A Comparison of Wear of 36 mm and 28 mm Metal-on-Highly Cross-Linked Polyethylene Articulations in Primary Total Hip Replacements

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Abstract

Total hip replacement is one of the most frequently performed and successful surgical procedures. Its most common modes of failure identified in joint registries are dislocation in the short term and aseptic loosening associated with wear and osteolysis in the long term. Therefore, the ideal articulation would have both a low incidence of dislocation and low wear.

Metal-on-highly cross-linked polyethylene (HXLPE) articulations of 36 mm diameter have been demonstrated in a randomised controlled trial to have a significantly lower incidence of dislocation at one year postoperatively compared to 28 mm articulations. Historically, large articulations (femoral head size ≥32 mm) have been associated with increased wear rates of conventional polyethylene compared to smaller articulations. Advances in polyethylene manufacture with cross-linking for clinical use in total hip replacements has significantly reduced early wear rates compared to conventional polyethylene. This has prompted reconsideration of the ideal femoral head size to enhance the longevity of articulations.

This study aims to compare the wear of 36 mm and 28 mm metal-on-highly cross-linked polyethylene total hip replacements through a *post hoc* analysis of radiographs of patients enrolled in the randomised controlled trial referred to above. Comparison of wear rates between cohorts was undertaken by use of computer-assisted analysis (PolyWare™) of patient radiograph sets.

Radiograph sets for 326 patients, 164 with 28 mm and 162 with 36 mm articulations, were analysed. 36 mm metal-on-HXLPE articulations were found to have a statistically significant higher magnitude of bedding-in and creep at three but not twelve months when compared to the 28 mm cohort. The mean annual two-dimensional wear rate from 1 year until final radiograph was 0.00mm/yr for both

cohorts. There were no differences between 36 mm to 28 mm cohorts in mean annual volumetric wear rates or significant differences in the proportion of patients in each cohort with two-dimensional wear rates ≥ 0.1 mm/yr or volumetric wear rates ≥ 80 mm^3/yr. These wear rates have previously been associated with osteolysis when using metal-on-conventional polyethylene articulations.

While the use of large articulations had been reported to be associated with comparatively greater wear rates of articulations incorporating conventional PE, this appears not to apply to large articulations incorporating HXLPE. The low wear rates measured combined with the findings of the RCT of a significantly reduced incidence of dislocation at one year of 36mm compared to 28mm articulations, support the use of 36 mm metal-on-highly cross-linked polyethylene articulations. Longer term follow-up is required to assess whether low wear rates are maintained for both 36mm cohorts and whether wear of HXLPE is associated with the development of periprosthetic osteolysis.

Declaration

This manuscript contains no material that has been accepted for any other degree in any university. To the best of my knowledge and belief, this manuscript contains no material previously published or written by any other person, except where due reference is given in the text. I give my consent for this copy of my thesis, when deposited in the university library, being available for loan and photocopying as well as being available for access as part of the digital thesis program.

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Abbreviations and glossary

2D	two-dimensional
2DWR	two-dimensional wear rates, analogous to linear wear rate
3D	three-dimensional
annealing	heating followed by gradual cooling applied to a material in an effort to allow recoil of polymer chains and relieve internal stresses
AOA NJRR	Australian Orthopaedic Association National Joint Replacement Registry
AP	antero-posterior
articulation	Interface where mobility occurs between components of the THR
arthroplasty	surgical modification of a native joint; in this thesis, this relates to total hip arthroplasty – replacement of the native joint with articulating prostheses
aseptic loosening	debonding of the component-bone interface that is not the result of infection; associated with increased volumes of PE wear debris
bedding-in	often discussed interchangeably or in combination with creep, but more strictly defined as loss of surface asperities left during manufacturing in the early postoperative period
BMI	body mass index
CAD	computer-assisted design
CAM	computer-assisted manufacturing
CI	confidence interval
CoCr	cobalt chrome (will generally refer to the material used for metal femoral heads upon PE)
conventional polyethylene	UHMWPE (non-cross-linked) utilised prior to the advent of cross-linking in the late 1990s
creep	time-dependent deformation of a material under stress that does not produce wear particles. Non-wear generating process of creep and settling in of the liner that dominates initial observed FHP and includes

	bedding-in. Often discussed interchangeably with bedding-in in the early postoperative period
CT	computed tomography
dislocation	an episode of disarticulation of the prosthetic joint requiring reduction to restore joint mechanics
e-beam	electron beam (method of irradiation of PE components, used exclusively by Zimmer™ in PE manufacture)
FHP	femoral head penetration; FHP after creep-dominated period may be referred to as steady-state linear wear
HXLPE	highly cross-linked polyethylene
in vitro	studies examining subjects outside their usual context; relating to articulations studied in a laboratory context.
in vivo	studies examining outcome of interest in living subject; in this context, relating to study of articulations implanted into patients.
Initial radial discrepancy	the initial radius between the edge of a reduced femoral head and the inner aspect of the acetabular component. This discrepancy is deliberate on the part of component manufacturer to ensure that manufacturing tolerances of the components allow reduction.
large articulation	greater than or equal to 32 mm articulation
mg	milligrams
mm	millimetres
mm^3	cubic millimetres
Mrad	megarad (equivalent to 10 kilogray doses of radiation energy)
negative wear	wear measurement over serial radiographs where the vector changes from the expected direction; typically a wear vector away from the acetabular component
osteolysis	resorption of bone in response to a pathology; in this context caused by host response to PE wear particles
osteolysis threshold	threshold of annual wear rates in conventional PE where osteolysis develops and below which osteolysis is rare

periprosthetic	relates to a process occurring around a prosthetic joint
PE	polyethylene
phantom model	a model of increments known to or adjusted by the assessor used as a reference point to test measurement tools with unknown performance
post hoc	retrospective examination of data following conclusion of the original part of a scientific process; implies that the original experiment was not designed with outcome of interest in mind
RCT	randomised controlled trial
revision	surgery undertaken subsequent to the primary (index) surgical operation replacing some or all of the components to address a problem that has since developed
RSA	Roentgen stereophotogrammetric analysis
standard articulation	articulation sized less than 32 mm
SD	standard deviation; square root of the variance from the mean
steady-state linear wear	FHP measured in the 2D plane following the bedding-in period
THR	total hip replacement (primary unless otherwise stated)
TIFF	tagged image file format
tribology	the study of the interaction between bearing surfaces of joints
UHMWPE	ultra-high molecular-weight polyethylene
UK	United Kingdom
USA	United States of America
VWR	volumetric wear rate
XLPE	cross-linked polyethylene manufactured using at least 3 Mrad (i.e. includes moderately as well as highly cross-linked PE)

Chapter 1: Introduction

Total hip replacement (THR) usually results in high patient satisfaction ratings (Anakwe, Jenkins & Moran 2011; de Beer et al. 2012), good functional outcomes (Röder et al. 2003) and good long-term results (Corten et al. 2011, Australian Orthopaedic Association National Joint Replacement Registry [AOA NJRR] 2014). The most common reason for early revision of THRs is dislocation (AOA NJRR 2014). THRs with a large articulation, that is ≥32 mm, present a potential solution to this problem given that 36 mm metal-on-highly cross-linked polyethylene (HXLPE) THRs have a significantly lower incidence of dislocation at one year than 28 mm articulations (Howie et al. 2012).

Lysis/loosening are the major reasons for revision of THRs in the long-term (AOA NJRR supplementary report 2014). Elevated wear of conventional PE has been shown to be associated with periprosthetic osteolysis (Sochart et al. 1999). This led to the development of cross-linked polyethylene (XLPE), which has been shown to have significantly lower wear than conventional PE (McCalden et al. 2009; Thomas et al. 2011). This has led to increasing use of articulations incorporating XLPE as well as increasing use of large articulations (AOA NJRR 2014). However, large metal-on-conventional polyethylene (PE) articulations were shown to have significantly higher PE wear rates than standard sized articulations (Hirakawa et al. 1997; Livermore, Ilstrup and Morrey 1990; Liu et al. 2011; Morrey & Ilstrup 1989; Shaju et al. 2005). Few studies have examined the relationship between wear of XLPE and articulation size.

The relationship between HXLPE wear and osteolysis remains to be determined because long-term outcomes of THRs involving HXLPE are not yet known. Elevated wear rates in this thesis are defined as two-dimensional wear rates (2DWRs)

≥0.1 mm/yr and volumetric wear rates (VWRs) ≥80 mm^3/yr, in accordance with the thresholds used in studies of conventional PE.

Four published studies have compared wear of HXLPE between large and standard metal-on-HXLPE articulations (Bragdon et al. 2013; Hammerberg et al. 2010; Lachiewicz et al. 2009; Nakahara et al. 2011). Importantly, patients in these studies were not randomised by articulation size leading to the possibility that factors potentially affecting wear were not equally distributed between articulation cohorts. The supervisors of this thesis (OTH and DWH) had undertaken a large multicentre RCT to examine the effect of articulation size on dislocation. The focus of this thesis is to examine the effect of articulation size on wear using radiographs taken during routine follow-up of patients in this RCT.

This thesis consists of five chapters. Chapter 2 reviews the relevant literature addressing the reasons for the development of HXLPE and the outcomes of THR involving HXLPE. It also examines current techniques of measuring PE wear and the advantages and disadvantages of different ways of reporting wear. Finally, the aims and hypotheses of the thesis are presented.

Chapter 3 describes the methodology of the study. Chapter 4 presents the results of the study with respect to wear of the 36 mm and 28 mm cohorts as well as relevant demographic and implant factors.

Finally, Chapter 5 discusses the results of the study in the context of the current literature. It also makes recommendations with respect to the most appropriate ways of reporting wear.

Chapter 2: Literature review

2.1 Content of the literature review

This literature review focuses on the wear and bedding-in/creep of primary metal-on-PE THRs. The literature review also examines first-generation HXLPE materials, because a first-generation highly cross-linked polyethylene (HXLPE) (Longevity™) is the subject of this thesis. While recognising that Roentgen stereophotogrammetric analysis (RSA) is the gold standard for wear measurement, the emphasis of this literature review is on computer-assisted techniques for wear assessment on plain radiographs, such as PolyWare™, because this was the method chosen to analyse patient radiographs retrospectively.

This review is limited to material that is published either in book form or in a peer-reviewed journal in the English language. MEDLINE, PUBMED and Google Scholar™ were the main databases utilised for the literature search, as well as The University of Adelaide's library catalogue for relevant books and eBooks. Keywords and medical subject headings utilised in search strategies included HXLPE, metal, femoral head diameter, large articulation, wear, creep, femoral head penetration (FHP), radiographic, Longevity™, PolyWare™, Devane's method and computer assisted methods.

2.2 Structure of the literature review

This literature review is structured to reveal different aspects of PE wear behaviour, measurement and reporting in the context of large metal-on-HXLPE THRs:

- Section 2.4 analyses contemporary and historical use of standard and large metal-on-PE THR articulations, including reasons for revision and current registry data.

- Section 2.5 considers problems with conventional PE, including the association between PE wear and periprosthetic osteolysis and scientific advancements in PE liner manufacture in the last two decades; it also introduces the rationale for the development of HXLPE.

- Section 2.6 outlines the literature on the wear, creep and associated osteolysis of metal-on-PE THRs.

- Section 2.7 discusses the tribology of metal-on-PE THR articulations and different factors affecting wear *in vivo*.

- Section 2.8 presents an overview of radiological methods for the assessment of wear; it includes their respective merits and limitations.

- Section 2.9 discusses different ways of presenting wear data, and the advantages and disadvantages of each method.

- Section 2.10 summarises the literature review to provide clarity and context for the methods used, and for the presentation and interpretation of results in this thesis.

- Section 2.11 presents the aims and hypotheses for this study.

2.3 Research questions and limitations of the literature

A search of the relevant literature was undertaken to help address the following research questions:

1. Is there a difference in the bedding-in and creep of 28 mm and 36 mm metal-on-HXLPE articulations in primary THRs?

2. Is there a difference in the 2DWRs and VWRs of 28 mm and 36 mm metal-on-HXLPE articulations in primary THRs?

3. Is there a difference in the proportion of 36 mm and 28 mm metal-on-HXLPE primary THRs that demonstrate wear rates significant for osteolysis in conventional PE i.e. 2D wear rates ≥0.1 mm/yr (Dumbleton, Manley & Edidin 2002) and VWRs≥80 mm^3/yr (Oparaugo et al. 2001)?

Since its introduction into THR, HXLPE has been the focus of much research. The wear and creep of metal-on-HXLPE, both *in vitro* and *in vivo*, are examined below. Relating to the research questions, three limitations in the current literature are acknowledged before the current tribology literature involving PE is examined.

First, the relationship of HXLPE wear to osteolysis in the mid-to-late term remains to be defined. Therefore, extrapolations of expected osteolysis prevalence taken from conventional PE wear literature and applied to HXLPE wear particles are based on assumptions. The relationship will likely be clarified in the next decade with follow-up studies extending to 20 years or more, as the seminal papers linking conventional PE wear rates to osteolysis prevalence were based on long-term follow-up of this magnitude of duration.

Second, it is difficult to compare wear performance between studies unless comparing similarly manufactured PEs within similarly sized articulations implanted in patients with comparable demographics assessed radiographically in the same way. It is very rare that an investigator will encounter another study for comparison with near identical attributes. For this reason, meta-analyses or systematic reviews in this area, such as that by Kurtz, Gawel and Patel (2011), must be analysed critically.

Finally, there remains no consensus on the optimal way to report wear results in a meaningful and uniform manner, and the subject of how to handle negative wear and outlier results remains controversial.

The status of the literature on this subject, including its limitations and gaps, has influenced the aims, design and conduct of the study in attempting to answer the research questions. This body of work will not only consider and draw from, but will also augment, the literature regarding large metal-on-HXLPE articulation THRs. The limited literature demands that the results and outcomes of the current wear study be presented and compared against similar studies in multiple different ways, not only for comparison but also to reflect on the effects of different ways of handling data. For completeness, it is important to present the advantages and shortfalls of each method of presentation and to recognise the multiple factors that can affect measured wear rates *in vivo*.

2.4 Metal-on-polyethylene total hip replacements

2.4.1 Total hip replacement surgery

Arthroplasty of the hip has been practised since the 19th century, with evolution to the current concept occurring in the 20th century (Amstutz and Kabo 1991; Learmonth, Young and Rorabeck 2007). Contemporary THR has evolved from technology developed by McKee (1951) and Charnley (1961); since 1962, the most widely accepted implant configuration has included a metal femoral head articulating against a polymer component fabricated from PE such as those developed by Charnley (Charnley 1963). Although THRs are among orthopaedic surgery's most successful procedures for painful arthroses (Learmonth, Young & Rorabeck 2007), many different bearing combinations have been trialled in the past four decades (such as metal-on-metal or ceramic-on-ceramic articulations) in an effort to improve

longevity of the construct (Amstutz & Grigoris 1996; Sandhu & Middleton 2005). While there are geographical variations, THRs involving metal-on-PE are arguably the international standard of care for degenerative joint disorders (Sandhu & Middleton 2005). Worldwide there are approximately one million metal-on-PE components implanted annually with the vast majority of which involve HXLPE (Schmidig et al. 2010).

PE has been used in THR articulations because of its good mechanical bearing properties and low coefficient of friction against metal or ceramic, and because it is neither toxic nor prone to third-body wear at revision surgery (Heisel et al. 2003, Schmidig et al. 2010). PE is a chemically and conceptually simple compound, produced by polymerisation of ethylene gas into a macromolecular carbon chain with pendant hydrogen atoms (Kurtz, Gawel & Patel 2011). Ultra-high molecular-weight polyethylene (UHMWPE) is a linear (non-branching) semi-crystalline polymer that is a two-phase composite of crystalline and amorphous phases (Sobieraj & Rimnac 2009). However, the PE liners in clinical use today, whether cross-linked by gamma or electron beam (e-beam) irradiation, and whether annealed or remelted by thermal treatments, are more complex than the gamma-air-sterilised non-HXLPE liners that were used routinely until the last decade (Kurtz, Gawel & Patel 2011). In this thesis, non-XLPE liners are referred to as conventional PE liners

HXLPE has been widely used in THR since its introduction at the end of the 20th century. According to the latest annual report of the Australian Orthopaedic Association National Joint Replacement Registry (AOA NJRR 2014), XLPE comprised 76.3% of all articulations incorporating PE and 87.3% of all implanted metal-on-PE articulations over the 12 years since the registry commenced.

2.4.2 Reasons for revision

Although metal-on-PE THRs remain among the most successful of orthopaedic operations, recurrent dislocation and aseptic loosening are leading causes for revision at early and later postoperative years, respectively (AOA NJRR Supplement 2014; Bozic et al. 2009; Kotwal et al. 2009).

The majority of dislocations (Amlie, Hovik & Reikeras 2010; Hailer et al. 2012; Williams, Gottesman & Mallory 1982) and revisions for recurrent dislocations (AOA NJRR 2014) occur within the first year. Within larger registries, recurrent dislocation of THRs is the most common cause of revision in the first three years post-implantation, with higher rates of revision in the AOA NJRR for recurrent dislocation of known primary THRs with articulations $\leq$28mm compared to those >28mm (AOA NJRR 2014). Recurrent dislocation accounted for 25% of revisions of known primary THR overall in the AOA NJRR (2014).

The most common cause of revision of primary THRs in the mid- to late-term is osteolysis and aseptic loosening from PE wear (Chiang et al. 2003; Harris 1995; Heisel et al. 2003; Maloney et al. 1997). Of all revisions of THRs reported in the last AOA NJRR Supplement (2014) report, the reason was listed as osteolysis and aseptic loosening in 49%. Although various theories for aseptic loosening have been proposed (Sundfeldt et al. 2006), the consensus in the literature is that increased wear rates of conventional PE components are associated with aseptic loosening (Clohisy & Harris 2001; McGee et al. 2000).

2.4.3 The role of large metal-on-HXLPE articulations

THRs incorporating large articulations offer the proven advantage of a reduced incidence of dislocation at one year (Howie et al. 2012), which would be expected to reduce revision for instability. Large articulations provide biomechanical advantages,

such as improved head-to-neck ratio, decreased implant impingement and an increased ‘jump distance’, which are all characteristics that help to reduce the risk of dislocation when compared with standard articulations (Amlie, Hovik & Reikeras 2010; Beaulé et al. 2002; Burroughs et al. 2006; Estok et al. 2007). The randomised controlled trial (RCT) from which the current study’s patients are drawn found a 0.8% incidence of dislocation at one year postoperatively in primary THRs incorporating 36 mm metal-on-HXLPE articulation compared with 4.4% in those with 28 mm articulations (Howie et al. 2012), a clinically and statistically significant difference. These results support earlier observations that were based on the AOA NJRR regarding increased revision for recurrent instability in articulations ≤ 28 mm compared with larger articulations (Conroy et al. 2008).

The use of large articulations involving conventional PE has been limited previously by reports of increased wear of the PE acetabular liner (Elfick et al. 1998; Hirakawa et al. 1997; Jasty et al. 1997; Kesteris et al. 1996; Liu et al. 2011; Livermore, Ilstrup & Morrey 1990; Shaju et al. 2005) and increased revision rates for aseptic loosening (Livermore, Ilstrup & Morrey 1990; Tarasevicius et al. 2006). Large frictional torque forces, bending moments and taper corrosion have also been reported as disadvantages relevant to articulations incorporating large modular metal femoral prostheses (Cooper & Della Valle 2014; Panagiotidou et al. 2013). However, the use of large articulations has been increasing with the advent of HXLPE as a wear-reducing advancement, and no increased wear rates have been reported with the use of large metal-on-HXLPE compared with standard articulations in simulator studies (Kelly et al. 2010; Muratoglu et al. 2001; Shen et al. 2011). Thus, in the last decade, there has been a reconsideration of the use of large metal-on-PE articulations for patients at risk of dislocation and those undergoing revision THR with reports of clinical use of articulations up to 40mm in size (Garbuz et al. 2012). As will be

discussed in Section 2.6, HXLPE has shown reduction in short-term wear rates compared to conventional PE. The four studies that have compared wear rates between standard and large metal-on-HXLPE THRs have reported no significant differences in 2DWRs and no evidence of an increased prevalence of osteolysis (Bragdon et al. 2007, 2013; Lachiewicz et al. 2009; Nakahara et al. 2011).

Patients in Australia are increasingly undergoing THRs with a large articulation, with the registry reporting that standard head sizes (<32mm) were shown to have over 3.5 times the rate of revision for instability compared with articulations ≥ 32 mm (AOA NJRR 2014). The most recent AOA NJRR (2014) report indicates that in 2013, over 50% of the primary THRs (of any femoral head material) incorporating XLPE had a femoral head size ≥ 32 mm. The increasing tendency towards using larger articulations was highlighted in this report where over 80% of primary THRs with metal-on-XLPE articulations incorporated femoral heads greater or equal to 32 mm compared with 6.9% in 2002 (AOA NJRR 2002, 2014). It must be emphasised, however, that while there is evidence that this combination reduces revision rates in the short term for instability, the long-term effect on revision rates from the use of a large metal-on-HXLPE THR articulation is currently unknown (AOA NJRR 2014).

2.5 Conventional polyethylene to cross-linked polyethylene

2.5.1 The clinical importance of wear rates of polyethylene liners

Despite the recognised efficacy of metal-on-PE THRs, conventional PE wear debris and the associated consequence of aseptic loosening has been a major barrier to the longevity of implanted components (Aram, Kadirkamanathan & Wilkinson 2013; Chiang et al. 2003; Dumbleton, Manley & Edidin 2002; Harris 1995; Maloney et al. 1997; Oparaugo et al. 2001; Sochart 1999; Wroblewski, Siney & Fleming 2009). With the exception of unusual cases where the metal bearing wears completely

through the PE liner, wear is only clinically important if it induces progressive osteolysis (Heisel et al. 2004). For example, a metal-on-conventional PE THR with an 2DWR of 0.1 mm/yr would theoretically take approximately a century to erode through a typical 10 mm-thick acetabular component (Kurtz et al. 1999). However, it is the generation of billions of microscopic conventional PE wear particles (from wear rates as little as 0.1 mm/yr) that is associated with osteolysis and loosening from bone loss around implants in the mid-to-late postoperative period (Aram, Kadirkamanathan & Wilkinson 2013; Revell 2008; Schmalzreid & Callaghan 1999; Sochart 1999).

The link between PE wear particulate and a subsequent host macrophage response was first explored by Willert and Semlitsch (1977). Howie et al. (1988) then described, in an animal study, how PE particles alone could cause bone resorption (osteolysis) in the absence of motion or infection. Inflammatory mediators released by the body in response to PE particles not only increase bone resorption but also suppress osteoblasts (cells responsible for bone formation), which results in ongoing loss of bony support (Schmalzried et al. 1992). Although there have been other processes cited to contribute to aseptic loosening, such as excessive periprosthetic micromotion (Ryd & Linder 1989), the theory of foreign body response to wear particles is generally accepted in the literature. Subsequent to Howie's (1988) study, the degree of wear from bearing surfaces in THR and the amount and size of PE particles produced from conventional PE liners has been shown to be strongly correlated with periprosthetic osteolysis and rates of aseptic loosening (Bragdon et al. 2003; Dumbleton, Manley & Edidin 2002; Oparaugo et al. 2001; Revell 2008).

Osteolysis can often progress asymptomatically with advanced disease causing component loosening, periprosthetic bone loss and pathologic fractures, which can result in component failure and complex revision surgery (Harris 1995; Nercessian et

al. 2003). The time taken for this process to be of the magnitude to noticeably affect survival rates in THR cohorts utilising conventional PE has been estimated to be between 10 and 25 years, based on studies such as those of Sochart (1999) and Tarasevicius et al. (2006). In addition, individuals younger than 65 years and men of all ages are disproportionately affected by osteolysis (Nercessian et al. 2003). It remains to be seen as to whether these trends will extend to HXLPE.

Knowledge of wear rates in the short term is useful in predicting joints at risk of significant osteolysis in the mid-to-late term and, in cohorts using conventional PE, increased wear rates are significantly associated with osteolysis at 10 years (Dowd et al. 2000; Dumbleton, Manley & Edidin 2002).

To date, Kuzyk et al. (2011) in their meta-analysis of first-generation HXLPE have demonstrated a reduced overall prevalence of osteolysis in HXLPE compared with conventional PE. While it is encouraging that reduced wear rates of HXLPE may also reduce osteolysis, current studies are only short- to medium-term and not all have used the most sensitive detection method, namely CT. Therefore, osteolysis may still be developing with HXLPE but lesions that are smaller are less readily detectable. However, it may be the case that there is a different threshold, possibly lower given the proportion of bioreactive particles per volume of HXLPE particulate, or no association of HXLPE wear rates to osteolysis. Also, with multiple different methods of manufacture, it is possible that HXLPE used in other studies could have different wear rates or bioreactivity, which would limit the generalizability of this study to other HXLPE articulations.

There has been some concern raised from retrieval studies that some first-generation HXLPE has shown unexpected mid-term oxidation which can affect the material properties of first-generation HXLPE and produce fatigue fractures (Currier et al.

2010). However, these concerns have not been clinically or radiologically evident as of a decade or more follow-up (Babovic and Trousdale 2013; Bragdon et al. 2013).

2.5.2 Defining clinically important wear rates

For THRs incorporating conventional PE acetabular liners, articulations with 2DWRs ≥ 0.1 mm/yr (Dumbleton, Manley & Edidin 2002) and VWRs ≥ 80 mm^3/yr (Oparaugo et al. 2001) in the short term have been shown to be associated with an increased risk of wear-related osteolysis and aseptic loosening in the mid-to-late term. Other authors report an increased likelihood of the development of osteolysis by a factor of four for every 0.1 mm/yr increase in the 2DWR of conventional PE, and by approximately a factor of three for each 40 mm^3/yr increase in VWR (Orishimo et al. 2003).

The subject of what constitutes clinically important wear rates of conventional PE liners has been well described by studies published in the last 15 years. Sochart (1999) is perhaps the most important original study at a late postoperative period to correlate radiographic wear to survivorship from aseptic loosening of metal-on-conventional PE THRs. The study found a statistically significant correlation between wear and decreased survivorship appearing after 10 years, based upon antero-posterior (AP) radiograph assessment of 22.25 mm metal-on-PE THRs. There was a 28% revision rate for aseptic loosening in the prostheses with a total wear of ≤1 mm compared with a 100% revision rate for aseptic loosening in prostheses with ≥2.5 mm wear at 25 years ($p<0.01$). This correlated to a mean annual 2DWR of ≥0.1 mm/yr across the 25 years. Conversely, the 20-year survivorship from revision of either the femoral or acetabular component for aseptic loosening was greater than 90% if the annual 2DWR was less than <0.1 mm/yr.

The study of Sochart (1999), among others, gave support to the 'osteolysis threshold', later proposed by Oparaugo et al. (2001), of an annual VWR of 80 mm^3/yr for the presence of clinically significant osteolysis. Dumbleton, Manley and Edidin (2002), in their review article, also conclude that an annual 2DWR of <0.1 mm/yr was rarely associated with osteolysis, and that osteolysis did not occur with annual 2DWRs below 0.05 mm/yr. They recognised that while the calculations of 2DWRs to VWRs used in the studies discussed above were based upon assumptions about wear direction and calculated from the AP pelvis radiograph only (they had used the Charnley and Halley [1975] formula in assessment of historical studies), it allowed broad comparisons of wear and osteolysis rates that could produce a clinically meaningful 'threshold'.

However, Harris (2003) raised five valid criticisms regarding the concept of an osteolysis threshold:

- Some of the studies used to justify the threshold had a follow-up of 10 years, which would be too short a time period to adequately quantify osteolysis, which has a gradual and insidious onset.

- A threshold implies no occurrence of the disease beneath the arbitrary figure, whereas osteolysis had been shown to occur in patients whose penetration rate was less than 0.1 mm/yr or 80 mm^3/yr (Sochart 1999; Wilkinson, Hamer & Stockley 2005; Vervest et al. 2005).

- Some reports used a limited definition of periprosthetic osteolysis that would tend to underestimate its prevalence, such as not including the type of lysis that is the cause of radiolucent zones at the interface between cement and the acetabular bone.

- Studies using plain radiography only would likely underestimate the prevalence of periprosthetic osteolysis, with several papers citing computed tomography (CT) to be superior to plain films for detection of peri-prosthetic osteolysis (Puri et al. 2002; Stamenkov et al. 2003; Walde et al. 2005).

- The term ‘threshold’ infers a direct association between wear rates and osteolysis without regard to other factors. Harris (2003) argues that the strong role of other factors was clear from matched pair studies; for example, Goetz et al. (1994) reported that femoral osteolysis developed in 29% of the hips with a HG™ femoral component compared with none that had the Precoat™ cemented femoral component despite similar wear rates, implying a mechanical contribution.

Others have explored further factors that could determine the host response of a set volume of wear particles to produce periprosthetic osteolysis, including the access of particles to periprosthetic bone (Schmalzried & Callaghan 1999), idiosyncracies of the host immune system (Granchi et al. 2003, Wooley et al. 1997) and the size and shape of the PE particles (Ingram et al. 2004; Minoda et al. 2007; Williams & Clarke 2009).

In the absence of any current evidence of a causal relationship between wear rates of the HXLPE component and periprosthetic osteolysis, the literature on excessive wear in conventional PE articulations gives an indication of what may occur as HXLPE THRs approach two decades postoperatively and beyond. While the classification of those with ‘elevated’ or ‘clinically significant’ wear rates in metal-on-HXLPE articulations is arbitrary without scientific support, it is a necessary step to attempt to assess those that *may* be at risk of wear related complications while awaiting the long-term relationship of HXLPE wear to osteolysis to be defined.

2.5.3 The development and chemistry of cross-linked polyethylene

For more than 30 years after the introduction by Charnley of metal-on-PE low-friction arthroplasty, advances in PE manufacture had only a modest effect on annual wear rates. However, the ongoing failure of prostheses attributed to clinically important wear rates and associated osteolysis stimulated studies into the structure, morphology and mechanical properties of the polymer at every stage of its production, from original resin into stock material to its final fabricated form (Kurtz, Gawel & Patel 2011). This led to polymer scientists advocating alternative or 'enhanced' UHMWPEs to improve the wear resistance of the polymer, culminating in the development of intentionally and widely used cross-linked UHMWPE (Kurtz et al. 1999).

The caveat 'intentional and widespread usage' is deliberate: there are two reports in the literature regarding the previous use of metal-on-gamma irradiated XLPE THR. *Inadvertent* use in South Africa in the 1970s was initially reported in the *Journal of Bone and Joint Surgery, British Volume* (Grobelaar, Du Plessis & Marais 1978), and *intentional* cross-linking by Oonishi et al. in Japan in the 1970s was later abandoned because the company that had provided the cross-linking technology became bankrupt (Oonishi, Kadoya & Masuda 2001).

Intentional cross-linking of UHMWPE is achieved by irradiation resulting in one long, branched molecule (Costa & Bracco 2009). When exposed to ionising radiation, two structural changes occur in UHMWPE: chain scission (carbon–carbon breakage) of the taut 'tie' molecules, and the reaction of the free radicals (produced by the breakage of the carbon–hydrogen bonds) with each other to the hydrogen free radicals forming cross-links between adjacent molecule chains (Lewis 2001) (Figure 2.1). Elimination of the free radicals tends to reduce the amount of reaction with

oxygen and the subsequent poor wear performance that would otherwise result (Lewis 2001), while cross-linking results in rigidity (Baker, Bellare & Pruitt 2003). The latter is advantageous for wear behaviour and reduced adhesion. However, it can predispose the material to mechanical failure due to reduced mechanical properties such as increased brittleness (Baker, Bellare & Pruitt 2003).

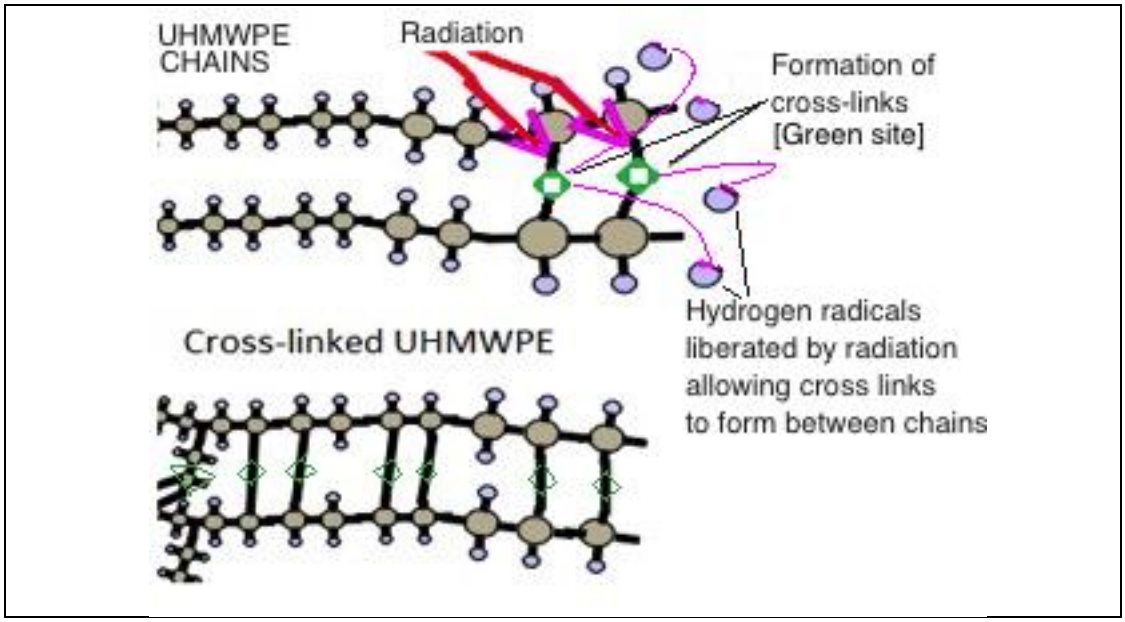

Figure 2.1: Schematic representation on role of radiation in achieving conversion from UHMWPE to XLPE

HXLPE was introduced into wider clinical use in December 1998 (Kurtz et al. 1999), which followed United States Food and Drug Administration approval after several companies had developed modification on their existing UHMWPE. While 10 megarad (Mrad) is used in the manufacture of most XLPE to achieve cross-linking (see Figure 2.1), various differences in other aspects of XLPE manufacture, such as gamma versus e-beam irradiation, remelting and annealing cycles, and sterilisation methods, have been implemented to reduce wear (see Table 2.1). For example, Marathon™ and Duration™ liners are moderately cross-linked with only 3 and 5 Mrad used, respectively, in their manufacture and are thus not further discussed in this thesis. Some studies have highlighted the degree to which the manufacturing process can affect wear and mechanical properties (see Section 2.7).

