



## CHSS Data Center Fall 2015 Work Weekend Summary

The fall 2015 Work Weekend was held November 20-22 in Toronto. There were 54 participants, 35 in person and 19 by Webinar. 29 institutions were represented. The attendees are listed in the Appendix. We had two keynote addresses.

The first was “Understanding the Physiologic Phenotype” by Dr. Peter Laussen, Director of the CCU at HSC. His talk described a real-time electronic physiologic monitoring and analysis platform under development at HSC. This platform is predictive, in that it alerts clinicians when physiologic trends are likely to result in an acute event, such as cardiac arrest, allowing clinicians to prepare for, if not circumvent the event. One of Laussen’s observations is that loss of variability in certain vital signs is predictive of impending arrest.

The second was “Challenges of Determining Authorship: An Editor’s Viewpoint”, by Dr. Richard Weisel, Editor-in-Chief of the Journal of Thoracic and Cardiovascular Surgery. Drawing on the analogy of the Cardiothoracic Surgical Trials Network (CSTN), Dr. Weisel presented very useful guidelines for determining authorship in the context of multi-institutional studies, such as those we carry out at the Data Center. These guidelines are much in line with those developed by the Research Committee this past year and can be found on the Data Center website ([www.chssdc.org](http://www.chssdc.org)). In practice, these criteria include (1) the researcher has participated significantly in either the conception, development or execution of the study AND (2) the researcher has participated in some significant phase of the manuscript writing AND (3) if the researcher is a CHSS member, the researcher’s CHSS institution has contributed patients to the study cohort. Extra weight will be given to a researcher from the highest-contributing CHSS institution (normalized to volume category). The PI of the study will recommend the author list for approval by the Research Committee. Many journals have author number limits, either “hard” or “soft” limits. We will work with each journal to negotiate inclusion of as many qualifying authors as possible. We are also working with journals to permit additional author recognition through an appendix-based participant list (which still leaves the question of how the citation databases will handle this.) When we are dealing with a “hard” limit, we will continue to ask for member cooperation in “splitting up” authorship among the (typically 2-3) papers we produce from each major study.

Finally, Kathryn Coulter, our Data Center regulatory chief, gave a comprehensive review of current regulatory structures both for the US and Canada, including the common, privacy, security and enforcement rules.

The remainder of the Weekend consisted of further development of CHSS studies, projects and cohorts. The format was variable depending on the objectives. Jim Meza, the Kirklin/Ashburn Fellow, conducted some whole group sessions while others were conducted by PIs of the studies. We also conducted break-out sessions to achieve focused tasks, such as chart data extraction for AAOCA, or “finessing” enrollment data forms for the new Ebstein’s cohort. What follows is a brief review of the work achieved, and the current status of each study/project. One can view the approved research proposals themselves on the Data Center website ([www.chssdc.org](http://www.chssdc.org))—we will not describe them in detail here.

LVOTO Baseline Echo Dataset Studies: As we have described previously, HSC visiting fellow Dr. Martijn Sliker reviewed 650 echocardiograms garnered by the Data Center Imaging Core

Lab (ICL), identifying 201 anatomic and Doppler variables for each neonate enrolled in the LVOTO cohort.

Descriptive analysis: A Working Group has been formed to conduct an approved study based on this rich dataset with Luc Mertens as PI. The first part of the first study will be a pure descriptive analysis of the dataset. In the second part of the study, Using unstructured cluster analysis, relationships among echocardiographic variables will be analyzed. The spectrum of AV valve morphology, LV morphology and AO/LVOT morphology will be studied. Certain clinical variables will also be included.

Reports vs. Expert Review: By analogy to our recent JACC Imaging paper on AAOCA, it was proposed to compare LVOTO echo reports with expert review.

