Tranexamic Acid Administration in Knee and Hip Arthroplasty: A Clinical Practice Guideline.

Jahnavi Jaladanki

University of Maryland, School of Nursing

Abstract

Tranexamic acid (TXA) is an anti-fibrinolytic agent that has been shown to decrease blood loss and transfusion requirements during hip and knee replacements. The purpose of this Doctorate Nursing Practice (DNP) Scholarly Project is to develop and evaluate a clinical practice guideline (CPG) for the safe and efficacious administration of TXA in hip and knee arthroplasty. A CPG was created and revised with the aid of a multi-disciplinary subject matter expert (MSME) group. The DNP students presented a draft of the CPG along with graded evidence based on current literature to the stakeholders on the team. Following the meeting, an online version of the AGREE II Instrument was distributed to the MSME group to critique and appraise the CPG. The AGREE II tool was designed to evaluate the methodological rigor in guideline development. Following the AGREE II analysis and revisions to the CPG, the guideline was approved by the Chief Anesthesiologist at the institution and was presented to the entire anesthesia department for future implementation. Following this presentation, the Practitioner Feedback Questionnaire (PFQ) was distributed and collected in an anonymous manner. The PFQ analysis revealed that 100% of the end users agreed that there is a strong need for the CPG; however, it was noted that 9% of the end users strongly disagreed that the CPG would be used in their practice. New practice guidelines frequently experience resistance to change by end-users. Further end-user clinical development should focus on educating staff on evidence-based practice as the literature continues to expand.

Tranexamic Acid Administration in Knee and Hip Arthroplasty: A Clinical Practice Guideline

Approximately seven million Americans are living with hip and knee replacements; over a million hip and knee replacement surgeries occur annually (Kremers et al., 2015). A Healthcare Cost and Utilization Project conducted by the Agency for Healthcare Research and Quality showed that since 2001, knee arthroplasty has nearly doubled from 371,600 procedures to 718,500 procedures in 2011 (Weiss & Elixhauser, 2014). Hip replacement surgeries have increased by 40% since 2001 from 332,500 to 466,500 in 2011 (Weiss & Elixhauser, 2014). This increasing trend will continue to be seen in the future due to the aging population, incidence of osteoarthritis, increased life expectancy, and improved perioperative management of patients' comorbidities (Melvin, Stryker, & Sierra, 2015).

There are many hospitals in and around Baltimore, Maryland that are nationally and regionally ranked in the orthopedic specialty and perform numerous hip and knee replacements each year (US News & World Report, 2016). Compared to other elective surgeries, hip and knee replacements are associated with significant blood loss and transfusion rates (Poeran et al., 2014). Patients undergoing total hip arthroplasty (THA) and total knee arthroplasty (TKA) have a perioperative blood loss of greater than one liter, resulting in a greater need for transfusion (Gandhi, Evans, Mahomed, & Mahomed, 2013). Blood product administration to these patients is associated with increased costs, risks of transfusion reactions, hospital stay, morbidity and mortality, risks of disease transmission, and risks of peri-prosthetic infections (Melvin, Stryker, & Sierra, 2015). The average cost of one gram of TXA is $39.14, whereas a transfusion of one unit packed red blood cell a Baltimore, Maryland hospital is $82.59.

Tranexamic acid has been shown to significantly decrease blood loss and is considered a safe to use during hip and knee arthroplasties (Melvin, Stryker, & Sierra, 2015; Gandhi, Evans,

Mahomed, & Mahomed, 2013; Wei & Liu 2015). Patients that received intravenous TXA in a case control study showed a 95.38% reduction in blood transfusions and there was a 53.9% reduction in hospital costs when IV TXA was used (Moskal, Harris, Capps, 2014). Additionally, tranexamic acid reduces blood loss and transfusion requirements without increasing the risk of thromboembolic events (Melvin, Stryker, & Sierra, 2015; Gandhi, Evans, Mahomed, & Mahomed, 2013; Wei & Liu 2015). It is safe to administer one gram prior to surgical incision and one gram within one hour of the end of surgery. There are certain relative contraindications for the use of TXA that include colorblindness, seizure activity, coronary artery disease, and active thromboembolic disease (Melvin, Stryker, & Sierra, 2015).

In the orthopedic operating rooms of a large academic medical center located in the Mid-Atlantic region of the United States, the ambiguous patient selection criteria, administration methods and dosing of TXA is occurring among anesthesia providers. In the organization of interest, TXA administration varies by surgeon and there is no set guideline to follow. Currently, the orthopedic residents ascertain whether a patient is a TXA candidate. Blood transfusion rate is very low when TXA is administered. Blood loss is significantly less when TXA is used in the organization of interest. Unfortunately, many major institutions and hospitals in the United States do not have a clinical practice guideline (CPG) for the administration of TXA during hip and knee arthroplasty (Melvin, Stryker, & Sierra, 2015), like the organization of interest.

The purpose of this Doctorate Nursing Practice (DNP) Scholarly Project is to develop and evaluate a clinical practice guideline for the safe and efficacious administration of intravenous TXA in knee and hip arthroplasty. Anticipated outcomes include standardization of patient care and decreased blood loss and transfusion rates during hip and knee arthroplasty. The

secondary anticipated outcomes will include a shorter length of patient hospital stay and decreased hospital costs.

Theoretical Framework

This scholarly project utilized the Knowledge to Action framework (KTA) that was described by Graham et al. (2006) as the guiding framework. The KTA framework strives to bridge the gap between knowledge translation and knowledge action and application. The KTA model describes the acquisition of knowledge and formation of new interventions as a cyclical process. This cyclical process centers around a knowledge funnel that encompasses knowledge inquiry, synthesis, and tools. This part of the model seeks to refine and tailor to the needs of the knowledge end users such as the anesthesia providers and orthopedic surgeons. The action cycle of the KTA framework includes seven phases that start from identifying the gaps and ending with sustained knowledge use (Graham et al., 2006). The KTA theory was operationalized by guiding the development of interventions in the form of a clinical practice guideline.

This KTA theory was chosen to support the operationalization of this project because it allows for the synthesis and application of knowledge into action. This framework furthermore permits the tailoring to meet the specific needs of the stakeholders and allows for the dissemination of information to be refined to what would be the best practice at the site of interest. TXA has been proven to limit blood loss, but anesthesia providers, while being held responsible for its administration, have no set guideline in place for how and to whom it should be safely administered to. By utilizing the KTA framework, a clinical practice guideline can be implemented to aid clinicians in decision making and improve patient outcomes in the institution of interest.

Literature Review

The need for developing a clinical practice guideline in the administration of TXA in TKA and THA patients is the focus of the evidence in this literature review. This review will begin broadly by addressing the effect of TXA on blood loss in patients undergoing hip and knee arthroplasty. This discussion will be followed by a review of the contraindications to TXA. The review will conclude with current evidence of TXA in relation to improved patient outcomes, dosing considerations, and decreased costs to hospitals. Appendices A, B, and C contain an Evidence Review Tables with details of all studies discussed in the Literature Review.

