

Executive Summary
CHSS Data Center Spring 2015 Work Weekend (Toronto)
2015/04/10 to 2015/04/12

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This Work Weekend was attended either in person or by Webinar by 53 people, including 23 CHSS members outside the Data Center faculty, 15 additional MDs/PhDs students, residents, surgeons, cardiologists, critical care physicians, 4 data coordinators and echo technicians, and the 11 Data Center faculty and staff. The complete list is in a separate attachment sent to you. The following is a summary of the WW discussions in chronological order:

Friday April 10

New Ideas for the Research Enterprise of the CHSS

Jim Kirklin, new Chairman of the CHSS Research Committee (RC), reviewed the history of research participation, authorship & publication discussions. He had several recommendations that he will present to the executive for their consideration. Important among these is the role of the research committee in reviewing potential research proposals before they are undertaken by the Data Center.

Jim also focused on balancing work load with cost. New projects will require a budget. Further the budget will need to be assessed as to whether a project could be done with existing resources and if not, a mechanism for raising the required new funds.

Another important proposal is to consider sending out data for analysis in participating CHSS institutions that would bear the cost of those analyses. Publically funded agencies insist on this capability. The process would require revamping of our data use agreements and our REB approvals as well as de-identifying the data.

In addition, balancing the data center budget may require regular review of the value of ongoing projects. Accountability is not critical, as the number of proposed studies and the complexity of the research (including the addition of the imaging core lab (ICL) and biobanks) is increasing.

Action plan: Although we have already begun implementing many aspects of the proposed “research process”, Jim will present his ideas to the Executive Council at the AATS for revision and approval.

LVOTO Echo Descriptive Analysis and Research questions.

Luc Mertens' research fellow, Dr. Martijn Slieker, presented an overview of the 600 (of 750) echos of neonates admitted with a diagnosis of critical LVOTO. Martijn has recorded in Access approximately 200 echo data points from each initial diagnostic echos. He has recorded a wealth of clinically important data that will be a baseline for many future studies. The discussion expressed the intent of developing several papers from this work starting with an overview of the data, a "Best Practice" paper to outline how to obtain consistent diagnostic quality echos, correlation of echo parameters to clinical outcomes, etc. The group was very enthusiastic about Martijn's enormous dataset.

In subsequent discussion about process, we suggested that the Membership be informed of this new dataset and additional ideas for research be solicited, to augment the studies already proposed by Drs. Slieker and Mertens. A subsequent proposal (or proposals) would be sent to the Research Committee (RC), and working groups formed. We will proceed with this using the present dataset (freeze extraction), while Martijn continues to add data in the next few months to create the final dataset of about 750 patients. Dr. Blackstone presented a template for moving from a research proposal to a study design and delineation of project management (one step of the "architectural structure" of research management, to use his words). This Cleveland Clinic "Project Plan" will be beta tested on the studies proposed using this dataset.

Action Plan: We will send out an announcement to the CHSS membership describing this new data set and solicit members' ideas for and participation in subsequent studies. Meanwhile, Martijn will continue extracting data and building the final dataset over the next few months. The Data Center, with Martijn's continued involvement, will solicit proposals to be submitted to the RC.

LVOTO Post-op Echo Research Proposal

Alistair Phillips provided an overview of outcomes for the 1st 710 neonates enrolled. He is the PI in developing a research plan and proposes a study to measure RV & tricuspid valve function pre-stage 2 and pre-Fontan based on ICL (Image Core Lab) review of echos obtained from participating institutions. Alistair's plan, including potential cost implications needs to be reviewed and approved by the RC and a working group established.

Action Plan: Awaiting RC approval. Dr. Phillips will investigate funding sources for this study to include in the RC submission.

Technical Assessment/LVOTO

Tara Karamlou proposed to add TPS scores to the propensity-matched cohort of 168 Norwood-BT, Norwood-RVPA. Her research question is does surgeon preference, experience and institution for N-BT result in a better pre-discharge Echo TPS than for their N-RVPA procedures. In discussion it was pointed out that there would be few 'cross-overs'. The dataset also has no information about total surgeon or institutional experience, although that data might be

obtained from each institution. Further, the pre-discharge Echo would be biased by eliminating early post-op deaths.

