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ARTHROPLASTY

Using tranexamic acid for an additional 24 hours postoperatively in hip and knee arthroplasty saves money: a cost analysis from the TRAC-24 randomized control trial

P. N. Karayiannis,
A. Agus,
L. Bryce,
J. C. Hill,
D. Beverland

From Musgrave Park Hospital, Belfast, UK

Aims

Tranexamic acid (TXA) is now commonly used in major surgical operations including orthopaedics. The TRAC-24 randomized control trial (RCT) aimed to assess if an additional 24 hours of TXA postoperatively in primary total hip (THA) and total knee arthroplasty (TKA) reduced blood loss. Contrary to other orthopaedic studies to date, this trial included high-risk patients. This paper presents the results of a cost analysis undertaken alongside this RCT.

Methods

TRAC-24 was a prospective RCT on patients undergoing TKA and THA. Three groups were included: Group 1 received 1 g intravenous (IV) TXA perioperatively and an additional 24-hour postoperative oral regime, Group 2 received only the perioperative dose, and Group 3 did not receive TXA. Cost analysis was performed out to day 90.

Results

Group 1 was associated with the lowest mean total costs, followed by Group 2 and then Group 3. The differences between Groups 1 and 3 (-£797.77 (95% confidence interval -1,478.22 to -117.32) were statistically significant. Extended oral dosing reduced costs for patients undergoing THA but not TKA. The reduced costs in Groups 1 and 2 resulted from reduced length of stay, readmission rates, emergency department attendances, and blood transfusions.

Conclusion

This study demonstrated significant cost savings when using TXA in primary THA or TKA. Extended oral dosing reduced costs further in THA but not TKA.

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Keywords: Cost analysis, Tranexamic acid, Hip arthroplasty, Knee arthroplasty

Introduction

Blood loss associated with total hip (THA) and total knee (TKA) arthroplasty can have a significant impact on outcomes for patients.[1] Tranexamic acid (TXA) is now commonly used in THA and TKA to reduce blood loss in low-risk patient groups, with strong evidence in the literature to support its use.[2-7] High-risk patients such as those with previous venous thromboembolism (VTE), myocardial infarction (MI), and cerebrovascular accidents (CVAs) have been excluded from orthopaedic trials to date.[8] Various dosing regimens have also been described, with support in the literature for extending oral or intravenous (IV doses of TXA to reduce blood loss further and potentially improve patient outcomes.[9,10] The most effective regime, however, remains unclear.

The TRAC-24 randomized control trial (RCT) aimed to assess the impact of extending administration of TXA orally for 24 hours postoperatively. Importantly, it did not exclude high-risk patients. It was the first randomized study to do so, and also one of the largest trials regarding use of TXA in

Correspondence should be sent to Mr Paul Nicholas Karayiannis; email: pkarayiannis01@qub.ac.uk

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Table I. Unit costs of health service use.

Resource items	Unit cost, £	Source	Details
Tranexamic acid 5 ml ampoule (100 mg/ml)	1.55	Drug Tariff (NI, December 2018)[19]	Cost per ampoule based on a pack of 10 × 5 ml ampoules (£15.47/10 = £1.55)
Tranexamic acid 500 mg	0.13	Drug Tariff (NI, December 2018)[19]	Cost per 500 mg tablet based on a pack of 60 × 500 mg tablets (£8.00/60 = £0.09)
Hip arthroplasty	5,507.00	Belfast Health and Social Care Trust Finance department (2017/18)	Average cost per episode for very major hip procedure (HN12F CC 0 to 1) based on average LOS of 3 days
Hip arthroplasty excess bed day	573.00	Belfast Health and Social Care Trust Finance department (2017/18)	
Knee arthroplasty	5,664.00	Belfast Health and Social Care Trust Finance department (2017/18)	Average cost per episode for very major knee procedure (HN22E CC 0 to 1) based on average LOS 3 days
Knee arthroplasty excess bed day	571.00	Belfast Health and Social Care Trust Finance department (2017/18)	
Non-elective (long stay) bed day	602.25	Department of Health Northern Ireland HRG Unit Costs Schedules (2017/18)[18]	Based on the weighted average cost of non-elective (long stay) and weighted average LOS
Unit of red blood cells	136.64	Northern Ireland Blood Transfusion Service (2018)	Freedom of information request
Blood transfusion (day case)	488.00	Department of Health Northern Ireland HRG Unit Costs Schedules (2017/18)[18]	Single plasma exchange or other intravenous blood transfusion, 19 years and over (SA44A, day case)
ED attendance	185.00	Department of Health Northern Ireland HRG Unit Costs Schedules (2017/18)[18]	

ED, emergency department; LOS, length of stay.

orthopaedics. The results revealed that extended oral dosing of TXA (1 g IV and then four oral doses over a 24-hour period postoperatively) significantly reduced blood loss in TKA but not THA, compared to a single IV dose or no TXA.[11,12] No increase in adverse thromboembolic events was reported despite the inclusion of high-risk patients.

