ABSTRACT: This application seeks to develop a multi-platform clinical decision support system (CDSS) in pulmonary arterial hypertension (PAH) for physicians, PHORA (Pulmonary Hypertension Outcomes Risk Assessment), which can be used to: (a) guide therapeutic decisions and (b) optimize clinical trial design. We will achieve this goal by utilizing clinical trial data from several large databases of completed trials in PAH, an ongoing PAH registry (REVEAL), as well as observational sessions with physicians. The proposed aims co-create the CDSS with a multi-disciplinary group of specialties including: biomedical engineering, advanced PAH physicians, computer science (machine learning/data mining), human computer interaction, and allied health care experts. Our intention is to engage all stakeholders to achieve consensus and thereby assure the acceptance of PHORA into practice. Successful completion of this project will lay the foundation for a prospective, multi-center trial in which PHORA will be evaluated with respect to long-term patient outcomes. The ultimate aim is to disseminate this resource so as to improve the efficiency, efficacy, and cost-effectiveness of this treatment for PAH.
SPECIFIC AIMS
Pulmonary arterial hypertension (PAH) is a rapidly progressing, devastating chronic disease, characterized by abnormal vascular changes causing narrowing of the pulmonary vessel wall, increases in pulmonary vascular resistance, and ultimately right heart failure. Over the past decade, a variety of new therapies has emerged to enhance survival and quality of life, but PAH remains a highly fatal and morbid disease. In light of this, effective treatment requires early detection and selection of the optimal initial therapy for the individual patient. An increasingly accepted theory amongst PAH clinicians, however, is that the established surrogate endpoints used in clinical trials do not accurately reflect hard outcomes. This project will address this clinical deficiency by creating a dynamic, patient-specific, prognostic algorithm for managing treatment of PAH from first diagnosis throughout the course of care. This tool is titled PHORA (pulmonary hypertension outcomes research assessment.)

We are encouraged in this endeavor by the previous success with development of a risk equation and calculator, which has enjoyed excellent feedback from clinicians. However, as a first-generation model, it has room for improvement with respect its predictive power and usability. In particular, the existing algorithm is limited by the type of data from which it was derived, namely Registry to Evaluate Early and Long Term PAH Disease Management (REVEAL). Furthermore, this algorithm is based on traditional statistical methods, which are known to lack robustness with respect to complexity, sparsity and nonlinearities of the data. In addition, the calculator relies on a relatively primitive user interface which lacks several important features that would make it more practical and generalizable.

This project will address the former shortcomings by employing an advanced and sophisticated set of algorithms based on Bayesian networks (BNs) which belong to the most successful machine-learning tools for processing uncertainty. For an orphan disease state like PAH, the further advantage of BNs over traditional statistical methods is that they can adapt dynamically with the evolution of treatment options and expansion of the patient cohort. The algorithm will be further improved by combining the data from REVEAL with that derived from several large clinical databases of prospective trials in PAH. This will enable the algorithm to encompass other relevant outcomes, such as readmission; and interventions such as investigational drugs.

The algorithms will be packaged as a user-friendly computer program that identifies key decision points in the course of treatment and provides both physician and eventually patient (future version) with prognostic assessment based on the fusion of the aforementioned meta-analysis and expert knowledge. A further benefit of the proposed prognostic tool will be to support shared decision making between patients and physicians, which in turn will result in more appropriate, timely, and cost-effective use of therapy.

PHORA will be a versatile decision-support system for PAH that integrates software modules for: data mining, data management, user input, decision-making, and presentation of data. This will be achieved through completion of the following specific aims:

**Aim 1:** Utilize Bayesian networks to develop an improved prognostic model of outcomes for patients with PAH. Training, testing, and validation data for the model will include a combination of the REVEAL registry and several trial datasets from Bayer, Gilead, Actelion and United Therapeutics. In addition to mortality and morbidity prediction, the model will predict beneficial/deleterious effects of standard interventions & therapies.

**Aim 2:** Derive an expert-knowledge model for diagnosis and treatment of PAH, based on (1) existing documented best practices and (2) semi-structured focus group comprised of the clinical PAH team. The model will be validated and re-calibrated through prospective, observational studies of clinical encounters, both individually and collectively. {This aim will be conducted contemporaneously with Aim 1.}

**Aim 3:** Incorporate the prognostic and knowledge models from Aims 1 and 2 into a multi-platform, user-friendly clinical decision support application for physicians to (a) guide therapeutic decisions and (b) optimize clinical trial design. This application will be evaluated with respect to: clinical workflow integration, team dynamics/communication, and usability vis-à-vis metrics from user-centered design.

This proposed project represents the largest collaborative effort between industry and academia to derive and standardize a prognostic approach to PAH treatment. Successful completion of this project will result in the following three benefits in treating and managing PAH: (1) it will help physicians identify individualized treatment sequences that minimize patient risk and optimize outcomes, (2) it will help the care team effectively manage costly interventions (with medication costing between $60-150k/year) according to patient-specific risks, and eventually (3) it will empower patients to actively engage in their own clinical course, prepare their life plans, and participate and interact with their physicians more productively.
A. SIGNIFICANCE

Pulmonary Arterial Hypertension (PAH) is a chronic and rapidly progressive disease characterized by extensive narrowing of the pulmonary vasculature leading to progressive increases in pulmonary vascular resistance and eventual death. Approximately half a million persons in the USA will develop PAH over the course of their lifetime. Idiopathic PAH (IPAH) has survival rates at 1, 3, and 5 years of 68%, 48%, and 34%, respectively, with an average survival from onset of symptoms of 2.8 years if left untreated.\(^1,3\)

Even with treatment, the effective 5-year survival is only ~60% amongst those with PAH enrolled in the Registry to EValuate Early & Long Term PAH Disease Management (REVEAL).\(^4\) There has been explosive growth in treatment options available for PAH, with 3 new drugs approved by FDA in the last 18 months. PAH therapy using initial combination therapies is showing promise in the literature\(^6,7\). However, the growing number of options creates a dilemma for determining which treatment is best for a particular patient. This is further complicated by the significant heterogeneity among patients with respect to their clinical responses to available therapies. Therefore, there is a critical need for an accurate, patient-specific prognostic tool to permit tailored, timely, targeted and effective therapies in PAH.

During the course of PAH, there is an escalating degree of diagnostic data that can be distilled into a progressively accurate prognosis in response to available treatment options. (See Figure 1.) This proposal envisions a real-time computer application, PHORA (Pulmonary Hypertension Outcomes Risk Assessment) that is integrated with the electronic health record (EHR) and accessible at various points during the course of treatment to: (a) predict the risks of mortality and morbidity, (b) predict effect of various interventions, and (c) identify the need for additional diagnostic information and referral to a PH center of excellence.

