Scholarly Project

Development of the ESA Assessment for Safety Improvement (EASI) Online Decision Support Tool

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In partial fulfillment of the requirements for the Doctor of Nursing Practice

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Executive Summary
Development of the ESA Assessment for Safety Improvement (EASI) Online Decision Support Tool

This project supported initial validation of the ESA Assessment for Safety Improvement (EASI) online support tool. The purpose of this tool is to help clinicians navigate the complicated diagnostic and treatment guidelines developed by the National Cancer Care Network (NCCN) and the National Kidney Foundation (NKF) when prescribing erythropoietic-stimulating agents (ESAs). These guidelines emphasize patient safety and drive reimbursement from insurance.

Problem Statement

Initial clinical studies showed that aggressive use of erythropoietic-stimulating agents (ESAs) increased the risk for thrombosis and decreased overall survival in patients with cancer. As information evolved about the safe, more careful and conservative use of ESAs, safety guidelines were produced and frequently updated. These changes have led to providers underutilizing this treatment in fear of doing harm to patients and not being reimbursed for the treatment by insurers. At more than $1,500 to $3,000 for each injection, losses from lack of reimbursement have been significant to patients and providers.

Objectives:

- Determine whether an ESA decision analysis tool could have prevented treatment outside of clinical guideline recommendations.
- Determine whether an ESA decision analysis tool could have identified treatment outside of financial reimbursement requirements.
- Complete first draft of manuscript for submission to peer review journal

Literature review

Safety concerns are associated with all treatments for anemia. Current evidence indicates that ESAs are an appropriate and safe alternative to pRBC transfusions when used within NCCN and NKF guidelines. Clinical decision tools have also demonstrated improved patient safety, as well as, improved efficiency of clinician time and resources.

Implementation and evaluation

An historical cohort of 105 patients who received an ESA while undergoing chemotherapy was identified through the Huntsman Cancer Hospital (HCH) pharmacy. Diagnosis, characteristics and lab values for dates of treatment were entered into the EASI tool then compared to actual treatments rendered. The tool identified that overall 22% of treatments rendered were inconsistent with clinical practice guidelines. Based on today's cost of Aranesp® this translates to about $197,000 in savings from 2008 to 2013. A request has been sent to the American Journal of Hematology/Oncology for interest in this project manuscript.

Discussion

The EASI tool streamlines guidelines to help prescribers consider all the parameters required to safely prescribe ESAs. This tool brings expert decision making support to the web, thus expanding who can benefit from these medications.

Acknowledgements

Faculty advisor: Lauri Linder, PhD, APRN, CPON®. Content experts: Jeff Gilreath, Pharm.D, and George Rodgers, MD. IT design and consult: Ming Yuan Zhang and Kensaku Kowamoto, MD, PhD.

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Problem Statement

Erytropoietin Stimulating Agents (ESAs) are used in patients with anemia to stimulate the bone marrow to produce more red blood cells. They are used primarily in oncology and nephrology clinics where anemia is frequently a complication of disease or treatment. Unfortunately, there has been controversy and confusion related to prescribing these medications. Clinical trials have revealed that these medications, when used too aggressively, increase the risk for thrombosis and decrease overall survival in patients with cancer (Bennett, Becker, Kraut, Samaras, & West, 2009). As a result, the Center for Medicare and Medicaid Services (CMS) restricted payment for these medications unless certain laboratory and diagnostic criteria are met. As information evolved about the safe use of ESA's, safety guidelines and payment parameters changed. These changes lead to providers underutilizing this treatment in fear of doing harm to patients and not being reimbursed for treatment by insurers (Gilreath, S Stenehjem, & Rodgers, 2014). At more than $1,500 to $3,000 per injection, losses from not being reimbursed have been significant to patients and providers.

Purpose and Objectives

The National Comprehensive Cancer Network (NCCN) and the National Kidney Foundation developed clinical guidelines for the use of ESAs in patients with anemia from cancers (hematologic and solid tumors), chemotherapy induced anemia (CIA) and chronic kidney disease (CKD). These guidelines were used to develop the ESA Assessment for Safety Improvement (EASI) Online Decision Support Tool. The purpose of this project is to test this tool. Jeff Gilreath, PharmD developed a flow chart for which the tool was based. This can be seen in Appendix A. Mingyuan Zhang, Jeff Gilreath and

Mary Vietti developed the EASI tool online-form: A screen shot of a completed EASI tool assessment can be found in appendix B.

Objectives:

- Determine whether an ESA decision analysis tool, namely the *ESA Assessment for Safety Improvement* (EASI) tool, could have prevented treatment outside of clinical guideline recommendations.
- Determine whether an ESA decision analysis tool, namely the *ESA Assessment for Safety Improvement* (EASI) tool, could have prevented treatment outside of financial reimbursement requirements.
- Complete first draft of manuscript for submission for publication and query to peer-reviewed journal.

Clinical Implications

Anemia is associated with increased fatigue and decreased quality of life in patients with cancer (Knight, Wade, & Balducci, 2004; Mortimer et al., 2010). Though there are a variety of other factors that weigh in, fatigue is one symptom used to evaluate patients for symptomatic anemia. Other symptoms of anemia include dizziness, shortness of breath, hypotension and tachycardia. Cancer, CKD and MDS patients are at risk for anemia related to the disease process. In addition, cancer patients have additive anemic side effects related to treatment with chemotherapy and radiation. The main treatments for routine anemias include the nutritional supplements vitamin B12, folate, and iron. More complicated or severe anemias require red blood cell transfusion or erythropoietin stimulation agents (ESAs). There are risks associated with treatment with ESA's and transfusion; however, the risks associated with the use of ESA's can be minimized if delivered according to NKF and NCCN guidelines. In

addition, CMS has adopted these national institutions guidelines as the basis for reimbursement to providers: NCCN for anemias from cancers, MDS and other hematological malignancies and NKF for CKD.

Thesis Statement

Through the use of the EASI tool, nurse practitioners and other clinicians can increase patient safety through strict adherence to the current NCCN and NKF clinical guidelines for treatment. In addition the EASI tool's parameters are programmed to be in compliance with the qualifications for reimbursement as defined by the Medicare and Medicaid.

Literature Review: Treating Anemia

Recognizing the Parameters for Patient Safety

In April of 2013, the National Comprehensive Cancer Network (NCCN) updated their guidelines for the use of ESAs in hematology and oncology. These guidelines outline the best practices to minimize risk associated with the use of ESAs. It details appropriate diagnoses for treatment, as well as, qualifying parameters for initiation and ongoing treatment. Many providers are hesitant to use ESA treatment out of confusion over correct conditions for treatment as well as fear of not being reimbursed (Gilreath, Daniel, Jorgenson, & Rodgers, 2008).

Erythropoiesis

The response to ESAs is optimized when nutritional deficiencies do not exist. However, patients with either absolute or functional iron deficiency frequently benefit from the early addition of IV iron. Many patients can't tolerate oral iron supplements and others are iron deficient despite oral administration of iron. In these cases IV iron is a

warranted intervention. To complicate matters, ferritin has been the gold standard to measure iron stores, but cancer patients often have a functional iron deficiency. This is the inability to mobilize iron stores for erythropoiesis, in which case serum ferritin and iron will be normal yet erythropoiesis is inhibited. In addition, ferritin can be unreliable in cancer as it is an acute phase reactant causing an overestimation of actual iron stores. Therefore, IV iron often needs to be administered to assist with erythropoiesis. (Henry, Dahl, Auerbach, Tchekmedyian, & Laufman, 2007, p. 237)

pRBC Transfusions

Transfusions are recommended for the treatment of the symptomatic treatment of anemia for hemoglobin concentration of less than or equal to 8 g/dL (Carson et al., 2012). This is common in cancer patients undergoing chemotherapy or radiation, as well as in patients with MDS or CKD. Although transfusion increases hemoglobin concentrations and is associated with patient reports of increased wellbeing, transfusions carry considerable risks of harm to the recipient. The risks include transfusion reaction related to incorrect matching or low quality product, circulatory overload, iron overload, viral and bacterial infections, immune injury, hemolysis, and transfusion-related acute lung injury (Gilreath, et al., 2014). The increased costs associated with RBC transfusions include societal-economic costs, such as donor time and expense, and infrastructure for collection, processing, usage and administration. The average cost in the U.S. for one unit of packed red blood cells is $211. Transfusions for hemoglobin below 8 usually require 2 units of blood and more than 5 hours of infusion time. There has also been controversy as to whether there is increased tumor activity in patients with certain types of cancers. (Schrijvers, 2011)

In 2004, The FDA required Amgen to add warning labels that cautioned an increased risk of thrombosis with use of ESA's. In 2007 the first NCCN Guidelines for the use of ESA's called for reduced use of ESA's. This mandated that hemoglobin concentrations be kept lower that below 12 g/dL and not initiated until hemoglobin dropped below 9 g/dL. In 2007, the parameters were changed to restrict some hematological malignancies, restrict treatment goals based on diagnosis, and include qualifying lab parameters. This has resulted in reduction in the use of ESAs which in turn has led to an increase in the alternative treatment, packed red cell transfusion. As a result, there has been a significant impact on the US blood supply, (Vekeman et al., 2009).

Erythropoietin Stimulating Agents

ESA's raise the hemoglobin by stimulating the bone marrow to produce more red blood cells. This increase in hemoglobin has been shown to increase patient's sense of wellbeing, just as was reported for transfusions above. However, ESA therapy is also associated with risk such as increase thrombogenesis and risk of tumor progression (Bohlius et al., 2006). Many studies have confirmed an increased incidence of thrombosis in patients with cancers known to cause thrombogenesis, but there is not sufficient evidence indicating increased tumor activity. Therefor ESA's should be considered for the treatment of anemia (Dicato, 2008).

Another consideration is that, "anemia prevalence rises as diseases progress; thus, it can be difficult to separate the effects of anemia from the effects of disease severity," (Knight et al., 2004, p. 22) and thus any associated increase in poor outcome due to disease progression should not be correlated directly with increased ESA use in this population. Without good evidence that ESA's increase cancer activity, they

become an attractive treatment modality once the parameters to qualify for treatment are clearly articulated or standardized.

