Health Technology Assessment

Peer Review, Public and Washington State Agency Comments & Responses

Total Knee Arthroplasty

September 22nd, 2010

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1. SPECTRUM RESEARCH RESPONSE TO PEER REVIEW COMMENTS

No formal peer review comments were received by the closing date.
No comments were received from the Washington State Agency.
Letters to the editor were submitted by Mr. Mike L. McClure, Director/Strategic Reimbursement, Smith and Nephew, Inc. after the closing date. Those letters are included below.

2. SPECTRUM RESEARCH RESPONSE TO PUBLIC COMMENTS

Response to Dr. Bert J. Thomas, M.D.; Professor of Orthopaedic Surgery; Chief, Joint Replacement Service; David Geffen School of Medicine at UCLA

Comment 1

We chose the two metaanalyses that contained the most robust number of randomized trials (though non-randomized trials were also included).

Comment 2
We did not include data from case series.

Comment 3
We did not evaluate the one month outcomes of independent ambulation.

Comment 4
We updated our report with the p-value in table for Ek and a comment in the text on page 62.

Comment 5
Longstaff evaluates function and alignment in those that received CONV-TKA (no CN-TKA). We included the article by Choong that also evaluates the association between alignment and function using both CN-TKA and CONV-TKA.

Comments 6, 7
These outcomes were not part of our inclusion criteria.

Comment 8
This study is from an administrative database. In general, administrative databases contain data that have been gathered as a by-product of some other process; the data may be collected and entered by hundreds of individuals at many locations; usually, there are few, if any, quality checks on the data; records may have different lengths and structures within the same database; and missing data are common.(Lange, 1993; Baron, 2000) One of the most obvious disadvantages is that these systems were not created for research

purposes and, in most cases, researchers did not have input into the design or types of information collected by the systems. They may lack some of the details that researchers might want.(Cowper, 1999) These characteristics of large databases lead to the controversy over their use in epidemiologic and health services research and point to the need to consider validity and reliability issues.(Connell, 1987; Flood, 1990)

References:

Lange, L. L., Jacox, A.: Using large data bases in nursing and health policy research. J Prof Nurs, **9:** 204, 1993

Baron, J. A., Weiderpass, E.: An introduction to epidemiological research with medical databases. Ann Epidemiol, **10:** 200, 2000

Cowper, D. C., Hynes, D. M., Kubal, J. D. et al.: Using administrative databases for outcomes research: select examples from VA Health Services Research and Development. J Med Syst, **23:** 249, 1999

Connell, F. A., Diehr, P., Hart, L. G.: The use of large data bases in health care studies. Annu Rev Public Health, **8:** 51, 1987

Flood, A. B.: Peaks and pits of using large data bases to measure quality of care. Int J Technol Assess Health Care, **6:** 253, 1990

Comment 9,10

These references are from the Proceedings of meetings. We included only peer-reviewed articles.

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3. Public Comments

1. Bert J. Thomas, M.D

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To whom it may concern:

I am the chief of the joint replacement service at UCLA, and over the past 25 years have developed some rather strong opinions regarding hip, knee, and shoulder replacements, and how they should be performed. The improvement in patients' lives after unicompartmental, bicompartmental, and total knee arthroplasty, are nothing short of a miracle. My vision is to make these procedures so reproducible that every patient will be able to achieve the same outstanding results. Computer navigation and robotic assisted surgery are tools that can help to achieve this goal.
I believe that in the near future, computer technology will assist with virtually every orthopaedic reconstructive procedure, and that young surgeons will wonder how anyone could ever have considered not using these 'smart tools'. I have therefore, signed on as a consultant with Smith&Nephew as a consultant to help this belief to become a reality, and must disclose this as a potential conflict of interest.

I have had the privilege of reviewing the Washington State's Health Technology Assessment Report, and appreciate the opportunity to make the following observations.

While the Health Technology Assessment Report has done a thorough and exhaustive review of the available literature on computer-assisted/navigated surgery, given the growing body of evidence evaluating the improved patient outcomes provided by computer-assisted navigation on TKA, it can be argued that certain clinical results are not captured in the report. I believe that these additional results are relevant to the reimbursement decision for computer-assisted navigation of TKA and should be considered when rendering the final decision.

The specific relevant studies and data points that are not included in the Health Technology Assessment Report include:

Mason et al. (2007) and Brin et al. (2010) both undertook meta-analyses of the clinical literature and concluded that component orientation and postoperative limb alignment were improved with surgical navigation. These studies were referenced but not reported by the Health Technology Assessment Report, which only reports the two meta-analyses that include the most clinical trials. However, both the Mason study as well as the Brin study report on a greater number of TKAs than either of the two studies reported by the committee. Mason reports the results of 3,437 procedures and Brin reports the results of 4,199 procedures; while the two studies reported by the committee include 2,482 procedures and 3,423 procedures.

The Health Technology Assessment Report does not include data from Tingart et al. (2008) who conducted a prospective case series involving 1,000 patients. In the computer-assisted group 94.8% of patients had a postoperative leg axis within range of ±3° compared to 74.4% in the conventional group.

The Health Technology Assessment Report includes the non-significant data from Dutton et al. (2008), but provides no discussion of the fact that patients who underwent navigated TKA had shorter hospital stays, and at one month follow-up significantly more patients in the navigated group were able to walk independently for more than 30 minutes.