There have been multiple studies evaluating the effectiveness of TXA use in TKA and THA. De-Jie, Chen, Guo, & Yang (2013); Gandhi, Evans, Mahomed, & Mahomed (2013); and Wei & Liu (2015), concluded that TXA does limit blood loss and the need for allogenic transfusions in their meta-analyses. Collectively, these meta-analyses examined 94 well designed randomized control trials that included over 6,000 cases. All three meta-analyses sought out to compare the outcome measures of perioperative blood loss and incidence of thromboembolic events. The analysis of the three meta-analyses also concluded that TXA does not increase the risk of thromboembolic events such as deep vein thrombosis (DVT) or pulmonary embolus (PE). Please see Appendix A for detailed results of the meta-analyses.

De-Jie, Chen, Guo, & Yang (2013) examined the use of TXA in TKA cases only in which TXA reduced the average total blood loss by 435.41 ml in TKA and the average postoperative blood loss by about 406 ml ($P<0.01$). In patients undergoing knee and hip replacement, there was a 2% and 7% occurrence of transfusion requirements in patients treated with TXA compared to patients who were not treated at 18% and 33%, respectively (Gandhi et al., 2013). To account for the limitation of moderate study heterogeneity in these meta-analyses,

the authors utilized either a random effects model to explain the distribution or the I^2 statistic to indicate the percentage of variance in the meta-analysis which is attributable to study heterogeneity. Despite these limitations, these level 1A meta-analyses provide excellent support for the use of TXA during TKA and THA.

While the benefits of TXA are well established, there are inherent risks to its use. Since TXA can cause an increased risk of thromboembolic events such as DVT and PE, its use is contraindicated on those with active thromboembolic disease, seizure activity, hypersensitivity, or colorblindness (Melvin, Stryker, & Sierra, 2015). Colorblindness is one of the early signs of toxicity, hence if a patient already has it; it would limit the ability to monitor for it (Melvin, Stryker, & Sierra, 2015). Additional inclusion and exclusion patient criteria is presented in clinical practice recommendations developed by The Department of Veteran Affairs (2014), and is incorporated in the rough draft of our CPG that can be found in Appendix D. These recommendations were established as collaborative efforts between the Veterans Health Affairs Pharmacy Benefits Management Services, Medical Advisory Panel, the Veterans Integrated Service Network Pharmacist Executives and the National Surgery Office and are periodically updated.

Poeran et al. (2014) conducted a retrospective cohort study that included 510 hospitals with a total sample size of 872, 416 patients with total hip or knee arthroplasties to see if there were any adverse outcomes. This study examined how the there was a limitation with selective use of TXA in those who had thromboembolic stents and arterial stents. Numerous studies selectively did not include those that had thromboembolic history or arterial stents. Compared with patients who did not receive TXA, patients that received TXA had lower rates of all binary outcomes: allogeneic or autologous blood transfusion requirements (7.7% v 20.1%, $P<0.001$),

thromboembolic complications (0.6% v 0.8%, P=0.0057), combined complications such as stroke, myocardial infarction, and inpatient mortality (1.9% v 2.6%, P<0.001). Despite other studies showing no increase in thromboembolic complications with TXA (Melvin, Stryker, & Sierra, 2015; Gandhi, Evans, Mahomed, & Mahomed, 2013; Wei & Liu 2015), a contraindication list will be included in the CPG.

Tranexamic acid is not only beneficial in limiting blood loss, but also has beneficial financial implications. Moskal, Harris, and Capps (2014) conducted a case control study to see if the cost reduction with TXA administration had practical significance. With a sample of 2299 cases used from a study by Wind, Barfield, and Moskal (2013), the IV TXA group showed a 95.38% reduction in blood transfusions while the topical TXA group experienced 100% reduction in blood transfusions. There was a 53.9% reduction in hospital costs when IV TXA was used. Limitations to this study include all the cases being TKAs and from a single institution. Also, statistical analyses were not completed because their objective was not to determine if the results were statistically significant but to decide if there was a cost reduction that would have practical significance. Outcomes such as adverse events were not reviewed and could affect price estimates. Despite these limitations, their findings correlate with other studies in regards to the cost benefit of TXA (Moskal, Harris, & Capps, 2014). In another study, Poeran et al. (2014) found that the average cost of hospital stay was $14, 890 for the TXA group compared with $15,110 for the group not receiving tranexamic acid (P<0.001). There was a decrease in length of hospital stay from 5.3 to 4.7 days (Moskal, Harris & Capps, 2014). Transfusion reactions are also costly. It cost the hospital $1489 and 3.4 man hours for each transfusion reaction that occurred (Moskal, Harris & Capps, 2014). Fiscal responsibility has become exceedingly important and the research shows tremendous value in utilizing TXA.

Tranexamic acid not only benefits patients in the perioperative period by limiting blood loss, but also reduces the need for transfusion without increasing complications. Furthermore, there are favorable financial ramifications as a result. There is a plethora of studies to support TXA not causing adverse outcomes such as DVT and PE. However, until studies show that TXA can safely be used in those patients with the aforementioned contraindications, TXA will not be administered to those individuals.

Methods

Design and Setting

The design of this DNP quality improvement scholarly project incorporates the development and evaluation of a CPG for TXA use during hip and knee arthroplasty. The setting is a medium-sized, inner city, teaching hospital in the Mid-Atlantic region that supports a large orthopedic program that performs more than 1000 total hip and knee replacements and revisions annually. The organization has over 60 anesthesia providers that circulate throughout the orthopedic operating rooms.

Sample and Procedures

In this scholarly project, there were three stages with three different samples. The project was carried out once it gained approval by the DNP Project Committee and a query for determination of non-human subject research was submitted and approved by the Institutional Review Boards for both the academic institution and the hospital. Stage one occurred in the first month and the sample consisted of members of the organization that include an anesthesiologist that typically runs the orthopedic surgery operating rooms, the chief certified registered nurse anesthetist, a clinical pharmacist, and the director of the quality improvement who will grade the CPG. This sample will be referred to as the multidisciplinary subject matter expert (MSME)

group. Selection, for the MSME group was conducted by the doctoral students and required greater than three years of experience in the practice setting and greater than three years as a professional. Participation was voluntary and required a commitment of three, two hour meetings over a two month period. Participants were invited based on their clinical expertise, ability to meet the time commitment, and their interest. The participants were emailed two weeks prior to the MSME meeting with the CPG and Appraisal of Guidelines, Research, and Evaluation (AGREE) II tool (Appendix G). The email also described how to fill out the AGREE II tool and the students answered any questions that arose via email. They were asked to fill out the tool prior to the meeting so that they could discuss necessary revisions and can provide feedback on the CPG. The purpose of the project and the commitment of the MSME members' to their roles was established when they were approached initially to be part of the MSME group.