Table 2.1: Examples of manufacturing differences between first-generation moderately and highly cross-linked polyethylene used in total hip replacements

Product Name (Raw Material)/ Manufacturer/Launch Date	Radiation Dose and Type	Melting/ Annealing	Sterilisation/ Packaging
Duration™ (GUR 415)/ Stryker™/ 1998	3 Mrad gamma	50°C annealing	Gamma/ Vacuum packed/Nitrogen
Marathon™ (GUR 1050)/ De Puy™/ 1998	5 Mrad gamma	155°C remelt and 120°C annealing	Gas plasma/ Air
Crossfire™ (GUR1050)/ Stryker™/ 1999	7.5 Mrad gamma	130°C annealing	Gas plasma/ Nitrogen and additional 3 Mrad gamma
Durasul™(GUR1050) / Zimmer™/ 1999	9.5 Mrad e-beam	~125°C melt then remelt 150°C for 2 hours	Ethylene oxide/ Air
Longevity™ (GUR1050) / Zimmer™/ 1999	9.5 Mrad e-beam	150°C remelt	Gas plasma/ Air
ArComXL™ (GUR1020)/ Biomet™/ 2005	5 Mrad gamma	130°C annealing	Gas Plasma/ Air
XLPE™ (GUR1050)/ Smith and Nephew™/ 2005	10 Mrad gamma	150°C remelt	Ethylene oxide/ Air

Source: Adapted from Kurtz, Gawer & Patel (2011) & Kurtz (2009)

2.5.4 Proposed advantages of cross-linked polyethylene

It was believed that the reduction of wear rates in HXLPE observed in simulator and early clinical studies (see Section 2.6) would translate to a decreased risk of osteolysis and its associated risk of aseptic loosening compared with conventional PE. This supposition was based upon observations from conventional PE studies demonstrating a correlation between 2DWRs and osteolysis as previously discussed (Aram, Kadirkamanathan & Wilkinson 2013; Dumbleton, Manley & Edidin 2002; Harris 1995; Oparaugo et al. 2001; Sochart 1999). The low short-term wear rates of HXLPE also allowed re-consideration of larger articulations for use in those at risk of dislocation, which was previously unpopular because of the potential for accelerated wear rates (Livermore, Ilstrup & Morrey 1990).

The disadvantages of first-generation HXLPE are that it is more susceptible to *in vivo* oxidation than conventional PE (Dumbleton et al. 2006), and it is relatively brittle, making it more prone to fracture in the presence of component malalignment (Kurtz et al. 2011). Factors contributing to the latter include thin PE diameter at the cup rim, relatively vertical cup alignment that leads to rim loading, the presence of external fixation grooves on the liner (stress risers), and the use of an extended lip (Moore et al. 2008; Tower et al. 2007). Retrieval studies have confirmed, via optical and electron microscope inspection, that the crack initiation patterns are often characteristic of a fatigue process consistent with repeated focal loading (Furmanski, Kraay & Rimnac 2010), and manufacturers have since revised the PE locking mechanism.

Manufacturers of second-generation HXLPE have employed novel technologies in order to address the reduced mechanical properties seen in the first-generation HXLPE while retaining its wear reduction benefits. These include the addition of vitamin E to HXLPE, which is shown *in vitro* to improve mechanical properties and fatigue crack propagation resistance (Oral et al. 2006); sequential irradiation and annealing process, which preserves the mechanical properties of PE and demonstrates high survivorship in functional fatigue testing (Dumbleton et al. 2006); and high-pressure crystallisation after melting HXLPE (Simis et al. 2006). However, this thesis focuses on first-generation HXLPE because of the use of Longevity™ (Zimmer, Warsaw, Indiana, USA), a HXLPE liner, in the RCT from which radiographs for the current wear study are drawn.

2.5.5 Limitations of the current literature on cross-linked polyethylene

While the HXLPE technology has, in *in vitro* and mid-term *in vivo* studies, demonstrated reduced wear rates compared with conventional PE, unknown factors

remain in the relationship of HXLPE wear rates to osteolysis. In particular, the new material's bioreactivity (ability to incite an immunogenic response relative to volume of wear debris) and the association of its wear rate to the prevalence of osteolysis in the long term is uncertain.

Numerous studies show a strong association between conventional PE wear rates and their relationship to the pathogenesis of osteolysis; less is known about HXLPE wear particles *in vivo*. Some *in vitro* studies initially suggested that the quality and size of the particulates from wear of HXLPE may be more bioreactive than conventional PE (Endo et al. 2002; Green et al. 2000; Ingram et al. 2004). Other studies have proposed that the supposed difference in 'bioreactivity' from HXLPE wear may be the result of an overall higher proportion of submicron-sized particles per volume of wear particles rather than the quality or shape of the particles themselves (Ingram et al. 2004; Williams & Clarke 2009). In other words, HXLPE compared with conventional PE debris may well have the same or less volume of biologically active submicron-sized particles in a given sample, but these would be over-represented with reference to the proportion of larger, less active wear particles.

A retrieval study recently reported the bioreactivity, or 'functional biologic activity', of various HXLPE liners compared with a control cohort of conventional PE (Baxter et al. 2013). Analysis of functional biologic activity of PE particles within hip pseudocapsule samples confirmed that there was a higher proportion of submicron particles in HXLPE compared with conventional PE. Importantly, however, the study reported a proportionally lower functional biologic activity of the HXLPE compared with the retrieved conventional PE liner cohort. The *in vivo* response to HXLPE particles at the mid-to-late term remains to be seen.

Another limitation of HXLPE studies is that the different manufacturing methods of HXLPE liners (see Table 2.1) hinder the generalisation of wear results from one liner to another (Maloney & Elsbach-Richards 2010). This includes differing methods of ionising radiation, sterilisation and melting cycles. For example, temperature control and the manner of thermal delivery to the PE material can alter the rigidity of the lattice of the molecule and its ability to cross-link with adjacent chains (Lewis 2001). As such, there was recognition and compromise that annealing and melting of first-generation HXLPE had their advantages and disadvantages. Annealing potentially reduces loss of crystallinity and improves mechanical strength, but at the cost of an increased modulus and contact stress as well as increased residual free radicals that could adversely affect wear performance. Conversely, melting has improved wear characteristics, but reduced mechanical strength (Ries & Pruitt 2005).

2.6. Wear performance of total hip replacements

2.6.1 Wear terminology and concepts

Radiographic measurement of wear *in vivo* is a multifactorial and dynamic process (Digas 2005). Whether manual or digital, wear measurement techniques described in the literature involve measurement of any relative movement of the femoral head within the acetabular component between time points. The relative movement of the femoral head into the acetabular component, which commonly records as parts of a millimetre, is commonly referred to as femoral head penetration (FHP), or linear penetration, as assessed on serial plain radiography. The term FHP is frequently used interchangeably with linear wear, although wear technically refers to FHP that occurs following the bedding-in/creep period and, unless specified otherwise, refers to wear in the coronal plane (i.e. 2D wear measurement).

In early radiographic wear studies of metal-on-PE THR articulations, wear was assumed to occur at a constant pace in a cylindrical path (Charnley & Halley 1975). Clinical (Bragdon et al. 2007; Glyn-Jones et al. 2008; Röhrl, Nivbrant & Nilsson 2012; Sychterz et al. 1999), retrieval (Murtagolu et al. 2004) and simulation (Penmetsa et al. 2006) studies have since found initially high FHP rates in liners that reduce significantly with ongoing years (or gait cycles) into a slower, true-wear-dominated phase. This rapid change in FHP in the initial postoperative period has been ascribed to bedding-in and creep (Geerdink et al. 2008; Glyn-Jones et al. 2008; Muratoglu et al. 2004; Sychterz et al. 1997). This is depicted in Figure 2.2: the first scenario (the top three images, coloured red) demonstrates no wear (B to C) after the bedding-in/creep phase (A to B), whereas the second scenario (the bottom three images, coloured blue) demonstrates continued wear in the form of continued FHP (B to C) after the bedding-in/creep phase (A to B).

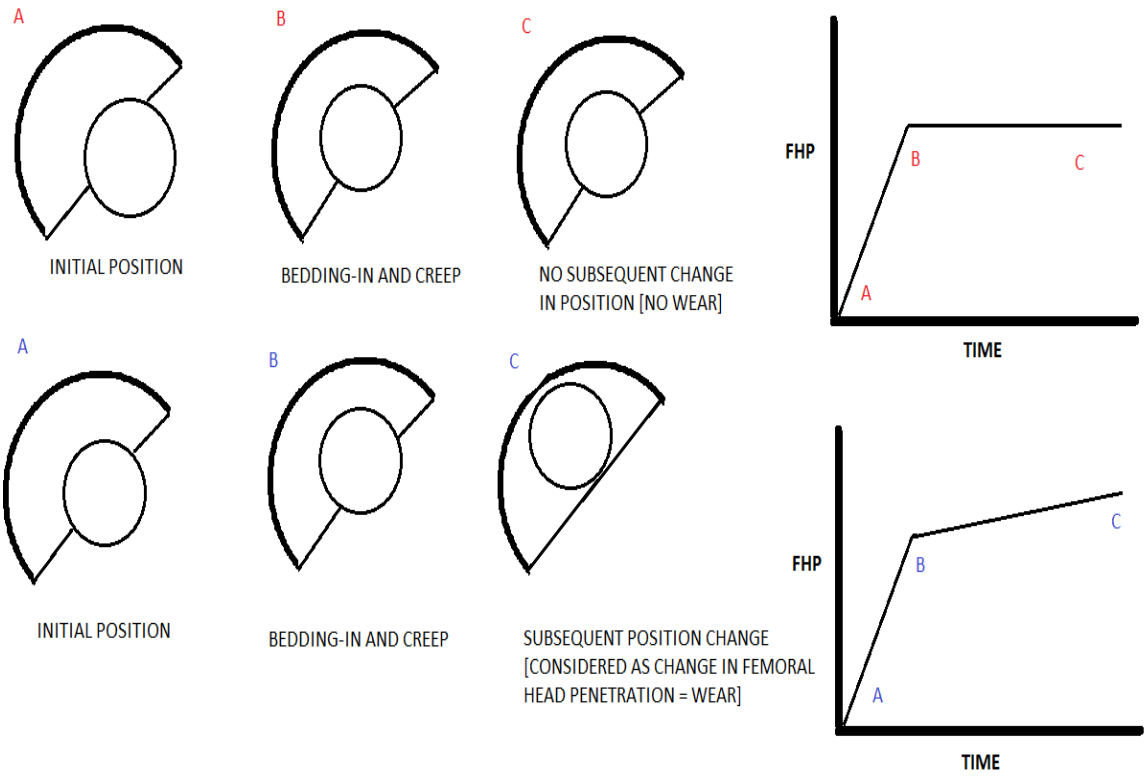

Figure 2.2: Relationship between change in the femoral head position (A, B, C in each scenario) and the observed 2D FHP over the serial time points analysed

Bedding-in, the settling in of the PE liner into the acetabular shell and screw holes, and creep, the non-wear-generating plastic deformation of material over time under cyclic load, are separate but simultaneous processes that occur early in the postoperative period (Sychterz et al. 1999). Although they contribute to measured FHP concurrently and are discussed herein as one entity, their effect on FHP is usually significantly diminished by the end of the first postoperative year, at which time the steady-state FHP phase, signifying true wear, emerges (Sychterz et al. 1999). While it is commonplace for studies to report on wear measured from radiographs between follow-up intervals, the distinction between creep/bedding-in and true osteolysis-generating wear is difficult, if not impossible, to determine at early follow-up. This is as there is no way to ascertain the relative contribution of either process from the observed FHP.

2D wear, or linear wear, in the literature refers to relative movement of the components measured from one radiograph in the AP (or coronal) plane, which, in effect, assumes wear as a vector that takes the product from a vertical and horizontal axis. Unless otherwise stated, wear measurements reported in this thesis are 2D with proximal/distal and medial/lateral movements in the coronal plane. Three-dimensional (3D) wear, which is arguably more realistic of the wear occurring *in vivo*, incorporates a third axis and requires another plane, typically provided by a lateral radiograph, to achieve its calculation. While proponents of 3D wear argue that it has higher fidelity to *in vivo* wear, 2D wear requires fewer radiographs, has been the main type of wear reported in the literature when correlating wear rates to osteolysis, is more precise, and has no reliance on variable quality cross-table laterals (Lewis 2000) (see Section 2.9).

The selection of time points used for wear measurements is critical, as this will inevitably influence the interpretation of data. For example, wear as either FHP or annual wear rate measured from immediate to five-year postoperative radiographs on the same patient cohort would be expected to be higher than that measured from one- to six-year postoperative radiographs. This is because, despite both scenarios involving a five-year period, the former would incorporate the initial bedding-in and creep of the liner into FHP measurement, which constitutes a large proportion of the total FHP. Once reaching a steady-state, wear rates in the short term in conventional PE have been shown to be predictive of wear rates in the mid- to late-term (Pedersen et al. 1998)

Different radiographic follow-up protocols have been used to describe the pattern of wear and steady-state wear rates depending on investigator preference and radiograph availability. While one may assume that more measurements would enable greater precision, this may not be the case where wear rates are reported to be

below the precision of instruments used to measure them, such as with HXLPE liners. It has been reported that the more radiographs taken, the higher the mean difference in readings (Stilling et al. 2009). There would be expected to be more variability in analysing wear in a cohort using one-, two- and five-year radiographs than one- and five-year radiographs alone. One potential solution advocated for this variability is the use of regression to produce annual wear rates (Bragdon et al. 2013; Nakahara et al. 2011).

It is critical to appreciate that extrapolations of *in vitro* simulator models to *in vivo* performance are limited (Oral et al. 2006). THRs *in vivo* are subjected to more complex kinematics than can be simulated and, further, lubricants such as bovine serum with additives may appear to produce clinically relevant wear rates but cannot be regarded as predictive for the behaviour of similar articulations containing human synovial fluid (Oral et al. 2006).

It is arguable that VWRs are of more clinical relevance than 2DWRs given that any host reaction to PE relates to the volumetric load of submicron PE particles (Ingram et al. 2004; Kubo et al. 2009). The importance of calculating VWRs in addition to 2DWRs is especially pertinent to the context of use of different-sized articulations. However, VWRs are less often reported in the literature. There are multiple methods of calculating volumetric wear, including conversion from 2D and 3D techniques, with varying accuracy when water displacement methods are used as a gold standard comparator (Kabo et al. 1993; Mizoue et al. 2003). While subsequent formulae have been reported to have superior accuracy to historical formulae (see Section 2.8), it is reasonable to still consider results according to historical formulae given that studies central to the wear rate to ‘osteolysis threshold’ correlation were based upon these older formulae (Oparaugo et al. 2001).

2.6.2 Clinical performance of first-generation cross-linked polyethylene

Clinical *in vivo* studies that have compared short-term wear rates of first-generation HXLPE to conventional PE liners in THR patients found that 2DWRs were significantly reduced with HXLPE (Digas et al. 2004, 2007; Dorr et al. 2005; Glyn-Jones et al. 2008; Olyslaegers et al. 2008; Triclot et al. 2007). This difference remains at the mid-term, with studies following HXLPE cohorts for 10 years or more reporting that HXLPE maintains a lower 2DWR than conventional PE liners (Babovic & Trousdale 2013; Bragdon et al. 2013).

The literature examining the comparative wear performance of HXLPE and conventional PE includes two RCTs involving a 28 mm metal on Longevity™ articulation, which is an articulation combination used in the current wear study. The first involved 100 patients and reported a lower mean steady-state 2DWR of 0.003 mm/yr (95% confidence interval [CI] ±0.027 mm) of the HXLPE (Longevity™) compared with 0.051 mm/yr (95%CI ±0.022 mm) with conventional PE liners, at a minimum of five years, measured using Martell Hip Analysis Suite™ (McCalden et al. 2009). In the second RCT, Thomas et al. (2011) completed an RSA of 54 hips assigned to either HXLPE (Longevity™) or conventional PE, and found a significantly reduced steady-state 2DWR of 0.005 mm/yr in the HXLPE cohort compared with 0.037 mm/yr with conventional PE. Furthermore, none of the 27 patients in the HXLPE cohort had a 2DWR ≥0.1 mm/yr, compared with three of 27 in the conventional PE cohort, although this did not reach statistical significance due to low numbers.

There are no known *in vivo* studies that compare large articulations using HXLPE to those incorporating conventional PE. However, large metal-on-conventional PE THRs *in vivo* compared to standard-sized articulations have been associated with

increased 2DWRs and VWRs of the acetabular liner (Elfick et al. 1998; Jasty et al. 1997; Hirakawa et al. 1997; Liu et al. 2011; Livermore, Ilstrup & Morrey 1990; Shaju et al. 2005) and increased revision rates for aseptic loosening (Elfick et al. 1998; Livermore, Ilstrup & Morrey 1990).

2.6.3 Bedding-in/creep and wear

While this section broadly discusses bedding-in and creep period for HXLPE, less is known about the effect of articulation size on bedding-in/creep, which will be discussed in the subsequent section.

Estok et al. (2005), in an *in vitro* study of 32 mm and 28 mm cobalt chrome (CoCr) heads on Longevity™ HXLPE liners and conventional PE, reported that the first 2.5 million simulated gait cycles were creep dominated and that there was a tendency for more creep in HXLPE compared with conventional PE liners, although this was not statistically significant for 32 mm articulations. Given that the average patient post-THR has been reported to undergo between 0.9 and 2.3 million gait cycles per year (Batteneberg et al. 2012), these findings support reports from *in vivo* studies that bedding-in/creep in Longevity™ liners is completed by one year (Glyn-Jones et al. 2008).

With respect to the magnitude of bedding-in/creep, studies have reported a range of 0.06 mm (Ayers et al. 2009) to 0.42 mm (Manning et al. 2005) of mean FHP at 12 months follow-up, using standard-sized articulations incorporating Longevity™ HXLPE liners (Tables 2.2 & 2.3). An RSA study reported that the bedding-in/creep of the Longevity™ HXLPE and conventional PE liners were similar in magnitude and lasted approximately six months in the latter and 12 months in the former, based on the transition in FHP direction signifying the end of the creep phase (Glyn-Jones et al. 2008).

The effect on wear rates in neglecting to characterise bedding-in and creep are highlighted in an *in vivo* study by Snir et al. (2014). Their study followed metal-on-first-generation HXLPE (Crossfire™) THRs over 10 years. They reported that the wear rate reached a plateau after approximately two years and that the mean annual 2DWR for years six to ten was 0.05 mm/yr, compared with the mean of 0.13 mm/yr when calculated for the entire ten year period. However, bedding-in and creep may not be the only reason why 2DWRs are initially higher in the first postoperative years given that gait cycles have been shown to reduce with age (Batteneberg et al. 2012). However, low steady-state wear rates have been reported in short-term studies of patients less than 65 years of age (Mall et al. 2011; Shia et al. 2009) which, pertinently, are wear rates comparable to those reported in studies involving patients of older mean age (See Table 2.2).

Options for characterising bedding-in and creep:

- Serial month-by-month radiographic assessment using edge-detection methods could be performed; while this would likely enable superior characterisation of the bedding-in/creep period compared to other edge-detection based methods below this is impractical and has the hazards of radiation exposure.

- Its magnitude could be determined by using RSA; this is the most accurate method and has the ability to observe for a change in direction, which can signify the end of bedding-in/creep. It is limited by the need for prospective bead insertion and specialised techniques required.

- It could be characterised from edge-detection software by the use of at least three radiographic time points, retrospectively, by looking for a plateau of the FHP rate of change for the cohort.

- Statistical modelling of the data could be used, which provides a reasonable assessment of when steady-state wear is reached; the transition point of no effect of time can be considered as the end of bedding-in/creep.

2.6.4 Comparative studies of large and standard articulations

2.6.4.1 Bedding-in/creep

While some studies do not attempt to measure bedding-in/creep, those that have done so for articulations incorporating Longevity HXLPE are described in Tables 2.2 and 2.3, have not produced definitive conclusions on the comparative bedding-in/creep.

The few authors examining creep and bedding-in for *in vivo* studies assessing larger compared with standard articulations have not reported a significant difference (Bragdon et al. 2007; Hammerberg et al. 2010; Nakahara et al. 2011). For example, Bragdon et al. (2007) in a RSA study of metal-on-HXLPE (Longevity™) articulations reported higher FHP at 12 months: 0.11 mm and 0.08 mm for the 36 mm cohort (using standard RSA and shell/marker methods, respectively) compared with 0.06 mm and 0.05 mm for the 28 mm cohort (Bragdon et al. 2007). However, this did not reach statistical significance, likely because of the low patient numbers. Hammerberg et al. (2010), who used manual methods to examine the bedding-in/creep and wear of 32 mm and 28 mm CoCr on Durasul™ THRs and found that the FHP measurements at three months (the bedding-in period defined in their study) and 12 months were 0.04 mm and 0.08 mm respectively, for both sizes.

In simulator studies, large and standard articulations have had wear measured with cumulative cycles as a surrogate for time, with no significant differences in FHP change after 1 million cycles, signifying the end of the bedding-in and creep (Kelly et al. 2010; Muratoglu et al. 2001; Shen, Lu & McKellop 2011).

2.6.4.2 In vitro wear rates

Hip simulator studies have shown similar steady-state 2DWRs and VWRs when standard and large metal-on-HXLPE articulations are compared. This trend extends to the extremes of large articulation sizes, with studies demonstrating this relationship up to diameters of 52 mm (Bragdon et al. 2005; Burroughs et al. 2006; Estok et al. 2007; Herrera et al. 2007; Muratoglu et al. 2001; Oral et al. 2006). Muratoglu et al. (2001) and Burroughs et al. (2006) reported no significant differences in 2DWRs and VWRs respectively, between different femoral head sizes ranging from 22 mm to 46 mm after 30 million cycles of simulated gait, which is equivalent to approximately 15 to 20 years of *in vivo* use.

Bragdon et al. (2005) reported 75 (± 0.85) mg of volumetric particulate wear per million cycles, which was consistent over a range of articulation sizes from 28- to 46 mm. Oral et al. (2006) and Estok et al. (2007), similarly, found no difference in material weight changes between large and standard metal-on-HXLPE articulations. Importantly, however, the latter study did report significantly higher mean VWRs with the use of large articulations on conventional PE compared with the HXLPE group.

Contrary to these findings, Galvin et al. (2010) reported that, after the exclusion of the first million cycles as initial bedding-in/creep, the steady-state VWR was 4.6 mm^3 per million cycles in the 28 mm articulations compared with 8.1 mm^3 per million cycles in the 36 mm articulations ($p<0.05$). While statistically significant, this is arguably a clinically minor difference given the magnitude of wear rates associated with osteolysis in conventional PE. As the average patient post-THR has been reported to undergo between 0.9–2.3 million gait cycles per year (Batteneberg

et al. 2012), the extrapolated annual VWRs are both still well below the volumetric osteolysis threshold proposed for conventional PE (≥80 mm^3/yr).

2.6.4.3 In vivo *wear rates*

A number of studies have examined the steady-state 2DWRs of large 36 mm and standard 28 mm metal-on-HXLPE articulations. Tables 2.2 and 2.3 summarise the nature of the studies, and the wear of 28 mm and 36 mm articulations respectively. In the interests of brevity and relevant comparison to the current study, only those studies examining Longevity™ HXLPE in either a 28 mm or large (≥32 mm) articulation have been tabulated. As seen in the tables, minimal steady-state 2DWRs have been reported for both 28 mm and 36 mm metal-on-HXLPE articulations. Steady-state 2DWRs range from –0.04 to 0.07 mm/yr in 28 mm articulations and from –0.06 to 0.08 mm/yr in large articulations. Studies have also directly compared 28 mm and 36 mm metal-on-HXLPE articulations and report no difference in 2DWRs; those studies that involve Longevity™, which is the HXLPE liner employed in the current wear study, are described in Tables 2.2 and 2.3.

To summarise the information in Tables 2.2 and 2.3, most studies have also reported no significant differences in VWRs with one exception. Specifically, Bragdon et al. (2013) reported statistically significant differences between articulation sizes for only one of three calculation methods with the difference in mean annual VWRs being minor. While a larger volumetric wear rate may be expected given that in volumetric wear formulae wear is proportional to the radius of the articulation, it is feasible that a larger articulation may still have the same or lesser VWR compared with a standard articulation provided it has demonstrated less linear wear.

Studies that compared large to standard metal-on-HXLPE not utilising Longevity™ also report no difference in 2DWRs (Hammerberg et al. 2010; Sayeed et al. 2011),

but Hammerberg et al. (2010) reported increased VWRs. In the latter wear study, however, there was no difference in mean VWRs between articulation sizes that were clinically significant (based on observations of conventional PE), though these were statistically significant (29.1 ± 14.8 [range, 8.4–112.8] for the 38/44 mm cohort compared with 16.7 ± 8.2 [range, 4.3–54.6] for the 28/32 mm cohort; $p = 0.0001$).

Lachiewicz et al. (2009) is the only study to report a clinically important (with regard to the conventional PE osteolysis threshold) and statistically significant difference in the VWR between larger and standard articulation sizes. However, they calculated the VWR from first (within the first eight postoperative weeks) to final radiograph (minimum five, maximum eight years) and they did not specifically measure bedding-in and creep. This may have incorrectly led to the conclusion that there are higher amounts of volumetric wear, without regard to true steady-state volumetric wear, in larger articulation sizes. Further, the reference time points, method of VWR calculation and treatment of negative wear rates were not specified.

Table 2.2: *in vivo* standard-sized CoCr-on-Longevity PE™ primary total hip replacement wear studies

Authors	Year	Cohort articulation size	No. of THRs completing follow-up	Min. years follow-up	Method of assessment	Mean bedding-in/creep at 12 months (mm)	Mean 2DWR in mm/yr (to 2 decimal places) [±95%CI if reported]
Ayers et al.	2009	28 mm	24	2	RSA	0.06	0.07¥
Digas et al.	2007	28 mm	19	5	RSA	0.08	0.05¥
Glyn-Jones et al.	2008	28 mm	26	2	RSA	0.26 (6 months)	0.06 ± 0.06¥
Thomas et al.	2011	28 mm	54	7	RSA	0.29 ± 0.07	0.01 ± 0.02¥
Lee et al.	2011	28 mm	113	6	PolyWare™	0.09	0.03 ± 0.01
Min et al.	2013	28 mm	162	5	PolyWare™	–	0.04
McCalden et al.	2009	28 mm	50	5	Martell	–	0.00
Mall et al.	2011	22/26/28 mm	48	5	Martell	–	0.03 ± 0.04
Manning et al.	2005	28 mm	30	2	Martell	0.42	0.01 ± 0.02
Shia et al.	2009	22/26/28 mm	70	2	Martell	–	–0.04
Whittaker et al.	2010	28 mm	36	5	Martell	–	0.03
Olyslaegers et al.	2008	28 mm	60	5	DICOM measure software	0.30 ± 0.13	0.05 ± 0.02
Yun et al.	2011	28 mm	55	5	Dorr and Wan (using digitised calipers)	–	0.05 ± 0.04 (measured from 6 weeks to final)
Babovic & Trousdale	2013	22/28 mm	54	10	Roman software	–	0.02
Beksaç et al.	2009	26/28 mm	40	4	Livermore method (using digital calipers)	–	0.0 ± 0.08

Notes. ¥ = proximal penetration rate – RSA technique

Table 2.3: *in vivo* large CoCr-on-Longevity™ HXLPE articulation (±standard comparison) primary total hip replacement studies

Author	Year	Cohort articulation sizes	Number of THRs completing follow-up	Minimum years follow-up	Method of assessment	Mean bedding-in/creep at 12 months (mm) [±95%CI if reported]	Mean 2DWR (to 2 decimal places) [±95%CI if reported]
Bragdon et al.	2007	28 mm	16	3	RSA	0.06 ± 0.04[¥] [median]	0.03 ± 0.02[¥] [median]
Bragdon et al.	2007	36 mm	14	3	RSA	0.11 ± 0.04[¥] [median]	0.00 ± 0.06[¥] [median]
Nakahara et al.	2011	26 mm	45	8	PolyWare™	–	0.03 VWR[#] 8.7
Nakahara et al.	2011	32 mm	45	8	PolyWare™	–	0.02 VWR[#] 10.1
Bragdon et al.	2013	28/32 mm	287 (28 mm and 32 mm)	5	Martell	–	0.00 VWR[#] 2.0
Bragdon et al.	2013	36 mm	297	5	Martell	–	0.00 VWR[#] 4.3
Bragdon et al.	2006	36 mm	45	3	Martell	–	–0.06 ± 0.41
Lachiewicz et al.	2009	28 mm	33	5	Martell	–	0.03 VWR[#] 53.8 ± 7.2
Lachiewicz et al.	2009	32 mm	35	5	Martell	–	0.01 VWR[#] 57.6 ± 11.2
Lachiewicz et al.	2009	36 mm/40 mm	15/5	5	Martell	–	0.08 VWR[#] 156.5 ± 21.2
Park et al.	2012	36 mm	70	3	PolyWare™	0.08 ± 0.03	0.03 ± 0.02

Notes: [¥] = proximal penetration rate – RSA technique; VWR[#] = steady-state mean annual volumetric wear rate (mm^3/yr)

2.6.5 Studies examining wear rates of younger patients

Studies in younger patients (under 65 years), albeit with shorter follow-up periods than the previously cited papers, have not reported excessive mean 2DWRs despite an expectation of higher gait cycles.

Shia et al. (2009) reported undetectable linear wear in a cohort of 70 THRs in 64 patients of age 50 years or younger with minimum 2.4 years follow-up in their study of CoCr-on-HXLPE (Longevity™) articulations. At a minimum of five-years follow-up, Mall et al. (2011), in a study assessing 2DWRs of THR patients under 50 years, reported reduced 2DWRs in HXLPE (Longevity™) compared with conventional PE. Similarly, Ranawat et al. (2012) reported low 2DWRs in a study of 112 CoCr 28 mm heads on HXLPE Crossfire™ THRs in patients 65 years or younger at a mean follow-up of 5.7 years.

2.6.6 Comparative prevalence of osteolysis in short- to medium-term

Significantly, studies have found a relatively lower prevalence of osteolysis with use of HXLPE compared with conventional PE at short- to mid-term follow-up. However, CT and magnetic resonance imaging, which are more sensitive modalities for detection of periprosthetic osteolysis around THRs than plain radiographs, are not routinely employed (Stamenkov et al. 2003; Walde et al. 2005) and clinically significant osteolysis tends to develop in the mid- to late-term with conventional PE (Sochart 1999).

To date, relatively few of the numerous metal-on-HXLPE THR studies have examined and specifically reported the prevalence of osteolysis, and even fewer have utilised CT. By analysis of plain radiographs, metal-on-HXLPE studies with the longest follow-ups (10–13 years) have reported no or minimal osteolysis (Babovic & Trousdale 2013; Beksaç et al. 2009; Bragdon et al. 2013; Olyslaegers et al. 2008) and

lower rates of osteolysis at a minimum of five years postoperatively, compared with conventional PE controls (Beksaç et al. 2009; Olyslaegers et al. 2008). Mall et al. (2011) used CT to compare 50 conventional PE and 48 HXLPE (Longevity™) THRs and reported a prevalence of osteolysis of 24% and 2%, respectively, at a minimum five-year follow-up. Importantly, they observed that the total FHP in the HXLPE THRs did not predictably correlate to the presence of osteolysis. Leung et al. (2007), in another CT study, found that 11 of 40 metal-on-conventional PE and two of 32 metal-on-moderately (Marathon™) XLPE THRs had periprosthetic osteolysis at a minimum five-year follow-up. Preliminary CT analysis of a minimum 7 year follow-up of patients from the same RCT from which this thesis' patients are drawn has been presented at an international meeting (Holubowycz et al. 2013). Post-operative development of acetabular lucency was demonstrated in 8 of 101 (8%) patients even in the presence of low median wear rates with median wear rates for patients who developed osteolysis being 0.04mm/yr with a range of 0.02-0.1mm/yr. More recently, Blakeney et al. (2015) reported a higher prevalence of 34% with peri-acetabular lucencies, albeit with a more comparatively inclusive definition compared to previous studies that included periacetabular cysts, in a CT study of 100 hips using XLPE liners.

A meta-analysis by Kuzyk et al. (2011) of 12 studies on the comparative radiographic prevalence of osteolysis between HXLPE and conventional PE reported a risk ratio for osteolysis, at a minimum of 2.3 years and a maximum of nine-years follow-up, of 0.40 (95%CI 0.27 to 0.58) favouring HXLPE. While encouraging, clinical studies have only reported a maximum follow-up to 13 years, and the *in vivo* behaviour of HXLPE and the sequelae from its associated wear particles beyond this are unknown.

2.7 Polyethylene wear

2.7.1 Wear of polyethylene acetabular liners

PE wear *in vivo* is multifactorial with a complex interaction of variables and the possibility of wear due to different mechanisms at different times (Schmalzried et al. 1998). Consequently, rates of PE wear observed between different patients and studies are also highly variable (Heisel 2005; Schmalzried et al. 1998) and further limit comparison. To clarify the interaction of different mechanisms and modes, McKellop (2007) proposes that wear in artificial joints can be better characterised and communicated when described as four general subject areas: modes, mechanisms, damage and debris.

2.7.1.1 Modes

McKellop and D'Lima (2008)describe four modes of wear as depicted in Figure 2.3. Specifically:

- Wear Mode 1 occurs when the two bearing surfaces are articulating against each other in the manner intended by the implant designer. Mode 1 is of the greatest relevance to this thesis, and how true *in vivo* articulation wear correlates with radiographic appearance is of central importance.

- Mode 2 occurs when a bearing surface articulates against a non-bearing surface.

- Mode 3 occurs when third-body abrasive particles have become entrapped between the two bearing surfaces.

- Mode 4 occurs when two non-bearing surfaces are wearing against each other.

The least wear occurs in Mode 1, whereas severe wear occurs in Modes 2, 3 and 4.

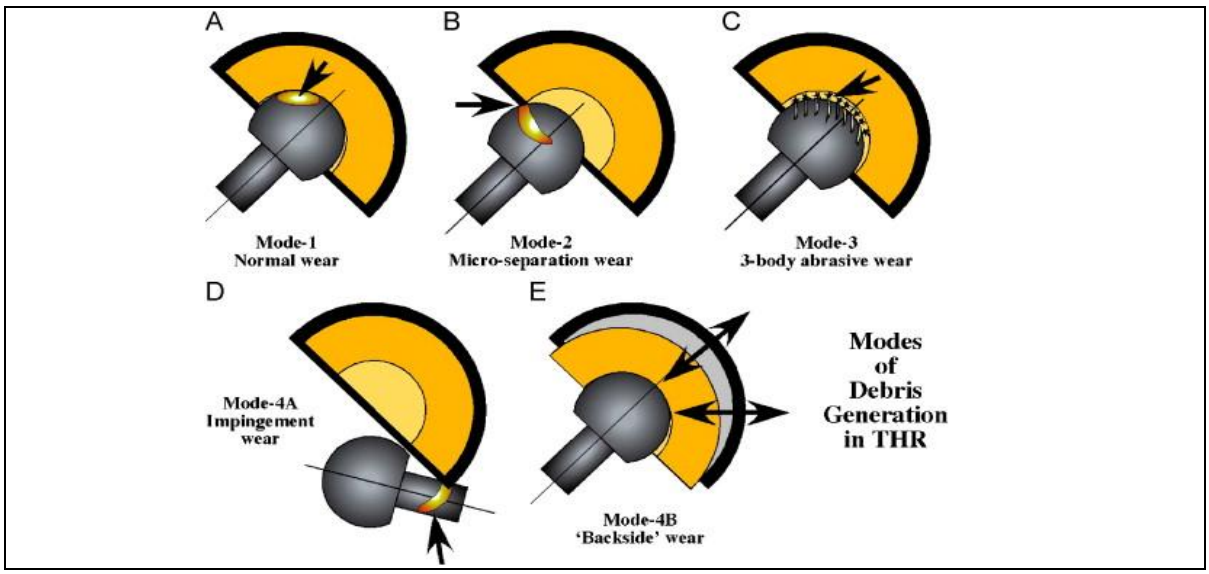

Figure 2.3: Different modes of wear in THR articulations

Source: McKellop and D'Lima (2008). Reproduced with permission and copyright © of the *Journal of American Academy of Orthopedic Surgeons*

2.7.1.2 Mechanisms

The classical wear mechanisms that apply to prosthetic joints include adhesion, abrasion and fatigue (Schmalzried & Callaghan 1999). These can occur in varying amounts in any of the four wear modes although wear debris in the ordinary setting is predominantly formed from the abrasion and adhesion induced by the sliding of a harder body, typically a metal or ceramic femoral head, on the surface of the PE component (Costa & Bracco 2009). For the typical wear scenario of articulating surfaces intended for each other, VWRs have been shown to be proportional to the contact area and sliding distance multiplied by the wear coefficient, which is a constant property of the articulating surfaces (Liu et al. 2011). Reduction of wear is achieved from the cross-linking process of PE, discussed in Section 2.5, which reduces the delamination of PE particles from the acetabular liner and is believed to alter the wear coefficient when it comes into contact with the harder femoral head component (Sobieraj & Rimnac 2009).