In addition to the clinical dilemma of PAH, the above exigency also represents a significant handicap to conducting clinical drug trials in PAH. Therefore, a validated prognostic algorithm that can provide a surrogate marker of survival could be used to validate the clinical benefits of new therapeutics and expedite their approval. This rapid approval paradigm for novel medicines is critical for the rapidly expanding field of treatment options for PAH. Incorporating redefined surrogate endpoints into a composite clinical decision tool will improve clinical prognostication, practical treatment stratification, and expedite new drug approvals.

Given the complexity of PAH, clinical decision making requires volume of information (demographics, labs, history, family support, clinical parameters, medical insurance, etc.) for patients who are often critically ill. This puts the applicability of existing patient-specific prognostic tools at odds with the rapidity with which some decisions must be made.

The existing tools for PAH stratification are so-called ‘risk scores’, which attempt to distill key variables into a single numerical index (e.g., REVEAL, Pulmonary Hypertension Connection Score, French National registry score, Scottish registry score, and NIH risk survival score\(^8-11\)). There are several limitations of such scores: (1) they require a fixed and complete set of data elements, which may not necessarily be available at one time, in which case the score cannot be computed; (2) they employ a static set of data which may be outdated with the patient’s changing clinical situation; (3) they are based on simple regressions, which do not account for the conditional dependencies and nonlinear relationships between variables; (4) they lack prospective validation (French and Scottish registry); and/or (5) they are derived from an older generation of treatment options, and in some cases have proven inaccurate when applied to the current generation of therapeutics.\(^11\) In addition, recent studies have shown that globalized risk scores on their own are ineffective at both modifying patient behavior and improving cardiovascular outcomes.\(^12\) Therefore, a further hypothesis is that a prognostic decision-support tool must be coupled to the patient’s electronic health records and must be self-calibrating to adapt to the most current data to be truly useful.
B. INNOVATION

We herein propose PHORA, a multi-platform clinical decision support system (CDSS) designed specifically for PAH, which can be used to guide appropriate diagnostic work up, stratify risk, tailor individualized therapeutic decisions, and optimize clinical trial design. Its predecessor is an analogous CDSS for Cardiac Outcomes in patients with advanced heart failure, titled CORA, now under development by a recent award by NHLBI to our co-I (Antaki, Kanwar). Whereas the latter derives its data from a large national registry for mechanical circulatory support, PHORA will utilize several large databases of completed trials in PAH, an ongoing PAH registry (REVEAL), as well as prospective, observational sessions with physicians and patients. To assimilate data from a myriad of clinical trials into one predictive tool and to validate its predictive power is novel, creative, and empowering for this orphan disease. This approach will change clinical practice, translational research, and drug development. The ultimate objective is to disseminate PHORA to improve the efficiency, efficacy, and cost-effectiveness of clinical management of PAH. Accordingly, to assure the acceptance of PHORA into practice, we aim to engage all stakeholders to achieve consensus during its development. Therefore, we have assembled a multi-disciplinary group of specialties including: biomedical engineering, PAH practitioners, computer science (machine learning/data mining), human computer interaction, and palliative care.

In addition, this proposal for the first time in PAH research, has convinced several competitive companies to work together with the investigator team, to advance our understanding of “clinical” PAH. The establishment of collaborative and interactive relations between competitive companies to foster the development of this algorithm is creative, efficient, and methodologically necessary for the project to be meaningful.

B.1 PHORA Dashboard: User-Configurable Clinical Decision Support System for PAH.

We wish PHORA to be accessible to a diverse range of providers, including the PAH team for stratifying and managing referrals, in-patients, and outpatients; independent primary care practitioners; and nurse practitioners. Accordingly, we plan to provide an interface (computer application) that is easily configurable according to the preferences, needs, and data access of the provider. Figure 2 illustrates a conceptual prototype of the PHORA Dashboard, depicting some of the possible data visualization panes, decision modules, and utilities that could be added, removed, or re-arranged by the user.

Within a healthcare setting, patient data will be imported directly from the EHR. It may be accessed in a group setting during weekly evaluation meetings, during a patient-physician appointment, or through remote, collaborative decision-making. It would be updated as new diagnostic information becomes available and issue an alert if relevant changes occur in key variable or outcome probabilities. Additional physician-specific features will include: (1) Detailed, technical view of all relevant clinical variables and risk scores; (2) “What If” capability enabling physicians to modify, add and ignore any clinical variable to test different scenarios and optimize to alternate theories; and (3) the ability for the user to customize both the layout of the interface, and structure of underlying decision logic to accommodate personal preferences or team-specific guidelines.

B.2 Advanced Data Mining and Machine Learning

The back-end logistics of the PHORA CDSS will be based on advanced algorithms rooted in the fields of Data Mining (DM) and Machine Learning (ML). Carnegie Mellon University (CMU) brings considerable expertise in this area, where their School of Computer Science is routinely ranked amongst the top 2 in the US.

DM refers to knowledge discovery from large databases, while ML refers to an important aspect of artificial intelligence, a system’s ability to learn and self-improve. ML technology can process complex, incomplete, interrelated and nonlinear patient data. The CMU DM&ML technology has been applied by the co-I (Antaki) to predict the survival and adverse events of end stage heart failure patients undergoing left ventricular assist device (LVAD) implantation. In the proposed project, we will employ two specific DM&ML methodologies namely Bayesian Networks and Decision trees. These techniques are summarized below.
A Bayesian Network (BN) is a probabilistic statistical tool that represents a set of random (clinical) variables and their conditional dependencies. (An example of a BN for right ventricular failure is shown in Figure 3.) BNs have several significant advantages over the traditional statistical analysis, such as univariate and multivariate assessment. Most importantly, BNs can model causal relationships or conditional correlations between complex clinical variables, as illustrated in Figure 3, which is key in clinical decision making. Whereas a standard multivariate risk score assigns an incremental level of risk for each variable, independent of the other variables, a BN can amplify or negate the influence of a given variable depending on synergistic or antagonistic relationships between them. For example, the relevance/influence of 6-minute walk distance would be different for a 24-year-old with BSI of 2.0 versus a 78-year-old obese patient.

Another important feature of BNs is their tolerance of missing or erroneous data elements: a common problem with clinical data. Whereas a traditional risk score is rendered ineligible for interpretation if any single data element were missing, BNs can substitute a collection of related variables for a missing variable. A further advantage of BNs is their representation by both a graphical structure and a quantitative component. This is accomplished by plotting variables as circles (nodes) interconnected by lines (arcs) depicting their interrelationship. This provides two benefits: First, it permits the model to be transparent to the user, and easily interpretable — it is not a "black box"; secondly, it permits the model to be constructed or modified manually by an expert, automatically through machine learning, or a combination of both.