In reporting the results of the study performed by Ek et al. (2008), the Health Technology Assessment Report includes the improved SF-12 scores in the computer navigation group, but does not additionally include the improved International Knee Score in the navigated group.

The Health Technology Assessment Report does not include data from Longstaff et al. (2009), whose data demonstrate that short-term function is improved by better alignment of the limb after TKR.

The Health Technology Assessment Report does not include data from Dillon et al. (2009), who used gait analysis to demonstrate that computer-assisted TKA improves knee function as compared to standard instruments.

The Health Technology Assessment Report does not include data from Saragaglia (2006), Han (2008), or Hakki (2009), all of which reported that computer navigation may allow a more quantifiable approach to soft-tissue balance, which according to Engh (2003) is a critical factor in restoring function after TKA, where failure to release contracted collateral ligaments can lead to accelerated implant wear.

The Health Technology Assessment Report does not include data from Browne (2010), who compared the early postoperative outcomes of computer navigated TKA to standard conventional TKA using a large nationwide database of 101,596 patients who underwent TKA in 2005. These authors reported no differences in postoperative mortality or complications, but did report a shorter length of stay and a lower rate of postoperative cardiac complications.

The Health Technology Assessment Report does not include data from Chambers et al. (2008), who found that patients who underwent TKR with surgical navigation on average reached oxygen saturation levels on air faster than the non-navigated group. These authors also reported that there was a lower need for oxygen and shorter length of hospital stay in the computer navigated group during the early post-operative period.

The Health Technology Assessment Report does not include data from Song et al. (2010), who reported mid-term clinical and radiographic outcomes of navigated TKR's as compared to the conventional technique. These authors reported that prosthetic loosening increases significantly when postoperative alignment exceeds 3° and implant survivorship improved when properly aligned.

<u>Key Question 1:</u> Evidence of efficacy and effectiveness of using computer-navigated total knee arthroplasty (CN-TKA) compared with conventional TKA

Overall Leg Alignment

The importance of varus/valgus alignment in total knee arthroplasty (TKA) has been documented extensively in the orthopedic literature over the years and is well accepted (Insall, 1985; Hungerford and Krackow, 1985; Moreland, 1988). In fact, Moreland went as far as to state that "Prosthetic alignment is the most important factor influencing postoperative loosening and instability… the major mechanisms of failure in TKA". Other investigators have further quantified the relationship between alignment and clinical outcomes, indicating that varus/valgus alignment in excess of 3° is strongly correlated to poor postoperative clinical results (Laskin, 1990; Ritter, 1994; Kumar and Dorr, 1997; Insall, 2002).

Ritter (1994) demonstrated that the highest rate of aseptic loosing occurred in knees with greater than ±4° of mal-alignment relative to the mechanical axis, and Jeffery (1991) demonstrated that the incidence of loosening over an 8-year period was 24% with a mechanical axis of greater than 3°, but only 3% with a mechanical axis of less than 3°. In regards to the relationship between alignment and survival of the implant, Rand and Coventry (1988) demonstrated a 10 year survival rate in excess of 90% with a varus/valgus alignment of less than 4°, which decreased dramatically to 73% with a varus/valgus alignment of more than 4°. In short, there is a significant body of clinical data to support the importance of postoperative leg alignment after total and partial knee replacement, where, for example, the above cited authors reported that:
The rate of implant loosening over 8 years was 24% in the mal-aligned group (with mal-aligned being defined as the mechanical axis exceeding ±3° from neutral) , but only 3% in the group where alignment was within 3°.
The 10-year survival rate of the implant was in excess of 90% when leg alignment was ±3° but only 73% when in excess of ±3°

Given the importance of postoperative leg alignment and its impact on implant longevity, anything that improves post-operative alignment should similarly impact implant longevity.
Many authors contend that computer navigation improves the accuracy of implanting the total knee prosthesis and therefore improves implant longevity. Published data also suggests that the incidence of implant mal-alignment is high and therefore a problem that must be addressed. For example, in 2004 Perlick reported a staggering 28% incidence of mal-alignment and Bathis similarly reported a 22% incidence of mal-alignment. There is a significant amount of evidence in the form of randomized controlled trials, prospective and retrospective case series and published reviews demonstrating that there is improved alignment when compared to conventional approaches (Jenny et al., 2001; Ritschl et al., 2002; Sparmann, et al., 2003; Bathis et al., 2004; Bolognesi and Hofmann, 2005; Chin, et al., 2005; Decking, et al., 2005; Haaker, et al., 2005; Keene, et al., 2006; Matziolis et al., 2007; Kamat et al., 2009; Luring et al., 2009; Weng, et al., 2009). Some authors have also reported that the use of computer navigation is associated with longer surgical times (Decking, et al. 2005; Bolognesi and Hofmann, 2005), as well as there being no difference in functional scores (such as Kamat et al., 2009). Most recently, Song et al. (2010) reported mid-term (5 years or greater) clinical and radiographic outcomes of navigated TKR's as compared to the conventional technique. The authors reported that prosthetic loosening increases significantly when post-operative alignment exceeds 3° and implant survivorship improved when properly aligned.