2.7.1.3 Damage

McKellop and D'Lima (2008) describe eight types of damage found on retrieved PE liners: burnishing, abrasion, scratches, plastic deformation, cracks, pits, delamination and embedded third bodies.

2.7.1.4 Debris

Assuming a normal wear mode, as would occur in the majority of well-positioned metal-on-PE articulations, the main debris released would be that of PE particles of different size and morphology. However, in the presence of contamination with various other particles within such an articulation, the size, type and shape of particles can change (Bragdon et al. 2003). Debris and contaminants can be diverse and can be from multiple sources, including cement particles, bone particles, porous coating particles and wires (Brown et al. 2009).

2.7.2 Polyethylene wear particle generation and periprosthetic particle migration

Factors reported to affect PE wear in THRs involving XLPE and conventional PE liners are summarised in Tables 2.4 and 2.5, respectively.

Table 2.4: The effect of different factors on cross-linked polyethylene wear generation

Factors	Relative effect on wear generation	Pertinent studies
Implant factors		
Articulation size	Larger size has increased VWRs but not 2DWRs compared to standard-sized articulations.	Bragdon et al. 2013; Lachiewicz et al. 2009; Nakahara et al. 2010
PE manufacturing	Remelting reduced wear but increased rim fracture compared with other methods.	Sobieraj & Rimnac 2009
PE irradiation	e-beam reduced wear compared with gamma irradiation.	Greer, King & Chan 2004; Muratoglu et al. 2001
PE thickness	Thinner PE thickness has indeterminate effect; minor increase in early wear compared with thicker liners.	Cho et al. 2013; Johnson et al. 2014; Rodriguez & Rathod 2013
Component modularity	Modular has presence of backside wear compared with none in non-modular.	Kreig et al. 2009; Ong et al. 2009
Femoral head surface	Rough, scratched and harder surfaces have increased wear compared with smooth and softer surfaces	Bowsher & Shelton 2001; Endo et al. 2002; Kim, Kim & Cho 2005; Lee et al. 2009
Surgical factors		
Contamination of articulation	Increased third-body wear with contamination compared with uncontaminated.	Baxter et al. 2013; Ingram et al. 2004; Kubo et al. 2009
Component positioning	Increased with malposition and deformation compared with ideally positioned and non-deformed.	Bjerkholt, Høvik & Reikerås 2010; Košak et al. 2011; Nakahara et al. 2010; Wang & Lee 2013
Femoral neck offset	Reduced offset has increased 2DWRs compared with higher offset.	Košak et al. 2011
Patient factors		
Age	No increased wear rates of patients <65 years of age compared with patients ≥65 years of age.	Mall et al. 2011; Shia et al. 2009
Gender	No increase in wear rates with males.	Lachiewicz et al. 2009; McCalden et al. 2009
Body mass index	No increase in wear rates in obese patients.	Lachiewicz et al. 2009

Table 2.5: The effect of different factors on conventional PE wear generation

Factors	Relative effect on wear generation	Pertinent studies
Implant factors		
Articulation size	Larger size had increased 2DWRs and VWRs compared with standard-sized articulations.	Hirakawa et al. 1997*; Kesteris et al. 1996; Livermore, Ilstrup & Morrey 1990; Liu et al. 2011; Morrey & Ilstrup 1989; Shaju et al. 2005
PE manufacturing	Base resin of GUR 1120, 1150 and 1900 had increased wear rates compared with GUR 1050 and 1020.	Pace et al. 2013; Schmidt & Hamilton 1996
PE sterilisation	Gamma had reduced wear compared with gas.	McKellop et al. 2000; Sychterz, Orishimo & Engh 2004; Xiong et al. 2007
PE packaging	Vacuum packaging had reduced wear compared with air.	McDonald et al. 2011; Sychterz, Orishimo & Engh 2004
Femoral head surface	Increased roughness/ scratching and harder bearing materials have increased compared with smooth articulations and softer bearing materials.	Agins et al. 1988; Minakawa et al. 1998; Unwin & Stiles 1993
Surgical factors		
Contamination of articulation	Increased third-body wear with contaminated compared with uncontaminated.	Minakawa et al. 1998
Component positioning	Increased with deformed and malpositioned compared with ideally positioned and non-deformed.	Bartel et al..1985; Lee et al. 2009
Femoral neck offset	Reduced wear if within 5 mm of native offset.	Little et al. 2009; Sakalkale et al. 2001
Patient factors		
Age <50	Increased with younger compared with older patients.	Della Valle et al. 2004; Dowdy, Rorabeck & Bourne 1997; Dunkley et al. 2000
High gait cycles/year	Increased with more-active patients compared with less-active patients.	Bjerkholt, Høvik & Reikerås 2010; Heisel, Silva & Schmalzried 2005; Schmalzried et al. 2000
Gender and body mass index	Increased with males and obese patients compared with females and patients with lower body mass index.	Della Valle et al. 2004

***** Correlated with higher volumes of wear particles in retrieved synovial tissue rather than radiographic correlation

2.8 Radiographic methods of polyethylene-wear measurement

2.8.1 A brief history of techniques and their utility

The measurement of *in vivo* wear is critical in assessing the performance of new bearing surfaces. Radiographic determination of the wear rate of the PE liner in THR is achieved by different methods. It was initially described using manual techniques employing rulers and slide-callipers (Charnley & Cupic 1973; Charnley & Halley 1975; Livermore, Illstrup & Morrey 1990).

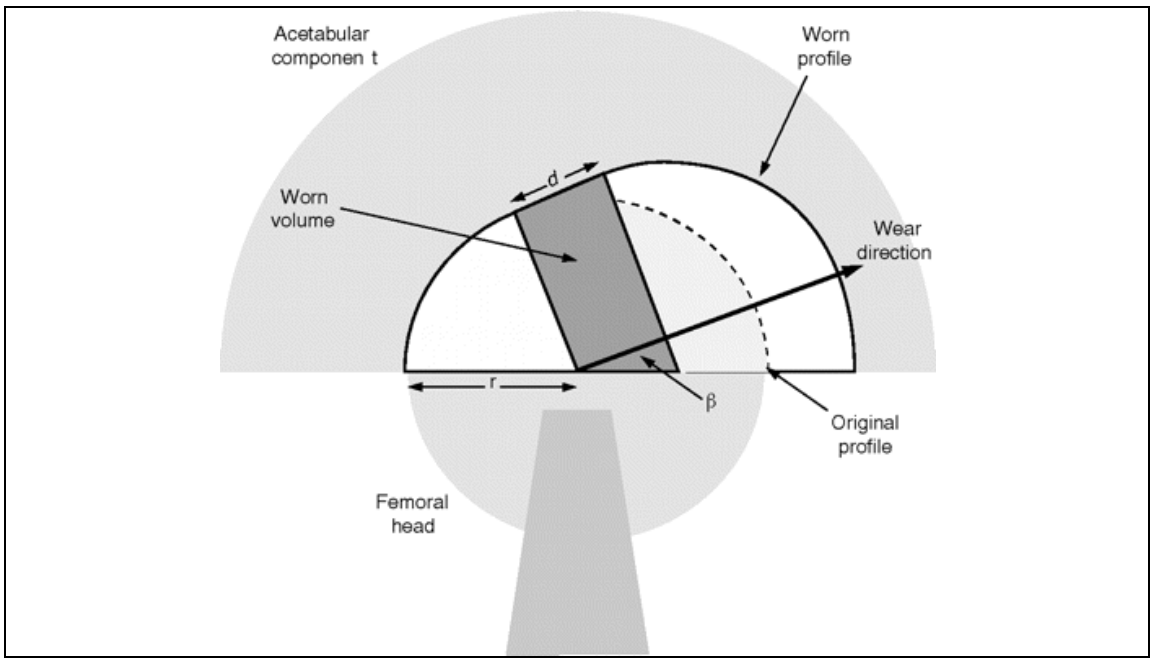

Figure 2.4: Wear theory proposed by Charnley and Halley (1975)

Notes: r = femoral head radius, ß = angle of wear direction to original profile, d = distance between the unworn and worn hemispheres i.e. the penetration depth

Source: Chuter et al. (2007). Reproduced with permission and copyright © of the British Editorial Society of Bone and Joint Surgery

Charnley and Cupic (1973) were the first to assess *in vivo* wear following THR which they did using a uni-radiographic technique measurement of relative component positions from a sole radiograph, dividing the total wear by the number of implanted years. Criticisms of the technique were that the wear was measured entirely within the direction of the plane of the opening of the acetabular component when, in fact, the maximum wear actually occurs in the weight-bearing area. Charnley and Halley (1975) subsequently refined their wear measurement technique by using a duo-radiographic technique. Thickness of the PE was measured from the most recent radiograph and subtracted from a similar measurement taken from the earliest radiograph at the same point (see Figure 2.4). Livermore, Ilstrup and Morrey (1990) as well as Dorr and Wan (1996) further refined manual measurement techniques following Charnley and Halley's (1975) initial methods. Livermore, Ilstrup and Morrey (1990) reported an accuracy of 0.075 mm (range, 0.0 to 0.4 mm), which is comparable to many computer-assisted techniques.

Computer-assisted techniques have superseded manual techniques because of generally superior precision as well as automation of magnification correction between radiographs (McCalden et al. 2005, Rahman et al. 2012). Using these techniques, femoral and acetabular edges are defined and magnification corrected, and superior inter-observer precision and accuracy have been reported (McCalden et al. 2005; Martell & Berdia 1997). One study opposed these generalisations for linear wear of less than 1 mm, reporting computer analysis to be less accurate than manual methods (Wan, Boutary & Dorr 2006). However, in the cited study the computer-assisted methods were hindered by the digital, as opposed to analogue, radiographs being affected by radiographic distortion and blurred edges.

PolyWare™ (Devane et al. 1995) and Hip Analysis Suite™ (Martell & Berdia 1997) are the most popular computer-assisted edge-detection methods for wear research and have been validated (Hui et al. 2003). Other programs have been developed but have not achieved widespread use, such as the MAXIMA™ program (Hardinge et al. 1991), EBRA™ technique (Ilchmann, Mjöberg & Wingstrand 1995) and Roman software™ (Geerdink et al. 2008). Each computer-assisted method can incorporate 2D and 3D measurement and has its own advantages and disadvantages. Significantly, the use of different computer-assisted measurement techniques leads to difficulties in making comparisons between different studies and makes interpretation of their data difficult (Hui et al. 2003; McCalden et al. 2005, 2009). The volumetric wear outputs of the programs do not allow separation of true volumetric wear from bedding-in/creep.

Although Devane and colleagues' (1995) PolyWare™ method and its modifications will be discussed in more detail because it is used in the current study, it is worth briefly discussing Martell's technique, namely, Hip Analysis Suite™ (Martell & Berdia 1997) given it is the other commonly used technique in wear studies with large cohorts. Hip Analysis Suite™ is an automated edge-detection software that calculates

the displacement of the femoral head where the penetration of the head and the angle of penetration are reported as the wear vector (mm) and vector angle (°) using a coordinate system similar to that of Livermore, Ilstrup and Morrey (1990). Wear direction out of the acetabular component in this program is presented as a negative value. This method of reporting has been analysed by Wan, Boutary and Dorr (2006) and Geerdink et al. (2008) who found, respectively, that 48% and 29% of measurements performed with Martell's Hip Analysis Suite™ gave negative wear values, which was attributed by the authors mainly to error in measurements. A 2D single measurement mode was chosen as Martell (2003) had reported that no accuracy is gained from the 3D analysis, which the software also provides.

RSA, developed by Selvik (1989), shares similar principles to these programs but requires intraoperative insertion of tantalum marker beads, expensive calibrated radiographic equipment and expertise. Due to the latter requirements, its use is limited to smaller, prospective studies, despite RSA having superior accuracy compared with other methods (Kärrholm, Gill & Valstar 2006) and a unique capability of being able to characterise creep-related FHP based on its direction (Glyn-Jones et al. 2008). Being constrained to small sample sizes is an important limitation when observing for relatively infrequent occurrences of excessive wear rates and, for this reason, computer-assisted methods remain valuable where a small cohort may miss such occurrences. If a research group's interest is upon comparing the magnitude of outliers between cohorts exceeding a wear threshold, then the degree of such accuracy is arguably less important than being able to recruit and follow large numbers of patients that techniques other than RSA can more easily allow. Some of the proposed advantages and disadvantages of RSA versus computer-assisted edge-detection techniques are summarised in Table 2.6 and further discussed in Section 2.9.4.

Table 2.6: Comparison of RSA and computer-assisted edge-detection techniques

	Traditional RSA	Computer-assisted edge-detection techniques
Gold standard for accurate determination of FHP rate and direction	Yes	No
Retrospective use	No	Yes
Intra-operative metallic bead insertion	Yes	No
Specialised equipment and radiographs required	Yes	No
Amenable to large sample sizes	No	Yes

McCalden et al. (2005), in an influential review of PE wear assessment techniques, asserted that PolyWare™ and Hip Analysis Suite™ were validated in the context of high wear rates (≥0.2 mm/yr). McCalden et al. (2005) cited the study of Hui et al. (2003), but the latter study did not clearly validate the use of these techniques for the evaluation of implants with lower wear rates or early follow-up; only RSA is likely to have sufficient precision in these contexts.

With regard to the relative utility of different methods, Ebramazadeh et al. (2003) compared the accuracy of modifications by Charnley and Halley (1975), Livermore, Ilstrup and Morrey (1990) and Kang et al. (2003) of the Dorr and Wan (1996) techniques to the PolyWare™ (Devane et al. 1995) and Hip Analysis Suite™ (Martell and Berdia 1997) automated software using retrieved liners and a coordinate measuring machine. Median error was least with Livermore, Ilstrup and Morrey's (1990) method and both computerised methods, followed by the Charnley and Halley (1975) and Dorr and Wan (1996) methods. The authors conclude that, in the setting of laboratory based phantom radiographs, computerised methods of PE wear measurement offered distinctly greater accuracy than manual methods. However, with clinical radiographs, computer-assisted methods offered only marginally better accuracy than manual methods, although both had sufficient accuracy for routine clinical assessment of wear.

2.8.2 PolyWare™

PolyWare™ (Devane et al. 1995) is a method validated by Hui et al. (2003) that involves assessing PE wear in metal-backed uncemented acetabular components by use of custom software that utilises AP and lateral radiographs to measure femoral head displacement from the centre of the acetabular component, allowing calculation of the minimum volume of wear (Devane et al. 1995; McCalden et al. 2005). This technique is based on computer-assisted technology to create a solid 3D model of the acetabular component and femoral head on the basis of point selection of back projection of the radiographs (shadow-casting) and computer-assisted design (CAD)/computer-assisted manufacturing (CAM) knowledge of the implant (See Figures 2.5 and 2.6). With this technique, 2D wear in the frontal plane is estimated on the basis of serial radiographs, and 3D wear is estimated by incorporating penetration as shown on lateral radiographs to data from the AP projection. In addition, an algorithm is used to estimate volumetric wear on the basis of the vectors of FHP in three axes.

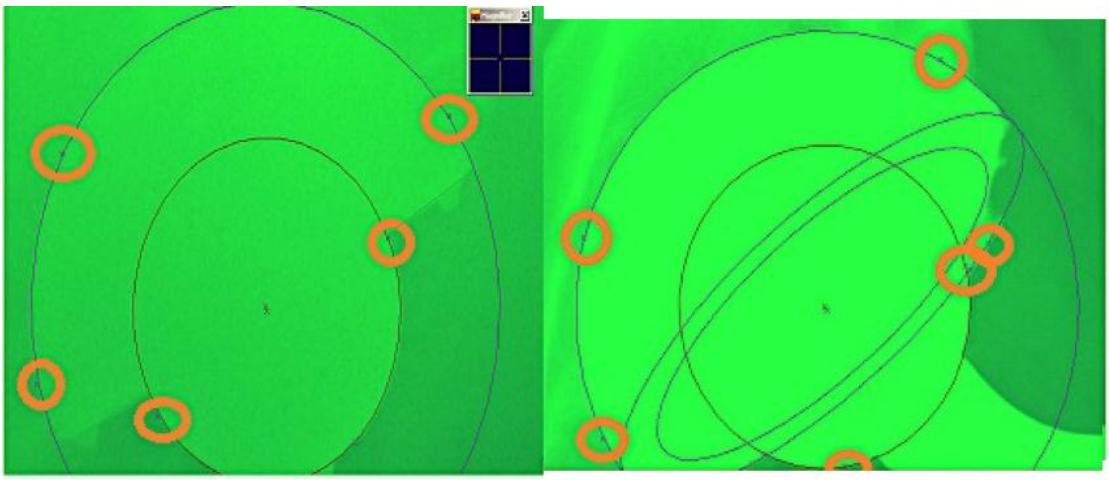

Figure 2.5: Examples of point selection (smaller, thicker circles) and resultant shadow-casting (thinner, larger circles) around an articulation using PolyWare™

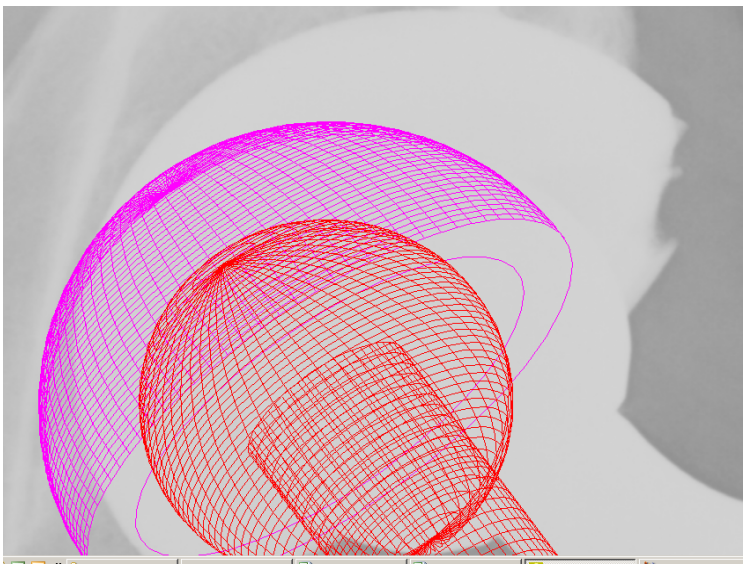

Figure 2.6: Display of the articulation modelling based upon data provided

Note: The CAD model produced and actual image used for point selection are not supposed to overlap on the image above.

In their original study, Devane et al. (1995) used an acrylic phantom model with a simulated head penetration of 8.55 mm, reporting a 3D accuracy in the order of ±0.15 mm (on the basis of the mean absolute difference between the measured and true displacements). Further, they demonstrated an inter-observer and intra-observer precision of ±0.077 and ±0.049 mm, respectively (on the basis of the 95%CI of the standard error), and a volume calculation that was within 8% of the actual amount of the PE removed. This is consistent with reported intra-observer precision of linear FHP with early PolyWare™ versions assessed with phantom images being 0.10 mm (Collier MB et al. 2003) and an accuracy of 0.15 mm (Kang et al. 2003).

Devane and Horne (1999) reported improved intra-observer precision of 0.001–0.042 mm and accuracy of 0.022–0.058 in association with a more automated imaging protocol involving the use of a phantom set-up consisting of two 38 mm-diameter steel balls. Stilling et al. (2009), also using a phantom model, report a precision of 0.02 mm, although other studies of the contemporary version (PolyWare Rev 4) were more conservative. Collier JP et al. (2003) report a 2D precision using mid- and low-pelvic radiographs of 0.21 ± 0.12 mm. Sychterz et al. (2001), assessed the impact of

radiographic quality on performance of wear measurements using a phantom model, and reported a measurement error of 0.09 ± 0.04 mm irrespective of whether suboptimal or optimal radiographs were used.

However, a study by Hui et al. (2003) on retrieved acetabular liners showed that 2D penetration rates derived from the use of Devane's technique differed from the control coordinate measuring machine by 18–20%, and that estimation of volumetric wear differed by 13%. In the same study, measurements using Martell's technique differed by 24%.

A completely automated version of PolyWare™ has been developed, with this version reported to have improved accuracy and precision compared with previous versions (Devane, Horne & Allanach 2004). The developers state that the sixth revision of the software further improves precision from the 0.028 mm for 2D measurements of previous versions (Devane & Horne 1999), although this data is yet to be reported in the scientific literature. Stilling et al. (2012) report that later PolyWare™ versions, such as PolyWare 3D Pro Version 5™, had sufficient precision to be of value with 2D (0.076 mm) but not 3D measurements (0.244 mm) in the clinical setting.

2.8.3 Volumetric wear measurement

Radiographic volumetric wear measurement of PE components is based on formulae that incorporate wear vectors and can be calculated from 2D or 3D contexts. Charnley and Halley (1975) originally attempted to calculate the volumetric wear from 2D methods via a formula incorporating the measured FHP multiplied by the radius of the femoral head multiplied by *pi*. They assumed that a uniform cylindrical wear track resulted in a constant direction that was the size of the diameter of the femoral head with time. Data reported by Dowling (1983) from retrieved conventional PE cups confirmed this assumption. Although simplistic in not considering the wear path

direction, and criticised by some authors for overestimating wear (Chuter et al. 2007; Mizoue et al. 2003; Rahman et al. 2012), it formed the basis for decades of studies reporting volumetric wear derived from plain radiographs. It was used in the seminal paper reporting increased VWRs of larger compared with standard articulations involving conventional PE and higher rates of failure for aseptic loosening (Livermore, Ilstrup & Morrey 1990). For instance, the derivation of osteolysis-associated wear rates stemmed from influential review papers such as that of Oparaguo et al. (2001) and Dumbleton, Manley and Edidin (2002) that acceded to this formula. This was in the absence of any other method in the studies that formed their reviews, although elaborate volumetric formulae from other authors had been published in the intervening period (Hall et al. 1995; Hashimoto et al. 1995; Kabo et al. 1993; Košak, Antolic & Paulovcic. 2003).

Part of the criticism of Charnley and Halley's (1975) formula is that true wear (wear volume) is significantly affected by wear direction (relative to the cup), the initial radial discrepancy, and the femoral head size (Chuter et al. 2007). Some authors, therefore, indicate that dependence on a single measurement (i.e. 2D FHP) may be unsuitable for comparison of wear between series of different types of HXLPE liners where small differences in measurement, such as initial radial discrepancy, will have substantial implications for interpretations of wear (Derbyshire 1998; Yamaguchi et al. 1999). In comparing linear radiographic wear to *in vitro* methods of fluid displacement, coordinate measuring and shadowgraphs found an overestimation of radiographic wear volume ranging from 4–17% in one study (Mizoue et al. 2003) to as much as 47% overestimation compared to a fluid displacement wear measurement method wear in another (Chuter et al. 2007).

Published formulae for estimating the wear volume of acetabular liners do not take the initial radial discrepancy into account, and are based on the assumption that the

femoral head displaces along a cylindrical path and lies at the limit of the cylinder when follow-up AP and lateral radiographs are taken (Yamaguchi et al. 1999). However, the initial radial discrepancy can markedly impact on calculated wear volume at penetrations of less than 1 mm (the magnitude of wear almost universally encountered with HXLPE) and particularly in the bedding-in/creep phase, with its neglect causing an *overestimation* of wear volume of greater than 100% (Derbyshire 1998). Since wear volume varies with wear direction, the wear measurement technique must be capable of correctly determining the wear direction. These issues are among the reasons for including an updated alternative volumetric wear formula in this study (Martell, Personal Communication via email, 3 March 2014), in addition to the historical formula provided by Charnley and Halley (1975).

The relationship between apparent 2DWRs and VWRs will depend on the size of the articulation studied, and studies have often focused solely on linear FHP as the wear surrogate. The limitations of this approach are illustrated by Hodgkinson, Shelley and Wroblewski (1988), who found that linear radiographic wear measured prior to revision THR was not necessarily accurately correlated with volumetric wear found intra-operatively. Nevertheless, while the gold standard of acetabular volumetric wear assessment remains retrieval studies and fluid-displacement analyses, radiological wear determination has a role as a method for estimating *in vivo* VWRs.

2.8.4 Two-dimensional versus three-dimensional wear measurement techniques

One limitation of 2D analysis is the inability to detect wear that occurs out of the plane of the AP radiograph, which was a reason for the development of 3D wear measurement techniques (Devane et al. 1995; Hui et al. 2003; Yamaguchi, Bauer and Hashimoto 1997).

However, 2D and 3D techniques are different in their precision, with 3D techniques arguably requiring increased resources without improvement in the ability to detect clinically relevant differences. Sychterz, Yang et al. (1999) were the first group to report on and make this assertion.

Hui et al. (2003), in a comparison of 2D versus 3D wear for PolyWare™, found that 2D wear measurement found approximately 10% less wear than 3D measurement but its intra-observer precision was four times superior to that of the 3D technique. This was largely contributed to by the quality of radiographs, particularly cross-table laterals. The authors conclude that the limited improvement in wear detection achieved with 3D analysis, coupled with its inferior precision, limits its clinical value. Hence, 2D measurements, based solely on an AP radiograph, may suffice in the clinical setting. Ilchmann, Reimold and Muller-Schauenburg (2012), from a study correlating *in vitro* fluid displacement measurement of retrieved liners to volumetric calculations from radiographic linear wear, also conclude that radiographic measurements of linear wear in the film-plane can provide a reliable estimation of the total wear volume. They propose that even the Charnley and Halley (1975) method, which generally overestimated wear, provided reasonable results compared with the gold standard *in vitro* fluid displacement comparison.

In summary, AP radiographs of THRs provide a reasonable estimate of the wear vector associated with the majority of linear wear (Sychterz, Engh et al. 1999) as well as volumetric wear (Ilchmann, Reimold & Muller-Schauenburg 2012). Although the shortcomings of this technique are acknowledged, the influential studies and reviews that linked conventional PE wear rates to the prevalence of osteolysis and implant survival are based primarily on extrapolations from 2D measurement techniques from the AP radiograph (Dumbleton, Manley & Edidin 2002; Oparaugo et al. 2001; Sochart

1999). On this basis alone, it is reasonable to utilise this as one of the methods for calculating VWRs.

2.9 Wear interpretation and wear study design

Factors influencing the interpretation of wear outcomes include occurrences such as negative wear and backside wear as well as discriminating bedding-in and creep from true wear and the issue of suboptimal diagnostic imaging (Bragdon et al. 2006; McCalden 2009).

2.9.1 Creep and bedding-in

As previously defined, creep is a normal superomedial remoulding process most prominent in the early postoperative period, and bedding-in is the settling in of the PE liner into the acetabular shell (McCalden 2009; Sychterz et al. 1997). Conversely, true wear is a pathological superolateral process that releases PE particles and has been associated with the pathogenesis of osteolysis (Bragdon et al. 2006; McCalden 2009; Sychterz et al. 1997).

While creep is more likely to be a function of cycles of gait rather than time in months (Liu, Fisher & Jin 2012), there is consensus amongst RSA studies that steady-state wear appears to be reached by one year postoperatively, if not earlier (Bragdon et al. 2007; Glyn-Jones et al. 2008; Röhrl, Nivbrant & Nilsson 2012; Sychterz et al. 1997). Therefore, one year is commonly chosen as the reference time point from which steady-state FHP is measured (Bragdon et al. 2007, 2013; Park et al. 2012; Röhrl, Nivbrant & Nilsson 2012).

Measurements derived from edge-detection methods cannot, at present, categorically distinguish true PE wear from initial creep and bedding-in (Geerdink et al. 2008; Glyn-Jones et al. 2008; Sychterz et al. 1997). However, it is optimal to assess whether

there is a common radiographic time point by which patients' plotted FHP plateaus, lest wear be overestimated. The inability to distinguish the contribution from creep and bedding-in against true wear has implications, as the steady-state wear follows the cessation of the creep-dominated period. Thus, studies of HXLPE that do not take these phases into account have overestimated 'true wear' and reported similar annual wear rates between conventional PE and HXLPE. This is because they rely on dividing observed total FHP across time points that include early bedding-in/creep-dominated periods (Geerdink et al. 2008; Stilling et al. 2010). A pertinent example is the study of Dai et al. (2000) who reported that the measured FHP in the first two postoperative years was approximately 60% of the FHP at 10-year follow-up and, similarly, the femoral head migration after a mean evaluation time of three to four months represented 56% of the two-year total.

The exact time point of where the creep-dominated phase for HXLPE ceases is unknown, but it would likely vary between articulations and require multiple measurements at short intervals. To characterise the end of bedding-in/creep with a high degree of accuracy would require monthly radiographs in patients, which would be a burden upon the patient and institution with additional radiation exposure and expenditure without significant gain. The caveat to this is that RSA studies can indicate, to a degree, the probability that FHP is creep- rather than wear-related based upon it being proximal rather than proximal, medial and anterior (Glyn-Jones et al. 2008).

2.9.2 Negative wear

Another problematic occurrence in wear studies is 'negative wear' in the context of contemporary studies dealing with relatively small wear rates approaching, or less than, the precision of the measurement tool being used (Bitsch et al. 2008; Bragdon et

al. 2006; Campbell, Field & Callary 2010; Engh et al. 2012; Manning et al. 2005; McCalden et al. 2009; Meftah et al. 2011; Ranawat et al. 2012).

While negative wear is thought to be the result of erroneous measurement, other plausible explanations have been described in the context of wear being a temporal phenomenon. First, Devane et al. (1995) described that wear of the femoral head into the PE acetabular liner is not necessarily a tight cylindrical path around the femoral head as was previously assumed, and the femoral head may not be located at the deepest point of the wear path at the time of the radiograph, thereby assuming an apparently more superficial position within the liner between different radiographs. Second, as discussed earlier, such apparent negative wear may be contributed to by the initial radial discrepancy, which can change following use of the articulation (Derbyshire 1998). Methodological limitations may also contribute to apparently negative wear with erroneous measurements that can be related to the software used, image quality, patient positioning and muscle tone, as well as random error in edge tracing (Bitsch et al. 2008; Ranawat et al. 2012).

Studies analysing 2D wear of articulations including HXLPE report varying amounts of negative wear. The proportion of hips recording negative wear rates have approached 50% when Martell's method is used to analyse wear rates in the vicinity of 0.1 mm, as reported by Wan, Boutary and Dorr (2006). Bitsch et al. (2008) reported negative wear rates occurred in 23% of patients in their cohort, again using Hip Analysis Suite™.

While multiple studies using Hip Analysis Suite™ and PolyWare™ methods have reported negative wear rates, the manner in which the data are handled and analysed presents an inconsistency in the literature. McCalden et al. (2009) commented that while several authors have noted negative wear rates, there is no consensus on how to

deal with them and not all authors state how they have dealt with negative wear results. This is critical, as the effect on wear results overall can be considerable depending on how negative wear is handled. For example, inclusion of negative wear results when calculating the mean will result in lower mean wear and have a broader SD range than when negative wear results are excluded or converted to a zero value. The significant effect on wear rates reported by different handling of negative wear results is later shown in Table 4.8. While the manner in which negative wear rates are treated is not as critical in this current study because the data are presented as scatterplots and proportions with elevated wear rates, the majority of wear studies that do report mean wear rates as their main outcome can be especially influenced by the manner of their treatment.

An example in the existing literature is the study of Ranawat et al. (2012) where, if negative wear rates were included into the mean wear rate calculation, the 2DWR was 0.014 mm/yr compared with 0.043 mm/yr if negative results were treated as zero values. Some studies have excluded negative wear results (Rajadhyaksha 2009; Reynolds et al. 2012) or not included them in the mean wear calculation. Others have factored them into their mean wear along with the positive values (Bragdon et al. 2013), assigned them a zero value (Engh et al. 2012) or have reported them by both including them as negative values or assigning them a zero wear value when calculating the man (Babovic & Trousdale 2013; Meftah et al. 2011; Ranawat et al. 2012).

2.9.3 Imaging technique and quality

Comparison between studies, with respect to the quality of image presentation for measurement, depends on the image acquisition and the edge-detection software used. Pixilation, picture compression and the type of viewer or software can play a part in

error and discrepancy (Sychterz, Young & Engh 2001). Geerdink et al. (2008) report, in an analysis of different edge-detection software used in FHP measurement, that a five-megapixel pelvic radiograph should be the minimum requirement, with lower resolution affecting interpretation. However, such image quality was not available for many of the historical wear studies. The authors further made comment that the edge-detection method used, specifically, Hip Analysis Suite™, had different performance depending on whether digital or scanned analogue x-rays were used. Image processing of digital x-rays was associated with improved accuracy and precision owing to the approximately 50% reduced pixel size of digital compared with analogue images (0.07 mm per pixel to use for measurements compared with 0.14 mm). It is important to note that this size per pixel approaches the precision of many of the measurement methods discussed with the exception of RSA.

Interpretation may also be impeded by the variable soft-tissue composition and positioning of patients when having radiographs (Clohisy et al. 2008). For example, pelvic orientation can change the geometry of distance measurements dependent on AP pelvic radiographs (2D measurements) although computer-assisted methods have reduced this issue compared with manual techniques as they commonly reorientate the cup in their wear calculations (Collier MB et al. 2003; Foss et al. 2008).

Studies investigating the potential influence of standing weight-bearing compared to non weight-bearing supine radiographs for PE wear analysis conclude that the measured differences in conventional PE wear between weight-bearing and non-weight-bearing radiographs are of no clinical relevance (Bragdon et al. 2006; Martell, Leopold & Liu 2000), although this may not be the case with HXLPE. Another important contributor to inaccuracies in edge detection is projectional distortion of the femoral head and acetabular shell on the radiographs, including the aberrant placement

of the x-ray tube and cassette. Contemporary software, however, has been able to minimise this problem with mathematical methods (Kraay et al. 2010).

