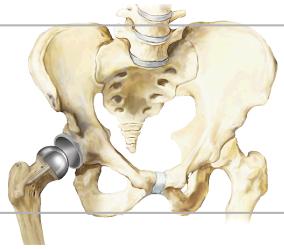
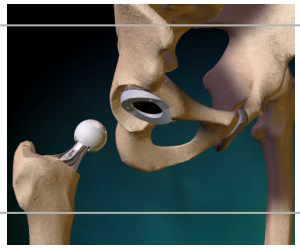
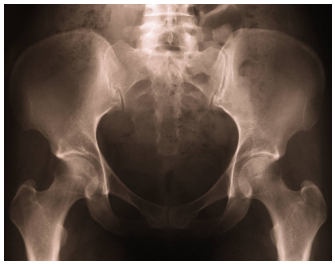
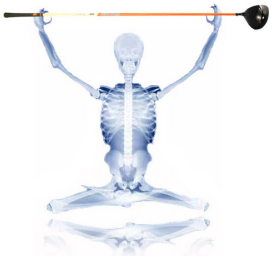


Alberta Hip Improvement Project

Preliminary Report on Early Results of Metal-on-Metal Resurfacing for Treatment of Degenerative Hip Disease in Alberta


November 1, 2010

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Alberta HIP

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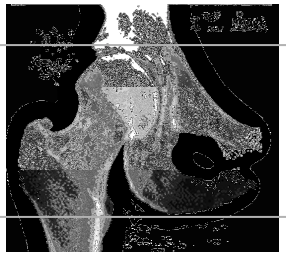

TABLE OF CONTENTS

1. Acknowledgements

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2. Introduction and Background

This report summarizes interim data collected as part of the Alberta Hip Improvement Project (HIP) to evaluate the effectiveness and safety of metal-on-metal (MoM) hip resurfacing arthroplasty (HRA) in young, active adults with degenerative hip disease. HIP, which started in 2004, will follow patients for 10 years from their date of surgery to determine whether HRA is an appropriate choice for select patients. A comprehensive report with detailed analyses is available from Alberta Bone and Joint Health Institute (ABJHI) (info@albertaboneandjoint.com; 403-670-0886).

Advanced hip arthritis is a common chronic condition causing severe joint pain and loss of joint function. Based on anecdotal and limited early published evidence mainly from the United Kingdom, HRA has emerged as an alternative to total hip arthroplasty (THA) internationally and in Alberta for younger and more active patients despite differences in clinical opinion about whether HRA is beneficial compared to THA. Some physicians believe that long-term outcomes of HRA have yet to be determined, and that resurfaced hips have unacceptably high failure rates. Others believe that HRA failure and adverse event rates are low and a return to normal function is more likely for patients who are appropriately selected for HRA than for patients who have THA. Little evidence on medium- and long-term risks and benefits of HRA or its cost-effectiveness compared to THA alternatives is available to support either view.

To provide Alberta-specific evidence for decision makers and clinicians on alternative hip bearing devices, ABJHI began working with health administrators and surgeons in 2004 to develop HIP, a provincial initiative to examine the clinical efficacy and long-term safety of alternative hip bearing surfaces, such as MoM HRA, compared to conventional THA in Alberta. HIP was designed to prospectively follow patients who have alternative bearing devices and provide the evidence needed to assess the safety and cost-effectiveness of HRA. The study initially recruited MoM HRA patients under 56 years of age, reflecting the evidence-based consensus of medical experts in Alberta that the procedure is most appropriate for young, active patients. HIP began recruiting THA recipients in 2005, applying the same age limitation to provide comparative results in a similar patient population. HIP's age criterion for MoM HRA and THA patients was modified in 2007, based on new information in the literature, allowing men under the age of 66 into the study. The age criterion for women was not changed.

HIP is being coordinated by ABJHI with oversight by the HIP Advisory Committee, which comprises surgeons and researchers from Edmonton and Calgary (see page 1). Without the safety and effectiveness information collected by HIP, the status of HRA recipients in Alberta would be unknown. This information is not available through administrative data or other sources. The rigorous safety review conducted by HIP is particularly important given the lack of information on the long-term safety of MoM HRA.

