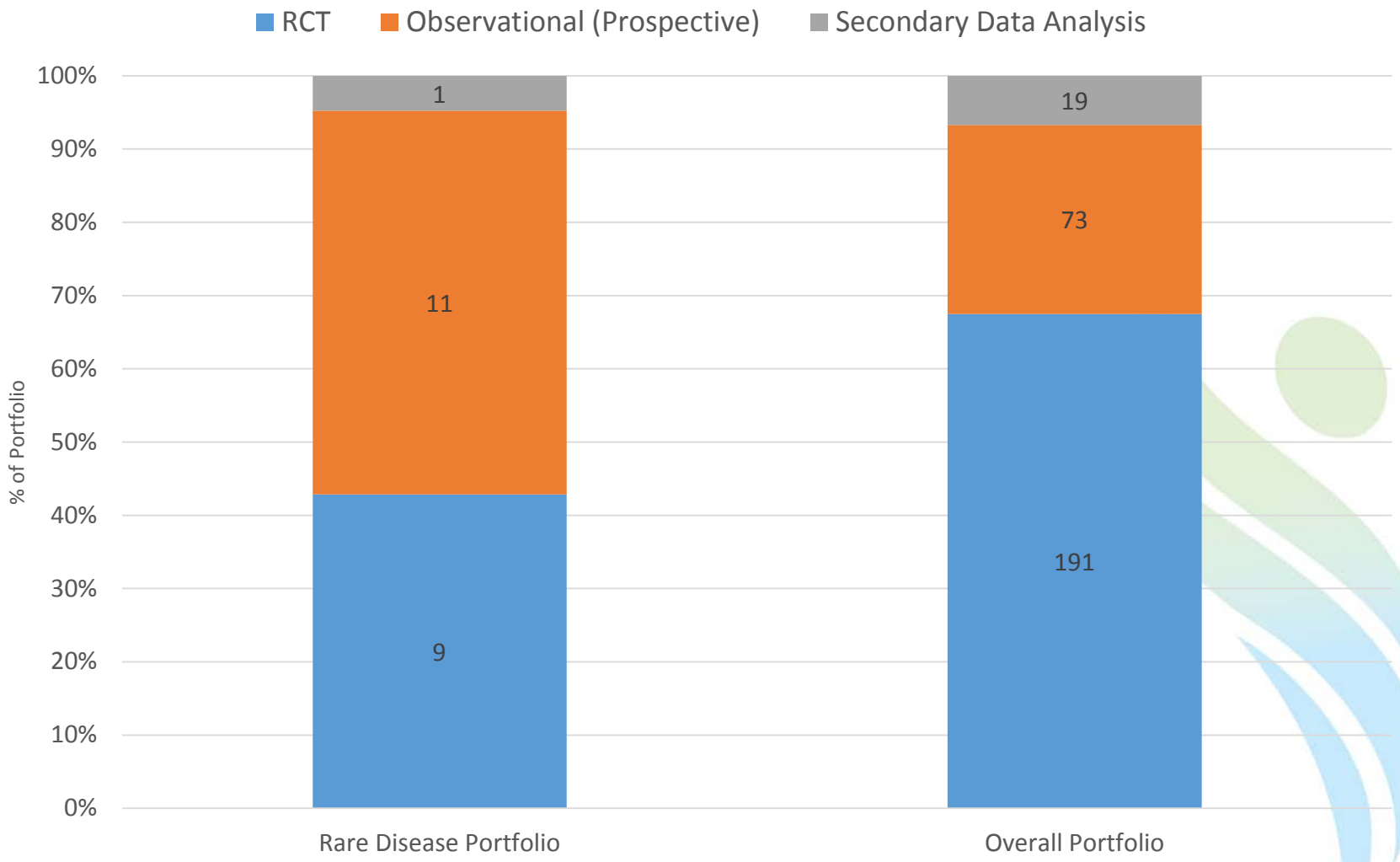
*includes projects in Improving Methods for Conducting PCOR

Study Goals in Rare Disease Broad and Pragmatic Portfolio (n=21)



Study Design in RD Portfolio (n=21) v. Overall (n=283)*



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*does not include projects in Improving Methods for Conducting PCOR

RD Portfolio Sub-Themes (N=21)