After revisions were made by the graduate students based on the MSME's feedback and the results of the AGREE II tool, another meeting was scheduled to review the revised clinical guideline prior to the start of the second stage. The second stage of the project had the chief of the anesthesiology department as the sample, who reviewed the finalized CPG. Further revisions were made based on recommendations by the chief and the MSME group was emailed a finalized copy of the guideline. The third stage of the project included a sample of anesthesia providers, both anesthesiologists and nurse anesthetists, with a projected sample size of 70. This sample received the Practitioners Feedback Survey (Appendix F) after being presented with the CPG during one of the anesthesia department's "grand rounds" meeting. This group will be responsible for evaluation of the CPG for implementation in the future. Voluntary participation in this group was based on position within the hospital's structure as titles and group names

describe. The second and third stages ensued over the second month. Please refer to Appendix E for a timeline of the scholarly project.

Data Collection and Analysis

The AGREE II tool (http://www.agreetrust.org/wp content/uploads/2013/10/AGREE-II Users-Manual-and-23-itemnInstrument_2009_UPDATE_2013.pdf) is widely used to assess the methodological rigor of clinical practice guidelines. The tool is made up of 23 items that are categorized within 6 domains, followed by two items that address the global assessment. A seven point Likert scale is utilized for the 23 items with 1 = "strongly disagree" to 7 = "strongly agree". Once they are independently scored, quality scores are calculated for each of the six domains which are scope and purpose, stakeholder participation, thoroughness of development, lucidity of presentation, applicability, and editorial independence (Brouwers et al., 2010a). Item scores in a particular domain are added together and the total is scaled as a percentage of the maximum possible score for that domain. Overall assessment involves rating the guideline's overall quality and whether it would be recommended for use in practice.

Construct validity of the instrument was established using a systematic analysis and all the mean ratings were found to be in the intended direction (Brouwers et al., 2010b). To report the reliability, Cronbach's alpha was used and ranged from 0.69 to 0.89. The inter-rater reliability was also reported as adequate and has been recommended as the revised standard for guideline development, reporting, and evaluation. The recommendations in the Agree II tool will be utilized in scoring and interpreting the results once the MSME group fills out and the tool and submits it to the graduate students for review at the meeting.

The Practitioner Feedback Questionnaire (Appendix F) was created as an instrument to assess clinicians' beliefs about guideline attributes in relation to end users' support and intentions

to use the CPG (Brouwers, Graham, Hanna, Cameron, & Browman, 2004). The instrument contains 21 items related to the quality, approval of the recommendations, applicability of recommendations, and comparative value. A 3 point Likert scale was utilized for items 2-23 (strongly agree – strongly disagree). Cronbach's alpha was used to report the reliability of this tool and ranged from 0.75-0.85 (Brouwers et al., 2004). Content validity was established using multilevel modeling techniques to show that the high variance in practitioners' support scores and intentions to use the guidelines was attributed to individual differences in beliefs compared to perceived differences in beliefs among the guidelines (Brouwers et al., 2004).

The modified version of the questionnaire can be found in Appendix F. No identifiers were collected to protect the subjects' anonymity. The paper questionnaire was distributed to the providers at the meeting and there were extra copies in the office for those who were unable to attend. Those who were not in attendance had a work email sent outlining the meeting and the CPG. The forms were collected at the end of the meeting and for those who were not present, they would turn it into a mailbox slot in the anesthesia office anonymously. Each day the student took and placed them in a locked file cabinet in the anesthesia office until all forms were turned in and were ready to be analyzed. Only the graduate students had access to this file cabinet. The item scores were calculated as percentages for each item. Two additional items in regards to whether the provider is a certified registered nurse anesthetist (CRNA) or Doctor of Medicine (MD) were added along with the clinical years of experience to aid in the comparison results between the different providers as well as other demographic variables. Descriptive statistics were used to describe demographic data.

This CPG development proposal was submitted to the University of Maryland Institutional Review Board (IRB) for consideration. The IRB determined that this was a quality

improvement project and is intended neither for generalizable knowledge nor to be applied to another health setting. In addition, this project was also submitted to the hospital IRB and it was which made the same determination as the University IRB.

Results

The AGREE II tool reported the clinicians' comments and general overall scores for each of the domains. Results of the AGREE II tool can be found in Appendix H. The domains with the highest overall percentages were "scope and practice" at 89% and "stakeholder involvement" at 86%. Other domains included "rigor of development", "clarity of presentation," and "applicability" that respectively scored 71%, 82%, and 60%. The lowest scoring domain was editorial independence at 58%. Following analysis of the written comments in the applicability domain, it was discovered that two MSME members reported low scores. Upon further analysis of those comments, it was apparent that these participants were wanting a more extensive review of the suspected barriers and facilitators in the CPG. In keeping the CPG clear and succinct for clinician ease of use, the barriers and facilitators were not included in the final approved guideline. The overall assessment score for the AGREE II showed that the average score was a 5.5, indicated a strong quality and recommendation for practice use.

Results of the Practitioner Feedback Questionnaire (PFQ) were analyzed using descriptive statistics. The PFQ results were placed in a table format that can be found in Appendix I. Approximately 60 questionnaires were distributed to the anesthesia providers comprised of both nurse anesthetists and anesthesiologists. Eleven questionnaires were completed and returned. All eleven questionnaires were completed by nurse anesthetists with an average of five years of clinical practice experience. Although there was a low return of PFQs, the PFQ analysis revealed that 100% of the end users agreed that there is a need for the CPG and

the current recommendations in the CPG were clear. It was noted that 9% of the end users strongly disagreed that the CPG would be used in their practice.

Barriers & Enablers

As with any clinical practice guideline, both enablers and barriers were present. The need for the TXA CPG was acknowledged by all the stakeholders and the end users. Enablers of the CPG included key stakeholders such as the Chief of Orthopedic Surgery and Chief of Anesthesia. Members of the MSME group were highly invested in the creation of the CPG due to its primary importance on patient safety. By having the end-users acknowledging there was a knowledge gap in how providers screened and administered TXA, this served as a window of opportunity for the DNP students. As the literature continues to expand, further end-user clinical development should focus on education and updating staff on evidence based practice.

New practice guidelines frequently experience resistance to change by end-users. Some potential barriers surfaced when the DNP students educated the end users in the department grand rounds. Despite the consensus on the need for the CPG, some providers were hesitant on being held responsible for ordering TXA. These providers felt that it was a surgical concern and that the orthopedic surgeons should order it. Moving forward, the anesthesia and orthopedic surgery department will work together to ensure that the orthopedic surgeons will order TXA for suitable candidates. The end users in the anesthesia department will ensure that TXA is administered according to the CPG recommendations. Another barrier that came up was screening for patients that were appropriate for receiving TXA. The DNP students created a TXA Candidacy Form that will be utilized for the pre-operative phase by the pre-operative nurses, anesthesia end users, and orthopedic surgeons. The TXA Candidacy Form can be found in Appendix J. The Chief of Anesthesia approved a test trial with the TXA Candidacy Form and

the DNP students received positive feedback. The form will be used more extensively once the CPG gets implemented in the future. Other barriers that had to be overcome included examining the cost effectiveness, efficacy, and feasibility of administering oral TXA. Pharmacy wanted the DNP students to examine the practicality of utilizing oral TXA. IRB approval was not sought out for this component and would not have been completed within the timeframe the DNP students were present.