ABJHI has performed an interim critical analysis of the Alberta registry data collected between 2004 and 2009. This data was collected from 609 patients who received the Birmingham Hip Replacement System (BHR), the resurfacing device most commonly used in Alberta, and from 303 THA recipients, including 204 THA patients who participated in the 2005-2006 Alberta Hip and Knee Replacement Pilot Project (see patient characteristics, table 1).

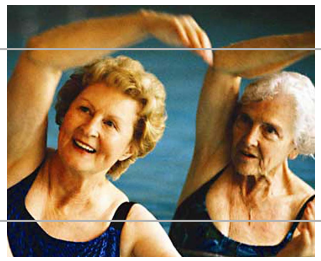
As of February 2010, ABJHI has synthesized the literature on this topic. Overall, the evidence available outside of Alberta was of insufficient quality to arrive at definitive conclusions about the safety and effectiveness of MoM HRA. Only two randomized controlled trials were found[1;2] and the bulk of available evidence was from lower-quality prospective comparative studies, case series and retrospective reviews. (See Appendix 1 for a comparison of levels of evidence.)

Though limited, the literature suggests resurfacing arthroplasties are appropriate in patients who have sufficiently high bone quality, but with cautious oversight, as reports in international joint registries, including registries in Australia, the U.K. and Sweden, suggest rates of failure and revision are higher than those of THA. However, these revision rates must be interpreted with caution, as they are reported over different follow-up periods, limiting comparability. Resurfacing revision rates vary from a cumulative 6.1% at 8 years post-surgery[3] to 11% at 9 years post-surgery[4]. These registries also suggest that hip resurfacing device failure rates differ from brand to brand. For example, data in the Swedish registry indicate that BHR, the most commonly used device in Sweden, had a revision rate of 4% while Durom had a revision rate of 10.7% at five years post-surgery.[5] In comparison, cemented THAs had a revision rate of 11.6% at 15 years and uncemented THAs had a revision rate of 33.6% at 16 years.[5] All of the 609 Alberta MoM HRA patients received the BHR, reducing variability of results in the HIP study.

A second safety concern is the elevated concentrations of cobalt and chromium ions in the bloodstream that have been reported in MoM arthroplasties, including MoM HRA, with high metal ion levels being associated with, and perhaps predictive of, implant failures that require revision. This issue has recently received media attention.[6] The long-term effects of elevated blood metal ion levels are unknown.

Since 2004, HIP has collected clinic and hospital information on consented patients to assess the safety and effectiveness of alternative bearing devices, primarily BHR, as compared to conventional THA. This information is stored in a secure database and used for analysis. All participants are asked to complete questionnaires, including WOMAC and SF-36 quality-of-life questionnaires, at the time of their consultation with a surgeon. ABJHI sends follow-up questionnaires to patients three months and one year following surgery, and annually thereafter. Following surgery, chart reviews are performed by ABJHI staff to confirm the type of prosthesis implanted and to capture adverse events and revisions. Administrative data from Alberta Health Services and Alberta Health and Wellness are used as a source of supplemental information to identify adverse events. Adverse events identified are assessed by the HIP Safety Committee (see page 1). Safety information in this report includes events that occurred up to December 31, 2009. A subset of 174 BHR patients has consented to have blood drawn annually to be tested for cobalt and chromium ion levels as well as markers of kidney and liver function. This report includes the values for blood samples collected up to July 2, 2009.

A cohort of 204 THA patients completed similar quality-of-life questionnaires at baseline, three months and one year following surgery as part of the Alberta Hip and Knee Replacement Pilot Project. These data were compared to the hip resurfacing cohort. An additional 99 THA patients were recruited to participate in HIP through long-term follow-up. This comparative group of 303 THA patients is small and may differ from the resurfacing group in terms of selection and patient characteristics. Increased recruitment into the comparative group is under way to improve the study quality.



3. Summary of Comparative Results from 2004 to 2009

Interim results of Alberta's HIP study comparing BHR and THA from 2004-2009 are summarized below and in table 2.

Safety: In the literature, femoral neck fracture was the most common reason for MoM HRA revision and most fractures occurred within the first year following surgery.[7;8] In the BHR cohort, two femoral neck fractures occurred, including one in the first year post-surgery. See tables 2 and 3.