Future studies: A number of possible future studies were suggested, including

- a. Obtain TEE echo tapes and do expert review, correlating baseline echo with TEE
- b. Use variables from the dataset in the “Timing of stage II” study (see below)
- c. What are the echo predictors of surgical strategy (this was Dr. Slieker’s second Aim in his original proposal): single ventricle vs. two-ventricle repair. This analysis obviously must include clinical, demographic variables and time-related as the strategy may change.
- d. What echo findings predict progression to stage II, stage III? What findings predict survival?
- e. Look at “rare” or “unusual” characteristics/clinical findings (e.g., intact atrial septum)—these could be the basis of smaller “focused” studies conducted by small working groups.
- f. Can a univ vs. biventricular repair “calculator” be further developed?

Members are encouraged to learn more about this LVOTO echo dataset and to formulate additional studies based upon it.

LVOTO: Optimal timing of Stage II. The Research Committee approved this proposal recently. The PI is Jake Jaquiss and Jim Meza will make this his U. Toronto thesis topic. Jim presented an initial analysis using the PHN SVR trial dataset and demonstrated that inter-operative time interval was not associated with either the outcome “survival” or the outcome “freedom from transplant”. However, it was associated with the composite outcome “survival & freedom from transplant”, the relationship raising the possibility of an “optimal” inter-operative time interval, or perhaps absolute age. Formulation of the analysis of the LVOTO cohort will continue. There are “triggers” (such as shunt stenosis, or volume overload due to repairable TR) that influence this timing, but the operation may or may not mitigate the risk associated with the trigger in some cases. It is these patients, rather than the “perfect interstage” patient in whom one wants to determine optimal timing of stage II. Drs. Blackstone and McCrindle discussed pertinent statistical methods such as “additive hazard”, informed censoring, and individualized dynamic risk profiling. The influence of home surveillance could be examined. A surgeon survey on institutional protocols for stage 2 timing may also be conducted. Jim is currently soliciting a Working Group for this study, the announcement for which was sent to the membership this week.

LVOTO: Arch re-obstruction: Pirooz Eghtesady, Tara Karamlou, Sarah Tabbutt, and Jeffrey Meadows and a provisional Working Group submitted a proposal to the RC to examine the prevalence and timing of arch re-obstruction and interventions for that in the LVOTO cohort. They proposed to look at the relationship between arch obstruction and AV valve and ventricular function, as well as other outcomes. The Work Weekend group discussed suggestions made by the RC for this proposal. The major suggestions made were to separate the submission into two proposals. The first would be a descriptive analysis of the occurrence of arch re-obstruction, e.g., what is the relationship between serial echocardiographic measurements and the timing of

intervention for arch re-obstruction? What are the risk factors for intervention on the arch? The second would be a study of the relationship between the time-related occurrence of arch re-obstruction and time-related AV valve and ventricular function. A revised proposal is under consideration by the RC as of this date.

AVSD: Cohort review: Dave Overman reviewed the progress and current plans for the AVSD cohort. The cohort formed in 2013. Enrollment is not limited to unbalanced AVSD. The inclusion criteria state, "Any patient less than one year of age at first intervention with complete AVSD, balanced or unbalanced, operated on at a CHSS institution is eligible for the study". To date, the cohort has accrued 205 patients. However, only 19 CHSS institutions have contributed patients. We have launched a campaign to try to enroll an additional 100 patients into the cohort by the end of March. The ICL has accrued roughly 420 baseline and follow up echocardiograms based on the cohort. This includes 205 baseline echos, 150 pre-discharge echos, and 68 echos obtained at one year follow up.

AVSD Cohort Proposal Aim 1: This proposal, based on Dave Overman's original cohort proposal, has been approved by the Research Committee. A Working Group has been solicited by email of the CHSS membership. A series of Webinars is planned over the next 6-8 months. The Aim is to characterize the full anatomic and functional spectrum of complete AVSD, and to identify anatomic relationships and develop novel indices to improve the ability to discriminate between unbalanced and balanced CAVC. Of the 420 echos described above, around 90 have been reviewed by the ICL. The goal is to have 200 echos reviewed by the Spring Work Weekend. To date, surgical data is entered for 163 patients.

