Purpose:

1. The primary endpoint of the study would be to determine the safety of dalteparin as prophylaxis against deep venous thrombosis (DVT) in orthopaedic oncology patients. Specifically, the goal of the study is to determine whether there are significantly increased bleeding complications at the surgical site after major oncologic operations in the lower extremity.

    a. The study would help establish specific parameters for use of dalteparin in complex orthopaedic oncology patients. Not all patients would be appropriate for this medication, particularly those with massive hemorrhage during surgery and those with underlying coagulopathies.
    b. It is likely that patients requiring limited tumor excision, particularly those with metastatic carcinoma, would be ideal candidates for dalteparin therapy.
    c. Patients who require radical resections of tumor may need stricter guidelines for the safe use of the medication, since the potential for post-operative bleeding may be greater.

Hypotheses:

1. Dalteparin may be used safely in complex group of patients such as orthopaedic oncology patients, provided that strict guidelines are followed with regard to indications for therapy.

2. Patents with metastatic carcinoma affecting the osseous skeleton would be good candidates for treatment since they generally have limited surgical resections and a pre-disposition to formation of DVTs.

3. The use of dalteparin would result in a low rate of DVTs that would compare favorably against historical controls.

Introduction:

It is well recognized that patients undergoing orthopaedic procedures such as total knee replacements and total hip replacements, are at increased risk of venous thrombo-embolic events.[1, 2] It is also known that cancer patients are at increased risk of venous thrombosis.[3-5] There have been little written about venous thrombosis in cancer patients undergoing major resections and orthopaedic procedures in the lower extremities. It is not well documented in the literature what the prevalence and extent of the problem is.

The largest previous study was performed at Memorial Sloan-Kettering Cancer Center. This study focused on the role of mechanical compression boots in orthopaedic oncology patients.[6] As expected, there is a high rate of proximal DVT's in the thigh even with mechanical prophylaxis (17%). This study did not address the potential use of low molecular weight heparins or other forms of anti-coagulation. Preliminary results from a

follow-up study recently presented at the Musculoskeletal Tumor Society Meeting showed promising results with the use of dalteparin and a significant reduction in the DVT rate.[7]

Although it would be preferable to improve the prophylaxis in this production, there is general concern among surgeons that the risk of bleeding would be high. Many of the patients undergo prolonged operations with substantial blood loss. These patients are somewhat coagulopathic immediately following surgery. In addition, there is often a large potential dead space for the accumulation of a hematoma. As a result, most surgeons do not use low molecular weight heparins or chemical anti-coagulation routinely following such operations. The current standard of care is still TED hose and mechanical compression stockings.

Dalteparin is a low-molecular weight heparin (LMWH) that has been shown to be effective as prophylaxis for deep venous thrombosis.[8] It was the second LMWH approved by the FDA for this indication, and the medication has been used widely in orthopaedic patients, particularly those undergoing hip and knee replacement. As a group, LMWHs are considered superior to unfractionated heparin in terms of bioavailability, longer half-lives, more predictable therapeutic response, and safety.[9] In one meta-analysis of total hip arthroplasty, LMWHs were noted to result in significantly less major bleeding complications compared to unfractionated heparin.[1] There are relatively few studies comparing dalteparin against other LMWHs such as enoxaparin, with regard to efficacy and bleeding complications. In one retrospective study on prophylaxis in hip and knee replacement dalteparin appeared to have a slightly lower bleeding complication rate and comparable DVT rate.[10] In another study, a prospective randomized trial was performed in patients with spinal cord injury. There was no statistically significant difference in rates of DVT or bleeding complications.[11] Similar findings were reported in another randomized trial in hip fracture patients.[12]

In spite of surgeons' concerns, it is reasonable to postulate that given the favorable safety profile of dalteparin, it can be used in this study population. The key to using the medication would be to establish firm criteria for the safe use of the drug.

The hypothesis is that the drug is safe for the patient population identified in this study. Most of the published safety data on the drug pertains to general orthopaedic patients and not to orthopaedic oncology patients. This study is intended to provide preliminary data on benefits and risks for orthopaedic oncology patients.

