CHSS Work Weekend Report
April 13 – 15, 2018

Goals & Objectives for Work Weekend *

1. **Cohort Updates - FYI session**
2. **Review of 2 AATS presentations:**
   AAOCA Ischemia Study
   Aortic Arch Re-intervention post Norwood
3. **Kirklin/Ashburn Fellow's visit to Cleveland – Statistical Methodology**
4. **Critical AS Calculator Issues & Future Direction**
5. **Data abstraction: A working session to extract LVOTO Data**
6. **Pulmonary Valve Conduit: Pseudo aneurysm project**
7. **AVSD research proposals; the next step(s)**
8. **CHSS Data Center Planning Follow-up conundrum**

** Final slide decks are available at https://chssdatacenter.box.com/s/lvkg9j7q6o3zy2i2onuavk6kojfh1pke*

1. Cohort Updates: FYI

Paul Devlin, John W. Kirklin/David A. Ashburn Fellow

Dr. Devlin reviewed the status of the 11 CHSS inception cohorts totaling 6,963 patients as listed below:

Diagnostic Cohort	Institutions	Accrual	Enrolled
Complete Transposition	24	1985-89	891
PA/IVS	33	1987-97	448
Interrupted Aortic Arch	33	1987-97	470
Coarctation of Aorta	36	1990-93	975
Aortic Valve Atresia	26	1994-2000	566
Critical Aortic Stenosis	28	1994-2000	422
Tricuspid Atresia	38	1999-present	411
Pulmonary conduit	29	2002-2014	632
Critical Left Heart Obstruction	27	2005-present	1066
Anomalous Aortic Origin of Coronary Artery	44	2009 - present	624
Atrioventricular Septal Defect	28	2012 - present	458

Paul reviewed the follow-up data currently available for each cohort and specific projects being pursued. Among these projects are the following:

TGA 1) Develop a link with the Alliance for Adult Research in Congenital Cardiology to have TGA patients born between 1984/12/15 & 1989/04/01 contact the data center to confirm their enrollment from that era (awaiting IRB/DUA approval)

2) Obtain current & retrospective medical records from CHSS institutions & other sources to study neo-aortic root problems, late atrial & arterial outcomes (an IRB problem) and search Death Index (may not be patient-specific).

Critical AS: 1) Correction of AS Calculator error and update calculator to present era (see discussion page 5)

2) Data collection of functional health data is not yet submitted for IRB approval.

Pulmonary Valve Conduit: Analysis of factors associated with pseudo-aneurysm (see discussion page 6 - 8)

Critical Left Heart Obstruction: Aortic Arch Re-intervention post Norwood presentation accepted for AATS 2018 (see page 3)

AAOCA: 1) AAOCA Ischemia Study for AATS (see page 2, 3)

2) Review of CT & MRI studies by Dr. Raj Krishnamurthy

3) Establish CT/MRI capability within a virtual Image Core Lab

Atrioventricular Septal Defect: Next steps in analysis? (See discussion page 8-10)

2. Review of 2 AATS presentations:
2.1 AAOCA Ischemia Study
Dr. Anusha Jegatheeswaran & Julie Brothers

Anusha presented a first draft of her AATS paper for feedback. She discovered 49 patients who presented with ischemia among the 560 AAOCA patients enrolled to December 31, 2016. Among the 49 are 18 who presented with a sudden cardiac event. Essential findings are that both anomalous right and anomalous left coronary anomalies were found among the ischemia patients and among those with sudden cardiac arrest. She compared these 49 with the larger group of 236 who were non-ischemic at presentation by provocative ischemia testing. Interestingly, about 50% of AAOCA patients (278) were not tested for ischemia, including some patients referred for surgery. Ischemia was more prevalent among patients with anomalous left coronary. Within the cohort with known ischemia status (236 patients without ischemia + 49 patients with ischemia = 285 patients) only 5% of patients with AAORCA (20/204, 10%) vs. 22% with AAOLCA (46/74, 62%), were found to have ischemia. The denominator for these two proportions, are patients with known ischemia status. Anusha found that associated morphologic variants in ischemic patients (slit-like orifice, high ostial takeoff, and intramural course) were different from anomalous right (longer intra-mural course). There were no significant morphologic variants identified with the sudden cardiac arrest group. These data suggest there are important morphologic variants other than left vs. right that account for ischemia at initial presentation.

