FRACTURES OF THE DISTAL RADIUS:

DOES OPERATIVE TREATMENT WITH A VOLAR LOCKING PLATE IMPROVE OUTCOME?

A RANDOMISED CONTROLLED TRIAL

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Abstract

Background and aims

The advent of volar locking plates designed specifically for fractures of the distal radius has resulted in a major shift away from percutaneous fixation of these injuries. However, comparative studies have not always demonstrated better outcomes than those achieved with less invasive and potentially less expensive established techniques.

The present study was a randomized controlled trial comparing the outcome of displaced distal radius fractures when treated with a volar locking plate or closed reduction and percutaneous wire fixation, with supplemental bridging external fixation when required. The primary research objective was to ascertain whether the use of volar locking plates improves functional outcome in the short and medium term. The secondary objective was to determine, through economic evaluation, whether the use of volar locking plates for distal radius fractures is of financial benefit to the health service.

Methods

A single-centre randomized controlled trial of pragmatic design, conducted in a tertiary care institution, with accompanying economic evaluation. 130 patients with displaced distal radius

fractures were randomised to either volar locking plate (n=66) or conventional percutaneous fixation methods (n=64). Outcome assessments were conducted at 6 weeks, 12 weeks and 1 year. The primary outcome measure was the PEM score at one year. Secondary outcomes included the *Quick*DASH, PRWE, EQ-5D and SF-12 scores, range of motion, grip strength, radiographic and cost parameters.

A cost-effectiveness analysis was performed from the perspective of the NHS, and in line with NICE guidance on the methods of technology appraisal. "Bottom up" micro-costing methods were used to calculate costs for each treatment pathway, prospectively collecting information on consumables, inpatient and outpatient resource use, complications and additional procedures up to a year post surgery.

Main findings

Patients in the volar locking plate group had significantly better PEM, *Quick*DASH, PRWE scores and range of motion at 6 weeks, with no differences at 12 weeks and 1 year. Grip strength was better for the plate group at all time points. The volar locking plate was better at restoring the radiographic parameters of palmar tilt and radial height. Despite the early functional advantage, patients did not return to work sooner.

Quality of life scores were marginally, but not significantly, better for the plate group at early follow-up. Both groups returned to baseline at one year. NHS costs for the plate group were significantly higher. For an additional £713, VLP fixation offered 0.018 additional QALYs in the year post surgery. The incremental cost effectiveness ratio (ICER) for VLP fixation at NHS list price was £40,068.

Conclusion

The current study showed that use of a volar locking plate resulted in better early post-operative function. However, there was no significant difference at, or after 12 weeks. The volar locking plate achieved better radiographic reduction and measured grip strength, but this did not translate to a difference in function at 12 weeks and 1 year. The earlier recovery of function may be of advantage to some patients. However, in spite of their increasing use and popularity, volar locking plates were cost-ineffective according to NICE threshold criteria.

Declaration

This is to certify that work submitted in this thesis is the result of original research. It has been conducted substantially by me with assistance as outlined below:

- The concept of a surgical randomised controlled trial comparing volar locking plate and percutaneous fixation (K-wires with or without bridging external fixation), was conceived by Professor Tim Davis.
- The economic evaluation was conceived by myself, and designed with the support of Professor David Whynes.
- Study design, ethical application, data collection, analysis, writing and general administration were conducted primarily by myself with support from of Professors Tim Davis, Brigitte Scammell and David Whynes.
- The statistical planning and analysis were executed by me, with the exception of conversion of SF-12 data to the SF-6D index and the Monte Carlo simulation, which requires specialist software and coding skills. This was performed by Professor Whynes with software held by the school of economics.
- There was no input from a clinical trials unit, bar the independent generation and management of the

randomisation sequence, which was done by the Nottingham CTSU for a fee.

- The study was administered full time by me in the first year, including recruitment and follow-up of patients, the administrative and clinical governance of the trial. In the second year, I was joined by a part-time research assistant (LItza Vera) who assisted with patient recruitment, data collection and upkeep of the trial database.
- The extraction of radiographic parameters was done by an independent assessor (Steven Clark), who was external to the design and execution of the study.

Supervision of this thesis was undertaken by Professors Tim Davis and Brigitte Scammell.