2.9.4 Clinical context of the utility of wear measurement techniques

As described in Section 2.8, traditional RSA has been reported as the gold standard technique in radiographic wear measurement of THR articulations. In the same way, some would advocate for 3D measurements over 2D as they are arguably higher fidelity. However, the ideal measurement technique for a specific study will depend on a variety of factors. This includes the design and aims of the study, especially whether it will be prospective or retrospective, and the proposed sample size desired for the study to demonstrate an outcome.

In the context of HXLPE, should an investigator want to focus on the infrequent occurrence of patients demonstrating excessive wear in a large cohort involving centres that may not have access to RSA, then computer-assisted edge-detection techniques may be an appropriate choice. Precision, afforded by 2D over 3D, may also be desired in this context over a higher capture of true wear. Supporting this, Stilling et al. (2010) report that PolyWare™ Version 1 is sufficient for retrospective determination of 2D wear from medium-term wear measurements above 0.5 mm with a clinical precision similar to that of RSA.

Conversely, it may be academically and clinically important to have accuracy of the order that will enable early monitoring of new implants demonstrating minimal wear rates, as observed in early follow-up of HXLPE THR cohorts, and more accurately define creep. In this context, RSA and/or 3D techniques may be the preferred option, but their many limitations would need to be accepted. RSA is limited by:

1. Being conducive only to smaller-sized cohorts

2. Being amenable only to prospective data collection
3. Requiring tantalum-bead insertion intra-operatively; and
4. Requiring acquisition of sophisticated and expensive RSA equipment and staff trained in its use.

The ability to carry out RSA research would then be subject to the availability of funding for the study as well as resource and expertise acquisition by the radiology and relevant departments. The need for tantalum-bead insertion and potential inconvenience of having patients travel to a specialised centre to have RSA radiographs taken may also need to be considered. While believed to be inert with good biocompatibility (Black 1994), there have been reports of migration and movement of tantalum beads from their intended position towards articulations (Eldridge et al. 1998) and, in theory, they may have the potential to contribute to third-body wear (Downing et al. 2004).

2.9.5 Reporting of wear outcomes and summary of limitations

Reporting of wear outcomes differs between studies, and the lack of consistency impairs comparisons and the clinical application of results. One of the primary benefits of uniform methods of obtaining, analysing and reporting wear outcomes is that it allows clinicians and researchers to extrapolate empirical results into the clinical arena. This would enable the clinician to make scientifically based decisions regarding implantation of optimally sized and manufactured articulations with the least risk of future revision. As discussed earlier in this chapter, the ideal implant combination for survivorship would reduce the incidence of dislocations while not having the disadvantage of a higher proportion of patients with elevated wear rates given that elevated short-term annual wear rates in conventional PE were closely correlated to

later revision for osteolysis and aseptic loosening (Dumbleton, Manley & Edidin 2002; Oparaugo et al. 2001; Sochart 1999).

The reporting of wear outcomes has tended to focus on mean 2DWRs as the most commonly reported outcome in THR wear studies. The shortcoming of this approach is that the mean wear rate can be skewed heavily by outliers. Furthermore, how negative wear is handled will affect the mean value, namely, whether it is included, excluded or converted to zero. Moreover, as seen in Figure 2.7, two studies may have the same mean 2DWR but should one cohort have a narrow spread of negligible wear rates and the other contain a large number of positive wear outliers, the clinical implications of the wear behaviour are very different between the cohorts. In Figure 2.7, the hypothetical cohorts whose distributions are indicated by the green and black outline have the same mean wear rates but differ in the proportion of patients with wear rates that may be clinically significant as indicated by the areas shaded yellow and purple for each cohort respectively. In this example, if only the mean wear rates for the cohort were to be reported, the clinically important fact that one cohort has a significantly greater proportion of patients with elevated wear is missed.

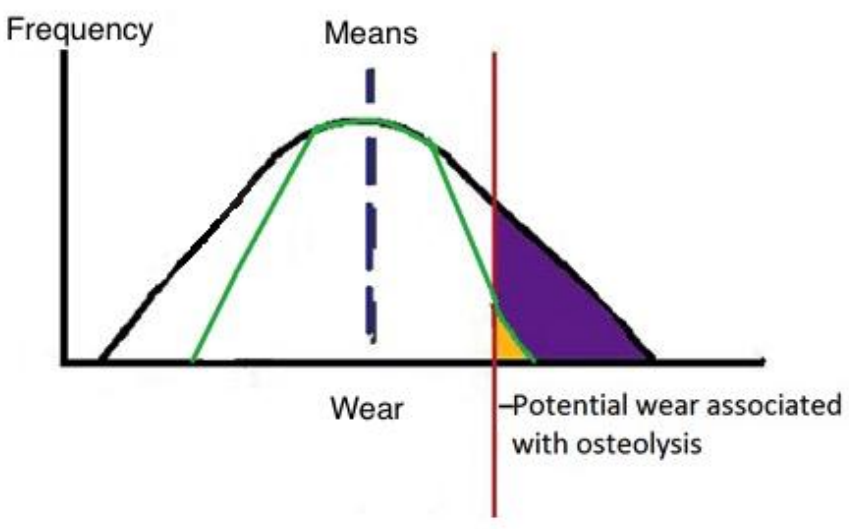

Figure 2.7: Implications of reporting mean wear rates only without regard to outliers exceeding the osteolysis threshold

Each method of reporting brings advantages and disadvantages and the choice of outcome reporting depends on the aims and methodology of the study as discussed above. The most commonly reported outcomes in wear studies are mean and median wear rates with the main advantage that they are convenient summary statistics for the comparison of central tendencies (Bragdon et al. 2013; Meftah et al. 2011; Ranawat et al. 2012). While median wear rates are less sensitive to the effect of outliers than mean wear rates, both will be significantly affected by whether negative wear rates are included (Bragdon et al. 2013; Meftah et al. 2011; Ranawat et al. 2012), excluded (Rajadhyaska et al. 2009; Reynolds et al. 2012) or treated as zero (Engh et al. 2012; Meftah et al. 2011; Ranawat et al. 2012).

Conversely, graphic methods enable full appreciation of the spread of the data. Scatterplots, in particular, not only show the data in their purest form, but enable a retrospective review of the data that retains meaning, both for cohorts and individuals. This is especially an advantage when the data are not normally distributed. Further, the depiction of the data is not subject to manipulation or interpretation. On the other hand, although histograms and boxplots show the spread of data in a meaningful way, particularly with respect to excessive wear rates, they do not display the wear rates of individuals as seen in a scatterplot.

Several other methods of reporting and handling data are valuable but not commonly used in the wear literature. Data modelling by statisticians gives statistically sound meaning to the data when comparing cohorts but is limited in application due to its complexity for the non-statistician to employ and comprehend. Outlier analyses in wear studies allow assessment of variables that may contribute to excessive wear rates that may not be appreciable across the cohort. However, outlier analyses are seldom reported in HXLPE, which is partly because the majority of studies involve sample sizes too small to characterise this infrequent occurrence, and also because the

definition and potential significance of excessive wear rates has not yet been reported in HXLPE. When further defined, assessing the proportion of individuals exceeding potentially clinically important wear rates will give data clinical relevance by assessing whether particular factors increase the risk of elevated wear rates.

2.10 Summary of the literature review

As has been described in this chapter, the rationale for the development of HXLPE liners is based on studies of conventional PE where excessive steady-state wear rates were correlated to periprosthetic osteolysis. While studies examining primary metal-on-HXLPE THRs report lower wear rates compared with conventional PE, the relationship between wear rates of HXLPE liners and osteolysis remains undefined.

The need to compare wear rates between articulation sizes in HXLPE arises from comparative studies in conventional PE, which report higher 2DWRs and VWRs with larger articulations (Hirakawa et al. 1997; Kesteris et al. 1996; Livermore, Ilstrup & Morrey 1990; Morrey & Ilstrup 1989; Shaju et al. 2005). Should higher short-term wear rates or a more substantial proportion of articulations exhibiting high wear rates be evident in large metal-on-HXLPE articulations, this would potentially be a disadvantage to be considered against the demonstrated benefit of a reduction in the incidence of dislocation at one year with large articulations (Howie et al. 2012). The limited studies have also not clarified the effect of articulation size on creep and bedding-in, and it is recognised that failure to appreciate this may lead to incorrect conclusions about comparing steady-state wear rates between different articulations.

Finally, wear studies continue to focus on mean wear rates as their primary outcomes. Although a convenient summary statistic for comparison, mean wear rates lack clinical meaning in isolation. Other additional statistics, such as the proportion of patients

exceeding certain levels of wear, should be reported to give clinical meaning to results and accurately identify patients with elevated wear rates.

The literature is lacking a study comparing wear rates between cohorts of patients randomised to large and standard articulation sizes and has focussed on mean wear rates as the primary outcome. The opportunity to analyse comparative wear and report wear data in clinically meaningful ways is available from use of radiographs of patients enrolled in an RCT comparing the incidence at one year between 36 mm and 28 mm metal-on-HXLPE articulations.

2.11 Aims and hypotheses

A large multi-centre RCT examining the effect of articulation size on dislocation was initiated by the supervisors of this thesis, Dr OT Holubowycz and Professor DW Howie , at the University of Adelaide. Specifically, the aim was to compare the incidence of dislocation at one year following THR between 36 mm and 28 mm metal-on-HXLPE articulations. The incidence of dislocation one year after primary THR with a 36 mm articulation was 0.8%, compared with 4.4% with a 28 mm articulation, which was a statistically ($p = 0.024$) and clinically significant difference.

The RCT involved radiographic examinations of patients at specified time points. This presented the opportunity to use patients' radiographs to assess and compare the PE liner wear of patients randomised to either 36 mm or 28 mm articulations, which is the focus of this thesis.

2.11.1 Aims

The aims of this thesis are to:

1. determine bedding-in and creep of 28 mm and 36 mm metal-on-HXLPE articulations at 3 and 12 months,

2. determine 2DWRs of 28 mm and 36 mm metal-on-HXLPE articulations at a minimum of two and maximum of five years following THR using computer-assisted wear analysis methods,

3. determine VWRs of 28 mm and 36 mm metal-on-HXLPE articulations at a minimum of two and maximum of five years following THR using computer-assisted wear analysis methods,

4. determine the proportion of patients in each articulation size cohort with elevated 2DWRs (≥0.1 mm/yr) and elevated VWRs (≥80 mm^3/yr), and

5. compare different methods of reporting wear rates.

2.11.2 Hypotheses

The specific hypotheses are that:

1. there are no significant differences at 3 and 12 months in creep/bedding-in between 36 mm and 28 mm metal-on-HXLPE articulations,

2. there are no significant differences in 2DWRs between 36 mm and 28 mm metal-on-HXLPE articulations,

3. there are no significant differences in VWRs between 36 mm and 28 mm metal-on-HXLPE articulations,

4. there are no significant differences in the proportion of patients in the 36 mm and 28 mm cohorts with elevated 2DWRs, and

5. there are no significant differences in the proportion of patients in the 36 mm and 28 mm cohorts with elevated VWRs.

Chapter 3: Methodology

3.1 Study conduct and data collection

3.1.1 Sample population and randomised controlled trial methodology

The study sample for this thesis was drawn from an RCT for which the primary aim was to compare the incidence of dislocation at one year between patients undergoing THR with either 36 mm or 28 mm metal-on-HXLPE articulations. The results of this RCT with respect to dislocation have been published (Howie et al. 2012). This publication and its associated electronic appendix (Appendix A) provide a detailed description of the RCT study methodology.

Following the granting of ethical approval at each centre, 14 centres in Australia and the United Kingdom (UK) recruited patients for the RCT (see Appendix B). Although both primary and revision THR patients were involved in the RCT, the current wear study involved analysis of radiographs of primary THR patients only. Importantly, the sample size for the RCT was powered for assessment of the incidence of dislocation at one year and not for determination of any differences in wear rates between the 36 mm and 28 mm articulation cohorts.

Inclusion criteria for primary THR patients were:

- age of at least 60 years,
- diagnosis in the index hip of either osteoarthritis, rheumatoid arthritis, inflammatory arthritis or surgery for previous fracture or dislocation involving the operated hip, and
- a posterior surgical approach.

Exclusion criteria for primary THR patients included variables that, although not common, are associated with an increased risk of dislocation, such as leg-length inequality and abductor muscle deficiency.

Primary THR patients in the RCT were eligible for the current wear study if a minimum of three radiograph sets were available for analysis. Specifically, at least one radiograph set was required from each of the following three time periods:

- up to three months postoperatively
- at 12 months
- at 24 months or subsequently.

These timelines were chosen based on previous literature, as described in Section 2.6, which reported that the majority of FHP due to creep and bedding-in was observed by 12 months. In other words, a transition to a steady-state FHP rate could be anticipated by 12 months, with the final two radiographs capturing a steady-state 'true-wear' phase of FHP.

3.1.1.1 Tabulation of patient information and component position

The patient's age, gender and body mass index (BMI) were tabulated along with the date of surgery, implants inserted and follow-up period, allowing comparison of the 28 mm and 36 mm articulation cohorts who had sufficient radiographs for analysis. Acetabular component positioning is also reported given that it has the potential to affect wear rates (see Section 2.7). Primarily due to a stratification and randomisation process applied to the RCT, neither significant differences in demographic factors nor significant differences in acetabular component position between entire articulation cohorts were expected. However, to confirm no significant differences with respect to

variables between cohorts in the current wear study, a two-tailed student *t*-test for interval data and *chi-squared* analysis for categorical data were undertaken.

3.1.1.2 Surgical protocol

All primary THRs were templated for planned component position and offset, and performed with the patient positioned laterally via a posterior surgical approach, with repair of the capsule and external rotators performed routinely.

3.1.1.3 Prostheses used

All primary THRs comprised an uncemented three-holed cluster acetabular shell (Trilogy™; Zimmer, Warsaw, Indiana) fixed with one or two screws, a 10-degree elevated 28 mm or 36 mm HXLPE liner (Longevity™; Zimmer) and a cemented femoral stem with a CoCr femoral head (CPT™; Zimmer) for all primary arthroplasties.

Following routine preparation of the acetabulum and femur, eligible patients received either a 28 mm or 36 mm articulation, according to randomization allocation specified in an envelope provided to the surgeon intra-operatively.

3.1.2 Clinical and radiographic follow-up

Follow-up varied between centres according to institutional protocol, and included a clinical assessment as well as a radiographic examination (see Section 3.1.2.1). Radiographs were taken according to local institutional practices at the centres involved. Radiographic follow-up practices varied between Australian and UK hospitals as shown in Table 3.1.

Table 3.1: Variation in radiographic follow-up practices between countries

Country	Day 4	6 weeks	3–6 months	12 months	24 months	36 months	60 months
Australian	x*		x	x	x		x
UK		x		x		x	x

Notes: * Royal North Shore Hospital patients had their first follow-up radiograph at six weeks.

Consent for cross-centre transfer of patients' radiographs was sought as part of patient enrolment in the RCT.

3.1.2.1 Radiographic protocol

Centres involved in the study were instructed that each radiographic assessment should include an AP pelvis centred below the pubic symphysis as well as an AP, cross-table and rolled-lateral radiograph of the operated hip. A minimum of an AP pelvis and lateral (either cross-table or rolled-lateral) of the hip was required for radiographic wear analysis. These were taken with the patient lying supine (non-weight-bearing) with standardised patient positioning, including pelvic orientation and exposure, with the goal of achieving radiographs of comparable quality between centres. Specifically:

- AP pelvis radiographs were taken with the patient supine and both legs internally rotated to approximately 15 degrees with the beam centred around the pubic symphysis.

- Rolled-lateral radiographs were taken with the patient supine and rotated posteriorly towards the operated side with the hip flexed and abducted approximately 45 degrees with the beam aimed perpendicular to the plate, centred on the femoral neck.

- The cross-table lateral had the patient supine with the non-operated hip flexed at 90 degrees, out of the path of the beam, and the beam centred on the femoral neck and perpendicular to its long axis.

3.1.2.2 Image acquisition

The centres varied in their modes of image capture and image storing. Some centres transported their study participants' early images in printed radiographic film format. The majority of radiographs taken before 2004 were analogue film radiographs, whereas the majority of images after 2004 were digitally captured (demonstrated in Table 4.3).

3.1.3 Data collection and image processing

The maximum pixel size for the cohort was 0.085 mm per pixel from radiographs, with the majority of institutions transferring images that enabled smaller pixel sizes. If hard-copy radiographs were sent by the institution, they were collated and then processed using a Royal Adelaide Hospital scanner (DiagnosticPro™, Vidar Systems Corporation, VA, USA) and stored as a tagged image file format (TIFF) with a minimum standard of 300 dots per inch (0.085 mm per pixel) resolution on a secure network drive. Digital images (DICOM) of smaller pixelation ranging from 0.04 to 0.06 mm per pixel were opened and similarly converted to TIFF files for program use and standardisation of format analysis using Paintshop Pro™ (Version 6, Corel, California, USA). The reason for selection of a uniform file type was for fairness of comparison, as pixelation can affect image analysis. The images were stored in a password-protected departmental research folder containing the categorised digital images of all trial patients.

3.2 Data analysis

3.2.1 PolyWare™ analysis

Analysis of radiographs of patients with a sufficient set of radiographs was undertaken with PolyWare Auto Rev 5™ (Draftware, Indiana, USA). A set of radiographs was deemed to be sufficient if there existed at least one quality AP radiograph of either the

operated hip or pelvis and one lateral radiograph of the operated hip at time points specified in Section 3.1. For consistency, the same type of radiograph was used across a patient's set. If AP pelvis and cross-table radiographs were available for each time point, they were used. However, if either the AP pelvis or cross-table radiograph was not available at a time point but the alternative radiographs were available (e.g. AP operated hip or rolled-lateral across a whole set), they were used instead.

The PolyWare™ program required the entry of patient demographics and implant details prior to carrying out the computer-assisted edge-detection method across the available set of patient radiographs. This included patient's age, gender and study number, date of procedure, magnification, make and size of acetabular components, size of femoral head and date of initial radiograph set.

All radiographs were analysed by the candidate using PolyWare™. The analytical technique was based on that of Devane and Horne (1999) and the PolyWare™ Rev 5 User Manual. An important goal was to achieve a reproducible technique that would lead to a minimal measurement bias or intra-observer errors. Specifically, the portion of the femoral head that was proximal to, and not obscured by, the acetabular shell was preferred for point selection over points within the shell, as this allows for more accurate point selection. This technique involved the lateral radiograph being analysed first, with the cross-table lateral (if available) preferred over the rolled-lateral, given the better ability of the former to demarcate the articulation outline from the patient's soft-tissue shadows.

A minimum of three femoral head points were entered and assessed for adequate shadow cast to assess if the ellipse formed was representative of what was presented on the radiograph (see Figure 3.1). Allowances were made for the Trilogy™ locking mechanism (notch in the upper right acetabulum in the images in Figure 3.1). In

Figure 3.2, the top-left and top-right figures represent the ideal point selection on lateral and AP images respectively (red stars for the acetabular and green outline/black stars for the femoral component), where the components are most spherical or rounded – this avoids the selection of points around the locking mechanism (blue star) and screw holes (purple) that can cause inaccuracy in shadow-casting. The visible area of femoral head available for ideal point selection (green square) in the 36 mm articulation (bottom left and right) is less than that of the 28 mm articulations because of the larger portion of the articulation that is non-spherical. If the point capture of the femoral component was accurate, then a minimum of three acetabular component points were again selected assessing for accurate shadow cast.

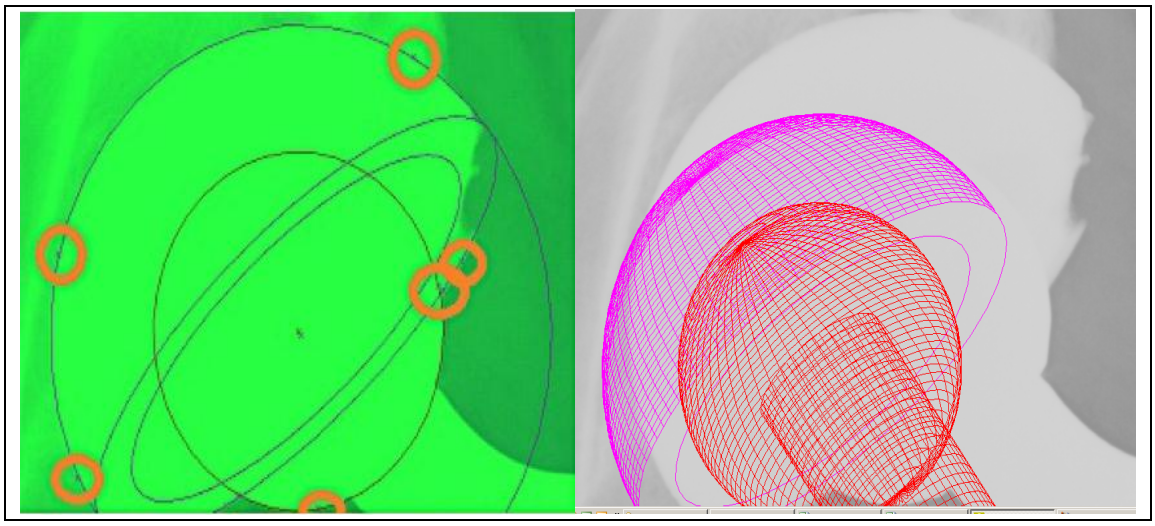

Figure 3.1: An example of a completed shadow cast following point entry and 3D model generated after entry into PolyWare™ of AP and lateral points, affirming acceptable point capture

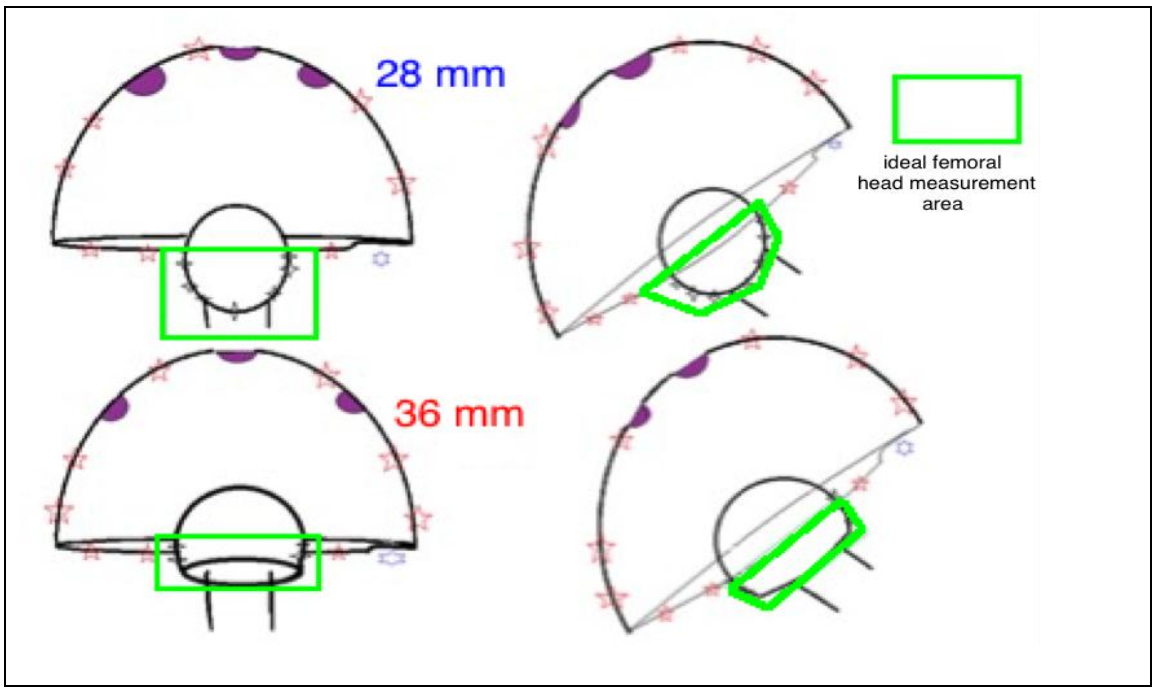

Figure 3.2: Schematic representation of the preferred process of analysing 28 mm and 36 mm articulations in the current study using the PolyWare™ software

If the lateral radiograph was of poor quality, it was still included in analysis, but more than three acetabular and femoral points were chosen to try to recreate component position as closely as possible, given that inclusion of the lateral radiograph allowed an accurate 3D model to be constructed for wear calculation and acetabular component positioning by the software.

For the analysis of AP pelvis images, the technique involved entering points to enable accurate pelvic orientation, with identification of pelvic coronal tilt and the central point of the radiograph. A minimum of three femoral head points were entered to enable an accurate shadow cast on the femoral head. A minimum of three points on the outer shell of the acetabular component and three rim points were entered, and attention was given as to whether the acetabular component shadow-casting accurately recreated the true acetabular component position on the radiograph (see Figures 3.1 and 4.2). If any of these shadow casts appeared inaccurate, the procedure was repeated using more points until accurate shadow-casting representative of the true component position on the radiographs was achieved (see Figure 3.3). This was then reaffirmed

by viewing the PolyWare™ generation of a 3D model and assessing whether this reflected the entered points before accepting the output data (see Figure 3.1). The overall input process was repeated at least once for each patient. The output selected depended on analysis of the most logical progression of results and a positive wear direction, referred to as the 'optimal' cycle (see Figure 3.4).

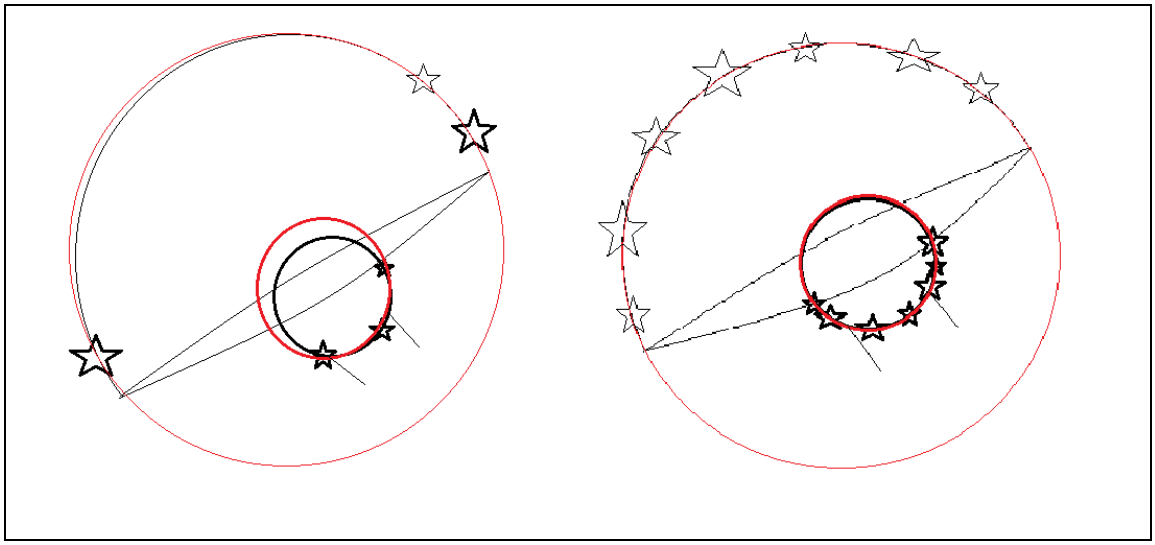

Figure 3.3: Schematic example of the occurrence and correction of shadow cast error

Notes: The image on the left depicts an AP image of an articulation – note the few points (represented by stars) from which the computer program needs to estimate a shadow cast and the resulting inaccurate representation from the points selected. On the right image, the same radiograph of the same articulation is then re-analysed using more point selection of the background articulation and a more accurate shadow cast is achieved.

	3 months	12 months	24 months	60 months
Patient A analysis 1	0.453	0.690	0.716	0.741
Patient A analysis 2	0.450	0.671	0.984	0.738

Figure 3.4: An example of 2D FHP (mm) outputs from 2 cycles of PolyWare™ analysis using the same patient radiograph sets

Notes: Here, analysis 1 is the 'optimal' cycle, as there is a more logical progression in FHP; analysis 2 is 'suboptimal', as there is a negative wear progression between penultimate to final radiographic periods. Analysis 1 is therefore favoured for inclusion in further calculations.

The 2D FHP for each patient at the available time points, as well as component positions, were entered into a Microsoft Excel™ spreadsheet for analysis. For reasons discussed in Section 2.8, 3D results were not entered into further analysis, although

available. Volumetric wear was also presented by the program but not directly recorded from it, as the program does not make any distinction as to the contribution of creep and bedding-in to the initial FHP, which would be expected to grossly overestimate wear, as discussed in Section 2.9.

3.2.2 Wear analysis

3.2.2.1 Bedding-in and creep phase

The 2D FHP phase dominated by bedding-in and creep was assessed using two methods. The first method, described by Sychterz, Yang et al. (1999), involved observing the FHP change over serial time points for a steady rate of change to be reached in the overall cohort. The time at which there was a transition to steady-state across these time points was selected as the end of the bedding-in period. In the second method, statistical modelling was used (see Section 4.2.2.5), with the beginning of steady-state wear rates adjudged to occur when there was no significant effect of time on FHP.

3.2.2.2 Steady-state wear rate calculation

The steady-state annual 2D rate of change of FHP after 12 months is referred to in this study as the 2DWR. As the reference time points in the steady-state wear period have the potential to affect measurements (see Figure 3.5), the 2DWRs were calculated by selection of the optimal cycle of data (see Figure 3.4) and using methods as outlined below.

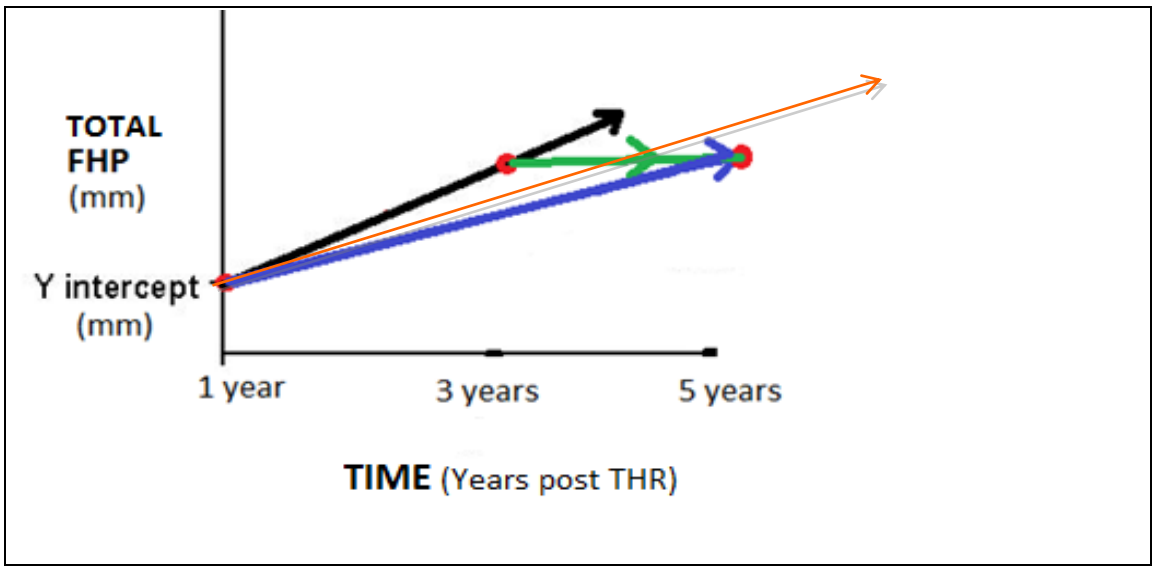

Figure 3.5: Schematic representation of possible wear rate slopes from use of three radiographic time points

Note: The same patient has radiographs at one, three and five years (indicated by red dots) with the one-year radiograph taken as the post-creep/bedding-in reference point

The first and preferred method of calculating wear is linear regression of the available FHP points over time for each patient.

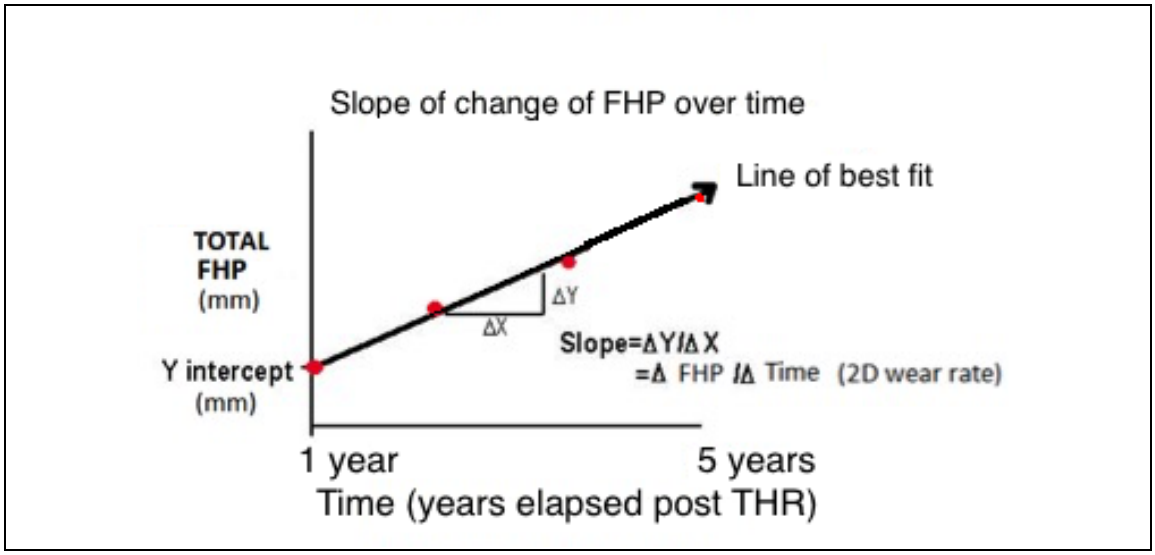

Figure 3.6: Schematic representation of individual regression for each patient

Note: The line of best fit through the FHP points gives a slope (2DWR in mm/yr)

This was done for each individual by calculating the slope of their FHP from one year using Microsoft Excel™ (see orange line on Figure 3.5 and the black line in Figure 3.6). Bragdon et al. (2013) and Nakahara et al. (2011) have reported use of such regression methods. Theoretically, as regression utilises more time points, the effect of

the inaccuracy of a single measurement on the central tendency should be less pronounced.

Given that individual regression was the preferred method for 2DWR calculation and reporting, it is important to note that the second and third methods below were used primarily to calculate 2DWR for the purpose of its application to the alternative, Martell (2014), volumetric wear calculation (see 4.2.2.4). This is because the Martell (2014) wear calculation requires assessment of vectors between two radiographs that is not possible when using regression for more than two radiographs. They were also used for later comparison of different methods of 2DWR calculation.

Accordingly, the second method of calculating 2D wear across time points that was used both for 2DWR and for the purpose of Martell (2014) volumetric wear calculation in this study was:

$$2DWR = \frac{\text{FHP final radiograph} - \text{FHP one-year radiograph}}{\text{Time in years elapsed from one year to final radiographs}}$$

Bragdon et al. (2013) utilised this method to report 2DWR. Should the patient have had a three-year radiograph as their final radiograph it would be represented by the black line on Figure 3.5, while if the patient had a five-year radiograph it would be represented by the blue line.

