AN ASSESSMENT OF THE USE OF ERYTHROPOIETIN STIMULATING AGENTS IN KENYATTA NATIONAL HOSPITAL

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A research dissertation submitted in partial fulfillment of the requirements for the award of a Bachelor's degree in Pharmacy from the University of Nairobi.

DECLARATION

The research dissertation is my original idea and to the best of my knowledge has not been presented elsewhere for project work.

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Signature: .....

Date: 17/10/2012

The research dissertation has been submitted for evaluation for research and examination with our approval.

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ACKNOWLEDGEMENT

I would like give my regards to Dr. N. Nyamweya for the guidance and support so far in my project development.

Special thanks to Dr. I. Weru, Senior Pharmacist in KNH, for taking her time to guide me and ensure that my project is at its level best with her diversity of opinions.

Many thanks to my family and friends for the endless support and help whenever I got stuck at some point.

Above all, I thank God for giving me the strength and endurance to finish my project to the end.

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LIST OF ABBREVIATIONS

ACE-I – Acteylcholinestarase Inhibitor

CERA – Continuous Erythropoietin Receptor Activator

EPOR – Erythropoietin Receptor

ESA – Erythropoietin Stimulating Agents

KNH – Kenyatta National Hospital

RBC – Red Blood Cell

EPO – Erythropoietin

ADME – Absorption, Distribution, Metabolism, Excretion

Hb – Hemoglobin

ABSTRACT

Background: Erythropoietin Stimulating Agents (ESAs) provide relief and decrease blood transfusion support among patients with anemia induced by chronic renal failure and cancer chemotherapy. However, there is risk of cardiovascular and thrombovascular events occurring in the course of treatment.

Objective: This study will seek to find out whether recommendations set out in Clinical Oncology Practice Guidelines are followed at Kenyatta National Hospital (KNH) and what monitoring parameters are considered in patients receiving ESAs.

Method: The study design will be hospital based descriptive retrospective study in which medical record files of patients to whom ESAs were dispensed from Kenyatta National Hospital Main pharmacy and inpatient pharmacies between January 2011 and December 2011 will be evaluated. The study variables will include patient demographics, diagnosis, indication for use of ESAs, the dosage, frequency, duration of therapy, laboratory parameters including Hb level and time to reach target Hb. Data collected will be analyzed and summarized using tables, graphs and summary statistics.

Intended use of results: It is hoped that the findings from this study will be used to improve the use of ESAs at KNH in order to achieve maximum benefit to the patients. The results will also be useful in developing an institutional protocol for the use of ESAs.

Results: The studies have shown that the use of erythropoietin in KNH is predominantly in renal patients (95.93%) and a very small percentage use in oncology (4.07%). It has enabled us to settle on a conclusion over the debate on whether ESAs are used rationally or irrationally. It is used irrationally due to poor patient monitoring and follow up. Further work needs to be done to improve on the use.

INTRODUCTION AND LITERATURE REVIEW

The physiological function of erythropoietin is quite significant in the body. It binds to erythropoietin receptors (EPOR), initiating signaling that stimulates growth, inhibits apoptosis, and induces the differentiation of erythroid progenitors to increase red blood cell mass. Erythropoietin has additionally been shown to exert tissue-protective effects on multiple tissues, suggesting a pleiotropic mechanism of action.

ESAs are used to treat symptomatic anemia associated with erythropoietin deficiency in chronic renal failure to increase the yield of autologous blood in normal individuals and to shorten the period of symptomatic anemia in patients receiving cytotoxic chemotherapy.

The various types of erythropoietin used include darbepoetinalfa, epoetinalfa and beta and methoxy polyethylene glycol-epoetin beta. The most commonly used ones are epotinalfa and darbepoetinalfa. Recommendations for their use is that patients undergoing myelosuppressive chemotherapy who have a hemoglobin (Hb) level less than 10 g/100ml, the American Society of Hematology and the American Society of Clinical Oncology Practice Guideline Update Committee recommends that clinicians discuss potential harms (eg, thromboembolism, shorter survival) and benefits (e.g., decreased transfusions) of ESAs and compare these with potential harms (e.g., serious infections, immune-mediated adverse reactions) and benefits (e.g., rapid Hb improvement) of RBC transfusions[i].

The major benefits of ESAs are their ability to significantly raise the hemoglobin levels and reduce transfusion risks. These benefits have shown to improve functional status, productivity and quality of life of patients[ii]. However, the major disadvantage is that they are very expensive.