In the BHR cohort of 609 patients, there were two cases of deep vein thrombosis (DVT) and four cases of pulmonary embolism (PE) within 30 days following surgery. Two of the four PEs occurred following a second unrelated surgery. No myocardial infarctions (MI) were reported. One dislocation occurred requiring closed reduction in the operating room (OR).

In the THA cohort of 303 patients, no cases of DVT, PE or MI were reported. One dislocation occurred requiring closed reduction in the OR. Femoral neck fracture is not a safety risk in the THA cohort because the total hip arthroplasty procedure requires removing the femoral neck.

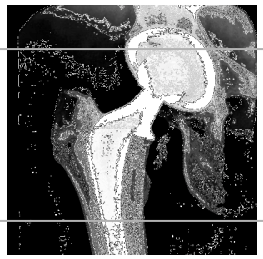
In this study, revision surgery is defined as the replacement, repositioning, repair or adjustment of a prosthetic device. (Exchange of the liner for debridement of an infection is not considered a revision.) There were six revisions in the BHR cohort of 609 patients (4 males, 2 females) with an average of 16 months elapsed post-surgery. Five revisions (4 males and 1 female) were performed in the THA cohort of 303 patients with an average of 17 months elapsed post-surgery. At four years post-surgery, revision rates are similar for the two groups (BHR=0.91%; THA=1.07%). See tables 4 and 5.

Reoperation is defined as a subsequent surgery at the same site for exploratory purposes, to retrieve a foreign body, debride or repair a bone fracture, but not to replace, reposition, repair or adjust the prosthetic device. There were 11 reoperations performed in the BHR cohort (1.6%, 3 males, 7 females; 1 patient received 2 reoperations) with an average of about 8 months elapsed post-surgery. Four reoperations (1.32%; 4 males) were performed in the THA cohort of 303 patients less than a month post-surgery. See tables 6 and 7.

Effectiveness: Average scores on the SF-36 physical function (PF) and bodily pain scales showed statistically significant post-operative improvement in the BHR cohort, and approached or exceeded Canadian norms (average scores for Canadians over 25 years of age)[9] within 12 months following surgery. In a propensity-matched cohort of 119 BHR and 119 THA patients, BHR patients had a greater improvement in SF-36 PF scores than THA patients at one year following surgery. BHR patients were more likely than THA patients to achieve a score of 90 or greater on the WOMAC and SF-36 PF (67% vs. 37% at one year post-surgery). See table 2.

Efficiency: Average OR time for BHR cases decreased from 150 minutes at the beginning of the study in 2004 to 131 minutes in 2009. Duration of hospital stay also improved, decreasing from an average of 4.5 days in 2004 to 2.7 days in 2009. The evidence indicates these improvements in efficiency did not have a detrimental effect on WOMAC and SF-36 patient functional outcomes nor on patient safety. See table 2.

Waiting times for surgery were within the ABJHI benchmark of 20 weeks after the decision to have surgery for 81%, or 496 of 609 BHR recipients. The most severely impaired patients proceeded to surgery more quickly, indicating that surgeons were prioritizing patients based on need. Waiting times did not change over time. See table 2.



Metal ion levels. There is concern in the literature about elevated cobalt and chromium ion levels in the blood of MoM HRA recipients, although the consequences of increased metal ion levels are unknown. A cohort of 174 BHR patients from HIP is being tested annually for metal ion levels. In the cohort, nine patients had metal ion levels higher than 10 micrograms per litre of blood, a limit recommended in other research.[10] These included three with elevated levels of cobalt, three with elevated levels of chromium, and three with elevated levels of both metals. Twenty-two had metal ion levels of five or more micrograms per litre at one or more times over the 2004-to-2009 period. Further research on these patients is being carried out in the form of clinical and diagnostic evaluation under a HIP sub-study. See table 2.

