VALIDATION OF THE HOSPITAL ASTHMA SEVERITY SCORE (HASS) IN CHILDREN AGES 2-18 YEARS OLD

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Introduction/Background and Significance:
Asthma is the most common chronic lung disease in children. According to the 2013 Centers for Disease Control report, 8% of all children under the age of 18 in the United States (over 6 million children) were diagnosed with asthma. Of those 6 million children, over half (58%) had at least one asthma attack, 1.8 million had emergency room visits, and 218 of those children died from their asthma. Boston Children's Hospital (BCH) cares for more than 2,000 children with a primary asthma diagnosis annually.

A key component of providing care to the asthmatic patient is the ability to assess and describe the severity of their illness at any point in time. While spirometry is considered the gold standard for measuring asthma severity, it is not considered a practical tool for use during a child's hospitalization, which can range from several hours to several days. The machine is large, making it difficult to maneuver around the hospital on a regular basis. Also, to achieve accurate measurements the patient must blow into the machine, which can be difficult for a patient when they are experiencing a severe asthma attack. A scoring tool provides a common language to describe the severity of illness and to determine proper treatment of and disposition for the child.

There are many asthma severity tools in existence. Amongst all of these scores, no score has been validated using construct validity for the entirety of the pediatric population, regardless of age or body habitus, and using a scoring system that needs minimal education to understand. It is for these reasons validation of the HASS tool is warranted (Boston Children's Hospital, 2012). One of the original asthma severity tools, the Pulmonary Index (PI) (Becker, 1984), was studied in a small sample of 40 patients in the emergency room aged 6 to 17 and validated against spirometry. Their results showed the mean PI correlated significantly ($p<0.01$) with the mean % Flow Expiratory Volume in 1 second ($\%FEV_1$) over Forced Vital Capacity (FVC). Limitations of this study were the small number of subjects and no testing in the preschool age group. Parkin et al., (1996) studied the Clinical Asthma Score (CAS) compared to pulse oximetry, in a prospective cohort study of 30 patients aged 1 to 5. These investigators found only a weak correlation between CAS and oxygen saturation (Spearman's rank correlation = -0.31, $p> 0.05$). In addition to the weak correlation, pulse oximetry is not considered a reliable predictor of asthma severity. Bishop, (1992) studied the Asthma Severity Score (ASS) using a prospective cohort of 60 patients' ages 6 months to 17 years. No relationship was found between peak expiratory flow rate (PEFR) and the ASS score for mild and moderate categories (Kruskal-Wallis test $p = 0.95$ and $p= 0.14$ respectively). Also the inter rater reliability for the ASS was marginal ($\kappa_w= 0.63$) and peak flow meter is not recommended by the American Thoracic Society (ATS, 1994) for evaluation of asthma severity. The Pediatric Asthma Severity Score (PASS), which was studied for use in a population of 852 children ages 1 to 18 years, was also tested using peak flow meter instead of the gold standard of spirometry (Gorelick, 2004). Results of this study showed weak to modest correlation between the PASS and PEFR (Spearman rho = -0.22 to -0.42). The Preschool Respiratory Assessment Measure (PRAM), has been studied multiple times (Ducharme, 2008; Chalut, 2000) to test validity in patients aged 2 to 17 years old. In the original research, Chalut looked at children aged 3 to 6 years (n=145) and used forced oscillation. Results showed significant correlation in responsiveness between the PRAM and a change from baseline respiratory resistance measurements at 8 Hz by forced oscillation (Rfo_8) ($r= 0.58$). Forced oscillation is a new technology that has not been studied well, and is not Food and Drug Administration (FDA) approved for use in the United States. It is not considered the

