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14. ABSTRACT- Goal of the project is to develop an Evidence-based Clinical Decision Support (EBM-CDSS) system and make it available at the point of care to improve prognostication of the life expectancy of terminally ill patients to improve referral of patients to hospice. In addition, the EBM-CDSS will be expanded with an evidence based pain management module (EB-PMM) to assist physicians managing patients with pain. So far our key research accomplishments are as follows (see details below). In brief, we have • Revised (and continue to revise) the software for the EBM-CDSS. Revised (and continue to revise) the user guide for the EBM-CDSS software and the training manual to assist research team for data collection in the prospective phase of the study (see appendix 11). Completed the initial paperwork to add Moffitt Cancer Center as a study site and submitted the study protocol and other required documents to Moffitt cancer centers' scientific review committee. • Submitted the amendment to the project reflecting changes in the study team, changes to the informed consent forms and the study protocol to University of South Florida institutional review board. • Completed the Tampa General Hospitals' (TGH) credentialing procedures for all (3) research personnel. • Completed the TGH electronic record system (EPIC) training for 3 research personnel. • Completed the training of research nurses regarding EBM-CDSS software and data collection procedures. • Started advertising our study at TGH and among USF physicians. • Opened enrollment in the prospective phase of the study. • Actively monitoring all aspects of the study• Further developed and completed internal testing the pain module of the EB-PMM module. • Published multiple peer reviewed manuscripts (see appendices 1-7).

15. SUBJECT TERMS- CDSS, SUPPORT, DEALE, Terminally ill, Hospice, Prognostication

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Introduction

The goal of the phase II of the project is to prospectively test the methods and techniques developed in phase I of the project. Evidence-based Clinical Decision Support system seeks to elicit patients' preferences and aid with prognostication of the life expectancy in terminally ill patients to improve referral of patients to hospice at the point of care. In addition, the EBM-CDSS will be expanded with an evidence based pain management module (EB-PMM) to assist physicians managing patients with pain.

Body:

Key research-related accomplishments (since the submission of previous annual progress report):

- We completed training and submitted the required documents for our nurses and other research personnel to complete TGHs' credentialing procedures. This step was essential to initiate the prospective phase of our study.
- We revised our case report forms and the EBM-CDSS software including its graphic user interface.
- We also revised the user guide for the EBM-CDSS software and the training manual to assist research team for data collection in the prospective phase of the study. We requested our research nurses and other research personnel to use the EBM-CDSS and review the user guide. Based on their feedback we revised the software and the user guide and again requested them to review it. After at least 4 iterations we have finalized EBM-CDSS software and user guide (see appendix 11). (NB there is continuing quality monitoring; depending on the feedback and the "situation on the grounds", we continue to revise and adjust our software while retaining the fidelity toward the study goals).
- We invested significant amount of time in training the research nurses in using the EBM-CDSS software and fine tuning their interviewing skills. We conducted a number of mock interview sessions in which our research nurses conducted interviews using the EBM-CDSS software, accompanying data collection forms (appendix 8), scripts (see appendix 9) and informed consents (appendix 10).
- Our research nurses have also completed their TGH electronic record system (EPIC) training.
- We have also completed a number of administrative requirements such as obtaining a University of South Florida (USF) Email IDs, TGH identification cards, parking permits and USF business cards for our research nurses. (Although these steps may appear small, in reality they are all time-consuming aspects of research activities, particularly because almost all modifications to the protocol require the USF IRB approval).
- We have also finalized the study advertisement flyer including obtaining related administrative permissions to advertise our study at TGH and among USF physicians. That is, we have obtained permissions from USF media relations department to use the "USF Health" logo on our flyer and clearance from TGH to post our flyer across TGH campus. See the flyer attached in appendix 12.
- We conducted a number of meetings with TGH palliative care team and presented our research study to the TGH palliative care team. These meeting were fruitful; especially in establishing trust and working relationship with TGH palliative care team, which is a key to facilitate the patients referral to our study. We are pleased that Dr. Howard Tuch, director of the USF TGH team joined our study as a key clinical collaborator.

- We have met with the number of the key physicians and their teams to explain the purpose of the study. This will be continuing effort on our part as the study cannot succeed without adequate referrals from the physicians at TGH.
- Based on the feedback received from health providers, including some patients and families, we have further revised and fine-tuned our CDSS:
    - Revised the user guide for the EBM-CDSS software and the training manual to assist research team for data collection in the prospective phase of the study.
    - Revised the script to guide the patient/proxy/provider interview.
    - Completed further training of research nurses regarding EBM-CDSS software and data collection procedures.
    - Further developed and completed internal testing of the pain module of the EB-PMM module.
- We have refined our EB-PMM to complement the EBM-CDSS. Our objective is to develop a reliable dosage conversion system as well as a knowledge based for each available pain medication. We have also incorporated evidence profiles for each drug to support the decision making using our pain management module. We have also created a survey to test usefulness of EB-PMM its users. Recently, the National Comprehensive Cancer Network revised their guidelines for management of adult cancer pain and we have revised EB-PMM accordingly. We have contacted the TGH palliative care team to review EB-PMM and provide feedback to us. Please see the user manual for EB-PMM and the EB-PMM evaluation survey in appendix 13 and 14 respectively.
- All these activities have been necessary to help us open the patient enrollment in the prospective phase of the study.
- Unfortunately, as we were to start enrollment, our research nurses left our study team. So, we are in the process of hiring new research nurses. We have already identified highly qualified candidates to replace the existing research team. Although we will have to train new research team again, the experience gained in the process outline above, will have proven invaluable to speed up training.
- We believe that we have been highly productive and we are on the right track to achieve of the objectives of the study. This is best reflected in our publication records (see next session). As it can be seen, these analyses were key to informing the prospective, phase II of our project.

Reportable outcomes

We have published/submitted 7 manuscripts for publication in peer-reviewed journals (see appendix 1-7): specifically:

- **Manuscript 1 (appendix 1):**
  Title: Towards a Classification Model to Identify Hospice Candidates in Terminally Ill Patient
  In brief: A Rough Set Theory based classification model to identify hospice candidates within a group of terminally ill patients. Unlike traditional data mining methodologies, this approach using an artificial methodology of rough set theory seeks to identify subgroups of patients possessing common characteristics that distinguish them from other subgroups in the dataset.
  Citation: Eleazar Gil-Herrera, Ali Yalcin, Athanasios Tsalatsanis, Laura E. Barnes and Benjamin Djulbegovic, "Towards a Classification Model to Identify Hospice Candidates in Terminally Ill Patients", to appear in the Proceedings of the Annual International Conference of the IEEE Engineering in Medicine and Biology Society, 2012

- **Manuscript 2 (appendix 2):**
  Title: A Flexible Alternative to the Cox Proportional Hazards Model for Assessing the Prognostic Accuracy of Hospice Patient Survival
  In brief: We applied the Palliative Performance Scale to demonstrate that a novel survival model predicted hospice patient survival more closely than a commonly used Cox proportional hazards model. Unlike the Cox proportional hazards model, it uses splines and the probit link function to model patient baseline survival. This model will be integrated in the prospective phase of the project.
  Citation: Miladinovic B, Kumar A, Mhaskar R, Kim S, Schonwetter R, Djulbegovic B, A flexible alternative to the Cox proportional hazards model for assessing the prognostic accuracy of patient survival. PLoS ONE 2012(in press)

- **Manuscript 3 (appendix 3):**
  Title: Natural History of Patients With Lung Cancer Without Treatment: A systematic Review. This manuscript is currently under review by Supportive Care in Cancer journal.
  In brief: The purpose of this study was to conduct a systematic review and meta-analysis of the natural history of patients with confirmed diagnosis of NSCLC without active treatment. Studies were identified by search of electronic databases (MEDLINE and CENTRAL) and abstract proceedings. Data on mortality was extracted from all included studies and pooled proportion of mortality was calculated. The meta-analysis included seven cohort studies (4,418 patients) and 15 randomized controlled trials (1,031 patients). The pooled proportion of mortality without treatment in cohort studies was 0.97 (95% CI: 0.96 to 0.99) and 0.96 in randomized controlled trials (95% CI: 0.94 to 0.98) over median study periods of 8 and 3 years, respectively. There was no statistically significant difference between these subgroups. For NSCLC patients undergoing no treatment, mortality is very high. Although limited by study design, this finding provides the basis for future trials to determine optimal expected improvement in mortality with innovative treatments. The results will also inform the aspects of phase II part of our studies related to cancer patients.
  Citation: Wao, H., Mhaskar, R., Kumar, A., & Djulbegovic, B. Natural history of patients with lung cancer without treatment: A systematic review. Journal of Supportive Care in Cancer, 2012 (under review).

- **Manuscript 4 (appendix 4):**

Title: External validation of a web-based prognostic tool for predicting survival in patients in hospice care

In brief: This study was undertaken to assess whether another prognostic model (a popular model Prognostat) should be integrated in the phase II of our project. Prognostat is an interactive Web-based prognostic tool for estimating hospice patient survival based on a patient's palliative performance scale score, age, gender, and cancer status. The tool was developed using data from 5,893 palliative care patients collected at the Victoria Hospice since 1994. This study externally validates Prognostat on a retrospective cohort of 590 hospice patients in Lifepath Hospice Center, Florida, USA. The criteria used to evaluate the prognostic performance are the Brier score, area under the receiver operating curve, discrimination slope and Hosmer-Lemeshow goodness-of-fit test. Though the Kaplan-Meier curves show each PPS level to be distinct and significantly different, the findings reveal poor performance of the prognostic tool in our cohort of hospice patients. Before redeveloping a new prognostic model researchers are encouraged to combine survival estimates obtained using Prognostat with the information from their cohort of patients. To that end, Prognostat needs to explicitly report patient risk scores to be useful to clinicians. Hence, we will not use it in a prospective phase of the project.

Citation: Miladinovic B, Mhaskar R, Kumar A, Kim S, Schonwetter R, Djulbegovic B. External validation of a web-based prognostic tool for predicting survival in patients in hospice care. Journal of Palliative Care, 2012 (submitted).

- **Manuscript 5 (appendix 5):**
  Title: External Validation of Prognostic Models in Terminally Ill Patients.

  In brief: In the phase I of our project we retrospectively extracted data from 590 deceased patients enrolled in Tampa Bay Lifepath Hospice and Palliative Care starting January 2009 and going backwards to validate following 5 prognostic models commonly recommended in the literature for prognostication in terminally ill patients: 1) declining exponential approximation of life expectancy (DEALE) 2) study to understand prognoses and preferences for outcomes and risks of treatments (SUPPORT), 3) adjusted palliative performance scale (PPS), 4) adjusted Karnofsky performance scale index (Karnofsky) and 5) adjusted eastern cooperative oncology group performance status (ECOG).

  The models were tested against observed survival duration. We utilized several metrics to assess the performance of these models. Specifically, we used the Brier score and scaled Brier score (which is very similar to the Pearson correlation coefficient R2), the area under the receiver operating characteristic curve (AUROC), and the Hosmer-Lemshow goodness-of-fit p-value (HL). Based on our analysis we will use PPS and SUPPORT models for prognostication of life expectancy in the prospective phase of the study

  Citation: Mhaskar R, Miladinovic B, Tsalatsanis A, Mbah A, Kumar A, Sehwan K, Schonwetter R, Djulbegovic B. External Validation of Prognostic Models in Terminally Ill Patients. Blood; 1791: 4186, 2011

- **Manuscript 6 (appendix 6):**
  Title: Rough Set Theory based Prognostic Model for Hospice Referral

  In brief: Objective: The goal of this paper is to provide an accessible prognostic classification model for hospice referrals. Hospice care provides high-quality and cost-effective end-of-life care for terminally ill patients. In addition, the paper explores the application of Rough Set Theory (RST) for the development of clinically credible prognostic models.

  Methods: We utilize retrospective data from 9,103 terminally ill patients to demonstrate the design and implementation of a classifier based on RST for potential hospice candidates. RST provides methods for knowledge reduction, founded on the relational indiscernibility of

objects in a decision system, to describe required conditions for membership in a concept class. Decision rules for six-month patient survival classification are extracted from the dataset utilizing genetic algorithms for approximate reduct generation.

Results: The RST-based classifier performs comparably to other common classification methods, while providing significant advantages in terms of traceability and accessibility of the model. We are in the process of refining this model, and hope to make final decision regarding this acceptability for phase II of our project.

Citation: Eleazar Gil-Herrera, Garrick Aden-Buie, Ali Yalcin, Athanasios Tsalatsanis, Laura E. Barnes and Benjamin Djulbegovic, "Rough Set Theory based Prognostic Model for Hospice Referral", submitted to Journal of Artificial Intelligence in Medicine, Sept. 2012

- **Manuscript 7 (appendix 7):**

  Title: Extensions to Regret-based Decision Curve Analysis: An application to hospice referral for terminal patients

  In brief: Despite the well documented advantages of hospice care, most terminally ill patients do not reap the maximum benefit from hospice services, with the majority of them receiving hospice care either prematurely or delayed. Decision systems to improve the hospice referral process are sorely needed. We present a novel theoretical framework that is based on well-established methodologies of prognostication and decision analysis to assist with the hospice referral process for terminally ill patients. We linked the SUPPORT statistical model, widely regarded as one of the most accurate models for prognostication of terminally ill patients, with the recently developed regret based decision curve analysis (regret DCA). We extend the regret DCA methodology to consider harms associated with the prognostication test as well as harms and effects of the management strategies. In order to enable patients and physicians in making these complex decisions in real-time, we developed an easily accessible web-based decision support system available at the point of care. We present a theoretical framework to facilitate the hospice referral process. This method uses our dual visual analog scale (DVAS) to elicit the patient preferences and values regarding the hospice referral. It effectively represents a linchpin between prognostication and elicitation of the patient values regarding the choice they face in terminal phase of their lives. This is now integrated in our CDSS-EBM and will represent a cornerstone of phase II of our project.

  Citation: Tsalatsanis A, Barnes LE, Hozo I, Djulbegovic B. Extensions to Regret-based Decision Curve Analysis: An application to hospice referral for terminal patients. BMC Medical Informatics and Decision Making 2011, 11:77 (doi:10.1186/1472-6947-11-77)

Next Steps

- Our first step is hiring and training research nurses to continue enrollment of participants in our study.
- Our immediate and most important next step is to enhance enrollment of patients in the prospective phase of the study. This requires tackling and coordinating multiple logistical, regulatory and administrative issues, which so far we have been successfully addressing.
- Work very closely with TGH palliative team to accomplish the goals of the study.
- We will maintain the quality assurance and oversight necessary for successful execution of the study.
- We will continue to test the main module of the EBM-CDSS computer program and modify it as needed (per feedback received from the field).
- We will further develop and complete testing the EB-PMM (pain module).
- Complete the on-going manuscripts and submit for publication in peer-reviewed journals.

Appendix 1

Towards a classification model to identify hospice candidates in terminally ill patients

Eleazar Gil-Herrera, Ali Yalcin, Athanasios Tsalatsanis, Laura E. Barnes and Benjamin Djulbegovic

Abstract— **This paper presents a Rough Set Theory (RST) based classification model to identify hospice candidates within a group of terminally ill patients. Hospice care considerations are particularly valuable for terminally ill patients since they enable patients and their families to initiate end-of-life discussions and choose the most desired management strategy for the remainder of their lives. Unlike traditional data mining methodologies, our approach seeks to identify subgroups of patients possessing common characteristics that distinguish them from other subgroups in the dataset. Thus, heterogeneity in the data set is captured before the classification model is built. An alternative RST methodology is used to obtain the minimum set of attributes that describe each subgroup existing in the dataset. As a result, a collection of decision rules is derived for classifying new patients based on the subgroup to which they belong. Results show improvements in the classification accuracy compared to a traditional RST methodology, in which patient diversity is not considered. We envision our work as a part of a comprehensive decision support system designed to assist terminally ill patients in making end-of-life care decisions. Retrospective data from 9105 patients is used to demonstrate the design and implementation details of the classification model.**

I. INTRODUCTION

A. Hospice referral criteria

Hospice is designed to provide comfort and support to terminally ill patients and their families. According to Medicare regulations, a patient should be referred to hospice if his/her life expectancy is approximately 6 months or less [1]. However, most patients are not referred to hospice in a timely manner [2, 3] and therefore they do not reap the well-documented benefits of hospice services. A premature hospice referral translates to a patient losing the opportunity to receive potentially effective treatment, which may prolong their life. Conversely, a late hospice referral may deprive patients and their families of enjoying the benefits offered. Therefore, accurate prognostication of life expectancy is of vital importance for terminal patients as well as for their families and physicians.

B. Prognostic models for estimating survival of terminally ill patients

Survival prognostic models range from traditional statistical and probabilistic techniques [4-10], to models based on artificial intelligence such as neural networks [11, 12], decision trees [13, 14] and rough set methods [15, 16]. The primary goal of survival prognostic models is to provide accurate information regarding life expectancy and/or determine the association between prognostic factors and survival. Typically, the information derived by prognostic models is presented in terms of probability of death within a time period. Recent systematic reviews [17, 18] have highlighted the necessity of prediction models that can be easily integrated into clinical practice and facilitate end-of-life clinical decision-making.

Several important issues demand particular consideration when developing clinical classification models: First, clinical data, representing patient records that include symptoms and clinical signs, are not always well defined and are represented with *vagueness* [19]. Therefore, it is very difficult to classify cases in which small differences in the value of an attribute may completely change the classification of a patient and, as a result, the treatment decisions [20]. Second, clinical data may present *inconsistencies*, which means that it is possible to have more than one patient with the same description but with different outcomes. Third, the results of prognostic models should be readily interpretable to enable practical and posteriori inspection and interpretation by the treating physician or an expert system [21]. Finally, prognostic models should consider the heterogeneity in clinical data, i.e. the existence of patient diversity presented in terms of risk of disease and responsiveness to

treatment [22, 23]. This consideration will enable a prognostic model to identify possible subgroups of patients for which certain covariates do not influence their classification. The practical implications of such considerations are associated with the ability to customize the prognostic model for each subgroup of patients (e.g. expensive and/or potentially harmful tests may be avoided for particular subgroups).

Rough Set Theory (RST) [24], a mathematical tool for representing and reasoning about vagueness and inconsistency in data sets, has been used in a number of applications dealing with modeling medical prognosis [15, 16, 25-28]. For example, Tsumoto et al. [25], provide a framework to model medical diagnosis rules showing theoretically that the characteristics of medical reasoning reflect the concepts of approximation established in RST. Komorowski et al. [26], show that RST is useful to extract medical diagnosis rules to identify a group of patients for whom performing a test that is costly or invasive is redundant or superfluous in the prognosis of a particular medical condition. Recently, [28] highlighted features of RST for integrating into medical applications. For example, RST has the ability to handle imprecise and uncertain information and provides a schematic approach for analyzing data without initial assumptions on data distribution.

In our previous work [29], we proposed the use of RST to predict the life expectancy of terminally ill patients using a *global reduction* [30] methodology to identify the most significant attributes for building the classification model. However, we found that the number of attributes used in the model was barely reduced and therefore produced long decision rules. Moreover, considering the number of discretization categories associated with each attribute, the generated decision rules were built to describe each object in the training set and therefore, they were poorly suited for classifying new cases.

Here, we propose the use of an alternative attribute reduction methodology that aims to identify groups of patients that share common characteristics that distinguish them from the rest of the patients. As a result, we obtain subgroups of patients from which different sets of significant attributes are identified. The decision rules generated in this manner contain fewer attributes and therefore are more suitable to classify new patients. Moreover, by studying each subgroup, we can reason about how a different rule-set is applied to a particular patient.

The rest of the paper describes details of the proposed RST based methodology to provide a classifier that properly discriminates patients into two groups: those who survive at least 180 days after evaluation for hospice referral and those who do not. ROSETTA [31] software is used to perform the analysis described in the remainder of the paper.

II. Methodology

A. Data Set

The dataset used in this study consists of the 9105 cases from the SUPPORT (Study to Understand Prognoses and Preferences for Outcomes and Risks of Treatments) prognostic model dataset [30]. We consider all variables used in the SUPPORT prognostic model [3] as condition attributes, i.e. the 11 physiologic variables along with the diagnosis groups, age, number of days in the hospital before entering the study, presence of cancer, and neurologic function. Attributes names and descriptions are listed in Table I. As the decision attribute, we define a binary variable (Yes/No) "deceases_in_6months" using the following two attributes from the SUPPORT prognosis model dataset:

•   death: represents the event of death at any time up to NDI date (National Death Index date: Dec 31, 1994).

•   D.time: number of days of follow up

The values of the decision attribute are calculated converting the "D.time" value in months and comparing against the attribute "death" as follows:

- If "D.time" < 6 months and "death" is equal to 1 (the patient died within 6 months) then "deceases_in_6months" is "Yes". Otherwise, it is implicit that a patient survived the 6-month period; hence, "deceases_in_6months" is "No".

B. Rough Set Theory Data Representation

Based on RST, the data set is represented as:

$$T = (U, A \cup \{d\}) \qquad (1)$$

TABLE I.   CONDITION ATTRIBUTES

Name	Description
meanbp	Mean arterial blood pressure Day 3
wblc	White blood cell count Day 3
hrt	Heart rate Day 3
resp	Respiratory rate Day 3
temp	Temperature (Celsius)
alb	Serum Albumin
bili	Bilirubin
crea	Serum Creatinine
sod	Sodium
pafi	Pa02 / (.01 * FiO2)
ca	Presence of cancer
age	Patient's age
hday	Days in hospital at study admit
dzgroup	Diagnosis group
scoma	SUPPORT coma score based on Glasgow coma scale

where *T* represents the dataset in the form of a table. Each row represents an object and each column represents an attribute. *U* is a non-empty finite set of objects and the set *A* is a non-empty finite set of attributes called the condition attributes. In our case, an object designates a terminally ill patient and an attribute $a \in A$ designates each of the fifteen condition attributes that describe a patient (Table I). For every attribute, the function $a: U \rightarrow V_a$ makes a correspondence between an object in *U* to an attribute value V_a which is called the value set of *a*. The set T incorporates an additional attribute *{d}* called the decision attribute. The system represented by this scheme is called a decision system.

C. Development of the Classification Model

This process typically involves numerous steps, such as data preprocessing, discretization, reduction of attributes, rule induction, classification and interpretation of the results. Details on the data preprocessing and data discretization for this data set are described in [29]. The ultimate goal of this process is to generate decision rules, which are used to classify each patient as surviving or not surviving within the defined period of time. A decision rule has the form: *if A then B (A → B)*, where *A* is called the condition and *B* the decision of the rule.

Here, we are focusing on an alternative method of reducing the attribute dimensions and identify different subgroups of similar patients in the data set. In [32], two types of reducts are defined:

1) Global Reducts:

Consists of the minimal set of attributes that preserve the structure of the entire data set and can be used to generate decision rules and classify new cases. A set $B \subseteq A$ is called a global reduct if:

$$IND(B) = IND(A), \text{ where,}$$

$$IND(B) = \{(u_i, u_j) \in U^2: \forall a_k \in B, a_k(u_i) \neq a_k(u_j)\}$$

As an example, consider the following global reduct obtained from the data set containing 12 condition attributes:

G_RED = {age, dzgroup, scoma, ca, meanbp, wblc, hrt, resp, temp, bili, crea, sod}

Using *G_RED*, few patients will have exactly the same attribute-value combinations because the number of discretization categories associated with each attribute is high. Thus, the decision rules generated are too specific to the cases in the training set and therefore may not be able to classify new cases accurately. Moreover, the fact that global reducts represent the entire data set makes it difficult to detect the presence of heterogeneous groups in the data meaning that the causes of diversity between the patient outcomes will remain unknown.

2) Object related reducts (ORR):

Represents the minimal attribute subsets that discern an object $u \in U$ from the rest of objects belonging to a different decision class. Mathematically, an ORR $R_u \subseteq A$ is defined as:

$$\forall u_i \in U : d(u_i) \neq d(u_j) \Rightarrow \exists a_k \in R_u : a_k(u_i) \neq a_k(u_j), \text{ where } u_i \neq u_j .$$

An ORR is the minimal and vital information that is used to partition the universe of objects into smaller, homogeneous subgroups, where objects within a subgroup are related by means of information described by the ORR. Decision rules generated by this scheme will usually contain fewer attributes and are more suitable to classify new cases. Some decision rules contain a different set of attributes applicable for a particular subgroup of patients.

III. Results

Based on the decision rules generated, patients are classified as surviving or not surviving the six-month period. A standard voting algorithm [30] is used for this purpose. Table II, presents the performance of two classification models based on each type of reduct generation described. The performance of each classification model is represented in terms of *sensitivity*, *specificity*, *Area under the Receiver Operating Characteristic curve* (AUC) and *coverage* of the model. A 5-fold cross validation procedure was applied to estimate the performance of each classification model, where, the entire data set is randomly divided into five subsets (folds). Then, each fold (20% of the data set) is used once as a testing set, while the remaining folds (80%) are used for training. The process is repeated five times and the results are averaged to provide an estimate for the classifier performance.

TABLE II.   CLASIFICATION RESULTS – GLOBAL VS. ORR

Method	Sensitivity	Specificity	AUC	Coverage
Global Reducts	73.67%	44.05%	61.8%	86.43%
ORR	86.92%	39.2%	71.9%	100%

Compared to the Global reduct approach, the ORR approach has enhanced the classification performance in terms of AUC and sensitivity. Moreover the decision rules generated are able to classify all new cases.

IV. Discussion

Analyzing the information obtained from the ORR, we can identify groups of patients for whom it is possible to evade costly, invasive or even unnecessary tests required by the prediction model. For example, the following two ORRs generate rules independent of the *Pafi* score (associated with the patient's blood gases), without reducing the classification accuracy. The importance of such finding becomes apparent considering that in clinical practice *Pafi* is not collected routinely for patients outside the Intensive Care Unit (ICU).

- ORR = {Age, dzgroup, meanbp} generates the following decision rules:
  - if age= [45, 60) AND dzgroup = (Lung Cancer) AND meanbp=[60, 70) then: Survive = 22.86%, Die = 77.14%.
  - if age= [45, 60) AND dzgroup = (CHF) AND meanbp=[100, 120) then: Survive = 82.93%, Die = 17.07%.

- o if age= [70, 75) AND dzgroup = (COPD) AND meanbp=[80,100) then: Survive = 84.21%, Die = 15.79%.

- ORR = {Age, dzgroup, hrt, crea} generates the following decision rules:

  - o if age= [45, 60) AND dzgroup = (CHF) AND hrt=[100,110) and crea[1.95, *] then: Survive = 83.33%, Die = 16.67%.

  - o if age= [75,85) AND dzgroup = (CHF) AND hrt=[50,110) and crea[0.5, 1.5) then: Survive = 82.19%, Die = 17.81%.

Consequently, the use of *Pafi* test in patients that belong to one of those groups defined by the ORR's will not improve the prognostication accuracy.

Our approach demonstrates features that make it particularly suitable for use in clinical decision-making. It is a patient-centric methodology which is able to predict without the use of unnecessary, expensive and/or invasive procedures for certain subgroups of patients. Consequently, selection of attributes upon which a decision is to be made is critical to minimizing healthcare costs and maximizing the quality of patient care. Finally, considering that more than one ORR could discern each patient, the information acquired offers several options dependent on the attribute values available for each individual patient.

V. Future Work

The number of ORR and the decision rules generated depends on the number of condition attributes and its categories. For clinical datasets, which contain large numbers of condition attributes, the interpretation and analysis of the ORRs and their decision rules requires the use of a well-defined methodology. Therefore, we intend to incorporate this methodology into a patient-centric decision support system to facilitate the hospice referral process.

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Appendix 2

A flexible alternative to the Cox proportional hazards model for assessing the prognostic accuracy of hospice patient survival

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ABSTRACT

Prognostic models are often used to estimate the length of patient survival. The Cox proportional hazards model has traditionally been applied to assess the accuracy of prognostic models. However, it may be suboptimal due to the inflexibility to model the baseline survival function and when the proportional hazards assumption is violated. The aim of this study was to use internal validation to compare the predictive power of a flexible Royston-Parmar family of survival functions with the Cox proportional hazards model. We applied the Palliative Performance Scale on a dataset of 590 hospice patients at the time of hospice admission. The retrospective data were obtained from the Lifepath Hospice and Palliative Care center in Hillsborough County, Florida, USA. The criteria used to evaluate and compare the models' predictive performance were the explained variation statistic R^2, scaled Brier score, and the discrimination slope. The explained variation statistic demonstrated that overall the Royston-Parmar family of survival functions provided a better fit ($R^2 = 0.298$; 95% CI: 0.236-0.358) than the Cox model ($R^2 = 0.156$; 95% CI: 0.111-0.203). The scaled Brier scores and discrimination slopes were consistently higher under the Royston-Parmar model. Researchers involved in prognosticating patient survival are encouraged to consider the Royston-Parmar model as an alternative to the Cox model.

Keywords: Survival prognostication, Palliative Performance Scale, Royston-Parmar survival models, Cox proportional hazards, Internal validation
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I.   INTRODUCTION

Prognostic models are often used to estimate the length of patient survival and improvement in the accuracy of prognosis translates into superior quality of patient care. Precise prognosis of survival using modeling techniques requires rigorous methods for the development and testing of the accuracy of prognostic models. Developing a prognostic model entails having accurate patient data for prognosis, and selecting clinically relevant candidate predictors and measure(s) of model performance, usually in the context of a multivariable regression survival model[1]. This process produces patient performance scores that allow for classification of patients into different risk groups [2,3,4].

In the hospice setting, accurate prognostication of survival affords patients and their families a vital opportunity to attend to matters such as planning, prioritizing, and preparing for death [5]. Predicting patient survival is a complex decision making process involving numerous subjective and numerical factors that have substantial variation which may lead to poor prediction of life expectancy. Many physicians practice optimism or avoidance, thus overestimating survival at times by a factor of five[6]. Implementing appropriate statistical methodologies translates into improved accuracy of prognosis and superior quality of care. Predictions based on appropriate statistical modeling have been shown to be superior to physicians' prognostication [4,7].

The Cox proportional hazards (CPH) model[8] is the most commonly-used survival prediction model[4,9]. In the hospice and palliative settings, demographic and clinical covariates are often included in CPH to predict patient survival [10,11].   The appeal of the model is its analytic simplicity and that the baseline survival function does not need to be defined *apriori* -- it is absorbed when the likelihood function is maximized (note that "baseline" refers to zero values of the covariates, not to time equal to zero). It is possible to estimate the baseline survival function for the CPH model conditional on the estimated regression coefficients. However, this is highly rigid as the smoothing of the underlying function depends on the proportional hazards assumption, which may not be supported by the data and is often overlooked by the investigators[9]. Essentially, the CPH model was designed to measure the effects of covariates on the changing hazard function and not to model patient survival.

A flexible family of functions which allows for parametrically modeling the baseline survival function is more appropriate, especially if the proportional hazards assumption is violated in the CPH[12]. The baseline survival has for the most part been ignored because it is left undefined in the CPH model.

In this manuscript we compare CPH with an alternative method of estimating survival in the form of the class of flexible Royston-Parmar (RP) parametric functions[12]. We use the Palliative Performance Scale (PPS)[13] from a cohort of hospice patients. Results from systematic reviews have shown that the patient PPS score is an accurate measure of patient survival in the palliative setting [7,11]. Furthermore, PPS and CPH model have been used to construct meaningful hospice patient survival estimates in the form of a life expectancy table and survival nomogram [14].

In addition to PPS, other risk factors such as age, cancer status and gender have been reported to be significant predictors of palliative patient survival in several studies[11,14]. In our study we did not adjust for other risk factors because though they may be significant predictors of survival for the cohort of patients in our dataset, they may not be in other palliative settings. Our goal was to demonstrate that the RP family of parametric functions allowed for a direct and flexible modeling of the baseline survival and that it might be formulated so that the impact of the proportional hazard assumption is minimized. We determined if the overall performance and discriminatory ability of RP family of parametric functions is superior to CPH in the sample by using models that were derived and tested on the whole dataset (naïve internal validation) and using (internal) cross-validation. CPH has been widely used to validate prognosticating scales for hospice patient survival [15,16,17]. It is important to note that the RP parametric functions have not been applied to prognostic models in the hospice and palliative settings. It is also important to note that we did not perform external validation, which entailed using a different data set than the one used to create the model[3]. In the next section we briefly discuss PPS, introduce the statistical models and measures of model performance.

II. METHODS

Study sample and palliative performance

The patient data were obtained from the Lifepath Hospice and Palliative Care Center, licensed since 1983 to serve in Hillsborough County, Florida. Hospice care focuses on pain control and symptom management. To avoid selection bias, we retrospectively and sequentially extracted data for 590 patients who, as of January 2009 were deceased. This study was a retrospective review of the deceased patients' medical records. Only data pertaining to outcomes were collected; personal information was not collected and the data were de-identified prior to analysis. Since we did not collect any information that can identify deceased patients or their family members, under HIPPA rules and regulations (45 CFR 164.512) the requirement for consent does not apply. The study and consent procedures were approved by the University of South Florida Institutional Review Board prior to study initiation. Two research assistants extracted all data necessary to populate the model variables and two faculty members randomly checked 25% of the data for accuracy. The models were tested against observed survival duration.

The Palliative Performance Scale (PPS) was developed and reported by Anderson et al. [13] as a measure of palliative patients' functional status. The scale has 11 possible mutually exclusive levels, which are based on five domains: six levels of ambulation, six levels of activity and evidence of disease, five levels of self-care, five levels of food intake and four levels of consciousness. The scale ranges from PPS of 0% (deceased patient) to PPS of 100% (ambulatory and healthy patient). Numerous studies have studied its prognostic accuracy of survival in a variety of settings and found it provides meaningful estimates of patient survival [10,14,15,18,19,20,21,22,23]. PPS has been found to be both valid and reliable [24].

Model selection and validation

Validating a prognostic model is generally accepted to mean that given a patient population it works in a data set other than the one it is applied to[2,25]. In other words, the model needs to be tested using a different data set than the one used to create the model[3]. It is also generally accepted that the

validation process should follow guidelines and that un-validated prognostic models should not be applied in clinical practice [3,4,26]. When validating a prognostic survival model in the regression framework, most attention has been on the value of the prognostic index based on covariates, while the role of the baseline survival function has been largely ignored. The role of the baseline survival is significant as it quantifies the absolute patient survival probabilities over time. For a vector of covariates **x** and parameter vector **β**, the survival function S(t; **x**) at time t for the CPH model is commonly expressed as $S(t;x) = [S_0(t)]^{\exp(x\beta)}$, where S_0 (t) is the baseline survival function, i.e. survival function when all the covariates **x** are equal to zero. In the CPH framework, the estimation of the prognostic index **xβ** does not require the formulation of the baseline cumulative survival function S_0 (t), which itself can be estimated conditional on the covariate estimates. The two popular methods for estimating baseline survival S_0 (t) are the Breslow and Kalbfleisch-Prentice methods [27]. Both give similar results in practice, but can lead to "choppy" estimates of the baseline function and are dependent on the proportional hazards assumption.

When the goal of a survival analysis is to estimate hazard ratios (the effect of covariates on the changing hazard function), the baseline function is of no consequence. The CPH is appropriate as the baseline function gets absorbed when coefficient **β**s are estimates by the method of partial log likelihood. However, when the goal is to prognosticate patient survival, there is a need for more flexibility in modeling the baseline survival.

An alternative to the CPH is the RP family of models that resembles the generalized linear models and can be viewed as a parametric extension Cox proportional hazard models [12]. The models are framed to rely on the transformation g(.), such that $g(S(t;x)) = g(S_0(t)) + x\beta$. The transformation g(.) can be either from the proportional hazard, proportional odds, Aranda-Ordaz or probit families [12]. We did not consider the Aranda-Ordaz family in this study due to possible interpretational difficulties [12]. Under the proportional hazard link function, the hazard ratio estimates are nearly identical to those estimated under CPH. The attractive feature of the RP baseline

survival function is that its shape is preserved, but the location of the baseline distribution function can vary, which allows for flexible model recalibration. Also, the estimate $g(S_0(t))$ is implemented on log-time scale. It is generally gently curved and smooth, making survival estimates more accurate.

In the RP framework, if the proportional hazard assumption is violated, the probit-link function $g(s) = -\Phi^{-1}(s)$ can be applied, where $\Phi^{-1}(.)$ is the inverse standard normal distribution function. The baseline survival function $S_0(t)$ is approximated and smoothed by a restricted cubic spline function with m interior knots. Splines are piecewise polynomials that ensure the overall curve is smooth (see Royston and Parmar [12] for details). Spline-based survival models such as RP have been empirically shown to be superior when the proportional hazard assumption is violated[28]. The optimal number of knots and the comparison among different RP models can be found using the minimum combination of Akaike Information Criterion (AIC) Bayes Information Criterion (BIC) and explained variation statistic R^2[29,30]. The AIC is defined in the usual manner as - 2Log(likelihood) + 2(No. of model parameters), while BIC equals - 2Log(likelihood) + (No. of model parameters)*Log(n). In survival analysis n is interpreted as the number of events rather than the number of patients.

We compared RP and CPH by performing internal validation (assessing validity in the population where the development data originated from) on the whole data set (naïve) and using split-sample cross-validation. We performed 10-fold cross-validation by splitting the data into development and validation sets and repeating the process 20 times. The methods can be readily implemented in Stata [31,32] statistical software using the *stpm*[29] and *stpm2*[33] commands, or in open source statistical software R as *flexsurv* package[34].

Assessment of model performance

Model performance is the ability of the estimated risk score to predict survival and is assessed using the measures of explained variation, calibration, and discrimination. Calibration refers to how closely the predicted survival at a pre-specified time agrees with the observed survival. For cross-validation,

we compared the average fitted probabilities of survival under RP and CPH for the first 15 days to observed probabilities estimated non-parametrically using Kaplan-Meier curves[35].

The Brier score is a quadratic scoring rule that calculates the differences between the actual outcomes and predicted probabilities[36]. Given the predicted probability of survival p_i at time t for patient i, and Y_i binary (0-1, dead-alive) variable, the Brier score is defined as $\sum_i(Y_i\,(1-p_i)^2 + (1-Y_i)\,p_i^2)$. A Brier score of 0 indicates a perfect model, while 0.25 indicates a non-informative model (the value achieved when issuing a predicted probability of 50% to each patient). The Brier score may be scaled by its maximum $Brier_{max} = (1 - mean(p_i))\,mean(p_i)$ to obtain $Brier_{scaled} = \left(1 - \frac{Brier}{Brier_{max}}\right)100\%$. The scaled Brier scores range from 0% to 100% and have interpretation similar to the Pearson correlation coefficient[37].

For a particular risk score, discrimination is the ability to differentiate between the patients who died versus those who survived. The Kaplan-Meier plot of survival for patients in different risk groups can be used to test for separation, indicating that the different risk groups are well defined[38]. For a statistical model, the global measure of the model's discriminatory power is the explained variation statistic R^2, which measures the variation explained by the fitted model[39]. Higher values of R^2 indicate greater discrimination. In this study we implement R^2 for survival models, as described by Royston and Sauerbrei[40].

The discrimination or Yates slope is a measure of how well the subjects with and without the outcome are separated. It is defined as the absolute difference in mean predictions of survival (mean[p_i]) between those who died and those who survived at time t[2]. The scaled Brier scores and discrimination slopes were calculated separately for the (naïve) model using the whole dataset and the model derived using cross-validation.for t = 1, 2… 100 days. Higher scaled Brier scores and discrimination slopes represent better model performance.

All statistical calculation were performed using Stata version 11.2[31,32].

III.   RESULTS

Description of the data source

The patient characteristics of the retrospective cohort are summarized in Table 1. The cohort consisted of 293 males (49.7%) and 295 females (50.0%), and 2 (0.3%) with unknown gender. The data were collected starting from patients' entry into hospice care until death for all 590 patients. The mean, median and range of survival times for the patients by PPS at admission, age, gender, cancer status, and diagnosis category are given in Table 2. The table shows that the median survival was fairly evenly distributed across age groups and gender, but unevenly across the cancer status and initial diagnosis category. All patients were assigned PPS at the time of admission to hospice care. Since PPS score of 0% means that the patient is dead, the data were transformed so that the PPS score of 10% was set as the baseline. There were only 15 total observations for PPS = 60%, 70%, 80%, so they were combined with PPS = 50% to obtain meaningful survival estimates. Fourteen patients had missing values for PPS.

The time of admission was the starting point for survival time. The Kaplan-Meier curves stratified by initial PPS level are shown in Figure 1. The curves show good separation indicating that the different risk groups are well defined. The log-rank test for equality of survival curves was highly significant at P = 0.0001. The global test based on Schoenfeld residuals showed that the proportional hazard assumption was violated for PPS (P-value<0.001), which can also be seen from the un-parallel log-plot of survival curves (Figure 2).

Table 3 lists AIC, BIC and R^2 values for 5 knots under the proportional hazard, proportional odds and probit RP families; the minimum combination in each underlined. The number of optimal knots was found to be m=1 under the probit model. The improvement in fit with the probit model can be seen from the parallel survival curves of log-probit against log time (Figure 3).

R^2 was higher in the RP model (R^2 = 0.298; 95% CI: 0.236-0.358) than the Cox model (R^2 = 0.156; 95% CI: 0.111-0.203), indicating that the RP model explained significantly more variation than CPH. To illustrate the differences for the baseline function, Figure 4 shows plots of the CPH and RP

baseline survival functions. The CPH baseline survival is "choppy" to approximately day 12, while the RP is smooth. The two baseline functions converged at around day 12.

Cross-validation showed that the relation between the two predicted survival estimates is approximately linear, with RP model consistently estimating a higher probability, which is particularly evident for higher scores of PPS corresponding to longer survival times (Figure 5). Overall, the predicted probabilities under RP tended to be closer to the Kaplan-Meier estimates than CPH. The plot of the consistently positive differences between RP and CPH scaled Brier scores and discrimination slopes showed that the RP model discriminated better across patient survival times for both the full (naïve) (Figure 6a) and cross-validated models (Figure 6b). This suggested that the higher value of R^2 under RP was not due to over-fitting.

IV.   DISCUSSION

The results from our study show that RP family of models predicts survival more accurately than CPH through its flexible modeling of the baseline survival function. Using the RP flexible baseline function modeling would allow for more precise calibration in the prognostication phase than CPH. As Figure 5 illustrates, the predicted RP survival probabilities are consistently higher for higher values of PPS, and closer to the Kaplan-Meier estimates of survival. We suspect that both the robust modeling of baseline survival and overall model fit provide for better survival estimation.

There are limitations to our study, the primary one being the use of retrospective data. The RP family of parametric functions needs to be applied prospectively to assess accuracy of prognostic models through external validation. Furthermore, the dataset was limited to the hospice setting with no censored observations with majority of patients having a very short follow-up time. For future studies, application of the proposed methodology should account for these limitations, and comparisons with parametric prognostic survival models should be explored.

The flexible models discussed in this paper could greatly improve the ability of researchers to accurately predict survival. An advantage of RP is that it can be used to validate published models for which the original individual patient data are unavailable. If the scale used (hazard, probit or odds), the knot positions, and the estimates of prognostic indices are known, then it would be possible to use RP. In the case of CPH this is not possible, since the baseline function would not be available.

V.   ACKNOWLEDGMENT

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Figure Legends

Figure 1. Kaplan-Meier survival curves by initial PPS.

Figure 2. Test of proportional hazards assumption under CPH for initial PPS.

Figure 3. Test of the probit assumption under probit RP for initial PPS.

Figure 4. Baseline survival functions under CPH and RP models.

Figure 5. Predicted probabilities under RP, and Cox models, plotted against the Kaplan-Meier estimates of survival in the validation set.

Figure 6. Difference between Scaled Brier scores (6a) and discrimination slopes (6b) under RP and Cox full (naïve) and cross-validated models, as a function of patient survival times. Both are consistently higher for RP indicating better discrimination under both naïve and cross-validated models.

Table1. Patient Characteristics

Variable	Result
Total no. of patients	590 (100%)
Age at Treatment	
<45	37 (6.3%)
45-64	187 (31.7%)
65-74	110 (18.6%)
75-84	129 (21.9%)
85+	127 (21.5%)
Gender	
Male	293 (49.7%)
Female	295 (50%)
Unknown	2 (0.3%)
No. of patients with cancer/noncancer	
Noncancer	363 (61.5%)
Cancer	227 (38.5%)
Diagnosis category for cancer	
Brain	10 (1.7%)
Gastrointestinal	35 (5.9%)
Genital-female	12 (2%)
Genital-male	12 (2%)
Head and neck	8 (1.4%)
Hematopoietic	10 (1.7%)
Pancreas	25 (4.2%)
Respiratory	49 (8.3%)
Skin	2 (0.3%)
Urinary	4 (0.6%)
Other	61 (10.3%)
Diagnosis category for noncancer	
AIDS	12 (2%)
Cardiovascular	74 (12.5%)
Neurological	69 (11.7%)
Respiratory	37 (6.3%)
Other	118 (20%)

Table 1. Patient Characteristics

Table2. Survival time by age, gender, diagnosis and intitial PPS

Variable	Survival Times (in Days)		Range	No. of Patients (%)
	Mean (95% CI)	Median (95% CI)		
Total no. of patients				
Overall	14 (12, 17)	6 (5, 6)	1-371	590
Age at Treatment				
<45	15 (8, 22)	8 (4,12)	1-95	37 (6.3%)
45-64	14 (11, 17)	7 (5, 9)	1-114	187 (31.7%)
65-74	14 (8, 20)	5 (4, 6)	1-271	110 (18.6%)
75-84	14 (8, 20)	6 (5, 7)	1-371	129 (21.9%)
85+	15 (9, 21)	5 (4, 6)	1-313	127 (21.5%)
Gender				
Male	14 (10, 18)	6 (5, 7)	1-371	293 (49.7%)
Female	15 (11, 19)	6 (5, 7)	1-271	295 (50%)
No. of patients with cancer/noncancer				
Noncancer	12 (8, 16)	5 (4, 6)	1-371	363 (61.5%)
Cancer	17 (14, 20)	9 (7, 11)	1-113	227 (38.5%)
Diagnosis category for cancer				
Brain	27 (16, 39)	28 (14, 42)	3-55	10 (1.7%)
Gastrointestinal	21 (14, 29)	11 (5,17)	1-82	35 (5.9%)
Genital-female	15 (6, 24)	8 (1, 15)	2-55	12 (2%)
Genital-male	26 (7, 45)	13 (4, 22)	1-100	12 (2%)
Head and neck	10 (2, 18)	5 (1, 9)	1-36	8 (1.4%)
Hematopoietic	4 (2, 6)	3 (1, 5)	1-10	10 (1.7%)
Pancreas	18 (7, 29)	7 (3, 11)	1-113	25 (4.2%)
Respiratory	15 (10, 20)	10 (7, 13)	1-71	49 (8.3%)
Skin	11	11	11-11	2 (0.3%)
Urinary	25 (1-58)	9 (1-39)	4-76	4 (0.6%)
Other	17 (12, 22)	9 (5, 12_	1-103	61 (10.3%)
Diagnosis category for noncancer				
AIDS	18 (3, 33)	8 (1, 15)	1-85	12 (2%)
Cardiovascular	14 (5, 23)	5 (3, 7)	1-271	74 (12.5%)
Neurological	8 (5, 11)	5 (4,6)	1-77	69 (11.7%)
Respiratory	25 (1, 49)	3 (1, 5)	1-371	37 (6.3%)
Other	11 (1, 15)	5 (4, 6)	1-174	118 (20%)
Initial PPS Score				
PPS 10%	5 (3, 7)	3 (2, 4)	1-77	188 (32.6%)
PPS 20%	16 (8, 24)	5 (4, 6)	1-371	125 (21.7%)
PPS 30%	15 (11, 19)	7 (5,9)	1-140	123 (21.4%)
PPS 40%	24 (18, 30)	14 (11, 17)	1-147	96 (16.7%)
PPS 50-80%	28 (21, 35)	18 (9, 27)	1-76	44 (7.6%)

Table 2. Survival Time by Age, Gender, Diagnosis and Initial PPS.

Table 3. Choice of scale

No. of knots m	PH	PO	Probit
	AIC, BIC, R^2	AIC, BIC, R^2	AIC, BIC, R^2
0	$2033, 2042, 0.156$	$1887, 1896, 0.321$	$1872, 1881, 0.295$
1	$1889, 1902, 0.178$	$1883, 1896, 0.322$	$\underline{1858, 1871, 0.298}$
2	$1871, 1888, 0.170$	$1870, 1887, 0.312$	$1857, 1874, 0.296$
3	$1870, 1892, 0.172$	$1870, 1892, 0.311$	$1858, 1880, 0.297$
4	$\underline{1865, 1892, 0.171}$	$\underline{1865, 1891, 0.310}$	$1855, 1881, 0.296$
5	$1866, 1896, 0.171$	$1865, 1896, 0.309$	$1856, 1886, 0.296$

Table 3. Choice of scale under RP proportional hazard, proportional odds and probit models.