Other recent studies have similarly demonstrated that the use of computer navigation results in improved mechanical axis and component alignment, where there is a growing body of evidence to support previous findings. For example, Tingart et al. (2008) conducted a prospective case series involving 1000 patients (500 underwent computer navigated TKA and 500 underwent a conventional approach). In the computer-assisted group 94.8% of patients had a postoperative leg axis within range of ±3° compared to 74.4% in the conventional group. Similarly, Dutton et al. (2008) published the results of a prospective randomized trial (n=108) also demonstrating the benefit of computer navigation in improving postoperative alignment without short-term complications. The patients who underwent conventional TKA had shorter operating times, but longer hospital stays. These authors also reported that at one month significantly more patients in the navigated group were able to walk independently for more than 30 minutes compared to the conventional group. The difference was not significant at three and six months, and at six months similar improvements were noted in the mean scores of both groups, including the Oxford knee score, Knee Society score, and Short Form-36 scores.

A meta-analysis was undertaken by Mason et al. (2007) to examine alignment outcomes in computer-assisted TKR versus conventional TKR, where a systematic review of literature from 1990 to 2007 was performed. Based on the results, these authors concluded that alignment outcomes were significantly improved when surgical navigation is used. A meta-analysis was similarly performed by Brin et al. (2010), where 23 publications were reviewed. These authors also concluded that component orientation and postoperative limb alignment were improved with surgical navigation is used when performing TKA (analysis of component orientation included 3,058 TKAs, and analysis of limb alignment included 4,199 TKAs).

Functional Outcomes

In a prospective randomized trial of 108 patients, Dutton et al. (2008) reported that those patients who underwent navigated TKA had shorter hospital stays, and at one month follow-up significantly more patients in the navigated group were able to walk independently for more than 30 minutes. Another group of authors has reported that improved alignment from computer navigated TKR correlated with improved knee function scores and quality of life. Choong and colleagues (2009) reported the results of a randomized controlled trial comparing the alignment, function and patient quality-of-life outcomes between patients who underwent conventional and computer-assisted TKA (=115). Mean operating time was longer for the computer-assisted group, although there was no difference in blood loss between groups. Mean length of stay was 6 days for both groups. A total of 88% from the navigated group versus 61% of the conventional group achieved a mechanical axis within 3º of neutral. Patients with a mechanical axis within 3º demonstrated superior total International Knee Society (IKS) scores and Short-Form 36 scores at 6 weeks, 3 months, 6 months, and 12 months following surgery.

Another group of authors similarly reported improved functional and quality of life outcomes. Ek et al. (2008) reported the results of a matched-controlled retrospective study of 100 patients (50 in the navigated TKA group and 50 in the non-navigated group), in which the use of computer navigation resulted in better SF-12 and IKS scores, as compared to the non-navigated group. Longstaff et al. (2009) similarly reported that short-term function is improved by better alignment of the limb after TKR. In another recent study that was presented at the 2009 AAOS, clinical data was presented also demonstrating that computer-assisted TKA improves knee function as compared to standard instruments. In this study, Dillon et al. (2009) compared navigated, non-navigated, and non-TKR knee function as assessed by gait analysis. These authors reported that at 8 months maximum knee flexion was significantly better in the navigated group during walking, chair rising/sitting, and stairs ascent/stairs descent. Moreover, when analyzing other outcomes that are associated with normal daily activities (detection of a biphasic moment pattern, mean double stance support time, etc.), the computer navigated group was more similar to the control group (the non-TKR group).

Lastly, it is well recognized that soft-tissue balance and accurate gap balancing is a critical factor in restoring function after TKR. Engh (2003) reported that the failure to release contracted collateral ligaments can lead to accelerated implant wear, especially when treating severe deformity. Moreover, gap symmetry in both flexion and extension, joint line position, and posterior femoral offset needs to be fairly accurate for the joint to function optimally postoperatively. All of these parameters are interrelated, and the surgeon must ensure accuracy and precision while performing each stage of the procedure. To that end, Mullaji and colleagues (2009) reported that computer-assisted TKA provides excellent information regarding gap equality and symmetry throughout the knee ROM, and allows for precise release for deformities. Numerous other studies have similarly reported that computer navigation may allow a more quantifiable approach to soft-tissue balance (Saragaglia et al., 2006; Han et al., 2008; Hakki et al., 2009).

Key Question 3: Evidence of the safety of computer-navigated TKA or partial knee arthroplasty

Blood Loss and Transfusions

The blood loss that accompanies total knee arthroplasty (TKA) can be substantial. Many patients need perioperative blood transfusions. To avoid anemia and transfusion-related complications, the amount of blood loss and need for blood transfusions must be reduced. In a randomized controlled trial by Kalairajah et al.(2005) in which blood loss and rate of transfusions were assessed in a group of navigated TKA patients versus non-navigated TKA patients, blood loss was lower and fewer patients required blood transfusions in the navigated group. In more recent studies by Conteduca, et al. (2009) and Hinarejos et al. (2009) the investigators reported that intraoperative blood loss for patients who underwent navigated TKA was less than that of those who underwent conventional TKA. Most recently, in a study of 500 patients undergoing TKA, Schnurr et al. (2010) reported that the average blood loss in the drainages and the calculated total blood loss were significantly reduced in the computer navigated group. Moreover, these authors reported that the transfusion rate of the navigated group was almost halved.

Browne et al. (2010) compared the early postoperative outcomes of computer navigated TKA to standard conventional TKA using a large nationwide database and reported that after adjustment for patient characteristics. Using multivariate regression analysis the authors found no differences in postoperative mortality or complications for the majority of the measured outcomes, but nevertheless reported that computer navigation was associated with less postoperative cardiac complications in addition to a shorter length of stay and a trend toward fewer hematomas.