Orthopaedic oncology encompasses a wide array of patients. Some patients are healthy and normal except for their tumor. Other patients may be moribund with multiple co-morbidities. Some patients require a relatively small procedure to remove the tumor, while others require massive resections and reconstructions. The risk of post-operative bleeding complications for these patients would be expected to vary considerably.

As the first step toward establishing the use of dalteparin in orthopaedic oncology patients, it is proposed that two target populations be studied. One group of patients is

comprised of those with metastatic disease in the lower extremity. The other group of patients is composed of those who require major resection of sarcomas of the lower extremity.

The two groups of patients are inherently different. The patients with metastatic disease of the lower extremity are an important group since they encompass a large population of patients. These patients are believed to be at the highest risk for DVT. They tend to be older, more sedentary, less mobile, and have multiple c-morbid conditions. These patients may be ideal candidates for treatments with dalteparin. The patients typically undergo a limited excision or curettage followed by an intramedullary rod, plating, cementation, hip arthroplasty or knee arthroplasty. The patients typically do not have much post-operative bleeding or drainage, since the skeletal defect is filled with bone cement. There is typically no significant dead space after surgery in which a large hematoma or seroma could form.

The patients with large primary sarcomas form a more challenging group. These patients typically require major resections and reconstructions that could last 6 – 8 hours or more. The potential for intra-operative and post-operative bleeding is greater. A larger, potential soft tissue cavity is often present after removal of large portions of muscles. Post-operative drainage through surgical drains often persists for 2 weeks or longer. There is generally a much greater reluctance on the part of orthopaedic oncologist to treat such patients with low-molecular weight heparins.

It is proposed that strict guidelines be established for the use of dalteparin in this second group of patients. In the initial safety study, patients should be chosen that pose a moderate risk in terms of post-operative bleeding. Patients who have extremely large tumors or those who become coagulopathic during surgery as a result of massive hemorrhage ought to be excluded. Patients with superficial and small T1 (< 5 cm) tumors will also be excluded, since the soft tissue concerns are minimal in such patients. The goal is to establish the safe use of dalteparin in the moderate risk group first. This would become the starting point for a subsequent study on managing DVT risk in the patients at higher risk for complications.

It is important to note that the underlying DVT rate in the pre-operative population is not well-established. It is reasonable to hypothesize that there is a substantial rate of pre-existing DVTs in patients with skeletal tumors. However, there are currently no guidelines with regard to screening of such patients. Pre-operative Doppler ultrasound examinations are not yet considered to be standard of care. If a substantial rate of DVTs is found, then a compelling case may be made for not just pre-operative DVT screening, but also regular routine screening of cancer patients.

It is well recognized that duplex Doppler ultrasound does not detect all DVTs. It is most suited to detecting 95 – 100%.[13] However, in well-controlled studies, the sensitivity is less, approximately 80%, and this may depend in part upon the experience of the ultrasonographer. Venography is still considered superior in terms of sensitivity. The

disadvantages of Venography include invasiveness, difficulty in studying patients with fractures, and a small risk of adverse reaction to intravenous dye. The risk of a non-invasive doppler ultrasound study is negligible. The primary intent of the current safety study is to assess risk of prophylaxis with regard to bleeding complications in the wound as opposed to determining the absolute rate of DVT formation in the leg. The safety and ease of duplex doppler ultrasound study make it suitable as the method for detecting DVTs in this study.

This safety study is really part of an effort to develop a rational, comprehensive plan for management of DVT risk in a heterogeneous population of patients. An important part of the management algorithm is screening for DVT in high risk groups. Another important part of the management is developing different strategies for different types of patients. The initial phase of the study is geared towards establishing preliminary data on underlying rates of DVT, establishing the safe and effective use of dalteparin in certain patients with metastatic disease, and testing the safety of dalteparin in a subset of patients undergoing major sarcoma resections.

Background Drug Information for Dalteparin[14]

Use
Prevention of deep vein thrombosis which may lead to pulmonary embolism, in patients requiring abdominal surgery who are at risk for thromboembolism complications (i.e., patients >40 years of age, obese, patients with malignancy, history of deep vein thrombosis or pulmonary embolism, and surgical procedures requiring general anesthesia and lasting longer than 30 minutes).