Decision trees (DTs) are also intuitive models that depict the decision logic of the clinician. (See Figure 4 for an example DT for PH.) The technique that we employ automatically constructs the tree from the set of training data. Our algorithm can provide multiple trees with similar performance, allowing the clinician to select the one that best fits their logic. DTs typically perform more effectively with fewer variables; therefore, they will be used in PHORA to represent the over-arching expert decision logic reflecting best practices for stratification, including the initial work-up for a patient. Both learning algorithms are clearly superior to the current PAH scoring systems, such as the Pulmonary Hypertension Connection Score (PHCS), French National registry score, Scottish registry score, and NIH risk survival score, and REVEAL score. Because the latter scores are based on univariate and multivariate regressions, they cannot account for the interactions between variables. In addition, they rely on a fixed set of variables and are therefore unable to adapt to changing PAH risk factors and emerging treatment options. For example, the PHCS is based on only three hemodynamic factors (pulmonary artery (PA) pressure, right atrial pressure and cardiac index). By contrast, BNs can readily account for hundreds of inter-related variables in a single model. They are able to update dynamically as risk factors change and different drugs are introduced. Consequently, the PHORA CDSS can be configurable to individual institutions. The variables included in the model can be adjusted according to those considered by the PH medical team to be relevant to their practice. For example, if a certain lab test is not typically performed at a certain hospital, then it can be removed from the model. This same flexibility and customization does not hold true for the current risk scores or calculators such as REVEAL.

C. APPROACH

Development and validation of PHORA comprises three components, corresponding to the Specific Aims: (1) Derivation of the Bayesian prognostic model; (2) Construction of the expert model; and (3) Integration into a multi-platform software package that is coupled with most common EHR program (Epic). Successful completion of these aims will lay the foundation for a future, prospective, multi-center trial in which PHORA will be evaluated with respect to long-term patient outcomes. The currently proposed project will capitalize upon our preliminary work, summarized below, relative to outcomes prediction in PAH and development of other CDSS.
C.1 Preliminary Studies pertaining to Risk Prediction:
The PI and colleagues have worked individually and collectively over the past 10 years in the area of risk stratification in PAH. This basic research has gained us an extensive insight into the causative factors affecting PAH prognosis, and treatment efficacy. Highlights of the relevant portions of this work are summarized below.

C.1.1. Prognostic Factors Associated With Increased Survival in Patients With PAH Treated with Subcutaneous Treprostinil in Randomized Placebo-Controlled Trials: A retrospective review for 811 patients with New York Heart Association (NYHA) functional class II-IV PAH treated with subcutaneous treprostinil was conducted. Based on univariate and multivariate analyses, baseline predictors of disease-related death were found to be: disease etiology, NYHA functional class, pulmonary vascular resistance index, and mixed venous oxygen saturation. Patients who walked ≤295m at 12 weeks during their 6MWD had a significantly greater risk of death than those who walked farther, emphasizing the importance of a threshold value in disease prognosis. These data demonstrate the importance of several baseline and on-treatment variables in formulating a prognosis of patient outcomes. These prognostic indicators of disease will receive increased attention in the proposed PHORA CDSS for planning and optimizing treatment to improve patient survival.

C.1.2. Reappraisal of NIH Risk Stratification Equation: Consultant Dr. Mardi Gomberg et al. compared baseline predictors of PAH to the NIH equation. Through multivariable analysis in the PAH cohort, it was found that independent predictors of death were age, connective tissue disease, etiology, functional class, mean RAP, and cardiac index. When compared with reported observational literature, the non-responder equation closely predicted mortality. Therefore, these independent variables will also receive special emphasis in constructing the PHORA prognostic model.

C.1.3. Analysis of The Lung Allocation Score (LAS) for Risk of Death in Patients with PAH Using Data from the REVEAL Registry: We analyzed data from 2,967 patients in REVEAL to identify key prognostic parameters that may be incorporated into the LAS to improve waitlist mortality for patients with PAH. Univariable and multivariable analyses found two variables that were independently associated with increased mortality: mean right atrial pressure (mRAP) ≥14 mmHg and 6MWD ≤300m. A modified LAS system was then developed, updating the waitlist survival component of the calculation. The United Network of Organ Sharing is now incorporating these results as additions and updates to the LAS. We will likewise incorporate these findings into the PHORA algorithm.

C.1.4. Insights From the REVEAL Registry: Data from 2,716 patients with PAH enrolled consecutively in REVEAL were analyzed to assess predictors of 1-year survival. One-year survival from the date of enrollment was 91.0% (95% confidence interval [CI], 89.9–92.1%). In a multivariable analysis using Cox proportional hazards, variables independently associated with increased mortality included: pulmonary vascular resistance >32 Wood units (hazard ratio [HR], 4.1; 95% CI, 2.0–8.3), portal hypertension (HR, 3.6; 2.4–5.4), modified WHO FC IV (HR, 3.1; 2.2–4.4), men >60 years old (HR, 2.2; 1.6–3.0), and family history of PAH (HR, 2.2; 1.2–4.0), renal insufficiency, connective tissue disease, WHO FC III, mRAP, resting systolic blood pressure and heart rate, 6MWD, brain natriuretic peptide, percent predicted carbon monoxide diffusing capacity, and pericardial effusion on echo. Accordingly, all the above variables will be included in the Bayesian model for prediction of outcomes.

C.1.5. REVEAL Risk Score Calculator: Based on the above multivariable analyses, a prognostic equation was derived, validated by bootstrapping technique, and translated to a mobile “app” that can be freely downloaded for use in the clinic. (See Figure 5.) Risk strata were developed based on the score depicting annualized survival and plotted as levels of risk. Prospective data from patients with newly diagnosed PAH enrolled in REVEAL were used to validate a predictive algorithm for 1-year survival. The model was validated by comparing algorithm-predicted survival with observed Kaplan-Meier estimates for the complete cohort of 504 individuals with 6-minute walk distance of 308 ± 128 m. 61.5% and functional class III. As of mid-June, there were 338 downloads for this application in the US and 119 in the EU. This is particularly impressive given that there are only 100 centers in the world that specialize in the treatment of PAH. Conclusions: (1) There is a great appeal for an easy-to-use, accurate risk calculator for PAH. (2) The REVEAL predictive algorithm and others demonstrate good discriminatory ability in patients with newly or previously diagnosed PAH, but leaves substantial room for improvement.