- 10 projects (47%) focus on children, with an additional 3 general population studies (14%) that include children
- The proportions of racial and ethnic minorities (33%), low income populations (10%), and women (14%) are lower than in the overall portfolio
- 4 projects (19%) are on rare cancers
- 3 projects (14%) are on sickle cell disease

Stakeholder Partners in PCORI RD Portfolio

- Children's Oncology Group Patient Advocacy Committee (COG-PAC),
- Alex's Lemonade Stand Foundation (ALSF)
- Transverse Myelitis Association (TMA)
- United Spinal Association
- Crohn's and Colitis Foundation of America (CCFA)
- Arthritis Foundation (AF)
- Children's Sickle Cell Foundation
- Chiari and Syringomyelia Foundation (CSF)
- Conquer Chiari
- American Society of Pediatric Hematology
- American Society of Pediatric Oncology Nursing
- Scleroderma Foundation
- Scleroderma Research Foundation
- CURED Foundation
- Eosinophilic Family Coalition (EFC)
- Accord Alliance
- Lupus Foundation of America (LFA)
- National Urea Cycle Disorders Foundation
- Hydrocephalus Association (HA)
- National Organization for Rare Diseases (NORD)
- Genetic Alliance
- The COPD Foundation and NTM Info & Research (NTMir)
- American Partnership for Eosinophilic Disorders (APFED)

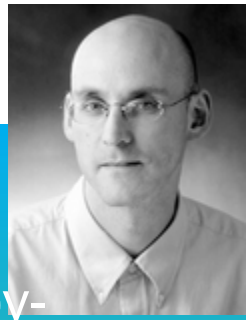
86% of Rare Disease Projects Identify a Patient Organization as a Partner

Discussion

- How can PCORI examine and conceptualize the rare disease portfolio to understand its impact?
  - What themes emerge from PCORI's rare disease portfolio?
  - What gaps emerge from PCORI's rare disease portfolio?
- What areas of rare disease research funded by PCORI could have the greatest impact?

Thank You

Home or Away from Home: Comparing Clinician and Patient/Family-Centered Outcomes Relevant to the Care of Pediatric Acute Myeloid Leukemia during Periods of Neutropenia



Engagement

- Engages a variety of stakeholders including a family consultant, a director of a large cancer advocacy foundation, and the patient advocacy committee from the Children's Oncology Group.

Potential Impact

- Infectious complications are a leading cause of treatment-related morbidity and mortality among AML patients. Identifying the best management strategy will have a substantial impact on care of these patients.

Methods

- Observational, prospective, and retrospective cohort

This study aims to evaluate outpatient versus inpatient management of chemotherapy-induced neutropenia among children and adolescents being treated for newly diagnosed acute myeloid leukemia. This will inform current treatment guidelines, and improve patient and provider decision making.

Richard Aplenc, MD, PhD
Children's Hospital of Philadelphia
Philadelphia, PA

Assessment of Prevention, Diagnosis, and Treatment Options, awarded April 2015

Intervention and Outcomes in Duarte Galactosemia

Engagement

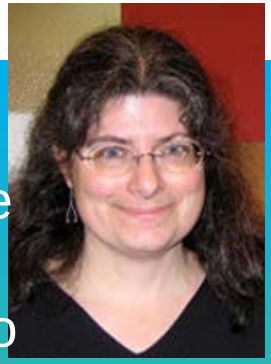
- Patient families will participate both as subjects and research partners

Potential Impact

- The results of this study will give families and clinicians an evidence-based understanding of likely developmental outcomes for their children with DG

Methods

- Multi-state, case-control observational study

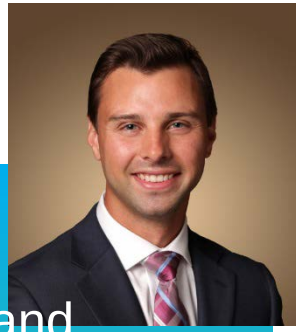


To assess developmental outcomes among school-age children with Duarte galactosemia (DG) relative to controls: determine whether school-age children with DG are at increased risk for disorders in physical, adaptive behavior, social-emotional, communication and auditory processing, or cognitive development.