Contraindications
Hypersensitivity to dalteparin or any component of the formulation; thrombocytopenia associated with a positive *in vitro* test for antiplatelet antibodies in the presence of dalteparin; hypersensitivity to heparin or pork products; patients with active major bleeding; patients with unstable angina or non-Q-wave MI undergoing regional anesthesia; not for I.M. or I.V. use.

Warnings/Precautions
Patients with recent or anticipated neuraxial anesthesia (epidural or spinal anesthesia) are at risk of spinal or epidural hematoma and subsequent paralysis.

Consider risk versus benefit prior to neuraxial anesthesia. Risk is increased by concomitant agents which may alter hemostasis, as well as traumatic or repeated epidural or spinal puncture. Patient should be observed closely for bleeding if dalteparin is administered during or immediately following diagnostic lumbar puncture, epidural anesthesia, or spinal anesthesia.

Not to be used interchangeable (unit for unit) with heparin or any other low molecular weight heparins. Use with caution in patients with known hypersensitivity to

methylparaben or propylparaben. Use with caution in patients with history of heparin-induced thrombocytopenia. Monitor patient closely for signs or symptoms of bleeding. Certain patients are at increased risk of bleeding. Risk factors include bacterial endocarditis; congenital or acquired bleeding disorders; active ulcerative or angiodysplastic GI diseases; severe uncontrolled hypertension; hemorrhagic stroke; or use shortly after brain, spinal, or ophthalmology surgery; in patients treated concomitantly with platelet inhibitors; recent GI bleeding; thrombocytopenia or platelet defects; severe liver disease; hypertensive or diabetic retinopathy; or in patients undergoing invasive procedures. Use with caution in patients with severe renal failure (has not been studied). Safety and efficacy in pediatric patients have not been established. Rare cases of thrombocytopenia with thrombosis have occurred. Multidose vials contain benzyl alcohol and should not be used in pregnant women. Heparin can cause hyperkalemia by affecting aldosterone. Similar reactions could occur with LMWHs. Monitor for hyperkalemia.

Adverse Reactions

1% to 10%

Hematologic: Bleeding (3% to 5%), wound hematoma (0.1% to 3%)

Local: Pain at injection site (up to 12%), injection site hematoma (0.2% to 7%)

<1% (Limited to important or life-threatening):

Thrombocytopenia (including heparin-induced thrombocytopenia), allergic reaction (fever, pruritus, rash, injections site reaction, bullous eruption), anaphylactoid reaction, operative site bleeding, gastrointestinal bleeding, skin necrosis. Spinal or epidural hematomas can occur following neuraxial anesthesia or spinal puncture, resulting in paralysis. Risk is increased in patients with indwelling epidural catheters or concomitant use of other drugs affecting hemostasis.

Drug Interactions

Drugs which affect platelet function (e.g., aspirin, NSAIDs, dipyridamole, ticlopidine, clopidogrel) may potentiate the risk of hemorrhage.

Thrombolytic agents increase the risk hemorrhage.

Warfarin: Risk of bleeding may be increased during concurrent therapy. Dalteparin is commonly continued during the initiation of warfarin therapy to assure anticoagulation and to protect against possible transient hypercoagulability.

Ethanol/Nutrition/Herb Interactions

Herb/Nutraceutical: Avoid cat's claw, dong quai, evening primrose, garlic, ginseng (all have additional antiplatelet activity).

Pharmacodynamics/Kinetics

Onset of action: 1 – 2 hours

Duration: >12 hours

Half-life elimination (route dependent): 2 – 5 hours

Time to peak, serum: 4 hours

Dosage

Adults: SubQ: 2500 units 1 – 2 hours prior to surgery, then once daily for 5 – 10 days postoperatively.

Monitoring Parameters

Periodic CBC including platelet count; stool occult blood tests (if clinically indicated with signs of gastrointestinal bleeding such as melena, vomiting of coffee grounds, abdominal pain, sudden drop of hemoglobin); monitoring of PT and PTT is not necessary.

Administration

Administration once daily beginning prior to surgery and continuing 5 – 10 days after surgery prevents deep vein thrombosis in patients at risk for thromboembolic complications.