Both THA and TKA are high-volume procedures with the potential for significant cost savings due to the cumulative effect of a large number of patients undergoing surgery.[13] Reduced costs associated with TXA in lower limb arthroplasty have been reported in retrospective studies. These savings are largely associated with a reduction in blood transfusions and their associated costs.[8,13,14] Reduced length of stay and improvements in early functional outcomes have also been reported.[15,16]

A cost analysis was undertaken in conjunction with this trial. The aim of this analysis was to assess the impact of the addition of TXA postoperatively on hospital resource use in comparison to an intraoperative intravenous bolus alone, or no TXA, for patients undergoing unilateral primary THA or TKA.

Methods

Trial design. TRAC-24 has been described in detail previously.[11,12,17] In brief, it was a phase IV, single-centre, open label, parallel group RCT. The Northern Ireland clinical trials unit (NICTU) coordinated the trial and four surgeons (DB, see Acknowledgements for others) from Musgrave Park Hospital enrolled their patients. The trial was registered on ClinicalTrials.gov (NCT03690037) and ISRCTN (ISRCTN58790500). The study was approved by the Office for Research Ethics Committees Cambridge East (16/EE/0068). Patients were eligible if aged between ≥ 18 and ≤ 100 years and were deemed fit for elective unilateral primary TKA or THA. Only patients with epilepsy, a metallic heart valve, known allergy to TXA, who were on renal dialysis, or could not/would not provide consent were excluded. Patients were randomly assigned to receive an intravenous bolus of TXA perioperatively plus oral TXA intervention (Group 1) or an intravenous bolus of TXA perioperatively (Group 2) or no TXA i.e. standard care/control (Group 3). Although TXA is known to reduce blood loss, TXA was not standard care in the unit, therefore it was included as a group but patients were allocated to the groups using a ratio of 2:2:1.

The analysis was undertaken from the perspective of secondary care and therefore only hospital-incurred costs were measured from the day of surgery until 90 days post-surgery. We included only non-elective hospital admissions and emergency department (ED) visits as these were likely to be related to their recent surgery. Outpatient attendances were therefore not included. As the analysis time horizon of the study was less than one year, discounting of costs was not necessary.

Data relating to the patient's primary hospital admission were collected prospectively via the case report form. This also captured any movements between units until primary hospital discharge. Readmissions, ED attendances, and transfusions in the period 90 days post-surgery were collected and recorded on the case report form, either directly from the patient via a follow-up phone call or by using patient information systems – electronic databases that record use of health and social

Table II. Hospital service use over 90 days by group for hip and knee patients. Values are number (percentages) of patients using the service.

	Group 1 (n = 471)		Group 2 (n = 476)		Group 3 (n = 134)	
Variable	**n (%)**	**Mean (95% CI)**	**n (%)**	**Mean (95% CI)**	**n (%)**	**Mean (95% CI)**
Primary admission including joint arthroplasty (mean days)	471 (100)	3.19 (2.93 to 3.45)	476 (100)	3.41 (3.16 to 3.66)	134 (100)	4.09 (3.24 to 4.94)
Non-elective hospital readmissions (mean days)	24 (5)	0.32 (0.15 to 0.49)	20 (4)	0.61 (-0.03 to 1.25)	12 (9)	0.75 (0.08 to 1.41)
ED (mean attendances)	51 (11)	0.15 (0.11 to 0.19)	45 (9)	0.13 (0.09 to 0.17)	24 (18)	0.21 (0.13 to 0.29)
Transfusions by 90 days	4 (1)	0	6 (1)	0	10 (7)	0

CI, confidence interval; ED, emergency department.

Table III. Mean (95% confidence interval) costs (£) of health service use over 90 days for hip and knee patients.