Emboli

In addition to reducing blood loss, studies have also shown that the use of computer navigation is correlated with a reduction in thromboemboli (Kalairajah et al., 2006; Ooi et al., 2008). Church et al. (2007) and Kalairajah et al. (2006) also reported a reduction in systemic emboli (as measured by trans-esophageal echocardiography) in a navigated TKR group as compared to a non-navigated group. Other authors have reported a reduction in post-operative confusion in patients who have received navigated TKR (Chauhan et al. 2004). There is also some evidence that the C-reactive protein level, a marker of systemic inflammatory response, is reduced with a navigated TKR (Shen et al. 2009). Lastly, a prospective study by Chambers et al. (2008) found that patients who underwent TKR with surgical navigation on average reached oxygen saturation levels on air faster than the non-navigated group. These authors also reported that there was a lower need for oxygen and a shorter length of hospital stay in the computer navigated group during the early post-operative period.

In summary, upon review of the clinical literature, it is clear that there are many benefits of navigated TKR as compared to the traditional technique. Some of these benefits include:
Reduced blood loss and incidence blood transfusion (Kalairajah et al., 2005; Conteduca, et al., 2009; Hinarejos et al., 2009; Schmurr et al., 2010)
Less postoperative cardiac complications in addition to a shorter length of stay and a trend toward fewer hematomas (Browne et al., 2010)
A reduction in the incidence of thromboemboli/systemic emboli (Kalairajah et al., 2006; Church et al., 2007; Ooi et al., 2008)

Key Question 5: Evidence of cost implications and cost-effectiveness of computer navigated

TKA or partial knee arthroplasty

Given the current healthcare economic environment which is characterized by increasing pressures to reduce the cost of care and/or improve efficiencies, the question has arisen as to whether the use of computer-assisted surgery can be a cost-effective tool to justify its added cost. Although variability in published outcomes introduces some level of uncertainty in determining the cost-effectiveness, Novak et al. (2007) demonstrated that computer-assisted surgery achieved cost-savings if the added cost of using the device is $629 or less per operation. As this seems to be within the range of what the navigation system manufacturers are willing to charge on a per-use basis, it may be that the use of surgical navigation for knee arthroplasty is cost-effective. Moreover, this cost savings is calculated based only on the probability of increased rate of revision (as a function of mal-alignment), and does not account for additional sources of additional cost savings such as the decreased cost of blood products and the reduced risk of venous thromboemboli.

In summary, computer technology offers a cost-effective tool to prevent outliers, decrease emboli, blood loss, cardiac complications, and hospital stay, while increasing the survival of knee reconstruction with unicompartmental, bicompartmental or total knee replacement.

Sincerely,

Bert J. Thomas, M.D.
Professor of Orthopaedic Surgery
Chief, Joint Replacement Service
David Geffen School of Medicine at UCLA

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2. Mr. Mike L. McClure

From: McClure, Michael [mailto:Michael.McClure@smith-nephew.com]
Sent: Tuesday, September 07, 2010 8:27 AM
To: Santoyo, Denise (HCA)
Cc: Frandsen, Tim; William Alkire
Subject: RE: HTA Updates: Total Knee Arthroplasty and Routine Ultrasound Draft Evidence Reports

Ms. Santoya,
I hope this email finds you well. I look forward to the October meeting regarding knee arthroplasty. I am fully aware the time has past for comments which could alter the draft assessment but I wanted to make you aware of an issue brought to my attention by Tim Frandsen Ph.D. M.B.A. who has responsibility for Computer Assisted Surgery at Smith & Nephew. I am providing a link to a response to an article concerning several meta analysis cited by Spectrum. The use and understanding of these meta-analyses leaves CAS in an unnecessarily unflattering light due to information in the analyses being interpreted incorrectly in the draft assessment. The link explains the issues with interpreting results of both Bauwens and Mason meta analysis. This is a fairly serious error in judging the evidence and presenting a fair and unbiased assessment of CAS to your panel.
I apologize for the tardiness of this information but there was insufficient time to respond to the initial draft assessment due to its length and complexity.

http://www.ejbjs.org/cgi/eletters/89/2/261#3881

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Letters to the Editor to:

Scientific Articles:
Kai Bauwens, Gerrit Matthes, Michael Wich, Florian Gebhard, Beate Hanson, Axel Ekkernkamp, and Dirk Stengel
Navigated Total Knee Replacement. A Meta-Analysis
J Bone Joint Surg Am 2007; 89: 261-269
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Dr. Katz & Dr. Losina comment on Navigated Total Knee Replacement.

17 September 2007

Jeffrey N. Katz, M.D., MSc
Orthopaedic & Arthritis Center for Outcomes Research, Brigham & Women's Hospital, Boston, MA 02115,
Elena Losina, Ph.D.

Send letter to journal:
Re: Dr. Katz & Dr. Losina comment on Navigated Total Knee Replacement.

E-mail Jeffrey N. Katz, M.D., MSc, et al.

To The Editor:

In their meta-analysis of the effectiveness of navigated total knee replacement, Bauwens et al.(1) found that navigation was associated with favorable results in terms of several radiographic parameters. The data were insufficient to evaluate effects on complication rates or functional outcomes. The article stimulated the above letter from Mason et al.(2) and a letter from Gregori and Holt(3), which prompted additional letters of clarification from Bauwens et al.(1).