The recommendation from discussion is to enter the essence of the TPS, rather than the score per se. Specifically arch obstruction, atrial septal defect restriction and shunt function could be added to the data set and analysed by multivariate analysis of all Norwood patients to determine their impact on outcome.

Action Plan: Tara will resubmit her proposal to the RC.

Mini-Projects

Gene Blackstone raised the issue of producing short focused papers (< 2800 words) rather than lengthy manuscripts. In essence, focus on each element of a simple or complex analysis thereby breaking up a major thesis into manageable shorter series of papers.

Katie Stackhouse's 2 manuscripts (see below) are examples. Jim Kirklin mentioned that this approach would facilitate institutions' involvement in carrying out some of the CHSS studies "from start to finish", i.e., based at the institution and not primarily the Data Center, and perhaps not involving the KA Fellow. This approach, while needing to leverage individual institutional resources (fellows, residents, students, data managers), could improve the overall productivity of the CHSS research enterprise.

Action Plan: The above concept being stated, await responses for ideas from the Membership.

AVSD- Progress and Problems

David Overman by Webinar: Enrollment in AVSD has been slow (188 total since 2011) likely compounded by the delay in setup of the ICL. Only 19 institutions have contributed patients to this cohort. The ICL is now operational. Therefore, all CHSS institutions are encouraged to enroll patients into the cohort. In discussion, the group thought that the data managers are the key to enrollment, not the surgeons.

A major challenge is collecting echos, especially pre-discharge and 1-year Echos. David's research proposal, "Unbalanced AVSD- a CHSS inception cohort study", is on file (& distributed in the WW binder), including the list of variables collected for the data set.

To date, 188 patients < age 1-year at admission for surgery are enrolled, 163 have been repaired. To date left dominant unbalanced are more prevalent than right but only by a small %.

Action Plan: Recommendation was made to initiate a descriptive analysis of the data accumulated so far (Aim 1a of Dr. Overman's proposal) and a paper be written. We will await RC approval of the remainder of the proposal, then create Work Groups for the studies based on Aims 1b, 2-4.

Review of AVSD ICL Echo Data

Luc Mertens & Cheryl Fackoury presented a review of their first 65 initial echoes of 188 total neonates enrolled. Cheryl identified technical echo deficiencies in 3 areas: What's Missing (sub-costal en-face views, & subcostal sweep); Colour box inadequate (too short, malposition, too narrow or too wide); Inadequate visualization of the ventricular free walls. Cheryl emphasized that most of the 65 echos reviewed to date are quite adequate, especially the more recent ones, but there may be a need for a "Best Practice" paper of simply more Webinar instruction to participating institutions.

Luc suggests that we need to define what constitutes a successful repair, other than survival and re-intervention. The ICL could contribute an assessment of ventricular and valve function as markers for success. Missing echos still compromise dataset robustness. Echos received in the data center to date are 96% of initial diagnostic echos, 60% of pre-discharge and only 31% of 1-year echos. CHSS institutions need to remind their research coordinators to follow the protocols carefully to maximize the follow up.

Action Plan: Dr. Overman will discuss echo acquisition challenge with Linda Lambert, Data Center Director of Institutional Research Coordinators.

Creating an App for Follow-up

Adam McKillop, a PhD student mentored by Brian McCrindle, has created an App for follow-up. The App is called "Safe Heart" and is designed to eliminate family uncertainty, begin a conversation about activity/exercise levels and promote activity. Adam outlined the trials and tribulations (& extensive delay in approval) of coping with ethics approval. But he has been successful. Kansas City also has developed an App for clinical monitoring of Stage I interval babies that has been very successful.

CHSS follow-up might be substantially improved by such a process but it was also noted that evolving social media is fickle and ever changing. So today's social media app may not be useful over the longer hall of life-long follow-up. But further thought about using social media for patient follow-up is needed.

Apple has recently released a Research Kit for Medical research that may be an appropriate start point.

Action Plan: Would like CHSS institutions to share their experience with using apps and social media to conduct clinical research, and to suggest ideas that would benefit the Data Center.