Variable	Group 1 (n = 471)	Group 2 (n = 476)	Group 3 (n = 134)
Primary admission including joint arthroplasty	5,695.54 (5,547.78 to 5,843.30)	5,821.40 (5,678.85 to 5,963.95)	6,209.37 (5,724.45 to 6,694.30)
Non-elective hospital readmissions	194.36 (92.96 to 295.75)	366.92 (-18.97 to 752.81)	449.44 (48.86 to 850.02)
ED	27.89 (19.85 to 35.93)	23.71 (16.49 to 30.93)	38.66 (23.61 to 53.71)
Transfusions	2.49 (-0.17 to 5.14)	3.16 (0.46 to 5.85)	24.62 (5.67 to 43.57)
TXA	4.05 (4.01 to 4.09)	3.27 (3.23 to 3.31)	0 (0)
Total cost (95% CI)	5,924.32 (5,736.80 to 6,111.84)	6,218.45 (5,790.59 to 6,646.32)	6,722.09 (6,085.98 to 7,358.20)
Mean difference in total cost (95% CI)			
Group 1 vs Group 2	-294.13 (-761.25 to 172.98)		
Group 1 vs Group 3	-797.77 (-1478.22 to -117.32)		
Group 2 vs Group 3	-503.63 (-1,295.60 to 288.33)		

CI, confidence interval; ED, emergency department; TXA, tranexamic acid.

care services. These include: Belfast Orthopaedic Information System, Northern Ireland Electronic Care Record, and Northern Ireland Patient Archiving and Communication System. The costs of TXA (both intravenous and oral) were included. We did not include the cost of administering the drug as this was considered to be minimal: it was always given by an anaesthetist into the existing IV infusion, so there was no extra cost for saline bags and no opportunity costs associated with the anaesthetist as they were already in theatre attending to the patient.

We obtained local unit costs where possible from either publicly available sources (e.g. Department of Health Northern Ireland Health Resource Group (HRG) Unit Costs Schedules (2017/18)),[18] Northern Ireland Drug Tariff,[19] or directly from the appropriate costing department (e.g. Belfast Health and Social Care Trust, Northern Ireland Blood Transfusion Service). We used unit costs for the financial year 2017/18 (Table I) and combined these with individual-level resource to estimate the total hospital costs for each participant.

Statistical analysis. The cost per patient was calculated for each of three study groups as previously described. Number (%) of patients using each hospital service, mean number of times service used (95% confidence intervals (CIs)), and the associated mean costs of each service type (95% CIs) were calculated for each treatment group. Differences in mean costs between groups were estimated using linear regression methods. Analyses were conducted on an intention-to-treat basis and significance was judged where the CIs of differential means excluded zero or $p < 0.05$. In keeping with the protocol, the analysis was repeated in knee and hip patients separately. A post-hoc sensitivity analyses assessed the impact of patients' risk of VTE (normal risk/high risk) on the cost estimates by adjusting for risk in the linear regressions. All statistical analyses were conducted using Stata/IC 15.1 (Stata Corp, USA).

Results

Following a scheduled interim analysis and a review of safety data, the data monitoring and ethics committee (DMEC) recommended stopping randomization to control Group 3.

In total, 1,086 patients were randomized: 474 to Group 1, 478 to Group 2, and 134 to Group 3. Five patients were excluded from the analysis: one patient (Group 1) was randomized in error and four patients did not have complete cost data up to 90 days. These included two patients (Group 1) who did not receive surgery and two patients (Group 2) who withdrew from the study. Thus, 1,081 patients were included in the economic analysis: 471 to Group 1, 476 to Group 2, and 134 to Group 3.

All patients (both hip and knee). Hospital service use by all patients (both hip and knee) over the 90-day study period and the associated costs are presented in Tables II and III, respectively. Group 1 (IV bolus and oral TXA) was

Table IV. Hospital service use over the 90-day study period by group for hip patients only. Values are number (percentages) of patients using the service, mean (95% confidence interval) use.