Caught in the crossfire, readers might well ask why a meta-analysis led to such editorial dueling. Of note, controversy over meta-analysis is long-standing(4). The debates stem in part from the methodological complexity of meta-analysis, a powerful but challenging analytic technique that permits pooling of estimates across studies. We will discuss a few of the many methodological complexities of meta-analysis to put the correspondence about navigated total knee replacement in perspective.

Why Pool? Meta-Analysis Compared with Traditional Literature Review

If pooling raises so many questions, why bother to pool estimates quantitatively across studies? In many reviews, the authors simply array the findings of separate studies in evidence tables without attempting to synthesize them quantitatively into single estimates of effect. A key rationale for pooling is that the available evidence may consist of small studies that show positive (or negative) effects but lack power to establish the associations with significance. Pooling these smaller studies may avoid false-negative results due to Type-II error.

A useful example of this application of meta-analysis was provided by Felson and Anderson in a meta-analysis of the effect of cytotoxic therapy and corticosteroids compared with that of corticosteroids alone for patients with lupus nephritis(5). Prior small studies had suggested a beneficial effect of cytotoxic therapy. The meta-analysis overcame the small sample sizes of the component studies and illustrated the beneficial effect of cytotoxic therapy across studies.

Pooling also permits the investigator to examine whether particular study characteristics are associated with the principal outcome. This technique is termed metaregression. The investigator develops a regression model in which each study serves as a single observation, contributing a single estimate of outcome and of each covariate. The investigator can weight studies differentially in order to give greater importance in the regression to those that have larger sample sizes or that are of higher methodological quality. Metaregression can yield insights about sources of variability in outcome measures across studies. For example, it may be that trial designs are associated with larger effects and nonrandomized designs, with smaller effects, or vice versa.

Why Not Pool?

Pooling the results of separate studies into single estimates of effect involves several assumptions that frequently are not satisfied by the literature under review. Clearly, the outcome variable must be consistent across studies. This constraint poses no problem when the outcome is unambiguously defined, such as thirty-day all-cause mortality following hip replacement. However, when studies measure satisfaction, pain relief, functional status, and other such complex outcome variables, the task becomes more complicated. These domains are often measured with different tools in different studies, or different cutoffs are used to define success. For example, the authors of some studies of the outcome of total knee replacement might use the WOMAC (Western Ontario and McMaster Universities Osteoarthritis Index) as the principal outcome measure whereas others might use the SF-36 (Short Form-36) or the Knee Society Scale. Attempting to synthesize results in these circumstances involves essentially combining apples and oranges and is not advisable. Standardization of outcome assessment and reporting in specific fields would assist investigators who wish to perform meta-analysis.

In addition, the underlying statistical methodology of meta-analysis assumes that each of the studies to be synthesized represents one observation from a single distribution of studies. This assumption is validated with tests of homogeneity of the odds ratios (or other effect estimates) across studies. If the group of studies to be synthesized appears to emanate from a single distribution, the homogeneity criterion is met and the studies may be synthesized in a meta-analysis. If, on the other hand, the assumption of homogeneity is not met, and the studies appear to be heterogeneous, then the investigators should be cautious about pooling. The investigators could simply choose not to pool the studies quantitatively. Alternatively, the investigators might wish to perform a metaregression to identify sources of heterogeneity. For example, it may be that higher-quality studies or a particular study design (e.g., trials) are associated with higher effect estimates.

What to Pool?

A meta-analysis is essentially an observational study of individual studies(6). As with all observational studies, the results are influenced by the selection criteria that dictate which studies are included in the meta -analysis and which are excluded. An issue that arises frequently, and was a major focus of contention about the paper by Bauwens et al.(1), is whether to include unpublished studies. Excluding unpublished studies risks publication bias, a form of selection bias in meta-analyses that arises because positive studies are, on the average, more likely to be published than negative studies. However, including unpublished studies that have not passed peer review risks the inclusion of studies with results that may not be credible.

Another important decision is whether to restrict the analysis to randomized controlled trials or to include observational designs. The advantage of restricting the analysis to randomized controlled trials is that randomization greatly reduces the risk of selection bias in each component study of the meta-analysis. Including observational studies permits the meta-analysis to simply propagate the biases inherent in the component studies. The disadvantage of restricting the sample to randomized controlled trials is that for many clinical problems, including navigated total knee replacement, there are few randomized controlled trials and most of the relevant literature includes observational designs.

Returning to Navigated Total Knee Replacement

Bauwens et al.(1) handled most of the above-mentioned issues with sophistication. They decided to pool because they were concerned that multiple underpowered studies would fail to establish an effect that might become apparent in a pooled analysis. They included nonrandomized trials because they were not comfortable restricting the analysis to randomized controlled trials. (An alternative approach would be to use metaregression to examine whether the magnitude of effect differed between randomized and observational studies; if it did, the meta-analysis could be done in subgroups.) The authors weighted the studies according to sample size and quality. They used appropriate analytic techniques to look for publication bias and, finding no evidence of such a bias, they restricted the analysis to published studies. In addition to stating the results of these analyses of publication bias, displaying the graphical evidence would have been helpful to readers.