It is important to recognize the shortcomings of the aforementioned risk algorithms that will addressed in the next generation tool proposed in these studies. These include: 1. Limited number of variables assessed without use
C.2 Preliminary studies pertaining to BN analyses:

PHORA will be built upon platform technology and graphic user interfaces developed and prototyped over the past 10 years by the co-I’s, Antaki, Druzdzel, and Padman. The collective research of our co-I’s encompass BNs for predicting probability for left ventricular recovery, LVAD weaning, short and long term survival, the need for right ventricular support, chronic kidney disease and diabetes, liver disorders, endocrinology, and cancer. Dr. Antaki currently is PI of a complimentary multi-center clinical decision-support project, titled CORA funded through NHLBI, for severe heart failure. Dr. Padman has collaborated with several healthcare organizations in the US, UK and India including IBM Research, and J&J to deploy and evaluate clinical and consumer healthcare decision support methods and tools. Details of relevant studies are summarized below.

C.2.1. Bayesian Models of Survival of Left Ventricular Assist Device (LVAD) Therapy: This study was the first application of Bayesian analysis to the comprehensive Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) Retrospective analysis was performed on 8,050 LVAD patients and 226 pre-implant variables. Separate Bayesian models were derived for mortality at each of five time endpoints post-implant (30 day, 90 day, 6 month, 1 year, and 2 year), achieving accuracies of 95, 90, 90, 83, and 78%, Kappa values of 0.43, 0.37, 0.37, 0.45, and 0.43, and area under the ROC of 91, 82, 82, 80 and 81%, respectively. (See Figure 5.) In comparison, the commonly used HeartMate II Risk Score (HMRS), had an ROC of 57 and 60% at 90-days and 1-year, respectively. Bayesian models can reliably represent the complex causal relationships of multiple variables on clinical outcomes in patients with end stage heart failure. This same platform technology will be employed to develop the multi-dimensional prognostic model for PHORA.

C.2.2. Decision Tree Models of RV Failure. An independent series of studies were conducted over 10 years to develop a prognostic model for the risk of RV failure: the leading adverse events following LVAD implantation. Most recently, a decision tree model was constructed based on retrospective analysis of 183 patients who received an LVAD at UPMC, with an optimal set of eight preoperative variables: TPG, age, RAP, INR, HR, WBC, ALT, and inotrope agents. The resultant decision tree, comprised of 14 leaves, identified RVAD+ pts with outstanding sensitivity of 87%, RVAD– pts with 83% specificity, and a ROC curve of 0.87. The success is attributed to the model’s ability to encode nonlinear, synergic interactions among preoperative variables and is its intuitive structure that more closely mimics clinical reasoning, and therefore can be readily interpreted. This technology will be used to represent expert knowledge. PHORA will also allow the user to toggle through a set of alternate decision trees with similar performance, to choose the one that best reflects their logic and/or the standard practices of their institution.

C.2.3. Development of a hybrid decision support model for optimal VAD weaning. A CDSS was developed based on a BN that combined expert knowledge with multivariate statistical analysis. Expert knowledge was derived from interviews with 11 members of the Artificial Heart Program at the University of Pittsburgh Medical Center. This was supplemented by retrospective clinical data from 19 LVAD patients considered for weaning between 1996 and 2004. Artificial Neural Networks and Natural Language Processing were used to mine data and extract sensitive variables. Three decision support models were compared: an expert-derived knowledge model, a data-derived model and a hybrid of the previous two models. The model exclusively based on expert-
derived knowledge was the least accurate and most conservative whereas the model derived exclusively from clinical data performed better. An expert-data hybrid model performed best, with a 97% accuracy (CI 75-99%), misidentifying only 1 pt weaned from support.\textsuperscript{25} Accordingly, using a hybrid approach is most valuable as it combines strengths/compensates for deficits in each model.

C.2.4. Learning and Visualizing Clinical Pathways from Electronic Health Records. This ongoing study aims to extract longitudinal sequences of the most common pathways of patients’ treatment interventions by mining electronic health record (EHR) data. In a pilot study, clinical visit data of 1,576 chronic kidney disease (CKD) patients who developed acute kidney injury (AKI) from 2009 to 2013 are extracted from the EHR. Each patient’s multi-dimensional clinical records were mapped into one-dimensional, chronologically ordered, longitudinal sequences using novel data modeling constructs designed to capture information on each visit’s (1) purpose, (2) procedures, (3) medications and (4) diagnoses. Analysis and clustering of these visit sequences identified distinct types of patient subgroups potentially following distinct clinical pathways. Characterizing visit sequences as Markov chains. Significant transitions were extracted and visualized into practice-based clinical pathways in each subgroup. (Figure 6.)\textsuperscript{5} We identified 31 patient subgroups whose extracted clinical pathways provide insights regarding disease progression, practices that are consistent with guidelines, and sustainable improvements in patients’ health conditions. The visualization of the pathways depicts the likelihood and direction of disease progression under varied contexts. These pathways can further be correlated with specific outcomes of interest such as hospitalizations, mortality, and functional status, and individual patient pathways predicted given history. In the present project, we will adapt this easily generalizable methodology to mine the EHR of patients diagnosed with PAH. In so doing, we believe this will both elucidate patterns of treatment, their relationship with outcomes, and eventually lead to a data-driven methodology to facilitate personalized, evidence-based care delivery, inform and educate the patient, and support patient engagement in shared decision making.

![Figure 6. Derivation of clinical path workflow for CKD from 1576 data records in EHR. Example clinical work flow pathway for subgroup of patients. Each node represents a medical intervention. (Yellow-office visit, Blue-education, Red-deceased. Line thickness reflects probability of transitioning between nodes.\textsuperscript{5})](image)

[C.2.5 Bayesian Model of REVEAL Risk Calculator]

Since the prior submission, our co-Investigators (Benza, Druzdzel and Antaki) working with Actelion and the REVEAL Team have already begun to develop a first-generation Bayesian model, based on the REVEAL registry data set with 2964 PAH patients aged ≥18 years. Using the same set of risk factors, albeit limited, we generated a Tree-augmented Naive (TAN) Bayes to model the 1-year survival (Figure 8, next page). This is provided in the amended Preliminary Data section. Based on 10-fold cross validation, this initial Bayesian network had an accuracy of 88.7% with an ROC AUC of 0.7412 compared to 0.71 for the original calculator. We are highly confident that this performance will increase significantly by adding independent variables, and further optimization of the model parameters.