Among the risks associated with ESAs are thrombosis, pure red cell aplasia, hypertensive encephalopathy, seizures and high blood pressure in 30% of the patients. The majority of the complications are associated with Hb concentrations greater than 12g/100ml. Another risk related to ESAs is the potential of increased mortality and tumor progression as observed in patients with advanced breast, head and neck, lymphoid and non-small-cell cancer[iii].

In order to avoid such risks and complication, the following factors need to be considered:

- Patients should not be treated with erythropoietin unless symptoms of anemia are present.
- The hemoglobin concentration should be maintained within the range 10-12g/100ml.
- Hemoglobin concentrations higher than 12g/100ml should be avoided.
- The aim of treatment should be to relieve symptoms of anemia in order to avoid blood transfusion and improvement of quality of life[iv].

Starting doses and dose modifications after response or non-response should follow US Food and Drug Administration-approved labeling. ESAs should be discontinued after 6 to 8 weeks in non-responders[iii].

Chemotherapy-induced anemia is a form of anemia that results from direct effect of cytotoxic agents on hematopoiesis including the red blood cells precursors in bone marrow or renal function. When administered for a long period of time causes renal dysfunction which progressively leads to decreased production of erythropoietin by the renal system thus reduced RBC production.

Chemotherapy may also impair erythropoiesis through gradual damage of stem cells in the bone marrow. Most cytotoxics induce stem cell impairment that last for as long as 3 years after treatment. This stem cell impairment may last much longer in patient treated with more potent myelosuppresive agents or those who have undergone high dose chemotherapy or radiotherapy to the marrow compartment.

A steady increase in rate and severity of anemia is observed with additional chemotherapy cycles due to accumulation of cytotoxic agents.

Anemia can lead to multiple symptoms such as fatigue, dyspnoea, dizziness, tachycardia, cognitive impairment and depression. It may also lead to adverse conditions such as cardiac and pulmonary impairment. The patients complain of dyspnoea on exertion and chronic fatigue thus impairs the patient's ability to perform daily activities[v].

Presence of anemia in cancer patients increases the risk of death and shortens their survival time than those who lack anemia. Tumor hypoxia resulting from reduced oxygen carrying capacity of blood has been hypothesized to be the major cause of reduced survival. It also reduces effectiveness of chemotherapy and radiotherapy thus leading to tumor progression.

Current treatment options include packed red blood cell transfusion, erythropoietin stimulating agents and iron supplements.

Chronic renal failure is a long standing and usually progressive impairment in renal functions. In several instances, no effective means are available to reverse the primary disease process. One of the major adverse effects is anemia which is presented by dyspnoea, dizziness, cardiac and pulmonary impairment.

Anemia is usually present in majority of the chronic renal failure patient. The factors that precipitate anemia include:Erythropoietin deficiency, increased blood loss, bone marrow fibrosis secondary to hyperparathyroidism, bone marrow toxins retained in renal failure, increased RBC destruction and the use of ACE inhibitors probably by interfering with the control of endogenous erythropoietin release.

Due to these multifactorial causes, management of anemia should be initiated as soon as the signs are observed. The replacement therapy of erythropoietin starting dose is 25-50 IU/kg three times a week.

In chronic renal failure therapy, newer experimental data suggest that long-term benefits of recombinant human erythropoietin could be due not only to antianemic effect, but also to a direct organoprotective effect of (rHu)-Epo mediated through a receptor complex different from the "erythropoietic" erythropoietin receptor. During the last decade, two alternative treatments for renal anemia have been approved: darbepoetin and CERA. Both are direct agonists of the "erythropoietic" receptors and both were derived from rHu-Epo[vi].

Molecularly, they differ from rHu-Epo in that they are much larger molecules (darbepoetin is genetically modified rHu-Epo with a higher sugar content and CERA is pegylatedrHu-Epo) with lower affinity for the erythropoietin receptor but with a longer circulating time. In terms of renal anemia correction, they are non-inferior to rHu-Epo and allow for less frequent dosing. They have never been compared to rHu-Epo regarding the long-term outcomes.

Future studies must take this into account (particularly the avoidance of transfusions) post chemotherapy. To quantify the impact of ESA therapy on transfusion avoidance, post chemotherapy trials need to continually consider the risks and benefits of supportive care therapy. Administrators should work closely with clinicians to determine the appropriate course of action to help ensure that patients receive the best possible care as new data and guideline updates emerge[vii].