Additional Information

Molecular weight: 5000; sulfur content: 11%

Dosage Forms

Injection:

Prefilled syringe: Anti-Factor Xa 2500 units per 0.2 mL; Anti-Factor Xa 5000 units per 0.2 mL

Multidose vial: 95,000 units anti-Factor Xa/Vial (9.5 mL vial) = 10,000 units/mL

Materials and Methods:

Patients

There will be two study groups:

Group A. Metastatic disease in the lower extremity requiring limited excision (curettage) of tumor as part of surgical treatment. Inclusion criteria would include all of the following:

1. Metastatic disease, myeloma, or lymphoma.
2. Pathologic fracture or impending pathologic fracture of the femur.
3. Intramedullary rod, plating, cementation, hip arthroplasty or knee arthroplasty.

Group B. Primary sarcoma of the lower extremity requiring radical resection of tumor. Inclusion criteria would include all of the following:

1. Primary sarcoma of bone or soft tissue of lower extremity.
2. T2 tumor (> 5 cm but < 20 cm).
3. Radical resection of tumor, which may necessitate major bone or soft tissue reconstruction.

Exclusion criteria for both groups would include the following:

1. Presence of DVT on pre-operative screening ultrasound study.
2. Massive tumor (>20 cm in greatest dimension)
3. Amputation of the affected leg as treatment for tumor.
4. Estimated blood loss >2 liters during surgery.
5. Surgical drain output >500 cc of bloody fluid during first 8 hours.
6. I.N.R. >1.3 pre-operatively or > 1.5 post-operatively.
7. Platelet count < 100,000 either pre-operatively or post-operatively.
8. Indwelling post-operative epidural catheter for pain control.
9. Age <30 years.
10. History of underlying bleeding disorder, such as hemophilia.
11. History of adverse reaction to heparin such as heparin-induced thrombocytopenia.
12. Severe liver or renal insufficiency.
13. History of hypertensive or diabetic retinopathy.
14. History of gastro-intestinal bleeding within 12 months.
15. Treatment with warfarin, clopidogrel, aspirin, NSAIDs, LMWH or other anti-coagulants for conditions.
16. History of stroke.
17. Women of childbearing potential having a positive serum or urine pregnancy test (hCG) at the time of pre-operative evaluation (within 7 days of surgery).
18. Women who are breast feeding.
19. Hemoglobin < 8.0 gm/dl
20. Platelet count < 100,000 /L
21. Alanine aminotransferase >100 IU/L
22. Aspartate aminotransferase > 100 IU/L

23. Direct bilirubin >0.5 gm/dL (the laboratory does not perform direct bilirubin if total bilirubin is below 0.2 mg/dl since direct bilirubin cannot be greater than total bilirubin).
24. Serum creatinine > 2.0 gm/dL
25. Patients taking COX-2 inhibitors.
26. Patients who have fragmented mechanical heart valves.

Study Design

The study design will be an open-label, non-randomized clinical trial involving 25 – 35 consecutive patients in each of the two groups. Historical controls from this institution will be used to compare peri-operative bleeding events, drainage, transfusion requirements, and re-operation rates in similar patients who did not receive chemical prophylaxis for DVT. Published historical controls will be used to compare the DVT rate. The rate of DVT will be measured in this study, but the primary objective is to examine bleeding complications at the surgical site. The sample size therefore is not calculated to establish efficacy, which has been demonstrated for patients in general in numerous previous articles.

The study design will be an open-label, non-randomized clinical trial involving 25 – 35 consecutive patients in each of the two groups. To analyze wound complications historical controls will be identified through the Surgical Database maintained by the Section of Orthopaedics from this institution and will be used to compare peri-operative bleeding events, drainage, transfusion requirements, and re-operation rates in similar patients who did not receive chemical prophylaxis for DVT. Data from surgery, including drain output, transfusion requirements, would complications, and re-operation for wound problems will be collected. To analyze DVT rates and to compare against patients who did not receive, data from the previously published article by Lin et. al. will be used for the control group of patients with mechanical compression stockings alone. Patients will receive a combination of dalteparin, bilateral TED hose, and bilateral mechanical compression stockings while in the hospital.