![Figure 7. Bayesian version of REVEAL model.](image)

[C.3 Specific Aim 1: Prognostic Model]

Development of the prognostic model will be performed under the supervision of Dr. Druzdzel and will consist of Training phase followed by Validation phase. The former will be derived from retrospective data, described below; and the latter will involve a combination of retrospective and prospective data.

C.3.1. Training Data for developing the prognostic model will include clinical data from three sources: (1) completed prior and contemporary PAH studies sponsored by Actelion, Bayer, Gilead, and United Therapeutics (bosentan, macitentan, selexipag, ambrisentan, tadalafil, riociguat and several formulations of treprostinil); (2) the REVEAL registry (managed by Actelion) and (3) pharmacogenomics data from Dr. Benza’s completed R01 Pharmacogenomics in PAH (5R01HL078946). The latter data set contains information on 1000 clinically phenotyped PAH patients with matching genomic data from a recently completed GWAS\textsuperscript{34}. The
REVEAL Registry is a multicenter, observational, U.S.-based registry of the clinical course and disease management of patients with WHO Group I PAH. The Registry is comprised of 54 US centers that enrolled 3,500 newly and previously diagnosed patients that were followed prospectively for a minimum of 5 years from the date of enrollment. The PI is a member of the steering committee of this registry; our consultants, Dr. Gomberg-Maitland is also an investigator, and Aimee Foreman is the lead statistician. All have an intimate knowledge of the construction/content and workings of the database. The REVEAL registry will be used to construct the initial prognostic model, with the other registry data being used to add, refine, and further develop the model. Genomics and pharmacogenetic information is of particular interest to the PI. (Dr. Benza) and pharmacogenomics information, derived from his R01 will be an essential component of the prognostic model.

C.3.2 Validation Data we be derived from three different sources: (1) the recent PATENT trial (riociguat) sponsored by Bayer (2) the recently published AMBITION trial sponsored by Gilead and Griphon trial (3) the newly launched REVEAL Registry (REVEAL 2.0). (Letters of collaboration from all industry sources are provided in the appendix: Gilead, Actelion, United Therapeutics and Bayer; as well as the REVEAL steering committee chair.) The AMBITION trial was a phase IV, randomized, double-blind study of comparing the safety and efficacy of first-line combination therapy (ambisentan and tadalafil) to first-line monotherapy in 352 subjects with WHO FC II and III PAH. GRIPHON was a multi-center, double-blind, placebo controlled phase study of 1156 patients randomized 1:1 to selexipag versus placebo. In addition to clinical data, Dr. Benza is acquiring DNA samples from the majority of the participants in the AMBITION trial under an agreement with Gilead and GlaxoSmithKline. These samples will serve as the validation set for his current pharmacogenomics work, but will also be used to help validate the genomic markers included in the PHORA prognostic model. Similarly, the new REVEAL registry will focus on biomarkers and genomics in PAH. This registry will collect DNA and plasma samples and conduct genomic analyses (i.e., BMPR2 status, etc.) and serum biomarker analyses on 500 newly diagnosed patients with PAH and follow them clinically for one year. (Dr. Benza is also a member of the steering committee for the REVEAL 2.0 study.)

C.3.3 Independent Variables for constructing the prognostic model are summarized in Table 1, and include cardiac and pulmonary function, etiology, demographics, laboratories, hemodynamics from right heart catheterization, ultrasound, and MRI, history, as well as genomics and pharmacogenetic information. We believe that an important input will be the presentation of PAH: i.e., slow indolent presentation vs. acute decompensation – like what we have done previously with our heart failure DSS. The inclusion of etiological factors as independent variables will allow the CDSS to customize treatment recommendations for the varying subtypes of PAH. These include: idiopathic (IPAH), connective tissue disease, congenital, cirrhosis, drugs and toxins, and heritable (HPH).

C.3.4. Outcomes and Endpoints. The Dependent Variables of the prognostic model will include (1) transplant-free survival (at 6 months, 1y, and 2y), (2) hospitalizations, as well as (3) a functional measure of efficacy. This later endpoint will include a combination of a 15% decline in 6MWD, an increase in WHO functional class. This endpoint is easy to obtain, is validated as a prognostically important outcome measure, and individually have logical interpretations; e.g., lower 6MWD, higher WHO FC all indicate worse prognosis. In clinical collective experience with PAH, most physicians believe that hemodynamics alone will not be as accurate as a multi-factorial assessment of outcomes measures.

C.3.5. Construction of the BN Model. The prognostic models for predictions of outcomes for patients with PAH will be derived using two software platforms: WEKA (an open-source machine learning software library) and GeNe (a modeling environment developed by our co-l (Druzdzel) at the Decision Systems Laboratory of the University of Pittsburgh.) Training and initial validation data will include a combination of the REVEAL registry and several trial datasets, listed above. We will evaluate at least two BN classification algorithms: the Naïve Bayes (NB) and the Tree-Augmented Naïve Bayes (TAN) (See, for example, Figure 3 and (Figure 7).), each based on a subset of clinical variables (called features) reduced from the original dataset of N variables. NB
allows for only a single parent node, i.e., PVR node connected to (associated with) survival. TAN allows two or more arrows to any single node, i.e., PVR node connected to (associated with) both survival and age.

The initial training of each of the candidate BN models will entail two components: (1) constructing the topology (structure) of the graph and (2) determining the breakpoints and classifications within each node. In the first step, the BN is constructed as a network of nodes, one for each attribute (e.g., age, gender, albumin), connected by directed arrows in such a way that there are no cycles. The arrows will represent conditional interdependence between the corresponding variables. (And lack of an arc will represent complete independence.) The classification of each attribute node defines a probability distribution quantified by conditional probability tables (CPTs). The joint probability distribution over a set of variables \( X = (X_1, ..., X_n) \) will be obtained by taking the product of all of these prior and conditional probability distributions:

\[
Pr(X) = Pr(X_1, ..., X_n) = \prod_{i=1}^{n} Pr(X_i | Pa(X_i)),
\]

where \( Pa(X_i) \) denotes the set of direct predecessors (parents) of node \( X_i \) in the graph.

C.3.6. Feature selection: We will initially consider the full set of independent variables aggregated from the data sources referenced above. These variables will be ranked by Chi-Square analysis, and then the most predictive variables will be included in the model. To avoid over-fitting the model, subsets of variables will be iteratively evaluated from approximately 10 (i.e. the top ten) to \( N \) (total number of variables), and the best performing set will be selected for the final model. As point of reference, the CORA model for advanced heart failure performs optimally with approximately 120 independent variables. However, it is capable of providing reasonably good results with as few as 12 variables.