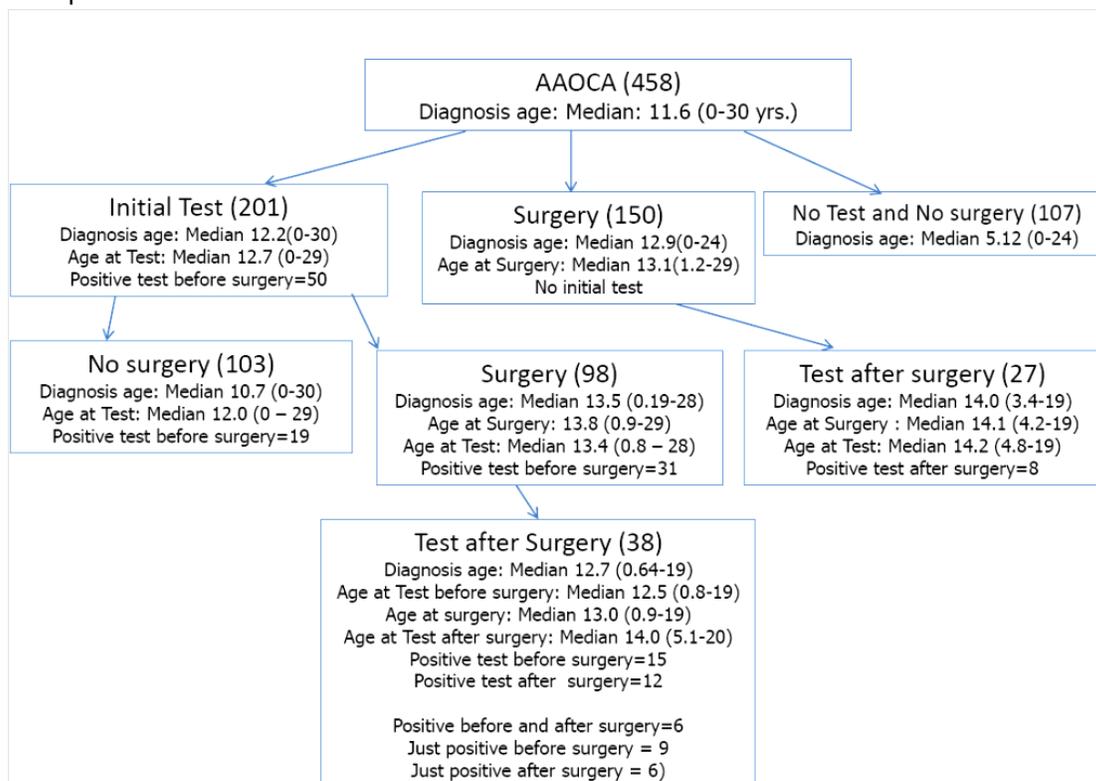
There was some discussion on how to increase enrollment, as a fairly large cohort is required to answer the Aims contained in the original cohort proposal. Dr. Blackstone suggested that if enrollment cannot proceed because the perceived workload is too great at the institutions, that we may consider enrolling only the unbalanced CAVC cases going forward, and use the existing 205 cases as (mostly) the group of balanced cases. It has been suggested that any surgeon member and any ICL working group member (institutional echocardiographers) seeking involvement in these studies (and potential authorship) require that their institution enroll most or all eligible patients. We will reassess enrollment in March. There are further Aims in the original cohort proposal. The Research Committee will consider these and other member proposals when Aim 1 is deemed achievable and analysis is proceeding.

AAOCA BMI Study: The AAOCA/BMI project has been a collaboration between the Data Center and Drs. Julie Brothers and Meryl Cohen. Both the CHSS and CHOP maintain an AAOCA registry. The CHSS cohort was analyzed to look at the relationship between exercise restriction and increase in body mass index. We briefly discussed the findings of the analysis of the CHSS cohort, which will be presented at the May 2016 AATS meeting. Of 440 patients in the registry at that time, exercise restriction status was recorded for 143 patients. Using linear mixed model regression, we did not find a link between exercise restriction status and increasing BMI over time. We also discussed the CHOP data. 82% of 72 patients were exercise restricted. Interestingly, exercise performance was a mean of 72% of normal. A provisional analysis also does not find a link between exercise restriction and increasing BMI over time.