Future Plans

Future recommendations and plans should involve examining and incorporating the latest in literary evidence as research is always expanding. The CPG should be implemented and evaluated at timed intervals in regards to improvement in patient outcomes, cost efficiency, and decrease in blood transfusions for patients undergoing hip and knee arthroplasty. Other future recommendations include utilizing an evaluation tool to audit for patients that are given TXA in comparison to those that were unable to receive TXA. Furthermore, TXA has been found to be useful and efficacious in postpartum hemorrhage and trauma patients. As the literature expands on the use of TXA, providers should examine how TXA can be further utilized to increase patient safety and improve outcomes.

References

Brouwers M.C., Graham, I.D., Hanna, S.E., Cameron, D.A., & Browman, G.P. (2004). Clinicians' assessments of practice guidelines in oncology: The CAPGO survey. International Journal of Technology Assessment in Health Care, 2(4), 421–426.

Brouwers M.C., Kho, M.E., Browman, G.P., Cluzeau, F., Feder, G., Fervers, B., Hanna, S.E., & Makarski, J. (2010a). AGREE II: Advancing guideline development, reporting and evaluation in healthcare. Canadian Medical Association Journal, 182 (18), E839-E842. doi: 10.1503/cmaj.090449. Retrieved from http://www.agreetrust.org/wp content/uploads/2013/10/AGREE-II Users-Manual-and-23-item Instrument_2009_UPDATE_2013.pdf

Brouwers M.C., Kho, M.E., Browman, G.P., Burgers, J.S., Cluzeau, F., Feder, G., Fervers, B., Graham, I.D., Hanna, S.E., & Makarski, J. (2010b). Development of the AGREE II, part 2: Assessment of validity of items and tools to support application. Canadian Medical Association Journal, 182 (10), E472-E478. doi:10.1503/cmaj.091716

De-Jie, F., Chen, C., Guo,L., & Yang, L. (2013). Use of intravenous tranexamic acid in total knee arthroplasty: a meta-analysis of randomized control trials. Chinese Journal of Traumatology 16(2), 67-76. doi:10.3760/cma.j.issn.1008-1275.2013.02.001

Department of Veterans Affairs. (2014). Clinical recommendations for using tranexamic acid for reducing blood loss and transfusion requirements in patients undergoing total knee or total hip arthroplasty. Retrieved from http://www.pbm.va.gov/PBM/clinicalguidance/clinicalrecommendations/Tranexamic_Aid_in_TKA_or_THA_Clinical_Recommendations.pdf

Gandhi, R., Evans, H. M., Mahomed, S., & Mahomed, N.N. (2013). Tranexamic acid and the reduction of blood loss in total knee and hip arthroplasty: A meta-analysis. BioMed Central Research Notes, 6(184). doi:10.1186/1756-0500-6-184

Graham, I., Logan, J., Harrison, M., Straus, S., Tetroe, J., Caswell, W., & Robinson, N. (2006). Lost in knowledge translation: Time for map? The Journal of Continuing Education in the Health Profession, 26, 13-24.

Kremers, H.M., Larsons, D.R., Crowson, C.S., Kremers, W.K., Washington, R.E., Steiner, C.A., Jiranek, W.A., & Berry, D.J. (2015). Prevalence of total hip and knee replacement in the United States. The Journal of Bone and Joint Surgery, 97(17), 1386-1397. doi:10.2106/JBJS.N.01141

Melvin, J. S., Stryker, L. S., & Sierra, R. J. (2015). Tranexamic Acid in Hip and Knee Arthroplasty. Journal of the American Academy of Orthopaedic Surgeons, 23(12), 732 740.

Melnyk, B.M. & Fineout-Overholt, E. (2011). Evidence-based practice in nursing and healthcare: A guide to best practice (2nd ed.). Philadelphia, PA: Wolters Kluwer Health.

Moskal, J.T., Harris, R.N., Capps, S.G. (2014). Transfusion cost savings with tranexamic acid in primary total knee arthroplasty from 2009 to 2012. The Journal of Arthroplasty, 30, 365-368. http://dx.doi.org/10.1016/j.arth.2014.10.008

Newhouse, R.P. (2006). Examining the support for evidence-based nursing practice. Journal of Nursing Administration, 36(7-8), 337-40.

Poeran J, Rasul R, Suzuki S, Danninger, T., Mazumdar, M., Opperer, M., Boettner, F., & Memtsoudis, M. (2014). Tranexamic acid use and postoperative outcomes in patients undergoing total hip or knee arthroplasty in the United States: Retrospective analysis of

effectiveness and safety. British Medical Journal (BMJ), 349. http://dx.doi.org/10.1136/bmj.g4829

U.S. News and World Report. (2016) Best hospitals for adult orthopedics. Retrieved from http://health.usnews.com/best-hospitals/rankings/orthopedics

Wei, Z. & Liu, M. (2015). The effectiveness and safety of tranexamic acid in total hip or knee arthroplasty: A meta-analysis of 2720 cases. British Blood Transfusion Society, 25, 151 162. doi:10.1111/tme.1221

Weiss, A.J., & Elixhauser, A. (2014). Trends in operating room procedures in U.S. hospitals, 2001-2011. HCUP statistical brief #171. Agency for Healthcare Research and Quality. Retrieved from http://www.hcup-us.ahrq.gov/reports/statbriefs/sb171-Operating-Room Procedure-Trends.pdf

Wind, T.C., Barfield, W.R., & Moskal, J.T. The effect of tranexamic acid on blood loss and transfusion rate in primary total knee arthroplasty. Journal of Arthroplasty, 28(7), 1080.

Appendix A
Evidence Rating Table

Author, year	Study objective/intervention or exposures compared	Design	Sample (N)	Outcomes studied (how measured)	Results	*Level and Quality Rating
De-Jie, Chen, Guo, & Yang, 2013	Investigate the efficacy and safety of the IV use of TXA in TKA	Meta-analysis	22 randomized control trials that included a total of 1361 patients Most of these trials were small but they were well designed and had a high quality	-Total blood loss, intraoperative blood loss, and postoperative blood loss - transfusion rates and volumes (number of units) were measured -Incidence of DVT was also measured in 21 of the 22 trials examined -Incidence of PE was reported in 13/22 trials	TXA reduced total blood loss by 435.41 ml in TKA and postoperative blood loss by about 406 ml P<0.01 TXA use also lowered the transfusion rate and transfusion volume The risks between the control and TXA group in developing deep vein thrombosis and pulmonary embolus were not statistically significant --TXA reduced the proportion of patients who needed transfusion by 30% --TXA decreased the average volume of blood transfusions examined by 0.95 unit.	IA
Department of Veterans Affairs	Clinical guideline to aid practitioners in clinical decision making and to	Expert Opinion	Not a true experiment Sample size	Blood loss is limited through the use of TXA reducing the	A guideline was established with strict inclusion and exclusion criteria for administering TXA to	7A