Figure 1
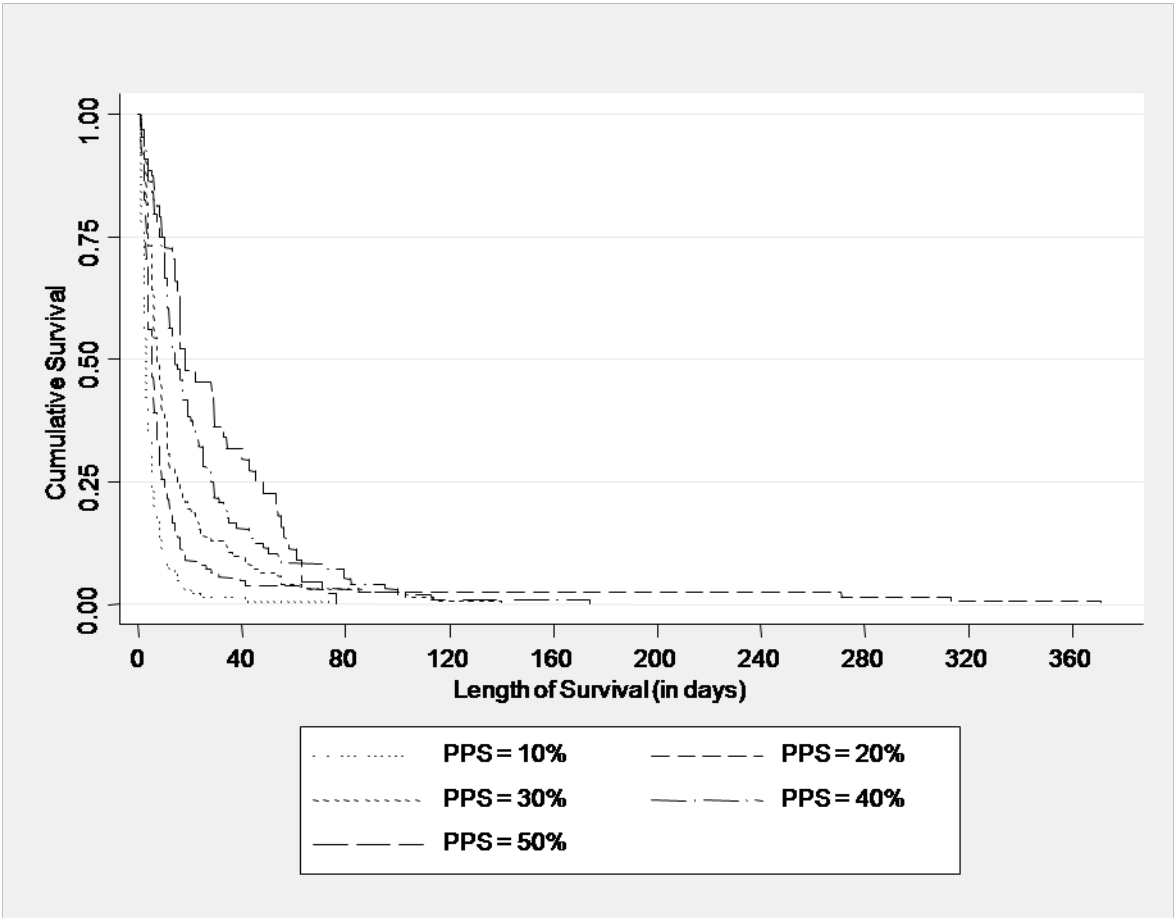
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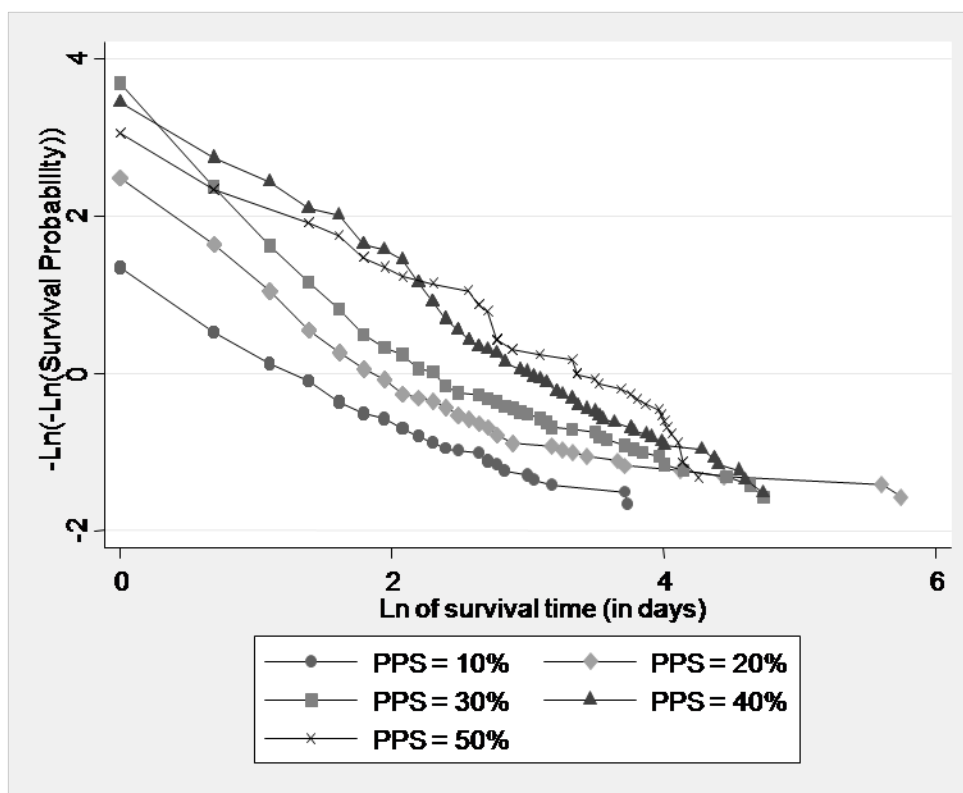
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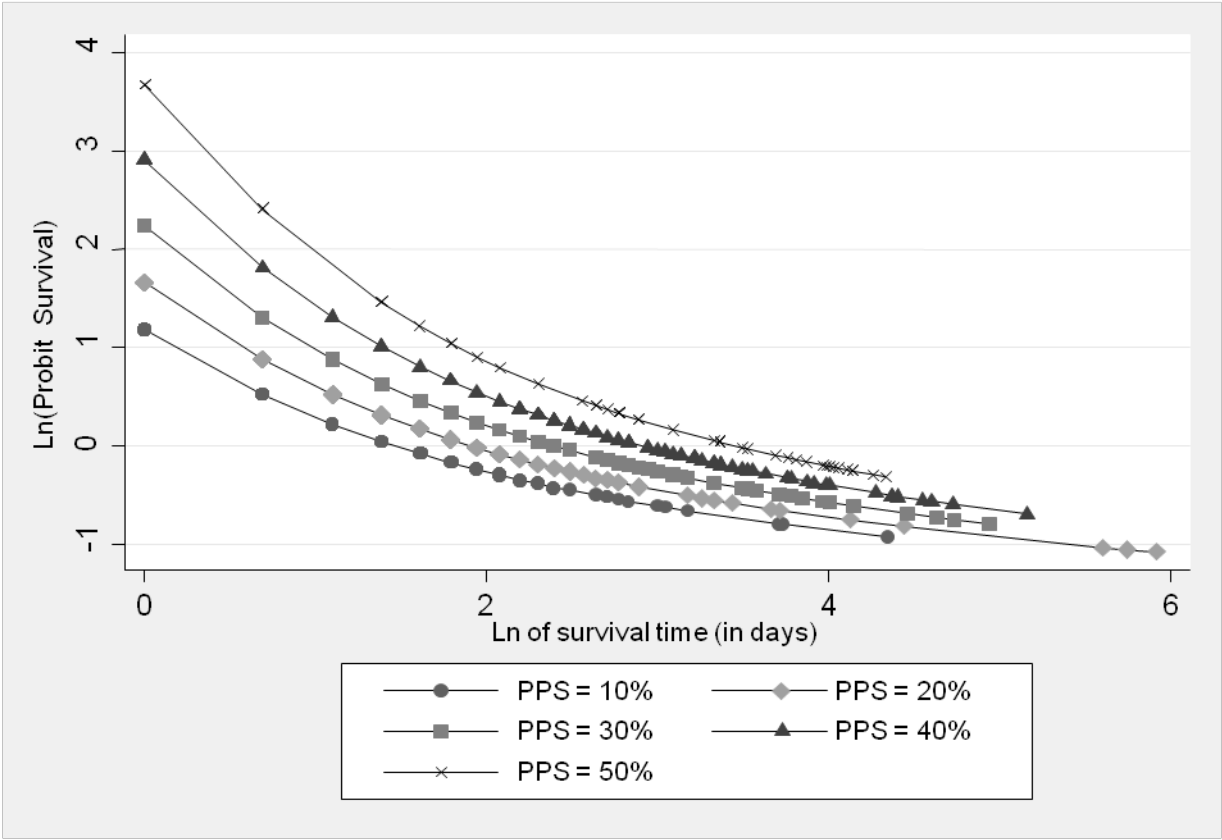
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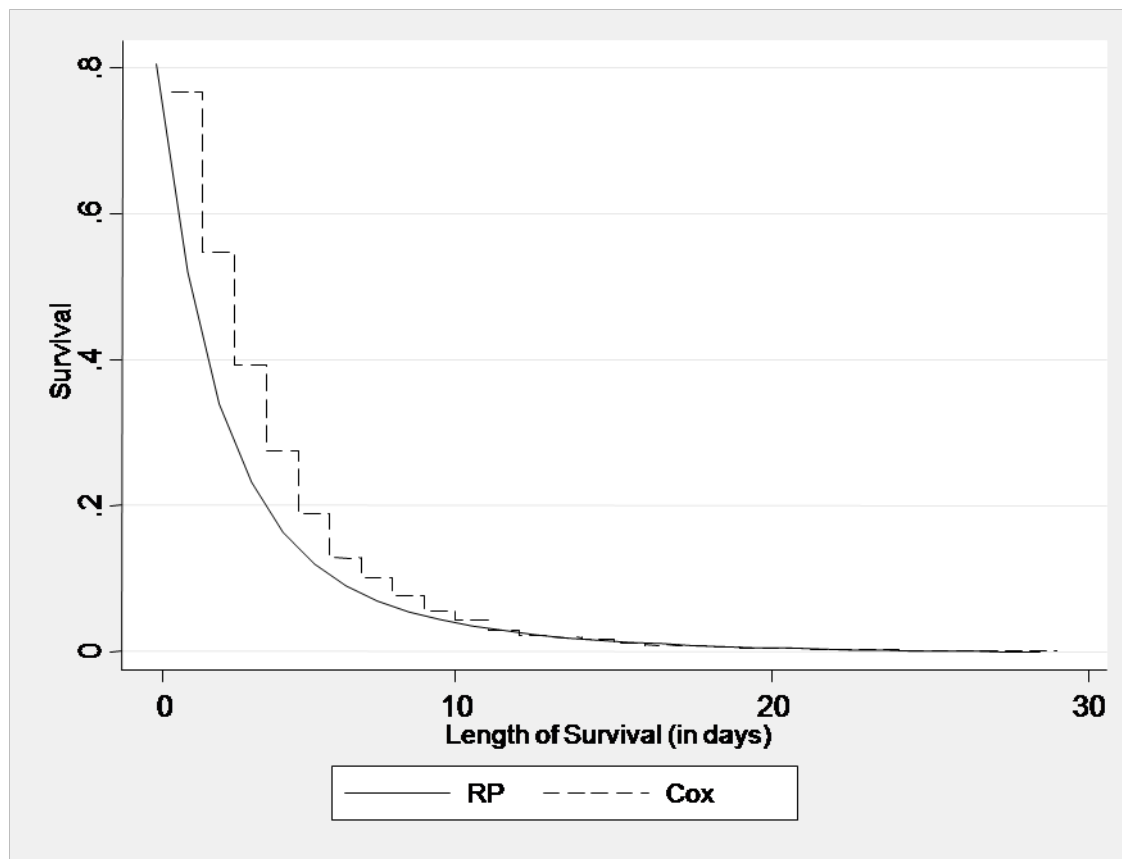
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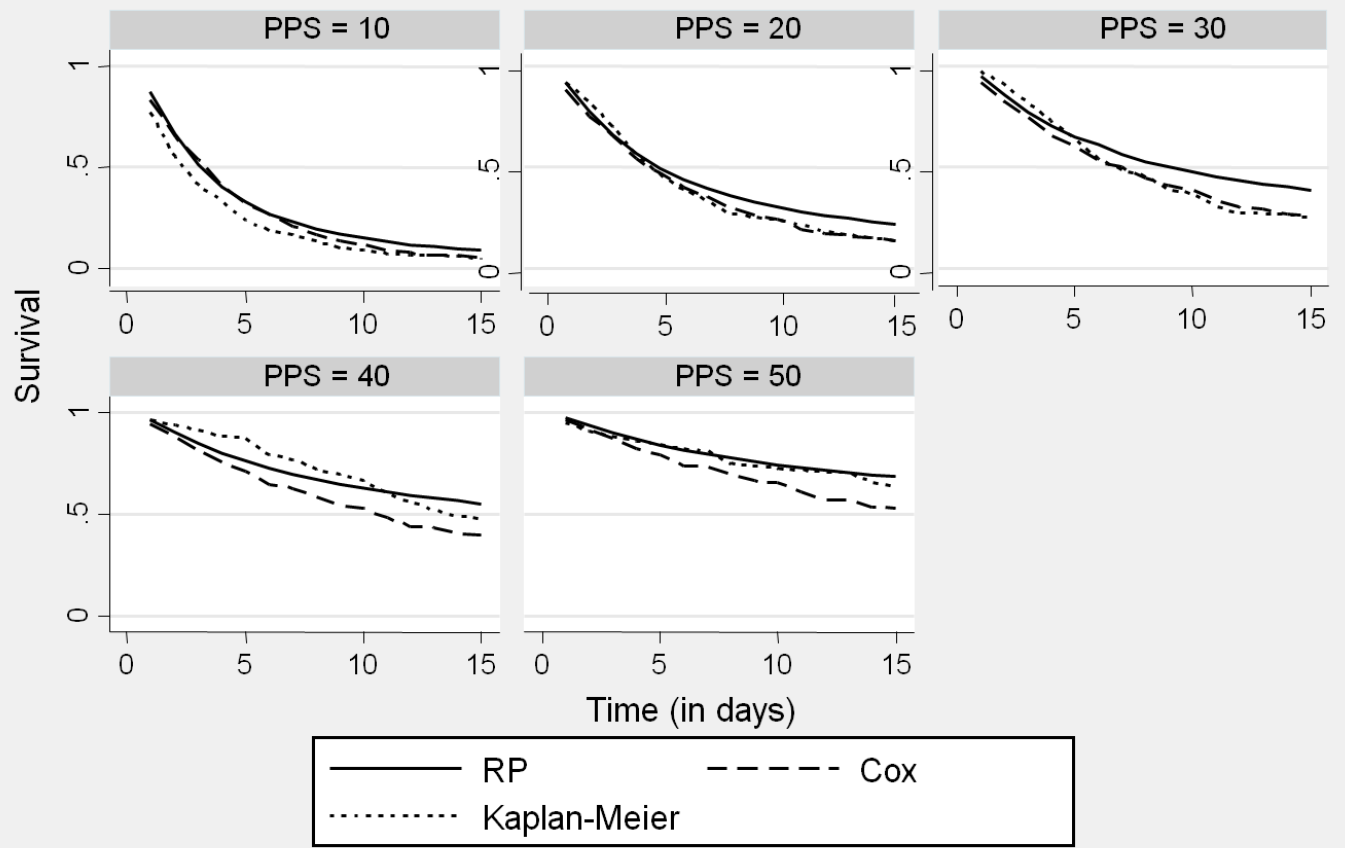
Figure 6

Appendix 3
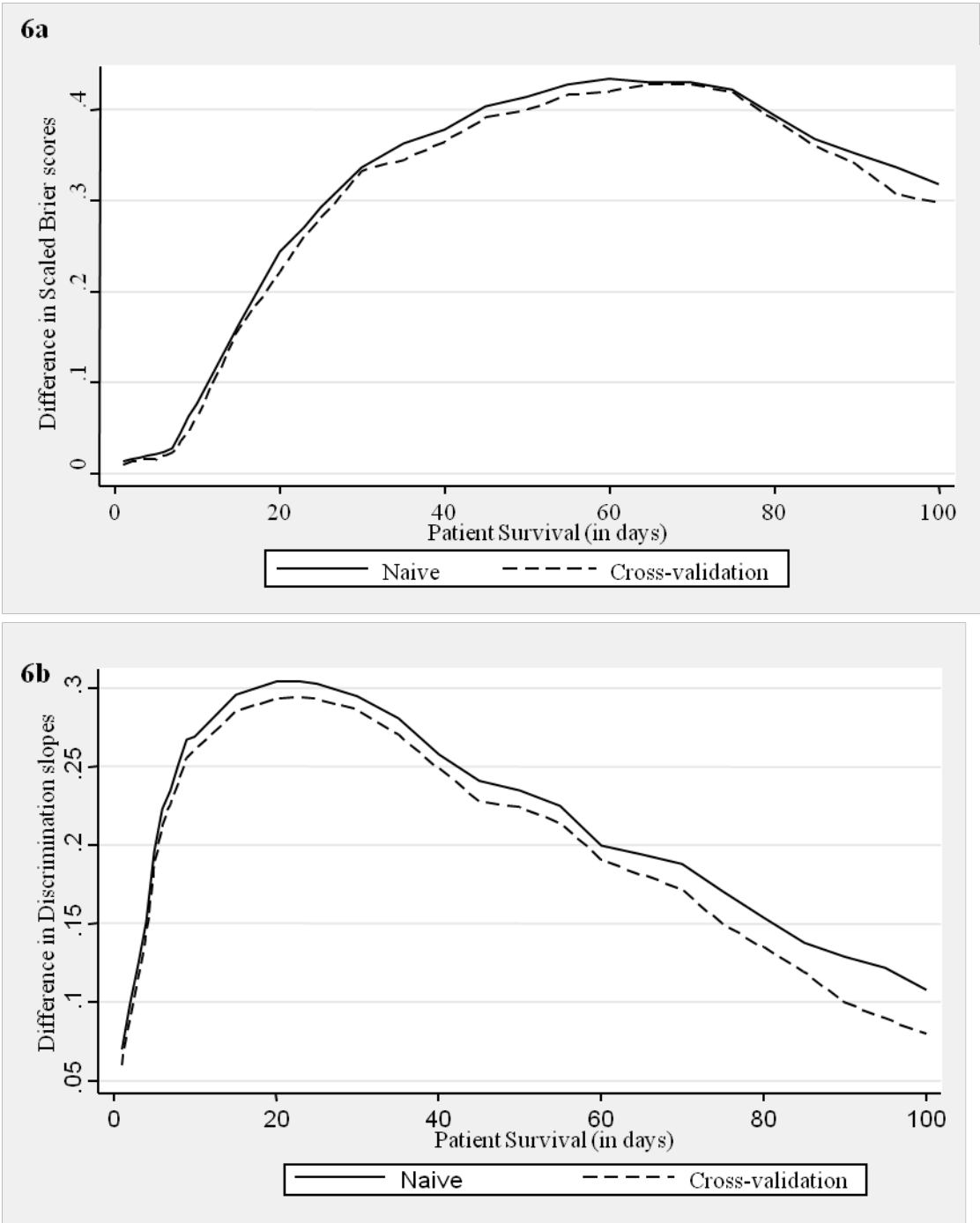
Natural History of Patients With Lung Cancer Without Treatment: A Systematic Review

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ABSTRACT

Purpose: To conduct a systematic review and meta-analysis of the natural history of patients with confirmed diagnosis of lung cancer without active treatment.

Methods: Relevant studies were identified by search of MEDLINE (PubMed) and CENTRAL electronic databases and abstract proceedings up to June 2011. All prospective or retrospective studies assessing prognosis of lung cancer patients without treatment were eligible for inclusion. Data on mortality was extracted from all included studies and pooled proportion of mortality was calculated as a back-transform of the weighted mean of the transformed proportions, using the random-effects model.

Results: Seven cohort studies (4,418 patients) and 15 randomized controlled trials (1,031 patients) were included in the meta-analysis. All studies assessed mortality without treatment in patients with non-small cell lung cancer (NSCLC). The pooled proportion of mortality without treatment in cohort studies was 0.97 (95% CI: 0.96 to 0.99) and 0.96 in randomized controlled trials (95% CI: 0.94 to 0.98) over median study periods of 8 and 3 years, respectively. The pooled proportion of mortality was 0.97 (95% CI 0.96 to 0.98) when data from cohort and randomized controlled trials were combined. Test of interaction showed a statistically non-significant difference between subgroups of cohort and randomized controlled trials. Overall the studies were of moderate methodological quality.

Conclusion: Systematic evaluation of evidence on prognosis of NSCLC without treatment shows that mortality is very high. Although limited by study design, these findings provide the basis for future trials to determine optimal expected improvement in mortality with innovative treatments.

INTRODUCTION

Cancer is a major public health concern globally. It is the most frequent cause of death in

economically developed countries.[1] Among all cancers, lung cancer is the leading cause of cancer

deaths worldwide. [2] In the United States, approximately 221,130 new cases of lung cancer (14% of all cancer diagnoses) are expected in 2011 out of which 156,940 deaths (27% of cancer deaths) are estimated due to lung cancer.[3] Given the incurative nature of lung cancer, it is considered a terminal illness with a 5-year survival rate of approximately 16% .[3]

Patients diagnosed with terminal illness such as lung cancer confront several decisions related to management of the disease. Opting for treatment (e.g. chemotherapy, radiotherapy, or surgery) instead of palliation or vice versa is one such critical decision. Depending on the stage of the disease, potential benefits of anticancer therapy intended to palliate specific tumor-related symptoms may be at the expense of treatment-related harms and the inconvenience associated with undergoing treatment. Other times, palliative care (e.g. pain medications or low dose radiotherapy)[4] rather than anticancer therapy may be preferable. Informed decision related to management of a terminal disease thus requires accurate prognosis of the disease with or without treatment.

Briefly, prognosis refers to the likelihood of an individual developing a particular health outcome over a given period of time, based on the individual's clinical and non-clinical profile.[5] Accurate assessment of prognosis is key to informed decision making. For example, if a patient is diagnosed with a terminal illness such as lung cancer, a prognostic question of critical concern to the patient, family, and the physician is how long the patient is expected to live. Other important outcomes may include disease progression, health-related quality of life, and treatment-related harms. Reliable prognostication of life expectancy can prevent subjecting patients to costly and unnecessary treatment for an unduly long period before transitioning to hospice care.[6] This in turn can help patients and their families prepare for the impending events and plan for the patient's remaining lifespan.[7] Accurate prognostic information can also help physicians decide on choice of curative versus palliative treatments. For instance, if evidence shows no effect of curative treatment on disease progression, significant treatment-related harms can be avoided in favor of palliative treatments.[7]

Accurate disease prognosis thus underpins all management decisions related to the disease including choice of treatment, planning of supportive care, as well as allocation of resources.

Despite the significance of disease prognosis in clinical decision-making, systematic assessment of prognosis in patients with lung cancer without treatment has not been performed. We are aware of only one narrative review on the subject.[8] Accordingly, this systematic review was undertaken to assess the natural history of patients with confirmed diagnosis of lung cancer without active treatment. Specifically, our aim was to estimate overall survival (natural history) in lung cancer when no anticancer therapy is provided.

METHODS

This systematic review was conducted as per the methods elaborated in a protocol that was developed *a priori.* An ideal study design to assess natural history of a terminal disease such as lung cancer is a cohort study. Specifically, an inception cohort whereby a well-defined group of patients at the same disease stage is assembled at first diagnosis and followed for a defined period of time.[9-11] However, given the availability of treatments for lung cancer in recent years, it would be unethical and logistically challenging to conduct such a study. An alternative approach is to assess prognosis from retrospective lung cancer registries, case series or from the control arm of individual RCTs that compare active treatment with either no treatment or placebo or best supportive care.[5,12] Thus, in this review, any retrospective or prospective cohort study assessing prognosis in lung cancer without treatment and any RCT assessing the role of treatment versus no treatment, were eligible for inclusion. A study was eligible for inclusion irrespective of language or publication type.

Search Strategy

We conducted a systematic search of PubMed and Cochrane library electronic databases, proceedings of major scientific meetings, and bibliographies of eligible studies to identify all relevant studies. To retrieve lung cancer prognosis studies in PubMed, we employed search strategies suggested by Wilczynski[13] that optimizes search sensitivity and specificity. Search details used

included: ("lung neoplasms"[MeSH Terms] AND "prognosis"[All Fields] AND "cohort"[All Fields] AND ("mortality"[Subheading] OR "natural course"[All Fields] OR "mortality"[All Fields] OR "survival"[All Fields] OR "survival"[MeSH Terms]).

To retrieve RCTs in PubMed, we employed strategies suggested by Haynes[14] with the following search details: ("lung neoplasms"[MeSH Terms] AND ("randomized controlled trial"[Publication Type]) AND ("palliative care"[All Fields] OR "hospice care"[All Fields] OR "supportive care"[All Fields] OR "best supportive care"[All Fields] OR "placebo"[All Fields] OR "symptomatic treatment"[All Fields] OR "no chemotherapy"[All Fields] OR "no treatment"[All Fields]).

In the Cochrane library, we utilized a free text search using the term "Lung cancer" to identify RCTs focusing on lung cancer. We manually searched abstracts of the American Society of Clinical Oncology (ASCO) and American Society of Hematology (ASH) meetings and utilized the snowballing procedure to identify other relevant studies. Studies published until June 2011 were included. No restrictions were made regarding the language of the publication.

Inclusion and Exclusion Criteria

A prospective or retrospective cohort study assessing overall survival as an outcome in lung cancer patients without treatment was eligible for inclusion. A RCT was included if it enrolled patients with confirmed diagnosis of lung cancer, compared treatment versus no treatment (e.g. supportive care, best supportive care, palliative care, placebo etc.), and assessed overall survival as an outcome.

A study in which patients had anticancer treatment prior to enrollment and subgroup analyses were excluded. Additionally, RCTs comparing two active treatments were excluded. Two reviewers read the titles and abstracts of identified citations to identify potentially eligible studies. Full text of potentially relevant reports were retrieved and examined for eligibility. Disagreements about study inclusion or exclusion were resolved via discussion until a consensus was reached.

Data Extraction

Data extraction was performed using a standardized data extraction form. Two reviewers independently extracted the following information from each included study: number of patients enrolled, number of deaths, median survival, funding source (industry versus public etc.), type of centers involved (single versus multicenter etc.), patient demographics, patients baseline clinical characteristics, and type of control arm (for RCTs only). For cohort studies, we extracted data on the number of deaths and total number of patients diagnosed with lung cancer. For RCTs, we extracted data on the number of deaths (all-cause mortality) and number of participants randomized to the control arm.

Assessment of Methodological Quality

To evaluate the methodological quality of included studies, a modified checklist of predefined criteria was developed on four methodological domains pertinent to minimization of bias. This modified checklist uses applicable elements from existing tools (Quality in Prognosis Studies tool,[15] Evidence-Based Medicine Group criteria for prognostic studies,[16] Newcastle-Ottawa Quality Assessment Scale,[31] and Cochrane Collaboration risk of bias criteria[17]) and related studies (Hudak et al[18] and Altman[19]). The four domains included *participation bias* (extent to which study sample represents the population of interest on key characteristics), *attrition bias* (extent to which loss to followup of the sample was not associated with key characteristics), *outcome measurement* (extent to which outcome of interest is adequately measured in study participants), *data analysis* and *reporting* (extent to which statistical analysis and data reporting are appropriate for the study design). The modified checklist contains 11 items for cohort studies and 14 items for RCTs. For each item, a study either fulfilled a certain criterion (scored "Yes") or failed to fulfill the criterion (scored "No"). To assess methodological quality of studies included, we focused on proportion of studies that fulfilled each quality criterion (Table 2).

Statistical Analysis

Data synthesis was conducted according to the study design separately as well as combined in the final stage (i.e., retrospective cohort and RCT).

For the purpose of meta-analysis, we used methods by Stuarts et al[20] to transform the proportions into a quantity according to the Freeman-Tukey variant of the arcsine square root transformed proportion. The pooled proportion was calculated as a back-transform of the weighted mean of the transformed proportions, using the random-effects model.

Heterogeneity of treatment effects between trials was assessed using the I^2 statistic[17] with the following thresholds for I^2 statistic values: low (25% to 49%), moderate (50% to 74%), and high ($\geq$ 75%).[21] We explored the potential causes of heterogeneity by assessing the differences between subgroups using the test of interaction. We assessed robustness of the results by conducting sensitivity analysis with respect to methodological quality criteria of reporting, study location, and funding source. RevMan Version 5.1[22] was used to perform the analyses.

RESULTS

Literature Search

A flow diagram of the literature search is shown in Figure 1. Initial search identified 1,562 potentially relevant citations excluding 71 duplicates. After initial screening of titles and abstracts, 1,489 records were not relevant for reasons depicted in Figure 1 and were excluded. Further assessment of full texts of remaining 73 studies led to exclusion of 51 studies. Altogether, 22 studies met the pre-defined inclusion criteria: 7 were retrospective cohort studies[23-29] and 15 were RCTs.[30-44]
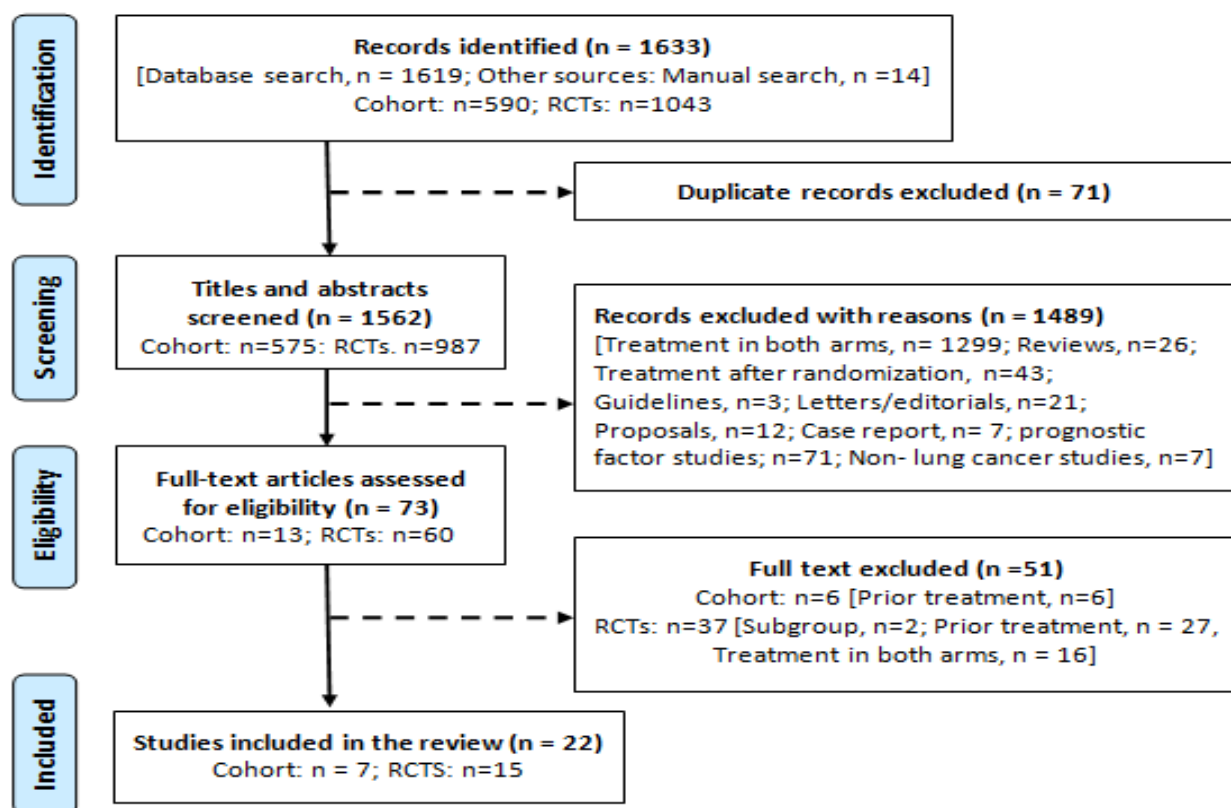
Figure 1 A flow diagram depicting the literature search process

Study Characteristics

We did not find any inception cohort study or a prospective cohort study assessing prognosis of patients with lung cancer without treatment. The seven retrospective cohort studies included 4,418 patients and the 15 RCTs enrolled 1,031 patients. Altogether, the 22 studies included 5,449 patients. All studies assessed prognosis in patients with NSCLC and were published between 1973 and 2009 (Table 1).

Cohort Studies: The median sample size in the cohort studies was 131 patients (range: 39 to 2,344 patients) with a median study period of 8 years (range: 5 to 13 years). Fifty-seven percent (4/7) and 29% (2/7) of the studies reported number of patients with stage I and stage II NSCLC, respectively. Forty-three percent (3/7) of the studies reported patients' cancer histology. Seventy-one percent (6/7) of the studies reported patient's gender. Forty-three percent (3/7) of the studies reported median age. Forty-three percent (3/7) of the studies were conducted at single institutions, 43% (3/7) were at multicenter national studies, and 14% (1/7) of the studies had unspecified study location.

Twenty-nine percent (2/7) of the studies were publicly funded, 14% (1/7) were funded by both public and industry, and 57% (4/7) had not specified funding sources.

RCTs: The median number of patients enrolled in the RCTs was 61 patients (range: 17 to 176 patients) with a median study period of 3 years (range: 1 to 7 years). Median follow-up was reported in 33% (5/15 of RCTs) and ranged between 2.7 and 43 months. Seventy-three percent (11/15) of the studies reported number of patients with stage III/IV NSCLC. Seventy-three percent (13/15) of the studies reported patients' cancer histology. Eighty-seven percent (13/15) of the RCTs reported patient's gender and median age. Twenty percent (3/15) of the RCTs were conducted at single institutions, 27% (4/15) were at multicenter national studies, 20% (3/15) were at multicenter international, and 33% (5/15) had unspecified study location. Seven percent (1/15) of the RCTs were funded by public, 33% (5/15) were funded by industry, 7% (1/15) were funded both public and industry, and 53% (8/15) had unspecified funding sources.

Types of control in RCTs: Three studies described *best supportive care* as comprising "symptomatic or palliative treatment excluding chemotherapy,"[45] "palliative radiotherapy, antibiotics, and corticosteroids,"[31] "palliative radiotherapy, opioid analgesics, and psychosocial support,"[38] or "radiation therapy, pain medication, nutritional and psychological support, thoracocentesis and/or tube thorascopy."[44] Three studies described *supportive care* as comprising "analgesics, an antitussive, relief of increased intracranial pressure, palliative radiotherapy, treatment of infections and pleural effusions,"[31] "symptomatic irradiation to involved fields,"[32] or "palliative radiation, analgesics, and psychosocial/nutritional support."[36] *Palliative care* consisted of "radiotherapy, antibiotics, coughs suppressants, and analgesics"[34] *Symptomatic treatment* included "glucocorticosteroids and anabolic steroids." [39] No descriptions were provided for *placebo* and "*no treatment*."

Table 1 Characteristics of studies included in the review

Study	N	Study period (years)	Disease Stage		Histology			Male	Median Age (years)
			I	II	squamous	adeno	large-cell		
(a) Cohort studies									
Raz 2007	1432	13	1432	NR	460	419	89	747	74

Study	N		III	IV					
Wisnivesky 2007†	2344	8	NR	NR	NR	NR	NR	1292	NR
Chadha 2005	39	11	23	13	18	88	5	4	77
Henschke 2003	131	7	131	NR	NR	NR	NR	NR	NR
McGarry 2002†	49	5	NR	NR	NR	NR	NR	49	NR
Vrdoljak 1994	130	7	55	56	61	35	34	120	60
Hyde 1973	293	8	NR	NR	NR	NR	NR	NR	NR
Total/[Range]	4418	[5-13]	1641	68	539	542	128	2211	
(b) RCTs			III	IV					
Goss 2009[m]	101	2 [0.23]	17	84	25	46	11	61	76
Anderson 2000	150	2	92	58	NR	NR	NR	91	64
ELVIS 1999 [m]	78	1 [1.08]	22	56	33	29	3	69	74*
Cullen 1999 [m]	176	8 [2.17]	88	88	103	42	6	122	64
Thongprasert 1999	98	4	49	49	31	49	12	NR	60
Helsing 1998 [m]	26	5 [3.33]	3	23	5	17	4	18	65
Cartei 1993	50	7	NR	50	25	17	8	36	57
Leung 1992 [m]	66	4 [3.58]	58	NR	31	18	7	48	62
Cellerino 1991	61	3	61	NR	38	18	5	59	62
Quoix 1991	22	3	NR	22	NR	NR	NR	NR	NR
Kaasa 1991	43	3	NR	43	16	16	11	31	62*
Ganz 1989	26	2	NR	26	9	17	NR	23	NR
Rapp 1988	50	3	50	NR	12	24	12	38	58
Cormier 1982	17	2	17	NR	8	2	6	16	60
Laing 1975	67	2	15	20	23	5	9	59	64
Total/[Range]	1031	[1-8]	472	519	359	300	94	671	[57-76]

Note: **N** = Sample size or number of participants enrolled; **NR**= data not reported; † = Sample includes stage I and II cancer; **adeno** = adenocarcinoma; **squamous** = squamous cell carcinoma; **large-cell** = large-cell carcinoma; *=we recorded mean age where median age was not reported or not extractable, **m** = median follow-up in parenthesis

Methodological Quality

Cohort: All seven cohort studies fulfilled 64% (7/11) of the quality criteria (Table 2). That is, adequate description of population of interest for key characteristics, adequate description of study setting/geographic location, adequate participation in the study by all eligible patients, reporting of patients with missing data, a priori and objective definition of outcomes, and presentation of frequencies of most important data (e.g., outcome) were reported in all studies. However, baseline sample was adequately described for key characteristics in 57% (4/7) of the studies, inclusion and exclusion criteria were adequately described in 71% (5/7) of the studies, follow-up was sufficiently long for outcome to occur in 86% (6/7) of the studies, and alpha error and/or beta error were specified *a priori* in 29% (2/7) of the studies.

RCTs: All 15 RCTs fulfilled 36% (5/14) of the quality criteria (Table 2). That is, adequate description of population of interest for key characteristics, adequate description of withdrawal (incomplete outcome data), a priori and objective definition of outcomes, and frequencies of most

important data were reported in all RCTs. However, study setting and geographic location were adequately described in 47% (7/15) of the RCTs, baseline sample was adequately described for key characteristics in 93% (14/15) of the RCTs, inclusion and exclusion criteria were adequately described in 93% (14/15) of the RCTs, patients were balanced in all aspects except the intervention in 93% (14/15) of the RCTs, follow-up was sufficiently long for outcome to occur in 53% (8/15) of the RCTs, proportion of sample completing the study was adequate in 60% (9/15) of the RCTs, characteristics of dropouts versus completers was provided in 13% (2/15) of the RCTs, alpha error and/or beta error was specified a priori in 47% (7/15) of the RCTs, and data analysis was based on intention to treat analysis principle in 53% (9/15) of the RCTs.

Table 2 Methodological Quality of Lung Cancer prognosis Studies

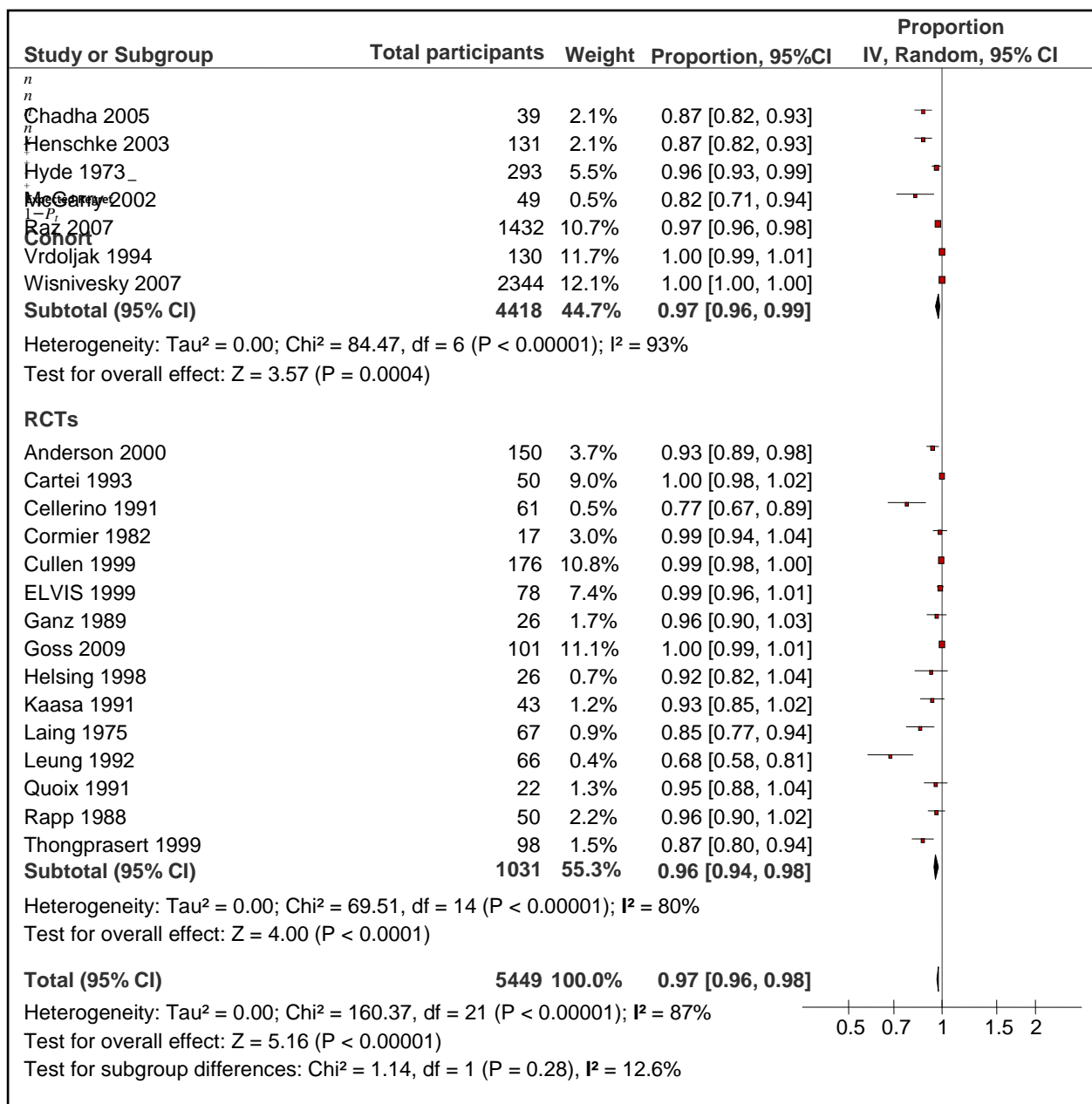| Study Design/Domain/Criterion	Criteria fulfilled	
	n/N	%
Cohort studies (11 items)		
Participation bias		
A Population of interest is adequately described for key characteristics[15]	7/7	100
B Study setting and geographic location is adequately described[15]	7/7	100
C Baseline sample is adequately described for key characteristics[15]	4/7	57
D Inclusion and exclusion criteria are adequately described[15]	5/7	71
E There is adequate participation in the study by all eligible patients[15]	7/7	100
Attrition bias		
F Follow-up is sufficiently long for outcome to occur ($\geq$ 6 months)[16,18,19,46]	6/7	86
G Patients with missing data were reported[15,17]	7/7	100
Outcome measurement		
H Definition of outcome is provided *a priori* [15]	7/7	100
I Objective definition of outcome is provided[15,16,18,19]	7/7	100
Data analysis and reporting		
J Alpha error and/or beta error is specified *a priori*	2/7	29
K Frequencies of most important data (e.g., outcomes) are presented[18,19,47]	7/7	100
Randomized Controlled Trials (15 items)		

	Participation bias		
L	Population of interest is adequately described for key characteristics[15]	15/15	100
M	Study setting and geographic location is adequately described[15]	7/15	47
N	Baseline sample is adequately described for key characteristics[15]	14/15	93
O	Inclusion and exclusion criteria are adequately described[15]	14/15	93
P	Patients were balanced in all aspects except the intervention	15/15	93
	Attrition bias		
Q	Follow-up is sufficiently long for outcome to occur (≥ 6 months)[16,18,19,46,48]	8/15	53
R	Proportion of sample completing the study is adequate (≥80%)[15,16,18,47,49,50]	9/15	60
S	Description of withdrawal (incomplete outcome data) is provided[15,17]	15/15	100
T	Characteristics of dropouts versus completers is provided[15]	2/15	13
	Outcome measurement		
U	Definition of outcome is provided *a priori*[15]	15/15	100
V	Objective definition of outcome is provided[15,16,18,19]	15/15	100
	Data analysis and reporting		
W	Alpha error and/or beta error is specified *a priori*	7/15	47
X	Data analysis was based on intention to treat analysis principle[17]	9/15	53
Y	Frequencies of most important data (e.g., outcomes) are presented[18,19,47]	15/15	100

Mortality

Cohort: Data on mortality was extractable from all seven cohort studies enrolling 4,418 patients. As shown in Figure 2, the pooled proportion of mortality for patients without anticancer treatment was 0.97 (95%CI: 0.96 to 0.99). There was a statistically significant heterogeneity among pooled cohort studies (I^2 =93%, P < 0.00001).

RCTs: Data on mortality was extractable from the control arm of all 15 RCTs (1,031 patients). Figure 2 shows that the pooled proportion of mortality for patients in the control arm (without active treatment) was 0.96 (95% CI: 0.94 to 0.98). There was a statistically significant heterogeneity among pooled control arm of RCTs (I^2 =80%, P < 0.00001).

Combined (Cohort and RCTs): Pooled proportion of mortality across the 22 studies

was 0.97 (95%CI: 0.96 to 0.98). Because these two designs are inherently different from

each other, we conducted separate analyses. However, as shown in Figure 2, test for

subgroup differences showed no statistically significant heterogeneity between the two study

designs (P = 0.28).

Study or Subgroup	Total participants n	Weight	Proportion, 95%CI	Proportion IV, Random, 95% CI
Chadha 2005	39	2.1%	0.87 [0.82, 0.93]	
Henschke 2003	131	2.1%	0.87 [0.82, 0.93]	
Hyde 1973	293	5.5%	0.96 [0.93, 0.99]	
McGarry 2002	49	0.5%	0.82 [0.71, 0.94]	
Raz 2007	1432	10.7%	0.97 [0.96, 0.98]	
Vrdoljak 1994	130	11.7%	1.00 [0.99, 1.01]	
Wisnivesky 2007	2344	12.1%	1.00 [1.00, 1.00]	
Subtotal (95% CI)	**4418**	**44.7%**	**0.97 [0.96, 0.99]**	

Heterogeneity: Tau² = 0.00; Chi² = 84.47, df = 6 (P < 0.00001); I² = 93%
Test for overall effect: Z = 3.57 (P = 0.0004)

RCTs				
Anderson 2000	150	3.7%	0.93 [0.89, 0.98]	
Cartei 1993	50	9.0%	1.00 [0.98, 1.02]	
Cellerino 1991	61	0.5%	0.77 [0.67, 0.89]	
Cormier 1982	17	3.0%	0.99 [0.94, 1.04]	
Cullen 1999	176	10.8%	0.99 [0.98, 1.00]	
ELVIS 1999	78	7.4%	0.99 [0.96, 1.01]	
Ganz 1989	26	1.7%	0.96 [0.90, 1.03]	
Goss 2009	101	11.1%	1.00 [0.99, 1.01]	
Helsing 1998	26	0.7%	0.92 [0.82, 1.04]	
Kaasa 1991	43	1.2%	0.93 [0.85, 1.02]	
Laing 1975	67	0.9%	0.85 [0.77, 0.94]	
Leung 1992	66	0.4%	0.68 [0.58, 0.81]	
Quoix 1991	22	1.3%	0.95 [0.88, 1.04]	
Rapp 1988	50	2.2%	0.96 [0.90, 1.02]	
Thongprasert 1999	98	1.5%	0.87 [0.80, 0.94]	
Subtotal (95% CI)	**1031**	**55.3%**	**0.96 [0.94, 0.98]**	

Heterogeneity: Tau² = 0.00; Chi² = 69.51, df = 14 (P < 0.00001); I² = 80%
Test for overall effect: Z = 4.00 (P < 0.0001)

| **Total (95% CI)** | | **5449** | **100.0%** | **0.97 [0.96, 0.98]** |

Heterogeneity: Tau² = 0.00; Chi² = 160.37, df = 21 (P < 0.00001); I² = 87%
Test for overall effect: Z = 5.16 (P < 0.00001)
Test for subgroup differences: Chi² = 1.14, df = 1 (P = 0.28), I² = 12.6%

0.5 0.7 1 1.5 2

Figure 2 Pooled proportion of mortality in lung cancer studies. The size of each square is

proportional to the weight of the study (inverse variance)

Sensitivity Analysis

To assess the robustness of overall results according to the study design (cohort vs. RCT) as well as

explore the reasons for observed heterogeneity in the pooled proportion of mortality, we conducted

additional sensitivity analyses. For both cohort studies and RCTs, we conducted sensitivity analyses

according to methodological quality criteria, funding source, and study location. For RCTs only, we conducted additional sensitivity analyses according to type of control. The results of sensitivity analyses are summarized in Figure 3. Overall, the results remained unchanged in the sensitivity analyses. There were no statistically significant differences in the proportion of mortality.

Cohort: In cohort studies, there was no statistically significant difference in the proportion of mortality according to any methodological criteria of reporting. With respect to study location, the pooled proportion of mortality in cohort studies conducted at multicenter national locations was 0.95 (95%CI: 0.89 to 1.01) and at single institution was 0.98 (95%CI: 0.95 to 1.01) whereas the pooled proportion of mortality in cohort studies conducted at unspecified locations was 0.87 (95%CI: 0.82 to 0.93). Test for overall interaction among these subgroups was statistically significant (P = 0.007). Regarding funding source, the pooled proportion of mortality in public-funded, unspecified funding sources, and public/industry-funded cohort studies were 1.00 (95%CI: 1.00 to 1.00), 1.00 (95%CI: 0.99 to 1.00), and 0.97 (95%CI: 0.96 to 0.98), respectively. The test for overall interaction among these subgroups was statistically significant (P < 0.0001).

RCTs: There was no statistically significant difference in the proportion of mortality according to methodological criteria of reporting, study location, and funding source. With respect to type of control, the pooled proportion of mortality in RCTs involving best supportive care, no treatment, placebo, supportive care, and symptomatic treatment as control were 0.90 (95%CI: 0.83 to 0.97) and in RCTs involving supportive care as control was 0.96 (95%CI: 0.92 to 1.00), 0.86 (95%CI: 0.81 to 0.92), 1.00 (95%CI: 0.99 to 1.01), 0.96 (95%CI: 0.92 to 1.00), and 0.97 (95%CI: 0.92 to 1.03), respectively. Test for overall interaction among these subgroups was statistically significant (P < 0.00001).

Subgroup	Number of studies/(participants)	Proportion, 95% CI	Proportion IV, Random, 95% CI
Study location (Cohort studies)			
Multicenter national	3/ (2768)	0.95 [0.89, 1.01]	
Single institution	3/ (1116)	0.98 [0.95, 1.01]	
Unspecified location	1/ (39)	0.87 [0.82, 0.93]	
Heterogeneity between sub-groups:I^2 = 80.1%			
Funding source (Cohort studies)			
Public	2/ (2637)	0.98 [0.95, 1.02]	
Public/Industry	1/ (1432)	0.97 [0.96, 0.98]	
Unspecified source	4/ (349)	1.00 [0.99, 1.01]	
Heterogeneity between sub-groups:I^2 = 94%			
Study location (RCTs)			
Multicenter international	3/ (329)	0.98 [0.95, 1.01]	
Multicenter national	4/ (313)	0.94 [0.88, 1.00]	
Single institution	3/ (163)	0.91 [0.86, 0.97]	
Unspecified location	5/ (226)	0.91 [0.84, 0.99]	
Heterogeneity between sub-groups:I^2 = 55.8%			
Funding source (RCTs)			
Industry	5/ (551)	0.97 [0.95, 1.00]	
Public	1/ (67)	0.85 [0.77, 0.94]	
Public/Industry	1/ (50)	0.96 [0.90, 1.02]	
Unspecified source	8/ (363)	0.95 [0.91, 0.99]	
Heterogeneity between sub-groups:I^2 = 57.6%			
Type of control (RCTs)			
Best supportive care	5/ (314)	0.90 [0.83, 0.97]	
No treatment	2/ (165)	0.86 [0.81, 0.91]	
Placebo	2/ (118)	1.00 [0.99, 1.01]	
Supportive care	4/ (215)	0.96 [0.92, 1.00]	
Symptomatic treatment	2/ (219)	0.97 [0.92, 1.03]	
Heterogeneity between sub-groups:I^2 = 87%			

0.01   0.1   1   10   100

Figure 3 Pooled Proportions of Mortality and Heterogeneity Between Subgroups

DISCUSSION

This is the first study to provide most comprehensive data related to natural history of lung cancer. The results show that prognosis of patients with lung cancer not receiving treatment is very high. Regardles of the study design (i.e. cohort versus RCTs) the findings were similar and did not differ according to disease severity. For example, all cohort studies assessed mortality in patients with early stage NSCLC (stage I/II) and all RCTs enrolled patients with advance stage NSCLC (stage III/IV). However, the mortality rates from cohort and RCTs essentially remained unchanged (97% vs 96%). Overall, included studies were of moderate methodological quality.