During the weekend, Dr. Krishnamurthy reviewed over 30 CTs and MRIs for the AAOCA cohort. While these data are not part of the AATS analysis, they will be an important additional component as a baseline for advanced imaging of the entire cohort when the virtual ICL is operational.

2.2 Aortic Arch Re-intervention post Norwood

Dr. Paul Devlin & Tara Karamlou

Arch re-intervention post Norwood is common (25% at 2 years) and may occur before, at, or after each subsequent palliation stage with similar prevalence. Among 593 babies enrolled, 146 had 1 or more re-interventions (total 228; 50 surgical & 128 catheter-based). Risk factors associated with 1st re-intervention are ≥ moderate TR whereas an interdigitation-type repair and not requiring an arch intervention before stage II are protective. The Rate of re-intervention post Stage I with an RV-PA conduit was not different than among the B-T cohort. Further re-intervention after a surgical repair was much less frequent than after a catheter intervention. Importantly, re-intervention for arch obstruction is not associated with increased mortality. There are major institutional variations of rates of re-intervention. Pressure gradient threshold for re-intervention also vary widely but there is insufficient measurement data to explain these differences.

Attendees were very helpful in suggesting constructive changes to both presentations. Each presentation was edited, reorganized and re-presented for further input.

3. Kirklin/Ashburn Fellow's visit to Cleveland – Statistical Methodology

Dr. Paul Devlin and Dr. Blackstone

Paul presented a comprehensive review of *Structured Approach to Survival Analysis* that he learned during his sabbatical in Cleveland. (In fact the 1½ hr. presentation only covered the first ½ of his prepared talk!)

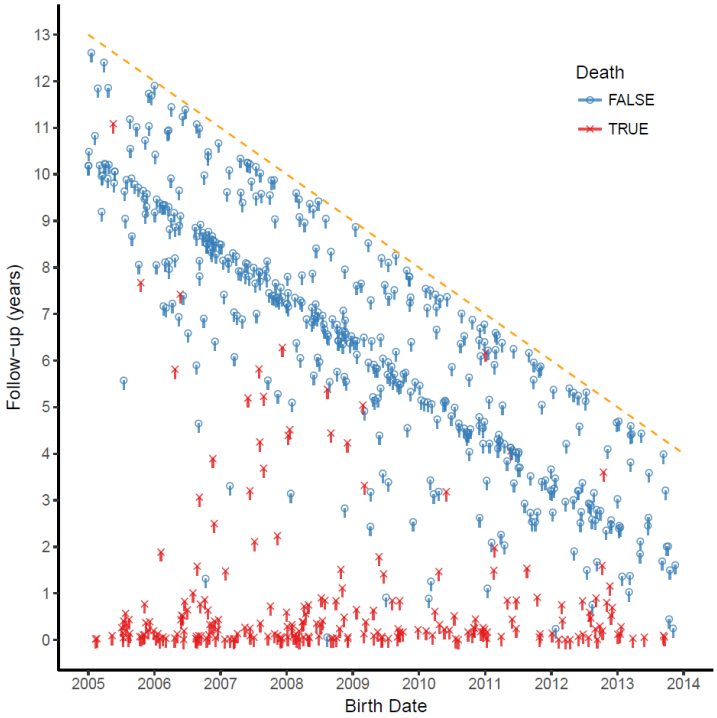
Every project in Cleveland begins with creation of a standard folder for the project. Each folder contains 8 standard sub-folders as follows:

Analyses	Distributions	Graphs
Datasets	Documents	Templates
Descriptive	Estimates	

The templates are software programs for specific statistical jobs that are organized in the same format for each study.

Each program is labelled with a 2 letter code that denotes the job. For example **tp** denotes that the program is a template program. These programs are adapted to work with on the specific project's data. Since each new project begins with a fresh set of template programs, there is no need to go digging into old projects to find code. Programs are run in batch so that output is regularly stored and saved.