Standardizing ESA treatment

Gilreath et al., (2008) proposed standardizing ESA treatments using a pharmacist run anemia clinic modeled after the Anticoagulation Clinic at the University of Utah. They proposed better adherence to NCCN guidelines and better compliance with the reporting requirements for reimbursement. The package labeling, NCCN guidelines and CMS criteria for ESA use are incongruent. Qualifying criteria for CMS-insured patients are more restrictive than ESA labeling or the NCCN recommendations for use. Unfortunately, many clinical providers are unaware of financial restrictions and prescribe ESAs under non-qualifying circumstances for reimbursement. As a result, Gilreath, et al. recommended that an oncology-trained clinical pharmacist who may be familiar with these intricacies of clinical and financial qualifying criteria serve in this capacity. However, not all centers have access to specialized clinical pharmacists or onsite hematologist to assist in clinical decision making. Gilreath et al. also found that clinicians struggle with defining hypo-responsiveness to treatment. Multiple criteria may be used to track patient response to treatment including a lack of Hb rise > 1 g/dL above baseline or a decrease in pRBC transfusion frequency by 50%. This leads to the condition where patients inappropriately received ongoing ESA treatment with little to no benefit, but continued risk, (http://www.cms.gov/medicare-coverage-database/details/lcd-details.aspx?LCDId=24301&ContrId=133, 2013). Many healthcare pathways have been standardized which has proven to increase patient safety and allow for measurement and evaluation of outcomes. Standardizing this complicated process would benefit patients, practitioners and institutions.

Benefits of Clinical Decision Tools

Clinical decision tools have been associated with increased patient safety, significant cost savings and increased efficiency of healthcare delivery (Goodnough, et. al., 2013), (Chaloub et. al., 2011). Decision tools offer algorithms to help clinicians navigate through the important details required for diagnosis and treatment of disease. These algorithms incorporate the latest evidence from clinical trials and industry specific guidelines. Decision tools are not intended to be used as substitutes for physical exam and clinical expertise, but only as an aide to consolidate patient data with current guidelines. Tools also provide standardization of treatment, which allow for better analysis of efficacy and efficiency of treatment rendered. Finally, tools based in current research provide references for treatment decisions, which are often the bases for reimbursement from insurance.

Future research

As mentioned above, standardizing treatment of cancer related anemia supports quantitative research related to outcomes from treatment. Other arenas for future research include defining anemia side effects as relates to specific hemoglobin levels; quality of life related to anemia; and ESAs effect on cancer related fatigue (Mortimer et al., 2010).

EASI online tool

The EASI tool is essentially a calculator that was designed By Jeff Gilreath, PharmD, Mingyuan Chen, IT specialist and Mary Vietti, DNP student. The calculator programming is based on the ESA decision tree charts of the NCCN and NKF clinical guidelines developed by Jeff Gilreath and George M. Rodgers, MD. (This is presented in appendix A). The EASI tool is designed to be accessed through the Internet. This

allows for the tool be centrally updated to reflect changes to the official guidelines as they occur. This creates a streamlined process to access the most current clinical guidelines and integrate them directly into clinical practice. This calculator is to be used to aid clinicians when considering treatment options for anemias.

The calculator was tested for reliability and validity using fictitious patient data to test the parameters inherent in the programing of the calculator. This data was detailed on spreadsheets with goals, test outcomes, and recommendations for changes. Improvements have included rewording for clarity, format changes for flow and one calculation change. The team met regularly to discuss ease of use and clarity, but most communication was through e-mail. The team for this phase of the project was Mingyuan Chen, IT specialist and programmer: Mary Vietti, DNP student and primary tester: and Jeff Gilreath, PharmD, content expert.

Theoretical Framework

The Donabedian Framework has been a staple in developing healthcare quality research for many years. This model simplifies the concepts into 3 categorical focuses: Structures of care, Process of Care, and Health Outcome.

The Structures of Care is the first stage of the framework and refers to the healthcare setting. For this project, the setting is the Huntsman Cancer Hospital outpatient clinics. This includes an onsite lab and pharmacy. Next, the Process of Care piece of the framework describes the proposed changes to care delivery and coordination of care. In this case, the clinicians will use the ESA calculator, a web based decision-making tool to assist with assessment of all patient information with regard to current recommended published guidelines. For this project the EASI tool was used on an historical cohort of patients that were treated at the Huntsman Cancer Hospital. And lastly, the Health

Outcomes part of this model was used for the analysis and reporting of the potential benefit from the proposed change in process or structure. This is the section where the majority of this project's objectives were met. The results revealed data related to the care that was actually given compared to the care that would have been recommended by the calculator. Estimate of losses from treatment given outside the appropriate guidelines was based on today's costs. (McDonald, et. al., pg 113)

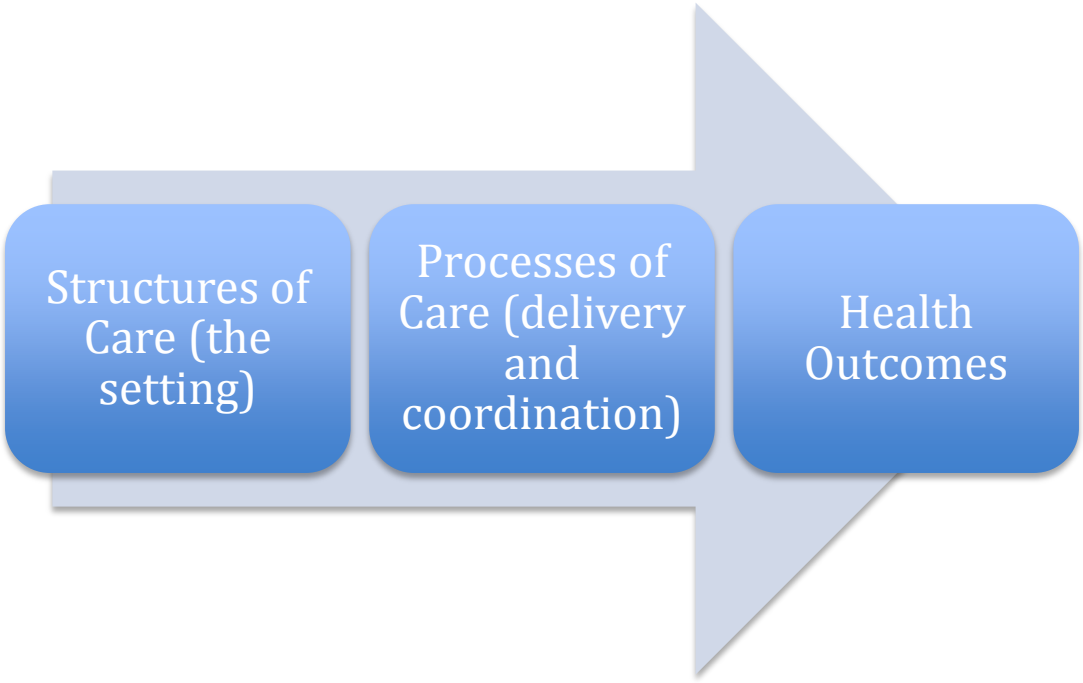

Figure adapted from (McDonald, et. al., pg 113).

Implementation

The Electronic Data Warehouse (EDW) attempted to identify subjects based on past receipt of erythropoietin, and the diagnosis of cancer or hematologic malignancy. Using icd-9 codes, the EDW identified 404 subjects; however, most were not treated for cancer, which made them ineligible for this project. Because there is the black box warning issued with ESAs, the nationally required Apprise system of informed consent

was devised to ensure patient education regarding the increased risk of thrombosis when for CIA. These consents collected by the Huntsman Cancer Hospital pharmacy identified an additional 121 subjects who received an ESA for anemia related to chemotherapy. The electronic medical record for each individual was accessed to obtain the data that are required by the EASI tool to determine ESA dosing per the current KDOKI and NCCN guidelines. The actual treatment decisions on the dates of service were also collected and compared to the recommendations determined by the EASI tool. Originally any patient data after January 2002 was eligible for inclusion in this project. Because the guidelines became much more stringent in 2008, and thus there were more complete patient records, we narrowed the eligible pool of patients to those treated after 2008 leaving 105 total patients for inclusion. All project-related data were recorded and saved on password-protected, encrypted devices and drives.

There were expected and unanticipated challenges to data collection. As expected, there was little documentation to support clinical decisions when a planned ESA was held. These were missed opportunities to test the tool's ability to identify instances where a dose should have been given or to confirm that the tool correctly identify when to hold a dose. In addition, many patients receive treatment or labs from multiple providers, which was difficult to identify in the electronic record. The biggest and unanticipated challenge was finding the dates where medication was actually delivered. To find dates of treatment a pharmacy database, Pharmnet was able to identify dates when the drug was dispensed.

A manuscript was started with the main writers being Mary Vietti and Jeff Gilreath. The Introduction and Background sections are nearly complete, with a rough draft of the rest of paper ready for the team review and edit.

Evaluation

The first objective was to compare the treatments received with the treatments recommended by the EASI tool. Each date of service, encounter, was evaluated for treatment rendered compared to the EASI tool recommendation. When the two groups matched, care was considered to be within the standard of care guidelines; when there was a discrepancy, the care was considered to be out of compliance. The encounters divided into two subgroups for data collection and analysis. The first was encounters to initiate treatment. These first treatments require more information about diagnosis, prognosis and current lab values than does the second subgroup, the return encounters. The percentage of treatments that were given outside the guideline standards were the measurement of efficacy of the tool. In addition, from the treatments differences we calculated the cost difference from the treatment given versus the treatment recommended. This total reflected pharmaceutical cost savings that would have been realized had the EASI tool been available. We did not be considering the cost savings related to provider time.

The third objective, writing the manuscript, is still in process. As detailed below, we feel the project and the paper will be stronger and of greater interest if we wait to publish with the inclusion of data related to the tools efficacy with myelodysplastic syndrome and chronic kidney disease.

Results

The EASI tool identified that in 22% of the combined patient encounters treatment was rendered outside the current guideline recommendations. As discussed earlier this represents patients being at higher risk for an adverse event related to the use of ESAs.

The subject pool included 105 patients representing a total of 130 visits for initiation of treatment and 294 treatment-related visits for monitoring and/or continuation of therapy. Of the patients evaluated for the initiation of treatment, 40% would not have qualified under current guidelines. The largest disqualifying factor was iron deficiency representing 56% of the total reasons for mismatch. Of note this is 22.3% of all initial assessments for use of ESAs for CIA. The other causes of mismatch included missing initial lab assessment (10.8%), hemoglobin out of range (8.5%), nutritional deficiency (1.5%), hemolysis/non-qualifying diagnosis (0.8%) and dose difference (0.8%). Overlapping criteria for mismatch accounted for 3.1%.

For return patients 14.8% of encounters resulted in treatment when the tool recommended either a hold or a dose reduction of encounters. Hemoglobin out of range was the major contributor at 12.9% of visits representing 87.2% of mismatches. Non-response to treatment (1.4%) and hyper-response requiring dose reductions (0.4%) accounted for the rest of the mismatches.

Overall, the EASI tool identified treatment outside guideline recommendations in the following categories: 1) Iron deficiencies 2) hemoglobin out of range, 3) non-responder, 4) hyper-responders, 5) disqualifying diagnosis, and, 6) vitamin deficiency. If these doses had been held, there could have been a $140,000 savings according to an average retail value of $1,500 per injection (Epocrates.com). The actual cost of Aranesp® according to the pharmacy at the Huntsman Cancer Hospital is closer to $2,300 per dose, which brings the total possible savings to about $197,000 for this cohort of patients from 2008 through 2013.