The third method of calculating 2D wear across time points that was used primarily for the purpose of Martell (2014) volumetric wear calculation in this study was:

$$2DWR = \frac{\text{FHP five-year radiograph} - \text{FHP one-year radiograph}}{\text{four}}$$

This utilised only those patients with maximal (five) years to follow-up postoperatively, assessing the one-year and five-year radiographs. However, this method, as illustrated in the box below, provides a limited number of patients for

analysis compared to Method 2 as it excludes those patients who have not had 5 year radiographs. 2DWR calculated by the difference in measured FHP between one year and five years or more has been used by multiple authors (Bragdon et al. 2013; Campbell, Field & Callary 2010; Lee et al. 2011; Mutimer, Devane & Horne 2010).

3.2.2.3 Manner of reporting results

As discussed in Section 2.8, reported mean and median wear rates depend on the handling of outlier and negative results. Although they are not preferred methods for reporting wear rates of cohorts in this thesis, means and medians are nevertheless reported to enable comparisons with existing studies that report their results in terms of mean and median 2DWRs. The effect of different methods of wear rate calculation on results is demonstrated, particularly by Table 4.8 in results and discussed in section 5.1.

Mean (arithmetic) and median 2DWRs were calculated according to the three methods described in Section 3.2.2.2. Individual regression that included negative wear values is the favoured method of reporting. It is the opinion of the candidate that individual regression including negative wear is the most robust method given the imprecision of individual measurements with an instrument such as PolyWare™. This is given that PolyWare™ is not intended to be able to measure amounts of wear to the level of nanometres, such as that reported in HXLPE, and a large proportion of wear rates would be expected to be negative.

Analysis was undertaken (with the use of methods 2 & 3 above) not only where the recorded negative value was included into calculations as described above, but also where the negative value was either excluded or ascribed the value of zero. These secondary calculations were undertaken with the specific aim of examining whether

the different handling of negative wear affected the conclusions reached on the research questions, as is later discussed in Section 5.1.

3.2.2.4 Wear analysis: Volumetric wear rate

Although the PolyWare™ program displayed total volumetric wear and VWRs, these were calculated from initial to final postoperative radiographs and therefore, do not differentiate between true wear and FHP due to the creep and bedding-in phase. This leads to an overestimation of the apparent contribution of wear to the observed FHP (see Section 2.9).

The following two methods of calculating volumetric wear were therefore undertaken instead, using FHP measurements derived from the steady-state period.

- Steady-state FHP rates calculated from Methods 1, 2 and 3 as described in Section 3.2.2.2 were selected for conversion to VWRs. The volumetric wear value was achieved by manual formulaic calculation from 2D measurement according to Charnley and Halley (1975), namely:

  $$\text{Volumetric wear} = \text{FHP} \times \pi \times \text{femoral head radius}^2.$$

  This assumes a cylindrical wear tract of the femoral head through the PE liner along a vector in the same plane as the radiograph. As stated previously, conversion of 2D wear from an AP measurement with this method is used in the review papers linking VWRs to the prevalence of osteolysis in conventional PE.

- The other method uses a formula developed by Dr John Martell (personal communication via email, 3 March 2014), who believes that traditional methods are difficult to calculate and either over- or under-estimate wear, as

wear direction was not considered. The technique involves taking the radius of the femoral head and known wear direction, using the beta angle (see Figure 3.7) and the 2D FHP calculated from computer-assisted software (one-year to final radiographs and one- to five-year radiographs) to characterise the volumetric wear. Although yet to be validated in the literature, this technique arguably gives a more accurate account of wear out of the plane of the radiograph, with less tendency to overestimate volumetric wear compared with the method described previously. Specifically, the beta angle is calculated by taking the coronal plane (x and y) coordinate points supplied by the PolyWare™ program between time points of interest (e.g. one-year and final radiographs) and determining the angle of the vectors between them (beta) by calculating the inverted cosine ($\cos^{-1}$) of the ratio of the vectors. The 2D FHP supplied by the PolyWare™ program and head size can then be entered into a computer-based program provided by Martell for an alternative volumetric wear measurement (Figure 3.8). The VWR can then be calculated by dividing the volumetric wear calculated by the program by the time elapsed between reference radiographs. It should be noted that wear vectors out of the cup using this method are treated as zero wear.

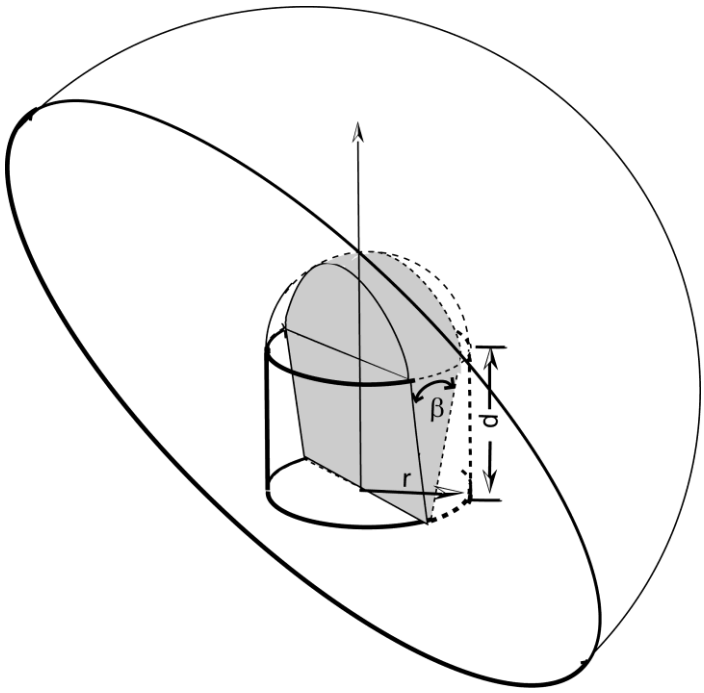

Figure 3.7: Schematic representation of a cylindrical wear path relative to a PE liner

Notes: Shaded portion = volume of material removed by wear of magnitude d in direction ß; longest arrow = direction of wear (not magnitude); r = radius of femoral bearing

Source: Reproduced with permission from Dr John Martell

```
Input beta, follow vector wear, and head size:

beta? (in degrees) 4.8

follow vector wear? (mms) .14

head size? (mms) 36

Case is 1, function is qsimp

beta (in degrees) is              4.800
beta (in radians) is              0.084
critical_beta (in degrees) is    89.554
critical_beta (in radians) is     1.563
follow_vector_wear is             0.140
head_size is                     36.000

     volumetric wear is 77.242898
```

Figure 3.8: Example of computer-assisted calculation of volumetric wear using a program based on the method of John Martell

Note: Using the first method described (Charnley and Halley 1975), the volumetric wear would be approximately double that given in this example with the same figures

3.2.2.5 Wear rates: Statistical calculations

Mean wear rates for 36 mm and 28 mm articulation cohorts were compared statistically using a two-tailed student *t*-test, with assumption of equal variance based

on a scatterplot of the data. Specifically, the program used was QI Macros™ for Excel™ (KnowWare, Colorado, USA).

The percentages of patients with elevated 2DWRs (≥0.1 mm/yr) and elevated VWRs (≥80 mm^3/yr) were compared between 28 mm and 36 mm articulations cohorts using the *chi*-squared statistic. Given that this study seeks to identify the proportion of patients potentially at risk rather than rely on central tendency statistics alone, this approach was considered desirable.

Demographic characteristics of those patients exceeding the above thresholds were also examined, as was their component position, to determine whether certain factors are potentially associated with elevated wear.

A consultant statistician undertook mathematical modelling to determine the effect of articulation size on FHP. All analyses were completed using SAS 9.3 (SAS Institute Inc., Cary, North Carolina, USA). The data were analysed using a linear mixed effects model, with patients treated as a random factor. Linear and volumetric wear figures were log transformed prior to analysis to meet the distributional assumptions of a linear mixed effect model. The data were transformed back to the original scale prior to reporting. Geometric means and the differences of least square means were analysed to assess a statistical equivalence or otherwise between articulation sizes and time points.

3.3 Inter- and intra-observer error

Inter- and intra-observer error was calculated using a random selection of the radiograph sets of 36 of the 326 patients (11%) who had undergone repeat measurements by one assessor as well as PolyWare™ analysis by a second trained assessor. For consistency, the 2D FHPs were measured from the reference time points

of one-year and final radiographs. Intra-observer error compared the results of an optimal cycle to a second cycle of analysis (by the candidate), enabling assessment of intra-observer variance. Inter-observer error used the results of a second assessor's analysis, enabling calculation of inter-observer correlation coefficient and agreement.

A Bland–Altman plot (Bland & Altman 1986, 1999), or difference plot, was used to show the limits of agreement, defined as the mean difference ± 1.96 times the SD of differences for intra- and inter-observer measurements.

For both methods, the coefficient of variance (Lehmann 1996) was also calculated by taking the SD for the differences between assessments and dividing it by the mean of the intra- and inter-observer differences.

Chapter 4: Results

4.1 Cohort demographics and component positioning

To undergo PolyWare™ analysis, patients were required to have a minimum radiographic set as detailed in Section 3.1.1. The reasons for patients not having minimum suitable radiographic sets for analysis are presented in Figure 4.1. There were no significant differences between 36 mm and 28 mm cohorts in the prevalence of reasons for not having minimum suitable radiographic sets for analysis by chi-squared analysis (X^2= 0.18, p = 0.73). There was also no significant difference in the proportion of patient radiographic sets that were comprised of digital only compared to digital and analogue images between the cohorts, as shown in Table 4.3. The mean follow-up was 3.7 years for 36 mm and 3.8 years for 28 mm (p = 0.39).

As can be seen from the Table 4.1, there were neither statistically significant differences between cohorts in age, gender, BMI and diagnosis, nor in component type or acetabular component positioning between the 36 mm and 28 mm cohorts. The only significant difference was a thinner PE liner for the 36 mm cohort. While there was no statistically significant differences in the distribution of outer diameters of acetabular shells [p=0.78] (Table 4.2), the difference in PE liner thickness is significant, as the use of a larger 36 mm femoral head necessitates a thinner liner than that possible for a 28 mm head for any given outer diameter of acetabular shell. Given that the only significant difference between articulation cohorts was PE liner thickness as was described above, the cohorts were therefore considered comparable and appropriate for an analysis of the effect of articulation size on polyethylene wear.

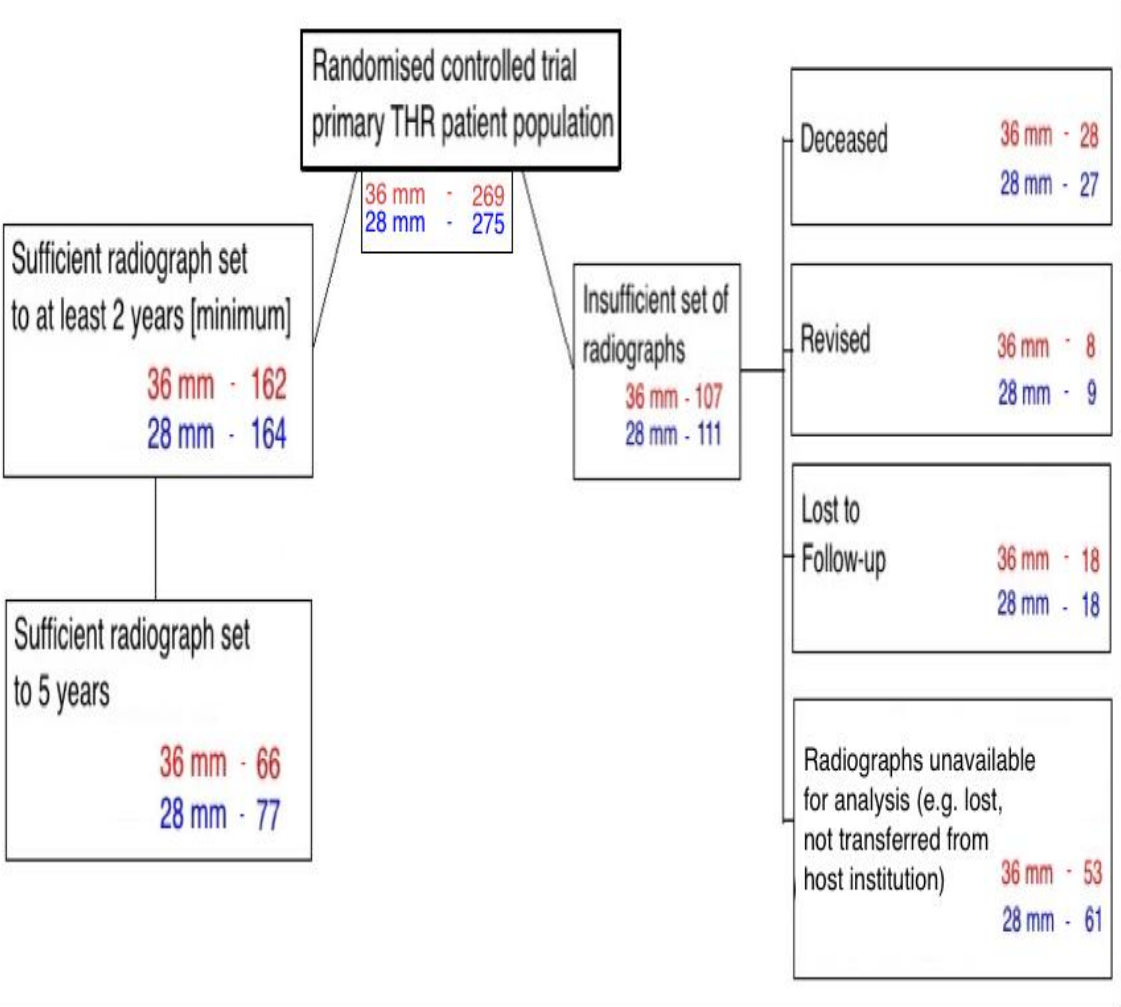

Figure 4.1: Representation of patients enrolled in RCT with either sufficient or insufficient radiograph sets for analysis

Table 4.1: Demographic characteristics at time of THR and component positioning for 28 mm and 36 mm patient cohorts

Variable	36 mm cohort (n = 162)	28 mm cohort (n = 164)	*p* value
Gender (% male)	43.8	39.7	0.45
Age (years)			
mean	71.1 (70.2–72.0)	71.7 (70.8–72.6)	0.52
range	60.3–87.1	60.8–88.0	
BMI†			
mean	27.9 (27.2–28.7)	28.3 (27.6–29.0)	0.38
range	16.8–43.3	18.8–40.9	
Primary or secondary osteoarthritis¥	98.0%	98.0%	0.83
Type of stem			
CPT 6°	45.1%	40.2%	0.38
CPT 12/14	54.9%	59.8%	
Acetabular component abduction angle			
mean	43.2 (42.1–44.3)	41.2 (40.2–42.2)	0.11
range	20–58	22–64	
Acetabular component anteversion			
mean	21 (19.8–22.2)	19.9 (18.8–21)	0.42
range	3–39	3–45	
Acetabular component ≥10° from abduction angle 45° or anteversion angle 20°	22.2%	21.0%	0.85

Notes: 95% C.I. in parentheses; † BMI recordings available at time of surgery for 127 of 28 mm and 121 of 36 mm articulation patients; ¥ Primary or secondary osteoarthritis without a previous fracture, traumatic dislocation or surgery to the index hip

Table 4.2 Outer diameter of acetabular components by articulation size

Acetabular component outer diameter	36 mm (n = 162)	28 mm (n = 164)
50 mm	24	18
52 mm	36	47
54 mm	31	37
56 mm	36	26
58 mm	22	18
60 mm	7	10
≥62 mm	7	8

Table 4.3: Makeup of radiograph type in patient radiographic sets by articulation size

	36 mm cohort (n, %)	28 mm cohort (n, %)	X^2, p
Patients with sets including digital and analogue radiographs	26 (16)	25 (15)	0.04, 0.82
Patients with sets including digital radiographs only	136 (84)	139 (85)	

4.2 Intra-observer and inter-observer reliability

Bland–Altman limits of agreement and variance coefficients (Bland & Altman 1986 & 1999) were used to test the reliability of 2D FHP PolyWare™ measurements. As explained in Section 3.3, these analyses were undertaken by comparing 2D FHP assessments (initial for inter-observer and repeated for intra-observer measurements) for a random selection of 36 patients using their one-year and final radiographs.

The Bland–Altman limits of agreement (Table 4.4) indicate that, based on the data provided to two decimal places, there is a 95% chance that the difference between the two intra-observer measurements truly lie within the range provided (from 0.04 mm less to 0.03 mm more for intra-observer measurements). Plotting of the data revealed that the larger the FHP change between radiographs, the more variation between readings. The 14% variation in intra-observer measurement gives an acceptable performance of the measurement tool in relation to the data. In the context of the study aims, focusing on patients with elevated 2DWRs ($\geq$0.1 mm/yr) rather than characterising wear to multiple decimal points gives an indication that reasonable confidence can be derived from serial intra-observer measurements should a truly excessive wear rate be found to occur in an individual.

However, inter-observer limits of agreement showed a wider variance in readings using the same patient radiographic time points and a higher coefficient of variance (Table 4.4 below). This would be expected, given the idiosyncrasies in point selection and judgement of shadow cast between assessors.

Table 4.4: Variance in 2D FHP measurement, Bland–Altman limits of agreement and coefficient of variance for intra- and inter-observer measurements

Mean change in 2D FHP between time points in selected sample	0.09 mm	
	Intra-observer	**Inter-observer**
Mean difference between repeated measurements	0.01mm	0.02mm
Bland–Altman 95% Limits of Agreement	-0.04mm to 0.03mm	-0.13mm to 0.09mm
Coefficient of variance	1.14 (14% variation between intra-observer measurements)	1.39 (39% variation between inter-observer measurements)

Notes: Calculations based on two decimal places

4.3 Two-dimensional femoral head penetration across points

This section presents 2D FHP measurements for both cohorts. Figure 4.2 presents the total 2D FHP measured from each patient's baseline initial radiographs to specific postoperative time points. The baseline radiograph varied between patients, depending on the centre and was either at four days, six weeks or three months. Although there was a higher proportion of patients in the 36mm cohort (58.7%) compared to the 28 mm cohort (53%) who had their baseline radiograph at either four days or six weeks postoperatively compared to baseline radiographs at three months, this was not a statistically significant difference ($X^2 = 1.9$; $p = 0.21$).

The 36 mm cohort reached a significantly higher mean 2D FHP at three months than the 28 mm cohort. Mean cumulative 2D FHP of patients with available radiographs is shown in Table 4.5 below. While there was no statistically significant difference in the cumulative 2D FHP between 36mm and 28mm cohorts after 3 months, higher mean FHP was recorded for the

36mm cohort at 24 and 36 months with p values approaching but not reaching statistical significance. However, given the heterogeneity of radiographs available for patients whose measurement contributed to the mean FHP at each timepoint, individual patient wear rates better characterise wear in each cohort and are presented in 4.6.

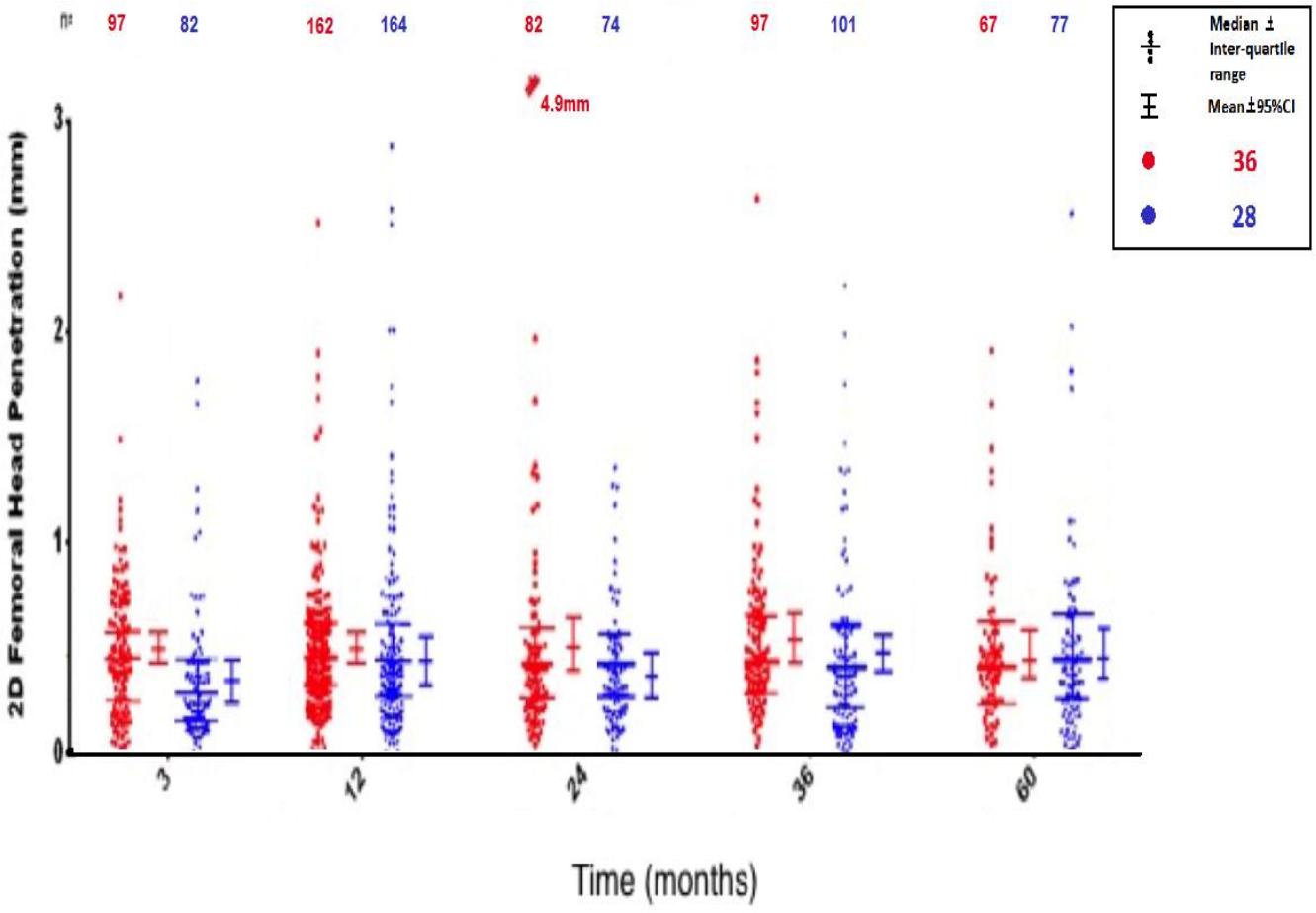

Figure 4.2: Scatterplot of total 2D femoral head penetration (mm) plotted against postoperative time elapsed (months)

Table 4.5 Mean two-dimensional femoral head penetration (±95%CI) at different radiographic time points by articulation size

	36 mm	**28 mm**	***p* value**
Three months			
n	97	82	
mean	0.53 mm (±0.07)	0.38 mm (±0.07)	0.003
Twelve months			
n	162	164	
mean	0.52 mm (±0.06)	0.49 mm (±0.07)	0.61
24 months			
n	83	74	
mean	0.55 mm (±0.14)	0.43 mm (±0.07)	0.1
36 months			
n	98	101	
mean	0.61 mm (±0.10)	0.45 mm (±0.09)	0.06
60 months			
n	68	76	
mean	0.55 mm (±0.09)	0.50 mm (±0.10)	0.5

4.4 Total volumetric wear across time points

Total volumetric wear, as converted from observed 2D FHP over different time points using the Charnley and Halley (1975) method, is presented in this section and summarised visually in Figure 4.3. In light of similar means in 2D FHP for cohorts, the total volumetric wear for 36 mm would be expected to be higher using this method, given that for a given FHP the product of πr^2 in converting 2D to volumetric wear is higher for the 36 mm articulation. Using this method, significant differences in mean total volumetric wear were found between 36 mm and 28 mm articulations at every time point.

Beyond 12 months, however, a stable relationship is observed for differences between the cohorts when a trendline is plotted through the median volumetric wear for each cohort (see Figure 4.3). This is expected given the minimal 2D FHP change from 12 months.

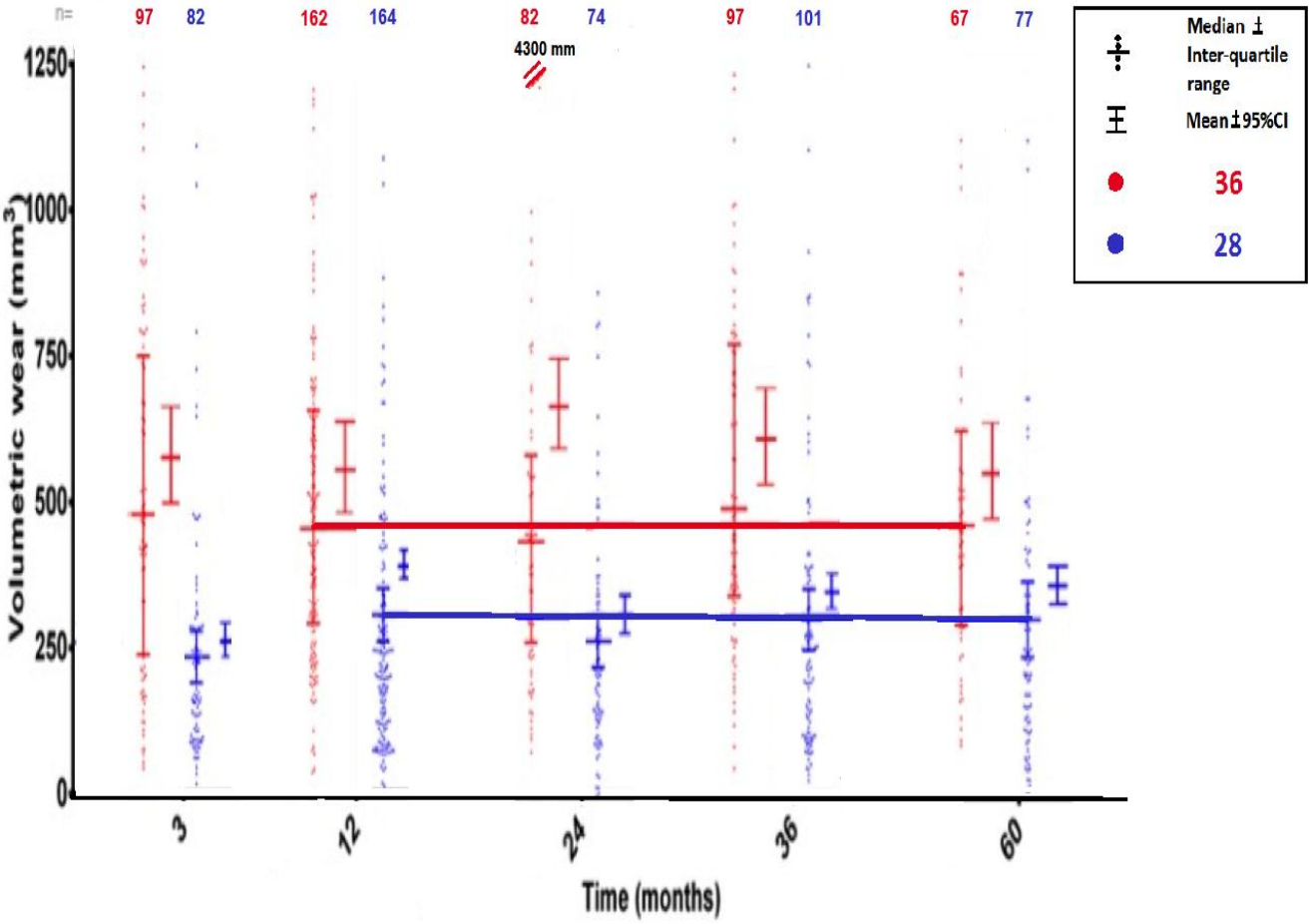

Figure 4.3: Scatterplot of volumetric wear over time by the Charnley and Halley (1975) method with superimposed trendline through medians from 12 months for each cohort

4.5 Bedding-in/creep

The contribution of bedding-in and creep to 2D FHP at the three- and twelve-month time periods is shown in Figure 4.2 and Table 4.5 while the contribution to volumetric wear converted from 2D FHP measurements at the three- and twelve-month radiographs is seen in Figure 4.3 above. As seen in Table 4.5, the mean 2D FHP at the three months of the 36 mm articulation cohort is significantly higher at 0.53 mm than that of the 28 mm cohort which was 0.38 mm ($p = 0.003$), whereas there was no significant difference at twelve months ($p = 0.61$).

4.6 Annual wear rates

4.6.1 Annual two-dimensional wear rates

Mean annual 2DWRs were calculated using the methods as discussed in Chapter 4.

Figures 4.4 and 4.5 show mean and median annual 2DWRs, where one-year radiographs were

used as baseline, given that the data in Sections 4.5 and 4.7 affirmed bedding-in/creep is completed by one year. While both methods used individual regression of all available radiographs from one year, they differed in the final time point used in analysis, being the final radiograph (Figure 4.4) or the five-year radiograph (Figure 4.5), respectively. Consequently, while all patients had a final radiograph, albeit at differing times, not all patients had a five-year radiograph, resulting in smaller numbers for the latter method. For all methods using regression, negative wear was included in calculations. Both methods used revealed no significant differences in mean wear rates between cohorts. The difference in 2D FHP between 1-year and final radiograph without regression is also presented in Table 4.6.

Table 4.6: Two-dimensional wear rate (±SD) calculated from different reference time points and methods (2 decimal places)

Time point references and calculation method	**36 mm**	**28 mm**	***p* value**
One-year to final radiograph by IR			
n	162	164	
mean	0.00 (±0.04) mm/yr	0.00 (±0.04) mm/yr	0.96
One-year to final radiograph			
n	162	164	
mean	0.01 (±0.02) mm/yr	0.01 (±0.02) mm/yr	0.85
One-year to five year radiograph by IR			
n	66	77	0.41
mean	0.00 (±0.09) mm/yr	0.00 (±0.09) mm/yr	

Note: IR = individual regression

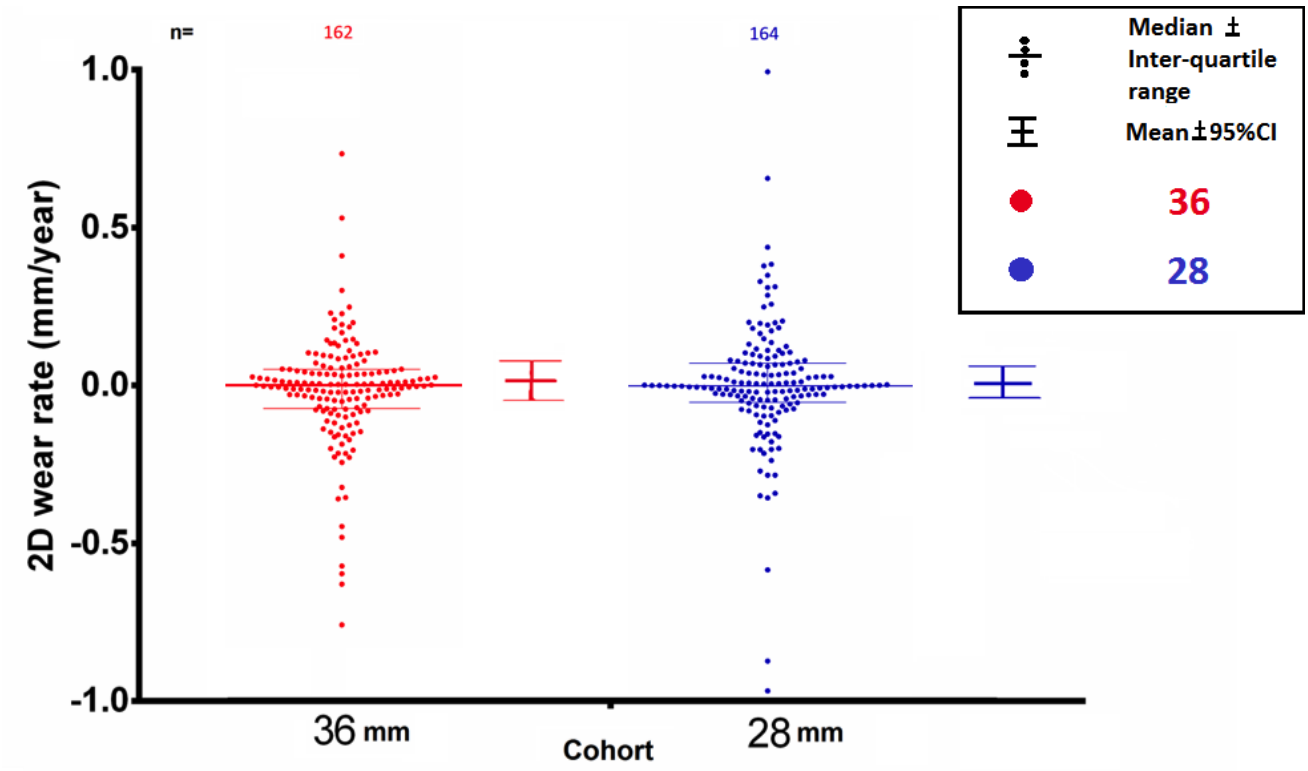

Figure 4.4: Scatterplot of 2DWR calculated using individual regression (slope) of one-year to final radiograph for each patient

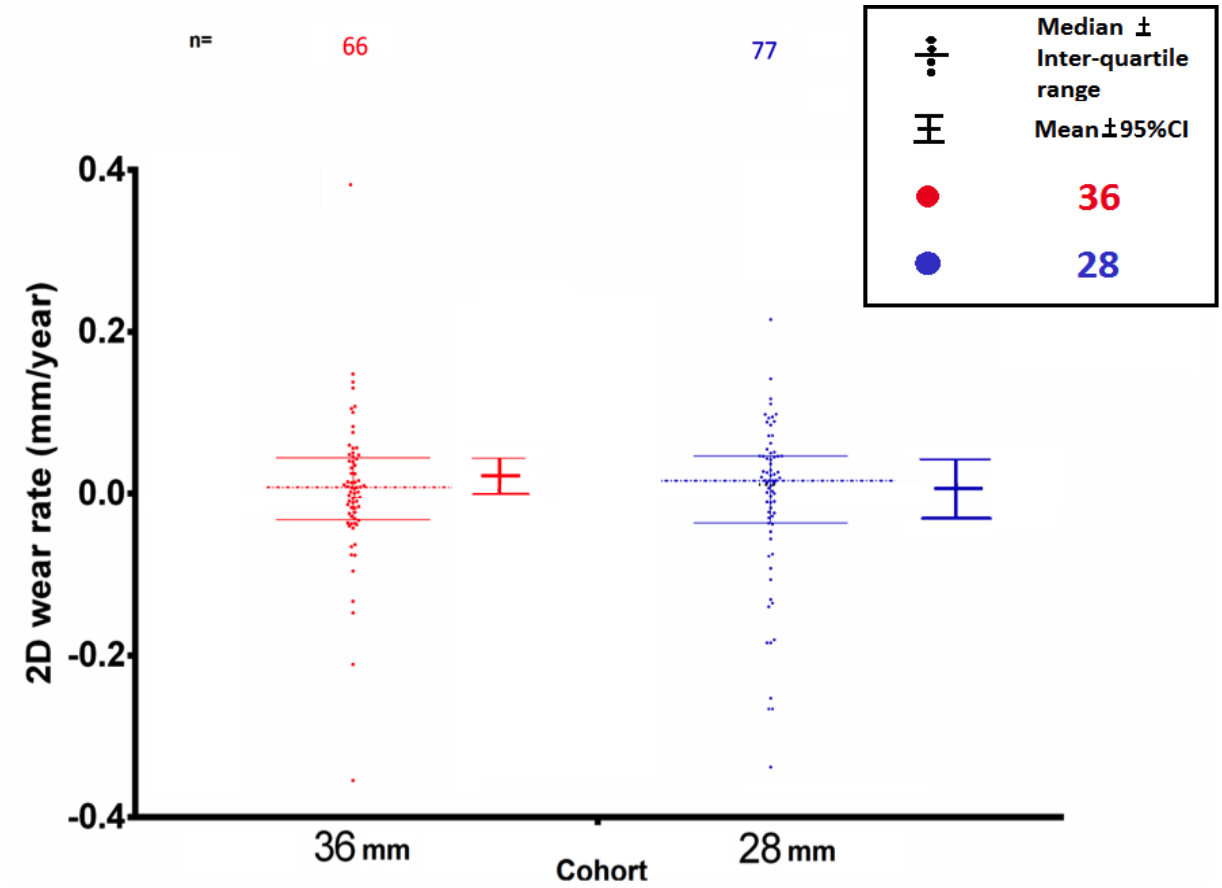

Figure 4.5: Scatterplot of 2DWR calculated from individual regression using one-year to five-year radiographs

4.6.2 Annual volumetric wear rates

Annual VWRs calculated by two methods described in Section 3.2.2.4 are represented in Figures 4.6 to 4.9, and in Table 4.7. There were no significant differences in mean annual VWRs, regardless of whether the calculations were based on the use of final- or five-year radiographs, as shown below in Table 4.7.