gold standard for comparison. In addition, the PRAM scale, which uses scalene retractions as a scored item in the tool, showed that less than 5% of patients actually have these retractions. This would suggest that it is not a relevant piece of data to capture (Chalut, 2000). Ducharme prospectively studied a cohort of 782 patients aged 2 to 17 years, and looked at predictive validity of the PRAM scale. Results of this study demonstrated a statistically significant moderate association between the PRAM and admission rates ($r = 0.4$, $p < .0001$), though the inter-rater reliability was unable to be determined because providers were not blinded -to each other's scores. In a prospective cohort study, Arnold et al. (2011) validated the Respiratory rate; Accessory muscle use; Decreased breath sounds (RAD) tool against spirometry and two other tools (the PRAM and PASS tools) for children ages 5 to 17. Findings for this study showed comparable criterion validity ($R^2 = 0.426$) for the RAD tool compared with the PRAM ($R^2 = 0.462$) and the PASS ($R^2 = 0.434$). However, in their comparison of the tool with $\%FEV_1$, findings for disposition to home, inpatient, or intensive care units were not statistically significant ($p = 0.61$).

The Hospital Asthma Severity Score (HASS) tool is currently used for inpatient management of asthma symptoms at Boston Children's Hospital (BCH). It was invented by Dr. Sarah McBride of BCH in 2009, to fill the void of a practical tool that used reliable clinical guides regardless of age or body habitus to accurately determine inpatient asthma management. She utilized the National Heart Lung and Blood Institute, National Asthma Education and Prevention Program, Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma (2007) recommendations to develop the tool. Dr. McBride secured an expert panel consisting of over 20 providers from the intensive care units, emergency department, and inpatient floors to help with this endeavor. The expert panel was multidisciplinary in nature with allergists, pulmonologists, intensivists, emergency room providers, respiratory therapists, nurses, and others. The panel was responsible for confirming the face validity of the HASS. A consensus of this panel was that the tool would allow for a provider to tell the story of their assessment using both subjective and objective data. An initial pilot of the HASS was completed with 140 patients (75 in the year 1 cohort and 75 in the year 2 cohort). In both years, there was nearly even numbers of males and females and most patients studied were of the white and black races. Face validity of the tool was demonstrated (the tool was subjectively viewed as covering the concept it measured), and high inter-rater reliability was observed (unpublished data). Kappa scores for inter-rater reliability were 0.6 in the first year and 0.89 in the second year data for a pooled kappa with a score margin difference of 1 point between raters. Nevertheless, reliability and validity testing of the tool is not complete. A more accurate assessment of the tool's validity is needed, comparing it against the gold standard for assessing asthma severity i.e.: spirometry.

Purpose Statement:
The purpose of this research will be to evaluate the reliability and validity of the HASS tool in a cohort of patients' ages 2 to18 years old against the gold standard of spirometry, , if possible, and the most similar validated tool, the PRAM.

Research Questions or Specific aims:
Primary Aim 1. To describe the inter-rater reliability for the HASS as scored by 2 individual health care providers

Primary Aim 2. To evaluate construct validity of the HASS tool in a cohort of patients' ages 7 to18 years old as compared to forced expiratory volume through spirometry

Primary Aim 3. To evaluate construct validity of the HASS tool in a cohort of patients' ages 7 to 18 years old as compared to the PRAM.

Secondary Aim 4. To evaluate construct validity of the HASS tool in a cohort of patients' ages 2 to 6 years old as compared to forced expiratory volume through spirometry

Secondary Aim 5. To evaluate construct validity of the HASS tool in a cohort of patients' ages 2 to 6 years old as compared to the Preschool Respiratory Assessment Measure (PRAM)

Hypotheses:
Hypothesis 1. The HASS tool will demonstrate moderate to high inter rater reliability when 2 individual health care providers provide scores for a single patient encounter

Hypothesis 2. HASS performs as well as spirometry for determining asthma severity in children ages 7 to 18 years old

Hypothesis 3. HASS performs as well as the PRAM for determining asthma severity in children ages 7 to 18 years old.

Hypothesis 4. HASS performs as well as spirometry for determining asthma severity in children ages 2 to 6 years old

Hypothesis 5. HASS performs as well as the PRAM for determining asthma severity in children ages 2 to 6 years old

Study Design and Methods:
Design: We will utilize a prospective cohort study design

Human Subjects: Approval will be sought from the nursing scientific review sub-committee and the Committee for Clinical Investigation prior to initiating the study procedures.