Judith Fridovich-Keil, AB, PhD
Emory University
Atlanta, GA

Assessment of Prevention, Diagnosis, and Treatment Options, awarded April 2015

Treatment Alternatives in Adult Rare Disease: Assessment of Options in Idiopathic Subglottic Stenosis



Engagement

- All patient partners and advocates are equal partners in this research and will be included in all aspects of design, implementation, analysis, and result dissemination

Potential Impact

- It will enable rigorous treatment strategy comparisons to determine how well the most commonly used treatments in iSGS work as well as the quality-of-life trade-offs that are associated with each approach

Methods

- Prospective observational cohort study

Idiopathic subglottic stenosis (iSGS) is a rare disease characterized by unexplained and recurrent narrowing of the upper trachea. This study intends to create an international, multi-institutional prospective cohort of iSGS patients through which the treatment effectiveness of the three most common treatments—endoscopic dilation, endoscopic resection, and tracheal resection—will be measured.

Alexander Gelbard, MD
Vanderbilt University

Assessment of Prevention, Diagnosis, and Treatment Options, awarded April 2015

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Anti-TNF Monotherapy versus Combination Therapy with Low-Dose Methotrexate in Pediatric Crohn's Disease

Engagement

- Parents and patients will provide input on all aspects of the trial: planning, conducting, and future dissemination.

Potential Impact

- Could address a significant knowledge gap and have substantial impact on patient decision making, care, and outcomes. The advantage of conducting this trial within ICN is that the same network that generates the research can also be used to implement evidence into practice.

Methods

- Randomized controlled clinical trial.

Compares which of two treatments provided—anti-TNF plus methotrexate or anti-TNF therapy alone—is more effective in inducing and maintaining long-term (two-year) steroid-free remission, and improving patient-reported outcomes among anti-TNF naïve patients with moderate-severe Pediatric Crohn's Disease (PCD).

Michael Kappelman, MD, MPH
University of North Carolina at Chapel Hill
Chapel Hill, NC

Assessment of Prevention, Diagnosis, and Treatment Options, awarded April 2015

Comparative Effectiveness of CARRA Treatment Strategies for Polyarticular Juvenile Idiopathic Arthritis

Juvenile idiopathic arthritis (JIA) is the most common pediatric rheumatic condition, affecting 1-4 in 1,000 children. The proposed study, Start Time Optimization in PJIA (STOP-JIA), aims to improve the lives of polyarticular JIA patients by comparing the clinical effectiveness of three different strategies for the introduction of biologic therapy in achieving clinically inactive disease.

Yukiko Kimura, MD
Hackensack University Medical Center
Hackensack, NJ

Engagement

- Two patient partners are members of the core research team. A stakeholder advisory committee, composed of patients, parents, pediatric rheumatology nurses, and research associates, will advise the research team on study design, engagement, and dissemination.

Potential Impact

- Biologics are highly effective, but can have side effects and toxicity, so knowing when they should be started to produce the best outcomes is critical.

Methods

- Prospective, observational cohort study

Assessment of Prevention, Diagnosis, and Treatment Options, awarded April 2015

Posterior Fossa Decompression with or without Duraplasty for Chiari Type I Malformation with Syringomyelia

Determine the best treatment for Chiari type I malformation + syringomyelia (CM+SM) in terms of change in symptoms, syrinx size, and QOL that optimizes clinical effectiveness and minimizes risk of harm to patients.

David Limbrick, MD, MS, PhD,
Washington University
Saint Louis, Missouri

Engagement

- Partnership with the patients and advocacy groups, who provided input on the study design and will continue to be engaged over the course of the study.

Potential Impact

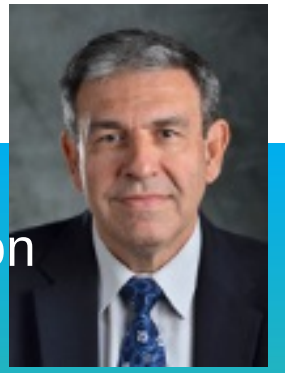
- Results will enable the creation of evidence-based treatment guidelines and, importantly, provide CM+SM patients and families with the information they need to make informed healthcare decisions.

Methods

- Randomized controlled trial

Assessment of Prevention, Diagnosis, and Treatment Options, awarded September 2015

Comparative Effectiveness of Therapy in Rare Diseases: Liver Transplantation vs. Conservative Management of Urea Cycle Disorders



Engagement

- Brings together investigators and those affected by urea cycle disorders in all aspects of study design and dissemination.

Potential Impact

- Could affect patient decision-making process on whether to opt for liver transplantation or remain on conservative treatment.