Bauwens et al.(1) concluded that the studies that they wished to synthesize were heterogeneous. Having established heterogeneity, the authors could have simply decided not to pool the studies at all. Alternatively, they could have developed a metaregression model, which would have been useful in identifying and ultimately controlling for sources of heterogeneity. They could have stratified according to such characteristics and tested whether the stratified meta-analysis would have yielded less heterogeneity. The authors did indeed perform a metaregression, but they did not use it to identify strata in which studies were more homogeneous, as discussed here. By documenting heterogeneity and not doing anything about it, the authors in a sense, made a diagnosis without offering a remedy.

Data Sharing

Synthesizing the results of various studies is ultimately a collaborative activity. The investigator will often wish to contact other scientists who have access to original trial data or who themselves have attempted a data synthesis. These collaborations can help move the field forward. In fact, the National Institutes of Health (NIH) and other research sponsors have developed specific provisions for facilitating data sharing in order to best leverage the precious data garnered in NIH-funded studies. In this regard, we were particularly impressed by the willingness of Bauwens et al.(1) to share their data and we were disappointed that Mason et al.(2) chose to communicate their observations in a letter to The Journal without discussing the findings with the original authors. Readers, and ultimately patients, were not served well by this failure to behave collaboratively.

Concluding Remarks

The meta-analysis by Bauwens et al.(1) prompted questions about selection of studies, choice of common outcome measures across studies, assessment and management of heterogeneity, interpretation of results, and approaches to collaboration. The lessons learned from these studies of navigated total knee replacement are that investigators should make individual studies as definitive as possible by using the most rigorous designs feasible, powering studies adequately, and using standardized measures of outcome. Pooling is a powerful method for aggregating information across studies, but it is ultimately a collaborative effort. Leaders in the field should designate standard measures of outcome to facilitate pooling, and investigators should work collaboratively with one another so that data syntheses move the field forward, bringing quality and value to patients.

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of their research for or preparation of this work. Neither they nor a member of their immediate families received payments or other benefits or a commitment or agreement to provide such benefits from a commercial entity. No commercial entity paid or directed, or agreed to pay or direct, any benefits to any research fund, foundation, division, center, clinical practice, or other charitable or nonprofit organization with which the authors, or a member of their immediate families, are affiliated or associated.

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1. Bauwens K, Matthes G, Wich M, Gebhard F, Hanson B, Ekkernhamp A, Stengel D. Navigated total knee replacement. A Meta-Analysis. J Bone Joint Surg Am 2007;89:261-269.

2. Bauwens K, Matthes G, Wich M, Gebhard F, Hanson B, Ekkernhamp A, Stengel D. Navigated total knee replacement. A Meta-Analysis. J Bone Joint Surg Am 2007;89:261-269. [Letter to The Editor] J Bone Joint Surg Am. epub 25 Jul 2007. http://www.ejbjs.org/cgi/eletters/89/2/261.

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"Review of Navigated Total Knee Replacement: A Meta Analysis by Bauwens et al."

25 July 2007

J. Bohannon Mason, M.D.,

To The Editor:

OrthoCarolina Hip and Knee Center, NORTH CAROLINA
,
Thomas Fehring, M.D., and Kyle Fahrbach, Ph.D.

Send letter to journal:
Re: "Review of Navigated Total Knee Replacement: A Meta Analysis by Bauwens et al."

E-mail J. Bohannon Mason, M.D., et al.

We read with interest and concern the article, Navigated Total Knee Replacement: A Meta Analysis by Bauwens et al.(1). We submitted a similar meta-analysis to the Journal of Bone Surgery over one year ago, which was appropriately rejected for publication due to the inclusion of abstracts and uncontrolled case series data. The reviewers and editors also expressed concern that our finding of an advantage for navigated total knee arthroplasty (TKA) versus conventional TKA based on radiographic alignment endpoints needed to be balanced against the lack of evidence comparing the two procedures on cost-effectiveness, complication rates, and long term outcomes.

We were in the process of updating our meta-analysis in light of more recent publications (excluding abstract and uncontrolled case series data), when the study by Bauwens et al.(1) was published. Having reviewed essentially the same database, we were perplexed by the authors' conclusions that “navigated knee replacement provided few advantages over conventional surgery on the basis of radiographic endpoints”, as our own meta-analysis revealed a significant improvement in radiographic endpoints with computer-assisted navigation.

Our concerns about the discrepancies between our findings and those of Bauwens et al. prompted us to investigate their source data. We contacted them, and they graciously provided us with the raw data for all studies included in their meta-analysis. Upon further review, we discovered multiple inaccuracies of data extraction and/or data entry in their analysis:

In four of the studies reviewed in the Bauwens article(2-5) the data for conventional techniques was entered into the navigated data set for analysis while the data for the navigated set was entered under conventional techniques.

In four additional studies(6-9) we were able to determine errors of data extraction, data entry, patient count or patient group assignment.

One paper(10) was included and counted as reporting mechanical axis data when this was not reported in the study.

A kinship study (i.e., a study sharing overlapping data with an already included study) was included that should have been excluded(11).

There were two additional studies (12,13) in which the numbers we extracted were slightly different from those in Bauwens et al; we note these only as discrepancies (not errors) in extraction.