The first method involved taking the individual regression of 2D FHP measurements across available radiographs for a patient, presented as either the use of final- or five-year radiographs in Table 4.7 below, and applying the Charnley and Halley (1975) multiplier method. The second involved using either the one-year to final radiograph or one-year to five-year radiograph for each patient only (without regression) and applying the Martell (2014) method. Wear rates calculated from patients who had both one- and five-year radiographs showed no significant differences and similar mean wear rates to methods analysing patients using their final radiograph, although it is acknowledged that lower numbers in the former calculation may have influenced the lack of statistical significance when comparing articulation sizes. Table 4.8 demonstrates the effect that different calculations can have on both the 2D and volumetric wear rates reported.

Table 4.7: Volumetric wear rate (±SD) calculated from different time points and methods by articulation size

Time point references and calculation method	36 mm VWR VWR (mm^3/yr)	28 mm VWR (mm^3/yr)	*p* value
One-year to final radiograph by IR [negative wear included];			
Charnley and Halley			
n	162	164	
mean	0.3 (±36) mm^3/yr	1 (±22) mm^3/yr	0.98
One-year to final radiograph			
(Martell VWR)			
n	162	164	
mean	24 (±38) mm^3/yr	26 (±47) mm^3/yr	0.67
One- to five-year radiograph by IR			
[Negative wear included];			
Charnley and Halley			
n	66	77	
mean	4 (±22) mm^3/yr	–4 (±12) mm^3/yr	0.45
One- to five-year radiograph			
(Martell VWR)			
n	66	77	
mean	29 (±60) mm^3/yr	24 (±47) mm^3/yr	0.053

Note: IR = individual regression, Charnley and Halley = Charnley and Halley (1975) method

Table 4.8: Mean wear rates (± SD) of 36 mm and 28 mm articulations using different radiographic time points and calculations

Radiographs used and negative wear (NW) treatment	Articulation size & patients with adequate radiograph set (n)	2DWR*	VWR#
1 year-Final by IR, NW included	36 mm (162)	0.00 ±0.04	0.3 ±36
	28 mm (164)	0.00 ±0.04	1 ± 22
1 year-5 year by IR, NW included	36 mm (66)	0.00 ± 0.09	4.2 ±22
	28 mm (77)	0.00 ± 0.09	-4.5 ±12
1 year-Final Martell Volumetric WR calculation (No NW)	36 mm (162)	-	24 ± 38
	28 mm (164)	-	26 ± 47
1 year-5 year Martell Volumetric WR calculation (No NW)	36 mm (66)	-	29 ± 60
	28 mm (77)	-	13 ± 24
1 year-Final by IR, NW=0	36 mm (162)	0.06 ± 0.15	63 ± 160
	28 mm (164)	0.08 ± 0.14	50 ± 89
1 year-5 year by IR, NW=0	36 mm (66)	0.02 ±0.06	29 ± 59
	28 mm (77)	0.02 ± 0.04	12 ± 24
1 year-Final by IR, NW Excluded	36 mm (76)	0.12 ± 0.20	125 ± 207
	28 mm (85)	0.16 ± 0.17	101 ± 105
1 year-5 year by IR, NW Excluded	36 mm (35)	0.05 ± 0.05	53 ±71
	28 mm (35)	0.04 ± 0.04	25 ± 24

Notes: NW = Negative wear, IR = Individual regression, *= Mean Annual 2 Dimensional Wear Rate (mm/yr) [2 Decimal places], # = Mean Annual Volumetric Wear Rate (mm^3/yr); Unless specified, calculated using Charnley and Halley (1975) method

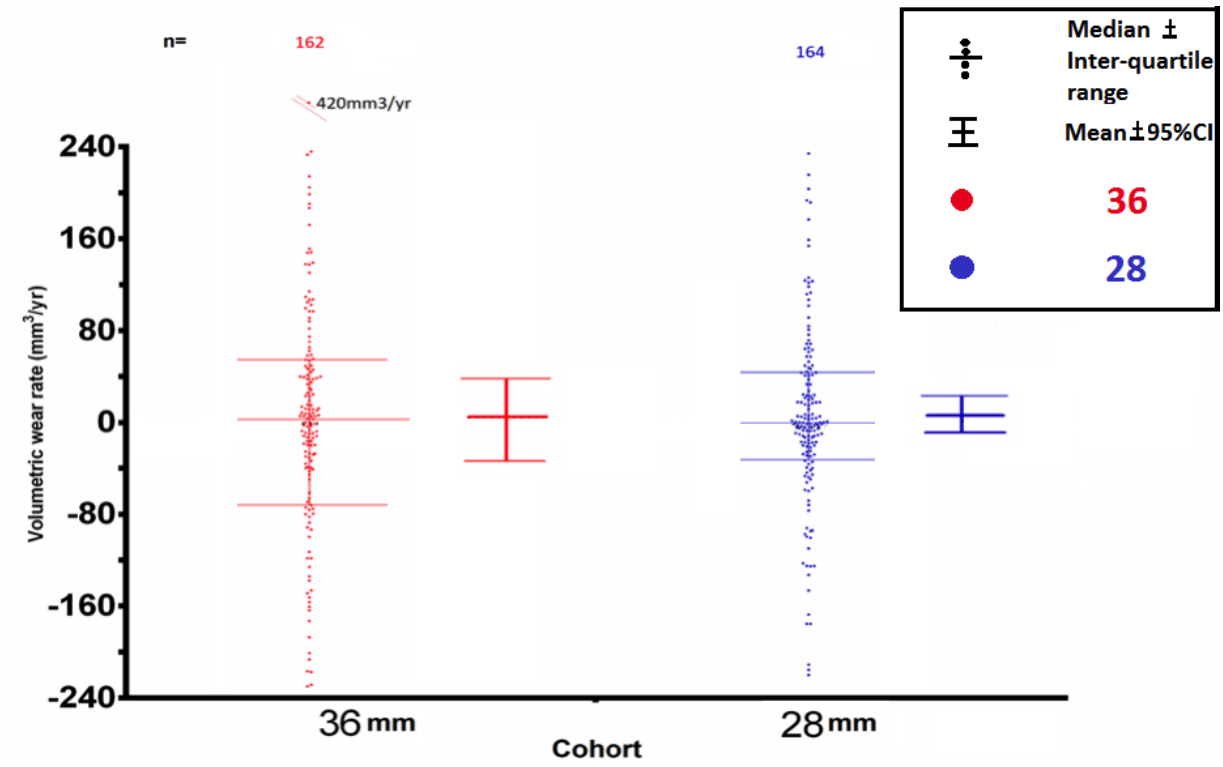

Figure 4.6: Scatterplot of VWRs calculated by the regression of FHP using radiographs from 1 year to final each individual

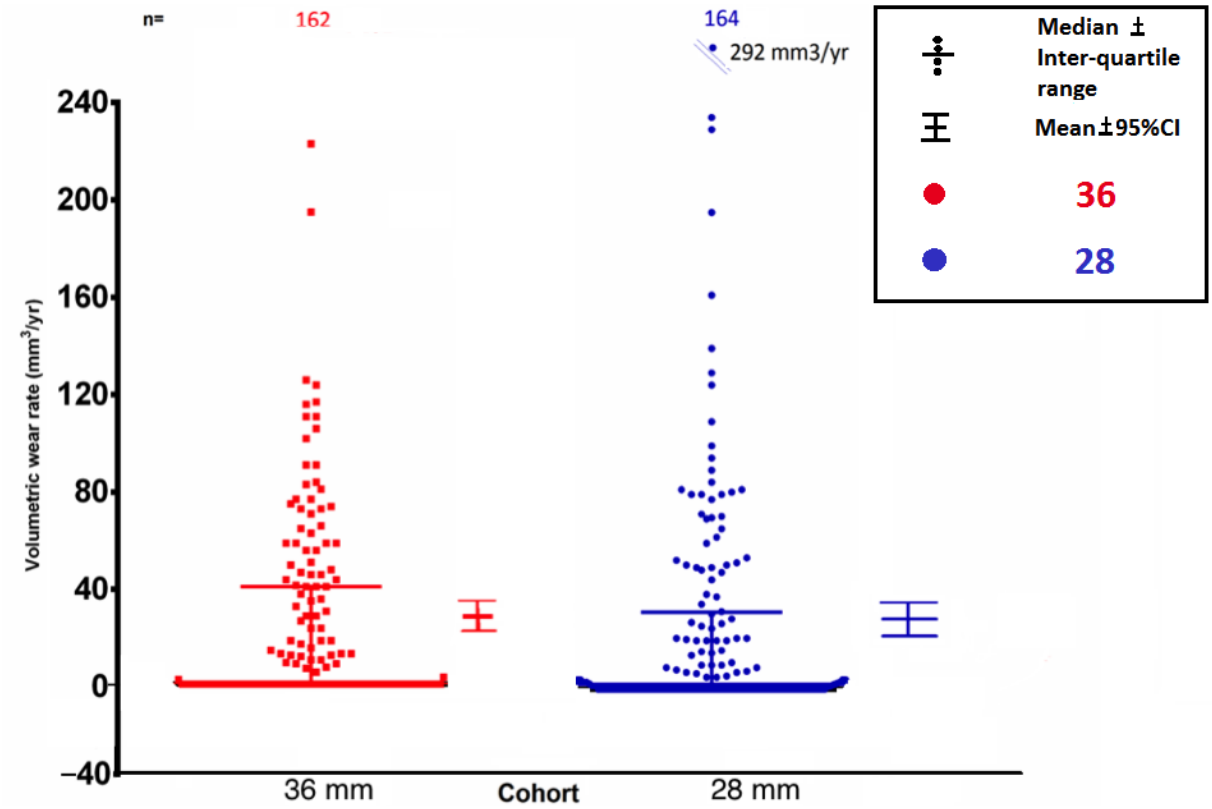

Figure 4.7: Scatterplot of VWRs calculated using Martell (2014) method from 1-year to final radiographs for each individual

Note: Upper bar superimposed on scatter represents 75% centile

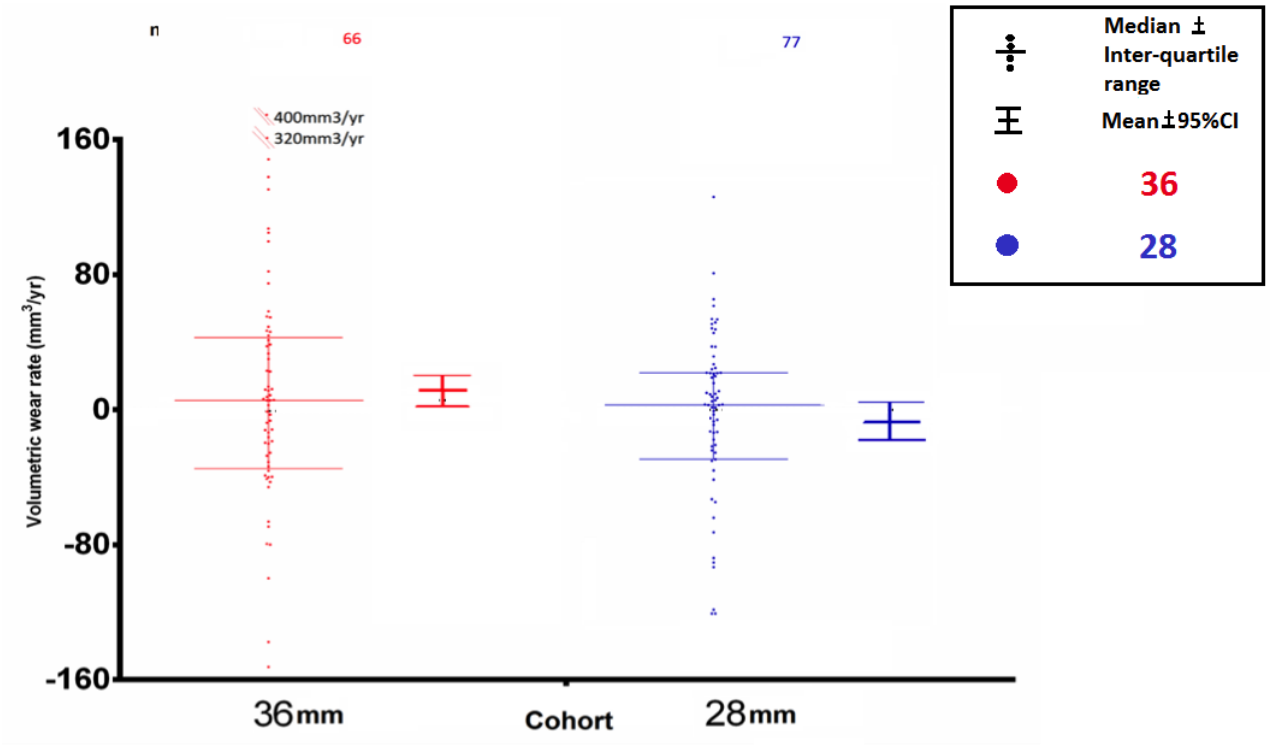

Figure 4.8: Scatterplot of VWRs calculated from individual regression using one- to five-year radiographs

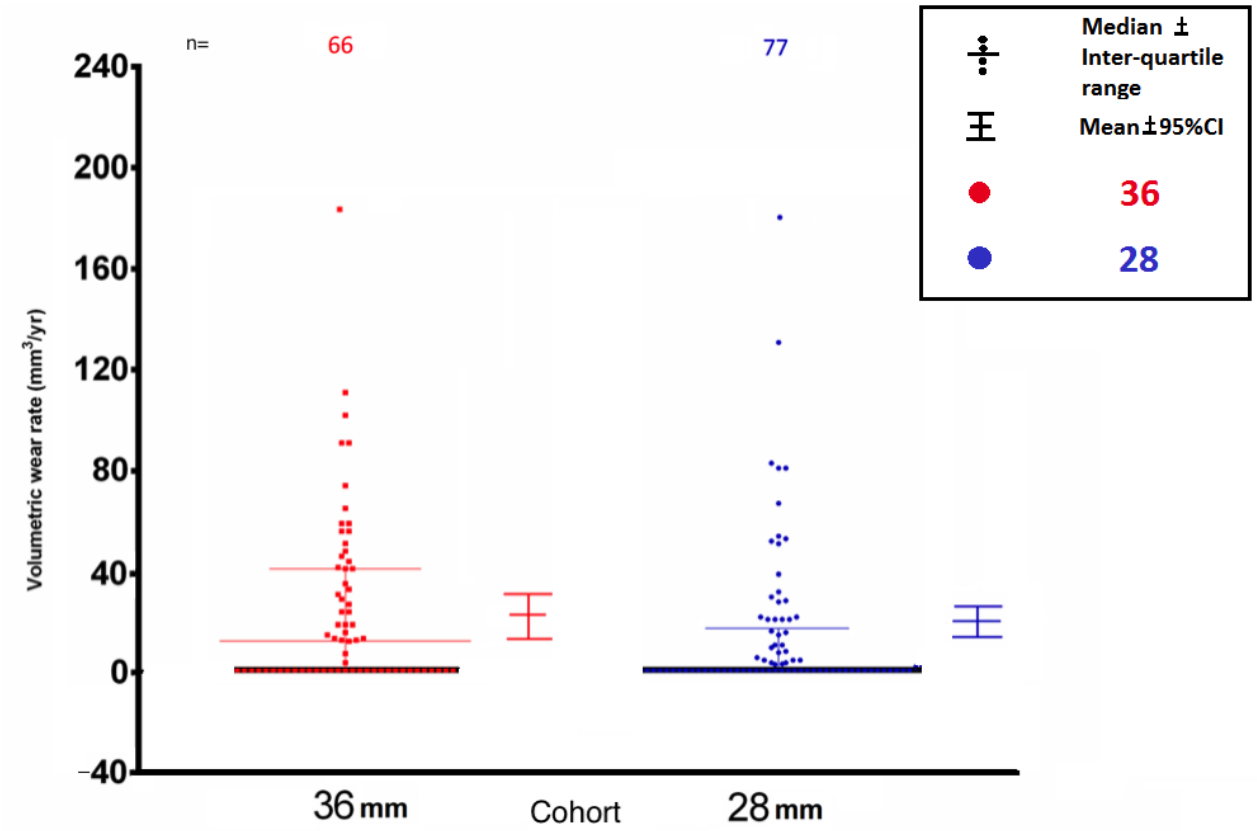

Figure 4.9: Scatterplot of VWRs calculated using Martell (2014) method from one- to five-year radiographs for each individual

Note: Upper bar superimposed on scatter represents 75% centile

4.7 Statistical modelling of the data (mixed linear effects model)

This section presents the results of a separate statistical analysis of the data undertaken using a linear mixed effects model. This was used as the data of interest were longitudinal and this method permitted assessment of change of 2D FHP over time (as discussed in Chapter 4). The ratio of the means technique was selected in order to assess differences between groups and across time points. Importantly, in the log-transformed data presented below, the mean differences represent the ratio of two geometric means and not the absolute difference between the means. Selected least square means are presented below in the interest of brevity with other statistical modelling calculations presented in Appendix D.

Table 4.9 shows that 2D FHP measurements were higher in the bedding-in/creep phase for 36 mm compared with 28 mm cohorts (p = 0.0009). However, beyond three months there was no significant effect of time on 2D FHP for either cohort (p = 0.65). In other words, while the absolute 2D FHP was higher in 36 mm articulations, there was no evidence of significant differences in wear rates in the steady-state period between articulation sizes (see Table 4.10). This also gives support to the bedding-in and creep process being completed by 12 months in both cohorts, as described in Section 4.5.

Table 4.9: Least square means for the effect of time on 2D FHP (mm) for 36 mm and 28 mm articulations

36 mm Articulations			
Time (months)	**Mean (mm)**	**Lower (mm)**	**Upper (mm)**
3	0.41	0.34	0.49
12	0.41	0.36	0.48
24	0.42	0.35	0.49
36	0.45	0.39	0.53
60	0.45	0.38	0.53
28 mm Articulations			
Time (months)	**Mean (mm)**	**Lower (mm)**	**Upper (mm)**
3	0.29	0.24	0.34
12	0.34	0.29	0.39
24	0.37	0.31	0.43
36	0.32	0.27	0.37
60	0.32	0.28	0.38

Table 4.10: Least square means for both the effect of time (independent of articulation size) and articulation size (independent of time) on 2D FHP (mm)

Effect	**Articulation size (mm)**	**Time (months)**	**Estimate (mm)**	**Lower (mm)**	**Upper (mm)**
Time	N/A	3	0.34	0.30	0.39
		12	0.37	0.34	0.41
		24	0.39	0.34	0.44
		36	0.38	0.34	0.42
		60	0.38	0.34	0.42
Articulation size	36 mm	N/A	0.42	0.38	0.47
Articulation size	28 mm	N/A	0.33	0.29	0.36

4.8 Proportion of cohorts with elevated 2DWRs and VWRs

There were no significant differences in the proportion of individuals with elevated 2DWRs (≥0.1mm/yr) or VWRs (≥80mm^3/yr). Elevated 2DWRs were observed in 16.7% and 17.1% of 36 mm and 28 mm cohorts, respectively ($X^2 = 0.01$, $p = 0.92$). Depending on the method of calculation used, elevated VWRs using Charnley and Halley (1975) were 17.3% for 36 mm

compared to 12.8% for 28mm ($X^2 = 1.28$, $p = 0.26$) while elevated VWRs calculated using Martell (2014) were 9.3% for 36 mm compared to 9.8% for 28 mm ($X^2 = 0.02$, $p = 0.88$). While the proportions of patients with elevated 2DWRs or VWRs were higher for both cohorts using the Charnley and Halley (1975) method (see Table 4.11), this was not unexpected, given that other authors have previously commented that this method tends to overestimate wear.

Table 4.11: Proportions of 36 mm and 28 mm Cohorts with 2DWR≥0.1 mm/yr and VWR≥80 mm^3/yr

Wear rate and calculation	36 mm (n,%)	28 mm (n,%)
≥0.1 mm/yr (one-year to final radiographs by IR)	27/162 16.7%	28/164 17.1%
≥80 mm^3/yr (Charnley and Halley [1975] method using one-year to final radiographs by IR)	28/162 17.3%	21/164 12.8%
≥80 mm^3/yr (Martell volumetric wear calculation using one-year to final radiographs)	15/162 9.3%	16/164 9.8%

Note: IR = individual regression

4.9 Demographic and component characteristics of patients with elevated 2DWRs and VWRs

Tables 4.12 to 4.14 compare patients who exceed annual 2DWR ≥0.1 mm/yr or VWR ≥80 mm^3/yr with those not exceeding these thresholds for each articulation size. This allowed assessment for differences in component positioning and demographics in those patients exceeding the above parameters. The range of total FHP measured at the final time point in those patients with elevated 2DWRs ranged from 0.34 to 4 mm of total wear (mean 1.2 mm).

The cohort of patients with 2DWR ≥0.1 mm/yr compared with those with <0.1 mm/yr (Table 4.12), had a higher proportion of males and acetabular component malposition with statistical significance. Age and BMI were not different between the cohort with 2DWR≥0.1 mm/yr compared with <0.1 mm/yr.

Tables 4.13 & 4.14 present the data on patients with VWRs ≥80 mm^3/yr using the Martell volumetric calculation for each articulation size, as this method is likely to be more accurate and less sensitive to spurious results than calculations based upon Charnley and Halley (1975). The only obvious difference with respect to demographics for patients with VWRs ≥80 mm^3/yr compared with those with VWR <80 mm^3/yr was the higher proportion of male patients (58% of those with VWRs ≥80 mm^3/yr compared with 42% in the overall cohort), but this did not reach statistical significance in the context of smaller numbers ($p = 0.19$). Note that Tables 4.13 and 4.14 do not present p values for analysis by articulation size as the numbers of patients for each articulation size with VWRs ≥80 mm^3/yr were small.

The investigators are aware of one fracture of the elevated lip of a HXLPE elevated liner. This occurred in a 67 year old male patient with a 36 mm articulation (outer diameter 56mm, which approached mean size for the 36 mm cohort), BMI 26, Charnley classification A and satisfactory acetabular component placement (abduction angle 36 degrees/anteversion 22 degrees) who presented with mechanical symptoms and dislocation. His analysis showed very large changes in FHP over serial radiographs up to revision (>4mm) but was subsequently excluded from further analysis due to a revision with liner change at 3 years without having the minimum study requirement of a radiograph of at least 24 months post-operative follow-up (missing set) prior to revision.

Table 4.12: Comparison of all patients with 2DWR ≥0.1 mm/yr (one- year-final radiograph by individual regression) compared with the overall cohort of patients <0.1 mm/yr

Factor	2DWR ≥0.1 mm/yr (n = 46)	2DWR <0.1 mm/yr (n = 280)	*p*
Age (mean, range)	74.9 (65–86)	72.7 (60.3–88)	0.08
Gender (% male)	56	39	0.02
BMI (mean, range)	28.9 (18.8–41)	28.4 (16.8–43.3)	0.65
Acetabular anteversion (mean, range)	21.4 (3–37)	20.7 (3–45)	0.48
Acetabular abduction angle (mean, range)	42.2 (29–59)	42.0 (22–64)	0.77
Acetabular component ≥10º from abduction angle 45º or anteversion angle 20º	45%	20%	0.0003
Cup outer diameter median (% sized 50-54 mm)	54 (55)	54 (53)	0.71

Table 4.13: Demographic and component variables of 36 mm articulations with VWR ≥80 mm³/yr compared with <80 mm³/yr

Factor	36 mm ≥80 mm³/yr (n = 15)	36 mm <80 mm³/yr (n = 147)
Age (mean, range)	74 (65–86)	71 (60–85)
Gender (% male)	60	42
BMI (mean)	28 (20–35)	28 (17–40)
Acetabular anteversion (mean, range)	17 (10–34)	24 (5–45)
Acetabular abduction angle (mean, range)	40 (32–53)	43 (22–64)
Acetabular component ≥10° from abduction 45°or anteversion angle 20°	47%	28%
Cup outer diameter median (% sized 50–54 mm)	54 (53)	54 (45)

Table 4.14 Demographic and component variables of 28 mm articulations with VWR ≥80 mm³/yr compared with <80 mm³/yr

Factor	28 mm ≥80 mm³/yr (n = 18)	28 mm <80 mm³/yr (n = 146)
Age (mean, range)	74.3 (65–86)	71.4 (60–88)
Gender (% male)	55	46
BMI (mean)	28.4 (19.9–34.9)	28.3 (17–43.3)
Acetabular anteversion (mean, range)	17.3 (10–34)	20.2 (3–39)
Acetabular abduction angle (mean, range)	40.3 (32–53)	42.0 (20–58)
Acetabular component ≥10° abduction angle 45° or anteversion angle 20° (%)	44%	25%
Cup outer diameter median (% sized 50–54 mm)	54 (50)	54 (46)

4.10 Summary of results

This study demonstrated:

- Low mean annual wear rates for both articulation sizes.
- A statistically significant difference between articulations sizes in 2D FHP at 3 months (higher for 36 mm cohort) but not at 12 months.
- No statistically significant differences in mean annual 2DWRs and VWRs calculated using radiographs from one year onwards.
- Elevated wear rates demonstrated in 9.3-17.8% of patients in the 36 mm cohort and 9.8-12.3% of patients in the 28 mm cohorts depending on wear calculation used
- No significant differences between articulation sizes in the percentages of cohorts with elevated 2DWRs or VWRs.
- A higher proportion of patients who were male and/or had acetabular component malposition in the cohort of patients with elevated 2DWRs compared to the cohort of patients whose 2DWR was not elevated.
- A significant effect of the wear calculation method chosen on the reported wear rate, as illustrated principally in Table 4.8.

Chapter 5: Discussion

5.1 Synthesis of results to literature and their interpretation

This study is a radiographic wear analysis of a large cohort (326 patients) of primary THR patients drawn from a RCT in which patients were randomised to receive either 36 mm or 28 mm metal-on-HXLPE articulations. The design of the RCT was such that factors that may affect wear were controlled, allowing articulation size to be the only significantly different variable between cohorts for the purpose of wear comparison which allowed achievement of the study aims. It is important to highlight that this is a feature unique to this study when comparing the results to other studies in the literature referenced below where patients were not randomised according to articulation size.

The current study assessed 2D FHP in the early postoperative period to three months inclusive, finding a previously unreported *in vivo* difference between 36 mm and 28 mm articulations, with a higher mean FHP for the 36 mm cohort at three months but not at 12 months. This was also supported by the statistical modelling analysis, which showed no significant effect of time on FHP after three months for either articulation size. Measurements within the bedding-in/creep period for both articulation sizes are broadly comparable to other studies examining metal-on-Longevity™ HXLPE THRs. In the study cohort, 28 mm metal-on-Longevity™ articulations had a mean FHP of 0.38 mm at three months ([95%C.I.] ±0.07) and 0.49 mm at twelve months (±0.07), compared to the literature on 28 mm articulations, which varies from 0.26 mm at six months (Glyn-Jones et al. 2008) up to 0.42 mm at 12 months (Manning et al. 2005). There are, however, only two reports quantifying bedding-in/creep of 36 mm metal-on-HXLPE articulations at 12 months. These are reported as a mean of 0.08 mm, using PolyWare™ (Park et al. 2012), and a median of 0.11 mm using RSA (Bragdon et al. 2007). The reasons for the relatively large magnitude of mean FHP of the 36 mm cohort at 12 months (0.53mm) is unclear but may relate to time points and sample sizes used in addition to

measurement methods. Irrespective of magnitude, it is important to define the end of bedding-in and creep rather than assuming that the process is complete. To illustrate using the results, if the end of bedding-in/creep had been set at 3 months rather than 12 months, comparatively higher steady-state wear rates would have been apparent for 36 mm than for 28 mm articulations.

Findings in this study of no significant differences between 36 mm and 28 mm in bedding-in/creep of HXLPE at 12 months are supported by both *in vivo* and *in vitro* studies. With the exception of Hammerberg et al. (2010), however, studies have assessed early postoperative to one-year radiographs (Bragdon et al. 2007; Nakahara et al. 2011) rather than early postoperative to three-month radiographs. While the higher FHP measured in the time points prior to 12 months in this study may be related to a tribological reason from the use of a larger femoral head and correspondingly thinner liner, such as different contact pressures and sliding distances, it may equally be a product of other factors, such as a difference in initial radial discrepancy. For example, it is more difficult to calculate wear from radiographs of 36 mm articulations because there is less ideal point selection area than in 28 mm articulations. Given there was a higher proportion of baseline 4 day and 6 week radiographs compared to 3 month radiographs (although this was not statistically different) for 36 mm articulations, this may have further affected analysis, as quality radiographs are typically more difficult to achieve when taken in the early post-operative period due to patient discomfort with positioning and surgical soft tissue changes.

Mean annual steady-state 2DWRs were low and not significantly different between articulation sizes. Mean annual steady-state 2DWRs for cohorts ranged between 0.00 (±0.04) mm/yr and 0.12 (±0.20) mm/yr for 36 mm and 0.00 (±0.04) mm/yr to 0.16 (±0.17) mm/yr for 28 mm depending on the method of calculation, as was demonstrated in Table 4.8. 2DWRs in the literature for 36 mm articulations range between –0.06 ± 0.41 (Bragdon et al. 2006) and 0.03 ± 0.02 mm/yr (Bragdon et al. 2012) while 2DWRs for 28 mm

articulations vary between -0.036 mm/yr (Shia et al. 2009) and 0.065 mm/yr (Ayers et al. 2009).

Mean VWRs, while not differing significantly between articulation sizes, did contrast to some of the reported HXLPE literature although the differences in sample sizes and methodology must be considered in any comparison. Minor differences in calculations from 2DWR and negative wear rates being excluded or treated as zero can translate to large differences in VWRs given that the multiplication coefficient (πr^2) used to convert to 2D measurements to VWR using the Charnley and Halley (1975) methods is larger for 36 mm than 28 mm cohorts. Mean VWRs of 36 mm articulations ranged from 0.3 (±36) mm^3/yr to 125 (± 207) mm^3/yr (see Table 4.8). These VWRs are comparable to the literature, where 36 mm articulations range from 4.3 mm^3/yr (Bragdon et al. 2013) to 156.5 mm^3/yr (Lachiewicz et al. 2009). Mean annual VWRs for 28 mm articulations, depending on calculation, ranged between 1 (±22) mm^3/yr to 101 (±105) mm^3/yr (see Table 4.8) which compares reasonably to the literature where mean VWRs for 28 mm articulations range between 1.9 mm^3/yr (Bragdon et al. 2013) and 53.8 mm^3/yr (Lachiewicz et al. 2009).

Only one paper reports a difference in mean VWRs of clinical significance (with respect to conventional PE wear rates) between 36 mm HXLPE articulations and 28 mm articulations, where the 36 mm cohort had a significantly greater mean VWR of 156.5 mm^3/yr compared to 53.8 mm^3/yr (Lachiewicz et al. 2009). As previously discussed in the literature review, the Lachiewicz et al. (2009) VWR results are both discrepant with the other literature on 36 mm metal-on-HXLPE articulations and difficult to compare with the current study, where randomisation according to articulation size and large cohorts are features.

While most HXLPE papers comparing large and standard articulations report their outcomes relative to whether the mean wear rates exceed the osteolysis threshold of 0.1mm/yr for conventional PE (Bragdon et al. 2013; Lachiewicz et al. 2009; Nakahara et al. 2011) or report

whether proportions of cohorts of conventional PE compared to HXLPE exceed the osteolysis threshold (Grimm, Tonino & Heyligers 2012; Thomas et al. 2011), this study is unique in reporting the proportions of patients with elevated wear rates by articulation size. The results demonstrate that the comparatively elevated wear rates seen from use of large compared to standard articulations in metal-on-conventional PE (Jasty et al. 1997; Kesteris et al. 1996; Livermore, Ilstrup & Morrey 1990) do not appear to apply to primary 36 mm compared to 28 mm metal-on-HXLPE THRs. Applying the assumptions of an association to osteolysis similar to conventional PE, then the proportion of the cohorts with elevated 2DWRs and VWRs is as low as 9.3% and up to 17.8%, depending on the reporting method used, with no significant differences in these proportions between articulation sizes. Of interest is that CT analysis of a preliminary sample of patients enrolled in the RCT at 7 years has not found a strong correlation between the presence of radiographic lucencies and elevated annual wear rates as calculated using PolyWare™ (Holubowycz et al. 2013).

Analysis of patients with elevated 2DWRs or VWRs was undertaken to determine factors potentially associated with increased wear (see Tables 5.10–5.12). A higher proportion of patients with elevated wear rates who were male as was seen in this study has been reported in conventional PE but not HXLPE (Della Valle et al. 2004). Increased HXLPE wear rates associated with component malposition is, however, well described by authors (Bjerkholt, Høvik & Reikerås 2010; Košak et al. 2011; Nakahara et al. 2010; Wang & Lee 2013). These authors postulate edge loading and liner fatigue as contributing to higher wear rates in the presence of malpositioned acetabular components.