Method of DVT Prophylaxis

Patients will receive a combination of dalteparin, bilateral TED hose, and bilateral mechanical compression stockings while in the hospital.

The reason for employing both mechanical prophylaxis and dalteparin together is as follows. DVT prophylaxis is very difficult to achieve. The DVT rate is never zero. There is a very little, if any, adverse effects of using mechanical compression stockings. However, from the previous study at Memorial Sloan-Kettering, it is known that there is still a significant rate of DVT (17%) with mechanical prophylaxis. Dalteparin and other low molecular weight heparins may improve upon this rate. There is no contraindication to using both dalteparin and mechanical prophylaxis together. The study is not intended to show that dalteparin obviates the need for mechanical prophylaxis.

Patients should not receive other anti-coagulants, such as aspirin, non-steroidal anti-inflammatory drugs, and warfarin while on the study. Heparin should not be administered except for routine intravenous catheter flushes.

During surgery, patients will have TED hose and a mechanical compression stocking on the unaffected extremity. For the operative leg TED hose and mechanical compression stocking will be applied in the recovery room.

Patients will be mobilized out of bed with physical therapy as soon as deemed safe by the attending physician (generally post-operative day 1).

Patients will not continue dalteparin after discharge from the hospital. Patients are generally able to ambulate independently upon discharge, and are considered at reduced risk for DVT.

Dosing of Dalteparin

1. The unit dose will be 5000 units of dalteparin.
2. The dosing will be once a day.
3. The rouge of administration will be subcutaneous injection.
4. The medication will start 12 – 24 hours after surgery on post-operative day #1.
5. The medication will continue daily while the patient is in the hospital. A follow-up doppler ultrasound study will be obtained prior to discharge (post-operative day 5 – 14).

Screening for DVT

Each patient must have a pre-operative, bilateral doppler ultrasound study of the lower extremity veins, including the popliteal to the common femoral veins.

Patients will receive a post-operative bilateral doppler ultrasound study of the operative limb prior to discharge home (generally post-operative day 5 – 14).

The patients will be monitored by daily physical examinations while in the hospital. Signs of acute DVT include pain, tenderness to deep palpation, swelling and a positive Homan's sign. Both legs will be monitored by examination. Patients suspected of acute DVT will undergo emergent doppler ultrasound study. Signs of pulmonary embolus (PE) include shortness of breath, pleuritic chest pain, dyspnea, hypoxia, and an arterial-alveolar oxygen gradient. Patients suspected of acute PE will undergo emergent chest computed tomography and/or ventilation-perfusion lung scan.

Endpoints of Analysis

1) Post-operative blood loss, as measured by the number of units of packed red blood cells transfused after surgery and change in hemoglobin levels.
2) Post-operative drainage (cumulative) from surgical drains.
3) Re-operation rate for post-operative complications, including hematomas, seromas, and infections.
4) Rate of per-operative DVT in the study population.
5) Rate of post-operative DVT in the lower extremities.
6) Rate of clinically symptomatic pulmonary embolus.
7) Bleeding at distant sites, such as the gastro-intestinal tract.

Statistical Considerations

The main purpose of this safety study is to evaluate the safety of dalteparin in patients undergoing orthopaedic oncologic procedures. There is remarkably little information for the drug in patient population. The main concern is that the drug could lead to increased bleeding, hematomas, seromas, and wound problems. The safety study is intended to gather preliminary data that potentially could be used to formulate a larger study on DVT prophylaxis. For the safety study, it seems reasonable to institute a stop rule. The stop rule will terminate the study in case the drug leads to an unacceptable rate of adverse events. The stop rules should not be based upon an arbitrary amount of post-operative drainage or weeks is a much better measure to use. This is discrete event that is a common final outcome for unacceptable wound bleeding, large seromas and hematomas, and other wound problems.

Two groups of patients will be evaluated in 2 independent cohorts, 1) patients who require major resection of sarcomas in the lower extremity, and 2) patients with metastatic disease of the lower extremity. There is little information about safety and efficacy of dalteparin in these two patient groups. Knowledge gained from the treatment of these patients will be used to design larger, more definitive studies. Twenty-five patients will be treated in the metastatic cohort and 30 patients in the sarcoma cohort. A total of 50 – 70 patients will be accrued on this study.

