Pediatric Heart Network (PHN)

ISV RANDOMIZED CLINICAL TRIAL
PUBLIC USE DATASET

ABOUT THE STUDY

The NHLBI Infant Single Ventricle (ISV) randomized double-blind placebo-controlled trial was conducted by the Pediatric Heart Network (PHN) at 10 centers in the United States and Canada, enrolling patients in 2003-2007. This trial was designed to determine whether ACE inhibition improves ventricular function and hemodynamic status in infants with single ventricle physiology, thereby improving a clinically important outcome, somatic growth.

The PHN screened a total 1,245 infants < 45 days old with single-ventricle anatomy who had undergone surgical palliation, and enrolled 230 infants (115 in each group, 43% consent rate) who were randomized to receive enalapril or placebo. Patients were followed until 14 months of age to allow assessment of the effects of ACE inhibitor therapy for at least 6 months after the volume-unloading that occurs after the Stage 2 superior cavopulmonary connection (SCPC) surgery, which occurs by age 8 months in most infants (mean 5.1±1.8 months in this trial). A total of 185 infants completed the trial (45 withdrew, 17 of which were deaths or cardiac transplants). A 29% of patients (53/185) discontinued the study drug during the course of the study.

The primary outcome was weight-for-age z-score at 14 months of age. Secondary endpoints included other measures of somatic growth, Ross heart failure class, brain natriuretic peptide (BNP) concentration, ventricular geometry and function obtained by two-dimensional echocardiography, and neurodevelopmental and functional status. Echocardiograms were analyzed centrally by a single core laboratory observer. BNP concentration was determined by a central laboratory.

Adverse events were classified as non-serious, moderately serious and serious using the Common Terminology Criteria for Adverse Event v.3.0 categories. All serious adverse events were adjudicated by an independent physician who was unaware of treatment group assignment.

The study design has been summarized in Hsu et al. (*Amer Heart J* 2009) and in the study protocol (available to users with approved logins).Key findings were published in Hsu et al. (*Circulation* 2010) followed by a number of papers listed in the ‘study resources’ section below. Table 1 summarizes key anthropometric measurements collected in the trial.

Table 1. Weight and Height from Birth to Age 14 months

			Weight			Height	
Time Point	**n**	**Age (months)**	**kg**	**z score**	**n**	**cm**	**z score**
Birth	230	0	3.27±0.50	-0.15±1.06			
Baseline*	229	0.7±0.4	3.36±0.54	-1.27±1.27	229	51.1±2.4	-1.05±1.27
Day 4**	211	0.8±0.4	3.43±0.54	-1.40±1.23	209	51.4±2.4	-1.17±1.27
Two Weeks**	161	1.2±0.4	3.66±0.54	-1.63±1.07	160	52.5±2.4	-1.29±1.16
Pre-SCPC	197	5.1±1.8	6.06±1.05	-1.63±1.14	197	62.4±3.8	-1.29±1.27
Post-SCPC Restart***	118	5.8±1.6	6.34±1.08	-1.64±1.18	118	63.7±3.6	-1.27±1.22
Age 10 months	86	10.0±0.7	8.22±1.10	-0.81±1.13	86	70.1±3.4	-1.12±1.30
Age 14 months	185	14.1±0.9	9.45±1.24	-0.49±1.11	185	75.3±3.1	-0.93±1.16

*Study drug initiation (within 3 days of randomization)
**On study drug
***7 days after restarting study drug

STUDY DOCUMENTATION

The following datasets and descriptor files are available for download. A login and password (request access via http://www.pediatricheartnetwork.org) are required for download capability. Privacy protection of these data is described in Appendix A.

1. Annotated study data collection forms (PDF) – These contain the SAS variable names next to each data field on the form. These form documents also include some created variables and their definitions.

2. SAS version 9.3 datasets

3. The file *isvformats.sas7bcat* – Include this file in your program using:
```
options fmtsearch = (fmtlib.isvformats);
```
where fmtlib is specified using a libname statement as the path name.
The formats are 64-bit.

4. SAS Proc Contents for each dataset (PDF)

5. Excel datasets (with variable formats applied) – These data have a .csv extension, which means that the file may also be opened either in Excel, OR in a text editor, appearing as a comma-delimited file.