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1.1 Distal radius fractures

1.1.1 Demographics of distal radial fractures

Fractures of the distal radius and/or ulna are the most common fractures of the upper extremity (Wulf et al., 2007). They are also the most common fracture overall under the age of 75, when they are surpassed by hip fractures in the female population (Cummings et al., 1985). It has been estimated that, at 50 years of age, a Caucasian woman in Northern Europe has a 15% lifetime risk of a distal radial fracture. For men the risk is 2% (Cummings et al., 1985).

Distal radius fractures account for more than 20% of all fractures seen in the emergency department in the United States (Grewal et al., 2005), where these numbers do not include those treated by medical practitioners in the community. One in five patients with a distal radius fracture will require a hospital admission (O'Neill et al., 2001), with the majority of those admitted undergoing some form of intervention.

Distal radial fractures are more common in females overall (Larsen and Lauritsen, 1993), though the incidence appears to be higher in males around the second and third decades (Figure 1.1). The same

study described a fall as the mechanism of injury in 73% of cases, a direct blow in 22%, crush in 2% and insufficiency in 3% of cases.

Figure 1.1 Age- and sex-specific incidence rates of distal radial fractures per 10,000 inhabitants per year in the municipality of Odense, Denmark (with 95% confidence intervals) (Larsen and Lauritsen, 1993).

In the United Kingdom, a multi-centre study of patients aged 35 and above reported an annual incidence of 9/10,000 in men and 37/10,000 in women. This computes to 58 000 women and 13 000 men per year. One in 5 men and women (19.4%) were admitted to hospital. Below the age of 50 years, 22.6% of those with fracture required admission. Above 50 years the proportion admitted rose gradually with age, from 14.5% at age 50–59 years, to 26% at age 80 years and over (O'Neill et al., 2001).

Current and past clinical data indicate a gradual increase in the incidence of distal radius fractures in recent years. The origin of this increase is unclear (Nellans et al., 2012). However, when coupled with the expanding indications for operative fixation (Mattila et al., 2011, Chung et al., 2009) and the increasing use of expensive internal fixation implants over other techniques, it is likely that the impact of these fractures on NHS resources is significant. Nevertheless, as they are not associated with the high morbidity and mortality of, for example hip fractures, distal radius fractures are often overlooked as relatively minor injuries.

1.1.2 Classification systems: what are we treating?

Distal radial fractures were originally described by Pouteau in 1783 and then Colles in 1814 (Colles, 1814, Peltier, 1984). They were then associated with universally good outcomes. Colles, Barton and Smith are well known eponyms assigned to common fractures, but eponyms give little information on stability, treatment and prognosis of a particular fracture pattern.

Burnstein defined the ideal classification system as one that is reliable and repeatable (demonstrating intra- and inter-observer agreement), has a good correlation with clinical outcome and can be used as the basis for choice of treatment (Burstein, 1993). Over the years, several classification systems have attempted to address these criteria. Early attempts were made by Watson-Jones (Watson-Jones, 1962) and then Gartland and Werley (Gartland and Werley, 1951), the first to make a distinction between treatment of extra- and intra-articular fractures. Contemporary systems include the Older (Older et al., 1965), Frykman (Frykman, 1967), Melone (Melone, 1984), Universal (Cooney, 1993) , Mayo (Cooney, 1993), Fernandez (Fernandez and Jupiter, 2002) and Comprehensive classifications (Muller, 1995). It is worth noting that, though progress has been made from early eponyms, numerous studies comparing current systems have found them falling short in terms of repeatability and reliability (Naqvi et al., 2009, Andersen et al.,

1996, Kreder et al., 1996a, Illarramendi et al., 1998, Flikkila et al., 1998).

There is as yet no universally agreed gold standard classification (Diaz-Garcia and Chung, 2012). Important points to consider when assessing and planning treatment are:

- Fracture displacement
- Articular involvement
- Associated ulnar fracture or disruption of the distal radioulnar joint
- Comminution
- Bone quality

Equally, in evaluating radiographs the following parameters are noted:

- Radial length
- Radial inclination
- Volar / palmar angulation
- Intra-articular step-off or gap