Negative wear rates were in the order of 40% depending on the method of wear rate calculation. While the negative wear rate is seemingly high, the data in this study mirrors other studies with measurement tools that are generally unable to characterise minimal changes in FHP and the negative wear rates in this study are not dissimilar to other studies examining metal-on-HXLPE articulations. Bragdon et al. (2013) and Nakahara et al. (2011) both

reported steady-state mean 2DWRs that were negative, while Lachiewicz et al. (2009) did not report a percentage of negative wear rates but had a histogram depicting approximately 25% negative wear rates. The high prevalence of negative wear rates in the initial radiographs in this study may be partly explained by the occasional poor quality analogue lateral radiograph due to poor positioning because of pain and surgical soft tissue changes that would have had an impact on measurement of the initial radial discrepancy (Derbyshire 1998). The lower prevalence among radiographs after 12 months is likely related to the improved ability of patients to undergo adequate radiographs and the shift to digital image acquisition that occurred in both cohorts which facilitates accurate analysis. Exclusion or treatment of a negative wear rate as 'zero' will likely make 36 mm VWRs disproportionately higher than 2DWRs, because πr^2, used in converting 2D wear to volumetric wear (such as in the Charnley and Halley [1975] method) will be greater for 36 mm compared to 28 mm articulations, for which a clear effect is apparent in Table 4.8. Despite this, the VWRs between articulation sizes were not significantly different with use of the Martell VWR method which effectively excludes negative wear out of the cup.

The current study proposes that both proportions of cohorts with elevated wear rates and scatterplots are more appropriate ways to present wear data than mean wear rates alone. The ability of the method of wear reporting to influence interpretation of results, particularly the mean wear rates, is well demonstrated in this study by Table 4.8. For example, mean 2DWR calculation from 2 time points as opposed to linear regression can lead to different results, as was also seen in the study of Bragdon et al. (2012). A further example relates to VWR calculation, where any positive wear result for 36 mm articulations will be greater than for 28 mm when applying the Charnley and Halley (1975) method, which makes the inclusion or exclusion of negative wear results into calculation of the mean critically important. These examples reinforce the value of reporting scatterplots and proportions of cohorts with elevated 2DWRs or elevated VWRs in addition to mean wear rates.

5.2 Limitations of the study and measurement technique

This study was a *post hoc* analysis of an RCT that was powered for dislocation and not for demonstrating a difference in wear rates, which was a limitation in the study design.

Many patients, despite having some form of imaging in the follow-up period of interest, did not have a set of radiographs that was defined as being adequate for inclusion in the study. The RCT involved data collection from multiple centres in Australia and the UK with a timeline to follow-up of five years; both the breadth of and the length of follow-up led to challenges for data collection with the loss of some radiograph sets. However, the effect on the 36 mm and 28 mm cohorts was not significantly different.

Exclusion of those patients not having an adequate set of radiographs for assessment (not taken, misplaced or not retrievable, patient death), could have introduced a bias, in that there may have been different proportions of THRs with elevated 2DWRs or VWRs in those patients affected by exclusion, but there is no reasons to suggest that this was so.

Because of the change from analogue to digitised images, there was inconsistency between radiograph pixelation qualities in patients' sets of radiographs. Despite the protocol for imaging acquisition with regard to positioning and beam direction as well as quality of imaging, views taken, image quality and completeness of the series differed between and within patients over time. This led to difficulty, overall, in assessing comparable radiographs between patients and between serial radiographs of the same patient. Use of images of different pixilation and quality is likely to have resulted in small errors during analysis, due to variation in the placement of landmarks within the images and, therefore, the ability to consistently and accurately shadow cast. This is particularly so when the maximum size of a pixel approaches the precision of the instrument. Further, the RCT was undertaken over a period where digital image storage was being introduced, and the conversion to digital imaging from hard copy storage led to a loss of some of the original films. However, there was

no significant difference found in the relative frequency of digital compared to analogue sets for each cohort.

The gold standard for wear measurement is RSA. However, because the current study was designed as a retrospective review of standard radiographs, a computer assisted technique, such as PolyWare™ was required. PolyWare™ has been highlighted in the literature review as not having the gold standard accuracy to characterise typical short-term wear rates of HXLPE. However, Stilling et al. (2010) concluded, as Hui et al. (2003) had similarly reported, that early PolyWare™ versions are a valid method for detecting *larger* amounts (2DWRs of 0.2mm/yr and above and total 2D FHP of 0.5 mm and above) of 2D wear in medium-term follow-up of conventional PE, with a clinical precision similar to that of RSA. While many patients with elevated 2DWRs, therefore, had wear of a magnitude for which PolyWare Rev5™ is validated as having sufficient accuracy and precision to measure, this may not be the case for all patients with elevated 2DWRs given that some had wear rates between 0.1 to 0.2 mm/yr. Further, the precision of PolyWare™ within the current study, as demonstrated by the intra-observer limits of agreement of -0.04mm to 0.03mm, compares reasonably to the range of 0.045mm (Devane et al. 1995) to 0.21 mm (Collier JP et al. 2003) reported in the literature, in addition to a coefficient of variance of 14% between FHP readings.

The different shape of the 36 mm and the 28 mm femoral head is another factor that may have influenced measurement. The CPT™ 36 mm femoral head appears more like a hemisphere and the 28 mm like a full sphere; this meant that there were instances where it was more difficult to place points on the outline of the 36 mm articulation (see Figure 3.2). This was especially the case in the early postoperative period and with poorer quality scanned images derived from analogue films. In addition, a notch of the Trilogy™ locking mechanism was prominent in many of the radiographs and provided some heterogeneity for cup selection points (see example in Figure 5.1).

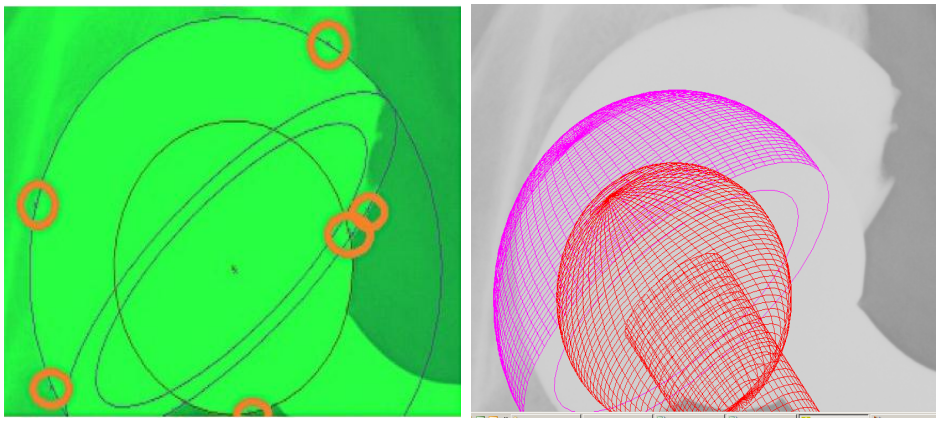

Figure 5.1: An example of a completed shadow cast following point entry and 3D model generated after entry into PolyWare™ of AP and lateral points, affirming acceptable point capture.

Notes: Allowances made for the Trilogy locking mechanism (notch in the upper right acetabular component in these images)

It is recognised that computer-assisted radiographic measurement of wear can be prone to error, in that some results will be near to the true wear value while others will be significantly different from the true value. A number of factors can make measurement error more likely, including poor quality radiographs for comparison, inconsistent angles of the radiograph taken and patient positions, different pixel sizes, increased soft tissue shadowing due to obesity and inconsistent magnification used between different radiography service providers.

There are several other sources of minor error that need to be acknowledged. For example, measurement is focused entirely on the movement of the femoral head within the acetabulum, and factors such as offset and femoral alignment and version cannot be measured with the technique used where it has been previously demonstrated that offset can modify wear rates (Little et al. 2009; Sakalkale et al. 2001). Also, unmeasured backside wear from the modular acetabular component also represents another source of minor error. However, there is no evidence to suggest that it should be over-represented in either articulation cohort, given no significant differences in the acetabular component outer diameters between articulation sizes.

Finally, another potential area for error was the presence of a HXLPE liner fracture, because a subclinical fracture may only be detected *in vivo* except by radiological observation. As discussed in results, the patient found to have a HXLPE liner fracture was discovered due to

frank mechanical symptoms and dislocation. While it may be the case that some of the outlier wear rates were a result of fatigue fractures (such as that which occurs in Longevity™ liners at the locking mechanism [Moore et al. 2008; Tower et al. 2007]), rather than unfractured but highly wearing articulations, the lack of a significant difference between sizes is reassuring. Even if there were HXLPE fractures in the presence of larger articulations and correspondingly thinner liners, the proportions of patients with elevated wear rates were similar in both articulation cohorts. Therefore, a detrimental wear effect of having thinner liners does not seem to afflict 36 mm articulations with any significant difference.

Given the minimal FHP occurring between time points and wear rates that approach the pixelation size, the slightest error and imprecision can produce large differences in the measured result and likely accounted for the 14% variance between intra-observer assessments. This is also the reason why some authors advocate factoring less radiographs into calculations and focusing on 2D rather than 3D wear (Martell et al. 2003, Stilling et al. 2009). This was a factor in calculating and comparing wear rates derived from two radiographic time points only, namely, one year to final or one- to five-year radiographs, or from individual regression of all radiographic sets available at each time point.

5.3 Significance

While the wear study itself was not designed or powered as an RCT to compare wear between different sized articulations, the patients and data are taken from the controlled setting of an RCT where articulation size was randomised, which enables robust assessment of annual 2DWR and VWRs between articulations. Therefore, this study is unique in that it has compared the radiographic wear of patients who were randomised according to articulation size, whereas other studies may have assigned a larger articulation size to patients who were at a higher risk for dislocation. There are potential uncontrolled factors and biases that may occur in other comparative studies that may not apply to this study.

The finding that 36 mm articulations were not associated with higher wear rates than 28 mm articulations up to five years support the use of 36 mm articulations for those patients where dislocation is of higher consequence than long-term wear related sequelae, such as patients of advanced age. Given that a reduced incidence of dislocation at one year has been reported with the use of 36 mm compared with 28 mm articulations in the RCT from which patients in the current study are drawn (Howie et al. 2012), large 36 mm metal-on-HXLPE articulations may have the benefit of stability and reduced risk of dislocation without the risk of elevated wear rates. Assuming that the benefits of reduced dislocation without increased VWRs continue to be borne out beyond the first decade of implantation, increased survivorship of the implant in the second and third decade would be predicted from a reduction in both osteolysis and associated aseptic loosening from volumetric wear in addition to fewer revisions for dislocation and instability.

However, it is possible that, unlike in metal-on-conventional PE THRs, wear rates are less clinically important for implant longevity than other sequelae from the use of large compared with standard articulations that involve metal-on-HXLPE. Biomechanical factors, such as the large bending moments and torque in using large articulations, higher forces on the trunnion of the femoral stem and the different bioreactivity of HXLPE may prove to be more concerning factors than wear rates themselves and have the potential to increase revision rates at the medium- to long-term (Cooper & Della Valle 2014). Demonstration of the importance of the biomechanical disadvantages of large articulations relating to large bending moments and frictional torque on acetabular components has been raised in other THR articulation types, such as metal-on-metal (Higgs et al. 2013), although it is yet to be determined with metal-on-HXLPE THRs.

The prospect of changes in the properties of HXLPE after the first decade, such as oxidation, physical degradation and different bioreactivity profiles, presents another uncertaint despite low short-term wear rates so far for large articulations combined with HXLPE. Also, it is

important to highlight that elevated wear rate parameters (2DWR ≥0.1 mm/yr or VWR ≥80 mm^3/yr) in this study are presumptive and may prove not to be relevant for HXLPE. Currently, whether reduction in HXLPE wear rates leads to a reduction in periprosthetic osteolysis is uncertain with further follow-up required in the mid-term using diagnostic standard CT assessment.

Radiographic studies such as ours and joint replacement registries both have the potential to aid decision-making for surgeons considering use of either a 36 mm or 28 mm metal-on-HXLPE articulation. The strength of registries are their strong participation and large numbers, enabling them to be sensitive to differences in revision rates between articulations. However, registries can only identify factors after the failures occur which require revision and articulations incorporating HXLPE have not been in clinical use long enough to make an adequate assessment of revision due to aseptic loosening. On the other hand, radiographic studies can measure predictors of failure applied to metal-on-PE articulations that cannot be assessed by registries. This includes the ability to assess and compare 2DWRs and VWRs between articulation sizes to identify patient cohorts with elevated 2DWRs or VWRs. Should an association be found in the future between HXLPE wear rates and osteolysis leading to aseptic loosening, then the current and other radiographic studies can be used to identify patients who may need closer follow-up or intervention due to elevated wear rates and identify implant designs with higher than expected wear rates.

There are over 75,000 THRs in Australia alone registered in the AOA NJRR (2014) who have large XLPE articulations (≥32 mm) and approximately three-quarters of these are metal-on-XLPE articulations. Reduced wear of HXLPE has lead to increased use of large HXLPE articulations (AOA NJRR 2014) The AOA NJRR (2014) demonstrates overall reduced revision rates in primary THR with the use of 32 mm or 36 mm metal-on-HXLPE articulations compared with 28 mm articulations in the first decade, primarily related to a reduction in revision for instability but it remains unknown whether this advantage will continue in the

longterm. Coupled the advantage of a proven reduction in the incidence of dislocation at one year from use of a 36 mm compared to 28 mm metal-on-HXLPE articulation (Howie et al. 2012), this wear study provides support for use of 36 mm articulations given no differences in short-term wear rates when compared to 28 mm articulations.

5.4 Conclusions and implications for further research

This study found low mean annual wear rates from one to five years post-operatively for both 36 mm and 28 mm metal-on-highly cross-linked polyethylene primary total hip replacements. Importantly, there were no statistically or clinically significant differences between articulation sizes in mean two-dimensional and volumetric wear rates. Furthermore, there were no differences in the proportions of patients with elevated two-dimensional or volumetric wear rates. Importantly, these findings support the study hypotheses. However, this study found that 36 mm compared to 28 mm metal-on-highly cross-linked polyethylene total hip replacements had higher bedding-in/creep at three months, although no difference in two-dimensional femoral head penetration between cohorts was evident at 12 months. Finally, patients with elevated two-dimensional or volumetric wear rates were more likely to be male and have an acetabular component that differed by at least 10 degrees from an abduction angle of 45 degrees or anteversion of 20 degrees.

These results support the use of 36 mm articulations in primary total hip replacement in older patients, in whom dislocation is a relatively more important consideration than wear. The randomised controlled trial from which patients were drawn for the current study reported a reduced incidence of dislocation at one year (Howie et al. 2012). The current study found no increased wear from use of a 36 mm articulation compared with a 28 mm articulation at mid-term follow-up.

This study is limited to mid-term analysis of wear and analyses in the long-term are required to assess whether wear rates remain low. Further studies to establish the effect of highly cross-linked polyethylene wear rates on the prevalence of periprosthetic osteolysis are also required. The results of such studies and further review of joint registry results are required prior to recommending 36mm metal-on-highly cross-linked polyethylene articulations for routine use, particularly in young or very active patients.

Appendix A: Published RCT Methodology

Source: Howie et al. (2012)

Appendix B: Evidence of Trial Ethics Approval and Registration

Australia New Zealand Clinical Trials Registry

Howie, Donald William; Holubowycz, Oksana T.; Middleton, Robert; The Large Articulation Study Group

Large femoral heads decrease the incidence of dislocation after total hip arthroplasty: A randomized controlled trial
Journal of Bone and Joint Surgery - American, 2012; 94(12):1095-1102

Large Femoral Heads Decrease the Incidence of Dislocation After Total Hip Arthroplasty

A Randomized Controlled Trial

Donald W. Howie, MBBS, FRACS, PhD, Oksana T. Holubowycz, PhD, MPH, Robert Middleton, MBBChir, MA, FRCS(Orth), and the Large Articulation Study Group

Investigation initiated and undertaken by the Discipline of Orthopaedics and Trauma, University of Adelaide, Adelaide, South Australia, Australia and performed at Royal Adelaide, St Andrew's, Glenelg, and Modbury Hospitals, Adelaide, South Australia, Australia; Whyalla Hospital, Whyalla, South Australia, Australia; Royal North Shore Hospital, Sydney, New South Wales, Australia; St. John of God and Ballarat Base Hospitals, Ballarat, Victoria, Australia; Geelong Hospital, Geelong, Victoria, Australia; Maroondah and St. Vincent's Hospitals, Melbourne, Victoria, Australia; Royal Bournemouth Hospital, Bournemouth, England; Southampton General Hospital, Southampton, England; and Ninewells Hospital, Dundee, Scotland

Background: The use of larger femoral heads has been proposed to reduce the risk of dislocation after total hip arthroplasty, but there is a lack of evidence to support this proposal. The aim of this multicenter randomized controlled trial was to determine whether the incidence of dislocation one year after total hip arthroplasty is significantly lower in association with the use of a 36-mm femoral head articulation as compared with a 28-mm articulation.

Methods: Six hundred and forty-four middle-aged and elderly patients undergoing primary or revision arthroplasty were randomized intraoperatively to receive either a 36 or 28-mm metal femoral head on highly cross-linked polyethylene. Patients who were at high risk of dislocation (including those with dementia and neuromuscular disease) and those undergoing revision for the treatment of recurrent hip dislocation or infection were excluded. Patients were stratified according to other potential risk factors for dislocation, including diagnosis and age. Diagnosis of hip dislocation required confirmation by a physician and radiographic evidence of a dislocation.

Results: Overall, at one year of follow-up, hips with a 36-mm femoral head articulation had a significantly lower incidence of dislocation than did those with a 28-mm articulation (1.3% [four of 299] compared with 5.4% [seventeen of 316]; difference, 4.1% [95% confidence interval, 1.2% to 7.2%]) when controlling for the type of procedure (primary or revision) ($p = 0.012$). The incidence of dislocation following primary arthroplasty was also significantly lower for hips with a 36-mm femoral head articulation than for those with a 28-mm articulation (0.8% [two of 258] compared with 4.4% [twelve of 275]; difference, 3.6% [95% confidence interval, 0.9% to 6.8%]) ($p = 0.024$). The incidence of dislocation following revision arthroplasty was 4.9% (two of forty-one) for hips with a 36-mm articulation and 12.2% (five of forty-one) for hips with a 28-mm articulation; this difference was not significant with the relatively small sample size of the revision group (difference, 7.3% [95% confidence interval, −5.9% to 21.1%]) ($p = 0.273$).

Conclusions: Compared with a 28-mm femoral head articulation, a larger 36-mm articulation resulted in a significantly decreased incidence of dislocation in the first year following primary total hip arthroplasty. However, before a 36-mm metal-on-highly cross-linked polyethylene articulation is widely recommended, the incidence of late dislocation, wear, periprosthetic osteolysis, and liner fracture should be established.

Level of Evidence: Therapeutic Level I. See Instructions for Authors for a complete description of levels of evidence.

Disclosure: One or more of the authors received payments or services, either directly or indirectly (i.e., via his or her institution), from a third party in support of an aspect of this work. In addition, one or more of the authors, or his or her institution, has had a financial relationship, in the thirty-six months prior to submission of this work, with an entity in the biomedical arena that could be perceived to influence or have the potential to influence what is written in this work. No author has had any other relationships, or has engaged in any other activities, that could be perceived to influence or have the potential to influence what is written in this work. The complete **Disclosures of Potential Conflicts of Interest** submitted by authors are always provided with the online version of the article.

Dislocation is the most common early complication following total hip arthroplasty and is one of the most common causes of early to intermediate-term revision of primary total hip arthroplasty[1,2].

The use of larger femoral heads has been proposed as a means of reducing the risk of dislocation because larger-diameter articulations have a relatively larger femoral head-to-neck ratio, which increases hip motion before impingement between components occurs[3,4]. Larger femoral head implants require a greater amount of femoral head displacement before dislocation occurs within a well-oriented acetabular component[4]. However, concerns about polyethylene wear in larger-diameter articulations, such as those involving 36 or 40-mm femoral heads, have prevented their use with earlier generations of ultra-high molecular weight polyethylenes. The development of highly cross-linked polyethylenes has now made the use of larger articulations feasible in total hip arthroplasty, given that the articulations involving the newer polyethylenes have shown less wear than the previous generation of polyethylenes in hip-simulator studies[5,6] and randomized controlled trials[7-10].

Two nonrandomized cohort studies of primary arthroplasty in which larger (≥30-mm) articulations were compared with 28-mm articulations suggested that increased femoral head size may be associated with a decreased risk of dislocation[11,12], whereas other studies have not conclusively shown this finding[13,14].

There are two important issues that need to be addressed when determining the potential magnitude of the effect of articulation size on the incidence of dislocation following hip arthroplasty. First, the risk of dislocation may be influenced by a number of other factors, including patient-related factors (such as diagnosis[14-16], age[16,17], and sex[15]) and surgical technique. Dislocation is more common in association with the posterior approach[11,17-19] and with a highly abducted acetabular component orientation[4] and is less common following soft-tissue repair[20,21]. Second, the rate of hip dislocation is frequently under-reported, primarily because of inadequate follow-up[22]. As the number of data sources used to identify episodes of dislocation increases, the capture rate increases significantly[22].

The aim of the present study was to examine the hypothesis that the incidence of dislocation at one year after total hip arthroplasty is significantly lower in association with a 36-mm femoral head articulation than with a 28-mm articulation. We undertook a randomized controlled trial in which a number of factors that may influence the risk of hip dislocation were controlled for by the study design and dislocation was tracked with a number of different methods.

Materials and Methods

The results of this trial are reported in accordance with CONSORT (Consolidated Standards of Reporting Trials) 2010 guidelines[23]. The study was undertaken as a multicenter, stratified, parallel-group randomized controlled trial involving fourteen hospitals (see Appendix). Consultants, or fellows or residents under their supervision, performed all procedures. The trial involved patients undergoing primary or revision total hip arthroplasty who were intraoperatively randomized to receive either a 28 or 36-mm femoral head articulation. Ethics approval was received from the institutional review board of every participating hospital. The trial is registered with the Australian New Zealand Clinical Trials Registry (ACTRN12609000678291).

Every patient who was scheduled to be managed with total hip arthroplasty by one of the collaborating surgeons was screened for inclusion in the trial. The reasons for, and the numbers of, preoperative exclusions are shown in the Appendix.

Eligible patients provided written informed consent if they were willing to participate in the trial. Patients were then stratified according to a number of factors to increase the likelihood that possible risk factors for dislocation would be distributed equally between patients randomized to a 36 or 28-mm femoral head articulation. The stratification and randomization procedures are described in detail in the Appendix.

The reasons for, and the numbers of, intraoperative exclusions for patients undergoing primary and revision procedures are shown in the Appendix. The randomization envelope was opened in the operating room after all exclusion criteria had been considered and it had been determined the patient was to be included. The envelope was opened after the acetabular component had been inserted and fixed with at least one screw but prior to the insertion of the stem. The patient received either a 36 or 28-mm articulation, according to the number in the envelope.

All arthroplasties were performed with use of uncemented acetabular components, which comprised a cluster three-holed acetabular shell (Trilogy; Zimmer, Warsaw, Indiana) fixed with one or two screws and a 10° elevated 36 or 28-mm-inner-diameter highly cross-linked polyethylene liner (Longevity; Zimmer). A cemented femoral stem was used for all primary arthroplasties (CPT; Zimmer). Either a cemented femoral stem (CPT; Zimmer) or an uncemented stem (ZMR; Zimmer) was used for revision arthroplasties. During the trial, the taper of the CPT femoral stem was changed from a 6° taper to a 12/14 taper by the manufacturer. When possible, each surgeon completed his allocated randomization block before commencing with the use of the 12/14 taper.

All primary arthroplasties were performed through a posterior surgical approach. Revision arthroplasties were performed through a posterior, transfemoral, or transtrochanteric approach. Repair of the capsule and external rotators was performed routinely during primary arthroplasties and, when possible, during revisions. The operative technique for insertion of the acetabular component through a posterior approach included reliance mainly on the alignment guide and confirmation by the surgeon's judgment that the component was reasonably positioned.

Determination of the incidence of hip dislocation required the use of a number of different approaches to ensure that all dislocations were identified. Prior to discharge, each patient was provided with a Dislocation Card, to be given to any physician who subsequently treated the patient for dislocation, with instructions for that physician to notify the study coordinator of the dislocation. Case notes were reviewed to check for inpatient episodes of postoperative dislocation. The patient was then reviewed at six weeks to three months and at one year, and any complications were noted. In addition, at each visit, the patient completed a Hip Instability Questionnaire, which we had previously developed and validated, and a Hospital Visit Questionnaire. The former included the item "hip came out of joint and was put back in by a physician," whereas the latter asked about all visits to an emergency room as well as any admissions. Dislocation was defined as an event requiring reduction by a physician or surgeon for which there was radiographic confirmation of a dislocation.

Patients, surgeons, and local study coordinators were not blinded to the articulation size received.

Radiographs showing the initial hip dislocation in every patient were assessed by one of the authors (D.W.H.) to determine the direction of dislocation. The position of the femoral head relative to the acetabular cup on the anteroposterior and lateral radiographs was used to determine the definite direction of the dislocation. If the lateral radiograph was unavailable or inadequate, the anteroposterior pelvic radiograph was used. The prominence of the lesser trochanter was compared to that of the contralateral side to determine the rotation of the femur and thereby the probable direction of dislocation. If only an anteroposterior hip radiograph was available, the prominence of the lesser trochanter was used to determine the possible direction of dislocation.

TABLE I Incidence of Dislocation One Year Following Total Hip Arthroplasty According to Type of Total Hip Arthroplasty or Type of Stem and Articulation Size

	Incidence of Dislocation					
	36–mm Articulation		28-mm Articulation			
	Number of Hips That Dislocated per Number of Hips in Group	Percentage*	Number of Hips that Dislocated per Number of Hips in Group	Percentage*	Difference Between Groups* *(%)*	P Value
Type of total hip arthroplasty						
All	4 of 299	1.3 (0.0 to 2.6)	17 of 316	5.4 (2.9 to 7.9)	4.1 (1.2 to 7.2)	0.012
Primary	2 of 258	0.8 (0.0 to 1.9)	12 of 275	4.4 (2.0 to 6.8)	3.6 (0.9 to 6.8)	0.024
Revision	2 of 41	4.9 (0.0 to 11.5)	5 of 41	12.2 (2.2 to 22.2)	7.3 (−5.9 to 21.1)	0.273
Type of stem						
CPT 12/14	2 of 163	1.2 (0.0 to 2.9)	8 of 178	4.5 (1.5 to 7.5)	3.3 (−0.6 to 7.5)	0.101
CPT 6°	1 of 117	0.9 (0.0 to 2.5)	7 of 120	5.8 (1.6 to 10.0)	4.9 (0.1 to 10.7)	0.072
ZMR	1 of 19	5.3 (0.0 to 15.3)	2 of 18	11.1 (0.0 to 25.6)	5.8 (−15.1 to 28.0)	0.542

*The 95% confidence intervals are given in parentheses.

The position of the acetabular component was assessed on the most recent anteroposterior pelvic radiograph that had been made prior to the dislocation. Inclination and anteversion of the acetabular component were measured with use of EBRA (Ein-Bild-Roentgen-Analyse) (EBRA-CUP, University of Innsbruck, Innsbruck, Austria).

Statistical Analysis

With use of a power of 80% and a two-sided alpha of 0.05, initial sample size estimates indicated that a total sample size of 650 patients would be required to detect a significant and clinically important reduction in the incidence of dislocation at one year from 8% in the 28-mm articulation group to 3% in the 36-mm articulation group, if such a difference were to exist. A planned interim analysis by an independent data-monitoring committee indicated adequate power for our data, even allowing for a 5% rate of patient attrition, and therefore a decision was made to stop recruitment after 644 patients had been randomized.

Poisson regression with, first, main effects of type of procedure (primary or revision arthroplasty) and articulation size (36 or 28 mm) and, second, type of stem (CPT 12/14, CPT 6°, or ZMR) and articulation size, was used to examine whether the primary outcome measure, the incidence of dislocation one year following total hip arthroplasty, was affected by articulation size. Log of the total number of patients was used as offset. An analysis with use of a Cox model was also undertaken to take into account the observed experience of patients who were lost to follow-up within the first year, either through death, revision, reoperation, or other reasons. Differences between means were assessed with use of an independent-samples t test, and differences in proportions were assessed with use of chi-square tests.

Source of Funding

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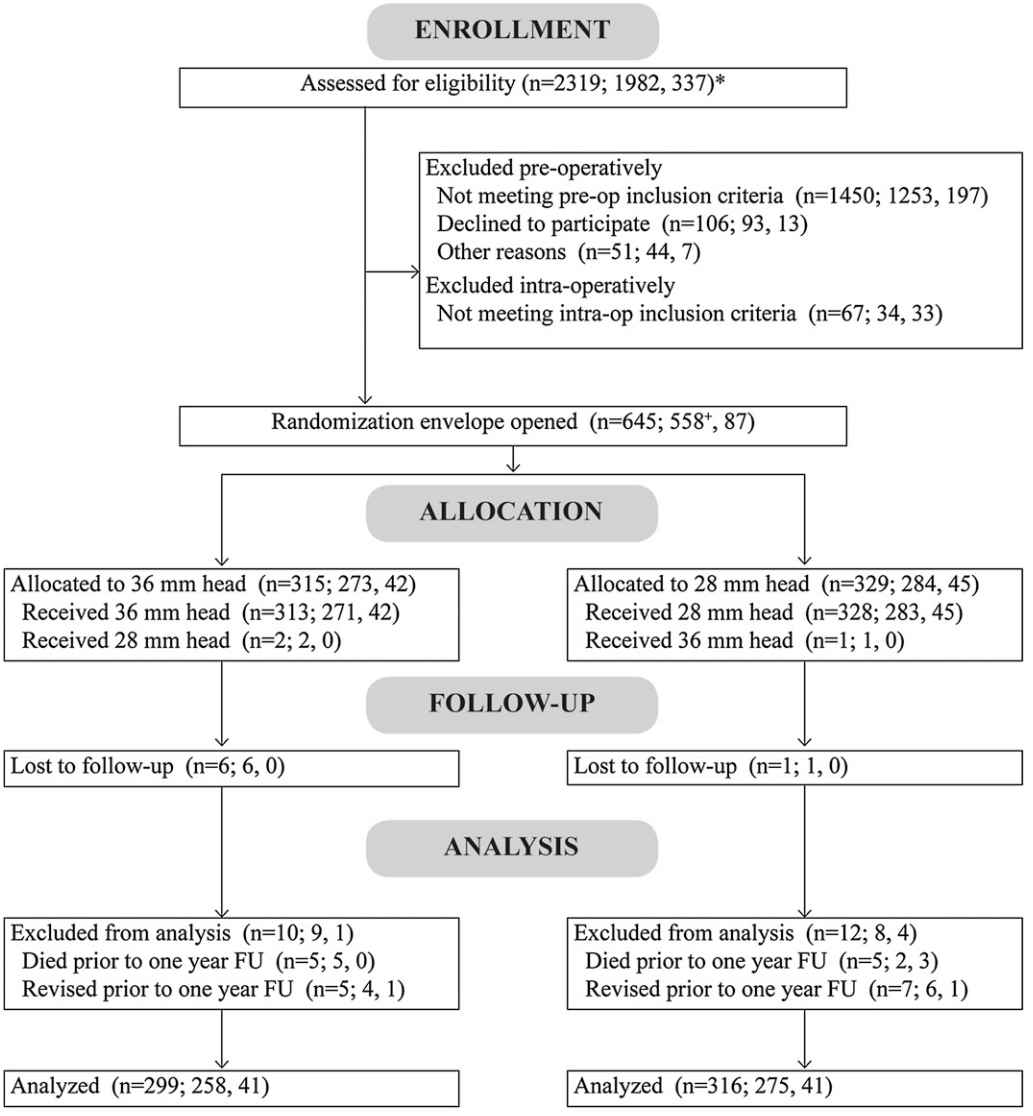
Results

Patients were recruited from September 2001 to June 2007. The numbers of patients who were assessed for eligibility, who were excluded preoperatively or intraoperatively, and who were randomized and included in the analyses are shown in Figure 1. Three patients received the wrong articulation size. These errors were due to breaches of protocol, with the envelope being opened prior to confirmation of the availability of all required components of the prosthesis and the required component in the allocated size subsequently being identified as not being available. These patients were included in the analysis according to their allocated articulation size; none of these patients had a dislocation. Seven (1.1%) of the 644 patients were lost to follow-up at one year and were excluded from the analysis. Another twenty-two patients were also excluded, ten because they died before the one-year follow-up without having a dislocation and twelve because they had undergone revision arthroplasty or reoperation, for reasons other than dislocation, that involved a change of implant or potential damage to the hip as a result of the surgery, which may have altered their risk of dislocation.

The incidence of dislocation at one year following hip arthroplasty was significantly lower in patients with a 36-mm femoral head articulation than in patients with a 28-mm articulation. One year following primary or revision arthroplasty, four (1.3%) of 299 hips with a 36-mm articulation and seventeen (5.4%) of 316 hips with a 28-mm articulation had dislocated (Table I). Controlling for the type of procedure (primary or revision), the articulation size was significantly related to dislocation ($\chi^2 = 6.4$, $p = 0.012$), with a significantly lower incidence of dislocation at one year in hips with a 36-mm articulation than in those with a 28-mm articulation. The incidence of dislocation at one year following primary hip arthroplasty was also significantly lower in hips with a 36-mm articulation than in those with a 28-mm articulation (0.8% [two of 258] compared with 4.4% [twelve of 275]) ($\chi^2 = 5.1$, $p = 0.024$). One year following revision arthroplasty, the



* (n=all THA pts; primary THA pts, revision THA pts)

+ One patient was withdrawn intra-operatively: the patient's randomization envelope was mistakenly opened at the onset of surgery, the patient then developed symptoms requiring surgery to be abandoned and the patient did not subsequently undergo surgery by a trial surgeon.

Fig. 1

CONSORT 2010 flow diagram. THA = total hip arthroplasty, FU = follow-up, pts = patients.

incidence of dislocation was not significantly different between hips with a 36-mm articulation and those with a 28-mm articulation (4.9% [two of forty-one] compared with 12.2% [five of forty-one]) ($\chi^2 = 1.2$, $p = 0.273$), most likely because of an insufficient number of revision procedures in the trial to achieve adequate power for this comparison. A Cox model stratified by the type of procedure (primary or revision) confirmed a lower risk of dislocation for hips with a 36-mm articulation during the first year following arthroplasty, taking into account the observed experience of patients who were subsequently lost to follow-up during the first year either through death, revision, reoperation, or another reason ($p = 0.005$). Controlling for the type of femoral stem, articulation size was significantly related to dislocation ($\chi^2 = 6.4$, $p = 0.012$). However, there was no significant difference in the incidence of dislocation between articulation sizes within any of the three stem types when

TABLE II Relationship Between Outer Diameter of Acetabular Cup, Articulation Size, and Dislocation Within One Year Following Primary and Revision Total Hip Arthroplasty

	Primary Total Hip Arthroplasty				Revision Total Hip Arthroplasty			
	36-mm Articulation (N = 255*)		28–mm Articulation (N = 275)		36-mm Articulation (N = 41)		28-mm Articulation (N = 41)	
Outer Diameter of Acetabular Cup *(mm)*	No. of Hips	No. of Hips That Dislocated	No. of Hips	No. of Hips That Dislocated	No. of Hips	No. of Hips That Dislocated	No. of Hips	No. of Hips That Dislocated
50	28		26		0		1	
52	58	1	68	3	4		1	
54	48		66	4	1		2	
56	58		54	5	5		2	1
58	34	1	27		8		6	1
60	15		22		8	1	7	
62	8		8		5	1	5	1
64	5		3		3		7	1
66	0		1		3		6	
68	1		0		1		1	
70					1		2	1
72					2		0	
74					0		1	

*The outer diameter of the acetabular cup was unknown for three patients.

considered individually, likely because of the smaller sample sizes in the individual analyses (Table I).