The findings from our study is similar to the study by Detterbeck and Gibson[4] which showed a 98% 5-year mortality rate for stage I/II lung cancer (median survival = 10 months). Despite the obvious similarity in results our study is significantly different in the conduct and analysis. For example, the study by Detterbeck and Gibson[4 4] did not employ a systematic approach to data collection and analysis (i.e. not a systematic review) and therefore the findings are not reproducible. The similarity in findings might be an artifact of play of chance. Furthermore, quantitative synthesis of results across included studies was not performed in the study by Detterbeck and Gibson[4] which was undertaken in our study. Another unique feature of our study lies in the inclusion of RCTs in addition to retrospective studies. None of the previous studies on the topic have utilized the approach of pooling data from one arm of RCTs for accurate assessment of prognosis. Therefore, due to the reasons enumerated here the study presented here is the most comprehensive to date reporting the natural history of lung cancer.

Our study has some limitations. For example, we observed a statistically significant heterogeneity in pooled results which we could not explain through subgroup analyses. We suspect that the observed heterogeneity is clinical and not methodological. Specifically in the case of RCTs, the constitution of control arm varied across pooled studies. For example, five RCTs employed best supportive care as control, four had supportive care, two had placebo, two had no treatment and another two had symptomatic treatment as control. While, the definitions are very clear on placebo

and no treatment, which was also explained by the sensitivity analyses (I^2 =0% for both subgroups), the composition of best supportive care, supportive care, and symptomatic treatment varied significantly across pooled studies. In these cases, the observed heterogeneity remained unexplained. The findings are also limited in terms of generalizability by the fact that all included studies enrolled patients with NSCLC due to which the results are not entirely applicable to all lung cancers. However, it is important to note that a systematic review is limited by the availability of data and we did include all available data related to prognosis of lung cancer patients without treatment.

Comprehensive data on the natural history of lung cancer is required for informed decision making by patients, physicians and researchers. For patients, it serves as the basis for their expected outcome with and without treatment, which is critical in cases of diseases with high mortality. For physicians, accurate and reliable information facilitates shared decision making with patients related to choice of interventions or no intervention. Most importantly, the findings are needed by researchers to avoid *optimism bias*.[51] Briefly, optimism bias refers to unwarranted belief in the efficacy of new therapies. A study by Djulbegovic et al. [51] assessed the role of optimism bias in a cohort of trials conducted by the National Cancer Institute Cooperative Groups and concluded that the optimism bias is the primary reason for inconclusive findings in the context of RCTs. Accordingly, the results from our study will help researchers determine the most optimal rate of expected improvement in mortality with innovative/newer treatments.

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Appendix 4

External validation of a web-based prognostic tool for predicting survival in patients in hospice care

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ABSTRACT

Prognostat is an interactive Web-based prognostic tool for estimating hospice patient survival based on a patient's palliative performance scale score, age, gender, and cancer status. The tool was developed using data from 5,893 palliative care patients collected at the Victoria Hospice since 1994. This study externally validates *Prognostat* on a retrospective cohort of 590 hospice patients in Lifepath Hospice Center, Florida, USA. The criteria used to evaluate the prognostic performance are the Brier score, area under the receiver operating curve, discrimination slope and Hosmer-Lemeshow goodness-of-fit test. Though the Kaplan-Meier curves show each PPS level to be distinct and significantly different, the findings reveal poor performance of the prognostic tool in our cohort of hospice patients. Before redeveloping a new prognostic model researchers are encouraged to combine survival estimates obtained using *Prognostat* with the information from their cohort of patients. To that end, *Prognostat* needs to explicitly report patient risk scores to be useful to clinicians.

Keywords: *Prognostat*, Survival prognostication, palliative performance scale, external validation

VI.   INTRODUCTION

Accurate prognostication of survival of patients in hospice care gives patients and their family members a vital opportunity to attend to matters such as planning, prioritizing, and preparing for death[1]. Predicting patient survival is a complex decision making process which is often affected by optimism or avoidance that may lead to poor prediction of life expectancy and overestimating survival at times by a factor of five[2]. Successful prognostication of patient survival depends on developing and testing prognostic models, which entails having accurate patient data for prognosis and selecting clinically relevant candidate predictors and measure(s) of model performance, usually in the context of a multivariable regression survival model[3]. This process produces patient performance scores that allow for classification of patients into different risk groups.

The usefulness and validity of a prognostic model is judged by how well it performs for patients that come from different centers[4]. Validating a prognostic model is generally accepted to mean that given a patient population it works in a data set other than the one which is used to develop

it [4, 5]. It is also generally accepted that the validation process should follow guidelines and that un-validated prognostic models should not be applied in clinical practice [6-8]. As the value of any prediction model is its generalizabilty to other groups of patients, our goal is to externally validate *Prognostat* [9], a Web-based interactive prognostic tool for estimating hospice patient survival, on a retrospective cohort of 590 hospice patients in Florida, USA. *Prognostat* gives estimates of survival based on the palliative patient's age, gender, diagnosis and palliative performance scale (PPS) score [10], which has been established as an accurate measure of patient survival in the palliative setting [11-15].

In the next section we discuss *Prognostat* and introduce the measures of model performance. Since predictive performance may decrease when Prognostat is tested in new patients compared to the performance estimated in the patients used to develop the model, we also discuss strategies for updating *Prognostat*.

VII.   METHODS

Study Sample and Survival Estimation using *Prognostat*

The patient data were obtained from the Lifepath Hospice and Palliative Care center, licensed since 1983 to serve in Hillsborough County, Florida. The data regarding 590 consecutive deceased patients was extracted starting January 2009 and going backwards. This study was a retrospective review of deceased patients' medical records and only data that pertained to outcomes was collected; personal information was not collected and the data were de-identified prior to analysis. The study was approved by the University of South Florida Institutional Review Board. Two research assistants extracted all data necessary to populate the model variables and two faculty members randomly checked 25% of the data for accuracy.

Prognostat is a web-based interactive prognostic tool developed at the University of Victoria using survival estimates of 5,893 palliative care patients collected at the Victoria Hospice starting in 1994. The variables or covariates found to be significant predictors of patient survival were the

patient's gender (male vs female), age group (19-44, 45-64, 65-74, 75-84, 85+), diagnosis (Lung Cancer, Breast Cancer, Colorectal Cancer, Prostate Cancer, Other Cancer, All Cancer, Non-cancer Illness) and PPS.

Palliative performonance scale was developed and reported by Anderson et al. [10] as a measure of functional status of patients receiving palliative care. The scale has 11 possible mutually exclusive levels, from PPS of 0% (the patient is dead) to PPS of 100% (the patient is ambulatory and healthy). Numerous studies have studied its prognostic accuracy of survival in a variety of settings and found it provides meaningful estimates of patient survival [11, 12, 14-20]. PPS has been found to be both valid and reliable[21].

Prognostat survival estimates were derived using the Cox proportional hazards (CPH) model. For a vector of covariates $\mathbf{x}$ and parameter vector $\boldsymbol{\beta}$, the survival function S ($\mathbf{t}$; x) for the CPH model is commonly expressed as

$$S(t; \mathbf{x}) = [S_0(t)]^{\exp(\mathbf{x}\boldsymbol{\beta})}$$

where S_0 ($\mathbf{t}$) is the baseline survival function, i.e. survival function when the all the covariates $\mathbf{x}$ are equal to zero. In the CPH framework, the estimation of the (linear) prognostic index $\mathbf{x}\boldsymbol{\beta}$ does not require the formulation of the baseline cumulative survival function S_0 (t), which itself can be estimated conditional on the covariate estimates using the Breslow and Kalbfleisch-Prentice estimators[22]. However, the full parametric estimation of S_0 ($\mathbf{t}$) is not possible, which makes prediction of baseline survival from the primary to the secondary data set not viable. At present, *Prognostat* does not explicitly report prognostic indices $\mathbf{x}\boldsymbol{\beta}$, which makes model calibration in other populations unfeasible.

Assessment of Model Performance

We analyzed *Prognostat's* predictive performance based on the ability of the estimated risk score to predict survival based on measures of accuracy, calibration and discrimination. Accuracy refers to the difference between the predicted probability of survival and observed patient survival. The Brier

score is a quadratic scoring rule that calculates the differences between the actual outcomes and predicted probabilities[23]. Given the predicted probability of survival p_i at time t for patient i, and Y_i binary (0-1, dead-alive) variable, the Brier score is defined as $\sum_i (Y_i (1 - p_i)^2 + (1 - Y_i) p_i^2)$. A Brier score of 0 indicates a perfect model, while 0.25 indicates a non-informative model (the value achieved when issuing a predicted probability of 50% to each patient). The Brier score may be scaled by its maximum $\text{Brier}_{max} = (1 - \text{mean}(p_i)) \text{mean}(p_i)$ to obtain $\text{Brier}_{scaled} = \left(1 - \frac{\text{Brier}}{\text{Brier}_{max}}\right) 100\%$ which has interpretation similar to the Pearson correlation coefficient[24].

Calibration refers to how closely the predicted survival at a pre-specified time agrees with the observed survival. Since calibration is essentially a test of fit, we also applied the Hosmer-Lemeshow (HL) test[25] on the dead versus alive binary outcome. The HL Chi-square statistic involves grouping of the observations (most commonly in deciles) based on the predicted probabilities and then testing the hypothesis that the difference between observed and predicted events is simultaneously zero for all the groups. This test is equivalent to testing the hypothesis that the observed number of events in each of the groups is equal to the expected number of events based on the fitted model. The higher the HL p-value, the better calibrated the model is. The HL calibration can be visually expressed by plotting deciles of predicted versus observed proportions of survival at each time point.

Discrimination is the ability of the model to differentiate between the patients who died versus those who survived at a pre-specified time. A rank order statistic commonly used to summarize discrimination with and without the outcome has been the area under the receiver operating curve (AUC)[26], which is a plot of the sensitivity (true positive rate) against 1 – specificity (false positive rate) for consecutive cutoffs of the probability of an outcome. The maximum value of AUC = 1 indicate a perfect prediction model, while a value of AUC = 0.5 indicates that 50% of the patients have been correctly classified (as good as by chance). As a rank order statistic, AUC is insensitive to errors such as difference in average survival.

The discrimination slope is a measure of how well the subjects with and without the outcome are separated. It is defined as the absolute difference in mean predictions of survival (mean[p_i]) between those who died and those who survived at time t[5]. In addition to the discrimination slope, we have assessed the extent to which survival differentiation at each time point is achieved using box plots. All statistical calculation were performed using Stata version 11.2[27]

VIII.   RESULTS

The patient characteristic of the retrospective cohort are summarized in Table 1. In addition to our cohort of 590 patients, in each column we present data information given in Prognostat (where reported) as a second cell entry. Even though the overall median survival times were not significantly different (6 vs. 8 days), the table shows significant discrepancies in the distribution of percentages for age and cancer status. There is also a significant discrepancy in the distribution of percentages and median survival times for PPS.

For our cohort, the Kaplan-Meier curves stratified by initial PPS level are shown in Figure 1. The curves show good separation indicating that the different risk groups are well defined. Fifteen patients with PPS score of 60% were dropped due to the crossing of the Kaplan-Meier estimate of PPS 50%. The log-rank test for equality of survival curves was highly significant at P = 0.001 for PPS and cancer status, but not for age and gender. Likewise, when adjacent categories of PPS were compared (PPS 10% vs 20%, 20% vs 30%,..etc), pair-wise log-rank tests were all significant at P = 0.05 level, except for PPS 40% vs PPS 50% (P =0.394), due to initial crossing of two survival curves and longer tail of the PPS 40% group. For our patients, the CPH model indicates that age and cancer status were not significantly related to the hazard for death. Patients who were 44 years old and younger did not have significantly lower hazard than other age groups, nor did male patients compared with females (Table 1).

The measures of accuracy, discrimination and calibration for days 1, 2, 4, 7, 14 and 30 are given in Table 2 and show poor performance of *Prognostat* overall. The discrimination slopes are low

and the HL p-values significant for all six days of measurement, and indicate poor calibration. In the HL calibration plot of predicted versus observed proportion of those who survived (Figure 2B) circles are mostly unaligned with the 45 degree line. They show that in our cohort of patients *Prognostat* consistently underestimates survival for days 1, 2, 4, 7 and 14, and overestimates for day 30. The larger circles indicate that these points are based on more data. The absence of circles in any given decile indicates that there were no predictions in that interval. The overlapping box plots (Figure 2A) confirm poor discrimination.

IX. DISCUSSION

In this manuscript we externally validated a web-based interactive prognostic tool *Prognostat* and found it performed poorly in our cohort of palliative patients. It is not uncommon for the predictive performance of a model to be decreased when it is tested in new patients compared to its performance in the cohort of patients used to develop the model, as patient populations will likely differ. This has been recognized in case of PPS possibly due to the differences in patient cohort characteristics, location of care, and misinterpretation regarding how to use the performance tool and the inter-reviewer discrepancy? [15, 28]. The difference between our cohort and the population used to develop *Prognostat* is pronounced for age at treatment, cancer status and PPS score.

However, instead of re-developing a new model, knowledge from previous studies should be used to update the existing prediction model using shrinkage and recalibration methods [29, 30]. The updating methods can range from adjustments of the baseline survival to adjustment of predictor weights using adjustment factors. This may entail re-estimating predictor weights and adding new predictors or removing existing predictors from the original model[7]. Ideally, the updated model should also be externally validated. For *Prognostat* to be useful to hospice and palliative care researchers, it should report explicit risk scores to be combined with new patient information, as well as guidance on how this should be done.

Prognostat is also restricted in the framework of the Cox proportional hazards model, especially due to the fact that it is impossible to directly model and report the baseline survival function. This is essential in calibrating survival estimates in a new population of patients. We have found that Royston-Parmar family of survival functions[31] is more accurate and flexible than the CPH model[32] by allowing for parametric modeling of the baseline survival function and relaxing of the proportional hazards assumption.

A limitation of our study is that it was confined to external validation of an existing model, which needs to be re-calibrated and tested prospectively on an independent data set from our patient population. Without explicit information from *Prognostat* regarding patient risk scores or linear predictors, this is not feasible at this time.

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Figure and Table Captions

Figure 1. Kaplan-Meier survival curves by initial PPS.

Figure 2. Box plot showing predictions by actual outcome (survival) for hospice patients (Figure 2A). Hosmer-Lemeshow calibration plot of predicted versus actual proportion of survival (2B). The 45° degree line denotes the perfect agreement between predicted and observed survival.

Table 1. Patient characteristics and survival time by age, gender, cancer diagnosis and PPS. The second cell entry (where available) marked with * is from the Victoria Hospice cohort of patients used to develop Prognostat.

Table 2. Prognostat performance measures. AUC = Area under the receiver operating curve. HL = Hosmer-Lemeshow.

Figure 1
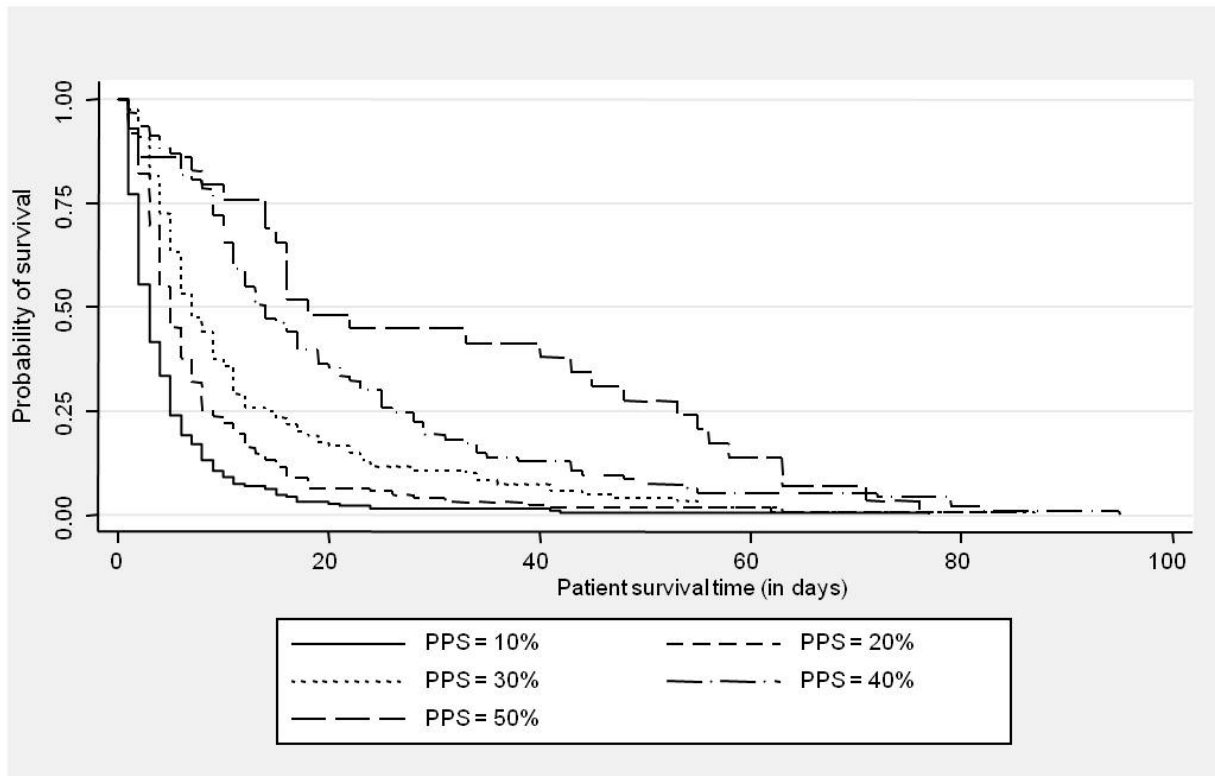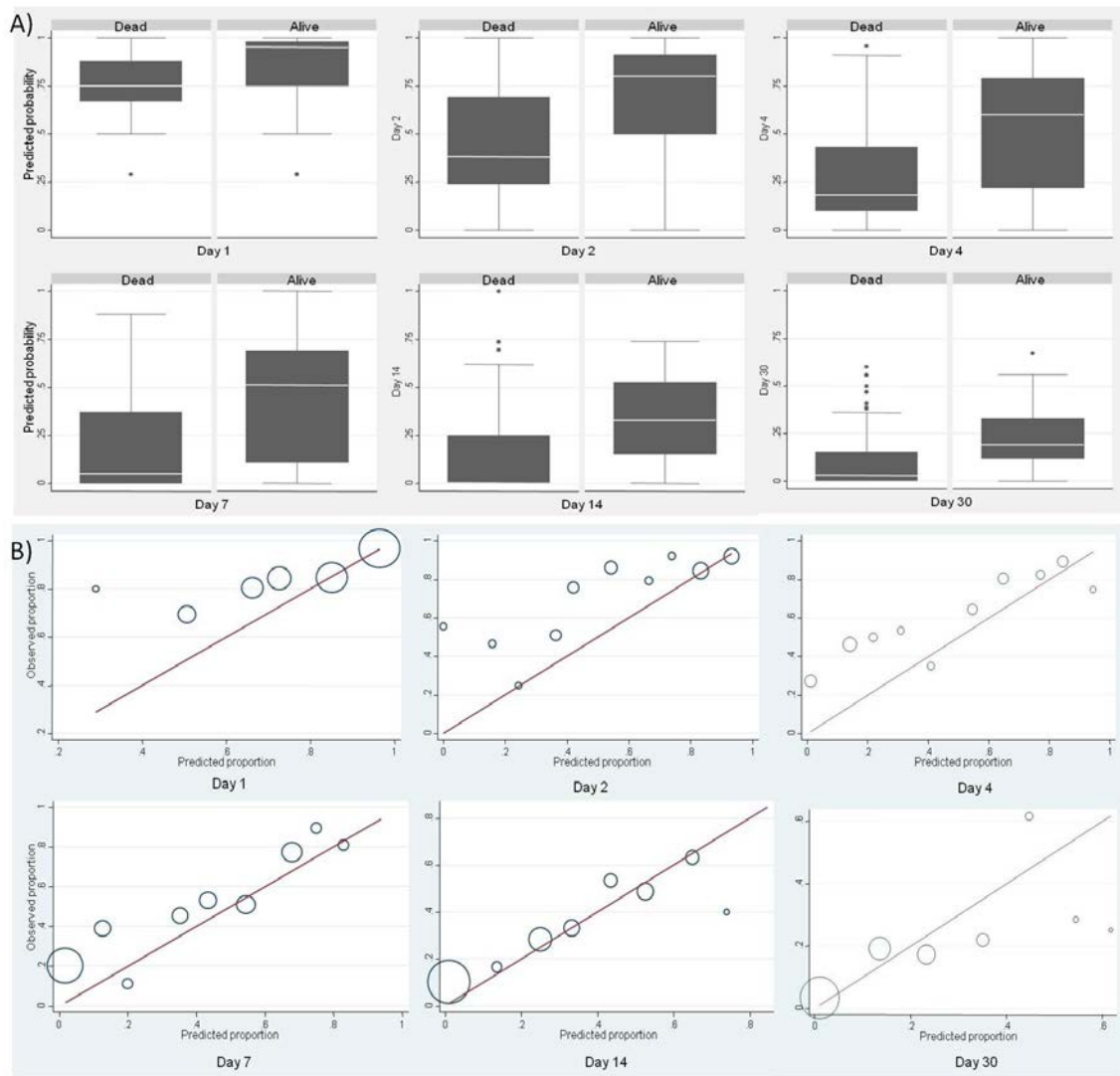
Figure 2

Table 1. Survival time by age, gender, diagnosis and intitial PPS

Variable	Survival Times (in Days)			No. of Patients (%)	HR (95% CI), P-value	Log-rank P-value
	Mean (95% CI)	Median (95% CI)	Range			
Total no. of patients						
Overall	14 (12, 17)	6 (5, 6), 8 (7.5, 8.5)*	1-371	590, 5893		
Age at Treatment					vs. < 45	0.65
<45	15 (8, 22)	8 (4,12)	1-95	37 (6.3%), 245 (4.2%)*	1	
45-64	14 (11, 17)	7 (5, 9)	1-114	187 (31.7%), 1270 (21.6%)*	1.032 (0.725, 1.469), 0.86	
65-74	14 (8, 20)	5 (4, 6)	1-271	110 (18.6%), 1489 (25.3%)*	1.199 (0.826, 1.742), 0.34	
75-84	14 (8, 20)	6 (5, 7)	1-371	129 (21.9%), 1945 (33.0%)*	1.146 (0.794, 1.653), 0.47	
85+	15 (9, 21)	5 (4, 6)	1-313	127 (21.5%), 944 (16.0%)*	1.135 (0.786, 1.637), 0.50	
Gender					vs Male	0.79
Male	14 (10, 18)	6 (5, 7)	1-371	293 (49.7%), 2822 (48.9%)*	1	
Female	15 (11, 19)	6 (5, 7)	1-271	295 (50%), 3071 (51.1%)*	0.979 (0.833, 1.152), 0.806	
No. of patients with cancer					vs Noncancer	< 0.001
Noncancer	12 (8, 16)	5 (4, 6)	1-371	363 (61.5%), 928 (15.7%)*	1	
Cancer	17 (14, 20)	9 (7, 11)	1-113	227 (38.5%), 4965 (84.3%)*	0.667 (0.563, 0.789), <0.001	
Diagnosis category for cancer						
Brain	27 (16, 39)	28 (14, 42)	3-55	10 (1.7%)		
Gastrointestinal	21 (14, 29)	11 (5,17)	1-82	35 (5.9%)		
Genital-male	15 (6, 24)	8 (1, 15)	2-55	12 (2%)		
Genital-female	26 (7, 45)	13 (4, 22)	1-100	12 (2%)		
Head and neck	10 (2, 18)	5 (1, 9)	1-36	8 (1.4%)		
Hematopoietic	4 (2, 6)	3 (1, 5)	1-10	10 (1.7%)		
Pancreas	18 (7, 29)	7 (3, 11)	1-113	24 (4.2%)		
Respiratory	15 (10, 20)	10 (7, 13)	1-71	49 (8.3%)		
Skin	11	11	11-11	2 (0.3%)		
Urinary	25 (1-58)	9 (1-39)	4-76	4 (0.6%)		
Other	17 (12, 22)	9 (5, 12)	1-103	61 (10.3%)		
Diagnosis category for noncancer						
AIDS	18 (3, 33)	8 (1, 15)	1-85	12 (2%)		
Cardiovascular	14 (5, 23)	5 (3, 7)	1-271	74 (12.5%)		
Neurological	8 (5, 11)	5 (4,6)	1-77	119 (20.2%)		
Respiratory	25 (1, 49)	3 (1, 5)	1-371	37 (6.3%)		
Other	11 (1, 15)	5 (4, 6)	1-174	121 (20.6%)		
Initial PPS Score					vs. PPS 10%	< 0.001
PPS 10%	5 (3, 7)	3 (2, 4), 1 (0.9, 1.1)*	1-77	188 (32.6%), 569 (9.6%)*	1	
PPS 20%	16 (8, 24)	5 (4, 6), 2 (1.8, 2.2)*	1-371	125 (21.7%), 732 (12.5%)*	0.527 (0.417, 0.664), < 0.001	
PPS 30%	15 (11, 19)	7 (5,9), 5 (4.6, 5.4)*	1-140	123 (21.4%), 1403 (23.9%)*	0.402 (0.318, 0.508), < 0.001	
PPS 40%	24 (18, 30)	14 (11, 17), 13 (11.9, 14.1)*	1-174	96 (16.7%), 1590 (27.0%)*	0.271 (0.209, 0.351), < 0.001	
PPS 50	30 (22, 38)	18 (14, 45), 28 (25.1, 30.9)*	1-76	29 (5.0%), 1003 (17.1%)*	0.223 (0.149, 0.334), <0.001	
PPS 60%	23 (14, 32)	18 (5, 29), 43 (37.9, 48.1)*	4-61	15 (2.6%), 453 (7.7%)*	0.271 (0.159, 0.461), <0.001	

Table 2. Accuracy, discrimination and calibration measures for model performance in predicting patient survival using Prognostat

Day (% patients survived)	Score	PPS adjusted
Day 1 (89.4%)	Brier	0.099
	Brier Scaled	18.30%
	AUC (95% CI)	0.699 (0.628, 0.771)
	Slope	0.119
	HL p-value	0.0023
Day 2 (77.6%)	Brier	0.187
	Brier Scaled	18.40%
	AUC	0.741 (0.689, 0.791)
	Slope	0.234
	HL p-value	< 0.001
Day 4 (59.7%)	Brier	0.244
	Brier Scaled	0.40%
	AUC (95% CI)	0.724 (0.682, 0.767)
	Slope	0.243
	HL p-value	< 0.001
Day 7 (42.4%)	Brier	0.211
	Brier Scaled	2.20%
	AUC (95% CI)	0.764 (0.724, 0.803)
	Slope	0.263
	HL p-value	< 0.001
Day 14 (24%)	Brier	0.155
	Brier Scaled	5.50%
	AUC (95% CI)	0.756 (0.709, 0.804)
	Slope	0.203
	HL p-value	< 0.001
Day 30 (10.8%)	Brier	0.088
	Brier Scaled	39.40%
	AUC (95% CI)	0.758 (0.696, 0.820)
	Slope	0.136
	HL p-value	< 0.001

CI: confidence interval, HL: Hosmer-Lemeshow statistic, AUC: area under the receiver operating curve

Appendix 5

External Validation of Prognostic Models in Terminally Ill Patients

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Background: Over one million Medicare beneficiaries receive hospice care annually. However, besides the well documented advantages of hospice, many Americans do not enjoy maximum benefit from the hospice care. The fundamental reason for this is related to the inappropriate and poorly timed referral of terminally ill patients to hospice. As a result, many patients die within a few days of referral, while some live many years after the referral was made. Improvement in the accuracy of prognosis translates into superior quality of care. Predictions based on statistical modeling have been shown to be superior to physicians' prognostication. However, very few of these statistical models have been externally validated in terminally ill patients. Here we report the external validation of 5 most commonly used prognostication models in a cohort of terminally ill patients: 1) declining exponential approximation of life expectancy (DEALE) 2) study to understand prognoses and preferences for outcomes and risks of treatments (SUPPORT), 3) adjusted palliative performance scale (PPS), 4) adjusted Karnofsky performance scale index (Karnofsky) and 5) adjusted eastern cooperative oncology group performance status (ECOG).

Methods: We retrospectively extracted data from 590 deceased patients enrolled in Tampa Bay Lifepath Hospice and Palliative Care starting January 2009 and going backwards to validate the prognostic models. Two research assistants extracted all data necessary to populate the model variables and two faculty members randomly checked 25% of the data for accuracy. The models were tested against observed survival duration. PPS, Karnofsky and ECOG risk scores were predicted using a flexible family of Royston-Parmar parametric models and adjusted for age, gender and presence of cancer. We utilized several metrics to assess the performance of these models. Specifically, we used the Brier score and scaled Brier score (which is very similar to the Pearson correlation coefficient R^2), the area under the receiver operating characteristic curve (AUROC), and the Hosmer-Lemshow goodness-of-fit p-value (HL).

Results: Brier scores were consistently below the non-informative level of 0.25 and AUROC significantly higher than the non-informative level of 0.5 for the adjusted PPS, Karnofsky and ECOG models (table 1). The HL p-value was consistently greater than 0.1 only for PPS. SUPPORT and DEALE models did not predict fit our data well for survival at day one and month one, two and six. The AUROC takes a value close to 0.5, even though the Brier scores were relatively low and HL p-value greater than 0.05, this value is significantly close to 0.5 for SUPPORT and DEALE models (table 1).

Conclusion: None of the prognostication models accurately predicated survival among our cohort of terminally ill patients. However, PPS consistently performed best in predicting survival in terminally ill patients followed by Karnofsky and ECOG.

Table 1 Discrimination and model performance statistics in survival prognostication						
	Model performance metrics	PPS	Karnofsky	ECOG	DEALE	SUPPORT
Day 1	Brier	0.089	0.089	0.106	0.106	0.106
	Brier Scaled	8.80%	4.30%	NA	NA	NA
	AUROC (95%CI)	0.747 (0.68, 0.813)	0.747 (0.693, 0.810)	0.709 (0.648, 0.771)	0.526 (0.467, 0.584)	0.62 (0.56, 0.68)
	HL p-value	0.26	0.17	0.11	0.44	0.58
Day 3	Brier	0.179	0.178	0.293	–	–
	Brier Scaled	16%	15.30%	0%	–	–
	AUROC	0.768 (0.726, 0.810)	0.778 (0.737, 0.818)	0.719 (0.676, 0.761)	–	–
	HL p-value	0.29	0.04	0.57	–	–
Day 6 (Median)	Brier	0.199	0.194	0.363	–	–
	Brier Scaled	20.10%	19.40%	NA	–	–
	AUROC (95%CI)	0.775 (0.739,0.816)	0.787 (0.749, 0.823)	0.721 (0.679, 0.764)	–	–
	HL p-value	0.43	0.008	0.44	–	–
Day 10	Brier	0.179	0.183	0.253	–	–
	Brier Scaled	26.70%	25.90%	4.70%	–	–
	AUROC (95%CI)	0.795 (0.757, 0.834)	0.798 (0.761, 0.836)	0.742 (0.697, 0.786)	–	–
	HL p-value	0.15	0.01	0.61	–	–
Day 30	Brier	0.122	0.127	0.095	0.099	0.1868
	Brier Scaled	37.80%	37.50%	12.30%	2.44%	11.20%
	AUROC (95%CI)	0.781 (0.725,0.838)	0.787 (0.734, 0.839)	0.722 (0.651, 0.794)	0.52 (0.467, 0.573)	0.56 (0.48, 0.64)
	HL p-value	0.62	0.25	0.484	0.92	0.23
Day 60	Brier	0.084	0.088	0.04	0.045	0.2
	Brier Scaled	47.40%	47.70%	18.70%	16.10%	13.80%
	AUROC (95%CI)	0.745 (0.653, 0.837)	0.781 (0.689, 0.871)	0.739 (0.62, 0.858)	0.543 (0.468, 0.616)	0.62 (0.5, 0.74)
	HL p-value	0.29	0.32	0.32	0.32	0.67
Day 180	Brier	0.041	0.05	0.006	0.1	0.27
	Brier Scaled	63.20%	58.60%	31.20%	NA	7.90%
	AUROC (95%CI)	0.55 (0.452, 0.648)	0.51 (0.314, 0.71)	0.59 (0.355, 0.83)	0.7 (0.386, 1)	0.58 (0.04, 1)
	HL p-value	0.59	0.54	0.22	–	0.09

CI: confidence interval, H-L: Hosmer-Lemshow statistics, AUROC: area under the receiver operating characteristic curve

Appendix 6:

Rough Set Theory based Prognostic Model for Hospice Referral

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Abstract

Objective: The goal of this paper is to provide an accessible prognostic classification model for hospice referrals. Hospice care provides high-quality and cost-effective end-of-life care for terminally ill patients. In addition, the paper explores the application of Rough Set Theory (RST) for the development of clinically credible prognostic models.

Methods: We utilize retrospective data from 9,103 terminally ill patients to demonstrate the design and implementation of a classifier based on RST for potential hospice candidates. RST provides methods for knowledge reduction, founded on the relational indiscernibility of objects in a decision system, to describe required conditions for membership in a concept class. Decision rules for six-month patient survival classification are extracted from the dataset utilizing genetic algorithms for approximate reduct generation.

Results: The RST-based classifier performs comparably to other common classification methods, while providing significant advantages in terms of traceability and accessibility of the model.

Conclusions: In contrast to widely used methods for prognostic classification models, RST provides several opportunities for adaptation of the model to personal healthcare preferences. In addition, the intuitive structure of the RST approach reflects the nature of decision-making and provides greater insight into the model process.

Introduction

Hospice care reduces the emotional burden of illness on terminal patients by optimizing pain relief strategies [1] and provides a demonstrated, cost-effective increase in the quality of end-of-life care when compared to conventional programs [2]. This increase in quality of care elevates in turn the quality of life of both patients and their families [3].

The advantages of hospice care are diminished for terminally ill patients who enter either prematurely or too late. In general, premature hospice referral represents a lost opportunity for the patient to receive potentially effective and life-prolonging treatment. Conversely, late hospice referral is not desirable and negatively impacts both the quality of end-of-life care and the quality of life of patients

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and their families [4, 5]. According to Medicare regulations, patient eligibility for hospice care is determined by a life expectancy of less than six months, as estimated by the attending physician and certified by the medical director of the hospice program [6]. Medicare claims data report that 14.9% of hospice care patients lived for more than 180 days after enrollment, while 28.5% were late referrals who died within 14 days [4, 6]. Accurate prognostication of life expectancy is crucial in end-of-life care decisions and is consequently of vital importance for patients, their physicians and their families. Prognostic models improve the accuracy of life expectancy estimation in critical clinical decisions and are shown to be superior to physicians' prognostication alone [7]. Models for estimating the life expectancy of terminally ill patients include the use of traditional statistical and probabilistic methods [8-16] as well as artificial intelligence techniques such as neural networks and support vector machines [17-19], decision trees [20, 21] and rough set methods [22, 23]. The objective of a prognostic model is to determine a quantitative relationship between covariates and a health-related outcome. Survival models [6, 10, 12, 14, 16, 20, 21] focus on estimating the probability that a patient will survive a finite period of time. Other models, based on neural networks, support vector machines and logistic regression [15, 17-19, 24], represent the survival outcome as a binary variable, predicting the status of a patient (e.g. survives/does not survive) at a critical point in time (e.g. six months). While prognostic models are an important instrument in prognostication, a significant barrier to their widespread practical use is their perceived lack of clinical credibility [25]. Clinical credibility requires a prognostic model to be both accurate and accessible; in addition to providing rigorous, objective information to physicians, the structure of the model should be transparent and its results should facilitate physician and patient interpretation. We hypothesize that accurate and accessible prognostic models based on rough set theory can be used to increase the clinical credibility and use of prognostic models. To this end, we will explore Rough Set Theory as it is applied to end-of-life care and hospice referral decision support models.

This paper is organized as follows: Section 2 presents a description of important considerations when analyzing clinical data that motivate the use of Rough Set Theory (RST). In Section 3, we present an overview of the fundamental theory of rough sets for analyzing datasets. Section 4 describes the dataset used for the demonstration of the proposed prognostic model. Section 5 presents the development of the prognostic model. Finally, Sections 6 and 7 reports the results, conclusions, and discusses limitations and future directions of our work.

Motivation

2.1 Inherent inconsistencies and complexity presented in clinical data

Clinical data, such as heart rate and blood pressure, represent the physiological state of a patient at a moment in time and are measured and recorded within a continuum of possible values. In order to facilitate interpretation, categorical variables representing each measured process are defined along a set of cut-points. For example, *mean blood pressure* can be expressed in three discrete categories: *high*, *normal* and *low blood pressure*, divided by the systolic blood pressure cut-points 120 mmHg and 90 mmHg. While this representation supports rapid decision making, difficulties arise when measured values are at or near the cut-points. In these cases, minor differences in the value of a measurement may change the categorization of a patient, leading to major changes in subsequent treatment decisions [26]. Moreover, within a dataset of numerous patients, multiple patients may have the same categorical descriptions, yet their outcomes may be varied, or *inconsistent*, and as a result the outcome variable is *vaguely defined* [27]. A prognostic model that attempts to categorize patients as potentially belonging to one of a number of outcome groups must address this vagueness.

The presence of an inconsistency is often assumed to be the result of noise or an entry or calculation error and can thus be eliminated from the dataset or corrected. Traditionally, data preprocessing procedures address these inconsistencies to create consistent datasets that are then used to train the prognostic model and test its performance [28]. In clinical datasets, however, inconsistencies are the

inherent result of the complex reality of illness and human physiology. A prognostic model trained with an inconsistent dataset performs better at classifying an inconsistent testing set than a model trained with a consistent dataset [29], and thus is expected to perform better at classifying new patients drawn from an inherently inconsistent reality.

Prognostic factors, contained in clinical datasets of patients' test results and physiological characteristics, have complex relationships with the outcome variable. For instance, temperature, mean blood pressure, cholesterol levels, and glucose levels–among others–all present non-linear relationships with the survival time of terminally ill patients. Statistical approaches make assumptions regarding the relationship between the prognostic factors and the outcome variable. When these assumptions are violated, the resultant model is no longer representative of the data. As an example of one such assumption, logistic regression assumes a linear relationship exists between a given prognostic factor and the logit form of the outcome variable [30]. If the relationship is not linear as assumed, the statistical significance of the logistic regression coefficient related to that prognostic factor will be inaccurate [31].

2.2 Clinical credibility and interpretation of prognostic models in clinical practice

Prognostic models, in conjunction with direct physician observation, increase the accuracy of prognostication when compared to physician observation alone [32]. A recent review [13] demonstrated that, despite the importance of accurate prognostication within the spectrum of medical care objectives, there is a lack of accessible and accurate prognostic models available to physicians in practice.

To withstand clinical trials, and to meet the needs of physicians and patients, a prognostic model must have clinical credibility. That is, however accurate or clinically effective a model is statistically, physicians must believe in the value of the model as a prognostic tool. As such, a successful model must be accessible, the data required for the model must be relevant and simple to collect with high reliability, the structure of the model should be apparent and its predictions should make sense to the physicians who rely on them. Physicians must be able to apply the modeling method correctly without violating the fundamental assumptions of the model.

For these reasons, black box models, such as those based on neural networks and support vector machines, are less suitable as they offer little insight into the process of prediction and are difficult to interpret. Similarly, logistic regression models require careful application without which results may be invalidated. The interpretation of regression model results requires complex calculations, limiting the accessibility of the model. Additionally, black box models and logistic regression models require collection of data and test results for all of the prognostic factors used in the model calibration, further reducing accessibility.

2.3 Rough Set Theory in medical prognostic models

Rough Set Theory [33] is a mathematical tool for data analysis that has been used to address vagueness and inconsistencies present in datasets [34]. In the medical field, applications of RST focus mainly on the diagnosis and prognostication of diseases, where it has been demonstrated that RST is very useful for extracting medical prognostic rules using minimum information. Tsumoto et. al. [35] argue that the concepts of approximation established in RST reflect the characteristics of medical reasoning, explaining why RST performs well in the medical field. For example, RST can be used to highlight non-essential prognostic factors in a particular diagnosis, thus helping to avoid redundant, superfluous or costly tests [36-40]. Recently, methods that combine survival analysis techniques and RST have been used to generate prognostic rules that estimate the survival time of a patient [22, 23]. RST provides a systematic approach for analyzing data without making assumptions common to statistical methods (such as a linear factor-outcome relationship). This advantage over statistical approaches makes RST suitable for integration into medical applications [41]. The information extracted from the dataset can be represented in the form of "if-then" decision rules—an intuitive

representation that offers significant advantage over "black box" modeling approaches [42]—increasing accessibility and thus clinical credibility.

Overview of Rough Set Theory

Rough Set Theory, introduced by Pawlak in [33], provides methods for knowledge reduction by exploiting the relational indiscernibility of objects in an information system. Central to RST is the notion that an observed object has a certain amount of information associated with it. When considered in relation to a cohort of observed objects, this information is used to group similar objects into information granules. Together, the information provided by the set of observed objects can be generalized to describe the conditions required for membership in a concept class.

Table 1. Example Decision Table

	Condition Attributes						Decision Attribute
Patient	c_1 Gender	c_2 Age	c_3 SystBP	c_4 HDL	c_5 Diabetic	c_6 Smoker	d Coronary Disease
x_1	F	H	M	L	No	No	No
x_2	M	L	L	L	No	Yes	No
x_3	F	M	M	H	No	No	No
x_4	F	M	M	H	No	No	Yes
x_5	M	H	H	L	Yes	Yes	Yes
x_6	M	H	H	L	Yes	Yes	Yes
x_7	F	M	M	H	No	No	Yes

Gender: Female/Male; Age: L = [54-59), M = [59-69), H = [69-74]; SystBP : L = <129, M = (129-139], H = (139-159]; HDL: L = 13, M = (44-60], H = (60-114]

3.1 Notation

The methods of RST act upon an information system of the form $= (U, A, V, f)$, where U is a non-empty finite set of objects, called the universe. $A = C \cup \{d\}$ is a set of attributes that describe a given object in U, comprised of a set C of condition attributes and an optional decision attribute d. When d is present, the information system is a decision system, and is typically presented in table form. Given an object $x \in U$, for every attribute $a \in A$, $f(x, a): a \rightarrow V_a$ maps the condition attribute of object x to its associated value $v \in V_a$ by the information function f. A value attribute pair (a, v) for a given object is referred to as a descriptor. The value set of attribute a is V_a, and the set of all values is V.
A data requirement for RST is that the attribute values must be in discrete or categorical form. Table 1 provides an example of a discretized decision table, where six prognostic factors, as the condition attributes, describe seven patients. The decision attribute, presence of coronary disease in the patient, is represented by the binary attribute $d \rightarrow \{Yes, No\}$.
Once discretized, the objects in a decision table can be grouped according to their descriptors. For example, patients x_5 and x_6 have the same attribute values and are thus indiscernible from each other. In general, two objects $x_i, x_j \in U$ are indiscernible with respect to set of condition attributes $B \subseteq A$ if $f(x_i, a) = f(x_j, a)$ for all $a \in B$. This relation is called an indiscernibility relation, given by $R(B) = \{(x_i, x_j) \in U: \forall a \in B, f(x_i, a) = f(x_j, a)\}$.
For example, the patients in Table 1 can be separated into four groups according to the indiscernibility relation $R(C)$: $X_1 = \{x_1\}$, $X_2 = \{x_2\}$, $X_3 = \{x_3, x_4, x_7\}$, $X_4 = \{x_5, x_6\}$. These groups of objects are referred to as equivalence classes, or conditional classes for $B \subseteq C$. An equivalence class for the decision attribute is called a decision class or concept, and in this example there are two groups:

$Y_{No} = \{x_1, x_2, x_3\}$ and $Y_{Yes} = \{x_4, x_5, x_6, x_7\}$. The equivalence class specified by the object x_i with respect to $R(B)$ is denoted as $[x_i]_B$.

3.2 Set Approximations

The goal of RST is to provide a definition of a concept according to the attributes of the equivalence classes that contain objects that are known instantiations of the concept. As such, in a consistent decision table, membership in a conditional class implies membership in a particular decision class. In Table 1, $x \in X_4$ implies $x \in Y_{Yes}$. Membership in X_3, however, does not imply Y_{Yes} as $x_4, x_7 \in Y_{Yes}$ but $x_3 \in Y_{No}$. Thus Table 1 is inconsistent as $d(x_4, x_7) \neq d(x_3)$.

To represent an inconsistent decision table, RST establishes an upper and lower approximation for each decision class, Y. The *lower approximation* is comprised of all objects that definitely belong to Y, while the *upper approximation* includes all objects that possibly belong to Y. It can be said that an object x_i definitely belongs to a concept Y if $[x_i]_C \subseteq Y$ and that x_i possibly belongs to a concept Y if $[x_i]_C \cap Y \neq \emptyset$. Thus, the lower and upper approximations are defined as follows:

$$\underline{R_B}(Y) = \{x \in U : [x]_B \subseteq Y\} = \bigcup \{[x]_b : [x]_b \in Y\}$$

$$\overline{R_B}(Y) = \{x \in U : [x]_B \cap Y \neq \emptyset\} = \bigcup \{[x]_b : [x]_b \cap Y \neq \emptyset\}$$

$$\overline{R_B}(Y) - \underline{R_B}(Y) = BND_B(Y)$$

The boundary region, $BND_B(Y)$, contains those objects that possibly, but not certainly, belong to Y. Conversely, the set $U - \overline{R_B}(Y)$ is the outside region containing those objects that certainly do not belong to Y. In our example, the lower and upper approximations for Y_{Yes} are $\underline{R_C}(Y_{Yes}) = X_4 = \{x_5, x_6\}$ and $\overline{R_C}(Y_{Yes}) = X_4 \cup X_3 = \{x_3, x_4, x_5, x_6, x_7\}$, and the boundary region contains the objects $BND_B(Y_{Yes}) = \{x_3, x_4, x_7\}$.

3.3 Reduct Generation

Within a decision system, not all of the condition attributes may be required to define object-concept allocation. If, for an attribute subset $B \subseteq C$, the indiscernibility relation $R_B = R_C$, then the set approximations remain the same, the structure of the decision system is preserved and the attributes in $C - B$ are said to be dispensable. There may be many such subsets, but if B is minimal (does not contain any dispensable attributes), then B is termed a reduct. {*Age*, *Smoker*} and {*SystBP*, *HDL*} are two such reducts from our example decision table that provide the same quality of information as the complete set of attributes.

Finding rough set reducts can be framed as a minimal hitting sets problem [43]. In this context, a discernibility matrix, $\mathcal{M}_A$, is constructed such that each entry in $\mathcal{M}_A(x_i, x_j)$ represents those attributes that differ, or discern, between object x_i and x_j with respect to the attributes in A.

$$\mathcal{M}_A(x_i, x_j) = \{a \in A : a(x_i) \neq a(x_j) \text{ and } d(x_i) \neq d(x_j)\}$$

If a multiset C is constructed from the non-empty entries in $\mathcal{M}_A$, the minimal hitting sets are rough set reducts. Let $C(S)$ be a mapping of $C : 2^U \to \mathbb{N}$ such that $C(S)$ counts the number of times a given set S appears in C, and let $h_X^C \to \{0,1\}$ be 1 if X intersects a set in C and 0 otherwise. Then $\alpha_w^C(X)$ is a measure of approximation for a set X with respect to C

$$\alpha_w^C(X) = \frac{\sum_{S \in 2^U} w(S) C(S) h_X^C(S)}{\sum_{S \in 2^U} w(S) C(S)}$$

where $w(S)$ provides a weight for each set S. An r-approximate hitting set of C is then a set $X \subseteq U$ such that $\alpha_w^C(X) \geq r$.

The computational cost for reduct computation is exponential with respect to the size of the decision table. Genetic algorithms, operating based on the principle of survival of the fittest, can be used to manage the computational complexity of the dimensionality reduction process [44, 45]. In this process, an initial population of elements is randomly selected from 2^A, and their quality as a reduct is

evaluated using a fitness function. In the case of rough set reducts, the fitness function rewards elements that hit more sets in *C* with an approximation greater than *r*. A process of combinations, mutations and random variations creates a new generation of elements, rewarding the more fit elements and discarding unfit elements. The stopping criterion is a lack of improvement in the average fitness of the population over a specified number of generations. The result is a collection of the *m* fittest individuals in *k* approximation intervals between *r* and 1.

3.4 Decision Rules

The reduct generation process may result in a number of reducts, which may then be filtered algorithmically or by the decision maker. Once the final reduct list has been established, each object in the decision table is used to generate a rule based on the attribute values of each object for each reduct. The collection of these rules can then be used to classify unseen objects – in the case of our example table, a new patient who may have cardiac disease.

A decision rule has the form: *if A then B* or $A \rightarrow B$, where *A* is called the antecedent and *B* the consequent of the rule. Each object-reduct pair contributes a rule. The antecedent is the logical conjunction of descriptors of the object for the attributes in the given reduct and the consequent is the decision attribute of the object. For example, object x_1 from our example in Table 1 yields the following rule for the reduct {*Age, Smoker*}: if *Age*=H and *Smoker*=No then *Coronary Disease* = No.

Dataset description

The dataset used for the development of the prognostic model to assist in hospice referral consists of 9,105 cases from the SUPPORT (Study to Understand Prognoses and Preferences for Outcomes and Risks of Treatments) prognostic model dataset [46]. The SUPPORT study included a prognostic model for 180-day survival estimation of seriously ill hospitalized adults based on cubic splines and a Cox regression model. As such, the dataset is ideal for the present research in regards to completeness of data, comparability of results and clinical applicability.

We consider as condition attributes the variables used in the SUPPORT prognostic model equation [10] to ensure consistency. The SUPPORT variables include ten physiologic variables in addition to the diagnosis groups, age, number of days in the hospital before entering the study, presence of cancer, and neurologic function. Attribute names, descriptions and value ranges are listed in Table 2.

The decision attribute, a binary (Yes/No) variable, *d.6months* (deceased in six months), was defined by comparing the values provided by the SUPPORT dataset for the variables *death* and *d.time*. The former represents the event of death up to a date 12 months after the conclusion of the SUPPORT study. The latter records the number of days of follow up in the study. If the follow up time for a patient was less than six months and *death=Yes*, then *d.6months=Yes*. Otherwise, it is implied the patient survived the 6-month period and *d.6months=No*, as study patients were followed for a minimum of 180-days.