JUSTIFICATION

The use of erythropoietin stimulating agents is important since its aim is to improve the functional status, productivity and quality of life of patients suffering from anemia induced by chemotherapy and chronic renal failure.

Erythropoietin is used in an effort to reduce the need and risks of blood transfusion. It has also shown to increase the Hb levels significantly in a short period of time thus alienate the symptoms associated with anemia.

If used irrationally, ESAs will increase risk of adverse effects to the patients and increased cost of treatment for a patient population whose cost of treatment is already unbearable.

This study will seek to find out whether recommendations set out in Clinical Oncology Practice Guidelines are followed at Kenyatta National Hospital and what monitoring parameters are considered in patients receiving ESAs.

Based on informal discussions, patients at KNH may be continued on ESAs for over 8 weeks even if they are non responders. It is also possible that there are some off-label uses of ESAs including prophylaxis for anemia in patients receiving radiotherapy. This study will therefore seek to discuss the overall use of ESAs at KNH, the safety issues that need to be considered and stimulate debate on the use of ESAs, rational or otherwise. Hopefully, this study will aid in the review and update of available guidelines on the use of ESAs at Kenyatta National Hospital.

OBJECTIVES

Broad objective

To evaluate the use of Erythropoietin Stimulating Agents in patients with chronic renal failure and cancer at Kenyatta National Hospital.

Specific objectives

- To describe the patient population for which erythropoietin is prescribed.
- To determine dose, frequency and duration of treatment with ESAs.
- To describe the factors contributing to change of dose or discontinuation of therapy with ESAs.
- To describe the mean hemoglobin initiation level and the average hemoglobin level at discontinuation of therapy with ESAs.
- To list any adverse effects observed with the use of ESAs.

METHODOLOGY

Study design
The study design was a hospital based descriptive retrospective study in which medical record files of patients to whom the ESAs were dispensed from Kenyatta National Hospital Main Pharmacy and Inpatient Pharmacies between January 2011 and December 2011 were evaluated.

Study area
The study was conducted in Kenyatta National Hospital which had a well attended outpatient and inpatient clinics. I was able to observe that it is also the largest referral hospital with specialized renal and oncology services.

Study population
The study population was conducted in patients of all age groups.

Inclusion criteria
i. Patients receiving erythropoietin stimulating agents.
ii. Patients dispensed to ESAs between January 2011 and December 2011.

Exclusion criteria
i. Patients not receiving erythropoietin stimulating agents.
ii. Patients who completed treatment with ESAs before January 2011.
iii. Patients whose medical records lacked the required information.

Sampling and Sample size
Universal sampling was used for all patients who received ESAs between January 2011 and December 2011. Estimates from the Main Pharmacy indicated that the average monthly consumption of ESAs from January 2011 to December 2011 was 180 syringes. Assuming that each patient received the medication at least twice a week for 4 weeks a month, the estimated number of patients was 22 patients per month.

Data collection and materials
Data was collected and entered into the predesigned data collection form (Appendix 1). Information collected included: the patient demographics, diagnosis, indication for use of erythropoietin, the dosage, frequency, duration of therapy, laboratory parameters including Hb level and time to reach target Hb.

Data analysis
The raw data was entered and analyzed using Microsoft Excel Software. The data was presented using graphs, pie charts and summarized statistics. The average starting Hb and target Hb was calculated.

Data handling
The raw data was kept under lock and key by the investigator for the entire duration of the study including the examination period after which the hard copies were shredded. All the data was entered in Microsoft Excel Software and was password protected on the investigator and supervisors computers. The data will be stored in this manner for possible use during publishing and presentation at scientific meetings.

Study limitations

This was a retrospective study therefore relying on pre-recorded data that may be incomplete or missing. This was overcome by reviewing a substantial number of files and by effectively utilizing the data available in making any conclusions and recommendations.

Ethical consideration

Permission to carry out the research was sought from the KNH/UoN ethics and research committee before the project was carried out. Patient names will not be used on the data collection forms. Instead, code numbers will be assigned to each patient.