AAOCA Ischemia Study: Prior to the Work Weekend, the Research Committee reviewed and approved a proposal by Julie Brothers, "Morphologic characteristics of cohort of children and young adults with AAOCA with evidence of myocardial ischemia or potentially lethal arrhythmia." The RC recommended further definition of "evidence of ischemia". This was discussed in the

session. The challenge is how to assign historical evidence of ischemia (e.g., report of chest pain). Jim Kirklin suggested having an “adjudication committee” to assign a pre-designed ischemia variable to each patient. During a break-out session, attendees undertook a chart review to clarify symptomatic status. They also assured that absence of chart evidence one way or another would be uniquely coded in the dataset.

Descriptive data analysis was performed by the Data Center. Among 458 enrolled patients in the AAOCA cohort, only 200 have been tested for ischemia, and 50 of these were “positive”. Of these 50, 31 had an operation. Among the 200 tested, 65 were tested post-operatively, and 26 were positive tests. The details are shown in the chart below:



The ICL began to determine the cases from which baseline echocardiograms need to be obtained and reviewed.

Note: In a follow-up meeting on January 7 attended by Drs. Brothers, Mertens, M. Jacobs, Williams, Meza and DeCampli, the decision was made to review echocardiograms in those patients who had definite evidence of ischemia or potentially lethal VT, according to the following criteria:

1. Sudden cardiac death
2. Aborted sudden cardiac death
3. Documented complex VT or VF
4. Myocardial infarction
5. Syncope during mid-stride exercise in the absence of vasovagal symptoms

This subgroup analysis would give the Working Group some idea of what the distribution of morphology is among this subgroup with “definite evidence of ischemia”. The group would then grapple with how to handle “weaker” historical evidence.

A previously organized Working Group developed this proposal over the course of several Webinars in the past year. The Working Group is still open to additional interested members.

**Ebstein's Cohort:** Joe Dearani presented the RC-approved proposal for creation of an Ebstein's cohort. This proposal can be viewed on the website. Initial study concepts were outlined in that proposal, written in part by Dr. Kim Holst (surgical resident at Mayo and research fellow under Dr. Dearani) under the supervision of Drs. Dearani, Knott-Craig, and Pizarro. At the Work Weekend, a break-out session was held to "finesse" the data collection forms. The next step is for the Data Center to reformat the proposal and data forms to create an REB document for submission and approval. The next step would then be to distribute the approved protocol to CHSS institutional data coordinators for subsequent production and submission of institutional IRB proposals. As these are approved, enrollment can begin. We estimate initial enrollment to occur in early summer of this year. The special challenge of building this cohort is the enrollment and follow up of those patients managed medically (a similar challenge exists in the AAOCA cohort). Marshall Jacobs suggested that the Working Group include not only surgeons, but also cardiologists, especially from higher volume programs, who could recruit interest among institutional cardiologists to enroll patients.

**Aortic Atresia Studies:** Under the leadership of Gene Blackstone, Brian McCrindle, Gosta Pettersson, and Jeevanantham Rajeswaran, Kathryn Stackhouse (surgical resident, Cleveland Clinic), has worked on two studies using the AA cohort. These are:

1. Quality of life and healthcare responsibility in adolescents after neonatal management of aortic valve atresia
2. 3-stage palliation or neonatal transplantation for aortic valve atresia? Answers from a CHSS inception cohort followed to adolescence

Drafts of these papers have been produced and were reviewed at the Work Weekend with Dr. Stackhouse attending by Webinar. A number of suggestions were made to revise the drafts. Writing groups for further drafts were solicited in emails to the CHSS membership following the Work Weekend. The goal is completion of these papers, #1 to be considered for JACC, or possibly Pediatrics or JAMA Pediatrics, and #2 to be considered for JTCVS.