A manuscript is being prepared for submission to a peer review journal. However, this project team does not want to submit without adding data to support the

use of this tool in Myelodysplastic Syndrome and Chronic Kidney Disease. The first of the manuscript without results data can be found in Appendix G.

Recommendations

The ability of this tool to streamline the decision points when prescribing ESA treatment for CIA indicates that other populations that use ESAs might benefit from this tool being adapted to their guidelines. This includes patient populations where disease or medications induce anemia. Clinicians in specialties such as nephrology with CKD, hepatology with chronic hepatitis and immunology with HIV are frequent prescribers of ESAs. The clinical guidelines and thus the EASI tool force the clinician to evaluate each patient for nutritional deficiencies, iron deficiencies, and kidney function. The EASI tool also reminds the user that these drugs should not be used with certain diagnosis or when there is evidence of hemolysis or bleeding.

The literature search illuminated the emerging importance of iron replacement as the primary consideration for treatment of anemias in conjunction with or as an alternative to ESAs or pRBC transfusion. The EASI tool confirmed that iron deficiency was a concern for about 1/5th of the patients being initiated on treatment in this study. More research needs to be focused on prevalence, identification, and diagnosis of iron deficiency; specifically, functional iron deficiency, which is not commonly understood according to Gilreath, et al. 2014. This is a diagnosis that might benefit more from iron supplementation rather than ESAs. The EASI tool identifies this group of patients and could be easily adapted to include recommendations for iron replacement.

This study should be expanded to include patients from the Huntsman Cancer Hospital who received ESAs for Myelodysplastic Syndrome (MDS) and Chronic Kidney Disease (CKD). In these diseases, the return patients take a more consistent and

predictable path, which would allow for better assessment of the tool in ongoing treatment. More testing is needed to assess the EASI tool's ability to identify non-responders and hyper-responders. This data and results would strengthen the utility of the EASI tool and should be added before the manuscript is submitted.

Discussion

As anticipated from the literature review, clinicians' use of ESAs has dropped severely since 2008. This decrease ESA usage and the continued prevalence of anemia, has lead to research indicating increased usage of transfusion in cancer populations, (Vekeman, et al., 2009). As cancer survival increases and is treated more like a chronic illness, there will be a growing number of patients with anemia and fatigue. The use of ESA's allows for maintenance of a higher hemoglobin, (although still well below normal), which can improve quality of life.

Limitations of this project include the subject selection process, which yielded a narrow pool of diagnoses. The majority of ESA recipients included in this project were receiving treatment from the Multiple Myeloma/ Bone Marrow Transplant clinics and the Kidney Transplant clinic. This may bring into question the generalizability of the project results. Being that the EASI tool is based on nationally accepted guidelines, the threat to external validity is an opportunity to involve more institutions to trial the tool. The results, as they are, confirm that the tool identifies the clinical guidelines created by the NCCN and the NKF, which are the same guidelines that drive reimbursement for treatment by CMS.

Conclusions

The EASI tool was able to assess appropriateness of ESA therapy for 105 patients with a total of 394 encounters assessed. Because of the intricacies involved

with ensuring patient safety when initiating ESA treatment and also with continued treatment and monitoring, this EASI tool offers a streamlined approach to aide clinicians in prescribing and monitoring these medications.

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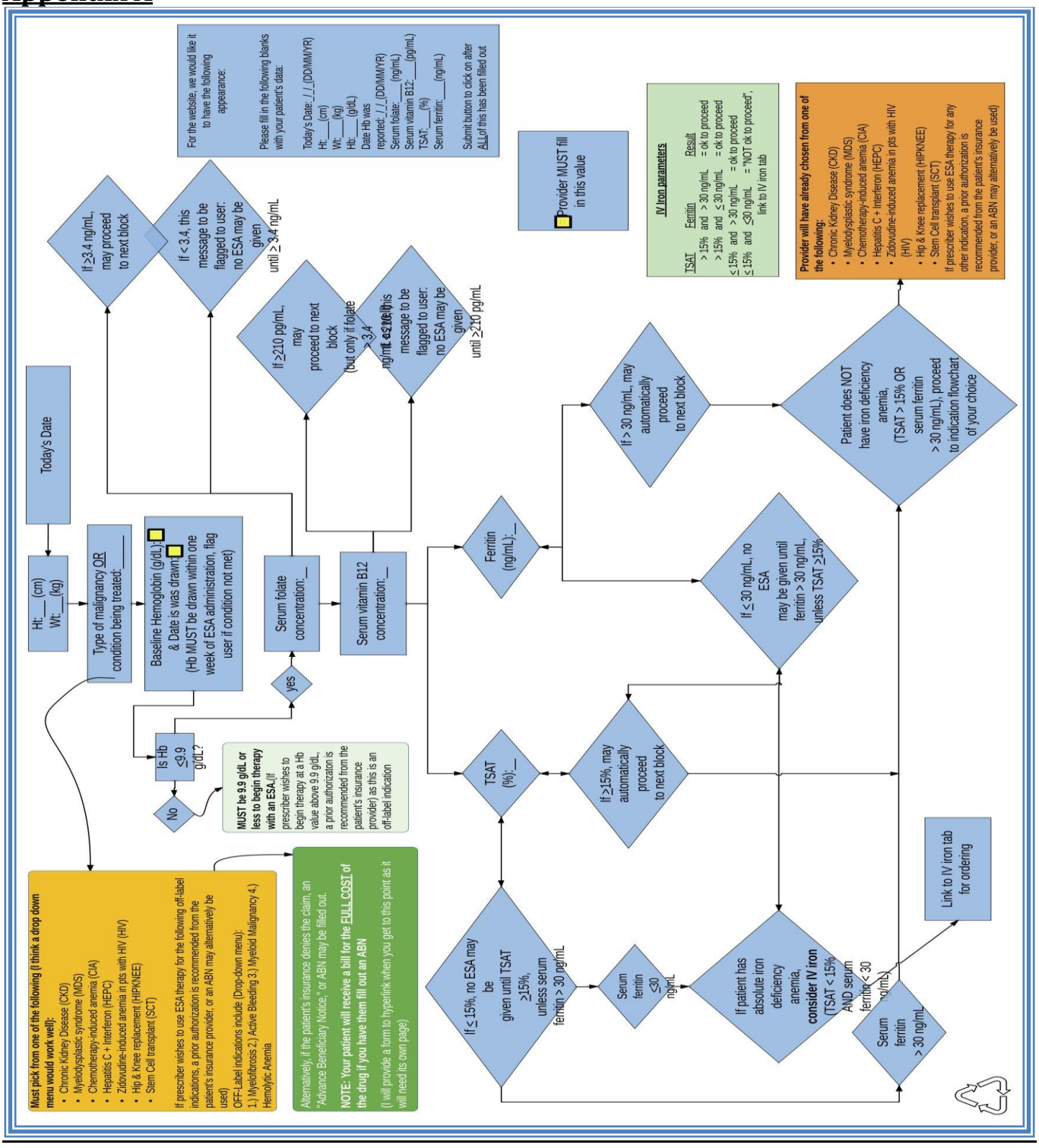
APPENDIX A:
ESA DECISION TREE

Created by Jeff Gilreath, Pharm.D.