Cost-effectiveness. Costing information is not collected in this study. However, ABJHI is collecting average prosthesis costs for an unrelated project. ABJHI data show BHR is among the most expensive devices at an average cost of $5,273, while the average cost of a conventional polyethylene-on-metal THA device is $3,440. There are differences of opinion about whether this higher expenditure is justified. Costing is a complex matter and must consider multiple factors in patient care and characteristics. For example, while the cost of the BHR device is higher than that of a conventional THA device, younger, more active patients such as those who typically have a BHR would receive a THA with a stronger bearing surface, such as cross-linked polyethylene, at a cost approaching that of the BHR device. ABJHI is developing a cost-effectiveness model to evaluate differences in prosthesis cost balanced with patient outcomes. The model is expected to be complete by mid-2011.

In summary, HIP results over the five-year period from 2004 to 2009 suggest BHR is an appropriate choice for young, more active patients with healthy bones. Older female patients, in particular, are much less likely to benefit from BHR and the existing recommended practice guidelines regarding appropriate patient population should be maintained. The Alberta evidence to the end of 2009 is level 2, and the literature is level 2 or lower (see appendix 1 for an explanation of the levels of evidence). Nevertheless, the Alberta evidence suggests that rates of adverse events among the two patient groups are similarly low and BHR in select younger individuals with severe hip arthritis produces outcomes that are equivalent to or better than those of matched THA patients. These findings must be interpreted carefully, as HIP results are limited by a small THA comparative group and a lack of longer-term (10 years) data. HIP will address these limitations by following patients for 10 years from their date of surgery and by recruiting more patients into the comparative group.

4. Recommendations

Safety

Current safety data support continuation of the study with further review as described below. These 2004-2009 interim results are limited by the period of follow-up, as longer-term surveillance is needed. Furthermore, data from additional THA patients would allow a more rigorous comparison of patients to adequately assess adverse events, revision rates and effectiveness.

Recommendation: Continue annual monitoring of patients for a total of 10 years from their date of surgery, including monitoring for adverse events to ensure any issues related to the safety of the device are identified as soon as possible.

Recommendation: Increase recruitment of age-matched patients who receive conventional THA devices to add approximately 200 to this comparative group.

Recommendation: Perform annual surveillance of the published literature regarding the safety and effectiveness of hip resurfacing, including registry reports, to ensure up-to-date information is available to care providers and decision makers.

Recommendation: Follow up with patients by telephone and email (to a maximum of three times) and offer completion of questionnaires by phone interview to improve response rates.

Recommendation: Continue monitoring metal ion levels in the cohort of 174 patients being tested, and alert surgeons to elevated levels. Continue to recall patients with elevated metal ion levels for clinical and diagnostic evaluation.

This information will support surgeon decision-making and will provide Alberta with a means of evaluating the safety of this relatively new orthopaedic surgical device.

Cost-effectiveness

Prostheses costs assembled by ABJHI show BHR, the most commonly used MoM HRA device in Alberta, is among the most expensive of all device types. Opinion differs on whether the higher expenditure for BHR is justified. However, comparisons must consider multiple factors in patient care and characteristics that can affect device costs. For example, THA devices for patients who, like typical BHR recipients, are young and physically active, generally have a stronger bearing surface at a cost approaching that of BHR.

Recommendation

Carry out a cost-effectiveness analysis comparing BHR to THA using clinical outcome measures that account for quality of life.

Appropriateness criteria

The HIP Advisory Committee initially recruited BHR patients under 56 years of age to the study, reflecting the evidence-based consensus of medical experts in Alberta that the procedure is most appropriate for young, active patients. The age criterion was modified in 2007, based on new evidence in the literature, to include in the study men under 66 who received a BHR. The age criterion for women was not changed.

Recommendation: Eligibility criteria should be re-evaluated as evidence is obtained to ensure appropriate patients are selected for this procedure based on functional outcome scores, adverse events and revisions. Additional appropriateness criteria for implanting the device beyond age and sex, such as BMI and a primary diagnosis of osteoarthritis, may be identified.