This study poses minimal risk to study subjects. Prior to enrollment, permission to participate in the study will be secured from the study participant's medical team. The study team will make every effort to include patients of non-English speaking background, so long as the child can follow the instructions given to them through an interpreter. Subjects (if applicable) and their parents will be consented to participate in a 1-time data collection of asthma severity that includes 1. an assessment by two providers using a asthma severity tools and 2. blowing into a spirometer a minimum of three maneuvers (subjects 7-18 years, and if possible subjects 2-6 years). Spirometry will be performed while the child is seated, with multiple efforts (three maneuvers at a minimum) until the patient has achieved adequate reproducibility of the FVC and the $\%FEV_1$. A nose clip will be placed temporarily on the subject's nose during spirometry that might be uncomfortable and leave a red mark for a short period of time. Should the subjects

experience an acute exacerbation of symptoms while participating in the study activities, healthcare providers in charge of their care will be easily accessible for treatment since all subjects will be receiving their care on inpatient units or in the emergency department.

Citi program trained, experienced research staff will be responsible for data entry and data checking. The data will be entered into a (RedCap) computerized database, housed behind the BCH firewall on a BCH desktop password protected computer.

Sample: 165 patients aged 7 to 18 years, and 30 patients aged 2 to 6 years; As part of the pre-screen for potential subjects, a brief chart review will be conducted to exclude patients on continuous albuterol and patients with acute conditions like pneumonia, croup, varicella, cystic fibrosis, broncho-pulmonary dysplasia, cardiac or kidney disease, or that were previously approached for participation in the study.

Sample Size Calculation: It is recognized that our sample includes two distinct patient populations (2-6 years and 7-18 years) that may require different evaluations. Also it is understood that enrollment of patients, and the evaluation of our aims for patients aged 2-6 may be limited. Thus we have primary and secondary study aims for which we have conducted separate sample size calculations.

Primary Aims: With a sample of 165, if a correlation of rho=.9 is observed between the two measures, the confidence interval around rho would be adequately tight (.85, .95) for descriptive purposes (Aim 1). An adequate level of observed agreement would be 80% of observations in agreement cells, 18% discordant, and 2% in grossly discordant cells. When the sample size is 165, a test of these proportions will have 81% power to detect an alternative hypothesis of, for instance, 73% agreement, 22% discordant, and 6% grossly discordant (Aim 2). For an ROC analysis, the $\%FEV_1$ gold standard measure will need to be treated as dichotomous (severe vs. less severe). The proportion of severe cases in the sample is unknown but, for the purposes of estimating power, we expect to find roughly 20% severe, 60% moderate, and 20% mild. In this case, a sample of 165 children (33 severe and 132 less severe) will give 90% power to show that an observed area under the curve of 0.9 is significantly higher than 0.75. In other words the confidence interval for the area under the curve would exclude 0.75.

Secondary Aims: A sample of 30, 2 to 6 year olds is proposed. If a correlation of rho=.9 is observed between the two measures, the confidence interval around rho would be (.73, .99) (Aim 4). For Aim 5, an adequate level of observed agreement between the HASS and PRAM would be 80% of observations in agreement cells, 18% discordant, and 2% in grossly discordant cells. With the sample size of 30, a test of these proportions will have 86% power to detect an alternative hypothesis of, for instance, 65% agreement, 25% discordant, and 10% grossly discordant.

Setting: Emergency room, inpatient floors, intermediate care program, and medical intensive care unit at a single free standing children's hospital in the northeast

Measurement Tools:

HASS: A 15 point scale with data points collected on saturation, auscultation of wheeze, retractions, dyspnea or respiratory effort while speaking, and respiratory rate based on age group
HASS scores of 1-6 are considered mild asthma, 7-9 are moderate asthma, and greater than 9 is severe asthma (Boston Children's Hospital, 2012).
PRAM: A 12 point scale with data points collected on saturation, auscultation of wheeze, suprasternal retractions, scalene muscle contraction, and air entry
PRAM has been tested and used in multiple studies, including studies comparing PRAM to spirometry to ensure its reliability and validity (Arnold, 2013, Ducharme, 2008, & Alnaki, 2014). Scores of 1- 4 are considered mild asthma, greater than 5 as moderate asthma, and the score greater than 9 is predicted to demonstrate severe asthma, though the precision could not be determined based on the number of children with severe asthma in the original PRAM tool study (Chalut, Ducharme, & Davis, 2000)
Spirometry: ComPAS software on a Morgan Scientific FVL spirometer
Spirometry is considered the gold standard for measuring asthma control and severity, as well as response to therapy (Reddel et al., 2009) Spirometry measures the percent predicted forced expiratory volume in 1 second $\%FEV_1$). Mild persistent asthma is classified as $\%FEV_1$>80% predicted, moderate persistent asthma is classified as $\%FEV_1$60-80% predicted, and severe persistent asthma is classified as $\%FEV_1$< 60% predicted.