Our further review of their paper also suggests that their labeling and description of results was misleading. Specifically, they describe their meta-analyses as those of “relative risk of malalignment”, and label their figures accordingly. Yet, in the discussion, they state that “the available data suggest that navigation reduces the relative risk of 3 degrees of malalignment by 25%”. This statement is in error, because their meta-analysis was not of the relative risk of malalignment, but rather the relative risk of alignment, (i.e., the chance that a patient has alignment after the procedure). It would, therefore, have been accurate for them to state that conventional total knee arthroplasty decreases the relative chance of alignment by 25%. When misfit is the outcome of choice, instead of fit, the results are quite different from those reported by Bauwens et al. Correctly stated, the risk of malalignment is approximately three times that with conventional replacement relative to CAS.

In conclusion, our findings of data extraction and entry errors cause us to challenge the conclusions in the article regarding the meta-analysis of radiographic endpoints in conventional versus navigated knee replacement surgery. A correct data analysis demonstrates overwhelming evidence of a much lower error rate with navigation. Reversal of some of the extracted data and misreporting relative risks for fit as risks of malalignment is partially responsible for the muted difference that Bauwens described between navigated and conventional total knee arthroplasty. These errors, however, do not obviate Bauwens’ other discussion points regarding methodological limits of the available trials, including a dearth of evidence on long term outcomes, quality of life, and costs.

While we recognize and understand the challenges inherent in performing meta-analyses, our intent is to bring these errors to the attention of the readers of the Journal to correct any erroneous impression this work may have left with the readership.

In support of their research for or preparation of this work, one or more of the authors received, in any one year, outside funding or grants in excess of $10,000 from Depuy, and Johnson & Johnson. Neither they nor a member of their immediate families received payments or other benefits or a commitment or agreement to provide such benefits from a commercial entity. No commercial entity paid or directed, or agreed to pay or direct, any benefits to any research fund, foundation, division, center, clinical practice, or other charitable or nonprofit organization with which the authors, or a member of their immediate families, are affiliated or associated.

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1. Kai Bauwens, Gerrit Matthes, Michael Wich, Florian Gebhard, Beate Hanson, Axel Ekkernkamp, and Dirk Stengel Navigated Total Knee Replacement. A Meta-Analysis J Bone Joint Surg Am 2007; 89: 261-269

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Dr. Stengel et al. respond to Dr. Mason.

25 July 2007

Dirk Stengel, M.D., Ph.D, MSc.
Center for Clinical Research, Department of Trauma & Orthopedic Surgery, Berlin, GERMANY,
Kai Bauwens, M.D, Gerrit Matthes, M.D., Michael Wich, M.D., Florian Gebhard, M.D., PhD, Beate Hanson, M.D., MPH, Axel Ekkernkamp, M.D., PhD.

Send letter to journal:
Re: Dr. Stengel et al. respond to Dr. Mason.

E-mail Dirk Stengel, M.D., Ph.D, MSc., et al.

We read with great interest the letter from Dr. Mason and colleagues. Since they raised substantial concerns about the validity of our findings, we carefully reviewed the dataset that formed the basis for all analyses and figures presented in the Journal.

We reviewed our references 2-5 and found that there was no data shift between the conventional and navigated groups. This was unlikely, since the forest plots consistently showed an advantage for the navigated cohort.

Mason et al. also claimed that they found additional errors of data extraction from our references 6 to 9, but unless they are more specific in their criticisms, we cannot respond properly.

We would refer the Dr. Mason et al. to the Methods Section of our paper, where we stressed that the numbers of patients were extracted from histograms whenever possible. This may explain most differences eventually noted between their and our dataset. Additional differences might be related to different handling of the unit of interest, that is, the patient or the knee. Indeed, Bolognesi and Hofmann(1) reported the alignment of the femoral and the tibial component rather than the mechanical axis. However, if navigation improves both femoral and tibial component alignment, it is very likely that the resulting mechanical axis will be optimized as well. Since the observed effects were consistent with others, we decided to include the study in our analysis. We definitely identified and excluded some kinship studies, but could not retrieve a dual publication published by Mielke and colleagues(2).

When posing a null-hypothesis it is important to define the accepted standard of care. Risk ratios and other relative measures are asymmetric. This was the reason why we also provided risk differences, that can be used for calculating the number needed to treat. Currently, navigation is an experimental add-on, and may either decrease the risk of malalignment, or increase the chance of alignment. It is, however, not justified to argue that conventional surgery would increase the relative risk of malalignment over navigated component placement. With regard to health policy decisions, this is a dangerous statement, since it would imply that all patients who are not operated on with computer assistance are at a higher risk of malalignment when compared to those who undergo conventional TKA by an experienced surgeon.

Importantly, our analyses and plots showed a significant advantage of navigated over conventional knee replacement in radiological surrogates, so we are in complete agreement with Dr. Mason. Yet, unless these advantages are consistent with improved outcomes, we feel that our conclusion "Navigated knee replacement provides few advantages over conventional surgery on the basis of radiographic end points" is valid.

Finally, we regret that Dr. Mason, after receiving our dataset (which shows our openness and willingness to engage in scientific debate), did not contact us again to compare both datasets, and to discuss, explore and resolve any possible differences jointly before submitting a Letter to the Editor challenging our scientific reputation. We are sorry that Dr. Mason's group could not publish their paper, but we are deeply disappointed in their behavior.