Statistical Methods for AAOCA Exercise Restriction vs. BMI study

Dr. Brian McCrindle reviewed the data collection in the AAOCA CHSS dataset to determine if the research question from CHOP (Meryl Cohen & Matt) of relating exercise restriction to changes in BMI over time could be addressed. The short answer is there is insufficient longitudinal data with repeated measures of BMI and inadequate information about whether or not 'exercise restricted' patients had important exercise restriction. There is no objective data that measures activity level.

Independent of the CHSS, CHOP is reviewing its own dataset of AAOCA patients. Brian does not have access to the data they have collected.

Action Plan: Brian will present the Data Center’s analysis to Meryl Cohen and Julie Brothers and discuss further plans.

Saturday April 11th

Genomics

Peter Gruber (via Webinar) reviewed progress in 3 areas:

1) **Biobank Registry** CHSS has created a “Registry of Biobank Registries” on our Website. Its purpose is simply to inform CHSS institutions how many specimens are available in CHSS institutional Biobanks, what diagnostic categories there are and in which institutions the samples are stored. The CHSS Registry contains no PHI. Researchers can use the Website to determine if a critical mass of specimen is available and then initiate a research proposal with those institutions willing & able to participate. Peter has data from 7-9 institutions and the Data Center needs to add that information to its Registry.

2) **Howard Jacobs** presented at the fall 2014 WW. He has reawakened his interest and offer to provide 3,000 whole genome sequencings free of charge to the CHSS. Discussion focused on what could be done to utilize Howard’s resource. At this time, it is most important that the Membership know about this opportunity and suggest ideas to the Data Center.

3) **Research Proposals:** Peter considered scenarios to link genomics with CHSS long-term clinical outcomes, either within the current cohorts or as a part of future inception cohorts. He has submitted grant applications with this in mind and welcomes anyone who volunteers to participate in a working group to contact him. Dr. Gruber has funding to perform 450 sequences, or 150 “trios” (patient and parents). The group discussed several possible links between available cohort clinical data and subsequent (prospectively obtained) genomic data, such as genomic correlates with (i) decreased RV function in single ventricle, (ii) success in bi-ventricular versus univentricular pathways, (iii) subsequent hypertension in repaired coarctation, (iv) stenosis/calcification in PA homografts, (v) early calcification in bicuspid AOV. An interest group would need to consider co-existing work, for example that of the PGC (with LVOTO, heterotaxy, conotruncal defects, and ASD cohorts) in proposing studies.

In general, the group agreed on the feasibility of obtaining tissue (blood, saliva) samples from patients in some of the CHSS cohorts.

Action Plan: (1) Peter will provide the data for the Data Center Biobank Registry from the handful of institutions with whom he has collaborated. (2) CHSS institutions are hereby encouraged to register their biobank with the Data Center registry, via the Website. Remember, you are not transferring PHI or individual specimen data. See the website—the process is very straightforward. (3) Dr. Gruber will solicit an “interest group” among CHSS members to review grant opportunities and to formulate a proposal for submission to the RC. Formal Work Groups will follow approval.

Aortic Valve Atresia

Katie Stackhouse is a PhD/MD student at Cleveland and has undertaken 2 studies:

1. 3-Stage Palliation or Neonatal Transplantation for Aortic Valve Atresia? Answers from a CHSS Inception Cohort followed long-term.
2. Quality of Life and Healthcare Responsibility in Adolescents after neonatal repair of Aortic Valve Atresia

Katie is mentored by Gosta Pederson and Eugene Blackstone (PI). Her research project is a successful example of outsourcing CHSS data and also of generating 2 Mini Projects from one cohort study.

Her presentation of 3-stage palliation vs. neonatal transplantation was of particular interest to the WW group. The late hazard for neonatal transplant is low and constant, unlike the 3-stage patient who have a rising late hazard starting at about 6-years. Survival at 16 years is 60% for the transplants (n=88) vs. 40% for the 3-Stage patients (n=453). Survival for the 68 patients transplanted as neonates is about 78% at 16 years compared to 50% for those transplanted secondarily after failed palliation. Is 3-Stage palliation the optimal term?

Action Plan: The QOL paper is close to completion and will be vetted by Brian McCrindle. Tara Karamlou and Linda Lambert will also contribute. EB will guide authorship. Several CHSS members asked to assist with further analysis and draft writing of the Palliation vs. Tx paper.