	Group 1 (n = 233)		Group 2 (n = 233)		Group 3 (n = 66)	
Variable	**n (%)**	**Mean (95% CI)**	**n (%)**	**Mean (95% CI)**	**n (%)**	**Mean (95% CI)**
Primary admission including joint arthroplasty (mean days)	233 (100)	3.10 (2.65 to 3.55)	233 (100)	3.34 (2.92 to 3.76)	66 (100)	3.58 (2.89 to 4.26)
Non-elective hospital readmissions (mean days)	11 (5)	0.34 (0.09 to 0.59)	14 (6.0)	1.14 (-0.16 to 2.45)	1 (2)	0.11 (-0.11 to 0.32)
ED (mean attendances)	19 (8)	0.12 (0.06 to 0.17)	24 (10)	0.14 (0.08 to 0.19)	5 (8)	0.09 (0.01 to 0.17)
Transfusion by 90 days	4 (2)	-	3 (1)	-	6 (9)	-

CI, confidence interval; ED, emergency department.

Table V. Mean (95% CI) costs (£) of health service use over 90 days for hip patients only.

Variable	**Group 1 (n = 233)**	**Group 2 (n = 233)**	**Group 3 (n = 66)**
Primary admission including joint arthroplasty	5,563.56 (5,305.77 to 5,821.36)	5,703.74 (5,463.47 to 5,944.01)	5,836.91 (5,443.85 to 6,229.97)
Non-elective hospital readmissions	204.20 (54.69 to 353.71)	687.55 (-99.20 to 1,474.30)	63.88 (-63.69 to 191.44)
ED	21.44 (11.29 to 31.58)	25.41 (14.82 to 35.99)	16.82 (1.42 to 32.22)
Transfusions	5.03 (-0.33 to 10.39)	4.11 (-0.64 to 8.85)	35.49 (0.99 to 69.99)
TXA	4.07 (4.03 to 4.11)	3.29 (3.24 to 3.34)	0 (0)
Total cost (95% CI)	5,798.29 (5,487.65 to 6,108.94)	6,424.09 (5,565.62 to 7,282.56)*	5,953.09 (5,532.00 to 6,374.18)
Mean difference in total cost (95% CI)			
Group 1 vs Group 2	-625.79 (-1,536.05 to 284.46)		
Group 1 vs Group 3	-154.80 (-690.93 to 381.33)		
Group 2 vs Group 3	470.99 (-460.38 to 1,402.37)		

*One patient within this group had an extended length of stay on readmission of 138 days, with a total cost of £90,912.86.
CI, confidence interval; ED, emergency department; TXA, tranexamic acid.

associated with the lowest mean total costs, followed by Group 2 (IV bolus only) and then Group 3 (standard care) with the highest mean costs. The difference between Group 1 and Group 3 (-£797.77 (95% CI -1,478.22 to -117.32)) was statistically significant. The main driver of costs was the duration of the primary hospital admissions and readmissions. In Group 1 the mean length of stay (LOS) was 3.19 days, in Group 2 3.41 days, and in Group 3 4.09 days. ED attendances in Group 3 were higher (3/184; 18%) compared to Group 1 (51/471; 11%) and Group 2 (45/476; 9%). Transfusion by 90 days was also lower in Groups 1 and 2 versus Group 3. The mean cost difference in TXA between the intervention groups (1 and 2) was only 78 pence per patient, but this was associated with a cost saving of over £290 per patient.

Hip patients. Hospital service use by hip patients only over the 90-day study period and the associated costs are presented in Tables IV and V, respectively. In keeping with the analysis of all patients, the lowest mean total cost was observed in Group 1 (IV bolus and oral TXA), however in contrast the highest costs were observed in Group 2 (IV bolus only) and not the standard care arm. The difference between Group 2 and Group 3 (standard care) was largely driven by a greater number of readmissions in Group 2. None of the cost differences were judged to be statistically significantly different based on the CIs of the differential means. There was one outlier in Group 2 of the hip patients, who had a readmission lasting 138 days. When excluded from the analysis, the mean costs for this group reduced to £6,060.

Knee patients. Hospital service use by knee patients only over the 90-day study period and the associated costs are presented in Tables VI and VII, respectively. The lowest mean total cost was observed in Group 2 (IV bolus only) followed by Group 1 (IV bolus and oral) with the highest observed in the standard care group. However, the difference in costs between Groups 1 and 2 was minimal (£26.41; 95% CI -251.31 to 304.13). The differences in costs between each intervention group and standard care were found to be statistically significant.

Overall total costs were higher for knee patients compared with hip patients. Adjusting for patients' risk of VTE had very little impact on the cost estimates (Supplementary Material).