Given the relatively small number of patients with larger acetabular cup diameters, the relationship between femoral head size, cup diameter, and dislocation risk could not be determined in this study (Table II). However, three of the twenty-one patients with a dislocation had a 28-mm articulation in an acetabular cup with a diameter of at least 62 mm, representing a radius mismatch of at least 17 mm, which previously was identified as a risk factor for dislocation[24].

In both the primary and revision arthroplasty groups, the patients who were randomized to a 36-mm articulation were

TABLE III Characteristics of Patients at Time of Primary Total Hip Arthroplasty According to Allocation to Articulation Size

	36-mm Articulation (N = 273)	28-mm Articulation (N = 284)	P Value	Total (N = 557)
Female* *(%)*	56.0 (50.2 to 61.9)	61.3 (55.6 to 66.9)	0.212	58.7 (54.6 to 62.8)
Age *(yr)*				
Mean*	72.3 (71.5 to 73.0)	72.3 (71.6 to 73.1)	0.891	72.3 (71.8 to 72.8)
Range	59 to 93	60 to 92		59 to 93
BMI†				
Mean*	28.0 (27.4 to 28.7)	28.4 (27.8 to 29.0)	0.371	28.2 (27.8 to 28.7)
Range	16.7 to 44.0	18.8 to 51.5		16.7 to 51.5
Primary or secondary osteoarthritis*† *(%)*	96.3 (94.1 to 98.6)	95.4 (93.0 to 97.9)	0.588	95.9 (94.2 to 97.5)
Type of stem* *(%)*			0.704	
CPT 12/14	59.3 (53.5 to 65.2)	60.9 (55.2 to 66.6)		60.1 (56.1 to 64.2)
CPT 6°	40.7 (34.8 to 46.5)	39.1 (33.4 to 44.8)		39.9 (35.8 to 43.9)

*The 95% confidence intervals are given in parentheses. †Data on BMI (body mass index) were available for a total of 484 patients (237 with a 36-mm articulation and 247 with a 28-mm articulation). ‡Primary or secondary osteoarthritis without a previous fracture, traumatic dislocation, or surgery to the index hip.

TABLE IV Characteristics of Patients at Time of Revision Total Hip Arthroplasty According to Allocation to Articulation Size

	36-mm Articulation(N = 42)	28-mm Articulation(N = 45)	P Value	Total (N = 87)
Female* *(%)*	45.2 (30.2 to 60.3)	48.9 (34.3 to 63.5)	0.733	47.1 (36.6 to 57.6)
Age *(yr)*				
Mean*	75.2 (72.7 to 77.7)	73.8 (71.5 to 76.0)	0.384	74.4 (72.8 to 76.1)
Range	54 to 89	56 to 87		54 to 89
BMI†				
Mean*	28.9 (27.3 to 30.5)	27.8 (26.4 to 29.2)	0.304	28.3 (27.3 to 29.4)
Range	21.6 to 44.6	21.8 to 42.9		21.6 to 44.6
Type of revision* *(%)*			0.591	
Revision of hemiarthroplasty	11.9 (2.1 to 21.7)	17.8 (6.6 to 29.0)		14.9 (7.5 to 22.4)
1st revision of total hip arthroplasty	78.6 (66.2 to 91.0)	68.9 (55.4 to 82.4)		73.6 (64.3 to 82.8)
≥2nd revision of total hip arthroplasty	9.5 (0.7 to 18.4)	13.3 (3.4 to 23.3)		11.5 (4.8 to 18.2)
Type of stem* *(%)*			0.880	
CPT 12/14	26.2 (12.9 to 39.5)	31.1 (17.6 to 44.6)		28.7 (19.2 to 38.2)
CPT 6°	28.6 (14.9 to 42.2)	26.7 (13.8 to 39.6)		27.6 (18.2 to 37.0)
ZMR	45.2 (30.2 to 60.3)	42.2 (27.8 to 56.7)		43.7 (33.3 to 54.1)

*The 95% confidence intervals are given in parentheses. †Data on BMI (body mass index) were available for a total of eighty-one patients (thirty-nine with a 36-mm articulation and forty-two with a 28-mm articulation).

similar to those who were randomized to a 28-mm articulation (Tables III and IV).

Overall, seventeen (81%) of the twenty-one hips that dislocated within one year after primary or revision arthroplasty had a 28-mm articulation (Table V). The majority (nine) of the fourteen hips that dislocated after primary arthroplasty did so within thirty days after surgery, whereas hips that dislocated after revision arthroplasty showed a tendency to dislocate later. Approximately one-third of dislocating hips redislocated. Within the first year after hip arthroplasty, revision surgery for the

TABLE V Characteristics of Patients Who Had Hip Dislocation Within One Year After Primary or Revision Total Hip Arthroplasty

	Primary Arthroplasty (N = 14)	Revision Arthroplasty (N = 7)
36-mm:28-mm articulation *(no. of hips)*	2:12	2:5
Female:male ratio *(no. of hips)*	9*:5*	3*:4*
Age† *(yr)*	73 (62 to 84)	76 (61 to 83)
BMI†	29 (20 to 39)	26 (23 to 34)
Primary or secondary osteoarthritis‡	12*	NA§
Type of revision (revision of hemiarthroplasty:1st revision of total hip arthroplasty:≥2nd revision of total hip arthroplasty) *(no. of hips)*	NA§	1:4#:2
Stem type (CPT 6°:CPT 12/14:ZMR) *(no. of hips)*	5:9#:NA§	3*:1:3*
1st dislocation (≤10 days:11 to 30 days:31 to 100 days:>100 days postop.) *(no. of hips)*	4:5*:3*:2	1:1:4*:1*
>1 dislocation *(no. of hips)*	5*	3
Revised because of recurrent dislocation *(no. of hips)*	2*	3
Closed reduction of 1st dislocation *(no. of hips)*	13#	6#

*Includes one patient with a 36-mm articulation. †The values are given as the median, with the range in parentheses. ‡Primary or secondary osteoarthritis without a previous fracture, traumatic dislocation, or surgery on the index hip. §NA = not applicable. #Includes two patients with a 36-mm articulation.

treatment of recurrent dislocation was required in two of the fourteen hips that dislocated after primary arthroplasty and three of the seven that dislocated after revision arthroplasty; another hip that had dislocated after primary arthroplasty was revised because of failed closed reduction of the dislocation.

Of the fourteen first dislocations that occurred after primary arthroplasty, three were classified as definitely posterior, seven were classified as probably posterior, one was classified as possibly posterior, and three were classified as probably anterior. Of the seven first dislocations that occurred after revision arthroplasty, two were classified as definitely posterior, two were classified as probably posterior, two were classified as anterior, and one was classified as having an indeterminate direction.

The median inclinations of the acetabular components used for primary and revision total hip arthroplasties with a 28-mm articulation that subsequently dislocated were 44° (range, 34° to 52°) and 45° (range, 41° to 51°), respectively, and the median anteversions were 15° (range, 7° to 32°) and 16° (range, 10° to 22°), respectively. The two hips with a 36-mm articulation that dislocated after a primary procedure both had an inclination of 48° and anteversions of 5° and 7°. The two hips with a 36-mm articulation that dislocated after a revision procedure both had an inclination of 43° and an anteversion of 10°.

Discussion

The purpose of the present randomized controlled trial was to determine whether a larger (36-mm) femoral head articulation significantly reduced the incidence of dislocation within the first year following total hip arthroplasty in comparison with a 28-mm articulation. The results of this trial indicated that the incidence of dislocation within one year after primary arthroplasty was five times lower in patients with a 36-mm articulation (0.8%) than in those with a 28-mm articulation (4.4%); this difference was both clinically important and statistically significant.

The use of larger femoral head implants for total hip arthroplasty has been increasing during the last decade[25-27], largely on the basis of the premise that larger articulations are efficacious for preventing dislocations. Our trial showed that a larger articulation significantly reduced the risk of dislocation following primary arthroplasty. The number of patients undergoing revision arthroplasty as part of the trial was relatively small, and therefore the difference in the incidence of dislocation between the 36 and 28-mm articulations did not attain significance. It should be noted, however, that initial sample size calculations estimated the total number of patients required for an analysis of the effect of articulation size on the incidence of dislocation rather than the numbers required to examine the effects in the primary and revision arthroplasty groups independently.

Our conclusion that a larger articulation decreased the risk of dislocation following total hip arthroplasty supports the findings of two cohort studies[11,12] as well as those of two registry studies that showed a decreased risk of revision for dislocation after total hip arthroplasty with larger articulations[18,28].

Although we have been able to determine the short-term benefits of a larger, 36-mm metal-on-polyethylene articulation in total hip arthroplasty, specifically in terms of decreasing the incidence of dislocation up to one year following arthroplasty, what is best at one year may not be best at ten years. This needs to be emphasized because the use of a larger articulation in a metal-on-polyethylene bearing is not without potential risks. In an acetabular component of a given outer diameter, a 36-mm liner will of necessity be thinner than a 28-mm liner, particularly at the rim. The polyethylene thickness for a 36-mm liner in an acetabular component with an outer diameter of 50 mm is 6.7 mm at the pole and 5.8 mm at 45°. This may increase wear or even wear-through compared with the smaller-diameter liner, although the findings of simulator studies have been encouraging[29,30]. However, even if cross-linking improves wear resistance, the mechanical properties of highly cross-linked polyethylenes are reduced, leading to increased fracture potential of such liners, irrespective of the inner diameter[31,32].

Wear has been used as a surrogate measure of osteolysis with previous generations of polyethylene implants. Given the same rate of linear wear, volumetric wear will be greater in a larger articulation. However, the relationship between head penetration, volumetric wear of highly cross-linked polyethylene, and osteolysis is not yet well defined[33].

The major strength of our randomized trial was the ability to control for other variables that may affect the risk of dislocation. We chose to exclude patients who had certain characteristics that, although not common, could significantly increase the risk of dislocation and could affect the results if not equally distributed across the 36 and 28-mm articulation groups. Importantly, patients who were to undergo revision were excluded if revision was being undertaken because of recurrent dislocation or infection. Patients were stratified by other factors that were also considered possible risk factors for dislocation.

One limitation of our study is that seven (1.1%) of the 644 patients were lost to follow-up at one year and that six of these patients had received a 36-mm articulation. For patients who had been lost to follow-up, reviews of hospital records and, when available, local physician records suggested that no dislocations had occurred. However, as it could not be confirmed that no dislocations had occurred, the patients were treated as having been lost to follow-up and were excluded from the analysis.

In our randomized trial, the incidence of dislocation in the first year after primary total hip arthroplasty with a 28-mm articulation was 4.4%. Although this figure is at the upper end of the range of incidences reported in large cohort studies, two factors are likely to have influenced this finding. First, the incidence of dislocation is known to be higher in association with a posterior approach[11,17-19]. Second, the reported incidence is higher when patients are routinely followed and when the number of methods used to track dislocation increases[22].

In conclusion, the present randomized trial showed that a larger articulation significantly reduced the incidence of dislocation in the first year after total hip arthroplasty with a metal-on-highly cross-linked polyethylene articulation. It must be emphasized that before a 36-mm metal-on-highly cross-linked polyethylene articulation is widely recommended,

particularly in younger patients or those at lower risk of dislocation, the incidence of late dislocation, wear, periprosthetic osteolysis, and acetabular liner fracture needs to be established.

Appendix

eA Tables showing a description of the study centers and the reasons for the preoperative and intraoperative exclusion of patients from the study and additional paragraphs describing the stratification and radomization preocedures are available with the online version of this article as a data supplement at jbjs.org. ■

NOTE: The Large Articulation Study Group: D. Howie, O. Holubowycz (Chief Investigators). Royal Adelaide Hospital: D. Howie, B. Allen, S. Brumby, M. Chehade, R. Clarnette, A. Comley, A. Mintz, R. Montgomery, A. Pohl, T. Savvoulidis, B. Solomon, J. van Essen (surgeons), A. Standen (Local Study Coordinator [LSC]). St. Andrew's Hospital: D. Howie (surgeon), M. Bennier (LSC). Glenelg Hospital: D. Howie (surgeon), M. Bennier (LSC). Modbury Hospital: S. Brumby (surgeon), S. Pannach (LSC). Whyalla Hospital: T. Savvoulidis (surgeon). Royal North Shore Hospital: A. Ellis, S. Ruff (surgeons), E. Cole (LSC). St. John of God and Ballarat Base Hospitals: J. Nelson (surgeon), C. Gear (LSC). Geelong Hospital: S. Williams, R. Angliss (surgeons), S. Beattie, U. Farago, C. Gleeson, A. Vanderveen (LSCs). St. Vincent's Hospital Melbourne: A. Dunin, B. Love (surgeons), M. Dowsey, M. Farley (LSCs). Maroondah Hospital: D. Booth, P. Gard (surgeons), J. Walsh (LSC). Royal Bournemouth Hospital: R. Middleton (UK surgeon coordinator), T. Wainwright, S. Sargeant (LSCs). Southampton General Hospital: D. Dunlop, J. Latham (surgeons), A. Wakefield (LSC). Ninewells Hospital: B. Clift, D. Rowley (surgeons), L. Johnston, L. McCormack (LSCs).

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TABLE E-1 Description of Study Centers

			No. of Patients (No. of Hips That Dislocated)	
Hospital	Type of Hospital	No. of Surgeons	Primary	Revision
Australia				
Royal Adelaide	Teaching, tertiary referral	12	135 (5)*	33 (3)
St. Andrew's, Adelaide	Metropolitan	1†	28	1
Glenelg, Adelaide	Metropolitan	1†	5	0
Modbury, Adelaide	Teaching, metropolitan	1†	10	0
Whyalla, Whyalla	Non-metropolitan	1†	5	0
Royal North Shore, Sydney	Teaching, tertiary referral	2	58 (1)	0
St. John of God, Ballarat	Non-metropolitan	1	45 (1)	1
Ballarat Base, Ballarat	Teaching, non-metropolitan	1†	8	0
Geelong, Geelong	Teaching, non-metropolitan	2	15 (1)	0
Maroondah, Melbourne	Metropolitan	2	11	0
St. Vincent's, Melbourne	Teaching, tertiary referral	2	8	3 (1)
England				
Royal Bournemouth	Teaching, tertiary referral	1	124 (2)	43 (3)
Southampton General	Teaching, tertiary referral	2	79 (3)	0
Scotland				
Ninewells, Dundee	Teaching, tertiary referral	2	26 (1)	6
All 14 hospitals		26	557 (14)	87 (7)

*A different surgeon operated on each of the five patients. †Surgeon also in trial at other listed hospital.

TABLE E-2 Numbers of Patients Excluded Preoperatively According to Exclusion Criteria, by Type of Total Hip Arthroplasty

	No. of Patients Excluded*	
Exclusion Criterion	Primary Total Hip Arthroplasty	Revision Total Hip Arthroplasty
Too young (<60 years old for primary procedures†; <50 years old for revision procedures)	559	20
Simultaneous bilateral total hip arthroplasty	2	0
Contralateral hip already in trial	50	6
Previous infection in hip	11	7
Diagnosis other than osteoarthritis, rheumatoid arthritis, inflammatory arthritis, or previous fracture/dislocation/surgery involving the hip	13	NA
Revision for hip instability	NA	34
Revision for infection	NA	17
Second stage of 2-stage revision or previous excision arthroplasty	NA	15
Not revision of hemiarthroplasty or conventional total hip arthroplasty	NA	5
Planned prosthesis		
Not Trilogy/CPT	455‡	NA
Not Trilogy/CPT or ZMR	NA	50
Planned approach		
Not posterior	4	NA
Not posterior, transtrochanteric, or transfemoral	NA	0
Intention to return to sports involving running or contact sports	0	0
Abnormal acetabulum	29	NA
Abnormal abductor mechanism	4	8
Likely postoperative leg-length inequality of >5 cm	1	1
Neuromuscular disease affecting hip	15	1
Primary or metastatic tumor involving index hip	10	1
Unable to provide informed consent (insufficient ability to communicate in English language/cognitive disorder/psychiatric illness)	73	15
Unable to complete follow-up (life expectancy <2 years/unable to complete English-language questionnaires/unable to return easily)	27	17
Total	1253	197

*Patients were excluded in a hierarchical manner, with only the first listed relevant exclusion criterion being recorded. NA = not applicable. †All Australian surgeons excluded patients less than sixty-five years old, one surgeon from the UK excluded patients less than seventy years old, and the other surgeons from the UK excluded patients less than sixty years old. ‡In one collaborating center, elderly, less-active patients received a cemented cup for cost reasons.

TABLE E-3 Numbers of Patients Excluded Intraoperatively According to Exclusion Criteria, by Type of Total Hip Arthroplasty

	No. of Patients Excluded*	
Exclusion Criterion	Primary Total Hip Arthroplasty	Revision Total Hip Arthroplasty
Surgical approach		
Not posterior	2	NA
Not posterior, transtrochanteric, or transfemoral	NA	0
Infection involving joint	0	0
Abnormal acetabulum	8	NA
Abnormal abductor mechanism	4	5
CPT or ZMR stem not inserted	2	11
Acetabular component not Trilogy with an outer diameter of ≥50 mm and fixed with at least one screw	8	14
Trial 28-mm liner not in place or trial stem not reduced	NA	2
Standard 28-mm or offset 36-mm liner not appropriate, or plan to use a long-neck skirted head	1	0
28 and 36-mm heads and liners for inserted shell not in operating room	9	1
Total	34	33

*Patients were excluded in a hierarchical manner, with only the first listed relevant exclusion criterion being recorded. NA = not applicable.

Appendix E-1

Prior to randomization, patients undergoing primary arthroplasty were stratified by surgeon, age (sixty to seventy-four years; seventy-five years or more), and diagnosis (previous fracture, traumatic dislocation, or surgery involving the index hip, irrespective of diagnosis; osteoarthritis without previous fracture, traumatic dislocation, or surgery; rheumatoid arthritis or inflammatory arthritis without previous fracture, traumatic dislocation, or surgery). If a patient had a diagnosis of osteoarthritis without previous fracture, traumatic dislocation, or surgery and was under seventy-five years old, he or she was also stratified by Charnley grade (A or B; C) and, if the patient was classified as Charnley A or B, he or she was further stratified by sex, resulting in eight strata per surgeon. Allocation of randomization sequences, with an allocation ratio of 1:1, was undertaken in block sizes of two, four, six, or eight on the basis of the anticipated prevalence of patients in each stratum, with larger block sizes being used for initial allocations. All ninety-eight possible allocation sequences were listed numerically, and each specific sequence was then chosen with random-number generation in Excel, without repetition, with use of the RANDBETWEEN command to choose from the required block size (block of two, sequences one to two; block of four, sequences three to eight, etc.). Each surgeon's unique randomization protocol initially allowed for forty-eight patients over the eight strata, with further allocations added subsequently if required. Sealed envelopes containing a folded piece of cardboard with either a "36" or "28" sticker were prepared in accordance with each consecutive allocation of a 36 or 28-mm articulation, over consecutive strata. Each envelope was then assigned a number with use of RANUNI, an SAS software random-number function (SAS Institute, Cary, North Carolina) programmed to generate forty-eight random numbers without replacement. The local study coordinator was notified of the next envelope number in the appropriate stratum, and that envelope was taken to the operating room.

Patients undergoing revision arthroplasty were stratified first according to the type of stem (cemented [CPT; Zimmer, Warsaw, Indiana] or uncemented [ZMR; Zimmer]) and then by whether they were undergoing revision of a hemi-arthroplasty or, if undergoing revision of a total hip arthroplasty, the number of previous revisions (first revision, second revision, or third revision [or greater]), resulting in four strata in each of the two randomization protocols, one being for revision with a CPT stem and the other for a ZMR stem. The randomization process for revision arthroplasty was the same as that described above for primary arthroplasty, except that each patient was allocated an envelope number from both the CPT and ZMR protocols, given that the decision to use a cemented or uncemented stem is occasionally made intra-operatively.

The Study Epidemiologist (O.T.H.) was responsible for every aspect of stratification and randomization. Participating surgeons and local study coordinators, who were responsible for enrolling patients, were not aware of the stratification and randomization

protocols. Local coordinators were advised by email of the allocated envelope number for each patient and ensured that this envelope was available in the operating room at the time of surgery. Envelopes allocated to patients who were excluded intraoperatively were returned unopened, to be reused when appropriate.

ANZCTR
Australian New Zealand Clinical Trials Registry

Questions in **bold** text are mandatory. **(*)**

Request Number:	364619
Current Page:	Review

Trial from ANZCTR

Trial ID	ACTRN12613000812796
Trial Status:	Registered
Date Submitted:	18/07/2013
Date Registered:	24/07/2013
	Retrospectively registered

Page 1

Public title	Outcomes 7 to 10 years following total hip replacement
Study title in 'Participant-Intervention-Comparator- Outcome (PICO)' format	Dislocation, osteolysis, polyethylene wear, acetabular component migration and other complications 7 to 10 years following randomisation to either a large 36 mm or standard 28 mm diameter metal on highly cross-linked polyethylene articulation in total hip replacement
Secondary ID [1]	Nil known
UTN	U1111-1145-7972
Trial acronym	

Page 2

Health condition(s) or problem(s) studied:	
Dislocation of total hip replacement	
Periprosthetic osteolysis	
Polyethylene wear	
Acetabular component migration	
Revision or re-operation of total hip replacement	
Condition category:	**Condition code:**
Musculoskeletal	Osteoarthritis
Musculoskeletal	Other muscular and skeletal disorders

Page 3

Descriptions of intervention(s) / exposure	The current study is a 7 to 10 year follow-up study of patients enrolled in the randomised controlled trial described in ACTRN12609000678291. Patients undergoing total hip replacement were randomised to receive either a large 36 mm articulation (intervention) or standard 28 mm articulation (control).
Intervention Code:	Treatment: Surgery
Intervention Code:	Treatment: Devices
Comparator / control treatment	Patients who, 7-10 years previously, underwent total hip replacement with a standard 28 mm articulation
Control group	Active

Page 4

Primary Outcome:	% of patients with osteolytic lesions exceeding 1 cubic centimetre, as measured by CT
Timepoint:	7-10 years following primary total hip replacement
Secondary Outcome:	Incidence of dislocation. Dislocation is measured initially through responses to a Hip Instability Questionnaire and Hospital Visit Questionnaire. Dislocations must then be confirmed radiologically.
Timepoint:	7 years following total hip replacement
Secondary Outcome:	Polyethylene wear, measured using PolyWare, a computer program which measures wear using plain radiographs
Timepoint:	7-10 years following total hip replacement

Secondary Outcome:	Acetabular component migration, measured using EBRA (Ein Bild Roentgen Analyse), a computer program which measures migration using plain radiographs
Timepoint:	7-10 years following total hip replacement
Secondary Outcome:	incidence of re-operation or revision of index total hip replacement
Timepoint:	7 years following total hip replacement
Secondary Outcome:	Other complications, such as infection, pain and loosening, as reported by patient
Timepoint:	7 years following total hip replacement

Page 5

Key inclusion criteria	Only patients involved in the RCT, ACTRN12609000678291, will be eligible for this study
Minimum age	67 Years
Maximum age	No limit
Gender	Both males and females
Healthy volunteers?	No
Key exclusion criteria	Not previously enrolled in the RCT, ACTRN12609000678291

Page 6

Study type	Interventional
Purpose of the study	Treatment
Allocation to intervention	Randomised controlled trial
Describe the procedure for enrolling a subject and allocating the treatment (allocation concealment procedures) Describe the methods used to generate the sequence in which subjects will be randomised (sequence generation)	
Masking / blinding	Open (masking not used)
Who is / are masked / blinded (choose all that apply)	
Assignment	Parallel
Other design features	
Type of endpoint (s)	Safety/efficacy
Statistical Methods/Analysis	The sample size is the number of patients still alive and able to undergo follow-up 7-10 years following enrollment in the randomised controlled trial. Confidence intervals will reflect the available sample size of each analysis.

Page 7

Phase	Not Applicable
Anticipated date of first participant enrolment	24/03/2010
Date of first participant enrolment	24/03/2010
Anticipated date last participant recruited/enrolled	15/06/2014
Actual date last participant recruited/enrolled	
Target sample size	300
Recruitment status	Recruiting

Recruitment in Australia

Recruitment state(s)	NSW,SA,VIC
Hospital:	The Royal Adelaide Hospital - Adelaide

Hospital:	Royal North Shore Hospital - St Leonards
Hospital:	St Vincent's Hospital (Melbourne) Ltd - Fitzroy
Hospital:	St John of God Hospital, Ballarat - Ballarat
Hospital:	Ballarat Health Services (Base Hospital) - Ballarat Central
Hospital:	Maroondah Hospital - Ringwood East
Hospital:	Barwon Health - Geelong Hospital campus - Geelong
Hospital:	St Andrew's Hospital Inc - Adelaide
Hospital:	Glenelg Community Hospital - Glenelg South
Hospital:	Modbury Hospital - Modbury
Hospital:	Whyalla Hospital - Whyalla

Recruitment outside Australia

Country:	United Kingdom
State/Province:	England
Country:	United Kingdom
State/Province:	Scotland

Page 8

Funding Source:	Government body
Name:	National Health Medical Research Council (NHMRC)
Address:	Level 1, 16 Marcus Clarke St Canberra ACT 2600
Country:	Australia
Funding Source:	Commercial sector/Industry
Name:	Zimmer
Address:	1800 W Center St Warsaw IN 46580
Country:	United States of America
Primary Sponsor	Individual
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Secondary Sponsor:	Individual
Name:	Dr Oksana Holubowycz
Address:	Department of Orthopaedics and Trauma, Level 4 Bice Building, Royal Adelaide Hospital, North Tce Adelaide SA 5000
Country:	Australia

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Has the study received approval from at least one Ethics Committee?	Yes
Ethics Committee name:	Royal Adelaide Hospital Research Ethics Committee
Address:	Royal Adelaide Hospital North Tce Adelaide SA 5000
Country:	Australia
Approval Date:	13/10/2009
Submitted Date:	
HREC:	RAH Protocol No. 090622
Ethics Committee name:	Northern Sydney Central Coast Health (NSCCH) Human Research Ethics Committee
Address:	Research Business Unit Level 2, Building 51, Royal North Shore Hospital Pacific Hwy St Leonards NSW 2065
Country:	Australia
Approval Date:	13/12/2010

Submitted Date:	
HREC:	1011-413M(QA)
Ethics Committee name:	Ballarat Health Services & St John of God Hospital HREC
Address:	Ballarat Health Services Drummond St N Ballarat VIC 3350
Country:	Australia
Approval Date:	25/05/2011
Submitted Date:	
HREC:	HREC/11/BHSSJOG/35
Ethics Committee name:	St Vincent's Hospital (Melbourne) Human Research Ethics Committee-D
Address:	Research Governance Unit St Vincent's Hospital Melbourne, Level 5, Aikenhead Bldg, 41 Victoria Pde Fitzroy VIC 3065
Country:	Australia
Approval Date:	23/03/2012
Submitted Date:	
HREC:	St Vincent's: HREC-A 001/12; SERP HREC: HREC/12/SVHM/22
Ethics Committee name:	Eastern Health Research and Ethics Committee
Address:	5 Arnold St Box Hill VIC 3128
Country:	Australia
Approval Date:	20/09/2012
Submitted Date:	
HREC:	HREC/12/SVHM/22 & Eastern Health Local Ref No: SERP25/1112
Ethics Committee name:	Barwon Health
Address:	Ryrie St Geelong VIC 3220
Country:	Australia
Approval Date:	03/05/2012
Submitted Date:	
HREC:	HREC/12/SVHM/22; SSA Ref: SSA/12/VICBH/13; Barwon Health Ref: 12/30
Brief summary	At 7-10 years after total hip replacement, this study will determine the incidence of bone loss around a primary total hip prosthesis with a metal head and polyethylene liner, as determined by CT, as well as the wear of the polyethylene and the movement of the acetabular cup, as determined by plain radiographs. The study will also examine the incidence of dislocation and other symptoms of hip instability, as well as the reasons for revision or re-operation. In addition, the study will show if there are any differences in these outcomes between prostheses with standard 28 mm and large 36 mm femoral heads.
Trial website	
Trial related presentations / publications	Howie DW, Holubowycz OT, Middleton R, The Large Articulation Study Group. Large femoral heads decrease the incidence of dislocation after total hip arthroplasty. A randomized controlled trial. J Bone Joint Surg Am. 2012;94:1095-102.
Public Notes	

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Appendix C: RCT Stratification

Strata	Characteristic patient
1	Age 60–74, OA, Charnley A/B (A:Uni- or B:Bilateral Hip disease without other functional impairment affecting walking), male
2	Age 60–74, OA, Charnley A/B (A:Uni- or B:Bilateral Hip disease without other functional impairment affecting walking), female
3	Age 60–74, OA, Charnley C (C: Bilateral hip disease and other joint disease or comorbidities affecting walking)
4	Age 60–74, Rheumatoid or inflammatory Arthritis
5	Age 60–74, Previous fracture, dislocation or surgery to index hip
6	Age 75+, OA
7	Age 75+, RA
8	Age 75+, previous dislocation/fracture/ Surgery to index hip

Appendix D: Statistical Modelling Tables

All analyses were completed using SAS 9.3 (SAS Institute Inc, Cary, NC, USA). The data were analysed using a linear mixed effects model, with subject treated as a random factor. FHP mm and Volumetric wear were log transformed prior to analysis in order to meet the distributional assumptions of a linear mixed effect model. The data were transformed back to the original scale prior to reporting. Thus, the reported means in Tables 2, 4, 6, 8 are geometric means and the differences of least square means reported in Tables 3 and 7 represent the ratio of two means.

FHP millimetres:

The output attached shows the effect of time and head size on FHP wear..

1. The interaction between time and head size on FHP wear was not significant (p=0.36) and this term was removed from the model. The means for each level of the interaction term are shown in Table 4.
2. Independent of head size, time was not significantly associated with FHP wear (p=0.65);
3. Independent of time, head size was significantly associated with FHP wear (p=0.0009)
4. The mean wear for Head = 36 is 1.3 times higher (95% CI: 1.11-1.52) than the mean wear for Head = 28

Table 1: Type III Effects

Effect	*NumDF*	*DenDF*	*F*	*p*
Time	4	321	0.61	0.65
HEAD	1	321	11.18	0.0009

Table 2: Least Square Means for the effect of time (independent of head size) and head size (independent of time) on FHP mm

Effect	*HEAD*	*Time*	*Estimate*	*Lower*	*Upper*
Time		03 months	0.34	0.30	0.39
Time		1 year	0.37	0.34	0.41
Time		2 years	0.39	0.34	0.44
Time		3 years	0.38	0.34	0.42
Time		5 years	0.38	0.34	0.42
HEAD	36		0.42	0.38	0.47
HEAD	28		0.33	0.29	0.36

Table 3: Difference of Least Square Means

Effect	*HEAD*	*_HEAD*	*Estimate*	*Lower*	*Upper*	*P*
HEAD	36	28	1.30	1.11	1.52	0.0009

Table 4: Least Square Means for the interaction between Time and Head size on FHP mm

Effect	*HEAD*	*Time*	*Mean*	*Lower*	*Upper*
HEAD*time	36	3 months	0.41	0.34	0.49
HEAD*time	36	1 year	0.41	0.36	0.48
HEAD*time	36	2 years	0.42	0.35	0.49
HEAD*time	36	3 years	0.45	0.39	0.53
HEAD*time	36	5 years	0.45	0.38	0.53
HEAD*time	28	3 months	0.29	0.24	0.34
HEAD*time	28	1 year	0.34	0.29	0.39
HEAD*time	28	2 years	0.37	0.31	0.43
HEAD*time	28	3 years	0.32	0.27	0.37
HEAD*time	28	5 years	0.32	0.28	0.38

Volumetric wear:

The output attached shows the effect of time and head size on FHP wear. The FHP mm data were log transformed prior to analysis in order to meet the distributional assumptions of linear models and the results were back transformed to the original scale prior to reporting. Hence, the means in Table 5 represent geometric means and the difference of least square means shown in Table 6 represents the ratio of two means.

1. The interaction between time and head size on Volumetric wear was not significant (p=0.33) and this term was removed from the model. The means for each level of the interaction term are shown in Table 8.
2. Independent of head size, time was not significantly associated with Volumetric wear (p=0.64)
3. Independent of time, head size was significantly associated with Volumetric wear (p<0.0001)
4. The mean volumetric wear for the 36 mm Head was 2.17 times higher the mean volumetric wear for the 28 mm head (95% CI: 1.85-2.53).

Table 5: Type III Effects

Effect	*NumDF*	*DenDF*	*F*	*p*
Time	4	321	0.63	0.64
HEAD	1	321	95.95	<.0001

Table 6: Least Square Means for the effect of time (independent of head size) and head size (independent of time) on volumetric wear

Effect	*HEAD*	*Time*	*Estimate*	*Lower*	*Upper*
Time		03 months	270.98	238.47	307.93
Time		1 year	293.32	265.92	323.55
Time		2 years	306.41	272.58	344.44
Time		3 years	298.93	268.14	333.25
Time		5 years	298.53	266.90	333.91
HEAD	36		431.81	387.12	481.65
HEAD	28		199.33	178.45	222.65

Table 7: Difference of Least Square Means

Effect	*HEAD*	*_HEAD*	*Estimate*	*Lower*	*Upper*	*p*
HEAD	36	28	2.17	1.85	2.53	<.0001

Table 8: Least Square Means for the interaction between Time and Head size on Volumetric wear

Effect	*HEAD*	*time*	*Mean*	*lower*	*Upper*
HEAD*time	36	3 months	416.85	350.07	496.39
HEAD*time	36	1 year	421.22	366.88	483.60
HEAD*time	36	2 years	424.64	361.03	499.47
HEAD*time	36	3 years	458.96	393.72	535.01
HEAD*time	36	5 years	454.29	386.42	534.09
HEAD*time	28	3 months	174.52	144.83	210.31
HEAD*time	28	1 year	204.36	177.77	234.92
HEAD*time	28	2 years	224.84	189.46	266.81
HEAD*time	28	3 years	195.18	167.59	227.31
HEAD*time	28	5 years	196.51	168.21	229.56

National and International Presentations

Poster presentation, Orthopaedic Research Society, New Orleans, USA, 13-17 March 2014.

Oral presentation, Australia New Zealand Orthopaedic Research Society Meeting, Adelaide, September 21st 2014

Oral presentation, Australian Orthopaedic Association Annual Scientific Meeting, Melbourne, October 2014.

Oral presentation, Australian Orthopaedic Registrars Association Annual Scientific Meeting, Melbourne, October 2014

[Allan Frederick Dwyer Prize, Runner-up for best paper at the Australian Orthopaedic Registrars Association Annual Scientific Meeting meeting]

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