Intended use of results

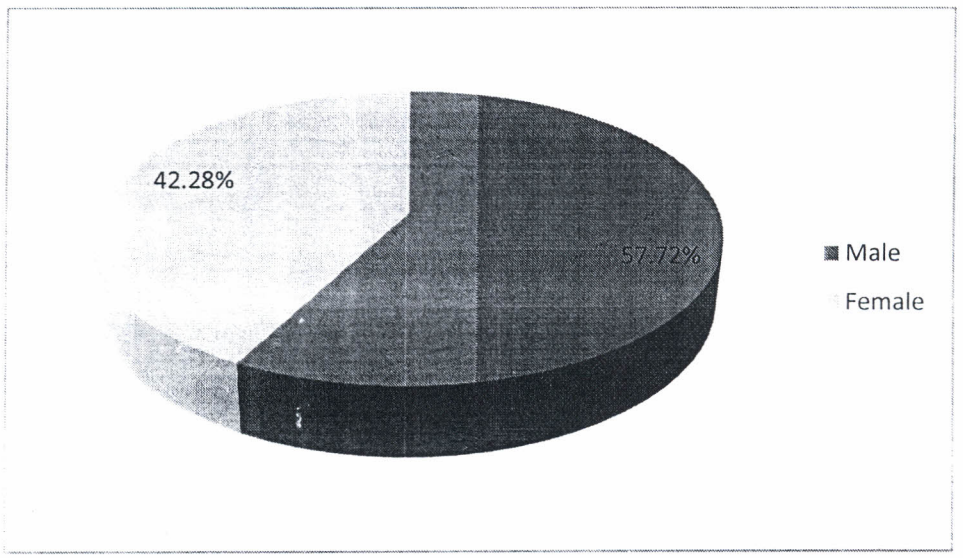
It is hoped that the findings of this study will be used to improve the use of ESAs at KNH in order to achieve maximum benefits to the patients. The results will also be useful in developing an institutional protocol for the use of ESAs.

DATA ANALYSIS

Patient Population

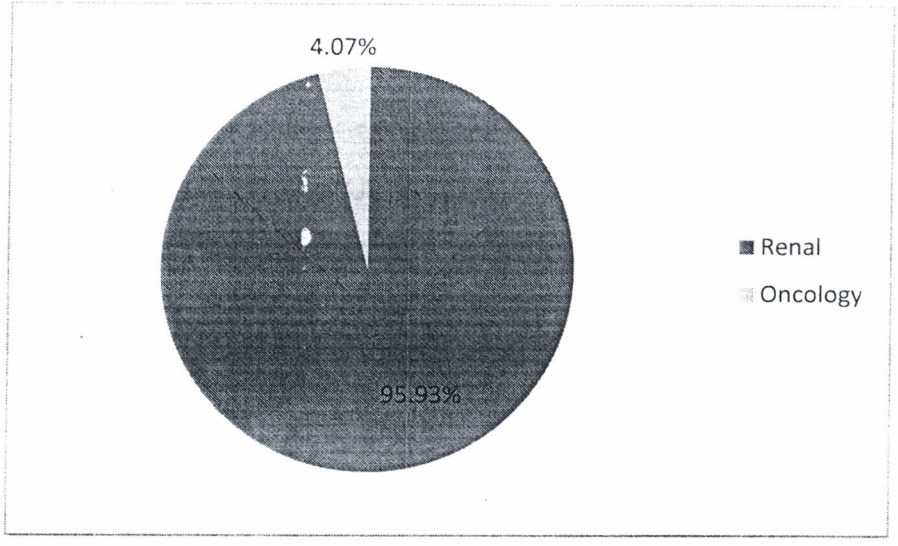
A total of 123 files were retrieved from the medical records and assessed between January 2011 and December 2011. The findings showed that the patients receiving Erythropoietin were 71 males and 52 females. Only 123 files out of the speculated 250 files were retrieved. Failure to attain the targeted patient population was due to missing files at the medical records, files currently being used at the medical wards and deceased patient files. The results were presented in a pie chart.

Figure 1: Patient population for which Erythropoietin was prescribed



The findings also showed that the patient population receiving Erythropoietin were 95.93% renal patients and 4.07% oncology patients. There were no other off-label uses observed.

Figure 2: Condition of patients on Erythropoietin



From the collected data, it was also observed that all the renal patients on erythropoietin therapy were on hemodialysis twice or thrice weekly. The oncology patients were all on chemotherapy at the moment of EPO therapy.

The oncology patients on erythropoietin therapy had the following cancer conditions:

Table 1

Condition	Number of patients
Prostate cancer	2
Cervical cancer	2
Breast cancer	1

Dose, Frequency and Duration of treatment with ESAs

The type of Erythropoietin used in KNH was Recormon. The findings from the medical files showed that all patients were on Recormon 2000IU twice weekly. The duration of treatment was not generalized. It varied depending on the patient response to therapy.