To illustrate the Cleveland process, Paul used the CHSS dataset 650 patients from the Critical Left Heart Obstruction Cohort that underwent baseline echo review by a single reviewer. He reviewed processes for dataset creation, data checking of categorical and continuous variable, data visualization, 'goodness' of follow-up graph (from 'R' statistical program) illustrated below:



Legend: The horizontal axis is year of enrollment, the vertical axis, years of follow-up. Each blue dote represents a single patient, the red a death. With 100% follow-up the blue dots would all be along the dotted line.

All of the above process precedes Standardized Application of Survival Analysis that Paul presented (be continued at the Fall Work Weekend) as outlined in the following list:

Structured research approach
Creating an analysis dataset and data checking
Survival Analysis
Kaplan-Meier Estimator
Parametric Hazard Modeling
Risk Factor Determination
Bootstrapping
Random Forests Survival
Time Varying Covariables
Competing Risks

The Step-by-step approach to survival analysis with parametric risk factor analysis consists of Kaplan-Meier survival estimates then matched to Parametric Hazard modeling. Candidate risk factors are the tested for relevance by bootstrapping samples to determine best fit for Variable selection and determination of final model. If imputed values are utilized, they need to be validated by re-runs with multiple imputed datasets and combined estimates.

The above short version does not do justice to Dr. Devlin's excellent presentation.

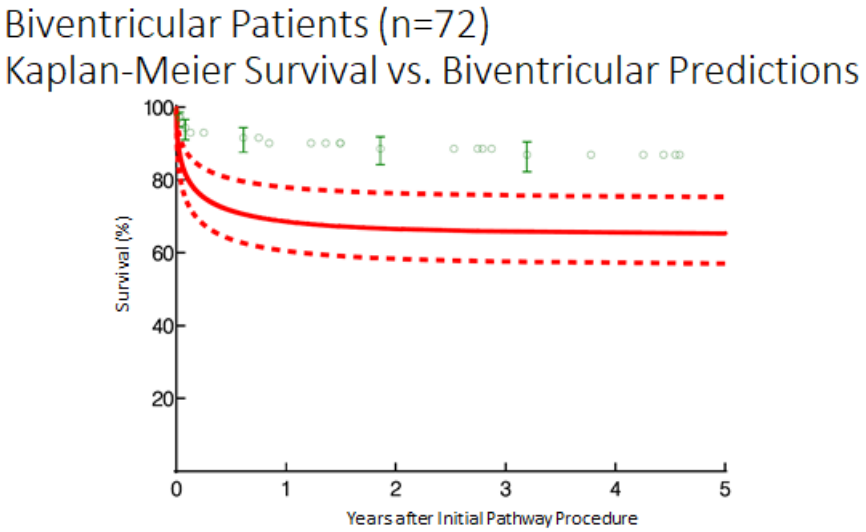
4. Critical AS Calculator Issues & Future Direction

Paul Devlin & Brian McCrindle

The initial version of the CHSS calculator to assist triage of babies with critical AS was developed from Gary Lofland's work published in 2000. A significant risk factor for death in that era was younger age at birth. The era preceded fetal diagnosis. The latter changed clinical practice by identifying the high-risk fetus resulting in urgent elective admission before onset of a circulatory collapse on day 0 or 1 of life.

Dr. Hickey's paper in 2007 identified slightly different risk factors when age was omitted, notably mitral stenosis. He updated the calculator to calculate the 5-year % survival difference (UVR – BVR). While the Website calculator program requests height in cm and LV length in mm. Each of the variables was incorrectly transformed in the algorithm. These errors have been corrected.

Data from the most recent cohort of isolated AS (2008 – 2013; n=115) shows that current survival is better in the current era for both UVR and BVR (the latter illustrated in the graph below:



Legend: Parametric survival estimated by the 2007 data is shown in red. Actual survival is portrayed by K-M in open circles with green error bars. A similar, but lesser improvement is also evident for UVR patients.

There are several possible explanations for this improvement; patients with MS (n=53) are not yet included, management algorithms have changed (more UVR to BVR transitions, more transplants, and increased use of hybrid management).