Data Collection and Management Procedures:
Education and Preparation for study team: All study team members engaged in the research will have completed CITI program training. Members of the study team will be educated on all aspects of the study by the PI, including how to use the HASS and the PRAM tools for those involved in data collection. Study staff will be assigned the responsibility of data collection. These study team members will be clinicians with the experience and knowledge of caring for critically ill patients, however they will not be directly involved in the care of the study subjects. To ensure that the members of the study team use the HASS and PRAM tools the same way, we will educate them on how to use the data collection tools and will conduct inter rater reliability testing to achieve 90% agreement across the measures prior to study roll out. By minimizing variability across measurers, we will help ensure that the HASS tool is evaluated using the most rigorous methods possible.

Pulmonary technicians will be performing the spirometry tests. As employees of Boston Children's Hospital, these bachelor's prepared technicians have received training in performance of spirometry with pediatric patients of all ages. These providers care for a large volume of pediatric patients on a regular basis where they perform this testing. Furthermore, this group of technicians serve as regular members of research study teams within the institution, thus they are adequately prepared to participate in this study.

In addition to the above procedures, participant admission and discharge dates will be collected to further characterize study participants.

Enrollment Procedures: To carry out this research, the project coordinator and/or primary investigator will screen subjects using a daily list of patients in the hospital available through the

face sheet in the electronic medical system. They will look for subjects with a primary diagnosis of asthma, aged 2 to 18 years old. The parents of children that qualify by meeting the pre-screening criteria will be approached for consent (after receiving clearance by their medical team), and assent will be obtained from the children when applicable.

Children aged 2 to 18 years old, for whom consent is received, will concurrently (but separately) have their asthma severity graded by 2 individual measurers using the HASS tool and the PRAM tool. When scoring the HASS and/or PRAM tools, the two measurers will be blinded to the findings of each other's scores. Scores sheets will be placed in separate envelopes by each measurer and sealed. The measurer will then sign their name over the seal. If the child is also consented to perform spirometry, the pulmonary clinic will be alerted to the patients for whom consent has been obtained. They will be performing the spirometry test after the tool(s) scores have been obtained. To obtain the spirometry measure, the pulmonary technicians will be using ComPAS software on a Morgan Scientific FVL spirometer. If the child cannot perform spirometry based on cooperativeness or inability to follow instructions, they will only have the two tool scores performed. To assure maximal results have been obtained, spirometry will be performed while the child is seated, with multiple efforts (three maneuvers at a minimum) until the patient has achieved adequate reproducibility of the FVC and the $\%FEV_1$.
After scoring is complete, the pulmonary technician will immediately perform the spirometry test. The PI will remain blinded to the spirometry results. (see study procedure algorithm 1)

Study team members (research assistant or coordinator) will collect the HASS/PRAM score sheets from the scorers and the spirometry test from the techs. They will also provide the pulmonologist with a copy of the spirometry test for interpretation.

The spirometry test will be interpreted by Dr. Jonathan Gaffin, a board-certified pediatric pulmonologist. As part of his responsibilities, he will prepare a report of the test and determine which tests are appropriate (interpretable or not) for use as study data. This criterion is based on the minimum of three forced airway maneuvers with flow-volume and volume-time curves meeting ATS criteria for start-of-test and end-of-test (ATS, 2007). There are two acceptable curves that will be collected; where the second highest FVC and FEV*t* are within 0.1 L or 10% of the highest value, whichever is greater. If a single acceptable maneuver is recorded, then these results will not be excluded only because of inability to repeat the maneuver. The number of technically satisfactory maneuvers and the repeatability results will be reported.