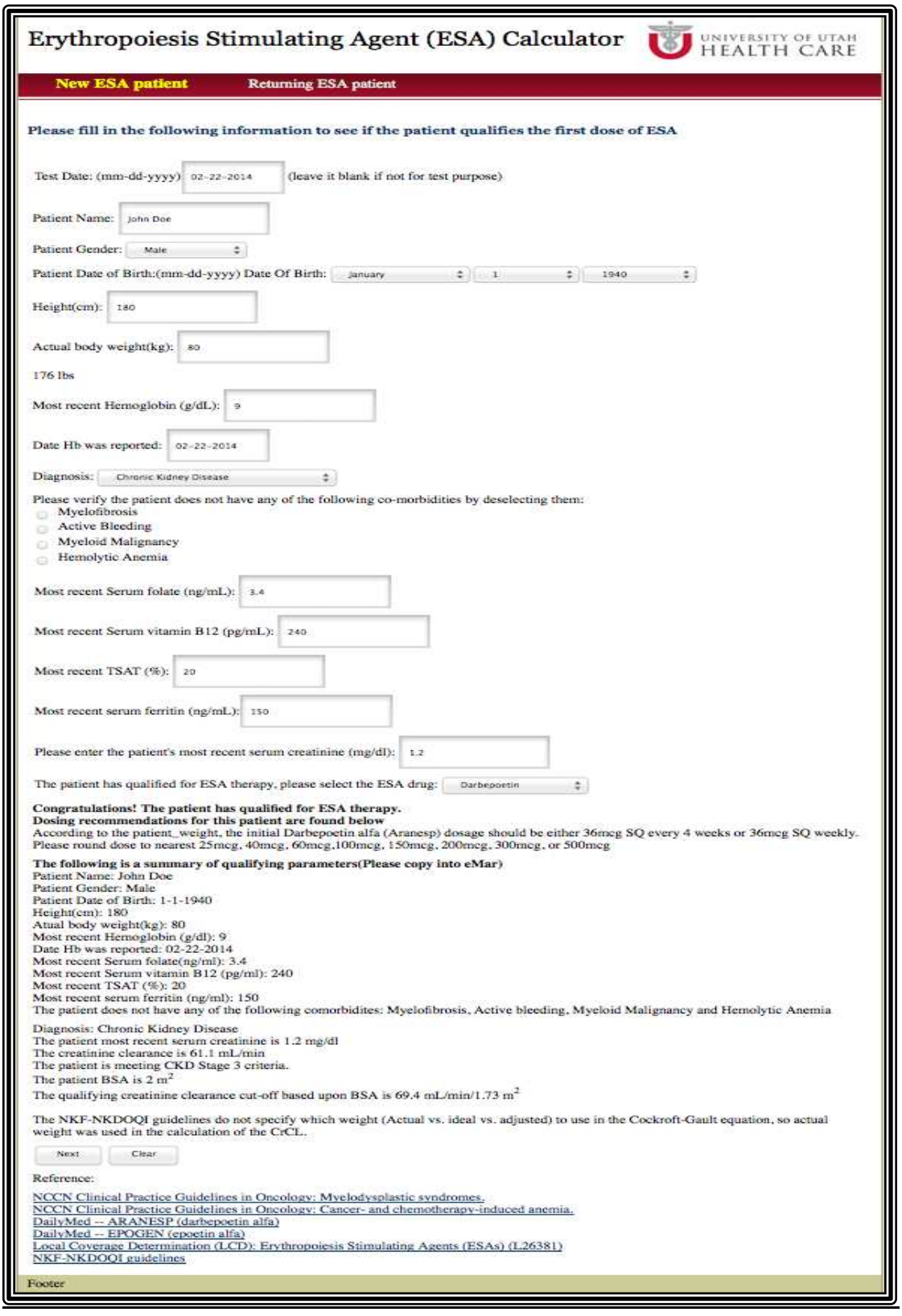
Appendix A


Today's Date
Ht:___ (cm)
Wt:___ (kg)
Type of malignancy OR condition being treated:____
Baseline Hemoglobin (g/dL): & Date is was drawn: (Hb MUST be drawn within one week of ESA administration, flag user if condition not met)
Is Hb ≤9.9 g/dL?
No
yes
MUST be 9.9 g/dL or less to begin therapy with an ESA.(If prescriber wishes to begin therapy at a Hb value above 9.9 g/dL, a prior authorizaton is recommended from the patient's insurance provider) as this is an off-label indication
Must pick from one of the following (I think a drop down menu would work well):
• Chronic Kidney Disease (CKD)
• Myelodysplastic syndrome (MDS)
• Chemotherapy-induced anemia (CIA)
• Hepatitis C + Interferon (HEPC)
• Zidovudine-induced anemia in pts with HIV (HIV)
• Hip & Knee replacement (HIPKNEE)
• Stem Cell transplant (SCT)
If prescriber wishes to use ESA therapy for the following off-label indications, a prior authorization is recommended from the patient's insurance provider, or an ABN may alternatively be used)
OFF-Label indications include (Drop-down menu):
1.) Myelofibrosis 2.) Active Bleeding 3.) Myeloid Malignancy 4.) Hemolytic Anemia
Alternatively, if the patient's insurance denies the claim, an "Advance Beneficiary Notice," or ABN may be filled out.
NOTE: Your patient will receive a bill for the FULL COST of the drug if you have them fill out an ABN
(I will provide a form to hyperlink when you get to this point as it will need its own page)
Serum folate concentration:__
Serum vitamin B12 concentration:__
Ferritin (ng/mL):__
TSAT (%):__
If ≥3.4 ng/mL, may proceed to next block
If < 3.4, this message to be flagged to user: no ESA may be given until ≥ 3.4 ng/mL
If ≥210 pg/mL, may proceed to next block (but only if folate ≥ 3.4 ng/mL as well)
If < 210 pg/mL, this message to be flagged to user: no ESA may be given until ≥210 pg/mL
If > 30 ng/mL, may automatically proceed to next block
If ≥15%, may automatically proceed to next block
If ≤ 30 ng/mL, no ESA may be given until ferritin > 30 ng/mL, unless TSAT ≥15%
If ≤ 15%, no ESA may be given until TSAT ≥15%, unless serum ferritin > 30 ng/mL
Serum ferritin ≤30 ng/mL
If patient has absolute iron deficiency anemia, consider IV iron (TSAT < 15% AND serum ferritin < 30 ng/mL)
Serum ferritin > 30 ng/mL
Patient does NOT have iron deficiency anemia, (TSAT > 15% OR serum ferritin > 30 ng/mL), proceed to indication flowchart of your choice
Link to IV iron tab for ordering
Provider MUST fill in this value
For the website, we would like it to have the following appearance:
Please fill in the following blanks with your patient's data:
Today's Date: _/_/_(DD/MM/YR)
Ht:___(cm)
Wt:___(kg)
Hb:___(g/dL)
Date Hb was reported: _/_/_(DD/MM/YR)
Serum folate:___(ng/mL)
Serum vitamin B12:___(pg/mL)
TSAT:___(%)
Serum ferritin:___(ng/mL)
Submit button to click on after ALL of this has been filled out
IV Iron parameters
TSAT Ferritin Result
> 15% and > 30 ng/mL = ok to proceed
> 15% and ≤ 30 ng/mL = ok to proceed
≤ 15% and > 30 ng/mL = ok to proceed
≤ 15% and ≤30 ng/mL = "NOT ok to proceed", link to IV iron tab
Provider will have already chosen from one of the following:
• Chronic Kidney Disease (CKD)
• Myelodysplastic syndrome (MDS)
• Chemotherapy-induced anemia (CIA)
• Hepatitis C + Interferon (HEPC)
• Zidovudine-induced anemia in pts with HIV (HIV)
• Hip & Knee replacement (HIPKNEE)
• Stem Cell transplant (SCT)
If prescriber wishes to use ESA therapy for any other indication, a prior authorization is recommended from the patient's insurance provider, or an ABN may alternatively be used)

APPENDIX B:

Example of EASI tool recommendation after all patient data has been entered.

Appendix B



Erythropoiesis Stimulating Agent (ESA) Calculator

UNIVERSITY OF UTAH HEALTH CARE

New ESA patient | Returning ESA patient

Please fill in the following information to see if the patient qualifies the first dose of ESA

Test Date: (mm-dd-yyyy) 02-22-2014 (leave it blank if not for test purpose)

Patient Name: John Doe

Patient Gender: Male

Patient Date of Birth:(mm-dd-yyyy) Date Of Birth: January 1 1940

Height(cm): 180

Actual body weight(kg): 80

176 lbs

Most recent Hemoglobin (g/dL): 9

Date Hb was reported: 02-22-2014

Diagnosis: Chronic Kidney Disease

Please verify the patient does not have any of the following co-morbidities by deselecting them:

- Myelofibrosis
- Active Bleeding
- Myeloid Malignancy
- Hemolytic Anemia

Most recent Serum folate (ng/mL): 3.4

Most recent Serum vitamin B12 (pg/mL): 240

Most recent TSAT (%): 20

Most recent serum ferritin (ng/mL): 150

Please enter the patient's most recent serum creatinine (mg/dl): 1.2

The patient has qualified for ESA therapy, please select the ESA drug: Darbepoetin

Congratulations! The patient has qualified for ESA therapy.
Dosing recommendations for this patient are found below
According to the patient_weight, the initial Darbepoetin alfa (Aranesp) dosage should be either 36mcg SQ every 4 weeks or 36mcg SQ weekly.
Please round dose to nearest 25mcg, 40mcg, 60mcg,100mcg, 150mcg, 200mcg, 300mcg, or 500mcg

The following is a summary of qualifying parameters(Please copy into eMar)
Patient Name: John Doe
Patient Gender: Male
Patient Date of Birth: 1-1-1940
Height(cm): 180
Atual body weight(kg): 80
Most recent Hemoglobin (g/dl): 9
Date Hb was reported: 02-22-2014
Most recent Serum folate(ng/ml): 3.4
Most recent Serum vitamin B12 (pg/ml): 240
Most recent TSAT (%): 20
Most recent serum ferritin (ng/ml): 150
The patient does not have any of the following comorbidites: Myelofibrosis, Active bleeding, Myeloid Malignancy and Hemolytic Anemia

Diagnosis: Chronic Kidney Disease
The patient most recent serum creatinine is 1.2 mg/dl
The creatinine clearance is 61.1 mL/min
The patient is meeting CKD Stage 3 criteria.
The patient BSA is 2 m^2
The qualifying creatinine clearance cut-off based upon BSA is 69.4 mL/min/1.73 m^2

The NKF-NKDOQI guidelines do not specify which weight (Actual vs. ideal vs. adjusted) to use in the Cockroft-Gault equation, so actual weight was used in the calculation of the CrCL.

Next Clear

Reference:

NCCN Clinical Practice Guidelines in Oncology: Myelodysplastic syndromes.
NCCN Clinical Practice Guidelines in Oncology: Cancer- and chemotherapy-induced anemia.
DailyMed -- ARANESP (darbepoetin alfa)
DailyMed -- EPOGEN (epoetin alfa)
Local Coverage Determination (LCD): Erythropoiesis Stimulating Agents (ESAs) (L26381)
NKF-NKDOQI guidelines

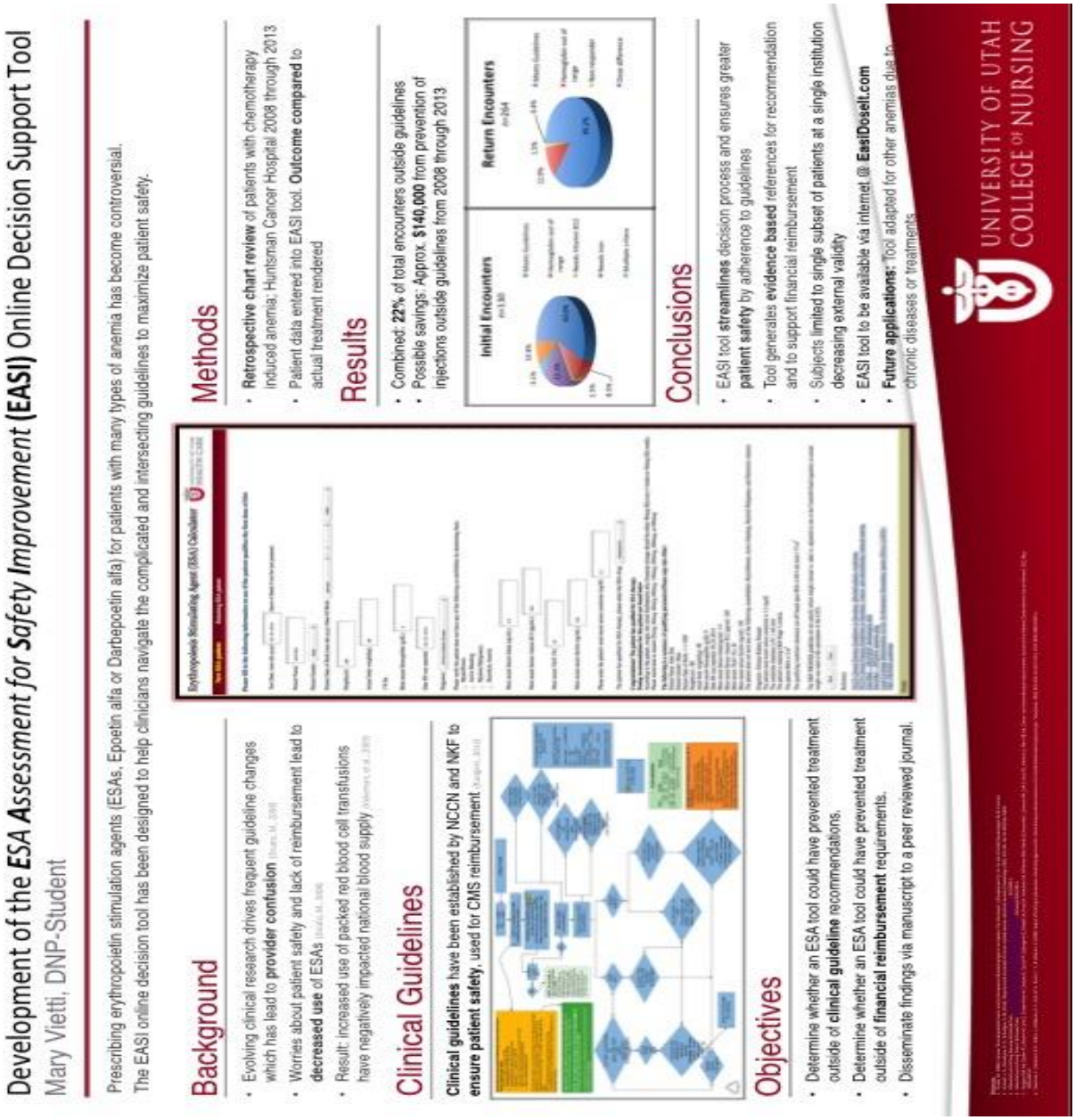
Footer

APPENDIX C:

Poster presented for School of Nursing 3/28/2014

Appendix C

Project poster presented 3/28/2014



APPENDIX D:

IRB Letter of Exemption

Appendix D – IRB Letter of Exemption

IRB: IRB_00069219

PI: Mary Vietti

Title: Development of the ESA Assessment for Safety Improvement (EASI) Online Decision Support Tool

Thank you for submitting your request for approval of this study. The IRB has administratively reviewed your application and a designated IRB member has determined that your study is exempt from further IRB review, under **Exemption Category 7**. Note the following delineation of categories:

- Categories 1-6: Federal Exemption Categories defined in 45 CFR 46.101(b)
- Categories 7-11: Non-Federal Exemption Categories defined in University of Utah IRB policy at http://irb.utah.edu/_pdf/IGS - Exempt Research 090113.pdf

You must adhere to all requirements for exemption described in University of Utah IRB policy (http://irb.utah.edu/_pdf/IGS - Exempt Research 090113.pdf). This includes:

- All research involving human subjects must be approved or determined exempt by the IRB before the research is conducted.
- All research activities must be conducted in accordance with the Belmont Report and must adhere to principles of sound research design and ethics.
- Orderly accounting and monitoring of research activities must occur.

Ongoing Submissions for Exempt Projects

- **Continuing Review:** Since this determination is not an approval, the study does not expire or need continuing review. This determination of exemption from continuing IRB review only applies to the research study as submitted to the IRB. You must follow the protocol as proposed in this application
- **Amendment Applications:** Substantive changes to this project require an amendment application to the IRB to secure either approval or a determination of exemption. **Investigators should contact the IRB Office if there are**

questions about whether an amendment consists of substantive changes. Substantive changes include, but are not limited to
    - Changes that increase the risk to participants or change the risk:benefit ratio of the study
    - Changes that affect a participant's willingness to participate in the study
    - Changes to study procedures or study components that are not covered by the Exemption Category determined for this study (listed above)
    - Changes to the study sponsor
    - Changes to the targeted participant population
    - Changes to the stamped consent document(s)
- **Report Forms:** Exempt studies must adhere to the University of Utah IRB reporting requirements for unanticipated problems and deviations: http://irb.utah.edu/submit-application/forms/index.php
- **Final Project Reports for Study Closure:** Exempt studies must be closed with the IRB once the research activities are complete: http://irb.utah.edu/submit-application/final-project-reports.php

If you have questions about this, please contact our office at 581-3655 and we will be happy to assist you. Thank you again for submitting your proposal.

Click IRB_00069219 to view the application.

Please take a moment to complete our customer service survey. We appreciate your opinions and feedback.

APPENDIX E:

Electronic Data Warehouse Request Form

Appendix E – Electronic Data Warehouse Request for Information

Data/Information Request Form
University of Utah Health Sciences Center

This form is used to request data/information from the University of Utah Health Sciences Center through the University Enterprise Data Warehouse (EDW). Data received from this source is covered under HIPAA regulation (46 CFR 164) and is subject to privacy law. Data requested for use in human subject research is also subject to review by the Institutional Review Board (IRB) under applicable federal regulation. For guidance completing this form, please see the document titled **Guidance for Accessing Protected Health Information** at http://www.research.utah.edu/irb/guidelines/investigator_guidance.html.

A. CONTACT INFORMATION

Name of Person Requesting Records:	Mary Vietti
uNID:	u0138288
Email:	mary.vietti@hci.utah.edu
Phone:	(206) 383-9369
Department:	DNP Student/ HCH Infusion
Campus Address:	1950 Circle of Hope, Clinic 2A

Contact Person:	Mary Vietti
Email:	mary.vietti@hci.utah.edu
Phone:	(206) 383-9369

Persons to have access to data (list below):

Name	*uNID*[1]
Mary Vietti	u0138288

B. REQUEST DETAILS

1. Purpose of the Request - *Select all that apply*

No form is needed for treatment or payment purposes.

- **X** QA/QI
- ☐ Accreditation
- ☐ HR Audit
- ☐ Teaching/training
- ☐ Audit (specify):
- ☐ Continuity of Care[2]
- ☐ Fundraising[3]
- ☐ Marketing
- ☐ Patient education
- ☐ Research Preparatory Activities
- ☐ Other (specify):

X Research (specify):

IRB #:	00069219	Consent Process:	☐ Consent Form **X** Waiver of Consent
Study Title:	Development of the ESA Assessment for Safety Improvement (EASI) Online Decision Support Tool		
Number of patients needed for enrollment[4]/analysis:	Target = 500, we will analyze > 500 if more are identified using our search		

	criteria

Data requested for research purposes:

- *This form must be completed and submitted to the IRB as part of your IRB submission. The approval watermark in the footer must be present in order to receive data.*
- *The information provided in this form must be consistent with your IRB application in order to receive approval.*
- *Do not use this form for research preparation or research on decedents' information. See IRB for appropriate form.*

2. Will patient(s) be contacted? ☐ Yes **X** No	Purpose: Evaluation of the EASI tool
3. Will this information be used in a formal presentation or publication? **X** Yes ☐ No	
4. Time period of records: 2002 - present	

C. DATA REQUEST

1. Data Elements Requested

De-identified data set	Limited data set	Identified data set
X DX (specify): Anemia, Cancer, Hematologic malignancy ☐ DRG (specify): **X** Procedure(s) (specify): Treatment with erythropoietin stimulating agents such as epoetin alfa (Epogen or Procrit) or darbepoetin alfa (Aranesp) **X** Age (year of birth)[6] ☐ Admission date (year) **X** Procedure date (year) ☐ Discharge date (year) ☐ Death date (year) ☐ Zip code[5] ☐ State	**X** Date of Birth ☐ Admission date (m/d/y) **X** Procedure date (m/d/y) ☐ Discharge date (m/d/y) ☐ Death date (m/d/y)	☐ Name/initials ☐ Phone/fax number ☐ Address ☐ Email address X MRN ☐ SSN ☐ Account number or ID number (specify type of number): ☐ Device/serial number ☐ Identifying images ☐ Other unique identifying information (specify):

Other data elements requested (please list): Additional data to will be collected from the patient electronic record as part of the study procedures.

Other data elements listed will be assessed for level of identification. In order to facilitate the collection of appropriate data elements, the following information may also be sent to the EDW Officials: (a) a protocol summary used for research, (b) a blank Excel spreadsheet with the columns/rows labeled according to the data you would like to receive, (c) an Excel spreadsheet with three columns specifying code, type of code (i.e., ICD9, CPT) and a description of code that needs pulled.

D. HIPAA COMPLIANCE

1. How does this request comply with HIPAA?

- ☐ This is for healthcare operations[7], as defined by HIPAA
- ☐ I have signed authorization from all patients (attach sample authorization, may be consent/authorization for research)
- X I have an IRB-approved waiver or modification of authorization
- ☐ I am requesting a limited data set (attach Limited Data Set statement and assurance if not reviewed by IRB)
- ☐ I am requesting de-identified data (attach Safe Harbor De-identification form if not reviewed by IRB)[8]

☐ I am requesting information for research preparation activities (attach a Research Preparation Form)

☐ Other (specify):

2. Will Protected Health Information[8] (PHI) be disclosed outside the University's Covered Entity? ☐ Yes X No
PHI may not be disclosed for research preparation activities.

E. REQUESTER'S REPRESENTATION

By signing* this form, I affirm the following:

a. I seek to review the indicated information solely for the purposes indicated;
b. The information for which I seek use or access is the minimum necessary for the purpose of this request.

Requesters Signature Date

***For submitting to the IRB, in lieu of a signature, check this box to agree:* X**

Requester's position/title: Mary Vietti, DNP Student/ PI

Signature of Dept. Chair, Attending Physician, or Responsible Faculty Date
**Not required for submitting to the IRB*

F. FOOTNOTES

1. PeopleSoft number
2. E.g., a provider is leaving the University and wants to contact current/former patients
3. Contact Stephen Warner, Asst. VP for Health Sciences Development, 585-7010
4. If you are using patient records for prospective recruitment and enrollment of patients into research, the number of records released to you will be based upon a 20% response rate to meet your enrollment goal. If additional records are needed to meet enrollment goals, EDW must be re-contacted.
5. All data from the following 17 3-digit zip codes must be combined together under "000" to be de-identified under HIPAA: 036, 059, 063, 102, 203, 556, 692, 790, 821, 823, 830, 831, 878, 879, 884, 890, 893. If these specific zip codes are needed for the study, please indicate on the form.
6. Ages over 89 must be combined in a single category of "Age 90 and older" to be de-identified under HIPAA. If these specific ages are needed for the study, please indicate on the form.
7. *Healthcare operations* include quality assessment and improvement, training, accreditation, certification, licensing, medical review, legal services, auditing functions, business planning and development, and business management and general administrative activities. This does NOT include research (45 CFR 164.501).
8. If your request involves an unusual disease or condition, attach a statement explaining 1) the incidence of the disease or conditions and 2) the potential of the information in

your request to be used to identify the individuals.

9. *Protected Health Information (PHI)* is information about the past, present, or future physical or mental health of an individual that identifies or could be used to identify the individual and is created or receive by a Covered Entity (45 CFR 160.301, 164.501). Information about the provisions of health care and payment for health care is included. Some educational and employment records are excluded.