STUDY RESOURCES

Resources posted on the pediatricheartnetwork.org website include:

- ISV trial bibliography (see http://www.pediatricheartnetwork.com/pubisv.asp)
- ISV trial Design paper and Main Results paper (see http://www.pediatricheartnetwork.com/publications/ISV.Design.AmHJournal.2009.pdf and http://www.pediatricheartnetwork.com/publications/ISV_CIRCULATIONAHA333-340.pdf?file_ID=85338)
- ISV trial protocol (with login access)

DATA USE POLICY

- REQUIRED ACKNOWLEDGEMENTS: All presentations and publications using these data must include the following statement: *"The NIH/NHLBI Pediatric Heart Network Infant Single Ventricle trial dataset was used in preparation of this work. Data were downloaded from https://www.pediatricheartnetwork.org//pud_login.asp?study_id=ISV on mm/dd/yyyy"."*
- *PAPER, ABSTRACT, and PRESENTATION TITLES*: Titles may, at the authors' discretion, mention the PHN database but should not imply that the work is from the PHN. An example of an acceptable phrase would be, "an analysis of the Pediatric Heart Network public database." Whether or not the title makes mention of the PHN, acknowledgement should be made as described above.
- All users are requested to send a copy of published abstracts and articles to the PHN Data Coordinating Center at New England Research Institutes (PHNpubs@neriscience.com) within one month of publication. This will allow the PHN and the NHLBI to document the continued impact of this study on the field.
- The login and password provided to each user are valid for 6 months. If a user decides to complete analyses leading to more than one presentation or publication in that time period, it is requested that they notify the PHN Data Coordinating Center at New England Research Institutes of their additional analysis topics, solely for the purposes of tracking.
- The login and password to access the public dataset is provided to a single user. If a colleague would like to access the public dataset for a different analysis topic, a separate request for login and password should be submitted via the www.pediatricheartnetwork.org website.
- As an approved user, you agree that you will not attempt to establish the identities of research participants through use of this dataset.
- As an approved user, you agree to not place these data in other public locations.

TIPS ON USING THESE DATA

- Identification numbers for study subjects and study sites have been re-assigned for privacy protection.

  blind_id: Subject ID ranging from 1 to 1245 (included in every form);
  blind_site: Ranges from 1 to 10 (included in S100)

- The study data are contained in a large number of individual forms. These may be used jointly by merging on *blind_id*.

- Some forms (S100, S101) include records for 1245 screened subjects. The majority of the forms are limited to the 230 randomized subjects. Many of the datasets, however, have multiple visit records for the 230 subjects.

- Randomization treatment assignment (along with the date of randomization) is recorded in the dataset 'randomization' (specially created for the public dataset, since the ISV trial was double-blind). The stratification variable (the presence or absence of hypoplastic left heart syndrome at the time of screening) may be found in S100 (question B5).

- Many measurements were performed longitudinally (i.e. repeated measurements were taken at different time points for the same subject). In particular, anthropometric measurements (weight, height and head circumference) were taken at baseline and at 6 follow-up visits (weight was additionally recorded at birth). The variable VISIT with the values 1 to 6 defines the follow-up visit and is included in the corresponding datasets.

- To improve precision, each of the anthropometric measurements was taken at least twice (or three times, if the gap between the first two measurements was larger than a certain threshold; see B1-B3 in S106 and S103) and the mean values were calculated.

- Another group of tests (BNP and Ross classification) was performed twice, at the pre-SCPC and 14-month visits. Echocardiography was performed at three time points (at the baseline, pre-SCPC and 14-month visits). The corresponding datasets include variable *VISIT* as well.

- The raw data collected are contained in the original variables (denoted by upper case variable names). Prior to analysis, these variables must have special values (typically negative numbers, see Appendix B) set to missing. Created variables (denoted by lower case variable names) already contain a SAS missing value if the measurement is unavailable.

- Anatomy: A key grouping variable that has been used for many study analyses is ventricular morphology (left, right, mixed). This variable is determined according to cardiac anatomic diagnosis and is called *vent_type (*Form S101 and S302). This variable is not the same as the echo core laboratory (Form S302) variable *vendom,* which does not take into account anatomic diagnoses involving reversed location of cardiac structures. All ISV Trial publications have utilized *vent_type*.