Discussion

For patients undergoing primary unilateral THA and TKA this study has shown that TXA decreases costs up to 90 days following surgery. This included patients deemed at high risk for VTE. The mean total cost for patients in Group 1 was £5,924.32, in Group 2 £6,218.45, and in Group 3 £6,722.09. The reduction in costs was associated with reduced length of stay, readmission rate, and ED attendances, as well as reduced blood transfusion requirements.

Table VI. Hospital service use over the 90-day study period by group for knee patients only. Values are number (percentages) of patients using the service, mean (95% CI) use.

	Group 1 (n = 238)		Group 2 (n = 243)		Group 3 (n = 68)	
Variable	**n (%)**	**Mean (95% CI)**	**n (%)**	**Mean (95% CI)**	**n (%)**	**Mean (95% CI)**
Primary admission including joint arthroplasty (mean days)	238 (100)	3.28 (3.02 to 3.54)	243 (100)	3.47 (3.20 to 3.75)	68 (100)	4.59 (3.05 to 6.13)
Non-elective hospital readmissions (mean days)	13 (5)	0.31 (0.08 to 0.54)	6 (2)	0.10 (0.00 to 0.20)	11 (16)	1.37 (0.07 to 2.66)
ED (mean attendances)	32 (13)	0.18 (0.12 to 0.25)	21 (9)	0.12 (0.07 to 0.17)	19 (28)	0.32 (0.19 to 0.46)
Transfusion by 90 days	0 (0)	-	3 (1)	-	4 (6)	-

CI, confidence interval; ED, emergency department.

Table VII. Mean (95% CI) costs (£) of health service use over 90 days for knee patients only.

Variable	**Group 1 (n = 238)**	**Group 2 (n = 243)**	**Group 3 (n = 68)**
Primary admission including joint arthroplasty	5,824.74 (5,676.76 to 5,972.72)	5,934.23 (5,775.94 to 6,092.51)	6,570.88 (5,690.18 to 7,451.58)
Non-elective hospital readmissions	184.72 (46.41 to 323.04)	59.48 (0.04 to 118.92)	823.67 (44.56 to 1,602.77)
ED	34.20 (21.75 to 46.66)	22.08 (12.16 to 31.99)	59.85 (34.85 to 84.85)
Transfusions	0 (0)	2.25 (-0.45 to 4.95)	14.06 (-3.21 to 31.34)
TXA	4.03 (3.97 to 4.09)	3.25 (3.19 to 3.31)	0 (0)
Total cost (95% CI)	6,047.70 (5,833.83 to 6,261.57)	6,021.29 (5,851.22 to 6,191.35)	7,468.47 (6,294.66 to 8,642.27)
Mean difference in total cost (95% CI)			
Group 1 vs Group 2	26.41 (-251.31 to 304.13)		
Group 1 vs Group 3	-1,420.77 (-2,579.95 to -261.59)		
Group 2 vs Group 3	-1,447.18 (-2,596.66 to -297.71)		

CI, confidence interval; ED, emergency department; TXA, tranexamic acid.

There are some studies which have analyzed hospital costs when using TXA in lower limb arthroplasty. In 2019, Wang et al[8] published a meta-analysis of four RCTs comparing oral versus IV TXA and its cost benefit in primary THA. They showed that oral dosing had a similar efficacy and safety profile as IV TXA but that costs were significantly increased in the IV group. It is important to note, however, that all of these studies excluded high-risk patients (previous VTE/CVA/MI). Tuttle et al[20] reviewed the use of topical TXA in in a retrospective cohort of 591 patients following primary THA and TKA. They noted reduced costs from a significant reduction in blood transfusions. Gillette et al[13] retrospectively reviewed 1,018 healthy patients undergoing primary THA and TKA; 580 received TXA and they noted a statistically significant reduction in overall costs in the TXA group. However, the group that did not receive TXA was significantly older. McGoldrick et al[15] also carried out a retrospective review of 200 patients, comparing 100 without TXA to 100 who did receive TXA following THA and TKA. They noted no significant difference between the groups' demographics, and showed a 20% reduction in blood transfusion rate and reduced LOS in the TXA group. This resulted in a significant cost saving in the TXA group.