	standardize and improve the quality of patient care		includes all patients undergoing TKA or THA in VA hospitals	need for allogenic transfusions	patients Instructions on how to administer and dilute TXA are strictly addressed	
Gandhi, Evans, Mahomed, & Mahomed, 2013	Primary goal was to review RCT's that compared patients undergoing hip or knee arthroplasty with and without TXA and examined total blood loss and the number of patients receiving allogenic blood transfusions	Meta analysis	33 randomized control trials were reviewed with a total sample of N=1957	Included total blood loss (measured intraoperatively and postoperatively), number of patients receiving allogeneic blood transfusions, and/or incidence of thromboembolic complications (DVT or PE occurrence)	TXA led to a statistically significant reduction in TBL TXA did not lead to an increase in thromboembolic events TXA groups showed statistically significant less transfusion rates	1A
Melvin, Stryker, & Sierra, 2015	Comprehensive review of randomized control trials and meta-analyses done with TXA administration for hip and knee arthroplasty	Expert opinion	57 quantitative and qualitative studies and meta-analyses reviewed for N=2044 in just the randomized control trials	Total blood loss Need for allogenic transfusions Occurrence of DVT/PE Cost savings	In both primary and revision THA and TKA, and abundant amount of randomized analyses show that TXA is safe and cost efficient. TXA decreased perioperative blood loss and transfusion requirements in both primary and revision THA and TKA	7A

					Relative contraindications to TXA are allergic reaction, epilepsy disorder, and active thromboembolic disease	
Moskal, Harris, Capps, 2014	Determine if there was a cost reduction with TXA administration in TKA and THA that would have practical significance	Case control study	N=2299	Number of transfusions that occurred Cost for transfusions Cost of TXA	IV TXA group showed a 95.38% reduction in blood transfusions while the topical TXA group experienced 100% reduction in blood transfusions 53.9% reduction in hospital costs when IV TXA is used With IV TXA, there is a 94.6% reduction in man hours when compared to patients who did not receive it	4A
Poeran, Rasul, Suzuki, Danninger, Mazumdar, Opperer, M., Boettner, & Memtsoudis, 2014	To determine the safety and efficacy perioperative use of TXA in U.S. patients undergoing hip and knee arthroplasty	Retrospective cohort study	510 hospitals with a total sample size of 872, 416 patients who had total hip or knee arthroplasty	Allogenic or autologous transfusion Thromboembolic events such as PE or DVT Acute renal failure Occurrence of CVA/MI/or in hospital	Pt's receiving TXA vs those that didn't showed lower rates of transfusions (allogenic or autologous) 7.7% vs. 20.1, thromboembolic complications (0.6% vs. 0.8%); acute renal failure 1.2% vs. 1.6; and combined complications (CVA/MI/in pt mortality) 1.9% vs. 2.6% TXA is associated with a decrease in blood	4A

				mortality -Secondary outcome variables include mechanical ventilation, ICU admission, length of hospital stay and cost of hospital stay in US dollars	transfusions, without increasing the risk of complications, that include thromboembolic events and renal failure	
Wei & Liu, 2015	To evaluate the safety and efficacy of TXA in TKA and THA	Meta-analysis 39 studies were included	All available randomized control trials regardless of how TXA was administered (IV/intra-articularly, topically, orally) N=2720	Total volume of blood loss following surgery=measurement of both intraoperatively and postoperatively blood loss Incidence of DVT and PE Secondary outcomes include the number of patients requiring allogenic transfusions	TXA significantly reduced allogenic transfusion need without increasing thromboembolic event	1B

*Rating system for the hierarchy of evidence (Melnyk & Fineout-Overholt, 2011)

Appendix B
Evidence Strengths and Weaknesses Table

Author, year	Study objective/intervention or exposures compared	Strengths	Weaknesses	Quality Rating
De-Jie, Chen, Guo, & Yang, 2013	Investigate the efficacy and safety of the IV use of TXA in TKA	Extensive literature search of medical journals and databases, sufficient sample size, Exclusion criteria included: RCTs of low quality, simultaneous bilateral TKA or TKA revision, original data not being enough for a meta-analysis Clearly defined inclusion/exclusion criteria Study protocol was clearly articulated Use of instruments with established reliability and validity Only focused on TKA to reduce heterogeneity of including other orthopedic surgeries Operational definitions were provided for all the outcomes measured Only included trials that had a placebo or control comparison	Some of the studies examined had the autologous blood before surgery due to confusion for determining blood loss based on the decrease of hemoglobin No consistency in how the follow up was done for determining what patients developed DVT and PE Publication bias may be present because the literature search was limited to major medical databases and did not include government reports, editorials, and other conventional literature Registration bias may be present with the use of billing codes and data Due to the administrative aspect of the data, they were only able to study complications that occurred during the patient's hospital stay.	A
Department	Clinical recommendations to	Clearly defined inclusion and exclusion	Only used two sources	B

of Veterans Affairs	aid practitioners in clinical decision making and to standardize and improve the quality of patient care	criteria for the administration of TXA Clearly defined dilution and administration methods for TXA Constantly gets updated based on new literature Government owned and updated guideline for administration to its veterans	Literature supports the interventions of the guideline	
Gandhi, Evans, Mahomed, & Mahomed, 2013	Main objective was to review RCT's comparing total blood loss and the number of patients receiving allogenic blood transfusions undergoing hip or knee arthroplasty with or without the use of TXA	Huge sample size Included both literature from English and non-English sources Used the Jadad Scoring system to analyze each RCT and assess the quality of the studies -Clearly defined inclusion and exclusion criteria	Used the Jadad score to assess the quality of the RCTs which would not show bias as allocation concealment Moderate study heterogeneity could be found however the authors conducted a sensitivity analysis	A
Melvin, Stryker, & Sierra, 2015	Comprehensive review of randomized control trials and meta-analyses done with TXA administration for hip and knee arthroplasty	26 level I studies, 4 level II studies, 12 level III studies, and 8 level IV studies were reviewed	Expert opinion-did not perform any experiments	A
Moskal, Harris, Capps, 2014	Determine if there was a cost reduction with TXA administration in TKA and THA that would have practical significance	Huge sample size One of the most thorough studies that examined the financial implications of TXA	Retrospective study that used data from a previous study -Study took place at a single institution so it may be hard to extrapolate the results -Selection bias may be present	A

			because high risk patients were administered topical TXA -Outcomes such as adverse events weren't reviewed and could affect price estimates	
Poeran, Rasul, Suzuki, Danninger, Mazumdar, Opperer, M., Boettner, & Memtsoudi, 2014	To determine the safety and efficacy perioperative use of TXA in U.S. patients undergoing hip and knee arthroplasty	Large sample size High generalizability due to data being from everyday practice Multivariable multilevel analysis controlling for individual level factors and hospital clusters	Analysis used data from administrative databases; clinical information details such as starting hemoglobin level or other transfusion triggers -Residual confounding may be present however the multilevel models showed high C statistics that showed good model discrimination between subjects for each income level	A
Wei & Liu, 2015	To evaluate the safety and efficacy of TXA in TKA and THA	-Large sample size -Novel literature data -Conclusion was consistent with other literature -Subgroup analysis of the methods of TXA administration showed that there was no significant differences between the different methods of administration, hence it was reasonable to pool all of the data of eligibility together -Well defined inclusion and exclusion criteria	Small sample size of each primary study and the significant heterogeneity in total blood loss and transfusion requirements Publication bias may be present because only English literature was used Some of the included trials excluded high risk factors such as patients with a history of cardiac disease	A