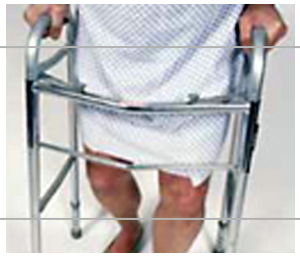


Table 1. Patient characteristics – Alberta HIP.		
Topic	**Measures**	**Findings**
Patient characteristics	Demographics	In general, BHR patients are younger than THA patients. In the HIP study, the ratio of males to females was three to one. Men were under the age of 66 and women were under 56, suggesting patients were selected appropriately based on the study criteria.
	Comorbidity and ASA scores	Comorbidity scores and ASA scores of BHR patients were lower than those of the THA comparative group of patients.

Table 2. Summary of interim results of Alberta HIP.		
Topic	**Measures**	**Findings**
Accessibility	Wait time	Most BHR patients (81%) had surgery within the 20-week benchmark. Patients with worse functional outcome scores had shorter wait times, indicating surgeons were prioritizing patients based on need.
Efficiency	OR time	OR time decreased from an average of 150 minutes in 2004 to 131 minutes in 2009, approaching the benchmark of an average of 125 minutes per case. This improvement likely reflected increasing surgeon skill in implanting the BHR, a relatively new device.
	Duration of stay	Duration of stay decreased from an average of 4.5 days in 2004 to 2.7 days in 2009. By January 2007, over 80% of patients met the benchmark of 3.0 days stay or less.
Effectiveness	Functional outcomes: WOMAC SF-36	Functional outcomes (WOMAC and SF-36) improved following surgery. The majority of patients achieved SF-36 scores close to or at Canadian normative scores one year following surgery (63.8% of patients achieved the norm for bodily pain and 66.2% for physical function). Although the most severely affected patients were less likely to reach Canadian norms after surgery, patients with the greatest disease severity showed the greatest improvement. BHR patients showed greater improvements than propensity-matched THA patients at one year following surgery.
Safety	Serious adverse events	Rates of adverse events were low.
	PE, DVT, MI, mortality	Among 609 BHR patients, there were four PEs and two DVTs in the 30 days following surgery. Two of the four PEs occurred following a second unrelated surgical procedure. No MIs and no deaths were reported in the 30 days following surgery.
	Revision rates	Six revisions, two due to femoral neck fracture, were reported in BHR patients and five revisions in THA patients. At four years post-surgery, revision rates are similar for the two groups (BHR=0.91%; THA=1.07%).
Metal ion levels	Cobalt and chromium levels	152 of 174 BHR patients tested for metal ions in their blood had levels under five micrograms per litre, the study's threshold for follow-up. Further research is being conducted through clinical and diagnostic evaluation of the 22 patients with metal ion levels of five or more micrograms per litre.
Cost-effectiveness	Model	Costing information on the different device types available in Alberta is not collected under this study. However, a cost-effectiveness model is being developed with the support of HIP and ABJHI. This model may offer opportunity to include cost-effectiveness among the criteria for selecting appropriate hip devices for patients.

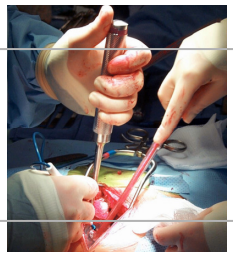


Table 3. Summary of serious adverse events requiring revision or reoperation at the surgical site. Events occurred prior to December 31, 2009.

	BHR (n=609)		THA (n=303)	
Event description	**Revision (n=6)**	**Reoperation (n=11)**	**Revision (n=5)**	**Reoperation (n=4)**
Femoral neck fractures	1	1*	N/A	N/A
Ongoing pain due to impingement	1	1	0	0
		1**		
Ongoing pain not yet diagnosed – suspicious for pseudotumor	1	0	0	0
Ongoing pain with unknown origin requiring surgery	1	2	0	0
Dislocation requiring closed reduction in the OR	0	1	0	1
Failed fixation of acetabular component (liner); and/or mal-position of acetabular component; and/or implant mismatch	1*	0	3	0
Subtrochanteric femur fracture	0	1	0	0
Mal-union of femoral neck fracture	1	0	0	0
Non-union of trochanteric osteotomy	0	1**	0	0
Deep infection	0	0	2	2
Hematoma requiring irrigation and debridement	0	1	0	0
Retained foreign object	0	2	0	1

*Same patient.
**Same patient.

Table 4. Revisions in the BHR cohort of 609 patients.