**Coarctation cohort outcomes:** It was suggested at the spring 2015 Work Weekend that the coarctation cohort be followed up. There are a number of obviously interesting questions concerning the long-term outcome of this cohort. The cohort contains 893 patients (some of these patients are IAA). Both enrollment and follow up were terminated a number of years ago. Christo Tchervenkov & Nancy Poirier and a few other participants suggested that a project to follow up the cohort be proposed.

The logistic and regulatory challenges of re-initiating follow up are formidable. The participants decided to take a provisional look at the cohort dataset. Amine Mazine, MD, a UT cardiac resident previously mentored by Nancy Poirier, is "deciphering" the variables. Additionally, Christo visited the Data Center following the Work Weekend to examine the data. We will provide progress reports on this effort during the year.

**Biobank Project:** Peter Gruber and Bill Williams reviewed the current status of the "registry of biobanks". This project is described on the website ([www.chssdc.org](http://www.chssdc.org)). As of this date, 10,500 patients' specimens are logged into the registry, with eight participating CHSS institutions so far. The legal DUA is approved, and final REB approval (stating, basically, that from their point of

view, IRB approval is not needed) will be finalized this month. The Data Center will mail these out to all CHSS institutions. This gives clearance for all CHSS institutions to enroll in the project, which is RedCap-based. Peter, Richard Kim and Dr. Williams will manage the project.

We discussed simple research questions on which to base a first study. Chris Caldarone and Peter Gruber emphasized that we should disseminate knowledge of our registry to genomics researchers (e.g., PCGC). In Calardone's words, "the CHSS is the broker of these data". Peter pointed out that the same is true of our clinical cohort data, which would be used along with the biobank data in many studies. He also encouraged some initial studies to proceed, as recruiting more institutions is not a "bottleneck" to initiating some studies.

Most samples so far are genomic DNA (blood). Rick Kim felt we should focus mainly on RNA-sequencing (transcriptome), as it is less costly. This would not answer questions of etiology, but may inform outcomes. However, it requires tissue to do expression analysis. Peter stated that, although we are underpowered to look at common genomic variants, we are good to do some *denovo* rare variants. With patient and parental tissue, such variants can be identified. Thus, acquisition of parental tissue is needed for this type, but not all types of studies. The cost of one whole genome sequence is currently about \$1500. However, CNVs, point mutations, chromosomes, i.e., intermediate structural variants are less expensive (of order \$100). Studies looking at "candidate gene" analysis are possible.

Technical Assessment Project: Bill DeCampi reviewed the RedCap-based data forms for the four operations tracked (VSD, TOF, AVSD, TGA ± VSD). He also demonstrated the graphical reports that surgeons can generate in real-time. He reminded participants that the application is "up and running". This is a quality improvement project, not a study. DSAs and IRB submission templates are available from the Data Center website ([www.chssdc.org](http://www.chssdc.org)). Individual institutions should return the signed documents to the Data Center and designate a "point person" who will likely enter most data. The Data Center will send the surgeon and point person an account with code. That surgeon/point person can now access the online app (RedCap).

STS/CHSS Linkage Project: Jeff Jacobs reviewed the STS/CHSS Linkage project. This project was intended to allow the Data Center to track CHSS institutions' number of patients eligible for enrollment in CHSS Data Center cohorts. The process used is described in the biannual STS Congenital Database Report. CHSS members are asked to do the following:

1. Make sure his/her STS data entry person fills in the query in the data entry form asking if the patient is enrolled in the CHSS cohort.
2. Upon receipt of an STS Database Report, send the Data Center the relevant tables (STS-CHSS Report 1: List of Potentially Eligible Patients) reporting the results of the tracking of their cases by the STS/CHSS Linkage process.

The next Work Weekend will be held March 18-20, 2016 at the Data Center, HSC, Toronto. Please let the Data Center know of your intention to attend, either in person or by Webinar. Webinar will be available throughout the duration of the weekend.