Table 2

Dose	**Frequency**	**Route of administration**
2000 IU	Twice weekly	Subcutaneously

Factors contributing to change of dose or discontinuation of therapy with ESAs.

The information was not clearly indicated in the patient files. It therefore raised the need to retrieve the information from the medical practitioners in the various wards. The main reasons for change or discontinuation of therapy were:

- Attainment of the required Hb levels thus preventing overtreatment of the patients.
- Patient financial constraint
- Pregnancy and child lactation in female patients
- Failure to respond to drug therapy after long duration of treatment
- Uncontrolled hypertension during treatment
- Clinical signs of pure red cell aplacia
- Hypersensitivity reactions
- Poor quality drugs thus resorting to blood transfusion instead

Mean hemoglobin level at initiation and discontinuation of therapy.

The mean hemoglobin level at initiation of therapy was found to be 7.5 g/dl while the average hemoglobin level at discontinuation of therapy was found to be 12.0 g/dl. According to the references, the Hb levels were attained within the speculated range and the level for initiation of therapy was also below 10.0 g/dl [iv]. Hb levels greater than 13.0 g/dl have shown to increase incidences of thromboembolism and increased blood pressure in patients using this drug [iii].

Adverse effects

Information on the adverse reactions was not recorded in the patient files.

DISCUSSION

The number of patients who were dispensed to erythropoietin according to the prescription register between January 2011 and December 2011 were about 240. Only 123 files were retrieved from the medical record. The study findings thus showed that the patients receiving erythropoietin were 57.72% males and 42.28% females (Table 1).

Out of these patients, 95.93% were chronic renal failure patients while only 4.07% were oncology patients (Table 2). This clearly indicated that the use of erythropoietin in oncology department has not been fully established. Information from the doctors in the oncology ward showed that its use has not been fully established since their biggest worry during chemotherapy is the reduction in the white blood cell count. After a debate late last year over the use of this drug, it was agreed upon by the practitioners that the best way to manage anemia in chemotherapy was blood transfusion. It involved less patient monitoring and reduced medical costs. They also argued that erythropoietin stimulation for a long period of time was not advisable since apart from quickly raising the Hb level, it causes a destabilization in the erythropoietin hormone balance. This led them to rule out its use.

The findings also showed that all the renal patients were on hemodialysis at the time of erythropoietin therapy. However, an increase in heparin dose during hemodialysis is frequently required during the course of therapy with Erythropoietin as a result of the increased Hb. Occlusion of the dialysis system is possible if heparinization is not optimal[viii]. Constant monitoring of blood pressure was also necessary.

The findings showed that the dose given was standard in all the patients (2000IU). According to the guidelines, treatment with Recormon is divided into two stages.

- Correction phase

- Subcutaneous administration (all dosage forms):

The initial dosage is 3 x 20 IU/kg body weight per week. The dosage may be increased every 4 weeks by 3 x 20 IU/kg per week if the increase of Hb is not adequate.
The weekly dose can also be divided into daily doses.

- Intravenous administration (powder and solvent for solution for injection and pre-filled syringes only):

The initial dosage is 3 x 40 IU/kg per week. The dosage may be raised after 4 weeks to 80 IU/kg - three times per week - and by further increments of 20 IU/kg if needed, three times per week, at monthly intervals.
For both routes of administration, the maximum dose should not exceed 720 IU/kg per week.

- Maintenance phase

To maintain a target Hb value of approximately 10-12 g/dl, the dosage is initially reduced to half of the previously administered amount. Subsequently, the dose is adjusted at intervals of two to four weeks individually for the patient (maintenance dose) [viii].

This indicates that there is poor erythropoietin dosing and monitoring in KNH which was attributed to various factors:

- There are few medical personnel enough to handle the large number of renal patients on hemodialysis, to carry out lab monitoring, patient care and record keeping.
- Some patients go back home with their lab results thus lack of reference in the files.
- Poor quality of the drugs with reduced potency leading to long duration of therapy.

The adverse drug reactions are not seriously monitored in KNH. A lot of adverse reactions data is missing in the medical files, thus raising the need to check out information from previous studies.

Anemic patients due to chronic kidney disease

The most frequent adverse drug reactions (common 1-10%), in particular during the early treatment phase with Recormon are hypertensive events including hypertension, hypertensive crisis with or without encephalopathy-like symptoms(e.g. headaches and confused state, sensorimotor disorders - such as speech disturbance or impaired gait - up to tonoclonic seizures). This increase in blood pressure can occur in normotensive patients or can be an aggravation of existing hypertension.