Year of BHR surgery	Days post-BHR surgery to revision	Reason for revision	Age	Sex	BMI	ASA score
2006	287	Ongoing pain; component impingement. Revised to a THA using a synergy stem with a modular BHR head.	46	M	32.2	2
2006	867	Mal-union of femoral neck fracture; femoral component slightly malpositioned with some retroversion and increased varus alignment of the femoral head. Revised using a synergy stem with a modular BHR head.	44	M	26.7	2
2006	14	Failed fixation of the acetabular liner. Revised to dysplasia cup with dysplasia screws.	51	M	32.6	1
2007	744	Ongoing pain. Revised to THA using a trabecular metal acetabular system with a highly crosslinked polyethylene acetabular liner, a synergy stem and a cobalt chrome femoral head.	48	F	19.8	1
2007	881 to stage 1 revision; 895 to stage 2 revision	Ongoing pain; no evidence of infection, rheumatoid arthritis or granulomatous disease; suspicious for pseudotumour. Surgery performed: components removed and antibiotic-impregnated cement spacer inserted. Antibiotic spacer removed. THA prosthesis implanted in stage 2 of revision using trabecular metal acetabular system with highly crosslinked polyethylene acetabular liner, synergy stem and aluminum femoral head.	51	F	21.9	1
2008	76	Femoral neck fracture. Revised to synergy stem with modular BHR head.	63	M	36.4	2

Table 5. Revisions in the THA cohort of 303 patients.

Year of THA surgery	Days post-THA surgery to revision	Reason for revision	Age	Sex	BMI	ASA score
2005	1317	Implant malposition; failed fixation of acetabular component (loosening with protrusio acetabuli); leg length discrepancy. Revised using tritanium porous acetabulum with extensive acetabular bone graft, highly crosslinked polyethylene acetabular liner and cobalt chrome head.	49	F	29.4	1
2005	69	Implant malposition. Revision of acetabular liner to ceramic liner.	50	M	21.9	1
2005	1089 to stage 1 revision; 1155 to stage 2 revision	Infection. Surgery performed: resection arthroplasty with insertion of temporary antibiotic-impregnated spacer. Antibiotic spacer removed. THA prosthesis implanted in stage 2 of revision using modular stem, tritanium acetabular system with alumina liner and V40 alumina femoral head.	42	M	23.0	2
2008	0	Implant mismatch. Liner replaced during a second surgery on same day.	57	M	26.5	1
2008	46	Deep infection: liner and head revised.	56	M	23.5	1

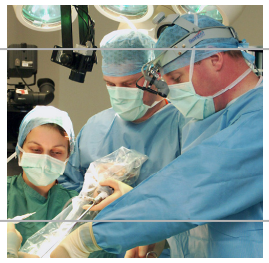
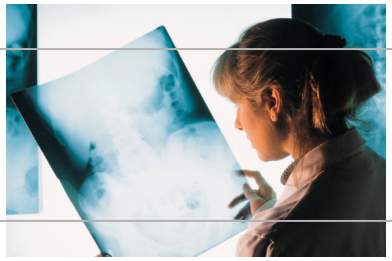


Table 6. Reoperations and reasons for reoperation in the BHR cohort of 609 patients.

Year of BHR surgery	Days post-BHR surgery to reoperation	Reason for reoperation	Age	Sex	BMI	ASA score
2004	99	Ongoing pain of unknown origin requiring exploration of surgical site. Arthrotomy performed as the femoral component was solidly fixed.	49	F	26.8	1
2004	2	Dislocation: closed reduction under general anaesthetic.	31	F	21.6	3
2005	54	Subtrochanteric femur fracture.	24	F	30.4	1
2006	0	Retained foreign object.	49	M	29.9	1
2006	0	Retained foreign object.	46	F	20.6	1
2006	792	Impingement and ongoing pain of unknown origin. Surgical dislocation and femoral osteoplasty performed.	42	M	28.5	1
	961 (169 days from first reoperation)	Non-union trochanteric osteotomy. Surgery performed: removal of hardware rt greater trochanter; bone grafting non-union rt greater trochanter; stabilization trochanteric fragment.				
2006	612	Femoral neck fracture. Repaired with 3 screws. Revision performed at a later date.	44	M	26.7	2
2007	636	Ongoing pain of unknown origin required arthrotomy. Revision performed at a later date.	51	F	21.9	1
2007	370	Ongoing pain due to impingement requiring tendon release. Revision performed at a later date.	48	F	19.8	1
2008	17	Hematoma requiring evacuation (irrigation and debridement).	41	F	31.9	1

Table 7. Reoperations and reasons for reoperation in the THA cohort of 303 patients.