Table 2. Description of attributes from SUPPORT dataset

Numerical Condition Attributes		Patient Distribution		
Variable Name	Description	Range	Mean	Std. Dev.
age	Age of the patients	18 - 101	62.65	15.59
alb	Serum albumin	0.4 - 29	2.95	0.87
bili	Bilirubin	0.1 - 63	2.55	5.32
crea	Serum creatinine	0.09 - 21.5	1.77	1.69
hday	Number of days in hospital at study entry	1 - 148	1.00	9.13
hrt	Heart Rate	0 - 300	97.16	31.56
meanbp	Mean arterial blood pressure	0 - 195	84.55	27.70
pafi	Blood gasses, $PaO_2/(.01 * FiO_2)$	12 - 890.4	239.50	109.70
resp	Respiration rate	0 - 90	23.33	9.57
scoma	SUPPORT coma score, based on Glasgow coma scale	0 - 100	12.06	24.63

sod	Sodium	110 - 181	137.60	6.03
temp	Temperature in ºC	31.7 - 41.7	37.10	1.25
wblc	White blood cell count	0 - 200	12.35	9.27

Categorical Condition Attributes		Patients	Percentage
dzgroup	Diagnosis group:		
	ARF/MOSF w Sepsis	3,515	38.60%
	COPD	967	10.60%
	CHF	1,387	15.23%
	Cirrhosis	508	5.56%
	Coma	596	6.54%
	Colon Cancer	512	5.62%
	Lung Cancer	908	9.97%
	MOSF w Malignancy	712	7.81%
ca	Presence of cancer:		
	Yes	1,252	13.75%
	No	5,995	65.84%
	Metastasis	1,858	20.40%

Decision Attribute		Patients	Percentage
d.6months	Death occurred within 6 months:		
	Yes	4,840	53.17%
	No	4,263	46.83%

While the median survival time for the patients in the study is 223 days, Figure 1 demonstrates that the majority of the patients fall into one of two extremes: death within 40 days of study entry (2,752 patients or 30% of all patients), or survival for more than a year (4,000 patients or 44%).
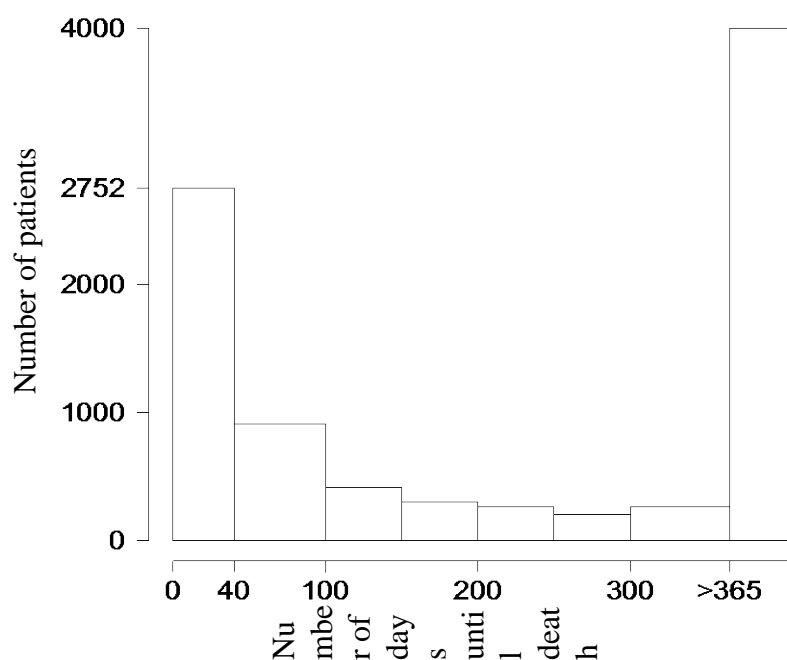
Figure 1. Distribution of patients with respect to number of days until death

General observations can be made regarding the influence of condition attributes on *d.6months* by analyzing the distribution of time until death by attribute. For example, the box-whisker plot in Figure 2 shows that a significant portion (75%) of patients with coma or multi-organ system failure with malignancy (MOSF w/ Malig) do not survive longer than 180 days, but patients with congestive heart failure (CHF) or chronic obstructive pulmonary disease (CPD) tend to live longer than 180 days. Thus, we can expect that *dzgroup* will be an important attribute in the decision table.

Note, also, that several *dzgroup* categories have a number of outliers, represented by circles in Figure 2. Whereas the information from these patients would be lost in a regression model, RST-based methods retain the information from these patients in the rule-generation and –application process. Given the number of outliers presented, however, it is reasonable to expect that a reduct approximation scheme will be necessary to generate meaningful reducts from the decision table.

Figure 2. Survival time in number of days vs. dzgroup

Diagnosis groups (dzgroup)
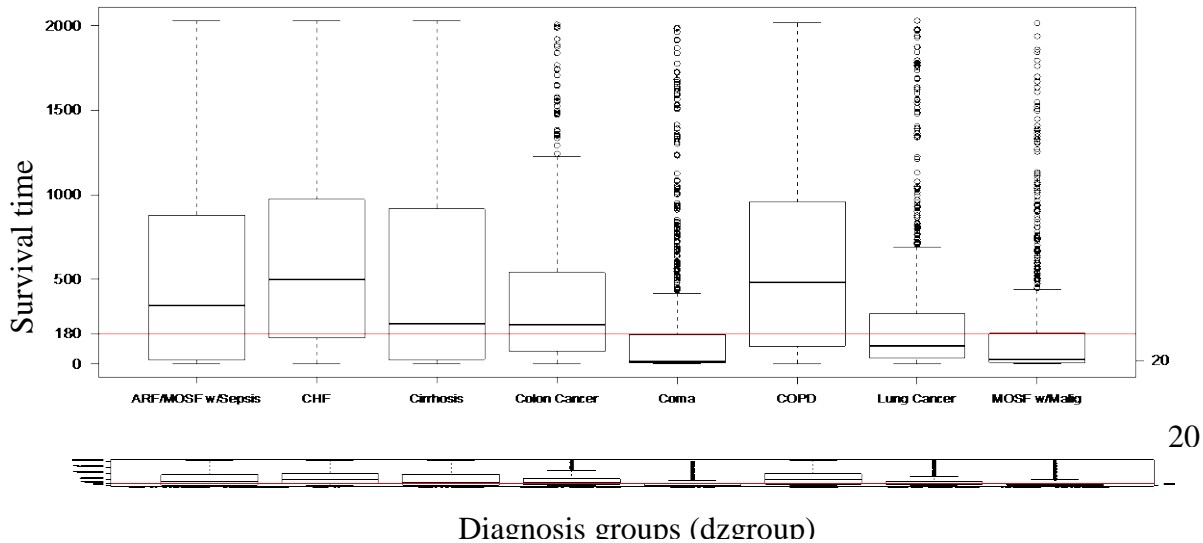
Development of the prognostic model

The objective of the presented research is to develop a classification model for life-expectancy prognostication using rough set methods. The proposed prognostic model was developed according to the following steps: data preprocessing, discretization, reduct generation, rule induction and rule application.

5.1 Data preprocessing

In its published form, the SUPPORT dataset contains 9,103 complete cases. Prior to publication, a series of analyses was done in [10] to determine the most appropriate approach for imputing missing values where needed. Missing physiologic variables were then imputed with a fill-in value within the normal range of the variable. A patient for whom it was not possible to establish a Glasgow coma score was given a *scoma* value of zero.

5.2 Discretization

As the indiscernibility relations are computed on categorical condition attributes, RST methods require that data be categorized. Discretization is the process by which appropriate categorical ranges are found for variables with a continuous value range.

There are a number of methods available for algorithmic discretization that operate without input from the decision maker and are based only on the information available in the data table. In this work, however, discretization was primarily performed using the APACHE III Scoring System [9], a clinically accepted scoring system designed to estimate the risk of death in ICU patients. This choice is founded on the principle that medically and contextually relevant classification rules will increase the clinical credibility of the proposed prognostic model.

Using the cut-points defined in APACHE III, nine physiologic variables and the age variable were discretized. The physiologic variables not categorized by APACHE III, *pafi* and *scoma,* were discretized using clinically accepted categorizations [47, 48]. The variable *hday* was discretized using

the *Boolean Reasoning Algorithm* [49] as implemented in the ROSETTA software [50]. Table 3 shows the categories obtained by this process.

Table 3. Discretized attributes not in APACHE III

Attribute	Description	Categorization
scoma	Minor	(*,9]
	Moderate	(9,44]
	Severe	(44,*)
pafi	Normal	[300,*)
	Severe defect in gas exchange	[200,300)
	Acute respiratory distress syndrome	[0,200)
hday	Boolean Reasoning Algorithm	(*,44]
	Results	(44,*)

Once discretized, the dataset contains a number of indiscernible patients with inconsistent decision attributes. For example, the lower approximation of the decision class *d.6months = Yes* contains 4,035 patients and the upper approximation contains 4,552 patients, leaving 517 patients in the boundary region.

At this point, the dataset is randomly divided into training and testing sets containing 7,282 (80%) and 1,821 cases (20%), respectively. The training set is used to develop the classification model while the testing set is reserved for evaluating the model's performance when classifying unseen cases.

5.3 Reduct Generation

There is exactly one minimal reduct for the SUPPORT dataset, which is the set of all condition attributes. Therefore, it is not possible to reduce the dimensionality of the decision table without affecting the indiscernibility relation. Ziarko outlined in [51] a method to allow an acceptable level of uncertainty in set approximations, called variable precision rough set method (VPRS), which has been used in various applications such as in EEG analysis, liver malfunction diagnosis, and corporate failure prediction [38, 52, 53]. VPRS allows for allocating equivalence classes in the boundary region to the lower approximation of the majority decision class for a given certainty threshold ($0.5 < \beta \le 1$). This method was explored, however the set of all condition attributes was found to be minimal for all β levels, indicating that reduct approximation methods would be more appropriate for rule induction.

Approximate reducts were obtained by applying the minimal hitting set method discussed in Section 3.3 using the genetic algorithm implemented in ROSETTA [50], at varying levels of approximation, as shown in Table 4. As an indicator of the level of importance of an attribute, the number of reducts in which an attribute appears is counted and used to rank each attribute. The sum of rankings across all levels of *r* indicates the overall importance of each attribute. It can be seen that *dzgroup*, *meanbp*, and *age* are the most important attributes for the 180-day survival classifier.

Table 4. Condition attributes ranked by appearance in reducts.

	$r = 0.1$		$r = 0.2$		$r = 0.4$		$r = 0.6$		$r = 0.8$		Rank
Attributes	%	Rank	%	Rank	%	Rank	%	Rank	%	Rank	Score
dzgroup	74.1%	3	78.4%	2	81.7%	3	94.8%	1	97.1%	1	10
meanbp	74.1%	2	77.8%	3	88.6%	1	92.9%	2	94.7%	2	10

age	74.6%	1	79.4%	1	88.0%	2	87.7%	3	92.6%	4	11
resp	58.4%	5	68.6%	4	78.3%	4	79.4%	4	89.5%	5	22
hrt	61.4%	4	65.0%	5	65.1%	6	79.4%	5	94.7%	3	23
pafi	49.8%	6	55.2%	6	72.0%	5	78.1%	6	86.3%	6	29
crea	39.6%	8	48.5%	7	58.9%	7	67.1%	7	85.3%	7	36
scoma	41.6%	7	46.4%	8	58.9%	8	61.9%	9	79.0%	8	40
sod	33.0%	10	42.3%	9	43.4%	10	52.3%	12	73.7%	9	50
alb	26.2%	12	28.4%	11	34.9%	13	66.5%	8	68.4%	11	55
ca	25.4%	13	18.6%	14	44.6%	9	56.1%	10	69.5%	10	56
bili	26.4%	11	24.7%	12	40.6%	11	54.8%	11	66.3%	12	57
wblc	35.0%	9	35.6%	10	39.4%	12	42.6%	13	62.1%	14	58
temp	18.8%	14	19.1%	13	30.3%	14	38.7%	14	66.3%	13	68
hday	7.1%	15	9.8%	15	22.9%	15	15.5%	15	13.7%	15	75
Total	197 reducts		194 reducts		175 reducts		155 reducts		95 reducts	

5.4 Rule Induction

For each *r*-approximate reduct set, every patient in the training set contributes to a decision rule of the form $if\ A \rightarrow B$ based on the reduced decision table for each reduct. For each rule, the left hand side (LHS) support is the number of patients in the table whose attributes match the antecedent, *A*, while the right hand side (RHS) support indicates the number of patients matching the consequent of the rule, *B*. The number and selection of descriptors in the antecedent varies according to the reduct generating the rule, thus the set of all *r*-approximate decision rules obtained from the training set will contain rules of varying number of descriptors.

Several decision rules are highlighted in Table 5. Rules 1 and 2 contain only two descriptors and therefore match more patients in the training set leading to a larger LHS support. Note that these rules match the expectations from our general observations from Section 4 about patients with CHF or MOSF with malignancy. Rules 3 and 4 contain six and four descriptors respectively, and are thus more specific.

Table 5. Selected decision rules for *r* = 0.1 approximate reducts.

Rule	LHS	RHS Support d.6months = Yes	RHS Support d.6months = No
1. *If dzgroup*=CHF AND *age*=(74,84] → *d.6months*={Yes,No}	254	73 (29%)	181 (71%)
2. *If dzgroup*=MOSFw/Malig AND *hrt*=(49,99] → *d.6months*={Yes,No}	192	128 (67%)	64 (33%)
3. *If dzgroup*=CHF AND *age*=(74,84] AND *resp*=(13,24] AND *alb*=(2.4,4.4] AND *crea*=(1.4,1.94] AND *sod*=(134,154] → *d.6months*={Yes,No}	8	6 (75%)	2 (25%)
4. *If dzgroup*=MOSFw/Malig AND *hrt*=(49,99] AND *meanbp*=(99,119] AND *resp*=(5,11] → *d.6months*={Yes,No}	7	1 (14%)	6 (86%)

5.5 Rule Application

A standard voting process [49] is used to allow all rules to participate in the decision process, arriving at a patient classification by majority vote. Thus, for a new, unseen patient, any rule whose antecedent descriptors match the patient descriptors "fires" by contributing as votes the RHS support for each decision class. Once all rules have "voted", the number of votes for each decision class is normalized against the total number of LHS support for all fired rules. The resultant ratio of RHS to LHS support is considered a frequency-based estimate of the probability that the patient belongs to the given decision class.

As an example, consider a patient whose profile includes the following descriptors: *dzgroup*=CHF, *age*=(74,84], *resp*=(13,24], *alb*=(2.4,4.4], *crea*=(1.4,1.94], and *sod*=(134,154]. If the prognostic model were applied to this patient, then both rule 1 and 3 would fire. Supposing rule 1 and 3 are the only rules that fire for this example patient, the probability that the patient will survive six months is estimated as $(181 + 2)/(254 + 8) = 69.8\%$. Any additional rules matching the patient's profile would contribute similarly to the estimated six-month survival probability.

A final classification is determined according to a threshold value, $\tau \in [0,1]$. A patient is classified as not surviving six months if the estimated probability of death in six months is greater than τ. In the event of an estimated probability equal to τ, or in the absence of any fired rules (no rule matches the patient profile), classification is not possible and the patient is labeled *undefined*.

Results

The performance of the model was tested by measuring the discriminatory power of each of the r-approximate sets of decision rules when applied to the reserved testing set. For our notation, a classification of *d.6months*=Yes is referred to as a positive classification, and *d.6months*=No is negative. *Sensitivity* is defined as the fraction of patients who did not survive six months and are correctly classified by the model, or the fraction of true positive classifications of all test patients who did not survive six months. Conversely, *specificity* is defined as the fraction of patients who did survive six months and were correctly classified by the model, or the fraction of true negatives of all test patients who did survive six months.

The overall accuracy of the classification model is reported in terms of area under the Receiver Operating Characteristic (ROC) curve, or *AUC*. The ROC curve graphs the sensitivity of the classifier, or the true positive rate, versus 1-specificity, the false positive rate, as the threshold probability, τ, for positive classification is varied from 0 to 1. The best overall classification performance is realized when AUC is equal to 1, while an AUC of 0.5 indicates a classifier performance no better than random selection. Best separation between decision classes is realized at the threshold corresponding to the point on the ROC curve closest to the point (0,1).

Also of importance is the coverage of the classification model, i.e. the percentage of testing set patients for whom a classification is possible. Coverage and AUC for each evaluated *r*-approximate reduct are shown in Table 6, and the associated ROC curve for each is illustrated in Figure 3. Clearly, *r* is a critical value in determining AUC, coverage and maximum sensitivity and specificity values. Classifier performance at a particular value of *r* is dataset-dependent, however, in general, *r*=1 represents a reduct generation approach strictly aimed at dimensionality reduction, while *r* closer to zero represents a more relaxed criterion for reduct acceptability.

Table 6. AUC and coverage for various levels of r-approximate reducts.

r	AUC (%)	Coverage (%)
0.1	70.3	100
0.2	69.7	100
0.4	69.5	100
0.6	65.9	98.7
0.8	61.3	66.9
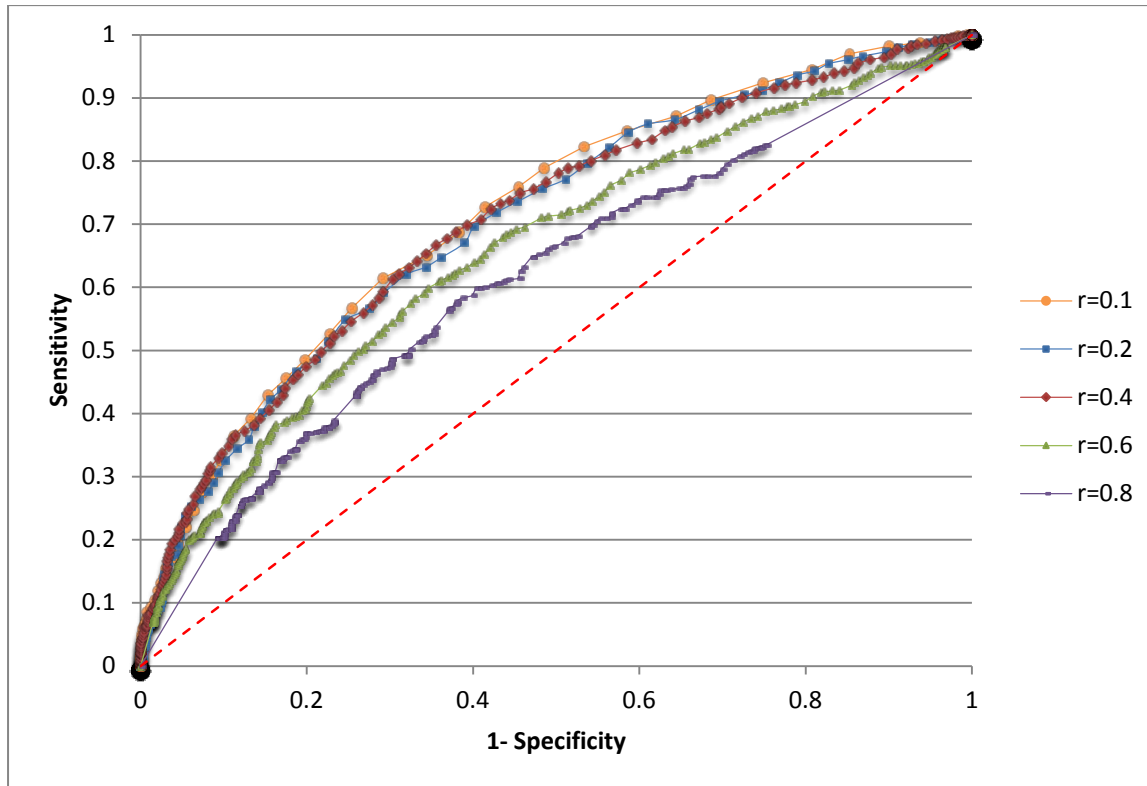
Figure 3. ROC curves for r-approximate reducts.

In order to estimate the stability of the classification model, a k-fold cross validation [54] procedure was applied. The entire dataset was randomly divided into five subsets, or folds, and then each fold (20% of the dataset) is used once as a testing set, with the remaining folds (80%) used for training. The results from each of the five fold configurations are averaged to provide an estimate for the classifier performance. Table 7 presents the results for the classification model for each fold arrangement for the three r-approximation levels with the highest AUC, r=0.1, 0.2, and 0.4. The AUC, sensitivity, and specificity for each fold are shown.

Table 7. K-fold validation results for r-approximate reducts, by reserved testing fold.

Testing Fold	$r = 0.1$ AUC (%)	Sens. (%)	Spec. (%)	$r = 0.2$ AUC (%)	Sens. (%)	Spec. (%)	$r = 0.4$ AUC (%)	Sens. (%)	Spec. (%)
1	70.34	65.28	66.22	69.74	62.78	67.04	69.53	62.78	67.96
2	71.78	58.94	74.56	68.47	62.59	63.34	68.12	60.35	67.97
3	71.91	68.74	64.90	71.99	61.93	69.48	71.23	67.90	65.51
4	68.37	66.86	61.08	68.97	60.93	68.03	67.77	63.66	63.64
5	70.18	61.77	68.93	70.28	64.57	66.24	71.02	67.49	65.26
Mean	70.52	64.32	67.14	68.89	62.56	66.83	69.53	64.44	66.07
Std. Dev.	1.44	3.95	5.02	1.34	1.34	2.29	1.60	3.22	1.87

6.4 Performance comparison with logistic regression and support vector machines

RST approaches in other diagnostic prognostic models have resulted in significantly higher discriminatory performance, with typical AUC near 90% [37, 43, 55]. To ascertain if the performance demonstrated by the present application is indicative of the unsuitability of RST for the problem or of the complexity of the dataset, the results are compared with two popular classification approaches: logistic regression and SVM. Table 8 shows the performance of the classification models, using the 5-fold cross validation scheme, in terms of sensitivity, specificity and AUC. All three models perform similarly, and an AUC of less than 75% for all three highlights the complexity of the estimation of life expectancy via a classification model.

Table 8. Performance of three classification models: Logistic regression, SVM and RST.

Method	Sens.	*Std. Dev*	Spec.	*Std. Dev.*	AUC	*Std. Dev.*
Logistic regression	59.20%	0.02	76.40%	0.01	74.10%	0.99
Support vector machines	65.52%	0.02	70.40%	0.01	73.40%	1.20
RST	64.32%	3.95	67.14%	5.02	70.52%	1.44

Discussion

7.1 Interpretation and usability of decision rules

Clinical credibility in prognostic models depends in part on the ease with which physicians and patients can understand and interpret the results of the models, in addition to the accuracy of the information they provide. While the performance of the RST-based prognostic model is comparable to similar methods, the if-then decision rule approach offers significant advantages by increasing both the traceability of the model and the amount of information included in its results.

Consider an example patient with MOSF with malignancy who is classified as not surviving six months with a probability of 66%. Among the list of fired rules presented to the physician are rules 2 and 4 from Table 5. Rule 2 indicates that of 192 patients with *dzgroup*=MOSF w/ Malig and *heartrate*=(49,99], 128 (67%) indeed did not survive six months. However, rule 4 shows more specifically that the example patient matches 7 patients when two additional physical conditions are considered, of whom 6 (86%), in fact, survived more than six months.

Thus, the gestalt survival expectation is presented without loss of contradictory information. This increases the transparency and traceability of the classification process, strengthening the accessibility, and hence credibility, of the model. This is in contrast to SVM, neural networks and other black-box methods, where the information provided is limited to a classification and a confidence interval. None of these methods provide traceable and accessible results as in the case of the if-then decision rule representation.

Additionally, logistic regression and other black-box models require the complete set of condition attributes, or prognostic factors, as those used in the formation of the respective model. Contrarily, the RST approach also offers the advantage of acceptable results should a particular prognostic factor be difficult or too costly to ascertain for a patient [36].

7.2 Decision analysis for hospice referral

Consider the costs – economic, emotional and physical – associated with the decision to enter hospice care. These costs are justified for patients who either enter hospice care at the appropriate time or for those who do not enter hospice care when they could benefit from curative treatment. These cases represent true positive and true negative classifications. A higher emotional and physical cost is born by patients sent to hospice care but who ultimately survive six months – a false positive. The highest cost of all, emotionally, economically and physically is born by the patient and his or her family when

costly treatment is prolonged for a patient who does not survive six months and who should have been referred to a hospice care program – a false negative. In this last case, some or all of the benefits of hospice care would be lost while the stresses and economic burden of aggressive treatment are endured.

In this light, the threshold parameter, τ (described in Section 5.5), can be seen as a representation of the patient and family's preference for hospice care treatment and their risk tolerance for a mistaken referral. The threshold parameter relates sensitivity to specificity and stipulates the required level of certainty for a positive classification. A higher threshold value requires a higher probability of not surviving six months for the classification of a patient as a hospice candidate, decreasing the sensitivity and increasing specificity (indicating a preference for continued treatment). Conversely, a lower threshold value increases sensitivity while reducing specificity, indicating a preference for avoiding the costly mistake of unnecessary treatment.

As this threshold value is a subjective matter and varies between physicians, patients and family members, one suggested approach [56] involves the measurement of the amount of regret the decision maker would have should an incorrect decision be made. As medical decisions must take into account the preferences of those ultimately affected by the decision, this application of regret theory allows for the formal treatment of those preferences by calculating the threshold value as a function of the measured anticipated regret.

Conclusions

Logistic regression models dominate clinical prognostic models, largely as a result of the simplicity of its application in widely available software packages, the history of usage with successful results in the field, and the ability to statistically interpret model parameters [57]. Logistic regression, however, is not able to identify non-linear structures in the dataset, and its results may be invalidated when its assumptions are not met in practice.

So-called black-box models have seen increased usage, with generally improved accuracy at the cost of drawbacks in the interpretability of the parameters and in the traceability of the model process. These drawbacks have limited the popularity of black-box models outside of domains in which accuracy is of much higher importance than interpretability.

This paper contributes to the growing body of research in RST as a prognostic modeling tool [37, 39-41] and highlights the strengths of this approach in terms of accessibility. RST is found to perform similarly to two common classification approaches, LR and SVM, while also offering more information. The intuitive structure of the RST approach, built on similarity relations and expressed in terms of if-then decision rules, offers both more insight into the model process and more opportunity for the knowledge extraction process to incorporate the personal preferences of those making and being affected by the decision.

There is an emergent trend towards personalized healthcare [58-60] – concurrent with advances in the field of data acquisition and storage – propelled by increasingly available personal healthcare data. In this respect, RST shows promising potential for data-driven prognostic models in medicine that are adaptive to personal healthcare preferences.

However, the performance of classification models is still a major issue for the targeted domain of life expectancy prognostication. Classifier performance, measured by AUC, is good but sub-optimal, which indicates a challenging problem in need of further research. The increased performance achieved by the reduct approximation approach indicates a dataset of highly diverse patients. Future research will explore methods to produce more accurate results by addressing this diversity.

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Extensions to Regret-based Decision Curve Analysis: An application to hospice referral for terminal patients

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Abstract

Background: Despite the well documented advantages of hospice care, most terminally ill patients do not reap the maximum benefit from hospice services, with the majority of them receiving hospice care either prematurely or delayed. Decision systems to improve the hospice referral process are sorely needed.

Methods: We present a novel theoretical framework that is based on well-established methodologies of prognostication and decision analysis to assist with the hospice referral process for terminally ill patients. We linked the SUPPORT statistical model, widely regarded as one of the most accurate models for prognostication of terminally ill patients, with the recently developed regret based decision curve analysis (regret DCA). We extend the regret DCA methodology to consider harms associated with the prognostication test as well as harms and effects of the management strategies. In order to enable patients and physicians in making these complex decisions in real-time, we developed an easily accessible web-based decision support system available at the point of care.

Results: The web-based decision support system facilitates the hospice referral process in three steps. First, the patient or surrogate is interviewed to elicit his/her personal preferences regarding the continuation of life-sustaining treatment vs. palliative care. Then, regret DCA is employed to identify the best strategy for the particular patient in terms of threshold probability at which he/she is indifferent between continuation of treatment and of hospice referral. Finally, if necessary, the probabilities of survival and death for the particular patient are computed based on the SUPPORT prognostication model and contrasted with the patient's threshold probability. The web-based design of the CDSS enables patients, physicians, and family members to participate in the decision process from anywhere internet access is available.

Conclusions: We present a theoretical framework to facilitate the hospice referral process. Further rigorous clinical evaluation including testing in a prospective randomized controlled trial is required and planned.

Background

Introduction

Hospice services have been proven to provide better quality of care to dying patients[1-3] by optimizing pain relief [4,5] and reducing emotional stress [1,6,7]. Furthermore, hospice care is associated with greater patient-family satisfaction[8], is shown to be cost effective[9,10], and most importantly, it has been attributed with increased survival in some patients [11]. Despite these well documented advantages, many terminally ill patients do not reap maximum benefits from hospice care. The fundamental reason for this is related to the less than optimal and frequently poorly timed referral of terminally ill patients to hospice [1,12]. As a result, many patients die within a few days of referral, or live many years after the referral was made [13].

According to Medicare regulations, a person should be referred to hospice if his/her "life expectancy (LE) is 6 months or less" [1,14]. Hence, the problem of meaningful referrals relates to the accurate estimation (prognosis) of death within approximately 6 months after evaluation for hospice care. However, statistical models designed to assist physicians in predicting life

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expectancy (LE), although beneficial [15,16], so far they failed to improve the quality of care at the end of life [17-21].

One such statistical model is SUPPORT (Study to Understand Prognoses and Preferences for Outcomes and Risks of Treatments), designed to calculate the probability of survival over a period of 180 days [22,23]. Although the SUPPORT model has been well validated [17,22] for prognostication of LE in terminally ill patients, a controlled trial of SUPPORT failed to demonstrate any impact on the overall quality of care for these patients [17,20]. We postulate that this lack of impact may be due to the fact that SUPPORT results, were not linked to any decision methodology that would translate the probability of survival to a hospice referral recommendation. Therefore, the full potential of the model's prognostication power remained unexploited.

In this work, we link the SUPPORT prognostication model with the recently developed decision methodology regret DCA [24] to facilitate the hospice referral process. Regret DCA relies on regret theory and decision curve analysis [25] to recommend the optimal management strategy for a patient, accounting for the personal attitudes and values of the particular patient or his/her surrogate.

Furthermore, we extend regret DCA to incorporate harms and effects of treatment as well as harms associated with the prognostication test to the decision model. The presented methodology is integrated into a comprehensive clinical decision support system developed to facilitate the hospice referral process.

Methods
Dataset
In our analysis, we utilized the entire SUPPORT dataset, both development and validation cohorts. The dataset is presented in detail elsewhere [22]. Medical records of 8,329 seriously ill hospitalized adults are included.

Support model
SUPPORT is a multivariable model designed to estimate probability of survival for seriously ill hospitalized patients over a period of the subsequent 180 days. The model variables include the patient's medical condition compatible with one of eight major diagnostic groupings (Acute Respiratory Failure, Multiple Organ System Failure, Chronic Obstructive Pulmonary Disease, Congestive Heart Failure, Hepatic Cirrhosis, Neurological Coma, Lung or Colon Cancer), the patient's current age, number of days in the hospital before study entry, neurologic status, and 11 physiologic measures recorded on day 3 after study entry [22].

The SUPPORT implementation for the estimation of survival probability is detailed in the appendix. Due to the nature of the hospice referral problem we also express the survival probability in terms of mortality. We can convert the estimated survival probability (SP) (equation A2) to probability of death within 180 days (denoted here as p) using the equation:

$$p = 1 - SP = 1 - P\{T \geq t | \text{disease group} = i\} \qquad (1)$$

where SP is the survival probability computed by SUPPORT, $i \in [1,8]$ the patient's disease group, T is the survival time in days, and t is an arbitrary time (typically expressed in days e.g. $t \in [1,180]$).

In terms of accuracy, the SUPPORT model has an area under the receiver-operating characteristics curve (ROC) for prediction of surviving 180 days of 0.79 in the phase I development cohort and 0.78 in the phase II validation cohort [22].

Decision model
Figure 1 depicts the decision tree summarizing the process of hospice referral. The four outcomes and their corresponding utilities (U) shown are:
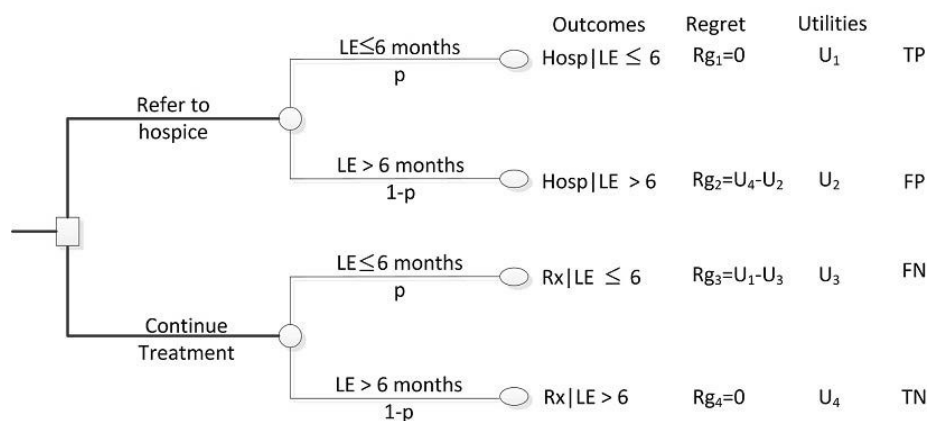
Figure 1 Decision tree for hospice referral. In this figure, p is the probability that a patient's LE is less than or equal to 6 months; 1-p is the probability that a patient's LE is greater than 6 months; U_i are the utilities associated with each outcome; Rg_i is the regret associated with each outcome.

1. U_1: Refer the patient to hospice and the patient's LE is less than or equal to 6 months (Hosp|LE ≤ 6).
2. U_2: Refer the patient to hospice and the patient's LE is greater than 6 months (Hosp|LE > 6).
3. U_3: Continue treating the patient and the patient's LE is less than or equal to 6 months (Rx|LE ≤ 6).
4. U_4: Continue treating the patient and the patient's LE is greater than 6 months (Rx|LE > 6).

p is the probability associated with the presence of an event (e.g. patient's LE ≤ 6 months) as predicted by the SUPPORT model, 1 - p is the probability associated with the absence of the same event (e.g. patient's LE > 6 months).

As with any decision, one may come to realize that, in retrospect, an alternative decision would have been preferable. This knowledge may bring a sense of loss or regret [26-32]. In this paper, we use this sense of regret to determine the preferences of the decision maker towards alternative management strategies. Specifically, we employ regret theory to estimate the threshold probability, P_t, at which the decision maker (patient, physician, or family member) is indifferent between continuation of treatment vs. hospice referral. Based on the concept of threshold probability, the patient should be referred to hospice if his/her probability of death is greater than or equal to P_t(e.g. p ≥ P_t), and he/she should continue receiving curative treatment otherwise (p <P_t).

The threshold probability is derived as [24]:

$$P_t = \frac{1}{1 + \frac{U_1 - U_3}{U_4 - U_2}} \qquad (2)$$

In (2) U_1-U_3 is associated with regret of omission (e.g. the patient was not referred to hospice, instead he/she continued receiving unnecessary treatment) and U_4-U_2 with regret of commission (e.g. the patient was unnecessary referred to hospice instead of continue receiving life-sustaining treatment) [24].

To elicit the decision maker's regret, and therefore threshold probability, we utilize the DVAS (Dual Visual Analogue Scale) method [24]. One visual analogue scale is used to capture the regret associated with failing to refer the patient to hospice (e.g. continue unnecessary treatment) and the second scale to measure the regret associated with unnecessary hospice referral (e.g. failing to provide life-sustaining treatment) (Figure 2).

Elicitation of threshold probability can be achieved through a set of questions such as:

1. On the scale 0 to 100, where 0 indicates no regret and 100 indicates the maximum regret you could feel, how would you weigh the level of your regret if
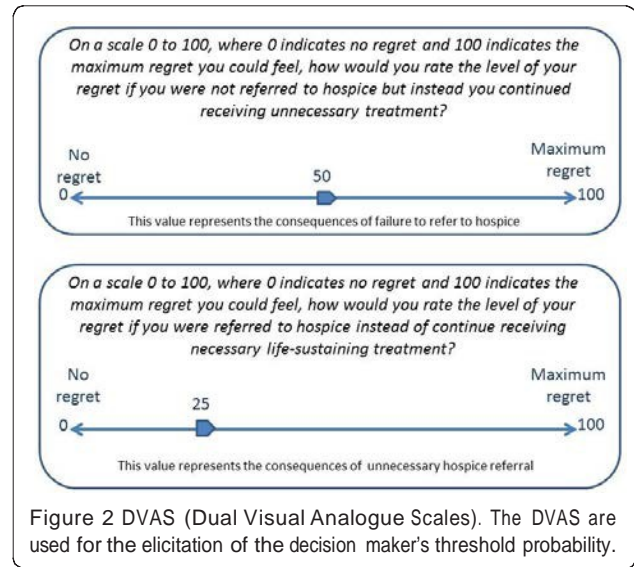
Figure 2 DVAS (Dual Visual Analogue Scales). The DVAS are used for the elicitation of the decision maker's threshold probability.

you were not referred to hospice but instead you continued receiving unnecessary treatment? That is, how much would you regret if you did not reap the benefits of hospice care? *Note that this value corresponds to U_1 - U_3.
2. On the scale 0 to 100, where 0 indicates no regret and 100 indicates the maximum regret you could feel, how would you weigh the level of your regret, if you were referred to hospice instead of continue receiving necessary life-sustaining treatment? That is, how much would you regret if you sustained harms from hospice care? *Note that this value corresponds to U_4 - U_2.

For example, suppose that the patient - who is aware of his/her terminal condition- answers 50 and 25 to the questions 1 and 2 respectively. This means that the patient considers 50/25 = 2 times worse not to be referred to hospice when necessary than receiving an unnecessary hospice referral. The threshold probability for this patient is (equation 2)

$$p_t = \frac{1}{1 + \frac{U_1 - U_3}{U_4 - U_2}} = \frac{1}{\frac{50}{25}} = 0.33 \text{ or } 33\% \ .$$

Regret DCA and extensions
The clinical problem we face in the situation of hospice referral is how to use reasonably accurate predictions of death, p, coupled with the patient's preferences (as expressed in terms of threshold probability, P_t) to arrive at the optimal decision for a specific individual. The problem is decomposed into three strategies: (1) act based on the prediction model (SUPPORT) (e.g. refer to hospice if p ≥ P_t and continue treating otherwise), (2)

refer all patients to hospice, and (3) continue current treatment for all patients (i.e. refer no patients to hospice).

Each of these strategies may inflict physiological and/or psychological damages to the patient. Specifically, a patient may suffer harms due to a treatment strategy (e.g. adverse effects) or harms due to the prognostication test (e.g. a test requiring invasive procedure). We express these harms as loss in utility associated with actions we may undertake. To that end, we define H_{Rx}, H_{Hosp} and H_{te} as the utility losses due to harms of the treatment, hospice, and prognostic test, respectively.

Figure 3 presents the decision tree describing the overall hospice referral problem. $p = P(D+)$ is the probability that the patient's LE is less than or equal to 6 months as estimated by the prediction model (SUPPORT); $1 - p = P(D-)$ is the probability that the patient's LE is greater than 6 months, and U_i, $i \in [1,4]$, are the utilities corresponding to each of the decision model outcomes (detailed in the previous section). The variables Hosp and Rx correspond to referring a patient to hospice and continuing current curative treatment, respectively. Rg, is the regret associated with an action, e.g. Rg(Hosp, D-) is the regret one may feel if the patient was referred to hospice when his/her LE was greater than 6 months. Finally, te designates that the patient received a prognostication test.

Considering the decision tree in Figure 3 we can compute the expected regret associated with each decision in terms of the utilities of each possible outcome as follows (detailed derivation is presented in the Appendix):
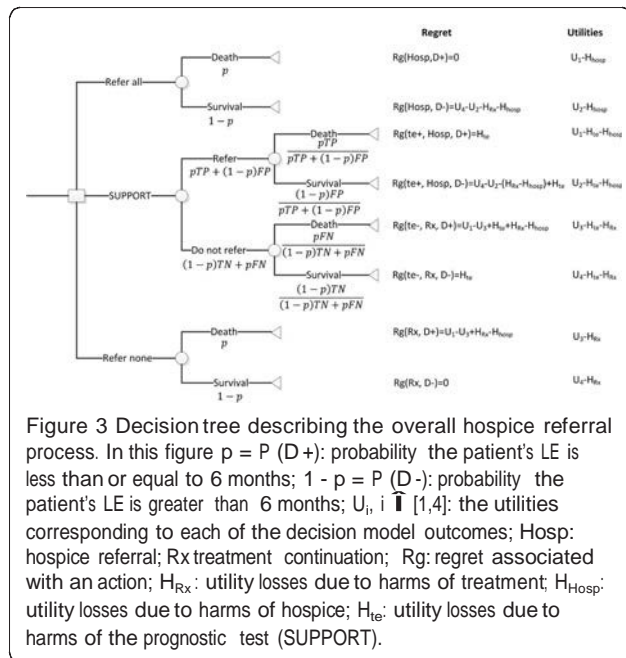
$$ERg[Hosp] = (1 - p) * (1 - RRR_{Hosp}) * \frac{P_t}{n} \qquad (3)$$

$$ERg[Rx] = p * (1 - RRR_{Rx}) \qquad (4)$$

$$
\begin{aligned}
ERg[SUPPORT] = \\
\big(1 - RRR_{Hosp} * (\#TP/n + \#FP/n) \\
- RRR_{Rx} * (\#FN/n + \#TN/n) \big) \\
* \frac{H_{te}}{U_1 - U_3 + H_{Rx} - H_{Hosp}} \\
+ (1 - RRR_{Hosp}) * \frac{\#FP}{n} * \frac{P_t}{1 - P_t} \\
+ (1 - RRR_{Rx}) * \frac{\#FN}{n}
\end{aligned} \qquad (5)
$$

In addition to harms, equations 3, 4 and 5 incorporate the effects of treatment and hospice care using measures of Relative Risk Reduction: and RRR_{Rx} RRR_{Hosp} respectively. The values for these measures are treatment specific and can be acquired from the literature. We have incorporated hospice effects because a recent study [11] has shown that early palliative care for patients with metastatic non-small cell lung cancer could increase survival. The variables TP, FP, FN, TN are related to the prognostic capability of the SUPPORT model (see appendix for detailed derivation) [24].

Since the regret of omission and regret of commission have been generalized to include effects and harms related to management strategies and testing, the function of threshold probability (equation 2) becomes:

$$ P_t = \frac{1}{1 + \frac{U_1 - U_3 + H_{Rx} - H_{Hosp}}{U_4 - U_2 - H_{Rx} - H_{Hosp}}} \qquad (6) $$

Where $U_1 - U_3 + H_{Rx} - H_{Hosp}$ corresponds to the regret associated with not referring the patient to hospice when necessary, and $U_4 - U_2 - H_{Rx} - H_{Hosp}$ corresponds to the regret associated with unnecessary hospice referral.

Choosing the optimal strategy

The optimal strategy is selected as the one which will bring the least amount of regret. The regret DCA algorithm expresses the regret associated with each strategy in terms of threshold probability and is implemented as follows [24]:

1. Select a value for threshold probability.
2. Assuming that patients should be referred to hospice if $p \geq P_t$ and should continue current treatment otherwise, compute #TP and #FP for the prediction model.
3. Calculate the ERg(SUPPORT) using equation 5.

Figure 3 Decision tree describing the overall hospice referral process. In this figure $p = P(D+)$: probability the patient's LE is less than or equal to 6 months; $1 - p = P(D-)$: probability the patient's LE is greater than 6 months; U_i, $i \in [1,4]$: the utilities corresponding to each of the decision model outcomes; Hosp: hospice referral; Rx treatment continuation; Rg: regret associated with an action; H_{Rx}: utility losses due to harms of treatment; H_{Hosp}: utility losses due to harms of hospice; H_{te}: utility losses due to harms of the prognostic test (SUPPORT).

Figure 4 Decision curves for hospice referral. In this figure, $RRR_{Hosp} = 0$, $RRR_{Rx} = 0$, $H_{Rx} = H_{Hosp} = H_{te} = 0$. At threshold probability equal to 10%, the optimal decision is refer the patient to hospice; at 40% the optimal decision is to use the SUPPORT model.

4. Calculate $ERg(Rx)$ using equation 4.
5. Compute the $ERg(Hosp)$ using equation 3.
6. Repeat steps 1 - 6 for a range of threshold probabilities.
7. Graph each expected regret function calculated in steps 3-5 against each threshold probability.

At each threshold probability, the action with the lowest value of expected regret corresponds to the most desired action. For example, in Figure 4, at a threshold probability equal to 10% (e.g. the patient considers 9 times worse not to be referred to hospice when necessary than to receive an unnecessary hospice referral), the optimal strategy is to refer the patient to hospice.

Figures 5, 6 and 7 depict the regret associated with alternative decision strategies as they relate to different

Figure 5 Decision curves as a function of RRR_{RX}. In this figure, $RRR_{Hosp} = 0$, $RRR_{Rx} = 2$ to 8%, $H_{Rx} = H_{Hosp} = H_{te} = 0$. As the effect of treatment increases, the regret associated with treating all patients and with the SUPPORT model slightly decreases. The strategy of using the SUPPORT model to refer a patient to hospice is the action with the least amount of regret for the wider range of threshold probabilities.

Figure 6 Decision curves as a function of RRR_{Hosp}. In this figure, $RRR_{Hosp} = 2\%$ to 8%, $RRR_{Rx} = 0$, $H_{Rx} = H_{Hosp} = H_{te} = 0$. As the effect of hospice care increases, the regret associated with hospice and with the SUPPORT model slightly decreases. As previously, the strategy of using the SUPPORT model to refer a patient to hospice is the action with the least amount of regret for a wide range of threshold probabilities.

values of hospice effectiveness (Figure 5), treatment effectiveness (Figure 6), and harms due to the prognostication test (Figure 7). As expected, when the harms due to the prognostication test are increased, then the area of threshold probability at which the prognostication model is the optimal decision is reduced (Figure 5). Even though, it is not expected that the SUPPORT model will actually create harms, at least physiological, to the patient, this is not always the case for other diagnostic tests that may be more invasive (e.g. screening for prostate cancer).

As can be seen from Figures 5, 6 and 7 the optimal decision is derived by the SUPPORT model for a rather wide range of threshold probabilities. Therefore, it appears that the SUPPORT model is the superior

Figure 7 Decision curves as a function of H_{te}. In this figure, $RRR_{Hosp} = 0$, $RRR_{Rx} = 0$, $H_{Rx} = H_{Hosp} = 0$ and $H_{te} = 0\%$ and 10%. As the harms associated to the prediction test increase, so does the expected regret of utilizing the SUPPORT model for hospice referral. Increasing the harms due to treatment or due to hospice care does not have an effect on the decision curves.
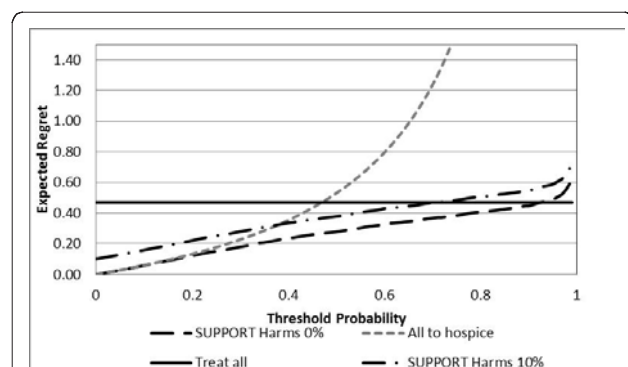
strategy for the vast majority of decision makers, regardless the effects of the alternative management strategies. However, since the threshold probability expresses the personal preferences of a particular decision maker, it is not unusual for specific patients to have smaller or greater threshold probability values than the majority of decision makers. This is the power of the proposed methodology, which allows for decision making at the individual level. For example, if the decision maker presents a threshold probability greater than ≈92%, the optimal decision would be to continue life-sustaining treatment even if it is deemed not to be effective(Figure 4). Similarly, for small values of threshold probability, the desired action would be to refer the patient to hospice.

Decision Support System

As our theoretical discussion highlighted, decisions about life and death are complex and difficult at both the emotional and cognitive level. Therefore, it is not surprising that the SUPPORT model originally failed to improve the quality of care for terminally ill patients despite its reasonable accuracy in prediction of probability of survival [17,20]. Any attempt to focus on a single dimension of the complex hospice referral process is not likely to succeed. An accurate prognostic model is only the first step. Having the apparatus to take into account trade-offs associated with the hospice referral decision while taking into consideration the patients' preferences represent further necessary steps to improve the care of terminally ill patients. In addition, we hypothesize that the SUPPORT intervention failed because it was not available at the point of care in real time. This is because the most desired outcomes are best achieved when decision-making occurs in real-time, at the point of care [33,34].

To facilitate the decision making process for the hospice referral at bedside, we propose a web-based clinical decision support system (CDSS) that computes the probabilities of survival and death for individual patients using the SUPPORT model, elicits personal preferences from patients and/or physicians, and utilizes regret DCA to suggest the optimal decision for a particular patient.

Features
Access
Our goal is to develop a CDSS that can be accessed by everyone and from anywhere regardless the operating system one uses. At the same time, it is desirable to develop a system that can eventually be integrated with various healthcare providers' electronic medical records (EMR). We concluded that a web-based implementation would fulfil such requirements.
Data storage
The CDSS performs the required computations without retaining or transmitting sensitive and identifiable information.

Results
In this section we present a prototype of the CDSS, developed to demonstrate the applicability of our theoretical framework for hospice referral. Each subsection describes the results of the methods shown in the previous section in conjunction with the description of the corresponding module. Figure 8 depicts the logical diagram that outlines the operation of the CDSS. Briefly, the operation begins by interviewing the patient or surrogate to elicit his/her threshold probability. Based on the value of threshold probability equation, the optimal strategy for the particular patient is derived (e.g. refer to hospice, continue treatment, or use of prediction model). If the optimal strategy is to follow the
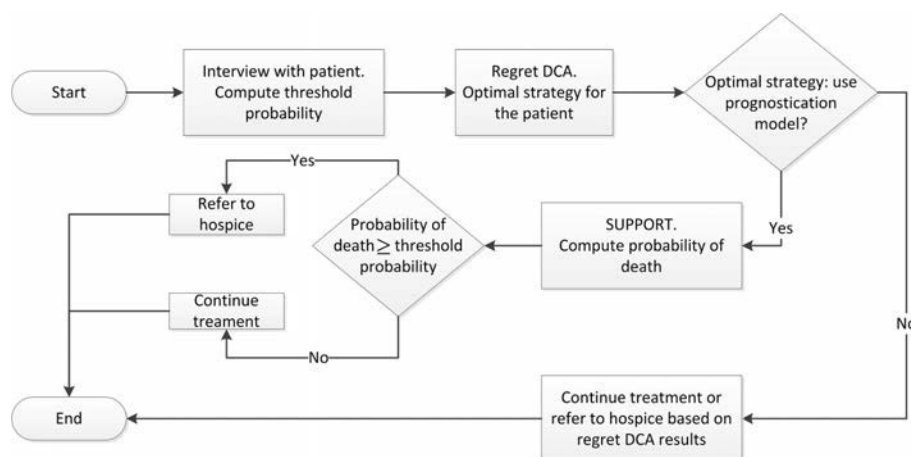
Figure 8 Block diagram outlining the operation of the DSS.

prediction model (SUPPORT), then using the equations A1, A2 and 1, the probabilities of survival and death are computed for the particular patient. The probability of death is then contrasted with the patient's threshold probability and the optimal decision is derived (refer to hospice, or continue treatment). At each step described, the patient selects the level of information he/she wishes to be exposed to. For example, the patient may not wish to know his/her threshold probability or probability of death. Instead he/she wishes to know only the optimal decision regarding his/her condition.

General implementation details

The proposed CDSS is a web-based application residing on the USF Health servers. The web address is http://health.usf.edu/research/ebm/decisionaids.htm. It has been developed based on the Adobe® ColdFusion® application technology and the interface has been designed using html and JavaScript programming languages. The hardware and software requirements from the user's point of view are modest. The system runs on any contemporary computer with net browsing capabilities. However, at this stage the CDSS is not optimized for use with handheld devices. The CDSS consists of 3 different modules as described below.

Elicitation of threshold probability module

The threshold elicitation module consists of the dual visual analogue scales, used to weigh the patient's regret in the case of wrong decisions. Each scale has 100 points where 0 corresponds to no regret and 100 to maximum regret. Depending on the role of the decision maker (e.g. patient/surrogate or physician) two different sets of questions are displayed. These questions are designed to capture the regret of omission and the regret of commission. For the remainder of this paper, we assume that the decision maker is the patient. As in pain scales [35], each visual analogue scale uses facial expressions to graphically represent variations in regret (Figure 9). A summary of the decision maker's preferences is presented for final verification. The threshold probability for the particular patient is derived using equation 2, however is not displayed until the decision maker requests it.