*Level of Quality based on Newhouse (2006)

Appendix C
Summary Evidence Rating Table

Evidence Based Practice Question (PICO): In adult patients undergoing hip and knee arthroplasty, is the administration of TXA effective in decreasing intraoperative blood loss and blood transfusion requirements, compared to patients who don't receive TXA?			
Level of Evidence	**Number of Studies**	**Summary of Findings**	**Overall Quality** (you may expand further)
1	3	All three meta-analyses concluded that TXA limited blood loss and the need for allogenic transfusion during joint surgery They also came to the conclusion that TXA does not increase the risk of thromboembolic events	A. All three meta-analyses performed a robust investigation of the most recent literature Despite study heterogeneity, being present, they utilized either the I^2 statistic or random effects model to display the degree of heterogeneity; definitive conclusions
4	2	Poeran et al. (2014) concluded that TXA limits blood loss without increasing the incidence of thromboembolic events or other complications such as MI, CVA or acute renal failure The retrospective study performed by Moskal, Harris, Capps (2014) concluded that TXA had favorable financial	A. Huge retrospective cohort study that has a high degree of generalizability A. Gave support that TXA is safe to use and limits blood loss. Despite the

		ramifications	study having occurred in one institution, costs of medications and transfusion remain the same, so the study's results can be extrapolated to other similar institutions. Other financial studies also came to the conclusion
7	2	Expert opinion was given after a comprehensive review of the literature in Melvin, Stryker, and Sierra, 2015 The clinical practice guideline developed by the Department of Veterans Affairs is the only documented guideline found in the literature. It was established based on the literature but only cited two sources	A. The Melvin et al. (2015) study is level A because it reviewed over 57 recent high quality randomized control trials and systematic reviews. Its conclusions were utilized in the formation of the CPG since it had such a robust literature review B. The CPG by the Department of Veterans Affairs is level B because it only utilized two sources; fairly definitive conclusions/recommendations based on a literature review that includes some reference to scientific evidence

Appendix D
Clinical Practice Guideline Draft

Tranexamic Acid for Hip and Knee Arthroplasty Clinical Practice Guideline (CPG)

1. Overview
    a. Purpose: to address the use of tranexamic acid (TXA) for total hip and knee arthroplasty to reduce total blood loss and decrease blood transfusions.
    b. Target Users: This CPG is intended to guide the anesthesia practitioner in administering TXA in this patient population. Orthopedic surgery attending physicians and trainees will be ordering TXA when indicated. Although not directly involved with the administration or ordering of TXA, knowledge of this CPG is critical for pharmacy, and perioperative nursing personnel.

2. Indications for Tranexamic Acid

A. Orthopedic procedures involving hip and knee arthroplasty (primary and revision)

B. **Exclusion criteria**

Absolute Contraindications (VHA Pharmacy Benefits Management Services, Medical Advisory Panel, VISN Pharmacist Executives & the National Surgery Office, 2014)

1. Allergy/Hypersensitivity
2. Coronary or vascular stent placed within the past six months (up to one year if appropriate)
3. Deep vein thrombosis, pulmonary embolus, myocardial ischemia or ischemic stroke within the past six months (up to one year if appropriate)
4. Seizure disorder (TXA is able to cross the blood brain barrier and has the potential to induce seizures secondary to reaction with the glycine receptors)
5. Subarachnoid hemorrhage
6. Bleeding disorders
7. Hypercoagulable state/disorder
8. Retinal vein or artery occlusion or colorblindness
9. Active intravascular clotting
10. Concomitant use of clotting factor concentrates or other anticoagulants

C. **Inclusion Criteria**

1. Patients undergoing total knee arthroplasty (TKA) or total hip arthroplasty (THA) and who do not have any exclusion criteria

2. **Other considerations:** TXA is a Pregnancy category B drug. There is limited evidence on the use of TXA for hip and knee arthroplasty during pregnancy and in pediatrics under the age of 18 (United States Food and Drug Administration, 2014).

C. Total Joint Arthroplasty TXA Candidacy Form

1. The Anesthesia provider will be responsible for completing this form for every patient undergoing hip and knee arthroplasty or revision.
2. This form will guide the provider in reviewing pertinent medical history questions to determine whether a patient is eligible to receive TXA.
3. A copy of this form will go into the patient's records and another copy will be placed with the anesthesia records for auditing purposes.

3. Administration

a. Timing

i. A repeat dosing regimen of intravenous TXA is superior, compared to a single dose alone in decreasing blood loss (Iwai, Tsuji, Tomita, Sugamoto, Hideki, & Hamada, 2013).

ii. There is no significant difference in outcomes between standardized dosing (1 gram) and weight-based dosing of intravenous TXA (Levine, Haughom, Belkin, & Goldstein, 2014).

b. Recommendations

i. When indicated, patients receiving TKA or THA, a standard 1 gram intravenous dose of TXA should be administered prior to incision, and a repeat 1 gram dose of intravenous TXA should be given at closure (Melvin et al., 2015)**.**

ii. When intravenous TXA is contraindicated, local or topical administration of TXA should be considered by the orthopedic surgeon (Melvin et al., 2015)**.**

Appendix E
Scholarly Project Timeline

- Submit Proposal to committee members by [April, 2016].
- Present Proposal to committee members on [May, 2016].
- Submit project proposal to UMB and hospital Institutional Review Boards (IRBs) by [June, 2016].
- Develop project from [July, 2016] to [August, 2016].
    - Meet with MSME group members to evaluate and amend the CPG
    - Meet with the Chief of Anesthesia to gain approval for distribution and presentation
    - Present at a grand rounds meeting and handout Practitioner Feedback Survey to the providers
    - Have an email sent out reiterating the information and Survey to those who were not in attendance.
    - Have extra forms available in the Anesthesia Office for those who were not there and have a mailbox slot where they can turn in completed forms
- Analyze, synthesize and evaluate data by [January, 2017].
- Submit final scholarly project manuscript to committee for review by [February, 2017].
- Present final scholarly project report to Committee by [March, 2017].

Appendix F
Practitioner Feedback Questionnaire

Check one **CRNA** ☐ **MD** ☐

Clinical Years of Experience _____

For each item, please check off the box that most adequately reflects your opinion.