Safety Monitoring. The primary endpoint for safety monitoring is the re-operation rate due to complications experienced by patients within the first 4 weeks after surgery. In the sarcoma group, surgery can be extensive and clinical experience indicates that approximately 10% of patients will require re-operation within 4 weeks.[15-17] A 25% re-operation rate in this group of patients would be considered excessive. For the metastatic patient group, the surgery is typically less involved and the re-operation rate during the first 4 weeks is near zero. [18] (we assume 3%) and a 15% re-operation rate would be considered excessive. We will monitor this endpoint separately for these two patient groups using the sequential probability ratio test (Goldman 1987). [19] We assume a type 1 error rate of 5% for both treatment groups. Table 1 contains the stopping rules for each patient group. For example, in the metastatic group, if 2 patients in the first 8 treated require re-operations to amend primary surgical complications, the protocol will stop accrual in this group. Similar, if 4 of the first 8 patients in the sarcoma group require re-

operation, accrual in this patient group will stop. The probabilities of detecting excessive re-operation rates if the true rates are as high or higher than stated above using these two stopping rules are 6% and 72% for the metastatic and sarcoma patient groups, respectively.

Table 1. Stop trial for excessive re-operation rate if the number of re-operations at or larger than listed (No. Re-operations) are necessary in the number of patients treated.

	Metastatic Patients			
No. Re-operations	2	3	4	
No. Patients	8	25	25	
	Sarcoma Patients			
No. Re-operations	4	5	6	7
No. Patients	8	16	26	30

Analysis Plan. Several additional safety and efficacy endpoints will be estimated. These include pre-operative DVT incidence, surgical drain output, the number of transfusions, post-operative DVT's and others. For continuous variables (e.g., surgical drainage, number of transfusions) data will be summarized using the mean (s.d.) and median (range). For categorical variables (e.g., DVTs, gender) data will be summarized in frequency tables. 95% confidence intervals will be estimated for all outcomes. For categorical outcomes, outcome estimates will be estimated with standard errors no larger than 9% and 10% for the sarcoma and metastatic patients, respectively.

Cost of Study

The major cost of this study is the Doppler ultrasound test to detect lower extremity DVT's. The cost is $475 per unilateral study and $950 per bilateral study at MD Anderson Cancer Center. The medication will be provided by Pfizer. The institutional tax is 25%, but this is waived for direct patient charges (i.e., ultrasound studies).

Seventy patients are used as the basis for the cost analysis. It is anticipated that there will be 50 patients on protocol in the study. The cost estimate includes an additional 20 patients for attrition from the study or exclusion from study as a result of a positive screening Doppler ultrasound test. It is noted however that these patients do provide useful data and information that is part of the study. If there is zero attrition and no pre-operative DVTs, up to 10 additional patients will be included in each study group.

Research Related Items	**Amount**	**Overhead (25%)**	**Notes**
Protocol Approval Fee	$1,000	n/c	Required institutional fee for review and approval of clinical trials.
PDMS User Fee	$10,500	$2,625	Required institutional fee for registration in PDMS - $150/patient minimum.
Experimental Pharmacy Fee	$7,000	$1,750	Required institutional fee for experimental pharmacy handling/inventory control; $100/patient
Diagnostic Imaging	$96,250	n/c	Projected cost based on current rate. One bilateral Doppler ultrasound scan ($950) + one unilateral scan ($475) per patient = $1375 per patient
Administrative and miscellaneous costs	$7,000	$1,750	$100/patient for unforeseen laboratory tests, document preparation, and non-institutional overhead costs.
Sub-total	$121,750	$6,125	
Total	**$127,875**		Direct cost per patient $1,739 Indirect cost per patient $87.50 **Total cost per patient $1,827**

Revised 9/7/04

References

1. Freedman KB, Brookenthal KR, Fitzgerald RH, Jr., Williams S, Lonner JH. A meta-analysis of thromboembolic prophylaxis following elective total hip arthroplasty. *Journal of Bone & Joint Surgery - American Volume.* 2000;82-A(7):929-938.