Methods

- Observational research

Provides scientific information to address risk of mortality and illness and quality of life measures for two treatment approaches: conservative management of urea cycle disorder with special diet vs. orthoptic liver transplantation.

Mendel Tuchman, MD
Children's Research Institute
Washington, DC

Assessment of Prevention, Diagnosis, and Treatment Options, awarded September 2015

Comparative Effectiveness and Safety of Inhaled Corticosteroids (ICS) and Antimicrobial Compounds for Non-CF Bronchiectasis

Engagement

- Representatives from national stakeholder groups, clinical experts, and a patient advisory panel are involved in study design, evaluating study progress, and providing perspective on the interpretation and dissemination of study results.

Potential Impact

- National dissemination efforts will provide information on relative risks and benefits of these common therapies, impacting the decision making and course of treatment for non-CF bronchiectasis patients.

Methods

- Retrospective observational cohort

Among a national Medicare cohort of non-CF bronchiectasis patients, we will compare the safety and clinical effectiveness of chronic ICS and antimicrobial therapies including macrolides. These findings will assist both clinicians and patients in evaluating the risks and benefits of chronic therapies for this patient population.

Kevin Winthrop, MD, MPH
Oregon Health and Science University
Portland, Oregon

Assessment of Prevention, Diagnosis, and Treatment Options, awarded September 2015

Break

2:45 – 3:00 p.m.

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PCORnet Update

Maryan Zirkle, MD, MS, MA
Program Officer, CER Methods and Infrastructure, PCORI

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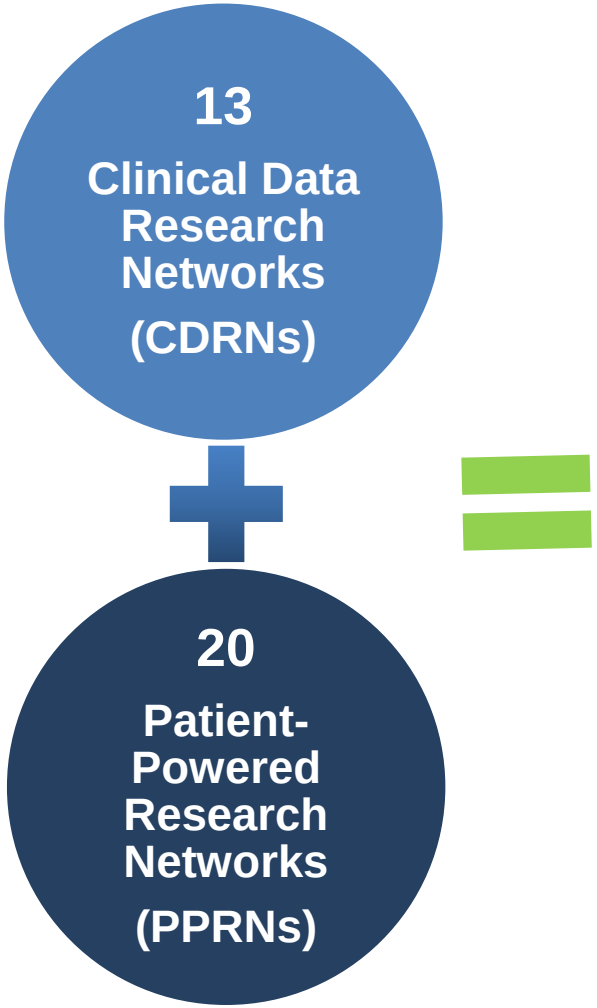
Why Did We Establish PCORnet?

- PCORI was established to fund comparative clinical effectiveness research (CER) that will provide needed evidence to help patients and their caregivers make better-informed decisions.
- However, the nation's capacity to conduct **CER rapidly and efficiently** remains extremely limited.

PCORnet's Goal

- PCORnet seeks to improve the nation's capacity to conduct **clinical research** by creating a large, highly representative, national **patient-centered** network that supports more efficient clinical trials and observational studies.