AATS Preview (8 minute presentation) Sano vs Norwood-B-T

Travis Wilder gave a test version of his AATS plenary session presentation to be given later this month. It generated much discussion, suggestions for revision and was followed by a 2-hour session on Sunday to add further organization and depth to the presentation. Included in the discussion is a suggestion for “story telling” (rather than the classic IMRD format) and starting with an overview of outcomes for the total cohort of 454 neonates selected by these 2 operations from 698 neonate total enrollment. The description of methodology in propensity matching could be limited and used only to confirm the better survival of Sano patients in the overall cohort. The late hazard of ventricular function needs to be clarified; late valve function seems straight forward. Early hazard before Stage II is dominant with little hazard and no important difference after Stage II.

Mock Deep Dive Session - Travis Wilder The new AATS format “Deep Dive” is to follow selected presentation 1 day later. 4 surgeons were selected as a mock panel for the deep dive (Van Arsdell, Kim, McKenzie, Kirshbom). They used the 20 minute time to discuss the inferences from Travis’ study to their practice. Interestingly, it generated very little cross-examination of Travis’ presentation & work.

Technical Assessment Project (TAP)

Tara Karamlou and John Karamichalis gave an update on the TAP that is ready to launch. CHSS members interested in using the TAP can register through the data center to begin entering non-PHI data, including discharge echo assessment, for 4 common operations (VSD, ToF, complete AVSD and TGA). The data center obtained QA approval for the study and also a Data Use Agreement. All of this documentation is available on our Website (www.CHSSdc.org) Individual institutional IRB's may accept this as a QI/QA project (there is non-PHI) or they may need to go through their IRB. Data will be input to an Internet database (RedCap) and reports are available for you at any time you wish comparing your individual data or your institution to all other participants. Tara & John downplayed the 'score' aspect of TAP because the reports will simply report the data and does not make any judgement about good, bad or indifferent results. It is a service to the members who wish to compare themselves to their colleague's results based on discharge echos.

Action Plan: The Working Group and Data Center will finalize the letter to the Membership instructing members how to enroll in this QA project. We will send the letter by April 24. The Work Group will also provide the template for institutional IRB approvals. This should include the ability of the project to expand the list of lesions tracked (currently four).

Ebstein's Inception Cohort

Joe Dearani presented a draft proposal for this emerging cohort that has been a topic of discussion at the previous few WW. A draft of his research proposal is included in the WW manual (& will be posted on the Website). Members interested in the project should contact Joe. He will present the proposal to the RC. An important component of the proposal will be to include cost estimates and funding for the project. Prospective collection of tissue (blood) samples for subsequent analysis was discussed.

Action Plan: Dr. Dearani will champion writing and submission of the final cohort proposal to the RC in the next couple of months. Drs. Pizarro, Knott-Craig and he will solicit a Work Group following RC approval. Data and regulatory forms will be developed by mid-Fall and the cohort enrollment will begin shortly thereafter.

Striving for Successful Enrollment in CHSS Studies

Linda Lambert, the Data Center's new Director of Institutional Data Coordinators, presented an excellent overview of what is required to participate in a CHSS cohort study. She emphasized the importance of institutional support for a study coordinator. These people are essential to consent patients, collect and transmit appropriate clinical reports and assist with follow-up when needed. Linda then led a discussion of the importance of obtaining patient follow-up. Ideas such as offering patient's incentive, email contact, electronic access by the data center to CHSS institutions (paradoxically perhaps, e-entry is more secure than allowing a person on-site access to medical records as the e-trail automatically records every move!), secure Web

transfer of data (the data center uses this), RedCap on-line patient questionnaires, search of government mortality records and social media follow-up. Regular progress reports (?quarterly instead of at the annual meeting) to each surgeon outlining the # of patients enrolled, data completeness, % follow-up, etc. were suggested and could be implemented.

Sunday April 12

Wrap-up Session

Travis' AATS Manuscript and Presentation Final Iteration and Thesis schedule were discussed at length. Adjustments arising from the discussion will prepare Travis for all!

Feedback from WW participants (virtual and by Webinar) are welcome. The data center belongs to CHSS members and we respond to your wishes. The group that participated was the largest ever and we thank them for the time, effort and considerable insight into your data center endeavours.

WGW and WMD