Year of BHR surgery	Days post-BHR surgery to reoperation	Reason for reoperation	Age	Sex	BMI	ASA score
2005	23	Infection (MRSA) of the prosthetic component requiring irrigation and debridement but not replacement.	59	M	22.0	2
2005	0	Retained foreign object.	53	M	25.2	2
2005	17	Infection of the acetabular component requiring irrigation and debridement with liner exchange.	48	M	25.5	2
2006	3	Dislocation of the joint requiring closed reduction in OR under sedation.	54	M	31.1	unkn



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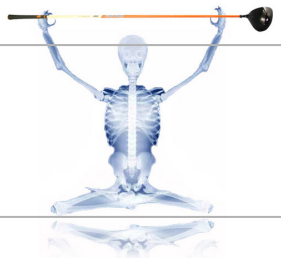

Appendix 1. Oxford Centre for Evidence-based Medicine Levels of Evidence (March 2009)

(For definitions of terms used see glossary at http://www.cebm.net/?o=1116)

Level	Therapy/ Prevention, Aetiology/Harm	Prognosis	Diagnosis	Differential Diagnosis/ Symptom Prevalence Study	Economic and Decision Analyses
1a	SR (with homogeneity*) of RCTs	SR (with homogeneity*) of inception cohort studies; CDR† validated in different populations	SR (with homogeneity*) of Level 1 diagnostic studies; CDR† with 1b studies from different clinical centres	SR (with homogeneity*) of prospective cohort studies	SR (with homogeneity*) of Level 1 economic studies
1b	Individual RCT (with narrow Confidence Interval‡)	Individual inception cohort study with >80% follow-up; CDR† validated in a single population	Validating** cohort study with good††† reference standards; or CDR† tested within one clinical centre	Prospective cohort study with good follow-up****	Analysis based on clinically sensible costs or alternatives; systematic review(s) of the evidence; and including multi-way sensitivity analyses
1c	All or none§	All or none case-series	Absolute SpPins and SnNouts††	All or none case-series	Absolute better-value or worse-value analyses ††††
2a	SR (with homogeneity*) of cohort studies	SR (with homogeneity*) of either retrospective cohort studies or untreated control groups in RCTs	SR (with homogeneity*) of Level >2 diagnostic studies	SR (with homogeneity*) of 2b and better studies	SR (with homogeneity*) of Level >2 economic studies
2b	Individual cohort study (including low quality RCT; e.g. <80% follow-up)	Retrospective cohort study or follow-up of untreated control patients in an RCT; derivation of CDR† or validated on split-sample§§§ only	Exploratory** cohort study with good††† reference standards; CDR† after derivation or validated only on split-sample§§§ or databases	Retrospective cohort study or poor follow-up	Analysis based on clinically sensible costs or alternatives; limited review(s) of the evidence or single studies; and including multi-way sensitivity analyses
2c	"Outcomes" research; ecological studies	"Outcomes" research		Ecological studies	Audit or outcomes research
3a	SR (with homogeneity*) of case-control studies		SR (with homogeneity*) of 3b and better studies	SR (with homogeneity*) of 3b and better studies	SR (with homogeneity*) of 3b and better studies
3b	Individual case-control study		Non-consecutive study or without consistently applied reference standards	Non-consecutive cohort study or very limited population	Analysis based on limited alternatives or costs, poor quality estimates of data but including sensitivity analyses incorporating clinically sensible variations
4	Case-series (and poor quality cohort and case-control studies§§)	Case-series (and poor quality prognostic cohort studies***)	Case-control study, poor or non-independent reference standard	Case-series or superseded reference standards	Analysis with no sensitivity analysis
5	Expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles"	Expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles"	Expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles"	Expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles"	Expert opinion without explicit critical appraisal, or based on economic theory or "first principles"

SR = Systematic review.
RCT = Randomized controlled study.
CDR = Clinical decision rule.
Produced by Bob Phillips, Chris Ball, Dave Sackett, Doug Badenoch, Sharon Straus, Brian Haynes, Martin Dawes since November 1998. Updated by Jeremy Howick, March 2009.