C.3.7. Imputation of missing data elements. It is inevitable that the training data sets will have missing entries. We will initially exclude variables from the model with “missingness” greater than 25%. The remaining missing data elements will be imputed by various methods, which are currently being evaluating as part of the CORA program. The simplest method is to use the means (for continuous variables) and modes (for discrete variables). These have worked reasonably well, but have also produced some anomalous results when extrapolated beyond the training set. Therefore, more sophisticated methods including: multiple imputation methods such as the Monte-Carlo method using Gibbs sampling, the Gaussian approximation, the Expectation-Maximization (EM) algorithm, and the use of normal values are being evaluated. At the time of an award, we should have a clear appreciation for the method most appropriate for the PHORA data set.

C.3.8. Model Validation & Verification: Validation and verification will occur in two stages. The initial optimization of the model will be performed using ten-fold cross validation using retrospective training sets from Actelion, Bayer, Gilead, and United Therapeutics, REVEAL Registry, and Dr. Benza’s R01 Pharmacogenomics in PAH. This methodology randomly partitions the records into two subsets: a training set (90% of the data) and a test set (10% of the data). This is repeated ten times. For each iteration, the BN model parameters are populated using the Expectation-Maximization algorithm on the training set. Then, the resultant BN predicts the outcomes of the test set. Comparing these predictions to actual outcomes yields a measure of BN predictive accuracy. Averaging the result of ten iterations of the algorithm results in an aggregate estimate of accuracy. The model is then optimized by adjusting the algorithm parameters (e.g. breakpoints, branches, etc.) and repeating the entire process until the specificity and accuracy metrics are maximized.

The methods above constitutes the initial validation of the model. The definitive verification will be performed using datasets from the PATENT and AMBITION clinical trials and the new REVEAL Registry 2.0 (See attached letters of support.) We will use the starting date as the time of completion of the respective randomized portion of the trials. All will require at least one-year follow-up. For all the training, verification, and validation steps, we will work with the specific statistical experts (or teams) as designated by each company, thus ensuring the integrity and privacy of the data. Datasets from the varying companies will not be combined to ensure that the final Bayesian model is generalizable across multiple patient populations.

C.3.9. Comparison with Gold Standard (REVEAL Score.) The final step in evaluating the prognostic models is to compare their performance with that of the REVEAL Score, which is a tool of choice for most PAH teams. A statistical power analysis will be performed to assure sufficient patient records to make this comparison. Assumptions include: Type I error rate of 0.05, the effect of interest (risk ratio) of 0.75, a 20% dropout rate during the recruitment. With these assumptions, a minimum of 1,000 patients are needed to achieve a statistical significance of \( p < 0.05 \). This is far less than the 6,000 patients represented in the total patient data collection.

C.4 Specific Aim 2: Expert-Knowledge Model

In parallel with Aim 1, we will construct an expert knowledge model that will essentially subsume the prognostic models. Whereas the latter provides a quantitative forecast of outcomes at a point in time, the knowledge model
will display the likely pathway of an individual patient over the natural course of diagnoses and treatments. This expert model will be derived from two initial data sources: (1) data mining of EHR, supplemented with (2) clinical practice guidelines (CPCs). The latter will include institution-specific written guidelines, and recently published National and international PAH guidelines. Once this initial model is established, we will develop a methodology to perform ongoing updates based on shifts in clinical practices, and emergence of new treatments and drugs. In other words, to avoid repeating the entire validation and verification process every several years, the algorithm will be re-calibrated on a regular/continual basis. This will be achieved by (a) ongoing mining of prospective EHR data in which older data is replaced by more recent data; (b) manual adjustments based on contemporary scientific literature (e.g. new clinical studies), and (c) continual user-feedback from the care team (physicians, nurses, psychiatry, palliative care and social work) and patients. This will permit customization to the specific practices of a given institution, and thereby facilitate widespread translation.

Data source (1), derived from the EHR, will form the backbone of the knowledge model. It will be constructed using the methodology developed by our co-I, Dr. Rema Padman, described above in Section C.2.4., which results in a collection of Clinical Workflow Diagrams. Briefly, this involves first partitioning the data records (patients) using a hierarchical algorithm into subgroups of “similar” patients based on both quantitative data (demographics, labs, comorbidities, medications) and treatment patterns – mined from the EHR. Then we extract treatment patterns from each subgroup by connecting significant transitions in the Markov chain. (Figure 6, top.)

The documented heuristic, and/or consensus based guidelines (data source 2) will be represented using decision trees, mapped directly from the respective written artifacts. To elicit the knowledge from clinical personnel, we will follow a procedure known as contextual inquiry to understand their clinical decision making process and to identify contextual barriers to interaction with our system. Prof. Zimmerman will be responsible for these studies. Contextual inquiry involves observations of work practices; semi-structured interviews that probe on information flow, roles and responsibilities, and decision making touchpoints; and focus groups with clinicians at AHN (Members of Dr. Benza and Kanwar’s clinical team) with a focus on initial patient assessment, consultation with colleagues, use of literature, and validation of the work practices and decision pathways we have observed. With respect to clinician-patient interactions, the contextual inquiries will address clinic appointments and hospitalization. Based on our observations, we will generate a set of service blueprints detailing the key decision touchpoints along a patient’s PAH journey.

We found this approach effective in our previous studies (in 2011 and 2015) related to end-stage heart failure. In this previous work, we identified several critical touchpoints in clinical decision making that might cause a patient to miss a window of opportunity for an aggressive intervention. One such insight is that attending physicians continually move throughout the clinical environment and must engage in near constant hand washing, making it a challenge to situate a computer-based decision support system in their practice. Additionally, they trust the advice of colleagues more than ‘intelligent systems’. We also observed that residents/fellows and nurse practitioners, who have considerably more interactions with EHRs and computers as well as attending physicians during rounding and weekly team meetings, to be an under-investigated pathway for placing computational decision support into the attention of the physicians. Finally, we observed many instances where exclusion criteria for a surgical intervention, such alcohol consumption, drug use, a lack of insurance, and a lack of effective social support should have been addressed months earlier so as not to complicate the life and death decision to do an implant.

In interacting with patients, we repeatedly saw that they underestimated the severity of their disease, and had unrealistic expectations that their health would dramatically improve with therapy. Although interviews with patients is beyond the scope of this project, we aim to develop a decision aid that will help clinicians engage in meaningful communication with their patients, helping them understand risk and benefits, and windows of opportunity for seeking interventions, hence engage the patients in decision-making.