Decision module

The decision module utilizes the decision maker's threshold probability and the regret DCA methodology to derive the optimal decision. For example, the preferences of the patient depicted in Figure 9, correspond to a threshold probability equal to 29%. From Figure 4 the
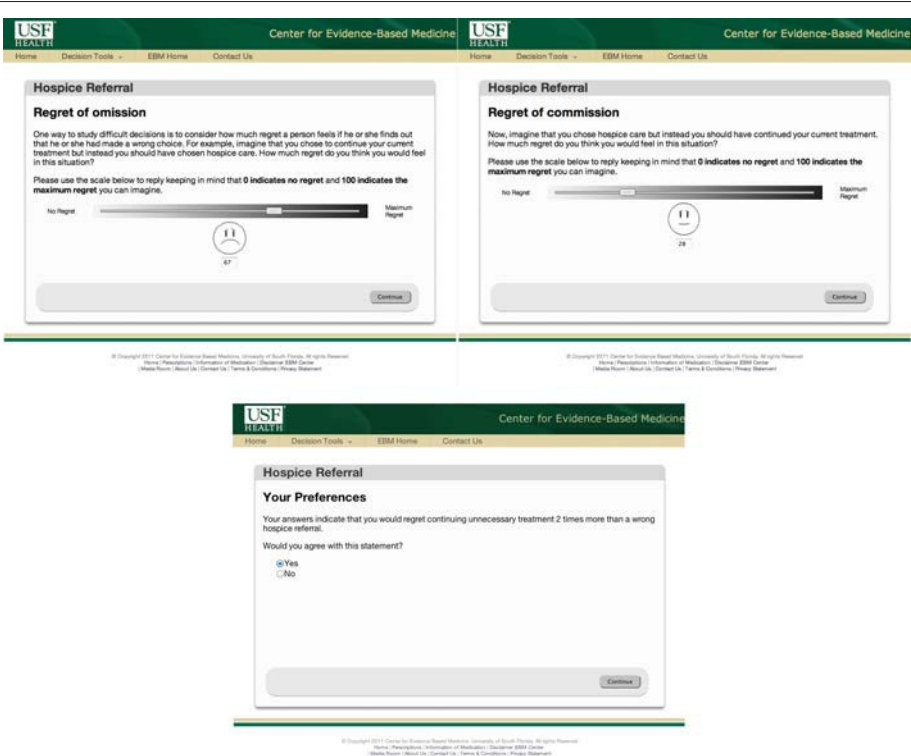
Figure 9 Elicitation of threshold probability. The user (patient/surrogate/physician) weighs the two alternative management strategies in terms of regret.

strategy that will bring the least amount of regret is to use the prognostication model (SUPPORT) for the hospice referral recommendation. In this case, the decision module initiates the SUPPORT module.

SUPPORT module

If the optimal strategy derived by the decision module is to utilize the prognostication model, the SUPPORT module is enabled. This module (Figure 10) is used to compute the probability of death for the particular patient based on the SUPPORT prognostication model. Currently, the user inserts all required information to the CDSS. In the future, this information will be captured automatically from the health care provider's electronic medical records system. Data validation restrictions have been imposed to protect the integrity of the collected data.

Once the values of all available variables have been inserted in the corresponding cells, the patient's life expectancy and probabilities of survival and death are computed. The decision module is employed again to display the optimal recommendation.

Decision justification module

The decision justification module explains in detail and at the user's request the reasons that led to a particular recommendation (Figure 11). It contains information regarding the decision maker's threshold probability, the optimal strategy associated with the threshold probability and the patient's probability of death (if applicable). Since people often misinterpret probabilities [36], we complement the results presented in terms of probabilities using frequency format (Figure 11). The latter format is currently considered the best way to represent favorable and unfavorable facts regarding medical interventions [37]. The justification module is highly technical and should only be reviewed by decision makers who wish to know more about their or their patient's condition.

Case Study

Figure 12 summarizes the decision process for a patient whose information is simulated in Figures 10, 11 and 12. The probability of death and the threshold probability of this patient have been computed as 85% and 29% respectively. At a 29% threshold probability, the optimal strategy is to use the prediction model for hospice referral (Figure 4). Therefore, since $p > P_t$ the patient should be referred to hospice. For completeness, all possible decision routes are depicted in Figure 12. The route corresponding to the specific simulated patient is shown using bold arrows.

Figure 10 SUPPORT user interface. The user enters all information regarding the particular patient to compute the probability of death and survival within the next 6 months. LE results are presented to the patient through the decision justification module after the patient's request.
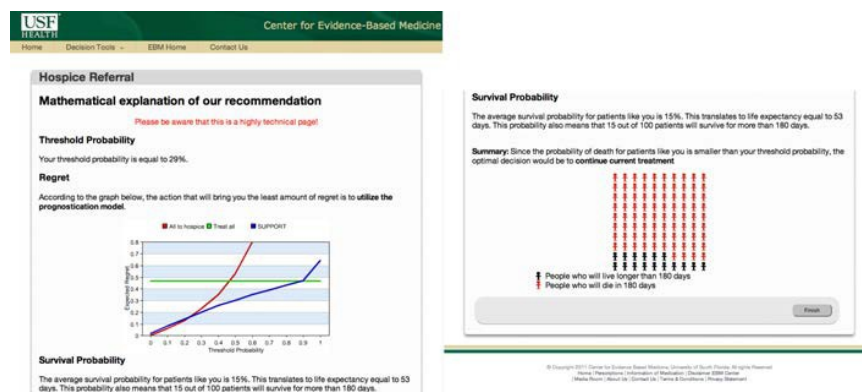
Figure 11 Justification of the hospice referral recommendation. The particular patient depicted has 29% threshold probability at which the optimal strategy is derived by the SUPPORT model. The patient has 85% probability of death in the next 180 days. Therefore, the optimal decision is to be referred to hopsice.

Discussion

In this article we describe both the theory and application behind a hospice referral clinical decision support system. To the best of our knowledge, this is the first CDSS that integrates two well established methodologies, one for prognostication (SUPPORT) and the other for decision making (regret DCA), to assist with the hospice referral decision-making process.

The recently developed regret DCA incorporates the decision maker's preferences towards alternative management strategies from the perspective of regret theory in terms of threshold probability. Such an approach promotes personalized patient care. We anticipate that the regret-based approach is more appropriate for the hospice referral process than other preference elicitation techniques, due to the nature of the problem where there are really no optimal options available- the optimal decision can be only considered as the one with the least regret.

Modern cognitive theories increasingly focus on the so called dual-processing theory in which both intuition (system 1) and analytical, deliberative process (system 2) are important for balancing risks and benefits in the decision-making process [38]. We believe that rational decision-making should take into account both formal principles of rationality and human intuition about good decisions[24,39,40]. One way to accomplish this is to use regret, a cognitive emotion, to serve as the link between systems 1 and 2 [24]. By taking into account the consequences of our actions as well as the circumstances under which we can live with our mistakes we anticipate that the goal of reconciling the formal
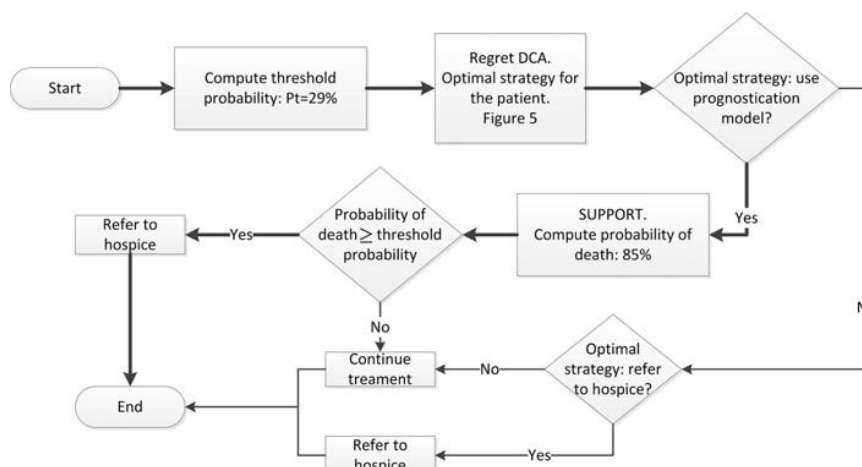
Figure 12 Block diagram summarizing the decision process. The bold route corresponds to the patient simulated in figures 10, 11 and 12.

Table 1 Values of Survival (S) as described in equation A2 for different disease types and varying survival times

t	$S_{ARF/MOSF}$	$S_{COPD/CHP/Cirrhosis}$	S_{Coma}	S_{Cancer}
0	0.994	0.998	0.993	0.993
30	0.691	0.889	0.630	0.578
60	0.601	0.837	0.609	0.407
90	0.562	0.800	0.581	0.264
120	0.532	0.772	0.569	0.190
1 50	0.508	0.751	0.551	0.135
177	0.493	0.733	0.545	0.108

principles of rationality and human intuitions about good decisions can be met [24,29,39,40]. This is particularly true in the situation of terminally ill patients.

Our web-based CDSS reflects modern cognitive theories to facilitate integration of the decision-making ingredients necessary for hospice referral decisions. The CDSS encapsulates all required information for the hospice referral process into a flexible software that can be used at bedside. Obviously, hospice referral decisions are complex and must be exercised with full compassion and deliberation. We advise against the use of our system as an automatic decision making tool that by-passes important personal interactions between the patient and his/her physician. It is important to stress that the elicitation of the threshold probability as described herein reflects the belief (also captured in recent legislation [41]) that patients and their families want to be told the "truth" about the patients' terminal sickness [22,41,42] and that physicians have ethical obligations to share this information with patients and their families [41,42]. Our system should be understood as an aid to facilitate decisions in terminal phases of patient lives.

Our approach has limitations as well. The main limitation of the proposed system remains the complexity of the SUPPORT model. Currently, the system still requires manual entry of data. In addition, failure to enter all data can jeopardize the accuracy of prediction and therefore, the decision process. To cope with this limitation, we plan to integrate our system into various health providers' EMRs. Based on each EMR, specifically designed queries will be used to retrieve lab values and patient demographics to be fed automatically into our system; a process that will reduce the amount of missing values and input errors.

The second limitation of the proposed system is that empirical data are not available to assess how the system actually works in practice. While we plan to undertake empirical testing of the system described here, we believe that a strong theoretical underpinning will enable better hospice referral decisions even in the current form. This is because our system will essentially

operationalize the decision-making process, which is supposed to occur in every day practice. Nevertheless, we need to firstly, identify the system's feasibility in real life settings and ultimately, if it appears to be usable and assessed favourably by all those involved in the hospice-referral decision-making process, to test it in randomized controlled trials against traditional care.

Our future plans include both empirical testing and implementation of multiple additional prognostication models which will be used in parallel to assess optimal decisions regarding hospice referral and take advantage of the regret DCA methodology. We anticipate that for a different range of threshold probabilities these models may perform better than the SUPPORT model. Furthermore, our intent is to develop a separate version of our CDSS optimized for mobile devices.

Conclusions

In this work we have presented the theoretical framework, accompanied by the associated CDSS, to facilitate end of life care decisions. Our work combines the prognostication power of the SUPPORT model, the simplicity of the DVAS methodology in eliciting people's preferences and the effectiveness of regret DCA at evaluating alternative management strategies to resolve the dilemma of choosing traditional vs. palliative care for patients at terminal stages. A clinical evaluation of the CDSS is planned.

Appendix
Support implementation
SUPPORT is implemented in two steps. First, the SUPPORT physiology score is computed based on equation A1 [22].

$$
\begin{aligned}
SPS = {} & 259.9\{ARF/MOSF\} + 263.4\{COPD/CHF\} \\
& + 241.4\{Cirrhosis/Coma\} \\
& + 281.5\{Lung/ColonCancer\} \\
& - 0.06174\min(PaO_2/FiO_2, 225) \\
& - 0.6316\min(MeanBP, 60) \\
& + 1.0205WBC - 0.3676(WBC - 8)_+ \\
& - 0.5631(WBC - 11)_+ + 0.2691\min(Alb, 4.6) \\
& + 0.2312Aresp - 2.362Temp + 1.326(Temp - 36.6)_+ \\
& + 2.473(Temp - 38.3)_n - 1.579 \times 10^{-1}HR \\
& + 9.770 \times 10^{-5}(HR - 55)_+^3 - 2.189 \times 10^{-4}(HR - 80)_+^3 \\
& + 1.518 \times 10^{-4}(HR - 110)_+^3 \\
& - 3.062 \times 10^{-5}(HR - 149)_n^3 + 0.9763Bil \\
& - 0.7481(Bil - 7)_+ - 6.8761Cr \\
& + 11.6058(Cr - 0.600)_+^3 - 21.8413(Cr - 1.000)_+^3 \\
& + 10.3574(Cr - 1.500)_+^3 - 0.1219(Cr - 5.399)_+^3 \\
& - 0.6167096Na + 0.0021118(Na - 128)_n^3 \\
& - 0.0036730(Na - 135)_+^3 + 0.0006126(Na - 139)_+^3 \\
& + 0.0009486(Na - 148)_n^3 \\
& - 6.278\{COPD/CHF\} \times \min(Alb, 4.6) \\
& - 11.45\{Lung/ColonCancer\} \times \min(Alb, 4.6) \\
& + \{ARF/MOSF\}[-2.3549WBC \\
& + 2.7494(WBC - 8)_+ - 0.4638(WBC - 11)_+]
\end{aligned}
\tag{A1}
$$

where: Alb: albumin; Aresp: APACHE III respiration score; Bil: bilirubin; Cr: Creatinine; Na: sodium; PaO₂: partial pressure oxygen in arterial blood; MeanBP: mean arterial blood pressure; WBC: white blood cell count in thousands; Temp: temperature in Celsius; HR: heart rate per minute; ARF: Acute respiratory failure; MOSF: Multiple organ failure; Cirrhosis: Cirrhosis; Coma: Coma; Lung: Lung cancer; ColonCancer: Colon cancer; COPD: Chronic obstructive pulmonary disease; CHF: Congestive heart failure. Also:

$$\{disease\ group\} = \begin{cases} 1, & \text{if patient in the disease group} \\ 0, & \text{otherwise} \end{cases}$$

$$(x)_+ = \begin{cases} x, & \text{if } x > 0 \\ 0, & \text{otherwise} \end{cases}$$

WBC = 9, if WBC < 9 and {disease group} ≠ ARF /MOSF
WBC = 40, if WBC > 40
Cr = 15, if Cr >15

The second step in implementing the SUPPORT model is to calculate the probability of survival for the individual patient based on equation A2 [22].

$$P\{T \geq t | \text{disease group} = i\} = S_i(t)^{e^{\dot{x_b}}} \tag{A2}$$

where T: survival time in days; t: arbitrary time; S described in Table 1[22] and

$$\begin{aligned} X_b^i = &-3.652 + 0.8356\{CHF\} + 0.9257\{Cirrhosis\} \\ &+ 0.6287\{LungCancer\} \pm 1.1803\{MOSFw/Malig\} \\ &+ 0.01434 Scoma \pm 0.01935 Age + 0.2413 Cancer \\ &- 1.863\ Hday + 3.4^{-1} + 0.08121 SPS \\ &+ Age[0.015261\{COPD/CHF/Cirrhosis\} \\ &+ 0.009047\{Coma\} - 0.008294\{Cancer\}] \\ &+ Age[-0.012498\{CHF\} - 0.004578\{Cirrhosis\} \\ &- 0.001435\{LungCancer\} \\ &- 0.013891\{MOSFw/Malig\} \end{aligned}$$

where Scoma: SUPPORT coma score (0-100); MOSFw/Malig: Multiple organ failure with malignancies; Hday: day in hospital when qualified for study; Cancer: Cancer by comorbidity or primary disease category (0 = no; 1 = present; 2 = metastatic) [22].

Derivation of the Expected Regret functions
As outlined in the Introduction, seriously and terminally ill patients may reap a number of benefits by the hospice program. Nevertheless, after enrollment into hospice, the patient (or the family, or the physician) may feel that this was a wrong decision, and subsequently may regret it. Similarly, the patient may feel regret for the treatment that he/she continues to receive because it is unnecessary, inappropriate, and/or harmful. Figure 3 represents our hospice decision tree in terms of regret from which we can compute the expected values of regret associated with each strategy as follows:

$$\begin{aligned} ERg[Hosp] = \\ (1-p)*(U_4 - U_2 - H_{Rx} - H_{Hosp}) \end{aligned} \tag{A3}$$

$$ERg[Rx] = p*(U_1 - U_3 + H_{Rx} - H_{Hosp}) \tag{A4}$$

$$\begin{aligned} ERg[SUPPORT] = &\ p*TP*H_{te} \\ &+ (1-p)*FP \\ &*(U_4 - U_2 - (H_{Rx} - H_{Hosp}) + H_{te}) \\ &+ p*FN*(U_1 - U_3 + (H_{Rx} - H_{Hosp}) + H_{te}) \\ &+ (1-p)*TN*H_{te} \end{aligned} \tag{A5}$$

The variables TP, FP, TN, FN are related to the probabilities $P(p \geq P_t \cap D+)$, $P(p \geq P_t \cap D-)$, $P(p < P_t \cap D-)$ and $P(p < P_t \cap D+)$ respectively, and are estimated as follows:

- $P(p \geq P_t \cap D+) \approx$ the number of patients who will die within 6 months and for whom the prognostic probability is greater than or equal to P_t (with #TP = number of patients with true positive results, $P(p \geq P_t \cap D+) \approx \frac{\#TP}{n}$, where n is the total number of patients in the study).
- $P(p \geq P_t \cap D-) \approx$ the number of patients who will survive for longer than 6 months and for whom the prognostic probability is greater than or equal to P_t (with #FP = number of patients with false positive results, $P(p \geq P_t \cap D-) \approx \frac{\#FP}{n}$).
- $P(p < P_t \cap D+) \approx$ the number of patients who will die within 6 months and for whom the prognostic probability is less than P_t (with #FN = number of patients with false negative results, $P(p < P_t \cap D+) \approx \frac{\#FN}{n}$).
- $P(p < P_t \cap D-) \approx$ the number of patients who will survive for longer than 6 months and for whom the prognostic probability is less than P_t (with #TN = number of patients with true negative results, $P(p < P_t \cap D-) \approx \frac{\#TN}{n}$).

To incorporate the effects of alternative treatments (e.g. treatment and hospice care) in equations A3-A5 we use the Relative Risk Reduction reported in literature for each strategy as follows:

$$ERg[Hosp] = (1 - p) * (1 - RRR_{Hosp})$$
$$* (U_4 - U_2 - H_{Rx} - H_{Hosp})$$
(A6)

$$ERg[Rx] = p * (1 - RRR_{Rx})$$
$$* (U_1 - U_3 + H_{Rx} - H_{Hosp})$$
(A7)

$$ERg[SUPPORT] =$$
$$p * (1 - RRR_{Hosp}) * TP * H_{te}$$
$$+ (1 - p) * (1 - RRR_{Hosp}) * FP$$
$$* (U_4 - U_2 - (H_{Rx} - H_{Hosp}) + H_{te})$$
$$+ p * (1 - RRR_{Rx}) * FN$$
$$* (U_1 - U_3 + (H_{Rx} - H_{Hospe}) + H_{te})$$
$$+ (1 - p) * (1 - RRR_{Rx}) * TN * H_{te}$$
(A8)

Since $TP + FN = 1$ and $FP + TN = 1$, we have:

$$p * TP + (1 - p) * FP + p * FN$$
$$+ (1 - p) * TN = p + (1 - p) = 1$$

Therefore, equation A8 becomes:

$$ERg[SUPPORT] =$$
$$(1 - p * RRR_{Hosp} * TP - (1 - p) * RRR_{Hosp} * FP$$
$$- p * RRR_{Rx} * FN - (1 - p) * RRR_{Rx} * TN) * H_{te}$$
$$+ (1 - p) * (1 - RRR_{Hosp}) * FP$$
$$* \left(U_4 - U_2 - (H_{Rx} - H_{Hosp}) \right)$$
$$+ p * (1 - RRR_{Rx}) * FN$$
$$* \left(U_1 - U_3 + (H_{Rx} - H_{Hosp}) \right)$$
(A9)

Scaling the equations A3, A4 and A9 with the quantity $(U_1 - U_3 + H_{Rx} - H_{Hosp})$ and replacing the expression $\frac{U_4 - U_2 - (H_{Rx} - H_{Hosp})}{U_1 - U_3 + H_{Rx} - H_{Hosp}}$ with $\frac{P_t}{1 - P_t}$, we derive the final equations for the expected regret (equations 3, 4, and 5).

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Authors' contributions
All authors contributed equally to this work. All authors have read and approved the final manuscript.

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The authors declare that they have no competing interests.

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Appendix 8 data collection forms

Patient Data Collection Form

Patient ID # [   ]

Physician ID # [   ]

Demographics

Who is being interviewed? (circle one)   Patient   Surrogate

Date of Birth: [   ]   **Date of Death:** [   ]   **Date of TGH Admission:** [   ]

Gender (check one): ☑ Male   ☑ Female

Ethnicity (circle one):   White   African American   Hispanic   Asian   Pacific Islander   Other:

Diagnosis

* Primary Diagnosis: [   ]

Date of Diagnosis: [   ]   **Patient Directives (circle one):**   Do Not Resuscitate (DNR)   Full Code

* Days in hospital when qualified for study (please circle one); if more than 10, write out.

    1   2   3   4   5   6   7   8   9   10   Other:

* Number of days in hospital: [   ]

	Vital Signs	Value	Date Collected
*	Systolic BP	mmHg	
*	Diastolic BP	mmHg	
*	Body Temperature	F	
*	Heart Rate	BPM	
*	Respiratory Rate	RR	

	Laboratory Data	Value	Date Collected
*	Serum Creatinine	mg/dl	
**	Serum Bilirubin	mg/dl	
*	Serum Sodium	mEq/lt	
*	Serum Albumin	g/dl	
	Blood Glucose	mg/dl	
	Hematocrit	%	
	Blood pH		
	24 Hour Urine Output	Cc/day	
*	White Blood Cell Count	K/UL	
	Alveolo-arterial p02 gradient (A-aD02)		
	Blood Urea Nitrogen (BUN)	mg/dl	
*	Partial Pressure Carbon Dioxide in arterial blood (PaCO2)	mmHg	
	Partial Pressure Oxygen in Arterial Blood (PaO2)	mmHg	
*	Fraction of Inspired Oxygen in a Gas (FIO2)		

Coronary Artery Bypass Graft (CABG) information (if applicable)

Emergency Surgery   Yes   No

Ejection Fraction

Diabetes (medication dependent)   Yes   No

CABG was redone   Yes   No

Number of grafts

Internal mammary artery used   Yes   No

Isosorbide mononitrate used   Yes   No

Co-morbidities

Acute renal failure/insufficiency   Yes   No

Acquired immunodeficiency syndrome   Yes   No

Cancer   Yes   No   Metastasis

Chronic obstructive pulmonary disease Yes   No

Congestive heart failure   Yes   No

Cirrhosis   Yes   No

Colon cancer   Yes   No

Coma   Yes   No

Hepatic failure   Yes   No

Immunosuppression(HIV,Trpl, neutrophil <1k/uL)   Yes   No

Lung cancer   Yes   No

Lymphoma   Yes   No

Leukemia   Yes   No

*Calculate using tables on page 3.

Multiple myeloma   Yes   No

* **Glasgow Coma Score:**

Multiple organ system failure w/ cancer Yes   No

Multiple organ system failure w/ sepsis Yes   No   * **PPS:**

Other co-morbidities

Patient interested in knowing the life expectancy calculated using the prognostication models?   Yes   No

Life expectancy estimate shared with patient?   Yes   No

Glasgow Coma Scale

The Glasgow Coma Scale provides a score in the range 3-15; patients with scores of 3-8 are usually said to be in a coma. The total score is the sum of the scores in three categories. For adults the scores are as follows (please circle on in each category):

Eye Opening Response	Spontaneous: open with blinking at baseline	4 points
	Opens to verbal command, speech, or shout	3 points
	Opens to pain, not applied to face	2 points
	None	1 point
Verbal Response	Oriented	5 points
	Confused conversation, but able to answer questions	4 points
	Inappropriate responses, words discernible	3 points
	Incomprehensible speech	2 points
	None	1 point
Motor Response	Obeys commands for movement	6 points
	Purposeful movement to painful stimulus	5 points
	Withdraws from pain	4 points
	Abnormal (Spastic) flexion, decorticate posture	3 points
	Extensor (rigid) response, decerebrate posture	2 points
	None	1 point

Palliatative Performance Scale (Please circle one PPS Level)

PPS Level	Ambulaton	Activity & Evidence of Disease	Self-care	Intake	Conscious Level
100%	Full	Normal activity & work, no evidence of disease	Full	Normal	Full
90%	Full	Normal activity & work, some evidence of disease	Full	Normal	Full
80%	Full	Normal activity with effort, some evidence of disease	Full	Normal or reduced	Full
70%	Reduced	Unable normal job or work, significant disease	Full	Normal or reduced	Full
60%	Reduced	Unable hobby/housework, significant disease	Occasional assistance necessary	Normal or reduced	Full or confusion
50%	Mainly sit/lie	Unable to do any work, extensive disease	Considerable assistance necessary	Normal or reduced	Full or confusion
40%	Mainly in bed	Unable to do most activity, extensive disease	Mainly assistance	Normal or reduced	Full or drowsy +/- confusion
30%	Totally bed bound	Unable to do any activity, extensive disease	Total care	Normal or reduced	Full or drowsy +/- confusion
20%	Totally bed bound	Unable to do any activity, extensive disease	Total care	Minimal sips	Full or drowsy +/- confusion
10%	Totally bed bound	Unable to do any activity, extensive disease	Total care	Mouth care only	Drowsy or coma +/- confusion
0%	Death	-	-	-	-

Physician ID # [ ]

Gender (check one): ☐ Male   ☐ Female

Ethnicity (circle one):   White   African American   Hispanic   Asian   Pacific Islander   Other:

Medical school name: [ ]

Medical practice specialty: [ ]

Years in practice: [ ]   **Average number of patients seen per year:** [ ]

Average number of patients referred to hospice in last 5 years: [ ]

Is/has the physician using/used a prognostication model for calculation of life expectancy for his/her patients?   Yes   No

Name(s) of prognostication model(s) being used: [ ]

Physician ID #

Date of Interview:

Patient ID #

Physician's prediction of survival (Please circle one):   Hours-days   Days-weeks   < 6 months   < 12 months

Please circle responses

Physician interested in knowing the life expectancy calculated using the prognostication models?   Yes   No

Life expectancy estimate shared with physician?   Yes   No

Usefulness of prognostication calculations (please circle responses)

Do you find our calculations regarding best advice in terms of continuing treatment/hospice care for your patient useful?

Yes   Somewhat   No

How strongly will these calculations influence your decision considering hospice referral for your patient?

Strongly   Moderately strongly   Somewhat   Not at all

How strongly do you agree with our best advice regarding continuing current treatment vs. choosing hospice care for your patient?

| Strongly agree | Moderately agree | Somewhat agree | Neither agree, nor disagree | Somewhat disagree | Moderately disagree |

Based on what you have talked about today, would you choose hospice care for your patient?

| Yes | Need more time to think it over | Need more time to discuss with family | Need more time to discuss with physician | No | Other (please specify): |

Appendix 9 Study scripts

Introductory Script

Good morning/afternoon. My name is _____. Dr. _____ (primary attending) told us you might be interested in participating in our research study aimed at helping you choose what type of medical care you want to have during the upcoming months.

Question: Would you like to hear more about our study? If no, STOP NOW.

Question: What has your doctor told you about your illness? *If patient does not understand that s/he has terminal disease, STOP NOW.*

I understand that you're going through a difficult time right now. One day most of us will likely find ourselves in a situation similar to the one you find yourself in today. Most people in this situation are uncertain how they want to spend the remainder of their lives. We have created a tool to help people and their doctors make the choices that they feel are right for them. The tool is designed to help patients like yourself decide whether to continue treatment targeting their disease, although the treatment may create additional discomfort, or whether to choose care through hospice focused more on providing comfort and symptomatic relief. Either of these approaches may or may not prolong your life.

Question: Did your doctor mention that you might want to consider hospice at this point? *If no, STOP NOW and notify referring physician.*

Question: Have you been contacted by hospice staff? Have you signed up for hospice? *If yes, DO NOT PROCEED UNLESS the patient and referring physician have requested us to do so (e.g., patient has doubt, wants to clarify his/her values, etc).*
Record answer on Checklist.

Question: Do you know what hospice is? Hospice is a type of care that provides support to people at the end of their lives. It can help people get their physical, emotional, and spiritual needs met.

If you choose to participate in our study, I will ask you to sign an informed consent form. It will allow me to take information from your medical records to help assess your current condition better. Your name and other identifying information will not be used. I will then interview you and record your responses. **There are no right or wrong answers.** Your responses will be completely confidential and will not be reported to anyone. Based on data we extract from your record and your responses, we can then provide you with a recommendation that may best represent your values and preferences regarding which approach (targeted treatment or hospice) you want to pursue.

Question: Would you like to participate? Before we begin, I will need to review this consent form with you.

Review the Informed Consent form with the patient. Allow the patient as much time as s/he needs to sign it.

Great. Let me ask you two questions before I go and review your medical records.

Question: When were you diagnosed with this condition?
Record answer on Checklist

Question: May I also have your phone number so that we can follow up with you?
Record answer on Checklist

Thank the patient and discuss when would be a convenient time for you to return to conduct the interview.

Hospice Decision Support Patient Scripts

Patient Script to Accompany the Hospice Referral Software

Enter data under Interviewee and Prognostic Models Tabs prior to returning to patient's room.

Software Tab: Current Choice

Thanks for taking part in our study. I would like to have an honest discussion about the choice(s) you face. This will include finding out your wishes, values and preferences about how you want to approach your illness. This will also include, *if you wish to know*, a conversation with you about how long you may live. Some people find talking about this topic to be difficult & distressing. If at any point during our conversation you feel upset and wish to stop, please don't hesitate to say so. Your decision to participate or not in this interview **will not** affect the care that you receive.

Question: Do I have your permission to proceed with the interview?

Exercise maximum tact, compassion & understanding. If the patient doesn't understand, please reword as appropriate. If in doubt, stop the interview and call the study coordinator/principal investigator. Proceed only if the patient/surrogate agrees to continue with the interview. Otherwise, thank the patient & conclude the interview.

The purpose of this study is to help people make decisions about continuing their medical treatment or choosing hospice care. As I mentioned, the main goal of hospice care is to improve the quality of patients' lives by focusing on pain and other symptom relief and emotional comfort. This means that treatments that are given to target your disease may be discontinued.

Question: If you had to choose right now, would you rather:

a) Continue with your current treatment that is focused on targeting your disease, even though you may experience some pain and discomfort, or,

b) Choose hospice care that is focused on relieving your pain and discomfort as much as possible, even though it may not affect your disease directly, or,

c) You don't know at this point.

As you arrived at your decisions and answered these questions you might have thought about many different things. One thing that may have occurred to you is, "Have I made the right choice?" As you know, we all make mistakes or errors from time to time. Some errors we can accept while others we may regret. In the case of choosing to continue your current treatment or hospice care, it is possible to make an error. One way to study difficult decisions is to consider how much regret a person feels if s/he found out that s/he had made the wrong choice. In a moment I will ask you about two possible scenarios and I want you to tell me about your feelings of regret.

Software Tab: Regret

Scenario 1: Now I want you to imagine that you chose to continue your current treatment but six months from now you feel you should have chosen hospice care (that is, care focused on comfort). How much regret do you think you would feel in this situation?

Hospice Decision Support Patient Scripts

Please indicate how much regret you would feel using the following rating scale where 0 indicates no regret and 100 indicates the maximum regret you can imagine.

Let the patient use the arrow keys to move the slider indicating his/her level of regret.

OK, thank you. Now let's flip the last question around.

Scenario 2: Imagine that you chose hospice care (that is, care focused on comfort) but six months from now you feel you should have continued your current treatment. How much regret do you think you would feel in this situation?

Please indicate how much regret you would feel using the following rating scale where 0 indicates no regret and 100 indicates the maximum regret you can imagine.

Let the patient use the arrow keys to move the slider indicating his/her level of regret.

Do you have any questions about this? Thank you for your help. We are almost done here. The choices that you just made will help us to come up with our best advice for patients like you about whether to continue current treatment or choose hospice care. We are now ready to share this information with you.

Question: Would you like to know what appears to be the choice about further treatment that is consistent with your values and preferences?

*Read the Summary at the bottom **only if** the patient/surrogate gives permission. Otherwise, thank the patient and click, "Next."*

Please understand that for us to make this recommendation we needed to calculate how long a patient like you may live. This is our best (guess) estimate of life expectancy for an "average" patient like you. Some people live longer that the estimate and others shorter. It is impossible for us to know if our estimate will be accurate in your specific case. Do you want to have a discussion about how long a patient like you might live?

Question: Would you like me to show you our best guess for how long a patient like you might live?

*Proceed **only if** the patient/surrogate gives permission. Otherwise, thank the patient and click, "No." The software will skip the Summary Tab and go to the Questionnaire Tab.*

Software Tab: Summary

If s/he gives permission, click "Yes," share results displayed on the screen, and on "Show Chart." Read the exact wording displayed on the screen, e.g. "Our best estimate is that there is a XX% chance that average patients like you would live for 6 months. That is, out of 100 patients like you, XX will still be alive after 6 months. This also means on average that (100-XX) patients like you will die within the next 6 months. Hospice care is considered to be better for these (100-XX) patients who are likely to die within the next 6 months."

Take a pause. Give some time to the patient to reflect on the situation. Exercise maximum tact, compassion and understanding.

Software Tab: Questionnaire

Hospice Decision Support Patient Scripts

Question: Thinking back on the choices you just made in the 2 scenarios (using the sliders), would you like to change your mind (your choices)?

Record the patient's/surrogate's answer. If the patient decides to change his/her choices, repeat the interview.

Question: Did you find this information helpful?

Yes? No? Somewhat?

Question: If your answer is "yes" or "somewhat," please indicate how strongly these calculations will influence your decision for considering hospice referral

We have four possible responses: Strongly? Moderately strong? Somewhat? or Not at all?

Question: How strongly do you agree with our best advice regarding continuing your current treatment vs. choosing hospice care?

We have 7 possible responses: Strongly agree? Moderately agree? Somewhat agree? Neither agree nor disagree? Somewhat disagree? Moderately disagree? or Strongly disagree?

Question: Based on what we have talked about today would you choose hospice care?

We have 5 possible responses: Yes? No? I need some more time to think this over? I need some more time to discuss this with my family? or I need some more time to discuss this with my physician?

Software Tab: Acceptable Regret

We will now continue with the last part of the interview if you wish to continue to participate. Sometimes the best way to clarify our own wishes, values and preferences is to imagine that we are in a position to advise other people who find themselves in the situation in which we find ourselves. There are two questions.

First, we would like to see under which circumstances you would **not** regret making a **wrong** decision. Imagine that there are 100 patients like you who will live as long as you will. Pretend that you are a doctor and you need to decide whether these patients will go to hospice care or they will continue their current treatment. This is akin as asking your doctor, "What would you do if you were me?" Please remember, there is no guarantee that your decision will be accurate. That is, like all of us, you can make mistakes. However, some people are better than others in *accepting* their mistakes. We would like to see how much you accept making a mistake in this situation without regretting it.

Question: _Read exact wording on screen,_ *e.g., "So let's pretend that you are a doctor. Based on our calculations, you would refer X patients out of 100 to hospice. It is likely that most of these patients will die within next 6 months. Therefore, they are expected to benefit from care through hospice. However, some of these patients may live longer than 6 months and hence should not have been referred to hospice. As a doctor, how many patients (out of X) would you be willing to incorrectly (wrongly) refer to hospice and still feel no regret?"*

Thank you. There is only one more question. Let's flip the last question around.

Question: <u>**Read exact wording on screen,**</u> *e.g.,* **"***Based on our calculations, you would recommend X patients out of 100 to continue current treatment. It is likely that most of these patients will live longer than 6 months. Therefore, they are expected to benefit from the current treatment. However, some of these patients may live less than 6 months and hence should have been referred to hospice. As a doctor, how many patients (out of X) would you be willing to incorrectly (wrongly) keep on current treatment and still feel no regret?"*

We truly appreciate your willingness to participate. Do you have any questions?

<u>Answer any questions you can and/or suggest the patient speak with their physician or hospice representative.</u>

I hope your participation has been helpful to you. We truly appreciate it. If it's still OK with you, we would like to contact you every month or so to ask you a few follow up questions. Thank you again.

<u>Software Tab: Final</u>

<u>Save the file.</u>

Hospice Decision Support Physician Scripts

Introductory Script

Good morning/afternoon. My name is _____. I'm working with Dr. Ben Djulbegovic, a Moffitt oncologist and USF Researcher. We would like to tell you about our Hospice Decision Support research study that we think can help you with current and future patients. As I'm sure you know, it's widely believed that patients are generally referred to hospice much later than they should be. Our decision support tool helps in two ways: It improves upon existing prognostication methods for determining terminal patients' remaining life spans and uses patients' values and preferences to help physicians better guide patients in choosing whether to choose targeted treatment of their disease or hospice care.

You recently referred a patient to us: Mr/s. _____ in Rm. _____. S/he was a _____ diagnosed with _____.

Question: Do you remember the patient? IF NO, thank him/her for the referral and his/her time today, and say that we'll try to catch him sooner on a future case.

We interview not only the patient but when possible their physician. The physician interview only takes about 10 minutes. ***There are no right or wrong answers.*** Your responses will be completely confidential and will not be reported to anyone. Based on data we extract from the patient's record and your responses, we can then provide you with feedback regarding this particular patient that you may find helpful.

Question: Would you like to participate? Are you available now or should we set up another time? I will need to review this informed consent form with you and get your signature.
Review the Informed Consent form with the physician. Allow him/her as much time as s/he needs to sign it.

Physician Script to Accompany the Hospice Referral Software

Software Tab: Interviewee
Enter patient's randomly assigned number and select "Physician."
Click through Prognostic Models Tab.

Software Tab: Current Choice
Thanks for taking part in our study. I would like to have a frank discussion with you about methods for estimating life expectancy in terminally ill patients. If you find talking about this topic to be difficult and distressing at any point during our conversation and wish to stop, just say so.

Question: Do I have your permission to proceed with the interview?

Offer to give the physician study material to read first. Proceed only if the physician agrees to continue with the interview. Otherwise, thank the physician and conclude the interview.

The purpose of this study is to find out how terminally ill people make decisions about choosing targeted treatment or hospice. We also want to study how physicians make decisions regarding recommending that their terminally ill patients choose targeted treatment or care through hospice. As you know, either choice may or may not prolong patients' lives. The main goal of hospice care is to improve quality of patient's life by focusing on pain and other symptom relief and emotional comfort. This means that treatment(s) that might extend a patient's life may be discontinued.

Question: If you had to choose right now, would you rather:

a) Continue with current treatment that is focused on extending your patient's life as much as possible, even though s/he may experience some pain and discomfort, or,

b) Choose hospice care that is focused on relieving your patient's pain and discomfort as much as possible, even though s/he might not live as long, or

c) You don't know at this point.

As you arrived at your decisions and answered these questions you might have thought about many different things. One thing that may have occurred to you is, "Have I made the right choice?" As you know, we all make mistakes or errors from time to time. Some errors we can accept while others we may regret. In the case of recommending continued treatment or hospice care for your patient, it is possible to make an error.

One way to study difficult decisions is to consider how much regret a person would feel if s/he found out that s/he had made the wrong choice. In a moment I will ask you about two possible scenarios and I want you to tell me about your feelings of regret.

Software Tab: Regret

Scenario 1: Now, I want you to imagine that you chose to continue your current treatment for your patient but six months from now you feel you should have chosen hospice care (care focused on comfort). How much regret do you think you would feel in this situation?

Please indicate how much regret you would feel using the following rating scale where 0 indicates no regret and 100 indicates the maximum regret you can imagine.

Let the physician move the slider or use the arrow keys to indicate his/her level of regret.

OK, thank you. Now let's flip the last question around.

Scenario 2: Imagine that you chose hospice care (care focused on comfort) but six months from now you feel you should have continued current treatment for your patient. How much regret do you think you would feel in this situation?

Please indicate how much regret you would feel using the following rating scale where 0 indicates no regret and 100 indicates the maximum regret you can imagine.

Let the physician move the slider or use the arrow keys to indicate his/her level of regret.

Do you have any questions about this? Thank you for your help. We are almost done here. The choices that you just made will help us to come up with our best advice for patients like the one you are treating about whether to continue current treatment or choose hospice care. We are now ready to share this information with you.

Question: Would you like to know what appears to be the choice consistent with your values and preferences about further treatment?

*Read the Summary at the bottom **only if** the physician gives permission. Otherwise, thank the physician and click, "Next."*

Please understand that for us to determine whether you should advise your patient to continue his current treatment or choose hospice care we needed to calculate how long a patient like the one you are treating may live. This is our best (guess) estimate for an average patient like him/her. As you know, some people live longer that the estimate and others shorter. It is impossible for us to know if our estimate will be accurate in your patient's case.

Question: Would you like me to show you our best guess for how long a patient like the one you are treating might live?

*Proceed **only if** the physician gives permission. Otherwise, thank the physician and click, "No." The software will skip the Summary Tab and go to the Questionnaire Tab.*

Software Tab: Summary

If s/he gives permission, click "Yes," share results displayed on the screen, and on "Show Chart." Read the exact wording displayed on the screen, e.g. "Our best estimate is that there is XX% chance that an average patient like the one you are treating will live for 6 months. That is, out of 100 patients like the one you are treating, XX will still be alive after 6 months. This also means on average that (100-XX) patients like him/her will die within the next 6 months. Hospice care is considered to be better for these (100-XX) patients who are likely to die within the next 6 months."

Take a pause. Give the physician time to reflect on the situation. Exercise maximum tact, compassion and understanding.

Use both the case report forms and the Hospice Referral software to record the physician's answers.

Software Tab: Questionnaire

Question: Thinking back on the choices you just made in the 2 scenarios (using the sliders), would you like to change your mind (your choices)?

Record the physician's answer using both the case report forms and the Hospice Referral Software. If the s/he decides to change his/her choices, repeat the interview.

Question: Did you find this information helpful?

Yes? No? Somewhat?

Question: If your answer is "yes" or "somewhat," please indicate how strongly this information will influence your decision for considering hospice referral for your patient.

We have four possible responses: "Strongly"? "Moderately strongly"? "Somewhat"? or "Not at all"?

Question: How strongly do you agree with our best advice regarding continuing current treatment vs. choosing hospice care for your patient?

We have 7 possible responses: Strongly agree? Moderately agree? Somewhat agree? Neither agree nor disagree? Somewhat disagree? Moderately disagree? or Strongly disagree?

Question: Based on what we have talked about today would you choose hospice care for your patient?

We have 5 possible responses: Yes? No? I need some more time to think this over? I need some more time to discuss this with the family? or I need some more time to discuss this with another physician?

Software Tab: Acceptable Regret

We have just two more questions. We would like to see under which circumstances you would **not** regret if you made a **wrong** decision. Imagine that you are treating 100 terminally ill patients. You need to decide whether these patients will go to hospice care or they will continue treatment. Please remember, there is no guarantee that your decision will be accurate. That is, like all of us you can make mistakes. However, some people are better than others in accepting their mistakes. We would like to see how much you accept making a mistake in this situation without regretting it.

Question: _Read exact wording on screen,_ *e.g., "Based on our calculations, you would refer X patients out of 100 to hospice. It is likely that most of these patients will die within the next 6 months. Therefore, they are expected to benefit from hospice care. However, some of these patients may live longer than 6 months and hence should not have been referred to hospice. How many patients (out of X) would you be willing to incorrectly (wrongly) refer to hospice and still feel no regret?*
Record the participating physician's answer. Take a pause.

OK, just one more question. Let's flip that last question around.

Question: _Read exact wording on screen,_ *e.g. "Based on our calculations, you would recommend X patients like the patient you are treating out of 100 continue their current treatment. It is likely that most of these patients will live longer than 6 months. Therefore, they are expected to benefit from the current treatment. However, some of these patients may live less than 6 months and hence should have been referred to hospice. How many patients (out of X) would you be willing to incorrectly (wrongly) keep on current treatment and still feel no regret?"*
Record the participating physician's answer.

I hope this information has been helpful to you. We truly appreciate your willingness to participate. Do you have any questions?
Answer any questions you can and/or refer the physician to Dr. Djulbegovic.

Thank you.
Software Tab: Final
Save the file.

Appendix 10 Informed consent forms

Informed Consent to Participate in Research and Authorization to Collect, Use and Share Your Health Information

For Patient

Information to Consider Before Taking Part in this Research Study

IRB Study # Pro00000220

Researchers at the University of South Florida (USF), Moffitt Cancer Center and Tampa General Hospital (TGH) study many topics. To do this, we need the help of people who agree to take part in a research study. This form tells you about this research study.

We are asking you to take part in a research study that is called:

"Proposal for development of evidence based clinical decision support system (EBM-CDSS) to aid prognostication in terminally ill patients"

We are approaching you to ask you to participate in this study because we were told that you have a terminal disease that may significantly shorten your life duration. You may participate in this study; only if you aware that you have a terminal disease.

The person who is in charge of this research study is Dr. Benjamin Djulbegovic. This person is called the Principal Investigator. However, other research staff may be involved and can act on behalf of the person in charge.

The person explaining the research to you may be someone other than the Principal Investigator.

Other research personnel who you may be involved with include: your consulting physician and or the following study personnel: Catherine Jahrsdorfer, Marlo Crawford, Rahul Mhaskar and Howard Tuch.

The research will be done at Tampa General Hospital, Moffitt Cancer Center and Tampa Bay Lifepath Hospice and Palliative Care and Moffitt cancer center.

This research is being paid for by the United States Army.

Purpose of the study

The purpose of this study is to help people in the final stages of their lives make decisions about continuing medical treatment targeting their disease or choosing hospice care. Hospice is a type of care that provides support to people at the end of their lives. The main goal of hospice care is to improve the quality of patients' lives by focusing on pain and other symptom relief and emotional comfort. This means that medical treatments that are given to target your disease may be discontinued.

This research study is aimed at helping you choose what type of medical care you want to have during the upcoming months. Most people in this situation are uncertain how they want to approach their illness. We have created a tool to help people and their doctors make the choice that they feel is right for them. The tool is designed to help doctors and patients like yourself decide whether to continue treatment targeting their disease although the treatment may create additional discomfort, or whether to choose care through hospice which is focused on providing comfort and symptom relief. Either of these choices may or may not prolong your life. We would also like to understand your wishes and preferences to help you make the choice that is right for you.

The tool that is being tested in this research is called an Evidence-based Medicine Clinical Decision Support System (EBM-CDSS). The EBM-CDSS is designed to be used by doctors at the bedside to better predict life expectancy in patients with terminal illness and to improve the timing and appropriateness of referral to hospice care.

We are asking you to take part in this research because you have an illness that may significantly shorten your life span.

How many other people will take part?

About 400 people will take part in this study.

Study Procedures

If you take part in this study: We will actively collect information from you until your demise. The study personnel or your attending physician will visit you twice initially and then once a month during the study period and will collect information from you. We do not expect the initial visits to last more than 30 minutes and the monthly visits to last more than 10 minutes.

If you take part in this study, you will be requested to sign this informed consent form:

- After signing the informed consent you will be requested by the study personnel to share certain information related to your health from your medical records. You may be requested to answer questions regarding your health.
- The interviewer will also ask you whether you would like to know your doctor's best estimate of your life expectancy.
- We will estimate your life expectancy based on our current best estimates for "average" patients like you (i.e. estimate of the average future lifetime for people like you)? We will ask you whether you would like to know the best estimates of your life expectancy with the current treatment targeted at your disease and without this treatment.
- To help you decide between hospice care and treatment targeted at your disease. We will also like to learn about your wishes and preferences regarding how you would like to approach your illness. We will do that by using our tool to understand your feelings of regret in case you made a wrong choice.
- The interviewer will also seek your opinion regarding your tolerance if your doctor is mistaken regarding whether to continue your present treatment (that may potentially cure your disease or

prolong your life) or to discontinue your treatment and refer you to hospice care. We will ask you a series of questions assuming that there is an error in prediction of your life expectancy with and without treatment targeted at your disease. We want to know how large an error you can tolerate and still not regret (magnitude of acceptable regret for you) your doctor's decision to be referred to hospice care. After you make the decision regarding choosing hospice care or continuing treatment we will ask you questions to obtain your opinion regarding the decision you made once a month until you pass away.

- We will ask you whether you changed your decision for enrolling / not enrolling in hospice care based on the information provided to you by us.
- You should know that we cannot tell you which of these choices (treatment targeted at your disease versus hospice care) will prolong your life. However, we may be able to tell you which of these choices is most compatible with your wishes and preferences for an average patient like you.

Alternatives

You do not have to take part in this study. Your decision to take part in this study or not to take part will not affect the medical care that you receive You can choose to fully take part in this study including the collection of your medical record information and the initial and follow up interviews.

You can also choose to **partially** participate in this study either by:

- allowing us to look at your medical records only and NOT take part in the interview process OR
- NOT allow us to look at your medical records or interview you but ONLY allow us to collect the date that you eventually pass away. .

You choice of whether to take part in the study fully or one of the partial options will be indicated on the last pages of this consent form. There is a separate signature area for each choice and only one of these sections should be signed.
Benefits

We don't know if you will get any benefits by taking part in this study. However, this study may improve doctor's accuracy to assess life expectancy. Many people find this important, which can be important for you too. Many people also find it helpful to clarify their wishes and preferences regarding how they would like to spend the reminder of their life.

Risks or Discomfort

This research is considered to be minimal risk. That means that the risks associated with this study are the same as what you face in the current phase of your life on an everyday basis. There are no known additional risks to those who take part in this study.

While many people in your situations want to have a frank conversation about doctors' best estimate of their life expectancy, we understand that talking about how to spend your remaining days of life is difficult and can be very distressing. If you find anything that we are about to ask you upsetting and distressing, you may request to discontinue your participation from the study. There is no funding to compensate you for treatment if "injury" occurs. There might be other unforeseeable risks that could occur which are unknown at this time. Your decision to withdraw from the study will not affect the

care you will receive in any form and or manner. If you wish to consult the study Principal Investigator and Co- Principal Investigator (who have extensive experience working with patients in similar situations) will immediately be available for counseling.

Compensation

You will receive no payment or other compensation for taking part in this study.

Cost

There will be no additional costs to you as a result of being in this study. However, routine medical care for your condition (care you would have received whether or not you were in this study) will be charged to you or your insurance company.

Conflict of Interest Statement

There is no conflict of interest.

Authorization to Use and Disclose Protected Health Information

Who will see your health information ?

In our research, we use and share your health information to the extent authorized by you. We know that this information is private. The federal privacy regulations of the Health Insurance Portability & Accountability Act (HIPAA) protect your identifiable health information. If you authorize us to use your information we will protect it as required by the law.

Research at Tampa General Hospital and Moffitt cancer center is conducted jointly with the University of South Florida. By signing this form, you are permitting Tampa General Hospital, Moffitt cancer center and the University of South Florida to use personal health information collected about you for research purposes. You are also allowing Tampa General Hospital and Moffitt cancer center to share your personal health information with individuals or organizations other than USF, Moffitt cancer center and Tampa General Hospital who are also involved in this research and listed below.