- To select for echocardiograms that have data acceptable for analysis, use ACPTECHO=1. Unacceptable echocardiograms have no qualitative or quantitative measurements recorded.

- The core laboratory echocardiographic measurement dataset Form S302 contains many created variables that are most commonly used in analysis. These variables express <u>total</u> ventricular size (e.g., *echoedv*) and function (e.g., *echoef*) and overall regurgitation grades

(*oavvregrg, slvregurg*). They incorporate, where available, measures from both ventricles, and measurements from left, right, and common atrioventricular valves. Echocardiographic z-scores (e.g., *echoedv_z, echoef_z*) accounting for body surface area or age that provide a reference relative to normal (two-ventricle) children are also included in this dataset.

- Anthropometric z-scores variables (weight-for-age, length-for-age, weight-for-length, etc.) are calculated based on the 2000 WHO standard (using macro downloaded in Oct 2008). The raw measurements used for z-score calculation are weight, height and head circumference (collected on multiple forms), as well as age, gender and race. Anthropometric z-scores were added to each of the datasets containing raw anthropometric measurements. Comparison of WHO and CDC methods can be found in M. de Onis, Garza C, Onyango AW, Borghi E. Comparison of the WHO child growth standards and the CDC 2000 growth charts. J Nutr 2007; 137(1):144-148).
- All neurodevelopmental assessment tests (Bayley, MacArthur-Bates and FSII-2(R)) were performed at the final 14 month visit.
- The second edition of the Bayley Scales of Infant Development® was used in the ISV Trial (BSID–II). See Bayley N. Bayley Scales of Infant Development, Second Edition. Second Edition ed. San Antonio, TX: The Psychological Corporation; 1993. The summary scores *PDISCORE* and *MDISCORE* are located in the S114 dataset.
- The functional status assessments are based on the manual by Drs. R. Stein and Dorothy Jessop (Albert Einstein College of Medicine of Yeshiva University, Bronx, NY, 1991). Calculated summary scores are added to the S113 dataset.
- The MacArthur-Bates assessments are based on MacArthur-Bates Communicative Development Inventories, User's Guide and Technical Manual, 2nd edition (L. Fenson et al., 2007, Paul Brookes Publishing). Calculated summary scores are added to the S115 dataset.
- Adverse events information can be found in the forms S200 and S205 (adjudicated events). To protect privacy of patients, detailed descriptions of events were removed from the public dataset.

ADDITIONAL ASSISTANCE

If you have questions about the study dataset that this documentation and the above resources (protocol, articles) have not answered, please email the PHN Mailbox at PHNmailbox@neriscience.com.

APPENDIX A

Implementation of Privacy Protection Rules for Public Use of the PHN Study Dataset

Variables that could lead to subject identification were eliminated in the public dataset. Steps included:

1. Removal of original study ID number (replaced with *blind_id*, a random consecutive numbering ranging from 1 to 1245), and removal of acrostic. Of note, no names, addresses, zip code, or medical record numbers were ever contained in the original study dataset.

2. Ten centers contributed data to the ISV trial. A new center identifier (*blind_site*), which represents a random consecutive numbering ranging from 1 to 10 was created, without formats (i.e., without center names).

3. All dates in the original datasets were removed, and replaced with "Age at event/intervention/procedure" in years (to 2 decimal places). Therefore, time intervals may be calculated by subtraction of two ages.

4. Free (write-in) text variables remain in the public dataset. These often provide highly relevant information for interpretation of the data. However, any write-in string that referred to a specific date, a particular medical center or a particular MD was blinded or omitted.

5. Outliers for continuous variables and small group sizes for categorical variables were retained in the dataset for public use due to their importance in interpretation of the data and low likelihood of unblinding any user to a subject identity unless the user already had access to the particular medical center’s data for valid reasons.

APPENDIX B

Special Value Codes

-9 = missing

-8 = don't know/indeterminate

-7 = refused to answer

-6 = not recorded

-5 = measurement could not be reliably recorded or is not interpretable (study technically inadequate)

-4 = illegible

-2 = programmed skipped field based on results of or response to a previous question

-1 = not applicable/structure not present

-77 = Not detectable below 4.0 pg/ml (BNP concentration)