FOR ADMIN USE ONLY **DATA/INFORMATION REQUEST APPROVAL**	
This information request has been reviewed and approved by the following applicable individuals/offices:	☐ University Privacy Office: Signature: _____ Date: _____ ☐ Health Information: Signature: _____ Date: _____ ☐ ITS: Signature: _____ Date: _____ ☐ Department Representative: Signature: _____ Date: _____ *IRB approval issued via the ERICA online system, indicated with stamp in footer.*

Original: Kept by the approving individual/office
Draft copy sent to: Enterprise Data Warehouse Officials, fax 801-585-9672, email EDW_DataRequests@hsc.utah.edu
(data will not be issued until final copy is received by EDW)
Final copies sent to: (1) HIPAA Privacy Office, 50 N Medical Dr., fax 801-587-9443
(2) Enterprise Data Warehouse Officials, fax 801-585-9672, email EDW_DataRequests@hsc.utah.edu

APPENDIX F:

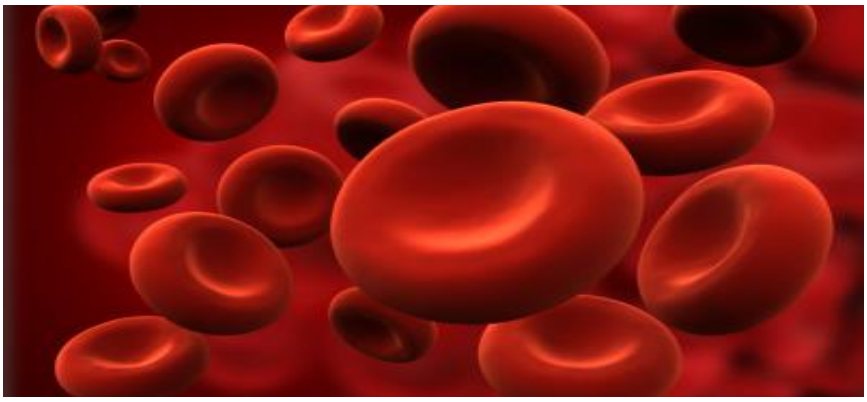
Defense Power Point Presentation for the School of Nursing
10/11/2013

Appendix F – Defense Power Point 3/10/2013

Development of the **E**SA **A**ssessment for **S**afety **I**mprovement (**EASI**) Online Decision Support Tool

In partial fulfillment of the requirements for the Doctor of Nursing Practice degree

10/10/2013



Background

- Anemia not correctable with iron, B12 or folate
  - Chemotherapy
  - Chronic Kidney Disease
  - Myelodysplastic Syndrome
- Clinicians hesitant to prescribe ESAs
  - Meta-analyses show ⇧ VTE & mortality with ESAs
  - Clinical controversy in patients with CKD
  - Time consuming
  - Frequent reimbursement rule changes
- Costs: ESA >$2,000 – 3,000 per dose
- Alternative treatment is blood transfusion
  - Usually reserved for Hb < 7-8 g/dL

VTE – Venous Thromboembolism

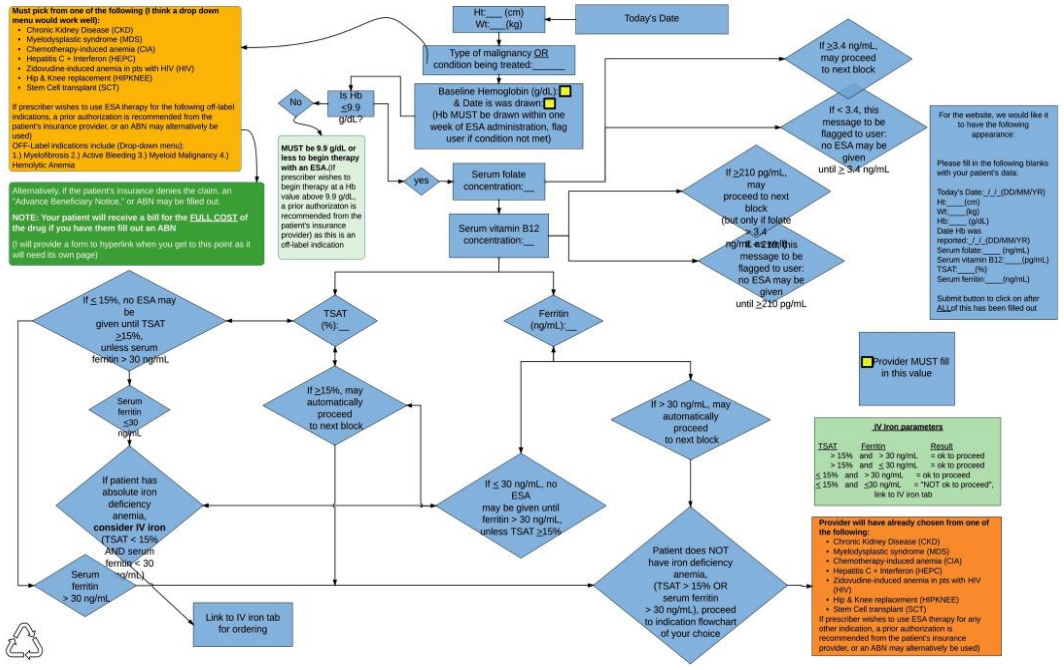
Background

- NCCN and NKF have issued clinical guidelines for treating anemia in patient with cancer, MDS, or CKD
- Since 2005, ESA safety data has lead to frequent guideline changes
- CMS uses NCCN and NKF guidelines for reimbursement
  - Other third party payers follow the CMS reimbursement structure
- As new research emerges, guideline recommendations change as do reimbursement parameters

NCCN - National Cancer Care Network
NKF - National Kidney Foundation
CMS - Centers for Medicare and Medicaid

MDS - Myelodysplastic Syndrome
CKD - Chronic Kidney Disease
ESA – Erythropoiesis Stimulating Factor

Current Guidelines



Problem Statement

- Treatments for anemia
  - Increase risk for adverse events
  - Are expensive
- Therefore we need to improve patient safety and financial efficiency

Purpose

- To develop an online EASI decision tool to help clinicians adhere to the treatment guidelines which increases patients safety

Clinical Significance & Policy Implications

Goal: standardize treatment and monitoring of anemia in patients with cancer

- Clinical Benefits of standardizing treatment:
  1) Increase patient safety
  2) Increase effectiveness of ESAs
  3) Reduce anemia-related side effects
  4) Early identification of patients not likely to respond

- Policy implications of standardizing treatment:
  1) Allow for measurement/evaluation of outcomes
  2) Early identification of patients not likely to respond
  3) Improve clinician efficiency in managing ESA treatment
  4) Increase reimbursement rate

Objectives

1. Determine whether an ESA tool could have prevented treatment outside of **clinical** guideline recommendations.

2. Determine whether an ESA tool could have prevented treatment outside of **financial** reimbursement requirements.

3. Complete manuscript for submission for publication.

Donabedian Framework

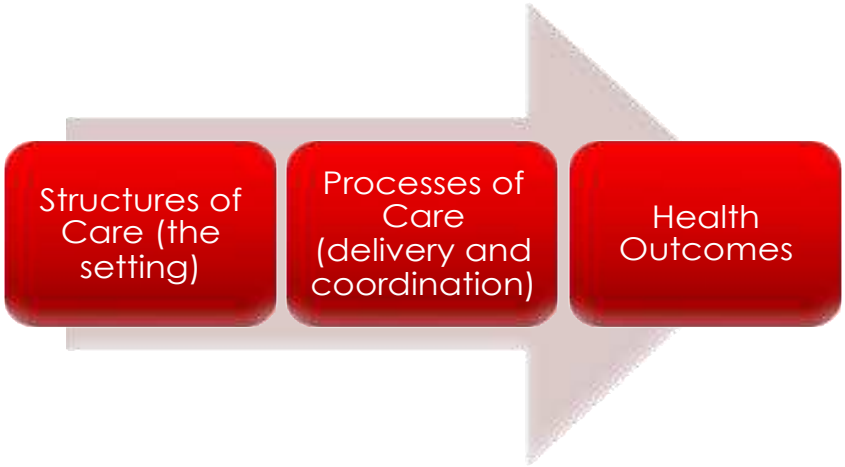


Figure adapted from (McDonald, et. al., pg 113).

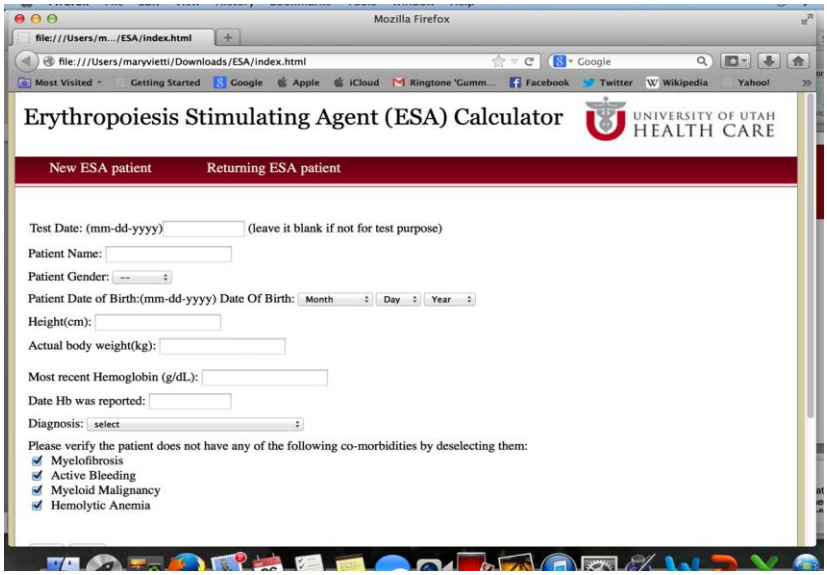
Literature Review

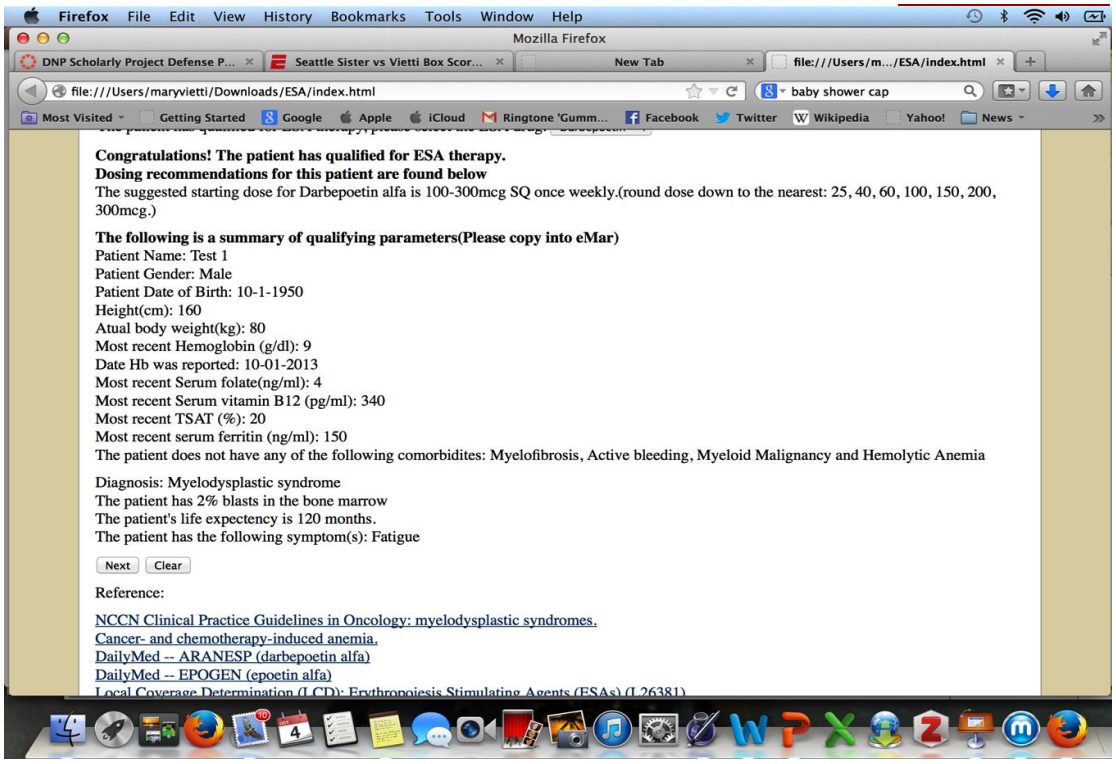
- Most information has been gathered from systematic reviews, meta-analysis and RCTs on the following subjects:
  - Treatment of anemias
    - CKD, MDS, Cancer, other
  - ESA efficacy and side effects
    - Adverse events and mortality
    - Dosing and diagnosis
  - Transfusion efficacy and side effects
    - Adverse events and mortality
- Valuable insight was gained through **2 specific studies**:
  - Gilreath et al (2008): Pharmacist lead anemia clinic
  - Vekeman et al (2009): Estimate of the impact the decreased use of ESAs has had on the national blood supply