Bill DeCampi & Bill Williams

**Appendix: Attendees of the fall 2015 CHSS Data Center Work Weekend**

2015-11-20	Institution	Role
<b>Data Center Staff</b>		
Bill Williams	The Hospital for Sick Children, Toronto	
Bill DeCampi	Arnold Palmer Hospital for Children, Orlando, Florida	
Brian McCrindle	The Hospital for Sick Children, Toronto	
Jim Meza	The Hospital for Sick Children, Toronto	
Sally Cai	The Hospital for Sick Children, Toronto	
Veena Sivarajan	The Hospital for Sick Children, Toronto	
Susan McIntyre	The Hospital for Sick Children, Toronto	
Annette Flynn	The Hospital for Sick Children, Toronto	
Irina Ristevska	The Hospital for Sick Children, Toronto	
Kathryn Coulter	The Hospital for Sick Children, Toronto	
<b>Confirmed - Yes</b>		
Eugene Blackstone	Cleveland Clinic, Ohio	Member
Constantine Mavroudis	Florida Hospital for Children	Member
Igor Bondarenko	Children's Hospital of Michigan	Data Coordinator
Gerhard Zeimer	University of Chicago Medical Center	Member
James Kirklin	University of Alabama	Member
Martijn Sliker	Netherlands	Non-member
Linda Lambert	Primary Children's Hospital	Data Coordinator
Phillip Burch	Primary Children's Hospital	Member
Diane Hersey	Nationwide Children's Hospital	Data Manager
Toshiharu Shinok	Nationwide Children's Hospital	Non-member
Kim Holst	Mayo Clinic	Fellow
William Douglas	University of Texas-Houston	Member
Jeffrey Jacobs	All Children's Hospital and Florida Hospital for Children	Member
Craig Fleishman	Arnold Palmer Hospital for Children, Orlando, Florida	ICL Co-director
Kamal Pourmoghadam	Arnold Palmer Hospital for Children, Orlando, Florida	Member
Susheel Kumar	Le Bonheur Heart Institute	Non-member
Amine Mazine	University of Toronto, Toronto	Resident
Anusha Jegatheeswaran	University of Toronto, Toronto	Non-member
Richard Kim	Children's Hospital of Michigan	Member
Michael-Alice Moga	The Hospital for Sick Children, Toronto	Non-member
Osami Honjo	The Hospital for Sick Children, Toronto	Member
Christopher Caldarone	The Hospital for Sick Children, Toronto	Member
Glen Van Arsdell	The Hospital for Sick Children, Toronto	Member
Rachel Vanderlaan	University of Toronto, Toronto	Resident
Haruki Ide	University of Toronto, Toronto	Fellow
<b>Webinar Participants</b>		
David Overman	The Children's Heart Clinic at Children's Hospitals and	Member

	Clinics of Minnesota	
Tara Karamlou	UCSF Benioff Children's Hospital San Francisco	Non-member
Brett Anderson	Columbia University	Non-member
Marshall Jacobs	John Hopkins	Member
Pirooz Eghtesady	St. Louis Children's Hospital	Member
Peter Gruber	University of Iowa	Member
John Nigro	Phoenix Children's Hospital	Member
Stephanie Fuller	Children's Hospital of Philadelphia	Member
Christo Tchervenkov	Montreal Children's Hospital	Member
Jake Jaquiss	Duke University	Member
Julie Brothers	Children's Hospital of Philadelphia	Associate Member
Luc Mertens	The Hospital for Sick Children, Toronto	Associate Member
Matt Elias	Children's Hospital of Philadelphia	Fellow
Katie Stackhouse	Cleveland Clinic	Resident
Gosta Pettersson	Cleveland Clinic	Member
Michael Mitchell	Children's Hospital of Wisconsin	Member
Camille Hancock-Friesen	IWK, Halifax	Member
Christian Pizarro	Dupont	Member
Joe Dearani	Mayo Clinic	Member