Notes

Users can add a minus-sign "-" to denote the level of evidence that fails to provide a conclusive answer because:

EITHER a single result with a wide Confidence Interval

OR a Systematic Review with troublesome heterogeneity.

Such evidence is inconclusive and, therefore, can only generate Grade D recommendations.

*	By homogeneity, we mean a systematic review that is free of worrisome variations (heterogeneity) in the directions and degrees of results between individual studies. Not all systematic reviews with statistically significant heterogeneity need be worrisome, and not all worrisome heterogeneity need be statistically significant. As noted above, studies displaying worrisome heterogeneity should be tagged with a "-" at the end of their designated level.
†	Clinical Decision Rule is an algorithm or scoring system that leads to a prognostic estimation or a diagnostic category.
‡	See note above for advice on how to understand, rate and use trials or other studies with wide confidence intervals.
§	Met when all patients died before the Rx became available, but some now survive on it; or when some patients died before the Rx became available, but none now die on it.
§§	By poor quality cohort study, we mean one that failed to clearly define comparison groups and/or failed to measure exposures and outcomes in the same (preferably blinded) objective way in both exposed and non-exposed individuals and/or failed to identify or appropriately control known confounders and/or failed to carry out a sufficiently long and complete follow-up of patients. By poor quality case-control study, we mean one that failed to clearly define comparison groups and/or failed to measure exposures and outcomes in the same (preferably blinded) objective way in both cases and controls and/or failed to identify or appropriately control known confounders.
§§§	Split-sample validation is achieved by collecting all the information in a single tranche, then artificially dividing this into "derivation" and "validation" samples.
††	An "Absolute SpPin" is a diagnostic finding whose specificity is so high that a positive result rules in the diagnosis. An "Absolute SnNout" is a diagnostic finding whose sensitivity is so high that a negative result rules out the diagnosis.
‡‡	Good, better, bad and worse refer to the comparisons between treatments in terms of their clinical risks and benefits.
†††	Good reference standards are independent of the test and applied blindly or objectively to all patients. Poor reference standards are haphazardly applied but still independent of the test. Use of a non-independent reference standard (where the 'test' is included in the 'reference', or where the 'testing' affects the 'reference') implies a Level 4 study.
††††	Better-value treatments are clearly as good but cheaper, or better at the same or reduced cost. Worse-value treatments are as good and more expensive, or worse and equally or more expensive.
**	Validating studies test the quality of a specific diagnostic test based on prior evidence. An exploratory study collects information and trawls the data (e.g. using a regression analysis) to find which factors are 'significant'.
***	By poor quality prognostic cohort study, we mean one in which sampling was biased in favour of patients who already had the target outcome, or the measurement of outcomes was accomplished in <80% of study patients, or outcomes were determined in an unblinded, non-objective way, or there was no correction for confounding factors.
****	Good follow-up in a differential diagnosis study is >80%, with adequate time for alternative diagnoses to emerge (for example 1-6 months acute, 1-5 years chronic).

Grades of Recommendation

A	Consistent Level 1 studies
B	Consistent Level 2 or 3 studies ***or*** extrapolations from Level 1 studies
C	Level 4 studies ***or*** extrapolations from Level 2 or 3 studies
D	Level 5 evidence ***or*** troublingly inconsistent or inconclusive studies of any level

"Extrapolations" are where data is used in a situation that has potentially clinically important differences than the original study situation.

Alberta Hip Improvement Project

FURTHER INFORMATION

Bone and Joint Clinical Network

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Early Results of Metal-On-Metal Resurfacing for Treatment of Degenerative Hip Disease in Alberta.
For the comprehensive report, please contact Alberta Bone and Joint Health Institute (403-670-0886 or info@albertaboneandjoint.com).