These data warrant further investigation. Echo images are being reviewed in the ICL to document ventricular function. Analysis of the new cohort is targeting the AHA deadline June 7th. A 3rd iteration of the calculator is planned.

5. Data abstraction: A working session to extract LVOTO Data

Work Weekend Attendees

Sally Cai constructed a copy of the CHSS Access file for critical left heart obstruction. Kate Pearson explained how to use the program and 17 attendees searched through 26 patient charts to extract 93 surgical operation reports during 2 working sessions of 3 and 2 hours each. A job much appreciated by the data center.

Special Presentation: The Art of Käthe Kollwitz

Dr. Brian McCrindle

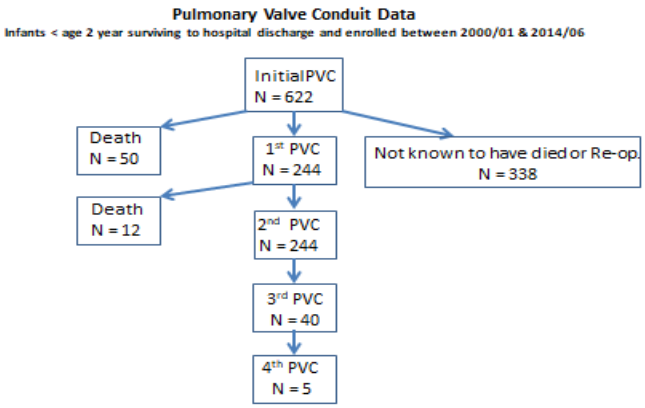
Dr. McCrindle gave a 1-hour description and interpretation of the life and art of Käthe Kollwitz. It is fair to say that the audience was mesmerized! Brian has collected her works since discovering her art during an afternoon off-service during his cardiology residency at Hopkins. He has recently donated > 200 of her drawings, wood etchings and sculpture to the Art Gallery of Ontario. The AGO is staging an 18 month exhibit of Kollwitz' art in 3 stages. (Unrelated to Fontan 3-stage palliation). Her art featured the common worker and family, often depicting women and children haunted by poverty. Brian described the context of many of her art works to help the audience understand their relevance. He also illustrated that in her art and in her life, Kollwitz was a humanitarian.

Following the lecture, the attendees toured the AGO exhibit prior to an evening dinner nearby.

6. Pulmonary Valve Conduit: Pseudo aneurysm project

Paul Devlin & Kristine Guleserian

The CHSS cohort of pulmonary valve conduits (PVC) consists of 622 infants < age 2 years at initial implant. Subsequent PVC replacements are shown in the following diagram:



Note that 338 infants are listed only as having initial PVC. But given the enrollment era of 2000 to 2014, one would expect more of these 338 to have had a 2nd PVC.

Among the 622 infants, 24 are known to have undergone 1 or more re-operations for false aneurysms. Risk factors for pseudo aneurysm will be sought and longer-term outcomes determined. But current follow-up must be obtained from institutional records before any definitive analysis can be performed. To do so, each institution must be IRB/REB compliant and have a Data Use Agreement (DUA) in place.