IMPLEMENTATION PLAN

Objective	Implementation	Evaluation
Determine whether an ESA tool could have prevented treatment outside of **clinical** guideline recommendations.	1. Using a retrospective design method, historical data from, (n=100), will be entered into the ESA calculator. 2. Collect actual treatment rendered data for each encounter for subject 3. Collect ESA calculator treatment recommendation for each encounter for each subject	1. Compare actual treatment data to ESA calculator recommendations. 2. Use descriptive statistics to determine significant differences between the groups.
Determine whether ESA tool could have prevented treatment outside the **financial** recommendations.	1. Use data collected for objective #1 2. Collect actual treatment costs for each encounter.	1. Compare actual treatment data to ESA calculator recommendations. 2. Determine cost of treatment given outside ESA calculator recommendation.
Complete manuscript in format for submission for publication..	Once data is collected and analyzed, the NP student will lead the team through writing the final manuscript. We will use a team approach with delegation of responsibilities, based on individual areas of strength and expertise.	Feedback from content experts, DNP faculty advisors and acceptance for final defense.

Calculator example





Summary

- The **EASI calculator** navigates guideline recommendations for treating anemia associated with chemotherapy, myelodysplastic syndrome, and chronic kidney disease
- The goal is to **improve adherence** to NCCN, NKF guidelines for treating anemias
- Adherence to guidelines will increase patient **safety** for some & **quality of life** for others
- Adherence to the guidelines also increases likelihood of **reimbursement** from third party payers, specifically CMS
- Implementation of a new process could show patient **results** in a few months with immediate financial savings
- Ultimately, the increase in patient well being will provides **confidence in treatment decision making**, as well as, peace of mind from worry of lack of reimbursement

Acknowledgements

Jeff Gilreath, PharmD
Huntsman Cancer Hospital
Department of Hematology

Lauri Linder, PhD, APRN, CPON
College of Nursing
University of Utah

References

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APPENDIX G:
First Draft of manuscript in process

Appendix G – First Rough Draft of Manuscript (Incomplete)

Version: 3/26/2014

Development of the ***E****SA* ***A****ssessment for* ***S****afety* ***I****mprovement* **(EASI)** Online Decision Support Tool

Principal Investigator
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BACKGROUND AND INTRODUCTION:

Introduction

Studies have shown that anemia is ubiquitously seen, occurring in as many as 90% of cancer patients (Knight, Wade, & Balducci, 2004). Symptoms of anemia that are associated with a decreased quality of life include fatigue, shortness of breath, dizziness, hypotension, and tachycardia. (Cella, & McDermott, 2004). Malignancy, chronic kidney disease (CKD), and myelodysplastic syndrome (MDS) are among many risk factors for anemia. In addition, treatment with chemotherapy and radiation increase the likelihood that cancer patients will need an intervention to combat anemia (Gilreath, Stenehjem, & Rodgers, 2014).

Treatment options for cancer-related anemia include iron, red blood cell (RBC) transfusion, or erythropoietin stimulation agents (ESAs). In primary care, B12 and folate supplementation are common treatments, however, there are little data to support the correction of nutritional deficiencies for the treatment of anemia in patients with cancer. After ruling out and correcting iron deficiency for all symptomatic patients with anemia, additional intervention is often required. As RBC transfusions and ESAs carry significant risks for patients, it is imperative that the risks and benefits of each option are carefully weighed.

Risks and Benefits of RBC Transfusions

Transfusions are recommended for the symptomatic treatment of anemia for hemoglobin (Hb) concentration of less than or equal to 8 g/dL (Carson, Grossman, Kleinman, Tinmouth, Marques, Fung, et. al., (2012). . This is commonly encountered in those receiving chemotherapy or radiation, as well as in patients with MDS and CKD. Although transfusion rapidly increases the Hb concentrations and is associated with patient reports of increased wellbeing, transfusions carry considerable risk of harm. The risks include transfusion reaction related to incorrect matching or low quality product, circulatory overload, iron overload, viral and bacterial infections, immune injury, hemolysis and graft versus host disease (Schrijvers, 2011). The increased costs associated with RBC transfusions include societal economic costs such as donor time

and expense, and infrastructure for collection, processing, usage and administration. The average cost (to patient) in the US for one unit of packed red blood cells ranges from $208 to $478, (Schrijvers, 2011). Transfusions for Hb below 8 usually require 2 units of blood and more than 5 hours of infusion time. By increasing appropriate ESA use and response rates, transfusion requirements may decrease.

Risks and Benefits of Erythropoietin Stimulating Agents

ESAs raise the Hb by stimulating the bone marrow to produce more red blood cells. This increase in Hb has been shown to increase patients' sense of well being. However, ESA therapy is also associated with risk such as thrombogenesis and a questionable risk of tumor progression (Bohlius et al., 2006). Many studies have confirmed an increased incidence of thrombosis in patients with cancers known to cause thrombogenesis, but there is not sufficient evidence indicating increased tumor activity (Dicato, 2008).

Another consideration is that, "anemia prevalence rises as diseases progress; thus, it can be difficult to separate the effects of anemia from the effects of disease severity," (Knight et. al., 2004) and thus any associated increase in poor outcome due to disease progression should not be correlated directly with increased ESA use in this population. Without robust evidence that ESAs increase cancer activity, and considering the increased risk associated with transfusion, ESAs remain an attractive treatment modality. However, providers will still be required to navigate through clinical and financial treatment parameters, which remain confusing and cumbersome.

The evolution ESA treatment guidelines have been directed by research regarding the risk of thrombosis with ESA treatment. Over the last decade this has lead to frequent changes in prescribing recommendations and reimbursement requirements. In 2004, the FDA required Amgen to add warning label that cautioned an increased risk of thrombosis with use of ESA's. In 2007 the NCCN Guidelines for the use of ESA's called for restricted use of ESA's. This mandated that Hb concentrations be kept below 12 g/dL and not initiated until Hb dropped below 9 g/dL. In 2007, the parameters were changed to restrict some hematological malignancies, restrict treatment goals based on

diagnosis, and include qualifying lab parameters. This has resulted in reduction in the use of ESA's which in turn has lead to an increase in the alternative treatment, packed red cell transfusion, and a significant impact on the US blood supply, (Vekeman, Bookhart, White, McKenzie, Duh, Piech, & Lefebvre, 2009).

Benefits of Standardizing treatment for anemia

Over concerns for risk to patient safety associated with transfusions, the Society for the Advancement of Blood Management (SABM), introduced a standardized process, the Patient Blood Management (PBM) program, to reduce the use of allogeneic blood transfusions for the treatment of anemia. The PBM process weighed the benefits and costs of transfusion when considering the complicated variables involved with the diagnosis and treatment of anemias. Their results showed a 17% reduction in the use of transfusions, (Shander, Ozawa, Gross, & Henry, 2013), thus improving patient safety through the reduction of the use of transfusion, (Goodnough, Shieh, Cheng, Khari, & Maggio, 2013).

Pharmacists at the University of Utah recognized the difficulties managing the treatment of anemia. They created a pharmacist-run anemia clinic to assess diagnostic criteria and appropriateness of treatment options as defined by the guidelines published by the National Kidney Foundation (NKF), American Society of Clinical Oncology/American Society of Hematology, and the National Comprehensive Cancer Network (NCCN). They found that having a dedicated clinician with a standardized approach to treatment for each individual patient increased adherence to the treatment guidelines. Adherence to these guidelines is the key to increasing patient safety with ESAs. In addition, they found that clinicians struggle with defining hyporesponsiveness to ESAs (Gilreath, Sageser, Jorgenson, James, & Rodgers, 2008). Multiple criteria may be used, including a lack of Hb rise > 1 g/dL above baseline or a decrease in pRBC transfusion frequency by 50%. Therefore, patients may inappropriately receive ongoing ESA treatment with little to no benefit, but continued risk.

To minimize the risks to patient safety and optimize anemia management, treatment should include the use of clinical guidelines, such as those published by the

NKF, ASCO/ASH, and NCCN. Because their recommendations may differ, clinicians find it cumbersome to navigate through several guidelines simultaneously (Bennett, Becker, Kraut, Samaras, & West, 2009). The EASI tool is being developed to help clinicians navigate the intricacies of the NKF, ASCO/ASH, and the NCCN guidelines.

Benefits of Clinician Decision Support Tools

Clinician decision support tools have become synonymous with efficient and high quality care. The time-consuming process related to navigating the guideline for the use of ESA lead the researchers at Henry Ford Hospital to formulate a standardized protocol for ESA dosing for CKD patients with anemia. The results showed that the use of this protocol increased consistency of dosing between providers, and resulted in an 84% decrease in clinician time spent evaluating and prescribing treatment. Hemoglobin goals were met for most (78%) patients (Chaloub,
Frinak, Zasuwa, Faber, Peterson, Besarab, & Yee, 2011). The success of this program demonstrates the value of standardized protocols for the clinicians as well as the patients. It should be noted that decision tools are not intended to be used as a substitution for physical exam or for clinician expertise, but rather as aides to reconcile patient data with current guidelines.