A vitally important final step in constructing the expert knowledge models (both the EHR-derived and observational/heuristic) is an assessment; a “reality check” that the system can deliver actionable information to the right people in the right place at the right time. This will be achieved in two ways for the two different parts of the system: prospective blind testing of the models and speed dating of the user interface. Prospective live validation will be performed by additional observational studies in which the predictions or suggestions of the model will be compared, blindly, with the clinical decisions at several settings throughout the course of care: such as PAH diagnosis and therapy planning, discussing individual patient cases, and design of clinical trials. The REVEAL steering committee and consultants Gomberg and Elliot will serve as the initial test subjects for our modeling sessions. The result will be an over-arching decision model that subsumes the prognostic models. The underlying architecture of the knowledge structure created by the end of Aim 2 will however be translated to the end-user in an understandable, natural-language like fashion – which is the objective of Specific Aim 3.
For the speed dating sessions, we will construct a simulated care environment and bring clinicians in to experience the interface and output of the expert model during a simulation treatment decision making for a patient. The speed dating sessions will investigate the forms of information for all the touchpoints and all the clinicians that participate in treatment decision making. This will follow an iterative, rapid prototyping process commonly used in software development, where the feedback from one session will be immediately integrated into new designs, allowing an effective interface to emerge through the co-design of clinicians who are the intended beneficiaries of the technology.

C.5 Specific Aim 3: Develop a Decision Support Tool for Healthcare Providers

The ultimate success of the prognostic and expert knowledge models detailed in Aims 1 and 2 depends on clinicians finding the information to be relevant to their decision-making process and the application to fit within their usual workflow. Therefore, the front-end application will allow users to visualize, navigate, and query the models. An important emphasis will be placed on providing transparency of both the data-sources and underlying logic of the decision model. For example, double-clicking or hovering over a node will reveal the associated portion of the guidelines, or expert source from which it was derived. Whereas Aim 2 focused on understanding and codifying the decision processes, Aim 3 focuses on how a user will interact with this information: hence their workflow, informational needs at the various touch points, the understandability of the information that is presented, and relevance/usefulness of the information in the course of treatment. Based on the contextual inquiry conducted in Aim 2, we will conduct two rounds of prototyping. First, we will develop a set of mockup screens (also known as wireframes) detailing the proposed interface for the system. (For example, see Figure 8 showing an envisioned forecasting window for PHORA.) We will then conduct experience prototyping with health care providers. For this step, will work with the Pulmonary Hypertension Association (PHA) and recruit practitioners from their certified Regional Clinical Programs. (See letter of support provided.) We will ask them to re-enact familiar decisions situations (a touch point) and provide them with the paper interface. We will document breakdowns that occur in terms of contextual factors, mismatch between our design and participants’ informational needs, inappropriate interpretations or confidence given to a machine learning inference, and to misinterpretations of visualizations. Based on this feedback, we will make improvements to the interfaces as functional website-style prototypes. We will then conduct a second assessment of the prototype using experience prototyping.

We expect that design improvements will continue throughout the course of this project (as is common with virtually any software product today.) On an ongoing basis, the performance of the interfaces will be assessed in terms of: (1) Learnability and retention – experimenting with different learning models, such as a workshop or self-service tutorial, and then evaluating the user’s ability to accomplish a variety of tasks, correctly; (2) Satisfaction – evaluating whether users actually like using it, and find it to be effective and helpful; (3) Effectiveness – evaluating whether decisions are made more correctly and/or consistently based on computational inferences, and (4) Error prevention - assuring that users do not inadvertently introduce errors. It is beyond the scope of this project to evaluate PHORA in terms of comparative effectiveness – i.e., long term outcomes. However, the successful completion of this project will provide the tools to begin a clinical trial.

Multi-Platform Implementation and Portability of PHORA. It is important to emphasize our eventual goal for making PHORA a public resource, which can be integrated into any EHR at any hospital. We also wish to emphasize that the software will have entry points for different stakeholders, including nurses, social workers, care givers, etc. For this purpose, the PHORA user interface will be programmed in HTML5 (using Ruby/Rails development architecture and MySQL database.) The secure, physician, version will reside on the institution’s server, and be accessible through proper authentication and login. It will provide tools for selecting specific patient(s), and a set of interactive visualizations and inferences as described above.

EHR integration. There will several data integration application programmer interfaces (APIs) to support extraction of the necessary clinical data from the providers EHRs. There will be sets of APIs for the most commonly used EHR (Epic), as well as a generic data integration API for sites that have custom systems. Additionally, an API to the PHORA application will be made available, enabling systems to more deeply integrate the PHORA algorithms into their own internal tools. For Epic systems, HL-7 interfaces or CCD/CCR feeds are possible. For other systems, a regional data integration application programmer interfaces (APIs) to support extraction of the necessary clinical data from the providers EHRs. The APIs will allow for the integration of PHORA into existing EHR workflows, facilitating the incorporation of PHORA into clinical decision support systems.
the primary conduits. All connections will be on encrypted channels, with a VPN or equivalent security setup between the primary PHORA servers and the EHR. The scope of data entry that can be eliminated using direct interface with EHRs may be variable, but based on our prior experience, we believe that this ability will increase usability and provider acceptance of the decision support tool.

**Scalability with respect to demands:** We recognize 3 aspects of the need for PHORA to adapt to increasing demands: (1) how the software can handle thousands of concurrent patients and clinics using it at the same time, (2) how the software deals with use cases and needs of diverse types of clinics and healthcare providers, and (3) how the software will be accessible on multiple platforms (desktop, web, mobile). To address all three of these aspects, PHORA will be built using Angular which is the same technology used to make widely used apps such as Healthcare.gov, Google Inbox, and Google+. To further facilitate scale-up, we will design PHORA to offload as much processing as possible to the cloud and by hosting the software at the Pittsburgh Supercomputing Facility which has sufficient computing power and storage capabilities for all PHORA’s future growth needs. The software can also be deployed to multiple servers and load balancing can be used to distribute load across servers.

**Pitfalls/Solutions:** Even though we will perform sensitivity analyses throughout our modeling, there is a chance that the model validation will demonstrate poor discrimination or calibration. If the discrimination for the prognostic model is weaker than the discrimination for a single variable or weaker than the discrimination based on REVEAL calculator alone, for example, this is also an important result. Such a finding would indicate that fewer tests are needed for most patients. There is also a chance that the validation for one of the data sources may not proceed at the preferred pace. One reason for selecting multiple data sources for the validation is to reduce the dependency on any single data source. If most of the validations are complete, per the original timeline, additional validation sets may be set aside. In addition, if logistical issues arise, we will also have a clinical consultant committee consisting of two experts in the field and a member from ICON (Foreman) to advise the primary team in all analyses and statistical correlations (see appended letters from Gomberg, Elliot and ICON, through a contracted service agreement).