2. Westrich GH, Haas SB, Mosca P, Peterson M. Meta-analysis of thromboembolic prophylaxis after total knee arthroplasty.[see comment]. *Journal of Bone & Joint Surgery - British Volume.* 2000;82(6):795-800.

3. Mandala M, Ferretti G, Cremonesi M, Cazzaniga M, Curigliano G, Barni S. Venous thromboembolism and cancer: new issues for an old topic. *Critical Reviews in Oncology-Hematology.* 2003;48(1):65-80.

4. Elting LS, Escalante CP, Cooksley C, et al. Outcomes and cost of deep venous thrombosis among patients with cancer. *Archives of Internal Medicine.* 2004;164(15):1653-1661.

5. Deitcher SR. Cancer-related deep venous thrombosis: clinical importance, treatment challenges, and management strategies. *Seminars in Thrombosis & Hemostasis.* 2003;29(3):247-258.

6. Lin PP, Graham D, Hann LE, Boland PJ, Healey JH. Deep venous thrombosis after orthopedic surgery in adult cancer patients. *J Surg Oncol.* May 1998;68(1):41-47.

7. Nathan SS, Simmons KA, Morris CD, Athanasian EA, Boland PJ, Healey JH. Deep venous thrombosis after orthopaedic surgery in adult cancer patients revisited--results of a prophylactic anticoagulation intervention program. Paper presented at: Musculoskeletal Tumor Society, 2004; Long Beach, CA.

8. Howard PA. Dalteparin: a low-molecular-weight heparin. *Ann Pharmacother.* Feb 1997;31(2):192-203.

9. Holzheimer RG. Prophylaxis of thrombosis with low-molecular-weight heparin (LMWH). *European Journal of Medical Research.* 2004;9(3):150-170.

10. Krotenberg R, Adler U, Pomeranz B, Miller JD, Russell MW. Dalteparin vs. enoxaparin as prophylaxis for deep-vein thrombosis after total hip or knee arthroplasty: a retrospective analysis. *American Journal of Physical Medicine & Rehabilitation.* 2001;80(12):889-895.

11. Chiou-Tan FY, Garza H, Chan KT, et al. Comparison of dalteparin and enoxaparin for deep venous thrombosis prophylaxis in patients with spinal cord injury. *American Journal of Physical Medicine & Rehabilitation.* 2003;82(9):678-685.

12. anonymous. Thromboprophylaxis in hip fracture surgery: a pilot study comparing danaparoid, enoxaparin and dalteparin. The TIFDED Study Group. *Haemostasis.* 1999;29(6):310-317.

13. Wells PS, Lensing AW, Davidson BL, Prins MH, Hirsh J. Accuracy of ultrasound for the diagnosis of deep venous thrombosis in asymptomatic patients after orthopedic surgery. A meta-analysis. *Ann Intern Med.* Jan 1 1995;122(1):47-53.

14. M.D. Anderson Cancer Center On-line Pharmacy Formulary and Therapeutic Index (www.inside.mdanderson.org). 2004-05.

15. Kunisada T, Ngan SY, Powell G, Choong PF. Wound complications following pre-operative radiotherapy for soft tissue sarcoma. *European Journal of Surgical Oncology.* 2002;28(1):75-79.

16. Scaife CL, Pisters PW. Combined-modality treatment of localized soft tissue sarcomas of the extremities. *Surgical Oncology Clinics of North America.* 2003;12(2):355-368.

17. O'Sullivan B, Davis AM, Turcotte R, et al. Preoperative versus postoperative radiotherapy in soft-tissue sarcoma of the limbs: a randomised trial.[see comment]. *Lancet.* 2002;359(9325):2235-2241.

18. Yasko AW, Lewis VO, Weber KL, Lin PP. Long-Stem Femoral Arthroplasty for Proximal Femoral Metastases. An Analysis of 160 Consecutive Patients. Paper presented at: American Academy of Orthopaedic Surgeons 71st Annual Meeting, 2004; San Francisco, CA.

19. Goldman AI. Issues in designing sequential stopping rules for monitoring side effects in clinical trials. *Controlled Clinical Trials.* 1987;8(4):327-337.