Study Procedure Audits: A research assistant or coordinator will audit the study procedures for every 20 subjects to ensure study procedures are being carried out correctly.

Data Management: Subjects will be aligned with a unique study ID. The study ID and patient names will be kept in a separate log from the database and only accessible by members of the research staff. Each data collection tool will include only the subject ID. Participants demographics, %FEV1/FVC scores from the spirometry data, HASS scores, and PRAM scores collected will be entered into a Redcap database along with the subject ID. This will then be prepared for analysis by the project coordinator. Double checks will be performed for every 10 participants to ensure accuracy of data.

A separate study log will be developed to record participant admission and discharge dates to calculate length of stay, this information will be aligned with participants' unique study IDs. On the same study log, we will record the day of assessment for study participants.

Data Analysis Plan and Outcomes to be evaluated:
Descriptive statistics will be used for preliminary analysis to describe the sample characteristics, outliers, and representativeness of the data.

Primary Aim 1. To describe the inter-rater reliability for the HASS as scored by 2 individual health care providers

Data Analysis 1. Use of an overall percentage of agreement, weighted and unweighted kappa and the intraclass correlation coefficient will show the inter-rater reliability of the HASS tool. For each measure, percent agreement between raters and Cohen's kappa statistic (rater agreement adjusted for chance agreement) will be reported.

Primary Aim 2. To evaluate construct validity of the HASS tool in a cohort of patients' ages 7 to18 years old as compared to forced expiratory volume through spirometry

Data Analysis 2. Treating the outcomes as continuous, a correlation coefficient will be computed for HASS and $\%FEV_1$. Sub-analyses will also be performed by age group and by $\%FEV_1$ severity level to see whether the correlation of HASS and $\%FEV_1$ is consistent across age and asthma severity strata. Treating the outcomes as categorical, if the HASS and $\%FEV_1$ are each categorized into three levels (mild, moderate, severe), then we could classify each of the nine cells of a 3X3 table (HASS X $\%FEV_1$) as either:

1. concordant (three cells; complete agreement: both tests say 'Severe', for instance),
2. discordant (four cells; e.g. one test says Moderate while the other say Mild) and
3. grossly discordant (two cells; one test says Severe when the other says Mild).

For the ROC analysis, the FEV will be dichotomized as Severe ($\%FEV_1<60\%$ predicted) versus Less Severe ($\%FEV_1\geq60\%$ predicted). In analyzing these data, the correlation (continuous), 3X3 table (categorical), and ROC (dichotomous $\%FEV_1$) treatments will be presented, with the continuous result considered primary. A high level of agreement is expected between the HASS and the spirometry severity score to make the case that the HASS can be used in place of the $\%FEV_1$ test.

Primary Aim 3. To evaluate construct validity of the HASS tool in a cohort of patients' ages 7 to 18 years old as compared to the PRAM.

Data Analysis 3. The Bland-Altman method will be used to assess the agreement between the two measures of the HASS and PRAM. Treating the outcomes as continuous, a correlation coefficient will be computed for HASS and PRAM. If the HASS and PRAM are each categorized into three levels (mild, moderate, severe), then we could classify each of the nine cells of a 3X3 table (HASS X PRAM) as either concordant, discordant, or grossly discordant (as described in Data Analysis 2). An adequate level of observed agreement would be 80% of observations in agreement cells, 18% discordant, and 2% in grossly discordant cells.

Secondary Aim 4. To evaluate construct validity of the HASS tool in a cohort of patients' ages 2 to 6 years old as compared to forced expiratory volume through spirometry.

Data Analysis 4. Treating the outcomes as continuous, a correlation coefficient will be computed for HASS and $\%FEV_1$. Treating the outcomes as categorical, if the HASS and $\%FEV_1$ are each categorized into three levels (mild, moderate, severe), then we could classify each of the nine cells of a 3X3 table (HASS X $\%FEV_1$) as concordant, discordant or grossly discordant (as described in Data Analysis 2). An adequate level of observed agreement would be 80% of observations in agreement cells, 18% discordant, and 2% in grossly discordant cells. In analyzing these data, both the correlation (continuous) and 3X3 table (categorical) treatments will be presented, with the continuous result considered primary. A high level of agreement is expected between the HASS and the spirometry severity score to make the case that the HASS can be used in place of the spirometry.