**Risk of Overfitting.** Considering the multiple large cohorts for derivation and validation, we acknowledge the potential for over-fitting the model exists. We hope to mitigate this risk with several precautionary steps to avoid over-fitting and increasing the generalizability of our models to different PAH populations. We will use two methods of training and testing the model: k-fold cross validation and leave-one-out cross validation, where the former is computationally more efficient and the latter is often more precise. To speak to the loss of sensitivity critique, we argue that although some sensitivity is lost when continuous variables are discretized, the model performance is not compromised. Hsu et al. compared performance of several discretization methods (10-bin, entropy based, error based) against each other and the use of continuous variables for the Naïve Bayes classifier. They concluded that the discretized Naïve Bayes models either outperformed or performed equally well compared to the continuous Naïve Bayes model.

**Adoption and Uptake.** The investigators acknowledge that there have been many unsuccessful attempts of introducing decision support systems into clinical practice, especially tools developed in the late 1990’s and 2000’s. However, the chief reasons are the lack of human-computer-interaction considerations for the workflow of healthcare practitioners and the associated information systems. Conversely, we attribute our positive experience to our rigorous use of user-centered design methodologies, which have become the standard of practice in computer science over the last 25 years, and which our co-l’s (Zimmerman and Padman) have successfully deployed in several healthcare settings.

To assess general interest in PHORA by the community, we conducted a survey of 58 patients and 48 medical providers at the 2014 PHA Meeting in Indianapolis. (See Figure 9.) Questions related to frequency and quality of patient-physician consultation, appropriate timing of treatment, and incidence of regret by patients. After being shown a mockup of the PHORA website with a brief description and asked their level of interest, 82% of patients, and 74% of providers, responded “absolutely” or “probably” be interested in using it. (In addition, members of the PH community from the US, Europe, Canada, and Australia have provided letters of support of the PHORA concept. (See Appendix.))

**Cloud compatibility:** To reduce IT burden on clinics, the PHORA software will be hosted in the cloud at the Pittsburgh Supercomputing Centre. All participating clinics can securely
access PHORA via any modern desktop browser without installing any software locally or involving IT staff. The backend is architected for multi-tenancy, meaning data for multiple clinics are stored in the same secure server and each clinic will only have access to their own patient data. A self-hosted option can also be provided for hospitals with strict requirements to store patient data in their own data centers.

{PHORA software’s accessibility and fee structure: For long-term success of PHORA, we recognize the need for a financial model to support, maintain, and continue to update the software. This is a challenge faced by a great number of prognostic models and risk-scores. For certain, we plan to provide a version of the model accessible to on a publicly accessible website (like the Framingham model and Seattle Heart Failure Model) and downloadable app (like the current REVEAL model.) We are exploring multiple financial plans to support the future ongoing maintenance of the model. One is to license the technology to an established EHR company or companies – in which case it will become their responsibility for its maintenance. On the other end of the spectrum, we are considering spinning out a small business that will derive income from customized versions of PHORA for individual practices or medical centers. We have previously competed successfully for a Phase-1 SBIR for our earlier-generation DSS app (then titled CHRISS), but we are deferring consideration for CORA or PHORA for the time being. In the latter two cases, a potential fee structure can be a $X per healthcare provider/month or a $X/patient/month.}

**Project Management.** The overall sequence of the above Aims are summarized in the Pert Chart below. Aims 1 and 2 will commence in Y2 once the prognostic and expert models have been initially validated. EHR integration is proposed for Y4 in preparation for a multi-center, comparative outcome, prospective trial clinical trial. Our team is located at three different performance sites, which poses challenges for efficient communication. Through our previous and ongoing collaborations, we have adopted practices for collaborating effectively. This includes bi-monthly face-to-face meetings, embedding a CMU investigator into the weekly patient-review meeting at AGH, and cloud-based project management software (i.e. Smartsheet) which facilitates sharing project milestones, task allocation, and tracking (accessible via web browser by all members, to report progress, annotate milestones, and share data.

**Dependence of Aims 1, 2, and 3.** Inasmuch as Aim 3 serves to translate the outcomes of Aims 1 and 2, we acknowledge that it is dependent on the success of those two aims. However Aim 2 is completely independent of Aim 1, inasmuch as it focuses on a complimentary Knowledge-Based model to the Bayesian (quantitative) model of Aim 1. Therefore, Aim 3 can be successful if either Aims 1 or 2 are successful. However we are confident that both Aims 1 and 2 will be successful for the following three reasons. Firstly, the protocols for developing both the Bayesian and Expert models are now well established as a result of the progress we have made with the current R01 study, CORA, for patients receiving ventricular assist devices. Co-investigators (Antaki and Kanwar) are now midway through this project, and have begun to publish promising results. As presented in the Preliminary Data section (C2.5), our initial first-generation Bayesian model of the REVEAL model has already exceeded the existing score with an **accuracy of 88.7% with an ROC AUC of 0.74.** This result was obtained prior to optimization of the parameters. We are highly confident that this performance will increase significantly by adding independent variables from the new data sources. The risks associated with the Expert Model (Aim 2) are mitigated by relying on two independent sources – either of which would serve as a valuable, useful model independently. The first source is merely existing best practices that we will codify into an appropriate data structure for the PHORA app. The second source, semi-structured interviews is a bit more speculative, but still a procedure well known to our co-Investigators.

**Future goals:** We intend to proceed on two fronts: a randomized clinical trial of the professional version of PHORA, and development of a patient version. It will be like the physician version, but provide information with less detail and in a more user-friendly format. For example, patients will be shown a “roadmap” of their treatment prospects with associated risks and outcomes. We envision the scenario wherein a patient is provided with the access to PHORA upon initial meeting with his/her physician, e.g., at dx of PAH. The patient would review the information, interact with the system at home with family or caregiver, and then review their decisions and questions with the physician at a follow-up visit. Our survey of ~ 60 patients and their caregivers at the 2014
PHA convention demonstrated an overwhelming positive response to this feature of the application.

In summary, completion of the above Aims will provide the health care team involved in management of PH with a quantitative, comprehensive, evidence-based guidance tool to help arrive on a timely and optimal course of treatment that will improve outcomes and quality of life of patients suffering from this devastating disease.
REFERENCES


Santelices L. Development of a clinical decision support system for optimal vad weaning. *Bioengineering*. 2005


66. Hayward RCDSTDTSC. Clinical decision support tools: Do they support clinicians? *Canadian Medical Association Journal*. 2004;170:66-68