Institutions Enrolling Infants in PVC cohort & Compliance

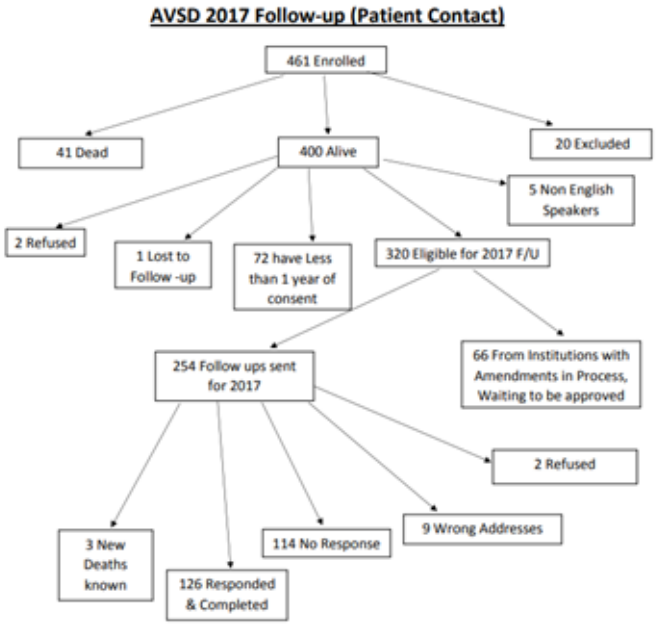
Institution	Infants	IRB Compliance	DUA
Yale - New Haven Hospital	1	1	1
University of Texas Health Science Center at San Antonio	2	0	1
Texas Children's Hospital	22	0	1
St. Louis Children's Hospital	6	1	1
SickKids	111	1	1
Rady Children's Hospital, San Diego	9	1	1
Primary Children's Hospital	117	1	1
Oregon Health Sciences University	5	0	1
Mott Children's Hospital	18	1	1
Montreal Children's Hospital	1	0	0
Milton Hershey Medical Center	5	0	1
Kosair Children's Hospital	27	1	1
Innova Fairfax Hospital for Children	4	0	0
Indiana University	20	1	1
Emory Clinic	27	0	1
DuPont Hospital for Children	14	0	1
Congenital Heart Institution of Florida	14	0	1
Comer Children's Hospital, University of Chicago	2	1	1
Cincinnati Children's Hospital Medical Center	13	1	1
Children's National Medical Center	3	0	1
Children's Mercy Hospital, Kansas City	35	0	1
Children's Memorial, Chicago	44	1	1
Children's Hospital Wisconsin	4	0	1
Children's Hospital of Philadelphia	51	1	1
Children's Hospital of Michigan	10	0	1
Children's Hospital LA	1	0	0
Children's Hospital Boston	38	0	1
Children's Heart Clinic, Minneapolis, MN	15	1	1
Arkansas children's hospital	13	1	1
Total	632	14	26

14 of the 29 PVC institutions have IRB compliance, and 26 institutions are DUA compliant. These 14 have enrolled 447 infants (70% of the cohort). Subtracted from the total will be the number known to have died and some with current follow-up. For the remainder, we need to ask these 14 institutions (or surgeon's office) for missing follow-up data (op reports, interval echos, cath interventions and most recent clinic reports including status). We will also endeavor to resolve the missing follow-up for patients from institutions not currently IRB compliant or without DUA in place.

7. AVSD research proposals; the next step(s)

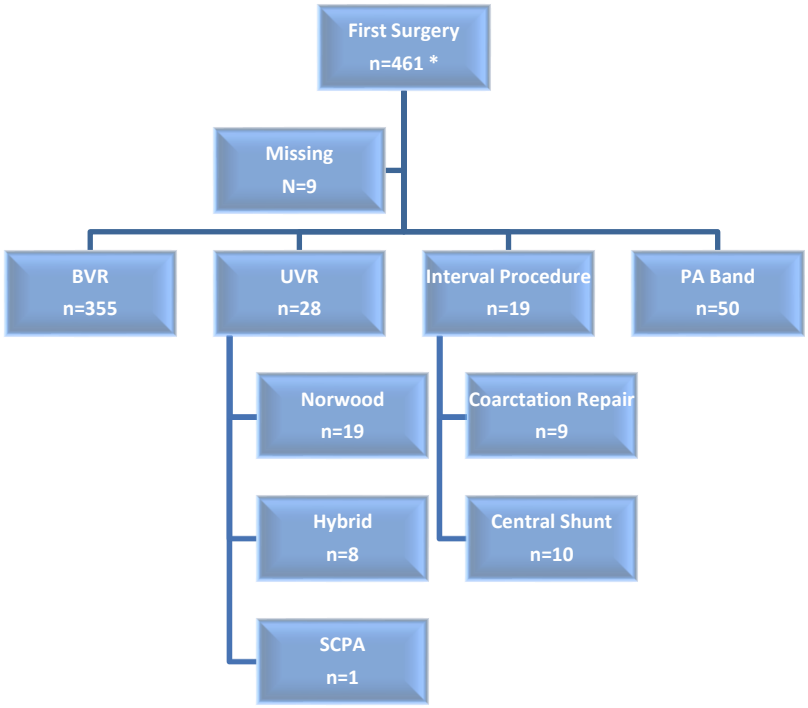
Paul Devlin & David Overman

Current status of the 465 babies' < 1-year with complete AVSD is as follows: 4 died without intervention, 461 had an index operation; 44 are known to have died