1. Are you responsible for the care of patients for whom this draft guideline report is relevant? This may include the referral, diagnosis, treatment, or follow-up of patients.	Yes ☐	No ☐	Unsure ☐
If you answered "No" or "Unsure", there is no need to answer or return this questionnaire. If you answered "Yes", please answer the questions below and return to **[enter expected destination of surveys]**.			
	Strongly agree	Neither agree or disagree	Strongly disagree
2. The rationale for developing a guideline is clear.	☐	☐	☐
3. There is a need for a guideline on this topic.	☐	☐	☐
4. The literature search is relevant and complete (e.g., no key evidence was missed nor any included that should not have been) in this draft guideline.	☐	☐	☐
5. I agree with the methodology used to summarize the evidence included in this draft guideline.	☐	☐	☐
6. The results of the evidence described in this draft guideline are interpreted according to my understanding of the evidence.	☐	☐	☐
7. The draft recommendations in this report are clear.	☐	☐	☐
8. I agree with the draft recommendations as stated.	☐	☐	☐
9. The draft recommendations are suitable for the patients for whom they are intended.	☐	☐	☐
10. The draft recommendations are too rigid to apply to individual patients.	☐	☐	☐
11. When applied, the draft recommendations will produce more benefits for	☐	☐	☐

patients than harms.			
12. The draft guideline presents options that will be acceptable to patients.	☐	☐	☐
13. To apply the draft recommendations will require reorganization of services/care in my practice setting.	☐	☐	☐
14. To apply the draft guideline recommendations will be technically challenging.	☐	☐	☐
15. The draft guideline recommendations are too expensive to apply.	☐	☐	☐
16. The draft guideline recommendations are likely to be supported by a majority of my colleagues.	☐	☐	☐
17. If I follow the draft guideline recommendations, the expected effects on patient outcomes will be obvious.	☐	☐	☐
18. The draft guideline recommendations reflect a more effective approach for improving patient outcomes than is current usual practice. (If they are the same as current practice, please tick NA). NA ☐	☐	☐	☐
19. When applied, the draft guideline recommendations will result in better use of resources than current usual practice. (If they are the same as current practice, please tick NA). NA ☐	☐	☐	☐
20. I would feel comfortable if my patients received the care recommended in the draft guideline.	☐	☐	☐
21. This draft guideline should be approved as a practice guideline.	☐	☐	☐
22. If this draft guideline were to be approved as a practice guideline, I would use it in my own practice.	☐	☐	☐
23. If this draft guideline were to be approved as a practice guideline, I would apply the recommendations to my patients.	☐	☐	☐

Adapted from: Brouwers, M.C., Graham, I.D., Hanna, S.E., Cameron, D.A., & Browman, G.P. (2004). Clinicians' assessments of practice guidelines in oncology: The CAPGO survey**.** International Journal of Technology Assessment in Health Care, 20(4), 421-6.

Appendix G
Appraisal of Guidelines for Research & Evaluation II (AGREE II)

DOMAIN 1. SCOPE AND PURPOSE

1. The overall objective(s) of the guideline is (are) specifically described.

1 Strongly Disagree	2	3	4	5	6	7 Strongly Agree

Comments

2. The health question(s) covered by the guideline is (are) specifically described

1 Strongly Disagree	2	3	4	5	6	7 Strongly Agree

Comments

3. The population (patients, public, etc.) to whom the guideline is meant to apply is specifically described.

1 Strongly Disagree	2	3	4	5	6	7 Strongly Agree

Comments

DOMAIN 2. STAKEHOLDER INVOLVEMENT

4. The guideline development group includes individuals from all relevant professional groups

1 Strongly Disagree	2	3	4	5	6	7 Strongly Agree

Comments

5. The views and preferences of the target population (patient, public, etc.) have been sought.

1 Strongly Disagree	2	3	4	5	6	7 Strongly Agree

Comments

6. The target users of the guideline are clearly identified.

1 Strongly Disagree	2	3	4	5	6	7 Strongly Agree

Comments

DOMAIN 3. RIGOUR OF DEVELOPMENT

7. Systematic methods were used to search for evidence.

1 Strongly Disagree	2	3	4	5	6	7 Strongly Agree

Comments

8. The criteria for selecting the evidence are clearly described.

1 Strongly Disagree	2	3	4	5	6	7 Strongly Agree

Comments

9. The strengths and limitations of the body of evidence are clearly described.

1 Strongly Disagree	2	3	4	5	6	7 Strongly Agree

Comments

10. The methods for formulating the recommendations are clearly described.

1 Strongly Disagree	2	3	4	5	6	7 Strongly Agree

Comments

11. The health benefits, side effects, and risk have been considered in formulating the recommendations.

1 Strongly Disagree	2	3	4	5	6	7 Strongly Agree

Comments

12. There is an explicit link between the recommendations and the supporting evidence.

1 Strongly Disagree	2	3	4	5	6	7 Strongly Agree

Comments

13. The guideline has been externally reviewed by experts prior to its publication.

1 Strongly Disagree	2	3	4	5	6	7 Strongly Agree

Comments

14. A procedure for updating the guideline is provided.

1 Strongly Disagree	2	3	4	5	6	7 Strongly Agree

Comments

DOMAIN 4. CLARITY OF PRESENTATION

15. The recommendations are specific and unambiguous.

1 Strongly Disagree	2	3	4	5	6	7 Strongly Agree

Comments

16. The different options for management of the condition or health issue are clearly presented.

1 Strongly Disagree	2	3	4	5	6	7 Strongly Agree

Comments

17. Key recommendations are easily identifiable.

1 Strongly Disagree	2	3	4	5	6	7 Strongly Agree

Comments

DOMAIN 5. APPLICABILITY

18. The guideline describes facilitators and barriers to application.

1 Strongly Disagree	2	3	4	5	6	7 Strongly Agree

Comments

19. The guideline provides advice and/or tools on how the recommendation can be put into practice.

1 Strongly Disagree	2	3	4	5	6	7 Strongly Agree

Comments

20. The potential resource implications of applying the recommendations have been considered.

1 Strongly Disagree	2	3	4	5	6	7 Strongly Agree

Comments

21. The guideline presents monitoring and/or auditing criteria.

1 Strongly Disagree	2	3	4	5	6	7 Strongly Agree

Comments

DOMAIN 6. EDITORIAL INDEPENDENCE

22. The views of the funding body have not influenced the content of the guideline.

1 Strongly Disagree	2	3	4	5	6	7 Strongly Agree

Comments

23. Competing interests of guideline development group members have been recorded and addressed.

1 Strongly Disagree	2	3	4	5	6	7 Strongly Agree

Comments

OVERALL GUIDELINE ASSESSMENT

1. Rate the overall quality of this guideline.

1 Strongly Disagree	2	3	4	5	6	7 Strongly Agree

Comments

2. I would recommend this guideline for use.

Agree II Tool

Appraisal of Guidelines for Research & Evaluation II

DOMAIN 1. SCOPE AND PURPOSE

1. The overall objective(s) of the guideline is (are) specifically described.
2. The health question(s) covered by the guideline is (are) specifically described
3. The population (patients, public, etc.) to whom the guideline is meant to apply is specifically described.