PCORnet Unites System-Based and Patient-Driven Research Networks



PCORnet:

A national infrastructure for patient-centered clinical research

PCORnet Overview: CDRN Awardee Organizations*

CDRN Name	Lead Organization	Principal Investigator
ADVANCE	Oregon Community Health Information Network	Jennifer DeVoe
CAPriCORN	The Chicago Community Trust	Terry Mazany
Greater Plains Collaborative	University of Kansas Medical Center	Russ Waitman
REACHnet	Louisiana Public Health Institute	Thomas Carton
LHSnet	Mayo Clinic	Veronique Roger
Mid-South CDRN	Vanderbilt University	Russell Rothman
NYC-CDRN	Weill Medical College of Cornell University	Rainu Kaushal
OneFlorida	University of Florida	Elizabeth Shenkmen
PEDSNet	The Children's Hospital of Philadelphia	Christopher Forrest
PORTAL	Kaiser Foundation Research Institute	Elizabeth McGlynn
pSCANNER	University of California, San Diego	Lucila Ohno-Machado
PaTH	University of Pittsburgh	Rachel Hess
SCILHS	Harvard University	Kenneth Mandl

**Each awardee works with multiple health systems*

Phase I: CDRN PFA Requirements for Rare Disease Cohort

- **Identify, characterize, and recruit** a rare disease cohort with defined conditions or symptoms using available electronic data
- Rare disease was defined by a **prevalence of less than one per 1,500 persons in the United States**.
- Applicants were encouraged to **reach out to and collaborate with the appropriate rare disease organization(s)** to identify and include additional individuals with the condition.
- Expected to work with other funded networks to ensure that methods of cohort construction **use data standards that support interoperability** and construction of similar cohorts elsewhere
- The cohort must be **contacted and recruited** to participate in the cohort and in a brief baseline **survey**.
  - The survey must assess the patient's level of interest in participating in research related to the condition being studied, including:
    - Interest in participating in randomized trials should an appropriate one be launched
    - Interest in participating in network development and governance
    - Interest in communicating with other patients about possible uses of the network

Phase II: CDRN PFA Requirements for Rare Disease Cohort

- Cohort identification and **preliminary analyses by running standardized queries against analysis-ready, standardized data**
- Continue development of the rare disease specific cohort initiated in Phase I, including:
  - Description of **planned expert working groups** during Phase II,
  - Projected **status of the cohort by the end of Phase II** (e.g., number of individuals expected to be accrued)
  - **Data** elements available
  - Ability to **contact individuals** for participation in research
  - Expectations and commitment **for research funding**

PCORnet CDRN Rare Disease Cohorts

Network	Disease/Condition
ADVANCE	Alpha-1-antitrypsin deficiency
CAPriCORN	Sickle cell disease; recurrent *C. difficile* colitis
GPC	Amyotrophic lateral sclerosis (ALS)
REACHnet	Sickle cell disease; rare cancers
LHSNet	Osteogenesis imperfecta
Mid-South CDRN	Sickle cell disease
NYC-CDRN	Cystic fibrosis
OneFlorida	Duchenne muscular dystrophy
PaTH	Idiopathic pulmonary fibrosis
PEDSNet	Hypoplastic left heart syndrome
PORTAL	Severe congenital heart disease
pSCANNER	Kawasaki disease
SCIHLS	Pulmonary arterial hypertension

Themes of CDRN Rare Disease Cohorts

- **Establishing Advisory Groups**
  - Includes patients, caregivers, clinicians, and researchers
- **IRB**
  - Slow to start: Various differences in local institutional practices
- **Identification**
  - Using computable phenotypes is not always accurate; results in false positives
- **Recruitment and Consent**
  - Populations can be accustomed to f2f recruitment and respond favorable to this methodology
  - Time intensive work toward novel, streamlined approach whereby patients could opt-out at the time of the recruitment
- **Data Collection: EMR and Survey**

Next Steps

Creating Template Table for Cohorts

I. Computable Phenotype
II. Pan-Disease Elements
    a) Completeness
    b) Demographics
    c) Coverage
III. Survey Elements
    a) Approach for ID
    b) Patients contacted
    c) Patients surveyed
    d) Response rate
    e) Participation
IV. Condition-Specific Elements

Questions/Comments/Feedback

Input on the template table?

What other information would be useful?

Recap and Next Steps

Vincent Del Gaizo
Co-Chair, Advisory Panel on Rare Disease, PCORI
Danielle Whicher, PhD, MHS
Program Officer, Clinical Effectiveness Research, PCORI
Parag Aggarwal, PhD
Senior Program Officer, Addressing Disparities, PCORI

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Thank You!

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