Shunt thromboses may occur, especially in patients who have a tendency to hypotension or whose arteriovenous fistulae exhibit complications (e.g. stenoses, aneurisms). In most cases, a fall in serum ferritin values simultaneous with a rise in Hb is observed. In addition, transient increases in serum potassium and phosphate levels have been observed in isolated cases [viii].

Cancer patients receiving chemotherapy with symptomatic anemia

Hypertensive events are common (1-10%) adverse drug reactions, in particular during the early phase of treatment.

In some patients, a fall in serum iron parameters is observed.

Clinical studies have shown a higher frequency of thromboembolic events in cancer patients treated with Recormon compared to untreated controls or placebo. In patients treated with Recormon, this incidence is 7 % compared to 4 % in controls. This is not associated with any increase in thromboembolic mortality compared with controls [viii].

CONCLUSION

The studies have shown that the use of erythropoietin in KNH is predominantly in renal patients (95.93%) and a very small percentage use in oncology (4.07%). It has also shown that other off-label uses are not incorporated in the institution. More male patients are on erythropoietin than the females.

There is a lot that needs to be improved concerning drug dosing and monitoring of Hb levels when patient is in treatment. The adverse drug reactions experienced by the patients were also not clearly recorded.

This study has enabled us to settle on a conclusion over the debate on whether ESAs are used rationally or irrationally. It is used irrationally due to poor patient monitoring and follow up. Further work needs to be done to improve on the use. Hopefully, this study will aid in review and update of available guidelines on the use of ESAs in Kenyatta National Hospital.

RECOMMENDATIONS

The findings have shown that ESAs are irrationally used in KNH. The following recommendations will hopefully help improve on their use and incorporate more use of it in other fields of medicine.

1. Improvement on the monitoring and follow up on the Hb levels and adverse drug reactions.
2. Educate other medical practitioners on the advantages of use of ESAs as compared to giving blood transfusion, with proper patient monitoring.
3. Ensure proper storage of the drug in cold temperatures to ensure maintenance of potency and efficacy of drug.
4. Proper record keeping for easier follows up and research studies.
5. Employment of more medical staff to suffice the high number of patients thus proper distribution of responsibilities.
6. Provide affordable medications for the patients since most of them are already going through other expensive therapies e.g. hemodialysis, chemotherapy.
7. Improve and increase the lab monitoring facilities and personnel for easier blood picture analysis.

APPENDICES

Appendix 1: Data Collection Tool

PATIENT DEMOGRAPHIC INFORMATION
Patient code: .....Age: .....Sex: .....
Weight: ..... Height: ..... BMI: .....

DIAGNOSIS
Type of condition.....
Age of patient at time of diagnosis.....

THERAPIES INITIATED PRIOR TO ESAs USE.

- Chemotherapy

Type used.....Duration of use.....

- Radiotherapy

Type used.....Duration of use.....

- Renal therapy

Type used.....Duration of use.....
Other renal therapies.....
Duration of therapies.. .....

THERAPIES INITIATED CONCURRENTLY WITH ESAs.

- Chemotherapy

Type used.....Duration of use.....

- Radiotherapy

Type used.....Duration of use.....

- Renal therapy

Type used.....Duration of use.....
Other renal therapies.....
Duration of therapies.....

TYPE, DOSE, FREQUENCY AND DURATION OF THERAPY
Type of ESA used.....
Dose .....
Dose frequency .....
Duration of therapy .....

LAB PARAMETERS

Hb level at initiation of therapy .....

Hb level during therapy .....

Hb level at the end of therapy.....

Blood pressure at initiation of therapy.....

Blood pressure at the end of therapy.....

Weight at initiation of therapy.....

Weight at end of therapy.....

FACTORS CONTRIBUTING TO CHANGE IN DOSE OR DISCONTINUATION OF DRUG

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MAJOR ADVERSE EFFECTS

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Appendix 2: Work Plan

Activity	March	April	May	June	July	August
Selection of topic and pre-writing of proposal						
Consultation and revision						
Preparation and final draft						
Ethical submission and approval						
Data collection						
Data analysis and interpretation						
Report writing						
Submission of the final draft						

Appendix 3: Budget

Budget Item	Cost (KShs)
Ethics Committee Fees	200
Printing and Binding	2000
Data collection forms	2500
Data entry and Analysis	10,000
Total	**14,700**

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