DOMAIN 2. STAKEHOLDER INVOLVEMENT
4. The guideline development group includes individuals from all relevant professional groups
5. The views and preferences of the target population (patient, public, etc.) have been sought.
6. The target users of the guideline are clearly identified.

DOMAIN 3. RIGOUR OF DEVELOPMENT
7. Systematic methods were used to search for evidence.
8. The criteria for selecting the evidence are clearly described.
9. The strengths and limitations of the body of evidence are clearly described.
10. The methods for formulating the recommendations are clearly described.
11. The health benefits, side effects, and risk have been considered in formulating the recommendations.
12. There is an explicit link between the recommendations and the supporting evidence.
13. The guideline has been externally reviewed by experts prior to its publication
14. A procedure for updating the guideline is provided.

DOMAIN 4. CLARITY OF PRESENTATION
15. The recommendations are specific and unambiguous.
16. The different options for management of the condition or health issue are clearly presented.
17. Key recommendations are easily identifiable.

DOMAIN 5. APPLICABILITY
18. The guideline describes facilitators and barriers to application
19. The guideline provides advice and/or tools on how the recommendation can be put into practice.

20. The potential resource implications of applying the recommendations have been considered
21. The guideline presents monitoring and/or auditing criteria

DOMAIN 6. EDITORIAL INDEPENDENCE
22. The views of the funding body have not influenced the content of the guideline.
23. Competing interests of guideline development group members have been recorded and addressed

OVERALL GUIDELINE ASSESSMENT
1. Rate the overall quality of this guideline.
2. I would recommend this guideline for use.

Appendix H

A Critical Group Appraisal of: Tranexamic Acid for Hip and Knee Arthroplasty Using the AGREE II Instrument

Domain 1	Domain 2	Domain 3	Domain 4	Domain 5	Domain 6	OA 1	OA 2
89%	86%	71%	82%	60%	58%	75%	Yes - 2, Yes with modifications - 2, No - 0

Domain 1. Scope and Purpose				
	Appraiser 3	Appraiser 2	Appraiser 1	Appraiser 5
Item 1	6	4	7	7
Item 2	7	4	7	7
Item 3	7	6	7	7
Domain 2. Stakeholder Involvement				
	Appraiser 3	Appraiser 2	Appraiser 1	Appraiser 5
Item 4	7	3	7	7
Item 5	7	4	7	7
Item 6	6	5	7	7

Domain 3. Rigour of Development				
	Appraiser 3	Appraiser 2	Appraiser 1	Appraiser 5
Item 7	5	3	7	7
Item 8	5	5	7	7
Item 9	1	3	7	7
Item 10	4	4	7	7
Item 11	5	4	7	7
Item 12	6	4	7	7
Item 13	1	5	6	7
Item 14	1	2	7	6
Domain 4. Clarity of Presentation				
	Appraiser 3	Appraiser 2	Appraiser 1	Appraiser 5
Item 15	5	3	7	7
Item 16	6	4	7	7
Item 17	7	4	7	7

Domain 5. Applicability				
	Appraiser 3	Appraiser 2	Appraiser 1	Appraiser 5

Item 18	2	3	7	5
Item 19	5	3	7	7
Item 20	4	2	7	7
Item 21	1	1	6	7
Domain 6. Editorial Independence				
	Appraiser 3	Appraiser 2	Appraiser 1	Appraiser 5
Item 22	4	1	6	7
Item 23	4	1	6	7

Overall Assessment				
	Appraiser 3	Appraiser 2	Appraiser 1	Appraiser 5
OA1	5	3	7	7

Appendix I

Practitioner Feedback Questionnaire Results

Practioner Feedback Questionnaire Results	n=	Totals Yes	% of total	Totals No	% of Total	Total Unsure	%of Total
Rationale for developing this guideline is clear	11	11	1	0	0	0	0
There is a need for a guideline on this topic	11	11	1	0	0	0	0
Literature search is relevant and complete	11	9	0.818181818	2	0.181818182	0	0
I agree with methodology used to summarize evidence	11	11	1	0	0	0	0
Results of the evidence described in this draft guideline are interpreted according my understanding of evidence	11	11	1	0	0	0	0
Draft recommendations in this report are clear	11	11	1	0	0	0	0
I agree with the draft recommendations as stated	11	7	0.636363636	3	0.272727273	1	0.090909
Draft recommendations are suitable for the patients for whom they are intended	11	10	0.909090909	1	0.090909091	0	0
Draft recommendation are too rigid	11	2	0.181818182	3	0.272727273	6	0.545455
When applied, the draft recommendations will produce more benefits for patients than harm	11	6	0.545454545	5	0.454545455	0	0
Draft guideline presents options that will be acceptable to patients	11	7	0.636363636	4	0.363636364	0	0
To apply the draft recommendations will require reorganization of services/care in my practice setting	11	6	0.545454545	3	0.272727273	2	0.181818
To apply the draft recommendations will be tenchincally challenging	11	5	0.454545455	2	0.181818182	4	0.363636
Draft guideline recommnedations are too expensive to apply	11	2	0.181818182	4	0.363636364	5	0.454545
Draft guidelines will be supported by majority of my colleagues	11	6	0.545454545	3	0.272727273	2	0.181818
Draft guideline recommendations, the expected effects on pt outcomes will be obvious	11	7	0.636363636	4	0.363636364	0	0
Draft guideline receommendations reflect a more effective approach for improving patient outcomes than is current usual practice	9	6	0.666666667	3	0.333333333	0	0
When applied, the recommendations will result in better use of resources than current usual practice	9	6	0.666666667	3	0.333333333	0	0
I would feel comfortable if my patients received the care recommended in the draft guideline	11	8	0.727272727	3	0.272727273	0	0
This draft guideline should be approved as a practice guideline	11	6	0.545454545	4	0.363636364	1	0.090909
I would use this in my own practice if this CPG were approved	11	6	0.545454545	4	0.363636364	1	0.090909
I would apply these recommendations to my patients if this guideline was approved	11	6	0.545454545	3	0.272727273	2	0.181818
CRNA or MD	11	11	1	0	0	0	0
Clinical Years of Experience	11		Age Mean	Age Median	Age Mode		
			4.909090909	3	1		

Appendix J
TXA Candidacy Form

	Yes	No
Allergy/Hypersensitivity to TXA		
Coronary or vascular stent placed within the past year		
Deep vein thrombosis, pulmonary embolus, myocardial ischemia, or ischemic stroke within the past year		
Seizure disorder		
History of Subarachnoid Hemorrhage		
Active hypercoagulable state		
Retinal vein or artery occlusion or history of colorblindness		
Patients taking hormonal oral contraceptives		
Recent or active cancer diagnosis		
Renal failure (Serum Creatinine > 1.5 mg/dL)		
Pt is eligible for TXA	Yes	No