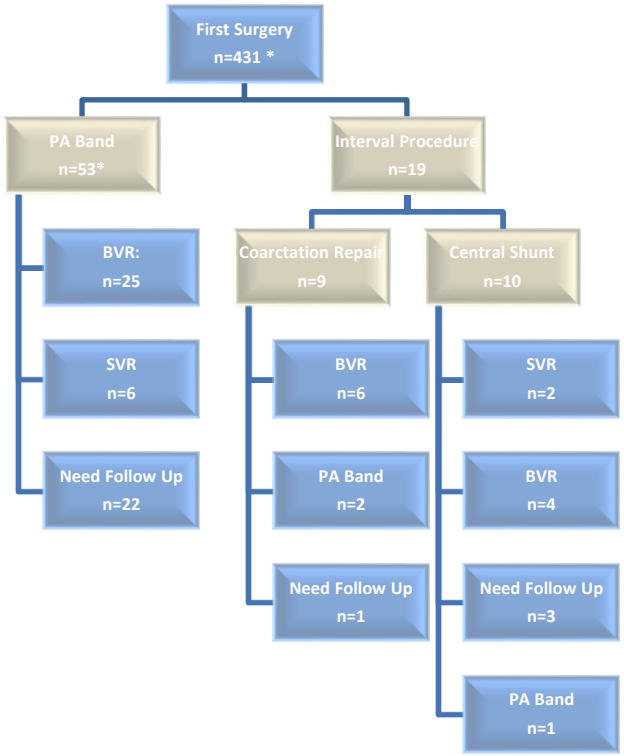


The above diagram represents patient questionnaire contact in 2017.

There are currently 465 patients enrolled, 4 died prior to surgery. Among babies who underwent an index operation: 355 had a BVR, and 28 started on a UVR pathway, 69 had an interval procedure, and 9 patients are missing surgical data. Please see the diagram below:



Of those who had interval procedures prior to BVR or UVR the breakdown is as shown below: (note that 3 patients who underwent PA band after either coarctation repair (2) or central shunt (1) are included on the diagram under interval procedures and also in the PA band group.



Current status of ICL echo review is:

Echo Type	Received	Read
Baseline	374	308
Pre-Discharge	337	246
Follow Up	158	56
Total	869	610

These echos are being processed at about 85 / month, but many follow-up echos have not been received in the data center. **The missing echos need to be identified and requests sent to institutions. The data center will also prepare QA reports for CHSS institutions in an effort to improve consistency of images.**

Discussion: How do we define success? Survival, morbidity (re-intervention), grade of AVV regurg, PA pressure, ventricular function, LVOTO, functional health – all of these ?

Perhaps a review of the above in a cohort doing clinically well at 5 or 10 years would define the characteristics of success? Otherwise 'success' wil be an arbitrary definition.

Does our database track modes of failure? (outcomes such as inflow obstruction, AVV regurg, LV failure, LVOTO, etc What is known about the cause of death?

We have enough data (barring complete follow-up) to assess outcomes of BVR. Likely not enough yet to determine outcomes for the complex group of non-BVR.

Volume estimates of LV must be done across the cardiac cycle. Likely best with CT/MRI.

Potential AVSD Research questions:

1) Do pre-op echo paramters predict successful stable echo parameters at discharge and at 1-year (need more echos in the latter 2 groups)

2) Among BVR patients, are AVVI and inflow angles distributed within a normal range? Do these outliers account for failures among BVR patients?

3) Does pre-op valve function affect outcomes of clinical result, ventricular function & post-op function?

4) How does valve function afffect failure of UVR?

5) What are predictors of BVR success?

6) Does imbalance lessen over time following PAB?

7) There is substantial mortality among BVR. Is that fruitful for analysis?