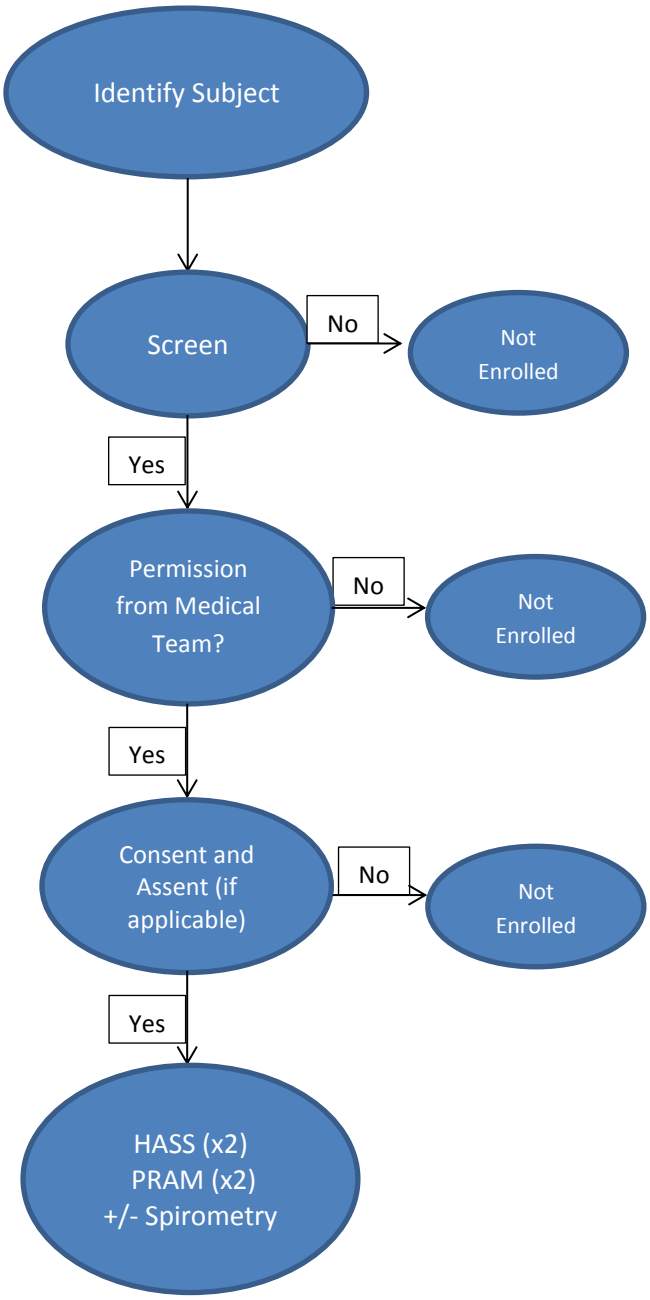
Secondary Aim 5. To evaluate construct validity of the HASS tool in a cohort of patients' ages 2 to 6 years old as compared to the Preschool Respiratory Assessment Measure (PRAM)

Data Analysis 5. Treating the outcomes as continuous, a correlation coefficient will be computed for HASS and PRAM. If the HASS and PRAM are each categorized into three levels (mild, moderate, severe), then we could classify each of the nine cells of a 3X3 table (HASS X PRAM) as either concordant, discordant, or grossly discordant (as described in Data Analysis 2). An adequate level of observed agreement would be 80% of observations in agreement cells, 18% discordant, and 2% in grossly discordant cells.

Timetable for implementation:

This study is proposed to take 2 years to complete as follows: Scientific Review: 2 months; IRB: 2 months; Database development: 1 month; Data collection: 1 year; Data analysis and Manuscript Development: 6 months.

Figure 1. Study Procedure Algorithm



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