Who will disclose (share), receive, and/or use your information?

To do this research, USF and the people and organizations listed below may use or share your information. They may only use and share your information:

- **With the people and organizations on this list;**
- **With you or your personal representative; and**
- **As allowed by law.**

In addition to the people and organizations listed below in the Privacy and Confidentiality section of this document, the following groups of people may also be able to see information about you and may use the information to conduct the research:

- The medical staff that takes care of you and those who are part of this research study;
- Each research site for this study. This includes the research and medical staff at each site and USF;
- The designated peer review committees such as the Tampa General Hospital and Moffitt cancer center Feasibility Committee;
- Additionally, there may be other people and/or organizations who may be given access to your personal health information. This includes Tampa Bay LifePath Hospice care.

Who else can use and share this information?
Anyone listed above may use consultants in this research, and for the purpose of this study may share your information with them. If you have questions about who they are, you can ask us. Individuals who receive your health information for this research study may not be required by the HIPAA Privacy Rule to protect it and may share your information with others without your permission. They can do so if permitted by the laws governing them. Example: The sponsor may share your information. If the sponsor or others share your information, your information may no longer be protected under the HIPAA Privacy Rule.

How Will My Information Be Used?
By signing this form, you are giving your permission to use and/or share your health information as described in this document for any and all study/research related purposes. Your authorization (permission) to use your health information will not expire until the end of this research study unless you revoke this authorization in writing.

As part of this research, USF may collect, use, and share the following information:

- Your whole research record
- All of your past, current or future medical and other health records held by USF, other health care providers or any other site affiliated with this study. This includes, but is not limited to, HIV/AIDs, mental health, substance abuse, and/or genetic information.

We may publish what we learn from this study. If we do, we will not let anyone know your name. We will not publish anything else that would let people know who you are.

Your Rights:

You can refuse to sign this form. If you do not sign this form:

- You will not be able to take part in this research and therefore not be able to receive the research related interventions. However, you can receive other treatments that are currently available for you as part of your regular medical treatment.
- This will not change your health care outside of this study.
- This will not change your health care benefits.
- This will not change the costs of your health care.

How Do I Withdraw Permission to Use My Information?

You can revoke this form at any time by sending a signed letter to USF at the address given below, clearly stating that you wish to withdraw your authorization to the use of your health information in the research. If you revoke you permission:

- You will no longer be a participant in this research study.
- We will stop collecting new information about you.
- We will use the information collected prior to the revocation of your authorization. This information may already have been used or shared with others, or we may need it to complete and protect the validity of the research..
- Staff may follow-up with you if there is a medical reason to do so.

To revoke this form, you must tell us in writing. Please write to:

Principal Investigator: Dr. Benjamin Djulbegovic

For IRB Study # **Pro00000220**

12901 Bruce B. Downs Blvd., MDC27

Tampa FL, 33612

While we are doing this research, we cannot let you see or copy the research information we have about you. After the research is done, you or a person designated by you have a right to see the information about you, as allowed by USF policies.

Privacy and Confidentiality

We will keep your study records private and confidential. Certain people may need to see your study records. By law, anyone who looks at your records must keep them completely confidential. The only people who will be allowed to see these records are:

- The research team, including the Principal Investigator, study coordinator, research nurses, and all other research staff**.**

- Certain government and university people who need to know more about the study. For example, individuals who provide oversight on this study may need to look at your records. This is done to make sure that we are doing the study in the right way. They also need to make sure that we are protecting your rights and your safety.

- Any agency of the federal, state, or local government that regulates this research. This includes the Food and Drug Administration (FDA), Florida Department of Health, and the Department of Health and Human Services (DHHS) and the Office for Human Research Protection (OHRP).

- The USF Institutional Review Board (IRB) and its related staff who have oversight responsibilities for this study, staff in the USF Office of Research and Innovation, USF Division of Research Integrity and Compliance, and other USF offices who oversee this research.

- The sponsors of this study The United States Army

We may publish what we learn from this study. If we do, we will not include your name. We will not publish anything that would let people know who you are.

Voluntary Participation / Withdrawal

You should only take part in this study if you want to volunteer. You should not feel that there is any pressure to take part in the study, to please the investigator or the research staff. You are free to participate in this research or withdraw at any time. There will be no penalty or loss of benefits you are entitled to receive if you stop taking part in this study.

New information about the study

During the course of this study, we may find more information that could be important to you. This includes information that, once learned, might cause you to change your mind about being in the study. We will notify you as soon as possible if such information becomes available.

You can get answers to your questions, concerns, or complaints

If you have any questions, concerns or complaints about this study, or experience an adverse event or unanticipated problem, call Dr. Benjamin Djulbegovic at 813-396-9178.

If you have questions about your rights as a participant in this study, general questions, or have complaints, concerns or issues you want to discuss with someone outside the research, call the Division of Research Integrity and Compliance of the University of South Florida at (813) 974-5638.

Consent to Take Part in this Research Study and Authorization to Collect, Use and Share Your Health Information

It is up to you to decide whether you want to take part in this study. If you want to take part, please sign the form, if the following statements are true.

Full Consent to Take Part in this Research, including medical record review, initial interview and follow up interviews:

I freely give my consent to take part in this study and authorize that my health information as agreed above, be collected/disclosed in this study. I understand that I am allowing the research team to access my health records for the purpose of this study and interview me regarding my health and my decision regarding enrolling to hospice. I understand that by signing this form I am agreeing to take part in research. I have received a copy of this form to take with me.

_____   _____
Signature of Person Taking Part in Study   Date

_____
Printed Name of Person Taking Part in Study

Partial Consent to Take Part in this Research, Without Participation in interview process

It is up to you to decide whether you want to take part in this study. If you want to take part, please sign the form, if the following statements are true.

I freely give my consent to take part in this study and authorize that my health information as agreed above, be collected/disclosed in this study. I understand that I am allowing the research team to access my health records for the purpose of this study. I understand that by signing this form I am agreeing to take part in research. I have received a copy of this form to take with me.

I am allowing the researchers to access my medical record and I am NOT willing to participate in the interview process.

_____   _____
Signature of Person Taking Part in Study   Date

_____
Printed Name of Person Taking Part in Study

Partial Consent to Take Part in this Research, <u>Without Participation in interview process or medical record review</u>

It is up to you to decide whether you want to take part in this study. If you want to take part, please sign the form, if the following statements are true. **I freely give my consent to take part in this study and authorize that my health information as agreed above, be collected/disclosed in this study.** I understand that I am allowing the research team to   collect the date that I eventually pass away for the purpose of this study. I understand that by signing this form I am agreeing to take part in research. I have received a copy of this form to take with me.

I ONLY ALLOW researchers to access medical records to collect the date that I eventually pass away.
.

_____   _____
Signature of Person Taking Part in Study   Date

_____
Printed Name of Person Taking Part in Study

Statement of Person Obtaining Informed Consent and Research Authorization

I have carefully explained to the person taking part in the study what he or she can expect from their participation.

I hereby certify that when this person signs this form, to the best of my knowledge, he or she understands:
- What the study is about.
- What procedures will be used.
- What the potential benefits might be.
- What the known risks might be.

   I can confirm that this research subject speaks the language that was used to explain this research and is receiving an informed consent form in the appropriate language. Additionally, this subject reads well enough to understand this document or, if not, this person is able to hear and understand when the form is read to him or her. This subject does not have a medical/psychological problem that would compromise comprehension and therefore makes it hard to understand what is being explained and can, therefore, give legally effective informed consent. This subject is not under any type of anesthesia or analgesic that may cloud their judgment or make it hard to understand what is being explained and, therefore, can be considered competent to give informed consent.

_____   _____
Signature of Person Obtaining Informed Consent / Research Authorization   Date

_____
Printed Name of Person Obtaining Informed Consent / Research Authorization

Informed Consent to Participate in Research and Authorization to Collect, Use and Share Your Health Information

<u>For Physician</u>

Information to Consider Before Taking Part in this Research Study

IRB Study # Pro00000220

Researchers at the University of South Florida (USF), Moffitt Cancer Center and Tampa General Hospital (TGH) study many topics. To do this, we need the help of people who agree to take part in a research study. This form tells you about this research study.

We are asking you to take part in a research study that is called:

"Proposal for development of evidence based clinical decision support system (EBM-CDSS to aid prognostication in terminally ill patients"

The person who is in charge of this research study is Dr. Benjamin Djulbegovic. This person is called the Principal Investigator. However, other research staff may be involved and can act on behalf of the person in charge.

The person explaining the research to you may be someone other than the Principal Investigator.

Other research personnel who you may be involved with include: your consulting physician and or the following study personnel: Catherine Jahrsdorfer, Marlo Crawford, Rahul Mhaskar and Howard Tuch.

The research will be done at Tampa General Hospital Moffitt Cancer Center and Tampa Bay Lifepath Hospice and Palliative Care.

This research is being paid for by the United States Army.

Purpose of the study

The main purpose of this study is to develop an Evidence-based Clinical Decision Support (EBM-CDSS) system available at bedside (for you) to improve prediction of the life expectancy of terminally ill patients and improve referral of patients to hospice. The EBM-CDSS is a tool that will include information using various health related data (including but not limited to laboratory values, disease type, age, sex, ethnicity/race, etc.) and also your patients' wishes and preferences made available to physicians (like you) at bedside to aid in better assessment of life expectancy of terminally ill patients.

We will also request you to share your preferences in terms of continuing treatment targeted at the disease versus hospice care for your patient(s).

Study Procedures

If you take part in this study: We will actively collect information from you in this study. The study personnel will visit you during the study period and will collect information from you. We don't expect each visit to last more than 15-20 minutes.

If you take part in this study, you will be requested to sign this informed consent form:

- You will be requested to explain the study in details to your patients and / or give permission to the study personnel to explain the study in details to your patients and seek their participation.
- You will be requested by the study personnel to answer questions related to your estimates regarding life expectancy of your patients.

- You will be requested to answer questions regarding referring patients to hospice care. Specifically, we would like to know your feelings of regret and how you weigh the relative harms of false-positives and false-negatives regarding your decision of referring patient to hospice care. For example: 1) Imagine that you chose hospice care but you should have continued current treatment for your patient. How much regret do you think you would feel in this situation? 2) Imagine that you chose to continue current treatment targeted at his/her disease for your patient but you should have chosen hospice care. How much regret do you think you would feel in this situation? We will also offer you our best guess regarding the life expectancy of a patient like the one which you are treating.
- We will also offer you our best advice regarding the choice of hospice care vs. continuing current treatment for a patient like the one which you are treating.
- You will be requested to answer questions to assess the impact of our calculations (of life expectancy and the recommendation of referring the patient to either hospice or continuing current treatment) on your clinical judgment.
- We will also seek your opinion regarding usefulness of EBM-CDSS in treating your patients.
- We will also offer our evidence based pain management module to you. We will also seek your opinion regarding usefulness of our evidence based pain management module in treating your patients.

Alternatives

If you decide not to take part in this study, that is okay.

Benefits

We don't know if you will get any benefits by taking part in this study. However, you may find the EBM-CDSS useful for making decisions in care of terminally ill patients. That's why we are doing this study.

Risks or Discomfort

This research is considered to be minimal risk. That means that the risks associated with this study are the same as what you face every day. There are no known additional risks to those who take part in this study.

We understand that talking about potential error in your clinical decision making (even imaginative one) can be unpleasant or distressing. If you find anything what we are about to ask you upsetting and distressing; you may request to discontinue your participation from the study. Your decision to withhold from the study will not affect your status in any way.

Compensation

You will receive no payment or other compensation for taking part in this study.

Cost

There will be no additional costs to you as a result of being in this study.

Conflict of Interest Statement

There is no conflict of interest.

Confidentiality of Information Used in the Study

Who will see the information that you give?

Not applicable

Who will disclose (share), receive, and/or use your information?

Not applicable

Who else can use and share this information?
Not applicable

How Will My Information Be Used?
Not applicable

For the Research Participant (you) to complete:

Not applicable

Your Rights:

You can refuse to sign this form. If you do not sign this form:

- You will not be able to take part in this research.
- This will not impact your status outside of this study.

How Do I Withdraw Permission to Use My Information?

You can revoke this form at any time by sending a signed letter to USF at the address given below, clearly stating that you wish to withdraw your consent to participate in the research and to the use of your information in the research. If you revoke this form:

- You will no longer be a participant in this research study.
- We will stop collecting new information about you.
- We will use the information collected prior to the revocation of your authorization. This information may already have been used or shared with others, or we may need it to complete and protect the validity of the research. Staff may follow-up with you if there is a medical reason to do so.

To revoke this form, you must tell us in writing. Please write to:

Principal Investigator Dr. Benjamin Djulbegovic

For IRB Study # Pro00000220

12901 Bruce B. Downs Blvd., MDC27

Tampa, FL 33612

While we are doing this research, we cannot let you see or copy the research information we have about you. After the research is done, you have a right to see the information about you, as allowed by USF policies.

Privacy and Confidentiality

We will keep your study records private and confidential. Certain people may need to see your study records. By law, anyone who looks at your records must keep them completely confidential. The only people who will be allowed to see these records are:

- The research team, including the Principal Investigator, study coordinator, research nurses, and all other research staff**.**

- Certain government and university people who need to know more about the study. For example, individuals who provide oversight on this study may need to look at your records. This is done to make sure that we are doing the study in the right way. They also need to make sure that we are protecting your rights and your safety.

- Any agency of the federal, state, or local government that regulates this research. This includes the Food and Drug Administration (FDA), Florida Department of Health, and the Department of Health and Human Services (DHHS) and the Office for Human Research Protection (OHRP).

- The USF Institutional Review Board (IRB) and its related staff who have oversight responsibilities for this study, staff in the USF Office of Research and Innovation, USF

Division of Research Integrity and Compliance, and other USF offices who oversee this research.

- The sponsors of this study The United States Army

We may publish what we learn from this study. If we do, we will not include your name. We will not publish anything that would let people know who you are.

Voluntary Participation / Withdrawal

You should only take part in this study if you want to volunteer. You should not feel that there is any pressure to take part in the study, to please the investigator or the research staff. You are free to participate in this research or withdraw at any time. There will be no penalty or loss of benefits you are entitled to receive if you stop taking part in this study.

New information about the study

During the course of this study, we may find more information that could be important to you. This includes information that, once learned, might cause you to change your mind about being in the study. We will notify you as soon as possible if such information becomes available.

You can get answers to your questions, concerns, or complaints

If you have any questions, concerns or complaints about this study, call Dr. Benjamin Djulbegovic at 813-396-9178.

If you have questions about your rights as a participant in this study, general questions, or have complaints, concerns or issues you want to discuss with someone outside the research, call the Division of Research Integrity and Compliance of the University of South Florida at (813) 974-5638.

Consent to Take Part in this Research Study

It is up to you to decide whether you want to take part in this study. If you want to take part, please sign the form, if the following statements are true.

I freely give my consent to take part in this study. I understand that by signing this form I am agreeing to take part in research. I have received a copy of this form to take with me.

_____   _____
Signature of Person Taking Part in Study   Date

_____
Printed Name of Person Taking Part in Study

Statement of Person Obtaining Informed Consent and Research Authorization

I have carefully explained to the person taking part in the study what he or she can expect.

I hereby certify that when this person signs this form, to the best of my knowledge, he or she understands:

- What the study is about.
- What procedures will be used.
- What the potential benefits might be.
- What the known risks might be.
- I can confirm that this research subject speaks the language that was used to explain this research and is receiving an informed consent form in the appropriate language. Additionally, this subject reads well enough to understand this document or, if not, this person is able to hear and understand when the form is read to him or her. This subject does not have a medical/psychological problem that would compromise comprehension and therefore makes it hard to understand what is being explained and can, therefore, give legally effective informed consent. This subject is not under any type of anesthesia or analgesic that may cloud their judgment or make it hard to understand what is being explained and, therefore, can be considered competent to give informed consent.

_____   _____

Signature of Person Obtaining Informed Consent / Research Authorization   Date

_____

Printed Name of Person Obtaining Informed Consent / Research Authorization

Informed Consent of Legally Authorized Representative (Proxy/Healthcare Surrogate) for Participation in Research

Information to Consider Before Taking Part in This Research Study

IRB Study # Pro00000220

Researchers at the Tampa General Hospital, Moffitt Cancer Center and University of South Florida study many topics. Our goal is to find better ways to help treat patients. To do this, we need the help of people who agree to take part in a research study.

We are asking you to take part in a research study that is called:
"Proposal for development of evidence based clinical decision support system (EBM-CDSS) to aid prognostication in terminally ill patients"

We are approaching you to ask you to participate in this study because we were told that you have a terminal disease that may significantly shorten your life duration. You may participate in this study; only if you aware that you have you have a terminal disease.

The person who is in charge of this research study is Dr. Benjamin Djulbegovic. This person is called the Principal Investigator. However, other research staff may be involved and can act on behalf of the person in charge. The person explaining the research to you may be someone other than the Principal Investigator.

Other research personnel who may be involved with you include: your consulting physician and or the following study personnel: Catherine Jahrsdorfer, Marlo Crawford , Rahul Mhaskar and Howard Tuch

The research will be done at Tampa General Hospital Tampa Bay Lifepath Hospice and Palliative Care and Moffitt cancer center.

This research is being paid for by the United States Army.

Finding the best person to give consent by proxy

Under certain circumstances, someone can give consent and research authorization for another person to take part in this research study. This person is the "subject by proxy." The proxy can make choices for the subject, if the subject is not able to make choices for him or herself. This person serves as the legally authorized representative. A proxy can be any of the people listed in A.

A. Look at the list and write Proxy in the space next to the description of the person who will give consent and research authorization for the person participating in this research. If, there is a person

with a higher authority, write in the space why that person is not available, willing, or able to act as proxy. This following is an example:

Health Care Surrogate: No one was named
Spouse: Spouse has died
Adult Child: Unable to reach by phone after several tries

Parent: PROXY

(1)   **Health Care Surrogate** named by person: _____

(2)   A **guardian** of the person, appointed by the court. He/she must be authorized to give consent to medical treatment:_____

(3)   The person's **spouse**: _____

(4)   An **adult child** of the person.   If the person has more than one adult child, a majority of the adult children who live near enough to be asked:_____

(5)   A **parent** of the person: _____

(6)   The **adult sibling** of the person. If the person has more than one sibling, a majority of the adult siblings who live near enough to know what is going on:
_____.

(7)   An **adult relative of the person who has shown special care and concern** for the person. This adult relative has kept regular contact with the person. He/she knows how the person feels about things, what the person likes to do, what the person's health is like, what the person believes and thinks is right
_____.

(8)   A **close friend** of the person: _____.

(9)   A **clinical social worker** licensed pursuant to Chapter 491, or who is a graduate of a court-approved guardianship program. Such a proxy must be selected by the provider's bioethics committee and must not be employed by the provider. If the provider does not have a bioethics committee, then such a proxy may be chosen through an arrangement with the bioethics committee of another provider. The proxy will be notified that, upon request, the provider shall make available a second physician, not involving in the patient's care to assist the proxy in evaluating treatment. Decisions to withhold or withdraw life-prolonging procedures will be reviewed by the facility's bioethics committee. Documentation of efforts to locate proxies from prior classes must be recorded in the patient record.

Proxy's Statement of Consent:

I understand that I am being asked to serve as the legally authorized representative for (name of participant) _____ and give permission for him/her to participate in this research study. My decision is based on what I believe the person would choose for him/herself and what I believe is now best for the person, based on the information I have been provided.

Should the person for whom you are signing consent take part in this study?

This form tells you about this research study. After reading through this form and having the research explained to you by someone conducting this research, you can decide if you think the person for

whom you are signing consent. Reading this form should help you decide whether the person for whom you are signing consent would want to take part in the study. If, at any time, you have any questions, feel free to ask the person explaining this study to you.

The remainder of this form is written as if you, the Legally Authorized Representative, were participating in the research. This helps you think in terms of what the person for whom you are signing consent would do or what is best for that person.

Before you decide:

- Read this form.
- Have a friend or family member read it.
- Talk about this study with the person in charge of the study or the person explaining the study. You can have someone with you when you talk about the study.
- Talk it over with someone you trust.
- Find out what the study is about.
- You may have questions this form does not answer. You do not have to guess at things you don't understand. If you have questions ask the person in charge of the study or study staff as you go along. Ask them to explain things in a way you can understand.
- Take your time to think about it.

It is up to you. If you choose to take part in this study, you will need to sign this consent form. If you **do not** want to take part in this study, you should **not** sign this form.

Why is this research being done?

The purpose of this study is to help people in the final stages of their lives make decisions about continuing medical treatment targeting their disease or choosing hospice care. Hospice is a type of care that provides support to people at the end of their lives. The main goal of hospice care is to improve the quality of patients' lives by focusing on pain and other symptom relief and emotional comfort. This means that medical treatments that are given to target your disease may be discontinued.

This research study is aimed at helping you choose what type of medical care you want to have during the upcoming months. Most people in this situation are uncertain how they want to approach their illness. We have created a tool to help people and their doctors make the choice that they feel is right for them. The tool is designed to help doctors and patients like yourself decide whether to continue treatment targeting their disease although the treatment may create additional discomfort, or whether to choose care through hospice which is focused on providing comfort and symptom relief. Either of these choices may or may not prolong your life. We would also like to understand your wishes and preferences to help you make the choice that is right for you.

The tool that is being tested in this research is called an Evidence-based Medicine Clinical Decision Support System (EBM-CDSS). The EBM-CDSS is designed to be used by doctors at the bedside to better predict life expectancy in patients with terminal illness and to improve the timing and appropriateness of referral to hospice care.

We are asking you to take part in this research because you have an illness that may significantly shorten your life span. Why are you being asked to take part?

We are asking you to take part in this research study because you are **one of the patients** being referred to hospice care.

What will happen during this study?

- If you take part in this study: We will actively collect information from you until your demise. The study personnel or your attending physician will visit you twice initially and then once a month during the study period and will collect information from you. We do not expect the initial visits to last more than 30 minutes and the monthly visits to last more than 10 minutes.
- If you take part in this study, you will be requested to sign this informed consent form:
- After signing the informed consent you will be requested by the study personnel to share certain information related to your health from your medical records. You may be requested to answer questions regarding your health.
- The interviewer will also ask you whether you would like to know your doctor's best estimate of your life expectancy.
- We will estimate your life expectancy based on our current best estimates for "average" patients like you (i.e. estimate of the average future lifetime for people like you)? We will ask you whether you would like to know the best estimates of your life expectancy with the current treatment targeted at your disease and without this treatment.
- To help you decide between hospice care and treatment targeted at your disease. We will also like to learn about your wishes and preferences regarding how you would like to approach your illness. We will do that by using our tool to understand your feelings of regret in case you made a wrong choice.
- The interviewer will also seek your opinion regarding your tolerance if your doctor is mistaken regarding whether to continue your present treatment (that may potentially cure your disease or prolong your life) or to discontinue your treatment and refer you to hospice care. We will ask you a series of questions assuming that there is an error in prediction of your life expectancy with and without treatment targeted at your disease. We want to know how large an error you can tolerate and still not regret (magnitude of acceptable regret for you) your doctor's decision to be referred to hospice care. After you make the decision regarding choosing hospice care or continuing treatment we will ask you questions to obtain your opinion regarding the decision you made once a month until you pass away.
- We will ask you whether you changed your decision for enrolling / not enrolling in hospice care based on the information provided to you by us.
- You should know that we cannot tell you which of these choices (treatment targeted at your disease versus hospice care) will prolong your life. However, we may be able to tell you which of these choices are most compatible with your wishes and preferences for an average patient like you.

How many other people will take part?

About 400 people will take part in this study.

What other choices do you have if you decide not to take part?

You do not have to take part in this study. Your decision to take part in this study or not to take part will not affect the medical care that you receive You can choose to fully take part in this study including the collection of your medical record information and the initial and follow up interviews. You can also choose to **partially** participate in this study either by:

- allowing us to look at your medical records only and NOT take part in the interview process OR
- NOT allow us to look at your medical records or interview you but ONLY allow us to collect the date that you eventually pass away.

You choice of whether to take part in the study fully or one of the partial options will be indicated on the last pages of this consent form. There is a separate signature area for each choice and only one of these sections should be signed.

Will you be paid for taking part in this study?

You will receive no payment or other compensation for taking part in this study. What will it cost you to take part in this study?

There will be no additional costs to you as a result of being in this study. However, routine medical care for your condition (care you would have received whether or not you were in this study) will be charged to you or your insurance company.

What are the potential benefits if you take part in this study?

We don't know if you will get any benefits by taking part in this study. However, this study may improve doctor's accuracy to assess life expectancy. Many people find this important which can be important for you too. Many people also find it helpful to clarify their wishes and preferences regarding how they would like to spend the reminder of their life.

What are the risks if you take part in this study?

There are minimal risks for participating in this study. While many people in your situations want to have a frank conversation about doctors' best estimate of their life expectancy, we understand that talking about how to approach your illness is difficult and can be very distressing. If you find anything that we are about to ask you upsetting and distressing, you may request to discontinue your participation from the study. There is no funding to compensate you for treatment if "injury" occurs. There might be other unforeseeable risks that could occur which are unknown at this time. Your decision to withdraw from the study will not affect the care you will receive in any form and or manner. If you wish to consult the study Principal Investigator and Co- Principal Investigator (they have extensive experience working with patients in similar situations) will immediately be available for counseling.

Conflict of Interest Statement

There is no conflict of interest.

Authorization to Use and Disclose Protected Health Information

Who will see your health information?

In our research, we use and share your health information to the extent authorized by you. We know that this information is private. The federal privacy regulations of the Health Insurance Portability & Accountability Act (HIPAA) protect your identifiable health information. If you authorize us to use your information we will protect it as required by the law.

Research at Tampa General Hospital and Moffitt cancer center is conducted jointly with the University of South Florida. By signing this form, you are permitting Tampa General Hospital,Moffitt cancer center and University of South Florida to use personal health information collected about you for research purposes. You are also allowing Tampa General Hospital and Moffitt cancer center to share your personal health information with individuals or organizations other than USF, Moffitt cancer center and Tampa General Hospital who are also involved in this research and listed below.

Who will disclose (share), receive, and/or use your information?

To do this research, USF and the people and organizations listed below may use or share your information. They may only use and share your information:

- With the people and organizations on this list;
- With you or your personal representative; and
- As allowed by law.

In addition to the people and organizations listed below in the Privacy and Confidentiality section of this document, the following groups of people may also be able to see information about you and may use the information to conduct the research:

- The medical staff that takes care of you and those who are part of this research study;
- Each research site for this study. This includes the research and medical staff at each site and USF;
- The designated peer review committees such as the Tampa General Hospital and Moffitt cancer center Feasibility Committee;
- Additionally, there may be other people and/or organizations that may be given access to your personal health information. This includes Tampa Bay LifePath Hospice care.

Who else can use and share this information?

Anyone listed above may use consultants in this research, and for the purpose of this study may share your information with them. If you have questions about who they are, you can ask us. Individuals who receive your health information for this research study may not be required by the HIPAA Privacy Rule to protect it and may share your information with others without your permission. They can do so if permitted by the laws governing them. Example: The sponsor may share your information. If the sponsor or others share your information, your information may no longer be protected under the

HIPAA Privacy Rule.

How Will My Information Be Used?

By signing this form, you are giving your permission to use and/or share your health information as described in this document for any and all study/research related purposes. For example, your information may be used as necessary for your research-related treatment, to collect payment for your research-related treatment (when applicable) and to conduct regular business operations. Your authorization (permission) to use your health information will not expire until the end of this research study unless you revoke this authorization in writing.

 As part of the research, USF may collect, use, and share the following information:

- Your whole research record
- All of your past, current or future medical and other health records held by USF, other health care providers or any other site affiliated with this study. This includes, but is not limited to, HIV/AIDs, mental health, substance abuse, and/or genetic information

We may publish what we learn from this study. If we do, we will not let anyone know your name. We will not publish anything else that would let people know who you are.

Your Rights:

You can refuse to sign this form. If you do not sign this form:

- You will not be able to take part in this research and therefore not be able to receive the research related intervention.
- This will not change your health care outside of this study.
- This will not change your health care benefits.
- This will not change the costs of your health care.

How Do I Withdraw Permission to Use My Information?

You can revoke this form at any time by sending a signed letter to USF at the address given below, clearly stating that you wish to withdraw your authorization to the use of your health information in the research. If you revoke you permission:

- You will no longer be a participant in this research study.
- We will stop collecting new information about you.
- We will use the information collected prior to the revocation of your authorization. This information may already have been used or shared with others, or we may need it to complete and protect the validity of the research.
- Staff may follow-up with you if there is a medical reason to do so.

To revoke this form, you must tell us in writing. Please write to:

     Principal Investigator Benjamin Djulbegovic
     For IRB Study # [Pro00000220
     12901 Bruce B. Downs Blvd., MDC27
     Tampa, FL 33612

IRB Number: Pro00000220 Version 3   IRB Consent Rev. Date: Aug 23 2012
IC Proxy Template – SocBeh Rev: 2008-10-14   Informed Consent Rev # 3
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Privacy and Confidentiality

We will keep your study records private and confidential. Certain people may need to see your study records. By law, anyone who looks at your records must keep them completely confidential. The only people who will be allowed to see these records are:

- The research team, including the Principal Investigator, study coordinator, research nurses, and all other research staff**.**

- Certain government and university people who need to know more about the study. For example, individuals who provide oversight on this study may need to look at your records. This is done to make sure that we are doing the study in the right way. They also need to make sure that we are protecting your rights and your safety.

- Any agency of the federal, state, or local government that regulates this research. This includes the Food and Drug Administration (FDA), Florida Department of Health, and the Department of Health and Human Services (DHHS) and the Office for Human Research Protection (OHRP).

- The USF Institutional Review Board (IRB) and its related staff who have oversight responsibilities for this study, staff in the USF Office of Research and Innovation, USF Division of Research Integrity and Compliance, and other USF offices who oversee this research.

- The sponsors of this study The United States Army

  We may publish what we learn from this study. If we do, we will not include your name. We will not publish anything that would let people know who you are.

What happens if you decide not to take part in this study?

You should only take part in this study if you want to volunteer. You should not feel that there is any pressure to take part in the study to please the study doctor or the research staff.

If you decide not to take part:
- You will not be in trouble or lose any rights you normally have.
- You will still have the same services you would normally have.
- You can still get your regular therapy/counseling/services from your regular therapist/counselor/social worker

You can decide after signing this informed consent document that you no longer want to take part in this study. **We will keep you informed of any new developments which might affect your willingness to continue to participate in the study. However, you can decide you want to stop taking part in the study for any reason at any time. If you decide you want to stop taking part in the study, tell the study staff as soon as you can.**
- We will tell you how to stop safely. We will tell you if there are any dangers if you stop suddenly.
- If you decide to stop, you can go on getting your regular care from your physician.

Even if you want to stay in the study, there may be reasons we will need to take you out of it. You may be taken out of this study if:

- We find out it is not safe for you to stay in the study. For example, your health may get worse.
- You are not coming for your study visits when scheduled.

You can get the answers to your questions, concerns, or complaints.

If you have any questions, concerns or complaints about this study or experience an adverse event or unanticipated problem, call Dr. Benjamin Djulbegovic at 813-396-9178.

If you have questions about your rights, general questions, complaints, or issues as a person taking part in this study, call the Division of Research Integrity and Compliance of the University of South Florida at (813) 974-5638.

New information about the study

During the course of this study, we may find more information that could be important to you. This includes information that, once learned, might cause you to change your mind about being in the study. We will notify you as soon as possible if such information becomes available.

Signature of Legally Authorized Representative (Proxy / Health Care Surrogate)

Full Consent to Take Part in this Research, including medical record review, initial interview and follow up interviews:

It is up to you to decide whether you want _____ (name of participant) to take part in this study. If you want this person to take part, please read the statements below and sign the form if the statements are true.

I freely give my consent to have _____ (name of participant) **take part in this study.** I understand that I am allowing the research team to access the patient's health records for the purpose of this study and interview me regarding the patient's health and his/hers decision regarding enrolling for hospice care. I understand that by signing this form I am agreeing for the individual named above to take part in research. I have received a copy of this form to take with me.

_____   _____

Signature of Legally Authorized Representative   Date

_____
Printed Name Legally Authorized Representative

_____

Partial consent to take part in the research, without participation in interview process

It is up to you to decide whether you want _____
(name of participant) to take part in this study. If you want this person to take part, please read the statements below and sign the form if the statements are true.

I freely give my consent to have _____ (name of participant) **partially take part in this study.** I understand that I am allowing the research team to access the patient's health records for the purpose of this study. I understand that by signing this form I am agreeing for the individual named above to take part in research. I have received a copy of this form to take with me.

I am allowing the researchers to access my medical record and I am NOT willing to participate in the interview process.

_____   _____

Signature of Legally Authorized Representative   Date

_____

Printed Name Legally Authorized Representative

Partial consent to take part in the research, Without Participation in interview process or medical record review

It is up to you to decide whether you want _____
(name of participant) to take part in this study. If you want this person to take part, please read the statements below and sign the form if the statements are true.

I freely give my consent to have _____ (name of participant) **partially take part in this study.** I understand that I am allowing the research team to access only the date of the individual's named above date of demise for the purpose of this study. I understand that by signing this form I am agreeing for the individual named above to take part in research. I have received a copy of this form to take with me.

I understand that I am allowing the research team to   collect the date that I eventually pass away for the purpose of this study. I understand that by signing this form I am agreeing to take part in research. I have received a copy of this form to take with me.

I ONLY ALLOW researchers to access medical records to collect the date that I eventually pass away.
.

_____   _____

Signature of Legally Authorized Representative   Date

_____

Printed Name Legally Authorized Representative

Determination of the Person's Ability to Give Consent

A.   I am (participant's name) _____'s _____(relationship).
I have examined this individual and have found that he/she is unable to give informed consent to take part in the research study.

_____   _____

Signature of Person Attesting to Limited/Diminished Autonomy of Participant   Date

_____

Printed Name of Person Attesting to Limited/Diminished Autonomy of Participant

-OR-

B.   I am a physician licensed in the State of Florida. I agree that this person is unable to give consent.

_____   _____

Signature of Physician   Date

_____

Printed Name of Physician

Paternal Consent
If you were pregnant or become pregnant, the particular treatment or procedure might involve risks to the embryo or fetus, which were currently unforeseeable.

_____   _____

Signature of father of unborn child   Date

The signature of the father was not obtained because:
☐ He was not readily available
☐ Other reasons: _____

Statement of Person Obtaining Informed Consent

I have carefully explained to the person who is giving consent for _____
who is taking part in the study what he or she can expect.

I hereby certify that when this person signs this form, to the best of my knowledge, he or she understands:
- What the study is about.
- What procedures/interventions/investigational drugs or devices will be used.
- What the potential benefits might be.
- What the known risks might be.
- How the information collected about the person will be used.

I also certify that he or she does not have any problems that could make it hard to understand what it means to take part in this research. This person speaks the language that was used to explain this research. This person reads well enough to understand this form or, if not, this person is able to hear

and understand when the form is read to him or her.

This person does not have a medical/psychological problem that would compromise comprehension and therefore makes it hard to understand what is being explained and can, therefore, give informed consent. This person is not under any type of anesthesia or analgesic that may cloud their judgment or make it hard to understand what is being explained and, therefore, can be considered competent to give informed consent.

_____   _____

Signature of Person Obtaining Informed Consent   Date

_____
Printed Name of Person Obtaining Informed Consent

Appendix 11 Prospective phase interview guidelines and software user manual

Interview guide

Please use the following interview guide for data collection from participating physicians and patients.

You will be using the Hospice Referral software in addition to the case report forms (hard copies: appendix 1) to record data obtained from participants. You will be provided with a laptop computer in which the *Hospice Referral Data Collection Software* (Hospice Referral software) will be pre-installed. The software will perform all computations required to derive the best advice for each decision maker (e.g. healthcare provider, patient or surrogate) according to the prognostication models and the decision maker's preferences.

Hospice Referral Data Collection Software – User guide

To run the Hospice Referral software, you need to locate it in the computer's desktop and then double click the shortcut associated with the software. The shortcut will be named: **Hospice Referral**. This shortcut will be depicted in the computer's desktop with the following icon:

Once the software has started you will see the following welcome screen:
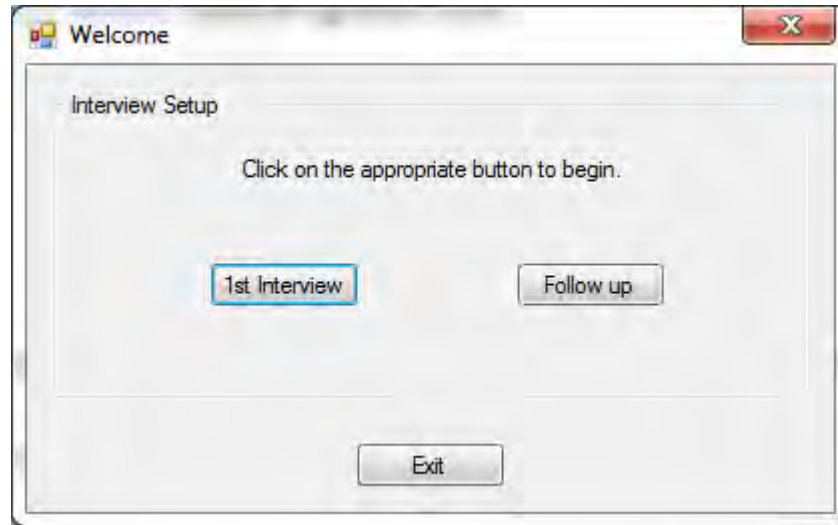
Click on "**1st interview**" button only when you interview a patient/surrogate for the first time or when you interview a healthcare provider regarding a specific patient for the first time (regret interview). Otherwise click on the "**Follow up**" button (post decisonal regret interview). The button "Exit" will terminate the software. The button "**1st interview**" is intended for patient/surrogate and healthcare provider interviews. The button "**Follow up**" is intended **only** for patient/surrogate interviews.

The "1st interview" button will lead you to the following screen:

The software uses tabs to present the information in an organized manner. To avoid confusion of switching between tabs, all tabs are invisible until needed. You can navigate **FORWARD** between tabs of the Hospice Referral software by clicking the **NEXT** button on the bottom of the screen. Once a tab is activated, it will remain this way until a new interview is initiated. You can navigate **BACKWARDS** between tabs by clicking on the name tag of the desired tab.

The **CANCEL** button, at the top left side of the screen, should be used ONLY if you would like to discard the data you entered. ALL data related to the current interview will be lost.

The "**follow-up**" button of the welcome screen will lead you to the following screen.

You need to enter the patient's id and click the "**Go**" button to enable the questionnaire. You must have interviewed the patient regarding regret (Welcome screen, "**1st interview**" button) before you use this questionnaire. You need to answer all questions. Click the "**Cancel**" button to discard the interview. Click the "**Save/Exit**" button to save your work and return to the Welcome screen.

Study recruitment and interview process (healthcare provider and patients)

You will collect data from healthcare providers and their (terminally ill) patients. The participating physicians will identify the "terminally-ill" patients who are potential candidates for participation in this study. Hence, the first step in the data collection process is the recruitment and data collection from healthcare providers.

Healthcare provider interview guidelines

Study recruitment (healthcare provider)

- We will provide a short summary of study procedures and expectations from the physicians to all physicians affiliated to TGH and Moffitt Cancer Center. (Via: email / a hard copy/flyer).

Tasks to be completed during the initial visit:

- Request the healthcare providers who are interested in participating in the study to sign the informed consent form (appendix 3).

- Please provide a photocopy of the signed informed consent form to the participating healthcare providers during the subsequent visit.

- Request the full name and the TGH/ Moffitt Cancer Center identification numbers for the patients that the participating physicians are providing services for.

- Further, request the participating physicians to identify the patients who are categorized as "terminally-ill" (potential hospice candidates) according to their clinical judgment at the current time.

- Inform the physician that you (or your fellow research nurse) will approach the potential participants (terminally-ill patients under his / her care) in order to request participation in this study. Also, inform the healthcare provider that you will see him / her again once you have obtained data and completed interview (s) of his/ her terminally-ill patients.

- Obtain the demographic and other information depicted in the healthcare provider demographics form (appendix 1).

- Thank the healthcare provider and make tentative appointment(s) to see him/her again.

Tasks to be completed during the interview (second visit):

- Please note that you will be using both the paper form and the Hospice Referral software to collect data and interview details.

- Obtain the healthcare providers' prediction of survival for the patient being discussed and note in the physician EBM CDSS usefulness case report form (appendix 6).

- Start the Hospice Referral software.

- On the Welcome screen (Figure 1) click on the "**1st Interview**" Button. This will lead you to the main interview window of the Hospice Referral software.
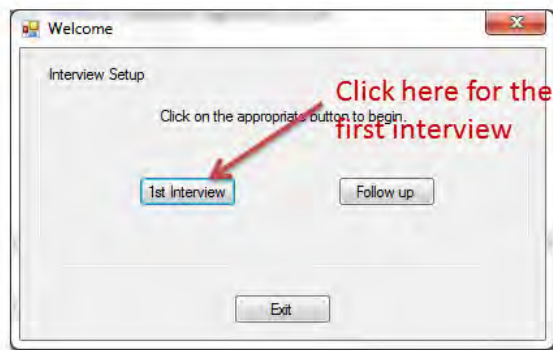
Figure 1. Welcome screen of the Hospice Referral Software

- Start the interview by providing the name and TGH/Moffitt Cancer Center ID of the patient you are going to discuss about.

- Use the Hospice Referral software to record the Physician's ID and the patient's ID (see figure 2).

- In the "Who is interviewed" dropped down menu select "Physician".

- Notice that the "Interview type" as well as the "Familiarity with hospice services" boxes are deactivated. The "Interview Type" box corresponds to the level of the interview the interviewee agrees to participate in (e.g. full: access to medical records and regret interview; partial: access to medical records; and minimum: access to date of death). Healthcare providers are participating only to full type interviews. The "Familiarity with hospice services" box is used to capture the patient's awareness of hospice care. Therefore, it is not applicable to healthcare providers.

Figure 2. Initial interview screen of the Hospice Referral software: Use this tab to enter the interview details.

- The **NEXT** button from figure 2 will lead you to the "Current Choice" tab, displayed in figure 3.

Figure 3. Current Choice: Use this tab to enter what the healthcare provider believes is the best action for the particular patient.

- Use the Hospice Referral software to record what the healthcare provider believes is the best treatment option for the particular patient by clicking the corresponding radio button.

- Click the **NEXT** button of the "Current Choice" tab (figure 3).

- The next tab will be the "Regret" (figure 4) tab. Click the "next" button to go to the regret tab (figure 3).

Figure 4. Regret Tab: Use this tab to enter the healthcare providers' regret level regarding each treatment option for the particular patient.

- Use the script provided to elicit the healthcare providers' regret levels (appendix 2).

- Use the Hospice Referral software to record the healthcare providers' regret levels by moving the corresponding sliders depicted in figure 4.

- Read the summary statement at the bottom of the "Regret" tab (figure 4 –"Summary" box) to validate the healthcare providers choice. If the healthcare provider does not agree with this statement, ask him/her to re-evaluate his/her regret estimates.

- You are now ready to move to the next tab (figure 5 - "Summary") by clicking the NEXT button depicted in figure 4.

- The next tab in the Hospice Referral software presents information regarding the assessment of our statistical model and decision methodology (figure 5). If the

healthcare provider wishes to learn our assessment as well as the probability of death for the patient, offer the information presented in this tab.
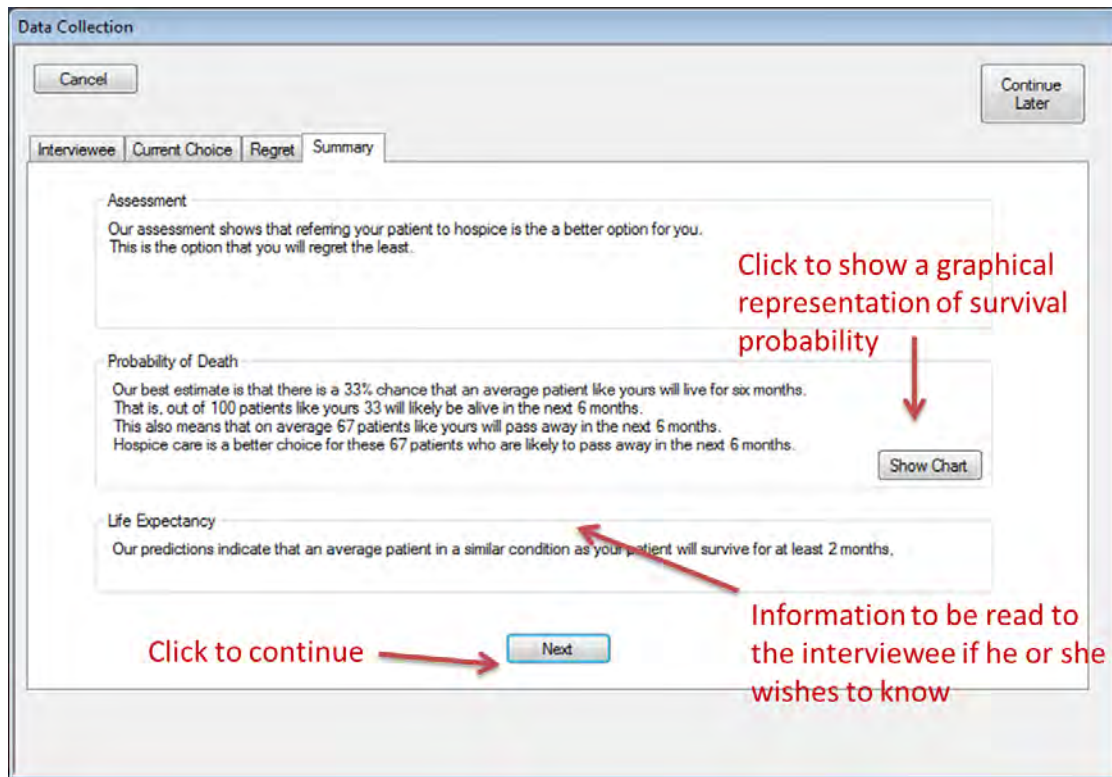
Figure 5. Summary tab: Use this tab to inform the healthcare provider regarding the details of our assessment.

- You may click the button "Show Chart" in the "Summary tab" to show a graphical representation of the survival probability computed by the software if the healthcare provider wishes to see it. The graphical representation appears as follows (figure 6):
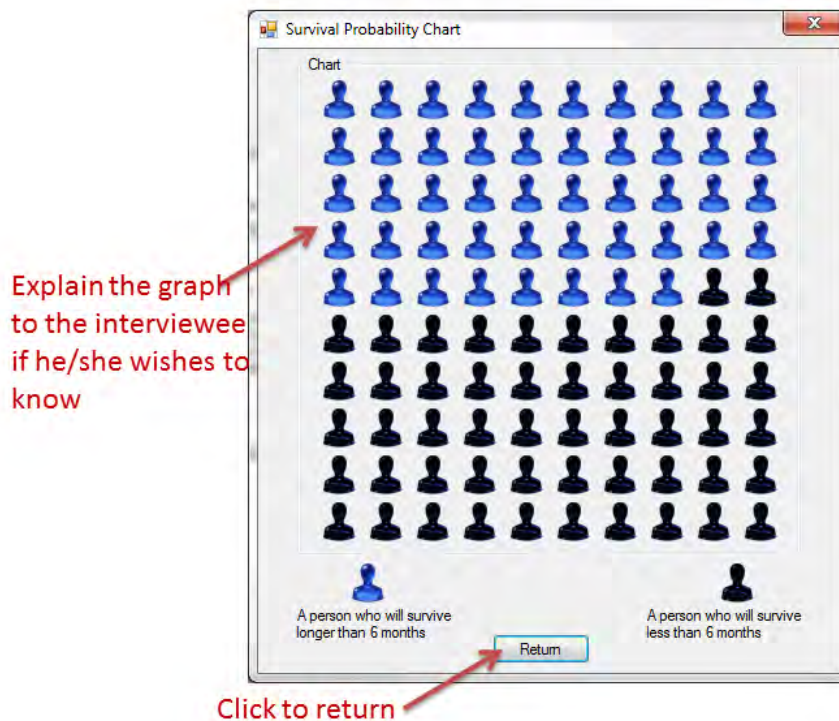
Figure 6. Graphical representation of survival probability.

- You can return to the "Summary" tab by clicking the "Return" button.

- You can now continue to the next tab "Questionnaire" by clicking the Next button in the "Summary" tab (figure 5)

- The "Questionnaire" tab contains questions regarding the usefulness of our statistical model in healthcare providers' decision-making (figure 7)

- Ask the healthcare provider if he/she would like to change his mind and therefore re-evaluate his regret levels.

- If the healthcare provider wishes to change his/her mind, click on the "Yes" button on the top of the "Questionnaire" tab. By clicking the "Yes" button, a new record will be created and the Hospice Software will return to the "Regret" tab (figure 4).

  o Repeat the procedure until you reach an agreement with the healthcare provider (he/she will not change his/her mind)

- If the healthcare provider does not wish to change his/her mind, click on the button "No". This will enable the questionnaire for filling out. To answer each question, click on the radio button that represents the healthcare provider's answer.

Figure 7. Questionnaire tab: Use this tab to get the healthcare provider's reaction to our recommendation. In this tab, the healthcare provider has the opportunity to change his/her mind regarding the regret he/she feels.

- When the physician answers all questions in the "Questionnaire" tab, you can move to the next tab by clicking the "Next" button in the bottom of the "Questionnaire" tab (figure 7).

- The next tab you will go to will be the "Acceptable Regret" (figure 8) tab.

Figure 8. Acceptable Regret tab: Use this tab to record the healthcare provider's acceptable regret

- Use the acceptable regret script for elicitation of healthcare providers' acceptable regret (appendix 2). Record the healthcare providers' values in the appropriate boxes (figure 8)

- You can now move to the last tab "Final" (figure 9) by clicking the "Next" button at the bottom of the "Acceptable Regret" tab (figure 10).
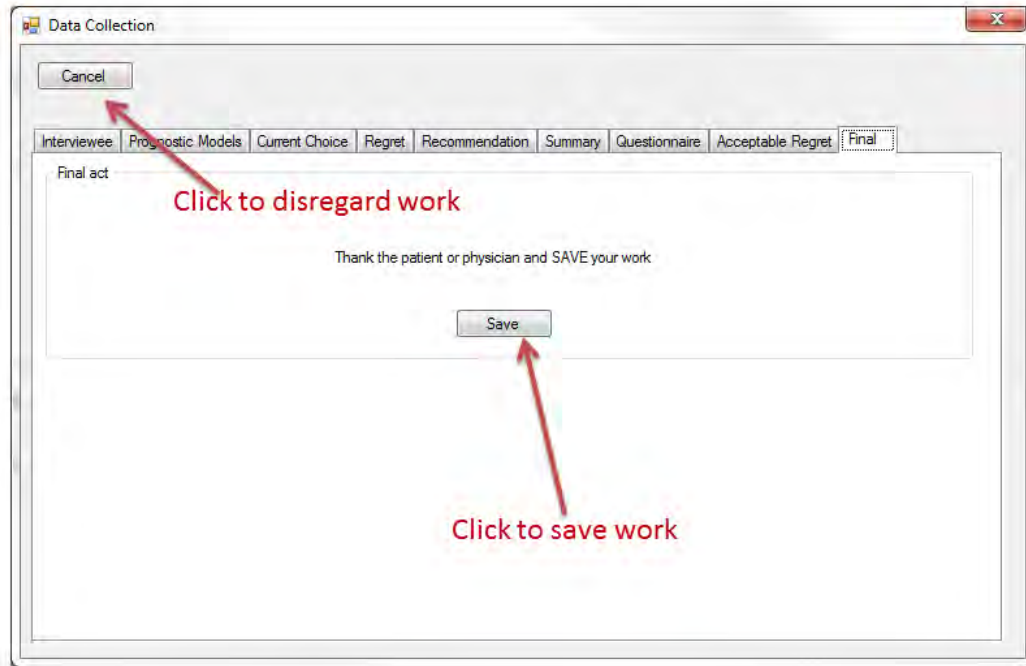
Figure 10. Final tab: Use this tab to save/cancel your work.