8) What can we learn from the different ways RV/LV inflow gradient was measured? (Previous echo review vs. ICL measurement)

The above discussion and potential research questions are prsented to the AVSD working group for decisions regarding the next steps in AVSD direction & analyses.

8. CHSS Data Center Planning Follow-up conundrum

The essence of CHSS studies is long-term (life-long) follow-up of inception cohorts. We have a track record of following patients for as long as 33 years (TGA cohort). Yet recent experience, fraught by increasing regulatory requirements has frustrated efforts to find patients.

We have previously discussed the regulatory requirement; consent (increasingly complex), assent (re-confirming the child as young as 4 years, their parent's decision to participate, Re-consent at age 18 years, semi-annual or annual renewal of previous IRB approval, amendment approval for any change in protocol or data collection, even for data already in hand). Confounding all of the above is the need for each of 82 CHSS institutions to obtain their own approval. And each institution must have a legal DUA in place. Further confounding the process is that each of our 11 cohorts may need individual IRB approval.

The data center is moving towards becoming a Registry. A Registry IRB application would be simply to do clinical research in patents with congenital heart disease. Each cohort would fall under that umbrella and not require separate submissions to IRB. Where possible data fields would include 'data from cath reports' and 'data from op records' rather than listing each individual data field thereby avoiding endless amendments when a data point is overlooked in the initial application.

In addition the data center plans to utilize a Single IRB (S-IRB), such as the Western IRB. The concept of an S-IRB is made possible by the NIH recognizing the complexity of multi-institutional IRB submissions. NIH now requires multi-center research to use S-IRB. CHSS institutions will need to buy into this new model (new as on January 2017) but most multi-center studies will go that route.

While we anticipate these changes will simplify process and workload (for us and IRB panels) other methods of contacting patients must be sought: Social media, email Apps, Website requests, and Adult Clinic cooperation with CHSS. A novel suggestion is to link with patient organizations to encourage research participation and consider including lay representatives as part of the working group and initial IRB application.

Monetary incentive for institutions is also considered and may be an option with a major NIH grant. In contrast, institutions that enroll patients not only pay the mandatory fee to support the data center; they also volunteer time & effort from their staff to supply clinical information reports to the data center

Addendum: Outstanding Issues not discussed

A QA report to all CHSS institutions enrolling patients in the AVSD cohort. Format of the report will be sent to assist institutions in improving consistency. Notable are missing images to assess AVVI and inadequate 1-year echo assessment quality.

Coarctation of the Aorta: A Long-term Follow-up Study

Ismail Bouhout/Nancy Poirier: Has been approved in principle by U of Montreal scientific committee. IRB approval to contact patients and to use social media/AI by UofM is pending next week.

Grant Opportunity for CHSS Projects: Eugene Blackstone brought to our attention the possibility of an NIH grant for major funding, including support to institutions for each enrolled patient: potentially a 'game-changer' for participation. It is in keeping with Gene's November WW quote: "**Make no little plans**. **They have no magic to stir men's blood**….".

Addendum: List of WW Attendees, April 13-15, 2018:

Members: Ali Dodge-Khatami, Anastasios Polimenakos, Christian Pizarro, Christo Tchervenkov, Donald Watson, James Hammel, Kamal Pourmoghadam, Marshall Jacobs, Mohsen Karimi, Osami Honjo, Petros Anagnostopoulos, Richard Kim, Suvro Sett, Tara Karamlou, William Douglas

Guests: Carlos Mery, Christoph Haller, Clauden Louis, Craig Fleishman, Damien LaPar, David Horne, Fernando Villegas, Igor Bondarenko, John Karamichalis, Linda Lambert, Liz McCullum, Michael Jiang, Parth Patel, Rajesh Krishnamurthy, Richard Lorber, Robert Hanfland, Silvana Mollossi, Yaroslav Mykychak

Data Center Staff: Bill Williams, William DeCampli, Brian McCrindle, Eugene Blackstone, Anusha Jegatheeswaran, Arti Singh, Brenda Chow, Julia Lo, Kate Pearson, Nabi Aghaei, Paul Devlin, Sally Cai