There are a number of potential factors that contribute to the costs savings seen when using TXA in THA/TKA. These include reduced blood loss in the peri- and postoperative periods.[3-6] The advantages of this include a higher haemoglobin level postoperatively, which is especially important in older patients.[7,21] This has been shown to have a significant effect on patient outcomes including quality of life scores postoperatively and readmission rate.[22] Functional improvements have also been demonstrated in a number of studies, particularly after TKA, and may in part explain the reduction in length of primary admission in Groups 1 and 2. Grosso et al[23] studied 560 patients undergoing TKA, 280 before and 280 after the introduction of a TXA protocol. They demonstrated early functional improvements in patients receiving TXA, with significant differences in the amount of activity and ambulation in the immediate postoperative period. Wang et al[24] reviewed 60 TKA patients, 30 receiving TXA via intra-articular injection after skin closure. They noted a statistically significant improvement in range of motion (ROM) at six weeks and reduced LOS in patients receiving TXA.

Extended dosing of TXA is increasingly supported by the literature although the ideal regime has not been identified. Lei et al[25] identified reduced blood loss, LOS, and improved ROM following extended dosing with TXA in patients undergoing THA. Zhang et al[26] showed that in TKA, prolonged IV dosing resulted in reduced blood loss and inflammatory parameters. In this study, the addition of a further 24hours of oral TXA (Group 1) cost an additional 78p per patient but was associated with a reduction in overall costs of £290 per patient compared

to IV TXA alone (Group 2). This difference was not statistically significant, but this simple and low-cost regime of oral TXA could result in considerable cost savings postoperatively.

When we compared THA and TKA costs, some differences were noted. For patients undergoing THA, although Group 1 patients still had the lowest costs, the highest cost was observed in Group 2. A substantial portion of this was associated with readmission costs, and one patient in this group had a complex postoperative infection with further revision surgery and an overall readmission LOS of 138 days and costs over £90,000. For patients undergoing TKA, there was almost no significant difference in costs between Groups 1 and 2, with a mean difference of only £26. Despite a shorter LOS in Group 1, the number of readmissions and ED attendances negated this saving.

A key strength of this study was that it was performed in conjunction with the main trial with data subject to clinical monitoring throughout, resulting in a high degree of accuracy. Data were also obtained from administrative records with no reliance on patient recall. The primary limitation of this study is that it was carried out at a single institution; the results obtained may not be extrapolated effectively to other institutions or networks. However, it is to our knowledge the largest prospective study in TXA in hip and knee arthroplasty that includes a cost analysis. Finally, although cost analyses can certainly inform evidence-based decisions on resource-planning, it is only through the comparison of both the costs and health benefits of different interventions that we can assess cost-effectiveness. The inclusion of a preference-based health-related quality of life instrument, such as the EuroQol five-dimension five-level questionnaire,[27] would have allowed us to estimate the cost per quality-adjusted life year (QALY) gained associated with TXA. The National Institute for Health and Care Excellence considers interventions that cost less that £20,000 per QALY cost-effective.[28]

In conclusion, the use of TXA was associated with significant cost savings up to 90 days for all patients. Extended oral dosing of TXA further reduced these costs. Differences were observed between patients undergoing THA compared to TKA with extending dosing reducing costs in THA but not TKA. These cost savings resulted from reduced length of primary admission, readmissions, and ED attendances.

Take home message

- Tranexamic acid (TXA) use in primary total hip arthroplasty and total knee arthroplasty significantly reduced associated hospital costs up to 90 days following surgery.
- Extended oral dosing of TXA postoperatively has shown promise in further reducing costs.

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Supplementary material

Mean (95% confidence intervals) costs (£) of health service use over 90 days for hip and knee patients, adjusted for risk.

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Author information:
- P. N. Karayiannis, MB BCh BAO, MRCSEd, MSc, Trauma and Orthopaedic Registrar
- L. Bryce, BSCNS, Research Nurse
- J. C. Hill, PhD, MEng, MSc, Research Manager
- D. Beverland, MD, FRCS, Professor
  Primary Joint Unit, Musgrave Park Hospital, Belfast, UK.
- A. Agus, BSc Hons, PhD, Health Economist, Northern Ireland Clinical Trials Unit, Belfast, UK.

Author contributions:
- P. N. Karayiannis: Investigation, Formal analysis, Writing – original draft.
- A. Agus: Investigation, Formal analysis.
- L. Bryce: Investigation, Writing – review & editing.
- J. C. Hill: Conceptualization, Formal analysis, Writing – review & editing.
- D. Beverland: Investigation, Conceptualization, Writing – review & editing.

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