- The "final" tab reminds you to thank the healthcare provider and save your work. Click on the "Save" button on the Hospice Referral software (figure 10). This will lead you back to the Welcome screen.

- Repeat these steps for each terminally –ill patient (whom you or your fellow research nurse have interviewed earlier) receiving care with the healthcare provider being interviewed.

- Thank the healthcare provider and conclude the interview.

Patient interview guidelines

Study recruitment (patients)

- Please contact potential patients (and / or their family members) in person.

- Please explain the purpose of the study using the recruitment script (which is a short summary of study procedures and expectations from the participants: appendix 1) to all the potential participants.

Tasks to be completed during the interview:

- After you have explained the study purpose and other details using the recruitment script, ask if the participant needs more time to think and wants you to come at later time etc. Exercise maximum tact, compassion and understanding.

- Please request patients who are interested in participating in the study to sign the informed consent form (appendix 3).

- Please provide enough time for the patient to read and understand the informed consent form. Also, inform the patients that you will be ready to answer any questions / concerns they may have.

- For the patients who are not in a state of being able to sign the informed consent form: request member of patients' family (a proxy / surrogate member) to sign the proxy informed consent form (appendix 3).

- Inform the patient that you will provide a photocopy of the signed informed consent form during the subsequent visit.

- Inform the patient that you will be extracting laboratory data from his/her hospital charts to calculate life expectancy.

- Please complete the demographics and other information in the patient case report form table 1 (appendix 1).

- Also, please obtain and complete data required in the tables 2, 3 and 4 in the patient case report form. Please use the patients' hospital charts and other hospital records to obtain these data. Contact the staff nurse if required.

- Thank the patient for his participation in the study and continue with the interview.

For patients who agree to participate in the complete study:

- <u>Start the Hospice Referral software.</u>

- On the welcome screen click on the "1st interview" button (figure 11)
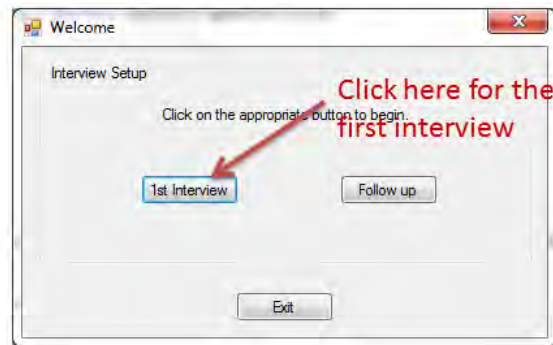
Figure 11. Welcome screen of the Hospice Referral Software. Click on the "1st interview" button for the first interview with the patient/surrogate.

- Obtain the full name and patient identification number and write it down on the case report form (appendix 1).

- Write down the identification number of the treating physician on the case report form (appendix 1).

- Use the Hospice Referral software to record the Physician's and the patient's identification numbers (see figure 12).

- In the "Who is interviewed" dropped down menu select "Patient or Surrogate".

- If the patient is <u>not</u> in a state being interviewed and his / her proxy has signed the appropriate informed consent form please select "Surrogate" from the drop down menu and proceed to interview the proxy individual.

- Per the informed consent form there are three types of interviews a patient/surrogate may agree to participate in: full (access to medical records and regret interview), partial (access to medical records), and minimal (access to the date of death). Based on the patient's/surrogate's response select the appropriate option button in the "Interview type" box (figure 12)

- Ask if the patient is aware of hospice services and if he was approached by a hospice nurse. If so, fill out the "Familiarity with hospice services" box (figure 12).

Figure 12. Interviewee tab: Use this tab to enter the physician's and patient's id and to select the interview type.

- Click on the Next button on the bottom of the "Interviewee" tab (figure 12) to move to the "Prognostic models" Tab (figure 13)

- At the "Prognostic models" tab enter the PPS Score and SUPPORT details (figure 13). Please use the guidelines for calculation of PPS document (appendix 1).

Figure 13. Prognostic models: Use this tab to enter physiological information regarding the patient.

- PPS Score is the only required data before you are allowed to move the next tab. However, use the patient's chart to fill out the remaining information (figure 13).

  - Hovering the mouse pointer on the label of each textbox (e.g. the word "Age", "Albumin" etc.) an information tooltip will appear showing you the range of **normal** values for each category. Use this information to get an estimate of the values required.

  - The drop down menu regarding the presence of cancer related to both the main disease (e.g. Colon cancer) and any comorbidity. Therefore, even if the main disease of the patient is not related to cancer (e.g. congestive heart failure) but the patient has cancer, you should note that in the "cancer" drop down menu.

- Once you complete entering the patient's information in the "Prognostic Models" tab, click on the **NEXT** button (figure 13). If there are missing values in the prognostic models tab, you will receive a notice as the one shown in figure 14. If you have more data to enter, click "No" and continue entering the data missed. If you have no more data to enter, click "Yes"

o   Note that you will **not** be able to return to this screen to enter missing values. Refer to the Troubleshooting section of this manual to learn how to handle missing values at a later time.
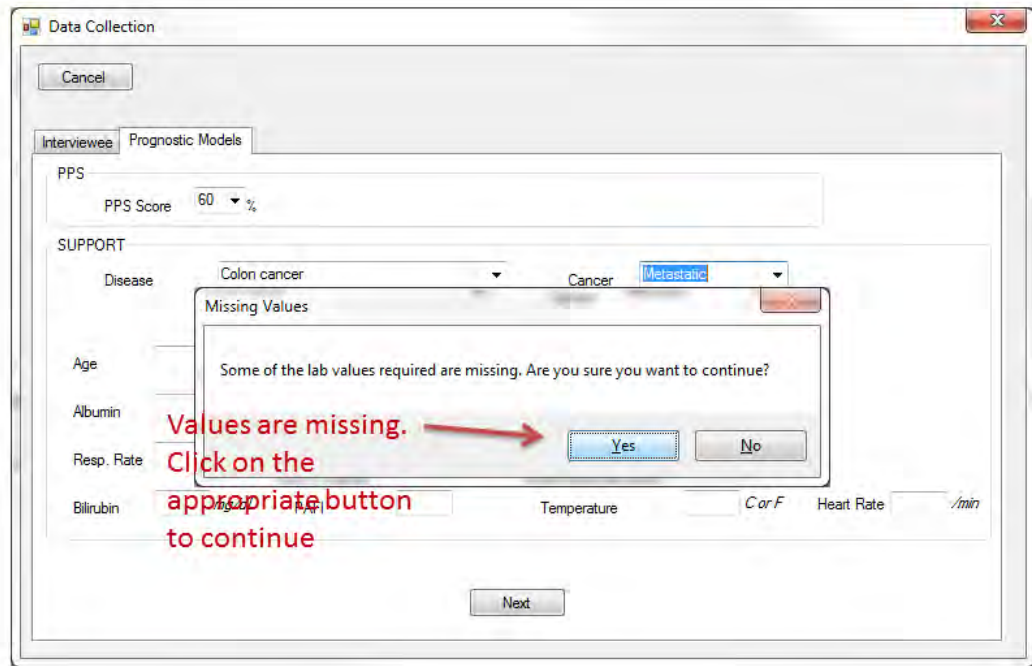
Figure 14. Warning related to missing data. Make sure you have no more data to enter.

- The next tab is associated with the "Current Choice" of the patient/surrogate, displayed in figure 15.

   o   Use the Hospice Referral software to record what the patient/surrogate believes is the best treatment option for the particular patient by clicking the corresponding radio button. Please use the regret script to elicit this information (appendix 2).

Figure 15. Current Choice: Use this tab to enter what the patient/surrogate believes is the best action for the particular patient.

- Click the **NEXT** button of the "Current Choice" tab (figure 15).

- The next tab is the "Regret" tab (figure 16), in which the interview regarding the regret levels of the patient/surrogate will be implemented.

Figure 16. Regret Tab: Use this tab to enter the patient's/surrogate's regret level regarding each treatment option for the particular patient.

- Use the script provided to elicit the patient's/surrogate's regret levels (appendix 2).

- Use the Hospice Referral software to record the patient's/surrogate's regret levels by moving the corresponding sliders depicted in figure 16.

- Read the summary statement in the bottom of the "Regret" tab (figure 16 –"Summary" box) to validate the patient's/surrogate's choice. If the patient/surrogate does not agree with this statement, ask him/her to re-evaluate his/her regret estimates.

- By clicking the "Next" button in the "Regret" tab the software will lead you to the "Summary" tab (figure 16), which presents details about our assessment as well as the probability of death for the patient. If the patient wishes to know our assessment offer him/her the details of this tab.

- If the patient wishes to know more regarding his probability of death you may offer a graphical representation by clicking the button "Show Chart". This will show the window depicted in figure 17.
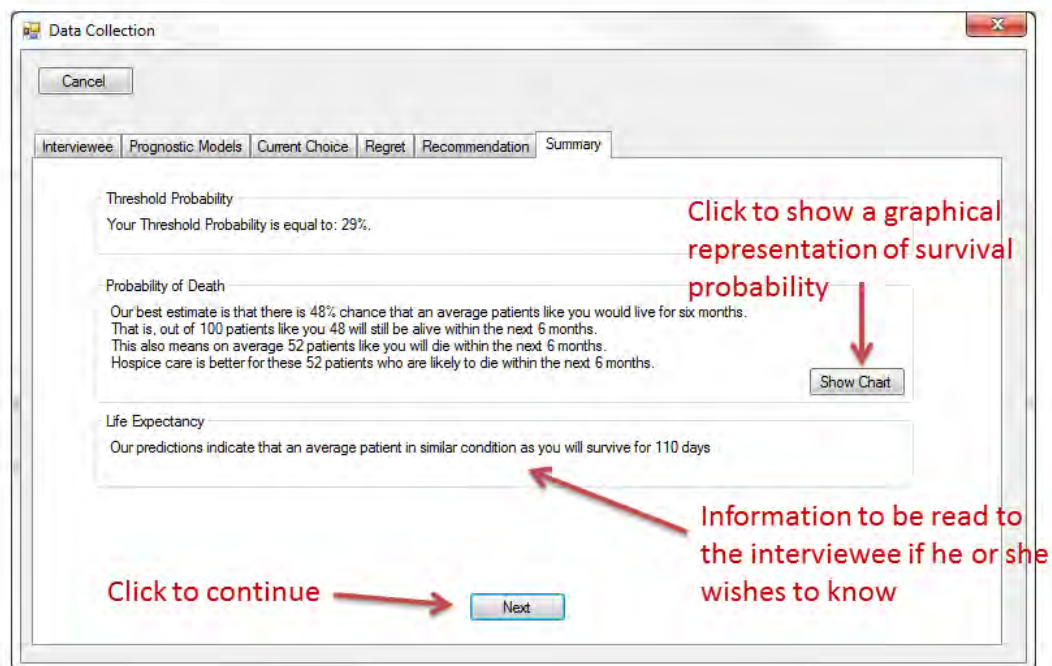
Figure 17. Summary tab: Use this tab to inform the patient/surrogate regarding the details of our recommendation.
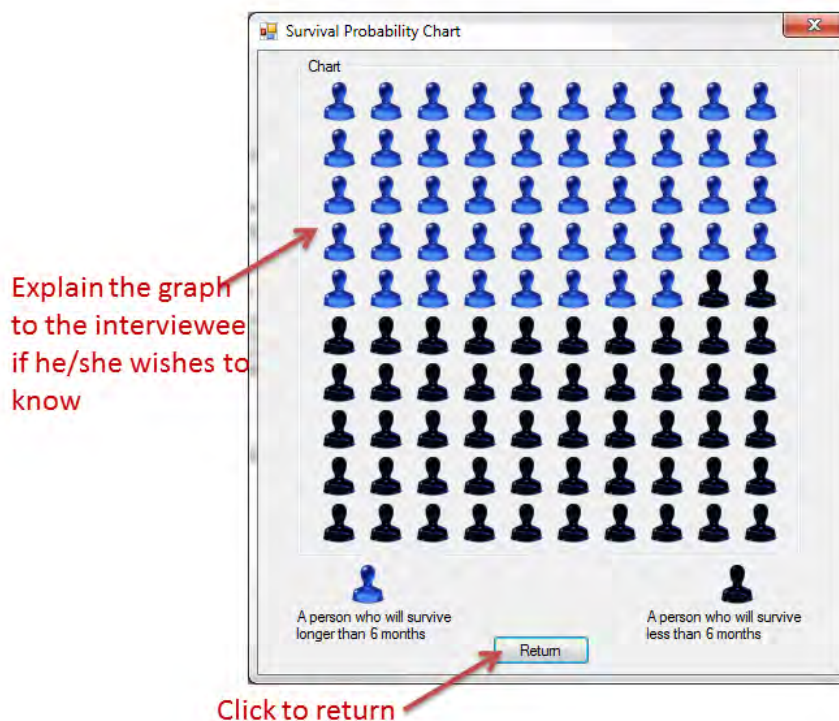
Figure 18. Graphical representation of probability of death

- In the chart window, click "Return" to return to the "Summary" tab.

- You can now continue to the next tab "Questionnaire" by clicking the "Next" button in the "Summary" tab (figure 19)

- The "Questionnaire" tab contains questions regarding the usefulness of our statistical prognostication model in patients'/surrogates' decision-making regarding choosing hospice care versus continuing current treatment (figure 19).

- Ask the patient/surrogate if he/she would like to change his/her mind and therefore re-evaluate his/her regret levels.

- If the patient/surrogate <u>wishes to change</u> his/her mind, click on the "Yes" button on the top of the "Questionnaire" tab (figure 19). By clicking the "Yes" button, a new record will be created and the Hospice Software will return to the "Regret" tab (figure 16).

  o Repeat this procedure until the patient/surrogate does not wish to change his/her mind.

- If the patient/surrogate <u>does not wish</u> to change his/her mind, click the "No" button to activate the questionnaire. To answer each question, click on the radio button that represents the patient's/surrogate's answer.

Figure 19. Questionnaire tab: Use this tab to get the patient's/surrogate's reaction to our recommendation. In this tab, the patient/surrogate has the opportunity to change his/her mind regarding the regret levels he/she feels.

- When the patient/surrogate answers all questions in the "Questionnaire" tab, you can move to the next tab by clicking the "Next" button at the bottom of the "Questionnaire" tab (figure 20).

- If the patient/surrogate has agreed to the acceptable regret interview (figure 13 – "Interview type"), the next tab will be the "Acceptable Regret" (figure 20).

- Please use the acceptable regret script for elicitation of patients' / surrogates' acceptable regret (appendix 2).

- Please record the patient's / surrogate's values in the appropriate boxes (figure 20).

Figure 20. Acceptable Regret tab: Use this tab to record the patient's/surrogate's acceptable regret

- You can now move to the last tab "Final" (figure 21) by clicking the Next button on the bottom of the "Acceptable Regret" tab (figure 20).
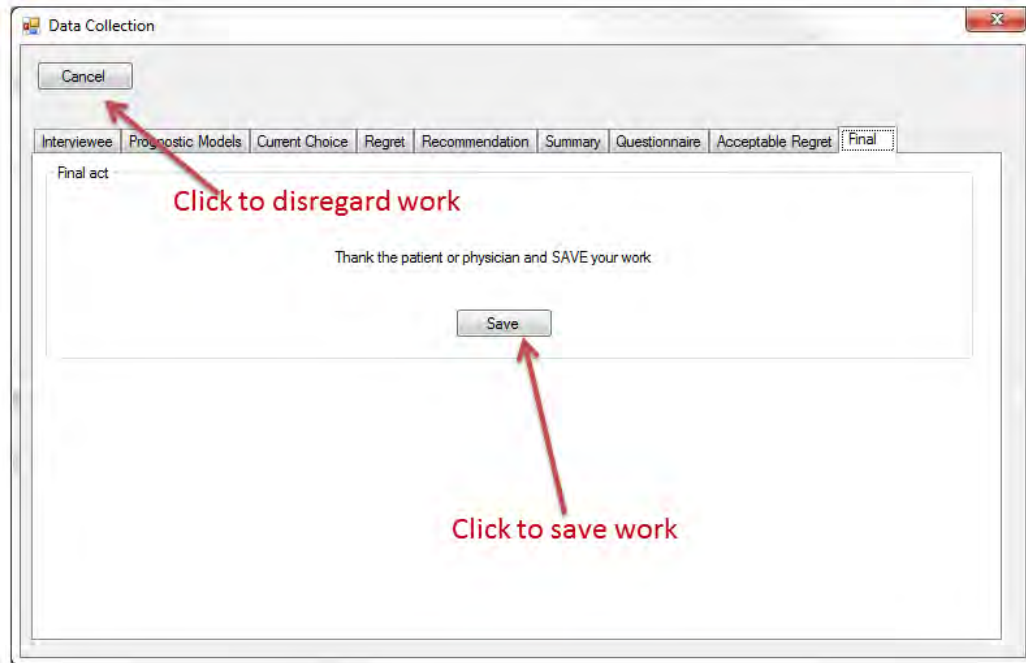
Figure 21. Final tab: Use this tab to save/cancel your work.

- The "final" tab reminds you to thank the patient/surrogate and save your work. Click on the Save Button (figure 21).

- Thank the patient and make a tentative appointment to see him/her after one month (the post-decision regret interview should take place after he / she makes his decision regarding choosing hospice care or continuing current treatment) to obtain the post-decision regret.

- For each post-decisional regret interview please use the post-decisional regret scale (appendix 2).

  o Start the Hospice Referral Software

  o On the welcome screen click the button "Follow up" (figure 22). This will bring the main questionnaire for the post regret interview (figure 23)

Figure 22. Welcome window of the Hospice Referral Software. Click on the "Follow up" button for post regret interviews

- o Enter the patient's ID on the appropriate box (figure 23). Click the "Go" button. The software will check if you have interviewed the patient regarding regret before. If so, the questionnaire will be enabled to fill out. If not, the software will inform you that you need to interview the patient about regret first.

- o After you fill out the questionnaire, click on the "Save/Exit" button to save your work and return to the "welcome" window. Or, click on the "Cancel" button to discard your entries.

- o Thank the patient and make a tentative appointment to see him/her after one month.

Figure 23. Post regret interview questionnaire.

Troubleshooting the Hospice Referral Software

How to run the Hospice referral software?

To run the Hospice Referral software, you need to locate the Hospice Referral shortcut on the computer's desktop. Double click the shortcut to start the software. If you cannot locate the Hospice Referral shortcut, ask the study personnel to re-install the software.

What are the Physician and Patient ID?

The physician's and patient's IDs are the coded numbers we have provided you referring to each physician and patient, respectively. Remember that these IDs are de-identified and do not include names or date of births. The IDs are of the form: XXXXXXXX.

What happens if a patient has more than one physician?

If a patient has more than one physician's then interview each physician who consents for the study.

What happens if I do not have all information related to the SUPPORT model?

If you do not have all information required for the SUPPORT model, then fill out as much as you can before continuing to the next tab.

I accidentally pressed Cancel and now I lost my work. Can I retrieve my work?

You will **_not_** be able to retrieve your work once you have clicked the "Cancel" button. However, before clicking the "Cancel" button a warning message will verify your action.

Can I edit a record I already saved?

You will **_not_** be able to edit a record once you have clicked the "Save" button. However, before clicking the "Save" button a warning message will verify your action.

Can I edit a record before I save it?

Once you have reached the "Final" form of your record you may navigate backwards to any of the tabs in the Hospice Referral software and you can edit all information entered. Remember that you will need to navigate forward by clicking the "Next" button located at the bottom of each tab.

Can I navigate to previous tabs?

You can navigate to previous tabs by clicking the name tag of each tab. Use the "Next" button at the bottom of each tab to navigate forward.

I cannot find the Save button to save my work

The "Save" button is located in the "Final" tab of the regret interview window. You need to navigate through all of the steps/tabs of the regret interview to reach the "save" button.

How can I terminate / close the software?

Use the "Cancel" button located at the top–right side of the Hospice Referral software to close the application and then click on the "Exit" button of the Welcome screen. ***Remember: any unsaved work will be lost***.

After the regret interview, I realized that I did not enter all lab values required in the Prognostication tab. Can I enter these values at a later time?

The values used in the "Prognostication" tab are necessary for the accurate estimation of life expectancy communicated during the interviews. Therefore it is imperative to record all of these values before an interview.

You will NOT be able to enter missing values after the interview. However, please use the appropriate paper base data collection forms to enter the missing values and notify the research personnel regarding the values missed and the patient id they correspond to.

Appendix 12 Study flyer

USF® HEALTH

"Hospice Referral Study"

EBM-CDDS (Evidence Based Medicine - Clinical Decision Support System)

Objective:

To aid prognostication in terminally ill patients using evidence based clinical decision support system

We want to evaluate the EBM-CDDS in patients that are eligible for hospice referral

How can you contribute?

- Call our research team for any patient you think may be eligible for hospice care.

How can you benefit?

- We will assess your patient's preferences and calculate his or her life expectancy to advise the patient if the referral to hospice is the "right choice" for him or her.

We are looking forward to your participation in this important research endeavor to improve prognostication and patient referral to hospice!

Contact Information

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Cell (813) 679-4930

Study PI: Benjamin Djulbegovic, MD, PhD

Appendix 13 EB-PMM User Manual

Pain Management Module

Instruction Manual

(Version 1.0)

Developed by: USF Center for Evidence Based Medicine

Table of contents

I. Overview

Welcome to the pain management module

The pain management module (PMM) has been designed to aid physicians in clinical decision making. It integrates highest quality of available evidence with NCCN physician guidelines to yield a comprehensive pain management system. The PMM enables the physician to assess patient's pain level, prescribe appropriate pain medication, calculate dosages for opioid conversion, manage adverse effects associated with pain medication, provide educational and psychosocial support resources, and easily access information for all available pain medications. The PMM aims to boost physician confidence in clinical decision making while providing patients with more effective pain management.

As it is based on NCCN guidelines, the PMM is primarily intended for use in patients experiencing pain associated with cancer. However, certain modules (i.e. pain assessment and opioid conversion) can be applied to managing 'any-source' pain. The NCCN guidelines have been supplemented by the highest quality of available evidence on each drug through a comprehensive literature search.

Disclaimer

Any program User is expected to use independent medical judgment in the context of individual clinical circumstances to determine patient's care or treatment. All calculations must be confirmed before use. The authors make no claims of the accuracy of the information contained herein; and these suggested doses are not a substitute for clinical judgment. University of South Florida – Division of Evidence-Based Medicine and Health Outcomes Research nor any other party involved in the preparation of this program shall be liable for any special, consequential, or exemplary damages resulting in whole or part from any user's use of or reliance upon this material.

Manual Structure

The manual is broken down into three components.

1) The introduction will provide the basis for the pain management module as well as the theory of evidence based clinical decision support.
2) Next, using the main page as a starting point, each possible path will be followed to the end
3) Finally, for experienced users, shortcuts to specific pages of the pain management module are provided.

Remarks:

Before using this program, we strongly recommend User be familiar with NCCN guidelines for "Adult Cancer Pain".

All program users are encouraged to try different scenarios, till they become very familiar with the program and its features. Also, pages contain additional explanations and tables (show/hide) and useful links. Please, try it.

By moving "mouse" over some of the table fields, program will pop-up small windows with instructions. This is useful in different conversions with more than one "operation".

II. What is the Pain Management Module?

Clinical decision support systems

Clinical decision support systems (CDSS) aim to provide physicians with higher confidence in clinical decision making by linking clinical observations with the best available evidence in the field.

Ideally a CDSS should be informed by the totality of evidence. In development of PMM, a systematic evaluation of all the currently available web-based resources related to choice of drug for pain management, route of administration, conversion between drugs and dosage was performed. When there was a lack of published evidence, suggestions from Package insert were used in providing dosing and administration routes for specific drugs.

Pain management in cancer

Pain management is a branch of medicine employing an interdisciplinary approach for easing the suffering and improving the quality of life of those living with pain. The typical pain management team includes medical practitioners, clinical psychologists, physiotherapists, occupational therapists, and nurse practitioners.

Pain is a common symptom experienced by patients with cancer. Whether as a result of the disease or a disease-related treatment, pain causes significant physical and psychosocial burdens.

NCCN reported that cancer pain can be well controlled in the vast majority of patients if evidence-based guidelines are applied, monitored, and individualized and patients engage in informed decision making for managing their pain.

NCCN guidelines

NCCN (National Comprehensive Cancer Network) guidelines are considered one of the most reputable professional guidelines and are widely used to manage patients with cancer and related conditions. NCCN guidelines are developed by 21 leading institutions in the US and are considered most reliable source of advice both for patients and physicians alike.[cite]

NCCN guidelines introduce several important components, such as: Pain intensity quantified by the patient (whenever possible), reassessment of pain intensity, availability of psychosocial support and provision of specific educational material. They also provide dosing guidelines for NSAIDs, opioids and co-analgesic. Finally, they provide suggestions for titrating and rotating opioids, changing dose and route of administration, and managing of opioid adverse effect.

III. Main page

After first opening the pain management module, the user should be able to see the screen below:

Figure 1
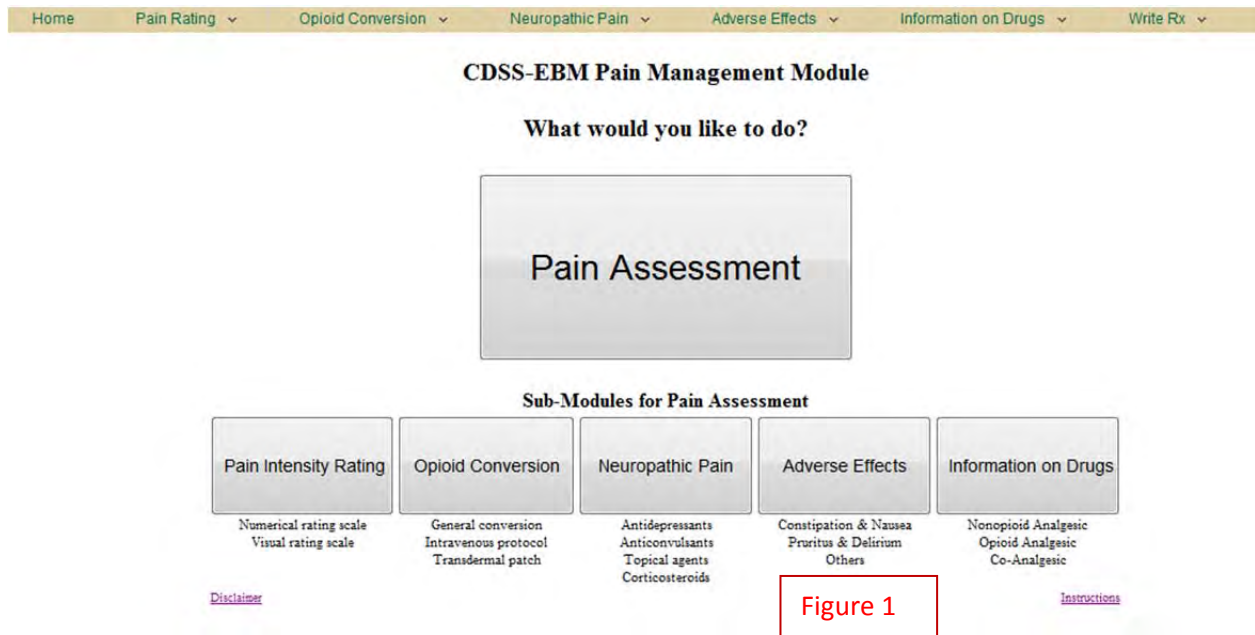
Some options on this screen are available on every page of the module and other options are specific to this page. First we will review options found on every page of the module.

<u>Options common to all pages of the pain management module:</u>

Figure 2

(1) Home

By selecting this option the user will be brought back to the first screen of the pain management module (figure 1, page 7).

(2) Pain Rating

By selecting this option the user will be taken to the pain intensity level assessment module (figure 11, page 14).

(3) Opioid Conversion

By selecting this option the user will be guided through calculating opioid conversion (figure 54, page 34).

(4) Neuropathic Pain

By selecting this option the user will be able to prescribe medication for management of neuropathic pain (figure 56, page 36).

(5) Adverse Effects

By selecting this option the user will be able to prescribe appropriate medication for managing common adverse effects associated with pain medication (figure 58, page 37).

(6) Information of Drugs

By selecting this option the user will be able to view specific information on available pain medications (figure 60, page 39).

(7) Write Rx

By selecting this option the user will have options to prescribe medication using suggested dose or to manually write complete prescription.

<u>Options specific to the main page of the pain management module</u>

The pain management module interface consists of the Pain assessment module (1) and five sub-modules.
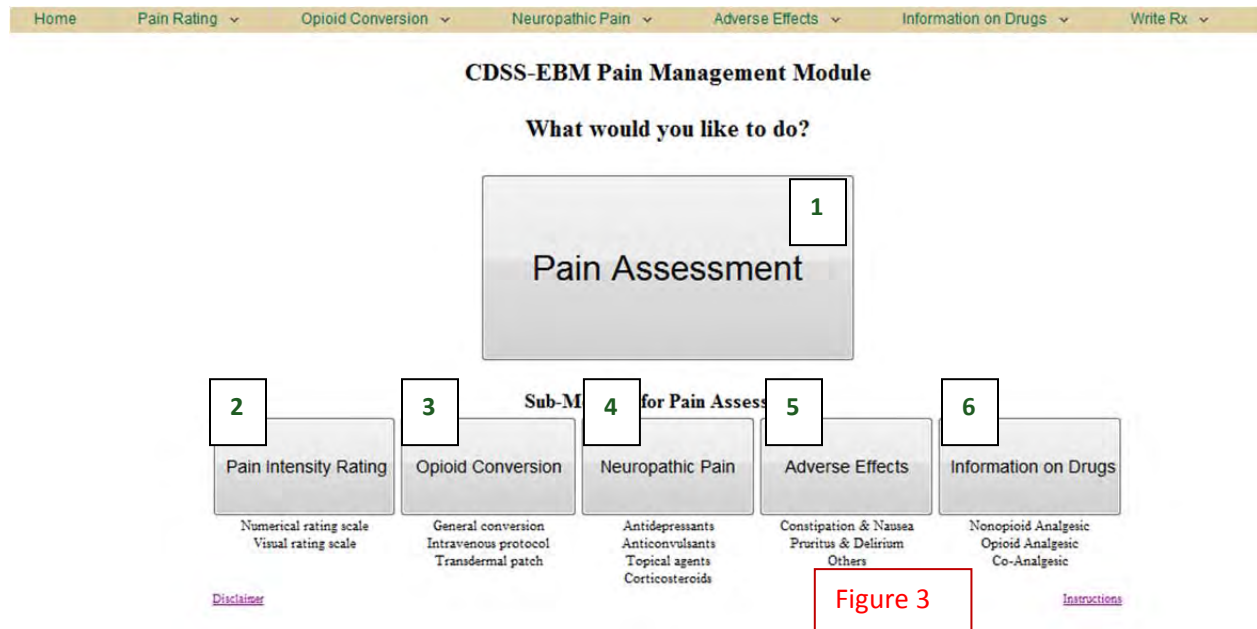
Figure 3

(1) Pain Assessment module

This module contains all components of the pain management tool. By selecting this option, user will be guided through pain assessment, patient drug history, and management recommendations.

There are practically "unlimited possibilities" for how to treat and follow-up with patients with chronic pain using the "Pain Assessment" algorithm.

Doctors are encouraged to try as much as possible and attempt different scenarios until they become very familiar with the program and its features.

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(2) Pain Intensity rating sub-module

This sub-module contains the pain intensity rating scales. By selecting this option, the user will be guided through assessment of patient's pain intensity using techniques provided by NCCN guidelines. (See page 33)

(3) Opioid Conversion sub-module

This sub-module contains the opioid conversion calculator. By selecting this option, the user will be able to calculate dosage conversions between different opioid drugs and routes of administration. (See page 34)

(4) Neuropathic Pain sub-module

This sub-module contains management options for neuropathic pain. (See page 35)

(5) Adverse Effects sub-module

This sub-module contains options for management of common adverse effects associated with pain medication. (See page 37)

(6) Information on Drugs sub-module

This sub-module contains information on available pain medications. (See page 39)

User Manual and Disclaimer

In order to access the user manual and disclaimer for the pain management module select the appropriate option as shown in figure 4.

Disclaimer   Figure 4   User Manual
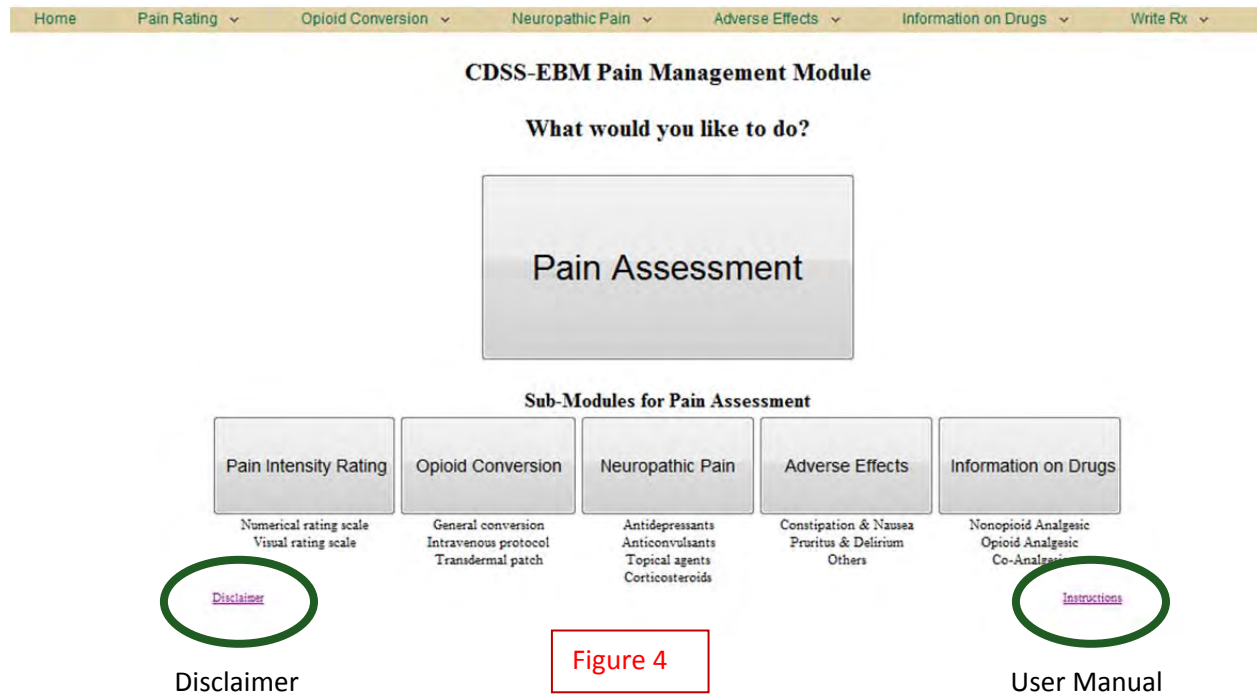
IV. Pain assessment

The pain assessment module contains all components of the pain management tool. It provides the user with complete pain management option starting from pain assessment and patient drug history followed by management recommendations and prescription writing.

To access the Pain Assessment module select Pain Assessment as shown in figure 5.

Figure 5

This will take you to…

Figure 6
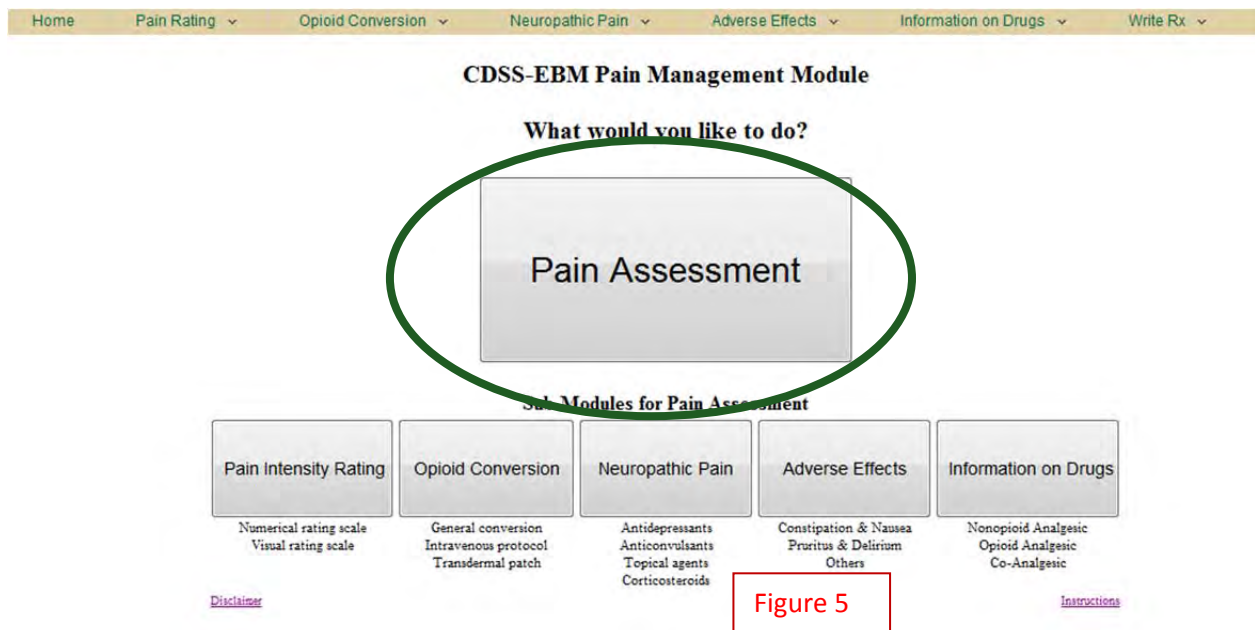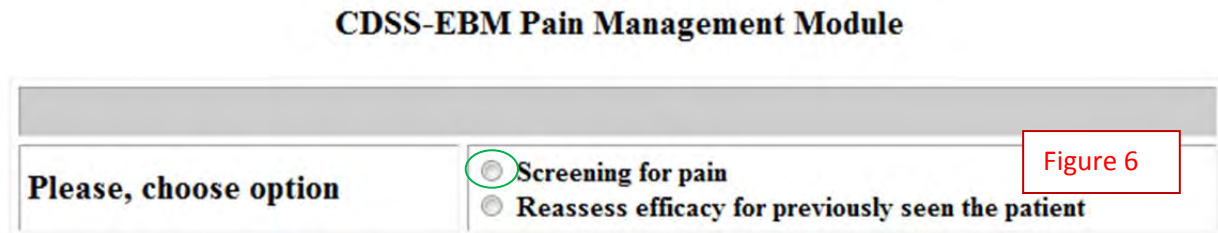
Let's select option "Screening for pain", and on next page we will have screen:

CDSS-EBM Pain Management Module

Screening for pain		
Is the patient currently experiencing pain?	○ Yes ○ No ○ No, but painful events or procedures are anticipated.	Figure 7

Let's select option "Yes", and on next page let's choose "No".

CDSS-EBM Pain Management Module

Assessment		
Is the pain related to oncologic emergency?	○ Yes ○ No	Figure 8

On next page, let's choose "Opioid naïve patient"

CDSS-EBM Pain Management Module

What is the patient status?	○ Opioid naive patient ○ Opioid tolerant patient	Figure 9

After selecting "Opioid naïve patient", next screen will appear:

CDSS-EBM Pain Management Module

Opioid naive patients		
Please choose option	○ Assess pain intensity ○ Skip pain intensity assessment and go to pain management	Figure 10

By choosing "Assess pain intensity", program will bring us to the page where we can define pain level for patient. There are two options for doing that, using numerical scale (clicking corresponding radio button and "clicking" submit button) or with face detection for nonverbal patient (moving slider to right, until face match pain intensity and "clicking" submit button).

13

CDSS-EBM Pain Management Module

show/hide Nonverbal patient	show/hide Linguistic assessment	**Pain Intensity Rating - Naive Patients**

On scale 0 to 10, how would you describe your pain? (You can choose numerical or face description)

○ null ○ one ○ two ○ three ○ four ○ five ○ six ○ seven ○ eight ○ nine ○ ten

| 0 = no pain; 1-3 = mild pain; 4-6 = moderate pain; 7-10 severe pain.[1] | | Submit |

How would you describe the level of your pain?

No pain

Worst pain you can imagine

0

| 0 | 2 | 4 | 6 | 8 | 10 |

[1] NCCN Adult Cancer Pain, V.1.2010; page: Pain-A, 1 of 2.

Figure 11

Submit

On next page, you have to confirm your selection.

CDSS-EBM Pain Management Module

Your selection indicates patient is in Severe pain (scale 7 - 10)   Figure 12   Confirm

After confirmation, you have to choose route of drug administration for short-acting opioids. Let's for learning purpose, choose "Tablets". Choosing Oral solution or Intravenous, there are similar procedures like for Tablets.

CDSS-EBM Pain Management Module

Opioid naive patient - routes	
Route of drug administration Figure 13	◉ Tablets (peak effect in 60 minutes) ○ Oral solution (peak effect in 60 minutes) ○ Intravenous (peak effect in 15 minutes)

CDSS-EBM Pain Management Module

Medication: (Opioid tablets)	Available dosage:
[▼] see opioid equivalency	[ ]
Choose a total daily dose: [▼]	1 day supply: [ ] ○
Single dose: [ ] *	7 day supply: [ ] ◉
[ ]	30 day supply: [ ] ○
Generate Prescription	* If single dose required "crushed" tablets, program will set lower dose available with tablet size.

After generating prescription, click here for more prescribing option, or go back to home page   Figure 14

You have to make three selections before generate prescription. You have to make medication selection, total daily dose and option for supply (1, 7 or 30 day). Button "Generate Prescription" will be "alive" only if you make correct selections.

CDSS-EBM Pain Management Module

Medication: (Opioid tablets)	Available dosage:
Morphine Sulfate [▼] see opioid equivalency	Tablets: 15, 30 mg IR, Typical initial dose is 15-60 mg, q3-4h as ▼
Choose a total daily dose: 90 mg [▼]	1 day supply: 6 (six) tablets ○
Single dose: 15 mg tabs *	7 day supply: 42 (forty two) tablets ◉
Take single tablet every 4 hours, as needed	30 day supply: 180 (one hundred eighty) tablets ○
Generate Prescription	* If single dose required "crushed" tablets, program will set lower dose available with tablet size.

After generating prescription, click here for more prescribing option, or go back to home page   Figure 15

15

CDSS-EBM Pain Management Module

Medication: (Opioid tablets)	Available dosage:
Morphine Sulfate ▾ see opioid equivalency	Tablets: 15, 30 mg IR, Typical initial dose is 15-60 mg, q3-4h as ▲▼
Choose a total daily dose: 120 mg ▾	1 day supply: 8 (eight) tablets ○
Single dose: 15 mg tabs *	7 day supply: 56 (fifty six) tablets ○
Take single tablet every 3 hours, as needed	30 day supply: 240 (two hundred forty) tablets ◉
Generate Prescription	* If single dose required "crushed" tablets, program will set lower dose available with tablet size.

After generating prescription, click here for more prescribing option, or go back to home page

Figure 16

After making necessary selection (most of them have default value), you need to hit "Generate Prescription" button and on next page you will have prescription page.

12901 Bruce B. Downs Blvd., MDC 33
Tampa, FL 33612

Phone:

ME #

Name: Saturday, June 04, 2011

Rx: Morphine Sulfate, Single dose: 15 mg tabs
Dosage: Take single tablet every 3 hours, as needed
Dispense: Month supply, 240 (two hundred forty) tablets

Refill: 0=☐ 1=☐ 2=☐ 3=☐ 4=☐ PRN=☐   DEA#

Send prescription to Pharmacist   Figure 17   Print this page

There are two options. One is to send e-mail direct to Pharmacist or to print prescription and give patient. When we finish with testing module, there will be option that doctors automatically select his name and in same time program will select Phone number, and numbers for ME# and DEA#. After finishing with prescription, we need to close prescription screen.
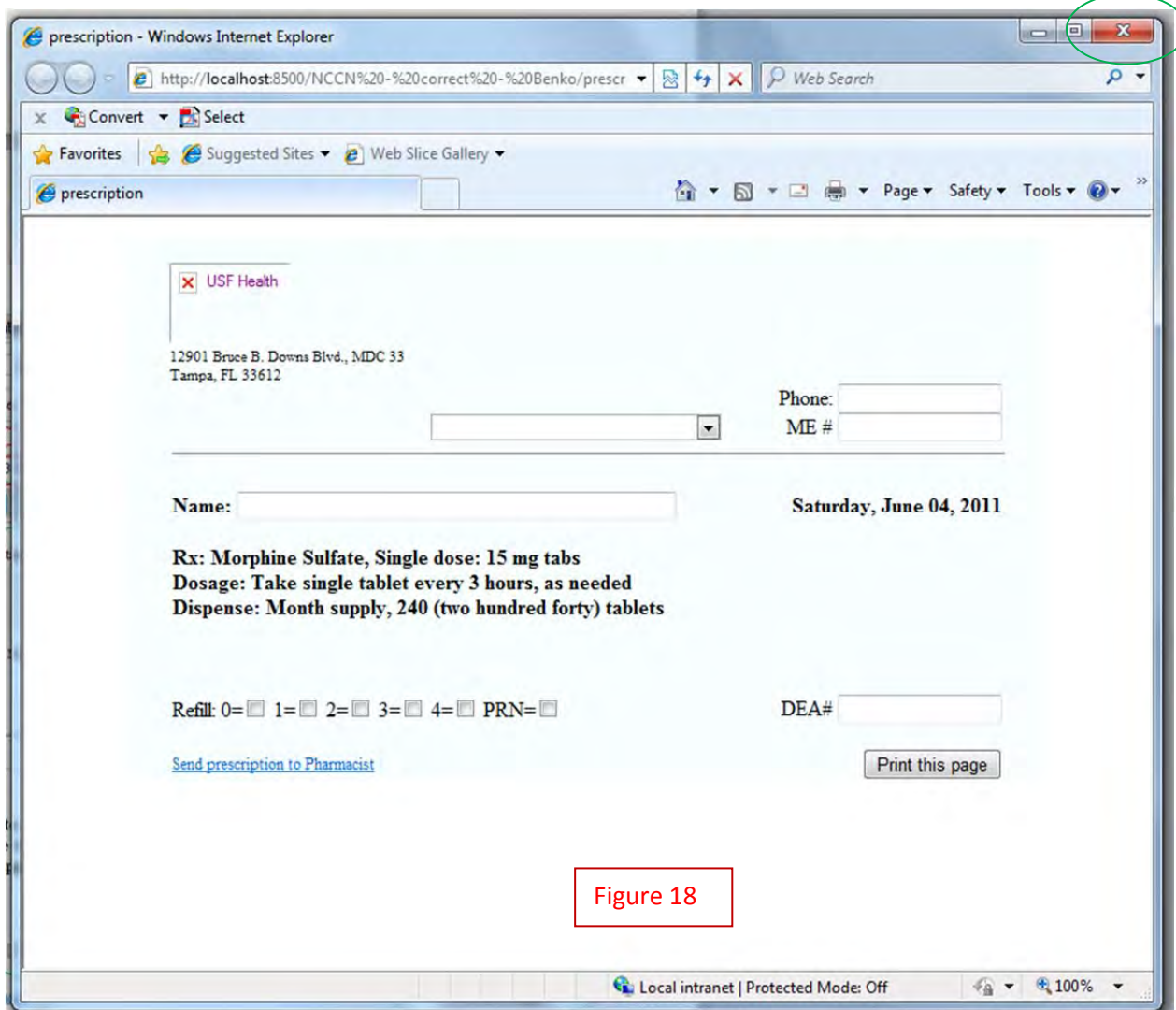
Figure 18

We will be back to following screen (shown on figure 16):

CDSS-EBM Pain Management Module

Medication: (Opioid tablets)	Available dosage:
Morphine Sulfate ▾ see opioid equivalency	Tablets: 15, 30 mg IR, Typical initial dose is 15-60 mg, q3-4h as
Choose a total daily dose: 120 mg ▾	1 day supply: 8 (eight) tablets ○
Single dose: 15 mg tabs *	7 day supply: 56 (fifty six) tablets ○
Take single tablet every 3 hours, as needed	30 day supply: 240 (two hundred forty) tablets ●
Generate Prescription	* If single dose required "crushed" tablets, program will set lower dose available with tablet size.

After generating prescription, click here for more prescribing option, or go back to home page

Figure 19

17

By selecting "click here" on figure 19, next screen will appear:

CDSS-EBM Pain Management Module

	Common to all pain level
Select option:	○ Prescriptions for neuropathic pain (co-analgesics/adjuvant) ○ Prescriptions for opioid adverse effects ○ Provide psychosocial support, including patient and family education

Figure 20

There are options for prescription for neuropathic pain, prescription for opioid adverse effect and psychosocial support. For learning purpose, let's choose neuropathic pain. Next screen will show up:

CDSS-EBM Pain Management Module

	Co-analgesics (adjuvant) medications for neuropathic pain
Select co-analgesic (adjuvant) medications see principles	○ Antidepressants ○ Anticonvulsants ○ Topical agents ○ Corticosteroids

Figure 21

Let's choose "antidepressants". Next screen will appear:

CDSS-EBM Pain Management Module

Antidepressants:		**Available dosage for selected antidepressants:**	
[▼] see example			
Choose a total daily dose: [▼]		1 day supply: [ ] ○	
Single dose: [ ]		7 day supply: [ ] ●	
[ ]		30 day supply: [ ] ○	
		Generate Prescription	Figure 22

Choosing one antidepressants, next screen will show up with default setting. There are possibilities to change daily dose and how many days of supply you want to prescribe.