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Navigated Total Knee Arthroplasty--a Meta-analysis

27 March 2007

Alberto Gregori, Consultant Orthopaedic Surgeon
Hairmyres Hospital, East Kilbride, Scotland, UK,
Graeme Holt.

Send letter to journal:
Re: Navigated Total Knee Arthroplasty--a Meta-analysis

E-mail Alberto Gregori, et al.

To The Editor:

In their recent meta-analysis(1), Bauwens et al. concluded that "navigated knee replacement provides few advantages......on the basis of radiographic end points". However, our analysis of this paper suggests that this conclusion is invalid.

While meta-analysis of randomised controlled trials represents the gold standard in validation of surgical interventions, overcoming the reduced statistical power of small sample sizes, it cannot compensate for poor scientific methodology in the analyzed papers. The authors (1) included not only randomised, but also quasi-randomized controlled trials, non- randomized cohort studies, studies with historical cohorts, and studies investigating the outcome of CT or image-free navigation systems for both unicompartmental and total knee arthroplasty.

A meta-analysis must use a predefined, documented search strategy allowing assessment of its completeness; this was not reported. "Mean straightness of mechanical axes" is an inappropriate outcome measure. The mean mechanical axis says nothing about the distribution of values that it represents without reporting standard deviations and range, though 95% confidence intervals were stated. However, two groups may have significantly different distributions of alignment values centered about similar mean values.

Navigation reduces the number of implants with a predetermined variance from the true mechanical axis, commonly defined as ±3o. The authors estimate a risk ratio of a deviation of >3° with navigated versus conventional knee arthroplasty at 0.79 and 0.76 for a threshold of 2o. Navigation reduced the relative risk of >3° malalignment by 25% thus avoiding one additional patient with unfavorable component positioning in any five patients managed with computer-assisted instead of jig-based methods.

The authors conclude that “the benefits of navigation diminished rapidly with increasing thresholds of proper implant positioning”. If we were to accept a deviation of up to 6 degrees from the true mechanical axis then both conventional jig and navigation based arthroplasty are almost equally efficacious; however, this degree of error is greater than most arthroplasty surgeons would accept.

Navigated total knee arthroplasty improves implant alignment, but consequent improved implant survival remains unproven. We are concerned that this meta-analysis(1) will be regarded by many as definitive evidence even though its methodological shortcomings and interpretation of results do not justify the conclusions reached.

The authors did not receive any outside funding or grants in support of their research for or preparation of this work. Neither they nor a member of their immediate families received payments or other benefits or a commitment or agreement to provide such benefits from a commercial entity. A commercial entity (Biomet & BBraun) paid or directed in any one year, or agreed to pay or direct, benefits in excess of $10,000 to a research fund, foundation, division, center, clinical practice, or other charitable or nonprofit organization with which the authors, or a member of their immediate families, are affiliated or associated.

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1. Bauwens K, Matthes G, Wich M, Gebhard F, Hanson B, Ekkernkamp A, Stengel D. Navigated total knee replacement - A meta-analysis. J Bone Joint Surg Am. 2007;89(2):261-9.

Dr. Stengel & Dr. Bauwens respond to Dr. Gregori & Dr. Holt

27 March 2007

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Head, Center for Clinical Research
Dept. of Trauma & Orthopedics, Unfallkrankenhaus Berlin, Berlin, GERMANY,
Kai Bauwens, M.D.

Send letter to journal:
Re: Dr. Stengel &

We read with great interest the comments of Alberto Gregori and Graeme Holt on our meta-analysis. We believe all the issues they raise were clearly addressed in the printed article and the electronic appendix, but we will be happy to respond to their letter in a point-to-point fashion.

1. We do not agree that the conclusion of the abstract conflicts with current best evidence. Most trials focused on alignment, not function, quality of life, or cost. We feel that all would agree that higher

Dr. Bauwens respond to Dr. Gregori & Dr. Holt

E-mail Dirk Stengel, M.D., Ph.D., MSc, et al.

precision in restoring the physiological limb axis is an advantage of navigated over conventional total knee replacement, but patient-centered and health-economic values have more weight in clinical and political decision making. In the Discussion, we stressed the need for high-quality trials aiming at investigating clinically relevant outcomes.

2. Meta-analyses (especially in orthopedics) are often criticized for including only RCT, thereby limiting the external validity of the results. We are very much aware of the discrepancy between methodological and clinical demands. In the methods section, we clearly pointed out that we conducted a meta-regression analysis to account for different study designs. There was no meaningful difference in effect estimates between RCT and other study settings.

All key features of our search strategy were mentioned in the methods section. Specifically, we (i) reported all databases searched, (ii) tried diligently to avoid a tower of Babel bias by including studies of all languages, (iii) did a manual search, (iv) reported the study selection in a QUOROM flow-chart, (v) assessed methodological features by two or more independent raters, (vi) tested for publication bias and statistical heterogeneity. If we had missed any important quality criterion of a valid meta-analysis (or a relevant paper that contradicts our findings), we would be pleased to be informed by Drs.Gregori and Holt.

4. In the Discussion, we admitted the limits of the chosen endpoints- however, as indicated in their letter, this was not a shortcoming of the quantitative summary, but the lack of reporting of other endpoints in the original manuscripts.

Dr. Gregori and Dr. Holt conclude that navigated total knee arthroplasty improves implant alignment, but consequent improved implant survival remains unproven. We are happy about this conclusion, since it perfectly agrees with the findings of our meta-analysis.