Lastly, many providers are hesitant to prescribe ESAs due to confusion over covered diagnoses, treatment parameters, and the fear of not being reimbursed (Gilreath, et. al., 2008). An average dose of an ESA is in excess of $2,000. A cost that accumulates quickly when prescribed weekly or bimonthly. In addition, the package labeling, NCCN guidelines, and CMS criteria for ESA use are incongruent. Qualifying criteria for CMS-insured patients are more restrictive than the ESA labeling. NCCN recommendations for use are also more specific than ESA labeling. Unfortunately, many clinical providers are unaware of these discrepancies as well as financial restrictions. This results in ESAs being prescribed under non-qualifying circumstances. Reimbursement criteria for CMS can be found in national coverage determinations (NCDs) or Local coverage determinations (LCDs) published by Medicare fiscal intermediaries. NCDs and LCDs recognize the guidelines published by the NKF for

chronic kidney disease and the guidelines published by the NCCN for cancers, MDS, and other hematologic malignancies as official compendiums for reimbursement. The EASI tool utilizes the same referenced support documentation for treatment decisions as used in NCDs and LCDs. This will benefit providers when submitting claims for reimbursement. Through the use of the EASI tool, we hypothesize that a greater percentage of claims will be submitted which adhere to NCD and LCD criteria thus resulting in an increase rate of reimbursement.

The EASI tool incorporates guideline-directed protocols used to formulate ESA dosing recommendations for cancer patients specifically. It is an online tool designed to be easily accessible. It will help clinicians navigate through the safety parameters and options for treatment of anemia in cancer. It addresses iron stores, hyporesponsiveness, increased risk related to cancer diagnosis and aligns the different treatment guidelines with reimbursement parameters. The aim of this study is to validate the *ESA Assessment for Safety Improvement* (EASI) Online Decision Support Tool, using a retrospective comparison of EASI recommendations with actual patient outcomes. The goal of the tool is to assess the differences in adherence to NKF and NCCN guidelines, which will ultimately increase patient safety.

OBJECTIVES:

Primary objective

To determine whether the *ESA Assessment for Safety Improvement* (EASI) tool, can identify clinical errors *a priori* and prevent treatment outside of clinical guideline recommendations for anemic cancer patients with CIA, CKD, or MDS.

Secondary objective

To determine whether the *ESA Assessment for Safety Improvement* (EASI) tool, can identify financial errors *a priori* and prevent treatment outside of financial guideline restrictions for anemic cancer patients with CIA, CKD, or MDS.

PARTICIPANT SELECTION CRITERIA:

Inclusion criteria

- All adult patients age 18 years and older with a diagnosis of anemia and cancer (both solid tumors and hematologic malignancies, including MDS)
    - Anemia will be defined as a Hb less than 12 g/dL
- Patients treated at the University of Utah Hospitals and clinics between 2002 - present
- Patients must have received at least 1 dose of an ESA

Exclusion criteria

- Subjects under the age of 18.
- Pregnant women
- Patients who do not have a cancer diagnosis
- Patients with CKD, without a diagnosis of cancer

DESIGN:

Research Methodology

This is a retrospective, un-blinded, single center research study involving patients with cancer and anemia who have been treated with ESAs.

Historical patient demographics to be collected include: DOB, gender, height, and weight. Diagnoses (cancer, anemia, CKD, CIA, MDS, myelofibrosis, bleeding, myeloid malignancy, or hemolytic anemia), chemotherapy received (dates and type, if applicable), intent of chemotherapy (curative or palliative) will also be collected. Historical laboratory data to be collected includes: Hemoglobin (Hb) and hematocrit (Hct), serum ferritin, transferrin saturation (TSAT), serum folate, red blood cell folate, serum vitamin B_{12} and serum creatinine, if available. Data on number and frequency of blood transfusions will also be collected for all patients. Additionally, receipt of IV iron and dose will be recorded when applicable. Lastly, the development of arterial or venous thromboses will be recorded (from radiologic imaging reports) and the date of

occurrence as it relates to ESA therapy. Overall survival will be collected from the date of first ESA administration to death.

IMPLEMENTATION

The Electronic Data Warehouse (EDW) attempted to identify of subjects based on past receipt of erythropoietin, and the diagnosis of cancer or hematologic malignancy. It was given icd-9 codes to narrow the pool. It identified 404 subjects; however, most were not treated for cancer, which made them ineligible for this project. Because there is the black box warning issued with ESAs, the nationally required Apprise system of informed consent was devised to ensure patient education regarding the increased risk of thrombosis when for CIA. These consents collected by the Huntsman Cancer Hospital pharmacy identified an additional 121 subjects who received an ESA for anemia related to chemotherapy. The electronic chart for each individual was accessed to collect the data that is required by the EASI tool to determine ESA dosing per the current KDOKI and NCCN guidelines. The actual treatment decisions on the dates of service were also collected and compared to the recommendations determined by the EASI tool. Originally any patient data after January 2002 was eligible for the study. Because the guidelines became much more stringent in 2008, and thus there were more complete patient records, we narrowed the eligible pool of patients to those treated after 2008 leaving 105 total patients for participation. All project-related data were recorded and saved on password-protected, encrypted devices and drives. The data collection guidelines can be found in appendix C.

There were expected and unanticipated challenges to data collection. As expected, there was little documentation to support clinical decisions when a planned ESA was held. These were missed opportunities to test the tool's ability to identify instances where a dose should have been given or to confirm that the tool correctly identify when to hold a dose. In addition, many patients receive treatment or labs from multiple providers, which was difficult to identify in the electronic record. The biggest and unanticipated challenge was finding the dates where medication was actually delivered. To find dates of treatment a pharmacy database, Pharmnet was able to identify dates when the drug was dispensed.

Evaluation

The objective was to compare the treatments received with the treatments recommended by the EASI tool. Each date of service, encounter, was evaluated for treatment rendered compared to the EASI tool recommendation. When the two groups matched, care was considered to be within the standard of care guidelines; when there was a discrepancy, the care was considered to be out of compliance. The encounters divided into two subgroups for data collection and analysis. The first was encounters to initiate treatment. These first treatments require more information about diagnosis, prognosis and current lab values than does the second subgroup, the return encounters. The percentage of treatments that were given outside the guideline standards was the measurement of efficacy of the tool. In addition, from the treatments differences we calculated the cost difference from the treatment given versus the treatment recommended. This total reflected pharmaceutical cost savings that would have been realized had the EASI tool been available. We did not be considering the cost savings related to provider time.

Results

The EASI tool identified that in 22% of the combined patient encounters treatment was rendered outside the current guideline recommendations. As discussed earlier this represents patients being at higher risk for an adverse event related to the use of ESAs.

The subject pool included 105 of patients were representing a total of 130 visits for initiation of treatment and 294 treatment-related visits for monitoring and/or continuation of therapy. Of the patients evaluated for the initiation of treatment, 40% would not have qualified under current guidelines. The largest disqualifying factor was iron deficiency representing 56% of the total reasons for mismatch. Of note this is 22.3% of all initial assessments for use of ESAs for CIA. The other causes of mismatch included missing initial lab assessment (10.8%), hemoglobin out of range (8.5%), nutritional deficiency (1.5%), hemolysis/non-qualifying diagnosis (0.8%) and dose difference (0.8%). Overlapping criteria for mismatch accounted for 3.1%.

For return patients 14.8% of encounters resulted in treatment when the tool recommended either a hold or a dose reduction of encounters. Hemoglobin out of range

was the major contributor at 12.9% of visits representing 87.2% of mismatches. Non-response to treatment (1.4%) and hyper-response requiring dose reductions (0.4%) accounted for the rest of the mismatches.

Overall, the EASI tool identified treatment outside guideline recommendations in the following categories: 1) Iron deficiencies 2) hemoglobin out of range, 3) non-responder, 4) hyper-responders, 5) disqualifying diagnosis, and, 6) vitamin deficiency. If these doses had been held, there could have been a $140,000 savings according to an average retail value of $1,500 per injection (Epocrates.com). The actual cost of Aranesp according to the pharmacy at the Huntsman Cancer Hospital is closer to $2,300 per dose, which brings the total possible savings to about $197,000 for this cohort of patients from 2008 through 2013.

A manuscript is being prepared for submission to a peer review journal. However, this project team does not want to submit without adding data to support the use of this tool in Myelodysplastic Syndrome and Chronic Kidney Disease. The first of the manuscript without results data can be found in Appendix G.

Recommendations

The ability of this tool to streamline the decision points when prescribing ESA treatment for CIA indicates that other populations that use ESAs might benefit from this tool being adapted to their guidelines. This includes patient populations where disease or medications induce anemia. Clinicians in specialties such as nephrology with CKD, hepatology with chronic hepatitis and immunology with HIV are frequent prescribers of ESAs. The Clinical guidelines and thus the EASI tool force the clinician to evaluate each patient for nutritional deficiencies, iron deficiencies, and kidney function. The EASI tool also reminds the user that these drugs should not be used with certain diagnosis or when there is evidence of hemolysis or bleeding.

The literature search illuminated the emerging importance of iron replacement as the primary consideration for treatment of anemias in conjunction with or as an alternative to ESAs or pRBC transfusion. The EASI tool confirmed that iron deficiency was a concern for about 1/5th of the patients being initiated on treatment in this study. More research needs to be focused on prevalence, identification, and diagnosis of iron deficiency; specifically, functional iron deficiency, which is not commonly understood

according to Gilreath, et al. 2014. This is a diagnosis that might benefit more from iron supplementation rather than ESAs. The EASI tool identifies this group of patients and could be easily adapted to include recommendations for iron replacement.

This study should be expanded to include patients from the Huntsman Cancer Hospital who received ESAs for Myelodysplastic Syndrome (MDS) and Chronic Kidney Disease (CKD). In these diseases, the return patients take a more consistent and predictable path, which would allow for better assessment of the tool in ongoing treatment. More testing is needed to assess the EASI tool's ability to identify non-responders and hyper-responders. This data and results would strengthen the utility of the EASI tool and should be added before the manuscript is submitted.

Discussion

As anticipated from the literature review, clinicians' use of ESAs has dropped severely since 2008. The drop in use is not likely due to there being fewer of these patients having anemia, as there is evidence of increased usage of transfusion in the cancer populations, (Vekeman, et al., 2009). As cancer survival increases and is treated more like a chronic illness, there will be a growing number of patients with anemia and fatigue. The use of ESA's allows for maintenance of a higher hemoglobin, (although still well below normal), which can improve quality of life.

Shortcomings for this study include the subject selection process, which yielded a narrow pool of diagnoses. The majority of recipients of ESAs in this study were focused in the Multiple Myeloma/ Bone Marrow Transplant clinics and the Kidney Transplant clinic. This limitation to a single institution with a subset of patients vs. multiple sites could be viewed as a threat to external validity for this tool. Being that the EASI tool is based on industry-wide guidelines, the threat to external validity is an opportunity to involve more institutions to trial the tool. The results, as they are, confirm that the tool identifies the clinical guidelines created by the NCCN and the NKF, which are the same guidelines that drive reimbursement for treatment by CMS.

Conclusions

The EASI tool was able to assess appropriateness of ESA therapy for 105 patients with a total of 394 encounters assessed. Because of the intricacies involved

with ensuring patient safety when initiating ESA treatment and also with continued treatment and monitoring, this EASI tool offers a streamlined approach to aide clinicians in prescribing and monitoring these medications.

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