CDSS-EBM Pain Management Module

Antidepressants:	Available dosage for selected antidepressants:
Amitriptyline ▾ see example	10, 25, 50, 75, 100, 200 mg tablets; Half-life: 10-50 h; Typical initial dose: 10-25 mg
Choose a total daily dose: 10 mg ▾	1 day supply: 1 (one) tablet ○
Single dose: 10 mg tablet	7 day supply: 7 (seven) tablets ◉
Take single dose at bedtime	30 day supply: 30 (thirty) tablets ○
	Generate Prescription Figure 23

After making necessary selections, hit "Generate Prescription" button. Next screen will show up:

12901 Bruce B. Downs Blvd., MDC 33
Tampa, FL 33612

Phone: _____
ME # _____

Name: _____   **Saturday, June 04, 2011**

Rx: Amitriptyline, Single dose: 10 mg tablet
Dosage: Take single dose at bedtime
Dispense: Seven day supply, 7 (seven) tablets

Refill: 0=☐ 1=☐ 2=☐ 3=☐ 4=☐ PRN=☐   DEA# _____

Send prescription to Pharmacist   Figure 24   Print this page

Explanation for figure 24 is same like for figure 17 (see page 16).
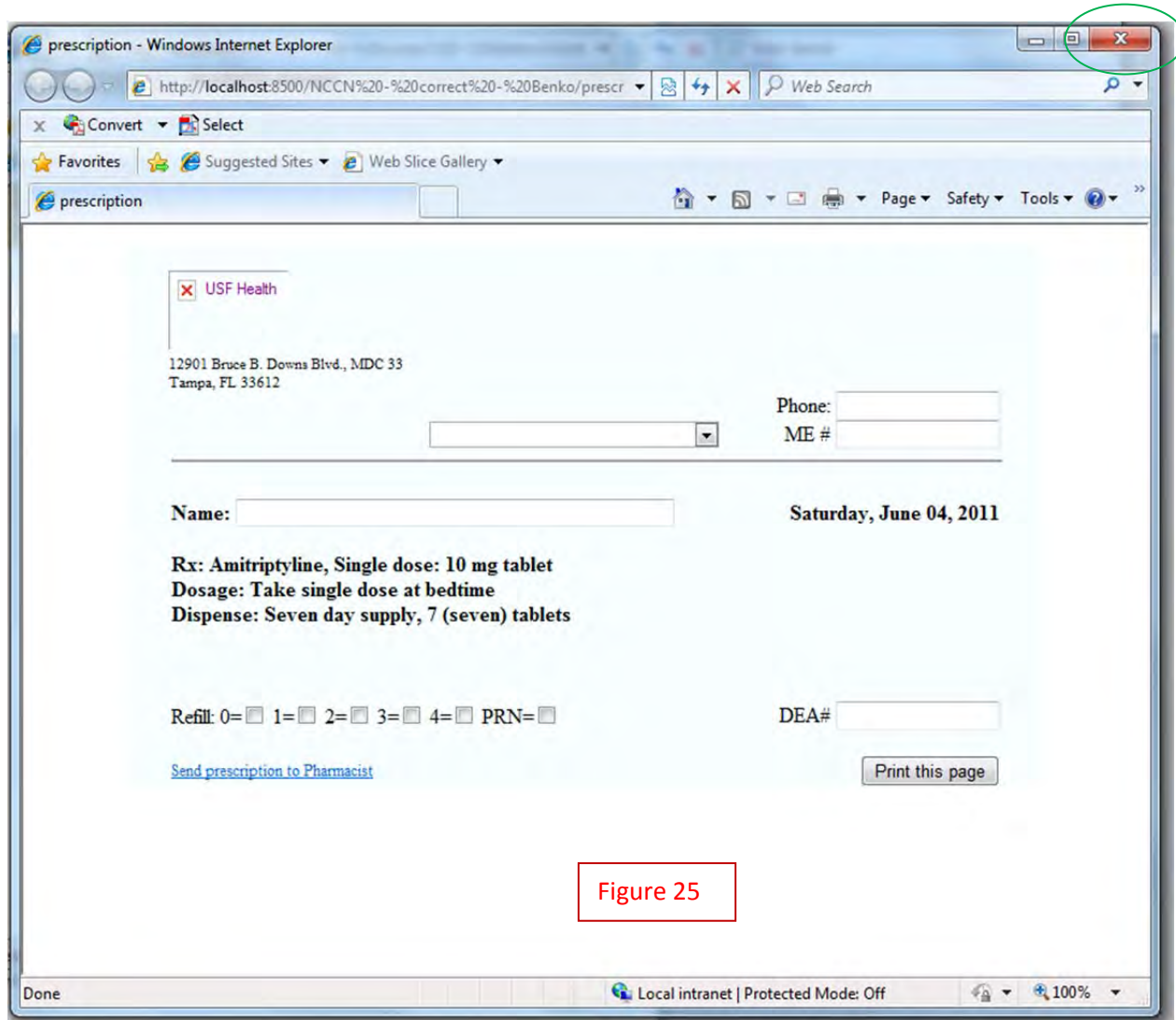
Figure 25

Let's close prescription page (figure 25) and Antidepressants page (figure 26).

Figure 26

We will be back to following screen (shown on figure 19, now marked like figure 27)):

Figure 27

By clicking "home page" program will return to home page, shown on figure 28.

CDSS-EBM Pain Management Module

What would you like to do?

Pain Assessment

Sub-Modules for Pain Assessment

Pain Intensity Rating	Opioid Conversion	Neuropathic Pain	Adverse Effects	Information on Drugs
Numerical rating scale Visual rating scale	General conversion Intravenous protocol Transdermal patch	Antidepressants Anticonvulsants Topical agents Corticosteroids	Constipation & Nausea Pruritus & Delirium Others	Nonopioid Analgesic Opioid Analgesic Co-Analgesic

Disclaimer   Instructions

Figure 28

Let's go back to figure 10 (see page 13). If you don't want to go through "Assess pain intensity", because you know pain intensity, you should choose second option "Skip pain intensity …" This option you can see on figure 29.

CDSS-EBM Pain Management Module

Opioid naive patients	
Please choose option	⦿ **Assess pain intensity** ⦿ **Skip pain intensity assessment and go to pain management**

Figure 29

After selecting "Skip pain intensity …" next screen will show up (figure 30).

There are several options, but let's say our patient has severe pain and we would like to prescribe short-acting opioid. In this case you should make selection shown on figure 30.

We are encourage users to try all different options and "familiarized" with program.

CDSS-EBM Pain Management Module

Management of pain in opioid naive patient	
For ALL pain levels	○ Recognize and treat adverse effects, including bowel obstruction ○ Prescribe co-analgesics (adjuvant medications) ○ Provide psychosocial support, including patient and family education
Severe Pain 7 - 10	See mangement for ALL levels of pain above, and ◉ Rapidly titrate short-acting opioid with opition for opioids conversion ○ Severe pain, full list of strong agonists
Moderate Pain 4 - 6	See mangement for ALL levels of pain above, and ○ Rapidly titrate short-acting opioid with opition for opioids conversion ○ Moderate pain medications, including weak agonists
Mild Pain 1 - 3	See mangement for ALL levels of pain above, and ○ Prescribe NSAID (Modify regimen to minimize adverse effects) ○ Prescribe short-acting opioid

After any treatment, Reevaluate patient's goals of comfort and function at each contact

Figure 30

After making selection on figure 30, next screen will show up (figure 31).

CDSS-EBM Pain Management Module

Short acting opioids - opioid naive patient	
Route of drug administration	◉ Tablets (peak effect in 60 minutes) ○ Oral solution (peak effect in 60 minutes) ○ Intravenous (peak effect in 15 minutes)

○ Additional details of opioid principles, prescribing, titration, and maintenance

Figure 31

Figure 31 is very similar to figure 13 (from "Assess pain intensity"). We can choose same option "Tablets", and we will have exactly same page (figure 32) like before (shown on figure 14).

CDSS-EBM Pain Management Module

Medication: (Opioid tablets)	Available dosage:
[dropdown] see opioid equivalency	[text area]
Choose a total daily dose: [dropdown]	1 day supply: [____] ○
Single dose: [_____] *	7 day supply: [____] ●
[_____]	30 day supply: [____] ○
Generate Prescription	* If single dose required "crushed" tablets, program will set lower dose available with tablet size.

After generating prescription, click here for more prescribing option, or go back to home page   Figure 32

CDSS-EBM Pain Management Module

Short acting opioids - opioid naive patient	
Route of drug administration	○ Tablets (peak effect in 60 minutes) ○ Oral solution (peak effect in 60 minutes) ○ Intravenous (peak effect in 15 minutes)
○ Additional details of opioid principles, prescribing, titration, and maintenance	Figure 33

Making selection like on figure 33, next (figure 34) screen will show up:

CDSS-EBM Pain Management Module

Opioid principles, prescribing, titration, and maintenance
General principles show/hide
Principles of maintenance opioid therapy show/hide
Opioid conversion, prescribing, titration, and maintenance   Figure 34

There are information on general principles and opioid therapy, but in the case that you want to make any conversion between opioids, you have to make selection shown on figure 34. Next screen will appear (figure 35).

CDSS-EBM Pain Management Module

Conversion	GRADE evidence profile
Select conversion option: show/hide references	○ General conversion [1, 3, 5] ○ Between intravenous (IV) medications [2, 6, 7] ○ Intravenous (IV) to oral medications (PO) ○ Multiple PO and fentanyl patch convert to intravenous medications ○ Between oral medications with rescue doses ○ Opioids to fentanyl transdermal patch (Duragesic) [4]

Figure 35

Let's make selection like on figure 35. After "clicking" radio button, next screen will show up (figure 36):

CDSS-EBM Pain Management Module

Current medications:			
Oral opioid 1 [▼]		Daily dose: [ ]	mg/day
Oral opioid 2 [▼]		Daily dose: [ ]	mg/day
Transdermal patch [▼]	[ ]*	Daily dose: [ ]	mg/day

New intravenous (IV) medications: [▼]

Equivalent morphine oral dose: [ ] mg/day	New IV daily dose: [ ] mg/day	Calculate

Intravenous (IV) Patient Controlled Analgesia (PCA)

IV PCA [▼]	Concentration: [▼]
Basal Rate: [ ] mg/h	Recommended [ ]
On-Demand: [ ] mg/dose	Recommended [ ]
Loading Dose: [▼]	Recommended [ ]
Lockout Interval: [▼]	Recommended [ ]	Generate Order Form

Figure 36

*Product insert for Duragesic (Fentanyl transdermal patch) use conservative conversion method: 60mg PO morphine equal 10mg IV morphine.

We will explain this table more details in our example C (see page 48), on the end this instruction manual.

For previously seen the patient, after pushing button "Pain Assessment" on figure 5 (see page 12), next screen will appear (figure 37): Let's this time select "Reassess efficacy …"

CDSS-EBM Pain Management Module

Please, choose option	○ Screening for pain ◉ Reassess efficacy for previously seen the patient

On figure 38, select "Yes" option. Figure 39 will appear.

CDSS-EBM Pain Management Module

Screening for pain	
Do you have pain?	○ Yes ○ No

Let's choose severe pain option (pain intensity 9), and click "Submit" button.

CDSS-EBM Pain Management Module

On scale 0 to 10, how would you describe your pain? (Doctor can choose numerical or face description)

○ null ○ one ○ two ○ three ○ four ○ five ○ six ○ seven ○ eight ○ nine ○ ten

0 = no pain; 1-3 = mild pain; 4-6 = moderate pain; 7-10 severe pain.[1] | Submit

How would you describe the level of your pain?

No pain   Worst pain you can imagine

0

0   2   4   6   8   10

[1] NCCN Adult Cancer Pain, V.1.2010; page: Pain-A, 1 of 2.

Submit
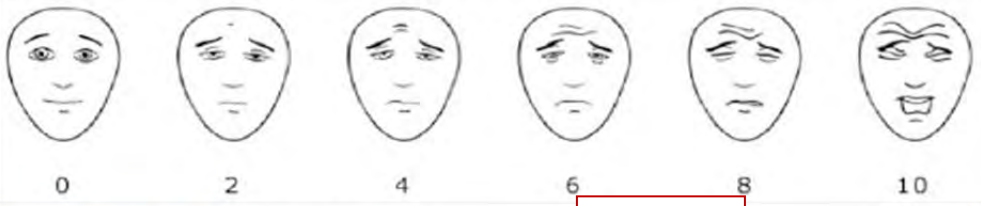
Next screen will show up. Let's assume that pain increase from last visit. Doctor has to select "Increase" option.

CDSS-EBM Pain Management Module

Severe pain
Compare with last visit, did your pain score: ⦿ Increased   ○ Unchanged   ○ Decreased

Figure 40

And because the patient is previously seen, let's assume that patient is "Opioid tolerant patient".

CDSS-EBM Pain Management Module

Pain level-severe & pain intesity-increase
What is the patient status?   ○ Opioid naive patient   ⦿ Opioid tolerant patient

Figure 41

After making selection on figure 41, next screen will appear:

CDSS-EBM Pain Management Module

Patient status-opioid tolerant & pain level-severe & pain intesity-increase	
Current drug administration	**Short acting opioids - routes:** ⦿ Tablets (peak effect in 60 minutes) ○ Oral solution (peak effect in 60 minutes) ○ Intravenous (peak effect in 15 minutes) **Full list of pain medications** (all routes in one table) ○ Prescribe NSAID for mild pain ○ Prescribe weak agonists for moderate pain ○ Prescribe strong agonists for severe pain

Figure 42

There are several options, but let's for beginning continue with prescribing short acting opioid in tablets. Figure 43 will appear:

CDSS-EBM Pain Management Module

Medication: (Opioid tablets)	Available dosage:
[blue dropdown] ▼ see opioid equivalency	
Choose a total daily dose: ▼	1 day supply: ○
Single dose: _____ *	7 day supply: ◉
_____	30 day supply: ○
Generate Prescription	* If single dose required "crushed" tablets, program will set lower dose available with tablet size.

First step: Increase dose 50 - 100 %

Second step: After 2 - 3 cycles (dose adjustment), consider:

○ **IV titration**
○ **Treatment evaluation and management for severe pain**

After generating prescription, click here for more prescribing option, or go back to home page

Figure 43

Let's assume that the patient previously was receiving total 120 mg/day. First step would be to increase dose 50% (choose option like on figure 44) and hit "Generate Prescription" button.

CDSS-EBM Pain Management Module

Medication: (Opioid tablets)	Available dosage:
Morphine Sulfate ▼ see opioid equivalency	Tablets: 15, 30 mg IR, Typical initial dose is 15-60 mg, q3-4h as
Choose a total daily dose: 180 mg ▼	1 day supply: 6 (six) tablets ○
Single dose: 30 mg tabs *	7 day supply: 42 (forty two) tablets ◉
Take single tablet every 4 hours, as needed	30 day supply: 180 (one hundred eighty) tablets ○
Generate Prescription	* If single dose required "crushed" tablets, program will set lower dose available with tablet size.

First step: Increase dose 50 - 100 %

Second step: After 2 - 3 cycles (dose adjustment), consider:

○ **IV titration**
○ **Treatment evaluation and management for severe pain**

After generating prescription, click here for more prescribing option, or go back to home page

Figure 44

Prescription screen will appear. Explanation about this screen you can find on page 15 (after figure 17)

Figure 45

If after several dose adjustments we still don't have successful results, we need to choose "IV titration" (shown on figure 46). Choosing this option, figure 47 will appear.

CDSS-EBM Pain Management Module

Figure 46

CDSS-EBM Pain Management Module

Intravenous (IV) Patient Controlled Analgesia (PCA)	Important explanation!

Opioid [▾] see opioid equivalency	Total daily dose: [▾] mg/day

IV PCA [▾]	Concentration: [▾]
Basal Rate: _____ mg/h	Recommended
On-Demand: _____ mg/dose	Recommended
Lockout Interval: [▾]	Recommended
Loading Dose: [▾]	Recommended
Generate Order Form	

Calculation was made according to Stanford University Medical School and Medical College of Wisconsin.

Figure 47

After generating order form, click here for more prescribing option, or go back to home page

Let's choose Morphine for IV medication. Next screen will appear:

CDSS-EBM Pain Management Module

Intravenous (IV) Patient Controlled Analgesia (PCA)	Important explanation!

Opioid Morphine (mg/day) [▾] see opioid equivalency	Total daily dose: 24 mg [▾] mg/day **1**

IV PCA Morphine [▾]	Concentration: 150 mg/150 ml NS (1 mg/ml) Standard Concentration [▾]
Basal Rate: 1 mg/h	Recommended 0 - 1 mg/hour **2**
On-Demand: 0.25 mg/dose	Recommended 0.5 - 1 mg/dose
Lockout Interval: 15 minutes [▾] **3**	Recommended 10 - 15 minutes
Loading Dose: 2 mg [▾] **4**	Recommended 2 - 4 mg
Generate Order Form **5**	

Calculation was made according to Stanford University Medical School and Medical College of Wisconsin.

Figure 48

After generating order form, click here for more prescribing option, or go back to home page

There are several possibilities for adjustment.

Total daily dose (1), concentration (2), lockout interval (3) and loading dose (4).

After making all selections, hit "Generate Order Form" button. Figure 49 will appear. Explanation for this screen is very similar to explanation on page 16, after figure 17.

Figure 49

If we choose "Treatment evaluation …" on figure 46, page 29, next screen will appear. There are full list of treatment possibilities for opioid tolerant patient.

CDSS-EBM Pain Management Module

Subsequent pain management and treatment in opioid tolerant patient	
For ALL pain levels	○ Recognize and treat adverse effects ○ Co-analgesic (adjuvant medications) ○ Provide psychosocial support, including patient and family education ○ Opioid conversion
Severe Pain 7 – 10	See mangement for ALL levels of pain above, and ○ Rapidly titrate short-acting opioid with opition for opioids conversion ○ Severe pain, full list of strong agonists ○ Reevaluate working diagnosis with a comprehensive pain assessment
Moderate Pain 4 – 6	See mangement for ALL levels of pain above, and ○ Rapidly titrate short-acting opioid with opition for opioids conversion ○ Moderate pain medications, including weak agonists ○ Reevaluate working diagnosis with a comprehensive pain assessment
Mild Pain 1 – 3	See mangement for ALL levels of pain above, and ○ Prescribe NSAID (Modify regimen to minimize adverse effects) ○ Prescribe short-acting opioid (Pain is under control with opioids)
After any treatment, Reevaluate patient's goals of comfort and function at each contact	

Figure 50

V. Pain intensity rating

This sub-module contains the pain intensity rating scales. By selecting this option, the user will be guided through assessment of patient's pain intensity.

Using NCCN (National Comprehensive Cancer Network) guidelines, we developed a submodule for universal and comprehensive pain assessment with both numerical and the faces pain rating scale detection (figure 11, page 14). Depending on the pain level, we also provided a suggested list with medications, dosage, duration and route.

Pain intensity must be quantified by the patient whenever possible. According to NCCN guidelines, pain intensity is divided in the following groups:

- No pain = 0
- Mild pain = 1 – 3
- Moderate pain = 4 – 6
- Severe pain = 7 - 10

By clicking on the radio button for pain level or moving the sliding button till we find the correct pain level and then pushing the corresponding "Submit" button will allow the program to jump to next page with suggested corresponding pain level medication. After choosing the medication, dosage, route and dispense, doctor will have the option to directly print the prescription and give it to the patients (or family member/ friend) or to send an e-mail to the pharmacist with the prescription data.

To access the Pain intensity sub-module select Pain intensity rating as shown below.

CDSS-EBM Pain Management Module

What would you like to do?

Pain Assessment

Sub-Modules for Pain Assessment

Pain Intensity Rating	Opioid Conversion	Neuropathic Pain	Adverse Effects	Information on Drugs
Numerical rating scale Visual rating scale	General conversion Intravenous protocol Transdermal patch	Antidepressants Anticonvulsants Topical agents Corticosteroids	Constipation & Nausea Pruritus & Delirium Others	Nonopioid Analgesic Opioid Analgesic Co-Analgesic

Disclaimer

Figure 51

Instructions

This will take you to the next screen (figure 52).

CDSS-EBM Pain Management Module

Options	
What is the patient status?	○ **Opioid naive patient** ○ **Opioid tolerant patient**
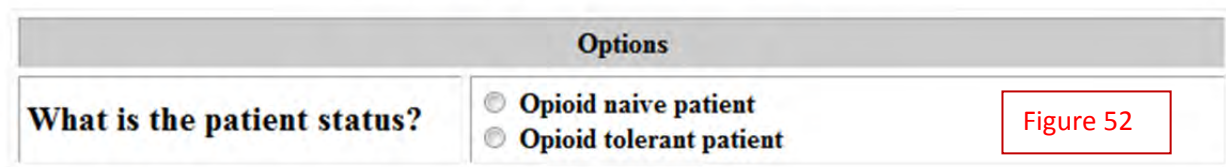
Figure 52

Selecting either options, program will bring us to pain intensity screen and from there is same procedure like was previously explained (figure 11, page 14).

VI. Opioid Conversion

This sub-module contains the opioid conversion calculator. By selecting this option, the user will be able to calculate dosage conversions between different opioid drugs and routes of administration.

There are different conversion types available:

- General conversion
- Between intravenous (IV) medications
- Intravenous (IV) to oral medications (PO)

33

- Multiple PO and fentanyl patch convert to IV medications
- Between oral medications with rescue doses
- Opioids to fentanyl transdermal patch (Duragesic)

To access the Opioid conversion sub-module select Opioid conversion as shown below.

Figure 53
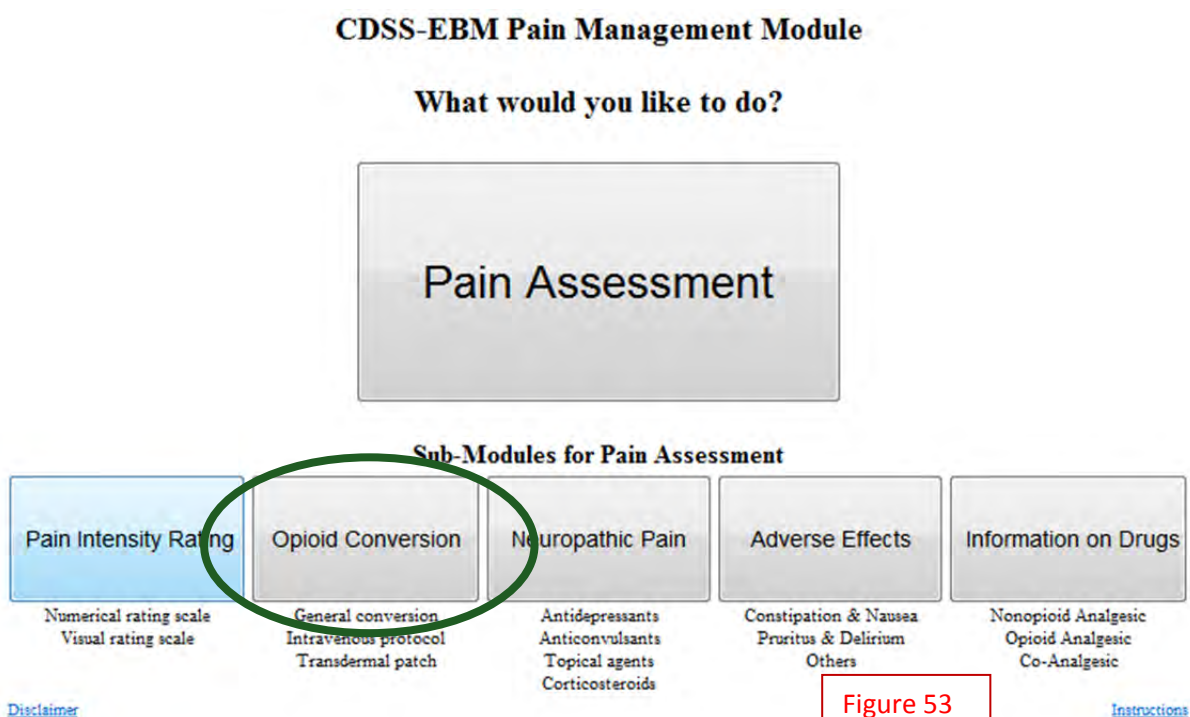
By clicking "Opioid Conversion" button, next screen will appear:

Figure 54
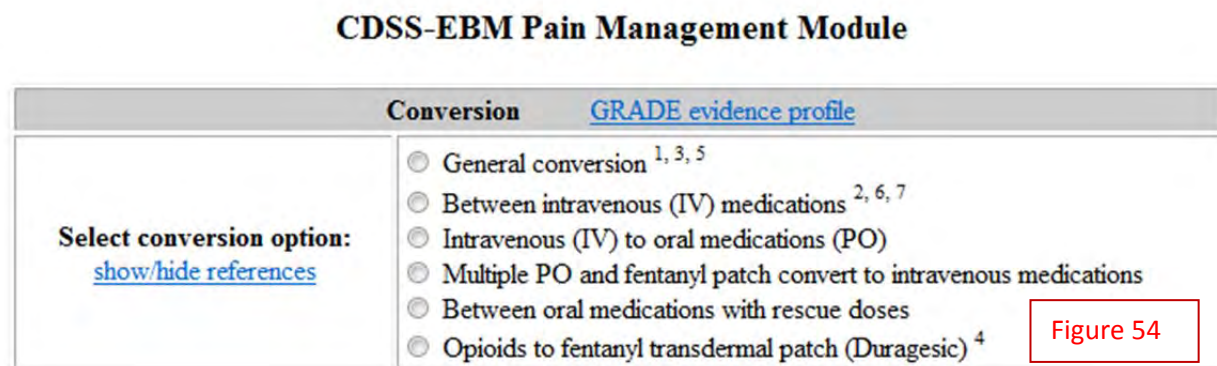
Base of our needs, doctors can choose any option by clicking corresponding radio button.

We are encourage users to try all different options and "familiarized" with program, before actual need.

VII. Neuropathic Pain

This sub-module contains four main groups:

- Antidepressants
- Anticonvulsants
- Topical agents
- Corticosteroids

For all these options, you need to select "Medication", and choose amount for "Total daily dose" and program will automatically display value for "Single dose", based on how often patients need to take the medication. After this, the button "Generate Prescription" will be "alive" and doctor will be able to generate prescription.

To access Neuropathic pain sub-module, select Neuropathic pain as shown below.

Figure 55

Next screen will show up:

CDSS-EBM Pain Management Module

Co-analgesics (adjuvant) medications for neuropathic pain	
Select co-analgesic (adjuvant) medications see principles	○ Antidepressants ○ Anticonvulsants ○ Topical agents ○ Corticosteroids

Figure 56

By choosing "Antidepressants" option, figure 22 from page 18 will appear. Explanation and how to continue was explained on page 18 – 21.

VIII. Adverse Effects

The most common types of adverse effects:

- Constipation
- Nausea and Vomiting
- Pruritus
- Delirium
- Motor and Cognitive Impairment
- Respiratory depression (The most serious Adverse effect)
- Sedation

Generating prescription procedure is similar to procedure for Neuropathic pain.

To access adverse effects sub-module, select adverse effects as shown below.

CDSS-EBM Pain Management Module

What would you like to do?

Pain Assessment

Sub-Modules for Pain Assessment

Pain Intensity Rating	Opioid Conversion	Neuropathic Pain	Adverse Effects	Information on Drugs
Numerical rating scale Visual rating scale	General conversion Intravenous protocol Transdermal patch	Antidepressants Anticonvulsants Topical agents Corticosteroids	Constipation & Nausea Pruritus & Delirium Others	Nonopioid Analgesic Opioid Analgesic Co-Analgesic

Disclaimer

Figure 57

Instructions

By clicking "Adverse effects" button, next screen will appear:

CDSS-EBM Pain Management Module

The most common types of adverse effects	
Select adverse effect which you would like to treat see principles	○ Constipation ○ Nausea and Vomiting ○ Pruritus ○ Delirium ○ Motor and cognitive impairment ○ Respiratory depression ○ Sedation

Picture 58
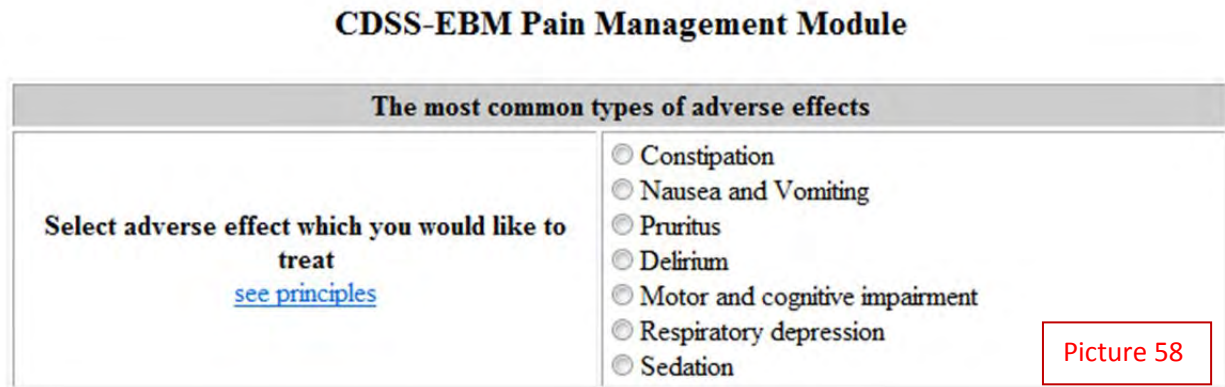
Base of the patient needs, doctors can choose any option by clicking corresponding radio button.

We are encourage users to try all different options and "familiarized" with program, before actual need.

IX. Information on Drugs

There are three main groups with corresponding sub-groups:

- Nonopioid Analgesic
  - Acetaminophen (Tylenol)
  - Salicylate
  - Non Selective NSAIDs (Non-steroidal anti-inflammatory drugs)
  - Selective COX-2 Inhibitor
- Opioid Analgesic
  - Strong full Agonists
  - Weak full Agonists
  - Weak Agonist/Reuptake Inhibitor
  - Partial Agonist and Mixed Agonist/Antagonists
- Co-Analgesic (Adjuvant medication) for neuropathic pain
  - Antidepressants
  - Anticonvulsants
  - Other Adjuvant

From each product insert for each of the most commonly used medications, we extracted data on dosage, cycles, route, duration of the medications, time to peak effect, and initial dosage. We then presented a summary on a separate table for a quick reference. On the same table, we also provided a link for each product insert for a more detailed explanation.

Drugs information sub-module is short cuts to explanation about dosage, routes and other useful information about drugs with option to access package insert.

To access drugs information sub-module, select information on drugs as shown below.

CDSS-EBM Pain Management Module

What would you like to do?

Pain Assessment

Sub-Modules for Pain Assessment

| Pain Intensity Rating | Opioid Conversion | Neuropathic Pain | Adverse Effects | Information on Drugs |

Numerical rating scale
Visual rating scale

General conversion
Intravenous protocol
Transdermal patch

Antidepressants
Anticonvulsants
Topical agents
Corticosteroids

Constipation & Nausea
Pruritus & Delirium
Others

Nonopioid Analgesic
Opioid Analgesic
Co-Analgesic

Disclaimer

Instructions

Figure 59

By clicking "Information on drugs" button, next screen will appear:

CDSS-EBM Pain Management Module

Drugs	
Information on drugs?	○ Nonopioid analgesic dosages and product insert for these medications
	○ Opioid analgesic dosages and product insert for these medications
	○ Co-analgesic dosages and product insert for these medications

Figure 60

Let's for explanation purpose, click on radio button for "Opioid analgesic …"

Screen bellow will appear:

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CDSS-EBM Pain Management Module

Figure 61

		Some opioid analgesics			
Drug	**Dosage forms**	**Durations**	**Half-life**	**Time to peak effect**	**Starting dose**
Strong full agonists					
Fentanyl					
Actiq	0.2, 0.4, 0.6, 0.8, 1.2, 1.6 mg transmucosal lozenges	> 1 hr	7 hrs	20-40 min	0.2 mg
Duragsic	12.5, 25, 50, 75, 100 mcg/hr transdermal patches	72 hrs/patch	17 hrs	20-72 hrs	25 mcg/hr
Fentora	0.1, 0.2, 0.4, 0.6, 0.8 mg buccal tabs	> 1 hr	2.6-11.7 hrs	15-30 min	0.1 mg
Onsolis	200, 400, 600, 800, 1200 mcg buccal films	> 1 hr	14 hrs	15-30 min	200 mcg
Sublimaze (Citrate)	50 mcg/mL; 2, 5, 10, 20 ml ampoules	> 1 hr	219 minutes	5-15 min	50-100 mcg
Hydromorphone					
Dilaudid	2, 4, 8 mg tabs; 5 mg/5 ml PO soln 5 mg/5 ml PO solution 1, 2, 4 & 10mg/mL ampoules	4-6 hrs 3-6 hrs	2.5 hrs	1.5-2 hrs	2-8 mg
Levorphanol					
Levo-Dromoran	2 mg tabs; 2mg/mL in 1ml ampoule	6-8 hrs	11-16 hrs	1.5-2 hrs	2-4 mg
Meperidine					
Demerol	50, 100 mg tabs; 50 mg/5ml PO soln 25, 50, 75 & 100mg//mL ampoules	3-4 hrs	2.5-4 hrs	1-1.5 hrs	50 mg
Methadone					
Dolophine	5, 10 mg tabs; 5, 10 mg/5ml PO soln, 10 mg/ml PO soln	8-12 hrs	8-59 hrs	1-7.5 hrs	2.5-10 mg

There are short extract data for dosage form, duration, half-life, time to peak effect and suggested starting dose. By clicking on highlight medication, program will move to short explanation about that drug with option to select and original package insert for that medication.

IX. Write Rx

If you want only to write a prescription, the fastest way is select "Write Rx" from menu option.

Clicking on "Write Rx" button, on next page you will have the choice to choose manual writing or options with suggested dosage (for ongoing care).

Example A: Converting IV morphine to IV hydromorphone

Patient is taking IV morphine at 6 mg/h and needs to be converted to IV hydromorphone.

To access IV conversion, select Opioid conversion sub-module as shown below.

CDSS-EBM Pain Management Module

What would you like to do?

Pain Assessment

Sub Modules for Pain Assessment

Pain Intensity Rating	Opioid Conversion	Neuropathic Pain	Adverse Effects	Information on Drugs
Numerical rating scale Visual rating scale	General conversion Intravenous protocol Transdermal patch	Antidepressants Anticonvulsants Topical agents Corticosteroids	Constipation & Nausea Pruritus & Delirium Others	Nonopioid Analgesic Opioid Analgesic Co-Analgesic

Disclaimer   Instructions

On next page, select "Between intravenous (IV) medications"

CDSS-EBM Pain Management Module

	Conversion GRADE evidence profile
Select conversion option: show/hide references	○ General conversion [1, 3, 5] ○ Between intravenous (IV) medications [2, 6, 7] ○ Intravenous (IV) to oral medications (PO) ○ Multiple PO and fentanyl patch convert to intravenous medications ○ Between oral medications with rescue doses ○ Opioids to fentanyl transdermal patch (Duragesic) [4]

By clicking on radio button, program will bring us to the next page:

CDSS-EBM Pain Management Module

Current intravenous (IV) medications:		New intravenous (IV) medications:	
Opioid [▼]		Opioid [▼]	
Current daily dose: [ ] mg/day		New daily dose: [ ] mg/day	[Calculate]

Intravenous (IV) Patient Controlled Analgesia (PCA)   see opioid equivalency

IV PCA [▼]	Concentration: [▼]
Basal Rate: [ ] mg/h	Recommended [ ]
On-Demand: [ ] mg/dose	Recommended [ ]
Lockout Interval: [▼]	Recommended [ ]
Loading Dose: [▼]	Recommended [ ]
[Generate Order Form]	[ ]

Calculation was made according to Stanford University Medical School and Medical College of Wisconsin.

Make selection for current IV medication (morphine) and new IV medication (hydromorphone).

CDSS-EBM Pain Management Module

Current intravenous (IV) medications:		New intravenous (IV) medications:	
Opioid [Morphine (mg/day) ▼]		Opioid [Hydromorphone (mg/day) ▼]	
Current daily dose: [ ] mg/day		New daily dose: [ ] mg/day	[Calculate]

Intravenous (IV) Patient Controlled Analgesia (PCA)   see opioid equivalency

IV PCA [Hydromorphone (Dilaudid) ▼]	Concentration: [▼]
Basal Rate: [ ] mg/h	Recommended [ ]
On-Demand: [ ] mg/dose	Recommended [ ]
Lockout Interval: [▼]	Recommended [ ]
Loading Dose: [▼]	Recommended [ ]
[Generate Order Form]	[ ]

Calculation was made according to Stanford University Medical School and Medical College of Wisconsin.

Program require daily dose for current IV medication.

(6 mg/h * 24 h = 144 mg/day)

Let's enter value in table.

CDSS-EBM Pain Management Module

Current intravenous (IV) medications:	New intravenous (IV) medications:
Opioid Morphine (mg/day) ▼	Opioid Hydromorphone (mg/day) ▼
Current daily dose: 144 mg/day	New daily dose: ____ mg/day **Calculate**

Intravenous (IV) Patient Controlled Analgesia (PCA) see opioid equivalency

IV PCA Hydromorphone (Dilaudid) ▼	Concentration: ▼	
Basal Rate: ____ mg/h	Recommended	
On-Demand: ____ mg/dose	Recommended	
Lockout Interval: ▼	Recommended	
Loading Dose: ▼	Recommended	
Generate Order Form		

Calculation was made according to Stanford University Medical School and Medical College of Wisconsin.

After entering value for Current daily dose, hit "Calculate" button.

CDSS-EBM Pain Management Module

Current intravenous (IV) medications:	New intravenous (IV) medications:
Opioid Morphine (mg/day) ▼	Opioid Hydromorphone (mg/day) ▼
Current daily dose: 144 mg/day	New daily dose: 21.599999 mg/day **Calculate**

Intravenous (IV) Patient Controlled Analgesia (PCA) see opioid equivalency

IV PCA Hydromorphone (Dilaudid) ▼	Concentration: 30 mg/150 ml NS (0.2 mg/ml) Standard Concentration ▼ 1	
Basal Rate: 0.9 mg/h	Recommended 0 - 0.2 mg/hour	
On-Demand: 0.225 mg/dose	Recommended 0.1 - 0.2 mg/dose	
Lockout Interval: 15 minutes ▼ 2	Recommended 10 - 15 minutes	
Loading Dose: 0.4 mg ▼ 3	Recommended 0.4 - 0.8 mg	
Generate Order Form		

Calculation was made according to Stanford University Medical School and Medical College of Wisconsin.

Before we generate order form, there are several possibilities for adjustment:

Concentration (1), lockout interval (2) and loading dose (3).

After making all selections, hit "Generate Order Form" button. Next screen will appear.

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Intravenous (IV) Patient Controlled Analgesia (PCA) - Standardized Order Form

USF HEALTH

12901 Bruce B. Downs Blvd., MDC 33
Tampa, FL 33612

Tuesday, 6/7/2011 11:33 AM

Name:

IV PCA: Hydromorphone (Dilaudid)
30 mg/150 ml NS (0.2 mg/ml) Standard Concentration
Basal rate: 0.9 mg/hour
On-Demand amount: 0.225 mg/dose
Lockout interval: 15 minutes
Loading dose: 0.4 mg

Phone: ME #   DEA#

Send order form to Pharmacist   Print this page

Example B: Converting oral Oxymorphone to transdermal fentanyl patch

Patient is taking 15 mg every 12 hours and needs to be converted to transdermal fentanyl patch.

Select Opioid conversion sub-module as shown below:

On next page, select "Opioids to fentanyl transdermal patch (Duragesic)"

By clicking on radio button, program will bring us to the next page:

CDSS-EBM Pain Management Module

Current medications:		Important explanation!
Opioid: ⊡ *	Total daily dose: [____] mg/day	Calculate
Fentanyl transdermal patch (Duragesic):	Available Dose: 25, 50, 75, 100 mcg/h transdermal patches	
Opioid: Fentanyl (Duragesic)	Transdermal patch: [____]	
7 day supply: [____] ⦿	30 day supply: [____] ○	
Generate Prescription	[____]	show/hide Recommended

*All Conversion was made according to package insert for Duragesic. That is different then NCCN guidelines for Adult Cancer Pain.

Make selection for current medication (Oxymorphone)

CDSS-EBM Pain Management Module

Current medications:		Important explanation!
Opioid: Oxymorphone (oral) ⊡ *	Total daily dose: [____] mg/day	Calculate
Fentanyl transdermal patch (Duragesic):	Available Dose: 25, 50, 75, 100 mcg/h transdermal patches	
Opioid: Fentanyl (Duragesic)	Transdermal patch: [____]	
7 day supply: [____] ⦿	30 day supply: [____] ○	
Generate Prescription	[____]	show/hide Recommended

*All Conversion was made according to package insert for Duragesic. That is different then NCCN guidelines for Adult Cancer Pain.

Program require daily dose for current medication.

(15 mg * 2 = 30 mg/day)

Let's enter value in table.

CDSS-EBM Pain Management Module

Current medications:		Important explanation!
Opioid: Oxymorphone (oral) ▼ *	Total daily dose: 30 mg/day	Calculate
Fentanyl transdermal patch (Duragesic):	Available Dose: 25, 50, 75, 100 mcg/h transdermal patches	
Opioid: Fentanyl (Duragesic)	Transdermal patch:	
7 day supply: ⊙	30 day supply: ○	
Generate Prescription		show/hide Recommended

*All Conversion was made according to package insert for Duragesic. That is different then NCCN guidelines for Adult Cancer Pain.

After entering value for Current daily dose, hit "Calculate" button.

CDSS-EBM Pain Management Module

Current medications:		Important explanation!
Opioid: Oxymorphone (oral) ▼ *	Total daily dose: 30 mg/day	Calculate
Fentanyl transdermal patch (Duragesic):	Available Dose: 25, 50, 75, 100 mcg/h transdermal patches	
Opioid: Fentanyl (Duragesic)	Transdermal patch: 50 mcg/h; Applied to intact non-irrita	
7 day supply: 3 (three) patches ⊙	30 day supply: 10 (ten) patches ○	
Generate Prescription	Replace patch every 72 hours	show/hide Recommended

*All Conversion was made according to package insert for Duragesic. That is different then NCCN guidelines for Adult Cancer Pain.

Hit "Generate Prescription" button. Next screen will appear.

USF HEALTH

12901 Bruce B. Downs Blvd., MDC 33
Tampa, FL 33612

Phone:
ME #

Name: Tuesday, June 07, 2011

Rx: Fentanyl (Duragesic), Single dose: 50 mcg/h; Applied to intact non-irritated skin; Each time applied to different skin site.
Dosage: Replace patch every 72 hours
Dispense: Seven day supply, 3 (three) patches

Refill: 0=☐ 1=☐ 2=☐ 3=☐ 4=☐ PRN=☐   DEA#

Send prescription to Pharmacist   Print this page

Example C: Converting multiple opioid to intravenous medication

Patient is taking 90 mg morphine Avinza (extended release) every 24 hours, 5 mg Oxycodone (Oxy IR) every 6 hours and transdermal fentanyl patch 50 mcg/hours. Because he is still in severe pain, he was admitted in hospital and doctor wants to convert all medication in intravenous morphine.

Select Opioid conversion sub-module as shown below:

On next page, select "Multiple PO and fentanyl patch convert to intravenous medication"

By clicking on radio button, program will bring us to the next page:

CDSS-EBM Pain Management Module

Current medications:		
Oral opioid 1 [dropdown]	Daily dose: [ ]	mg/day
Oral opioid 2 [dropdown]	Daily dose: [ ]	mg/day
Transdermal patch [dropdown]	[ ] *	Daily dose: [ ] mg/day
New intravenous (IV) medications: [dropdown]		
Equivalent morphine oral dose: [ ] mg/day	New IV daily dose: [ ] mg/day	[Calculate]

Intravenous (IV) Patient Controlled Analgesia (PCA)	
IV PCA [ ]	Concentration: [ ]
Basal Rate: [ ] mg/h	Recommended [ ]
On-Demand: [ ] mg/dose	Recommended [ ]
Loading Dose: [ ]	Recommended [ ]
Lockout Interval: [ ]	Recommended [ ] [Generate Order Form]

*Product insert for Duragesic (Fentanyl transdermal patch) use conservative conversion method: 60mg PO morphine equal 10mg IV morphine.

Program require daily dose for current medication.

Morphine Avinza: (90 mg/day)

Oxycodone Oxy IR: (5 mg * 4 = 20 mg/day)

Fentanyl patch: (50 mcg/h * 24 h = 1.2 mg/day)

Let's enter values in table and select new IV medication.

CDSS-EBM Pain Management Module

Current medications:		
Oral opioid 1 Morphine ▾	Daily dose: 90	mg/day
Oral opioid 2 Oxycodone ▾	Daily dose: 20	mg/day
Transdermal patch Fentanyl ▾	One patch 25mcg/h = 0.6mg/d: *	Daily dose: 1.2 mg/day

New intravenous (IV) medications: Morphine ▾

Equivalent morphine oral dose: ▢ mg/day	New IV daily dose: ▢ mg/day	Calculate

Intravenous (IV) Patient Controlled Analgesia (PCA)

IV PCA Morphine ▾	Concentration: 150 mg/150 ml NS (1 mg/ml) ▾
Basal Rate: ▢ mg/h	Recommended 0 - 1 mg/hour
On-Demand: ▢ mg/dose	Recommended 0.5 - 1 mg/dose
Loading Dose: 2 mg ▾	Recommended 2 - 4 mg
Lockout Interval: 15 minutes ▾	Recommended 10 - 15 minutes	Generate Order Form

*Product insert for Duragesic (Fentanyl transdermal patch) use conservative conversion method: 60mg PO morphine equal 10mg IV morphine.

After selecting opioids and entering value for daily dose, hit "Calculate" button.

CDSS-EBM Pain Management Module

Current medications:		
Oral opioid 1 Morphine ▾	Daily dose: 90	mg/day
Oral opioid 2 Oxycodone ▾	Daily dose: 20	mg/day
Transdermal patch Fentanyl ▾	One patch 25mcg/h = 0.6mg/d: *	Daily dose: 1.2 mg/day

New intravenous (IV) medications: Morphine ▾

Equivalent morphine oral dose: 300 mg/day	New IV daily dose: 100 mg/day	Calculate

Intravenous (IV) Patient Controlled Analgesia (PCA)

IV PCA Morphine ▾	Concentration: 150 mg/150 ml NS (1 mg/ml) ▾
Basal Rate: 4.167 mg/h	Recommended 0 - 1 mg/hour
On-Demand: 1.042 mg/dose	Recommended 0.5 - 1 mg/dose
Loading Dose: 2 mg ▾	Recommended 2 - 4 mg
Lockout Interval: 15 minutes ▾	Recommended 10 - 15 minutes	Generate Order Form

*Product insert for Duragesic (Fentanyl transdermal patch) use conservative conversion method: 60mg PO morphine equal 10mg IV morphine.

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Let's explain calculation:

From opioid conversion guidelines, 20 mg oral Oxycodone is equal to 30 mg Morphine.

From package insert for Duragesic (transdermal fentanyl patch) 50mcg/h is equal to

(135 +224)/2 = 179.5 mg/day oral morphine.

Equivalent oral Morphine dose is: 90 + 30 + 180 = 300 mg/day

Parenteral morphine is 1/3 oral morphine: 300/ 3 = 100 mg/day

Hit "Generate Order Form" button on page 46, next screen will appear.

Intravenous (IV) Patient Controlled Analgesia (PCA) - Standardized Order Form

USF
HEALTH

Tuesday, 6/7/2011 1:37 PM

12901 Bruce B. Downs Blvd., MDC 33
Tampa, FL 33612

Name: _____

IV PCA: Morphine
150 mg/150 ml NS (1 mg/ml)
Basal rate: 4.167 mg/hour
On-Demand amount: 1.042 mg/dose
Lockout interval: 15 minutes
Loading dose: 2 mg

Phone: _____   ME # _____   DEA# _____

Send order form to Pharmacist   Print this page

Appendix 14 EB-PMM Evaluation Survey

Default Question Block

I am a

- ⦿ Physician
- ⦿ Physician Assistant
- ⦿ Registered nurse
- ⦿ Other (please specify)

  [_____]

My area of practice is

- ☐ Family medicine
- ☐ Hematology
- ☐ Oncology
- ☐ Palliative medicine
- ☐ Other (please specify)

  [_____]

Typically, I make decisions regarding pain management _____ times per day. (Please, indicate number of times)

[_____]

In my practice, I currently use the following forms of clinical decision support

	Yes	No
Paper (i.e. guidelines)	⦿	⦿
Computer or Internet based information (i.e. on-line calculators)	⦿	⦿
Clinical decision support system (incorporated into institutional EMR)	⦿	⦿
I do not use any form of clinical decision support	⦿	⦿
Other (please specify) [_____]	⦿	⦿

The following statements refer to perceived usefulness of EB-PMM if it were made available in practice. Please, indicate the extent to which you agree/disagree with each statement.

	Disagree strongly	Disagree	Neutral	Agree	Agree strongly	Not applicable
Enhance my efficiency of prescribing	⦿	⦿	⦿	⦿	⦿	⦿
Improve my productivity	⦿	⦿	⦿	⦿	⦿	⦿
Improve the quality of care I can provide	⦿	⦿	⦿	⦿	⦿	⦿
Make my job easier	⦿	⦿	⦿	⦿	⦿	⦿

The following statements refer to perceived functions of EB-PMM. Please indicate the extent to which you agree/disagree with each statement.

	Disagree strongly	Disagree	Neutral	Agree	Agree strongly
To evaluate patients' pain intensity	⦿	⦿	⦿	⦿	⦿
To make decision regarding choice of treatment	⦿	⦿	⦿	⦿	⦿
To perform opioid conversion calculations	⦿	⦿	⦿	⦿	⦿

To obtain information on drugs used for pain management from package insert	○	○	○	○	○
To obtain information on treatment related adverse events	○	○	○	○	○
To obtain evidence on drugs used in pain management	○	○	○	○	○
To write prescriptions	○	○	○	○	○
To perform other tasks (Please specify below)	○	○	○	○	○

I would like to see the following functions added to EB-PMM. (Please specify)

I would like to see the following functions already in EB-PMM further developed. (Please specify the functions)

The following statement refers to perceived quality of EB-PMM. Please select the number which most appropriately reflects your impressions of using EB-PMM. If you have not had experience with certain elements, please select "not applicable" (NA).

	Hard to read										Easy to read	Not Applicable
	0	1	2	3	4	5	6	7	8	9	10	
Characters on screen (font, colors, arrangement) are												☐

	Inadequate										Adequate	Not Applicable
	0	1	2	3	4	5	6	7	8	9	10	
Amount of information displayed on screens is												☐

	Confusing										Clear	Not Applicable
	0	1	2	3	4	5	6	7	8	9	10	

Sequence of screens
for any specific task
is

☐

	Inconsistent										Consistent	Not Applicable
	0	1	2	3	4	5	6	7	8	9	10	
Use of medical terminology throughout EB-PMM is												☐

	Confusing										Clear	Not Applicable
	0	1	2	3	4	5	6	7	8	9	10	
On-screen instructions for commands or functions are												☐

	Impossible										Easy	Not Applicable
	0	1	2	3	4	5	6	7	8	9	10	
Finding solution to problem in technical manual is												☐

	Too many										Just right	Not Applicable
	0	1	2	3	4	5	6	7	8	9	10	
Number of steps needed to complete tasks are												☐

	Never										Always	Not Applicable
	0	1	2	3	4	5	6	7	8	9	10	
Steps to complete tasks follow logical sequence												☐

	Difficult										Easy	Not Applicable
	0	1	2	3	4	5	6	7	8	9	10	
Ability to correct mistakes (typos, incorrect selections) is												☐

	Poor										Excellent	Not Applicable
	0	1	2	3	4	5	6	7	8	9	10	
The overall quality of the EB-PMM interface is												☐

I have the following additional comments regarding EB-PMM interface quality: (Please specify)

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The following statements refer to your general impression about the EB-PMM. Please, indicate the extent to which you agree/disagree with each statement.

	Disagree strongly	Disagree	Neutral	Agree	Agree strongly
I felt very confident using EB-PMM	◯	◯	◯	◯	◯
I found that various functions of EB-PMM were well integrated	◯	◯	◯	◯	◯
I thought the system was easy to use	◯	◯	◯	◯	◯
I would use EB-PMM frequently if it was made available in practice	◯	◯	◯	◯	◯

Overall, I am satisfied with the EB-PMM

Disagree strongly	Disagree	Neutral	Agree	Agree strongly
◯	◯	◯	◯	◯

I have the following additional comments I would like to make regarding EB-PMM:
(Please specify)

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