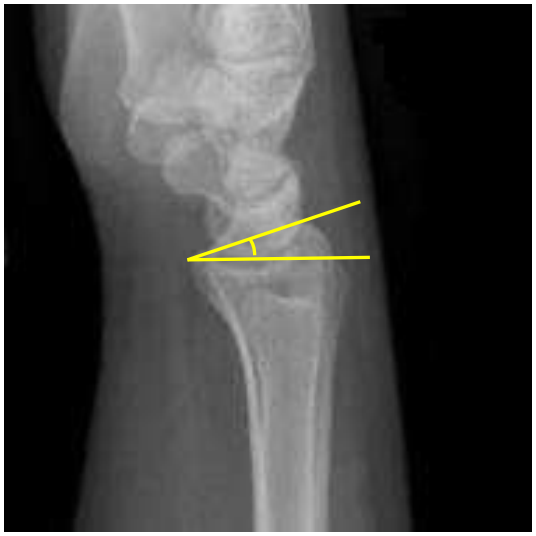
Definition of the three most commonly reported radiological parameters are reported in Table 1.1 and demonstrated in Figure 1.2.

Table 1.1 Definitions for key radiological parameters (Handoll, 2008)

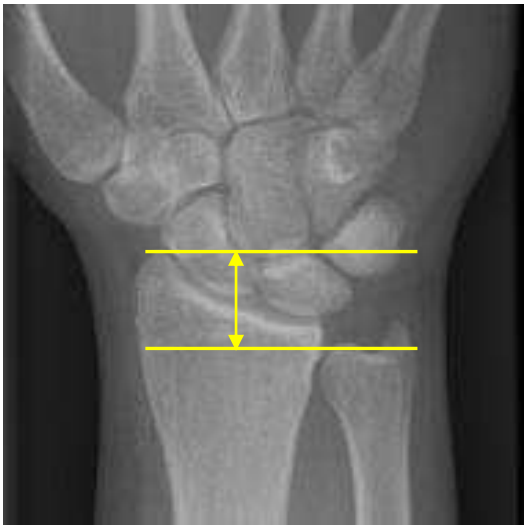
Parameter	Definition	Normal value
Dorsal angulation (dorsal or palmar or volar tilt)	Angle between a line which connects the most distal points of the dorsal and volar cortical rims of the radius and the line drawn perpendicular to the longitudinal axis of the radius. Lateral radiograph.	11 – 12 degrees where positive values indicate a palmar angulation and negative values indicate angulation dorsally beyond neutral
Radial length	Distance between a line drawn at the tip of the radial styloid process, perpendicular to the longitudinal axis of the radius and a second perpendicular line at the level of the distal articular surface of the ulnar head. PA* radiograph.	11 -12mm
Radial angle or inclination	Angle between the line drawn from the tip of the radial styloid process to the ulnar corner of the articular surface of the distal end of the radius and the line drawn perpendicular to the longitudinal axis of the radius. PA* radiograph.	22-23 degrees

*PA = Posterior to Anterior

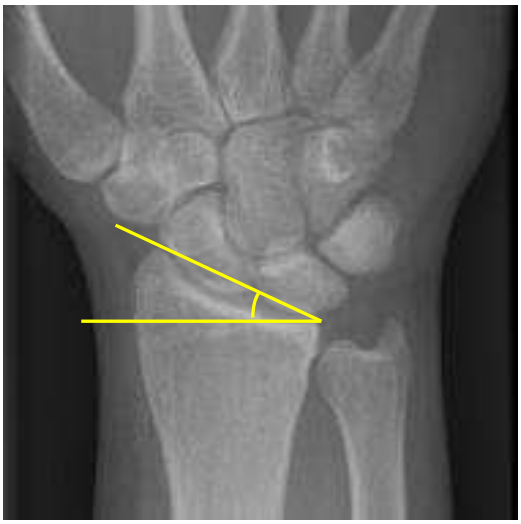
Figure 1.2 Key radiographic parameters.



A. Dorsal angulation (dorsal or palmar or volar tilt)



B. Radial length



C. Radial angle or inclination

1.1.3 The question of instability

Definitions of fracture instability can broadly be divided into two categories: those which refer to the behaviour of a fracture at presentation and those which refer to the outcome, usually radiographic, after initial treatment.

Below is an example of each:

Definition "at presentation"

"*Stable fractures are those who present in acceptable alignment and will not displace into unsatisfactory alignment if the limb is left free and mobilised… Unstable fractures are those which may unite into unacceptable alignment if treated by early mobilisation"* (Bruser and Gilbert, 1999).

Definition "after treatment"

"The definition of an unstable fracture …is usually made by observation of the behaviour of the fracture after initial treatment in a cast….Early instability was defined as a fracture that was displaced (or re-displaced following closed reduction) radiographically within two weeks after the injury. Late instability was defined as a fracture that was displaced radiographically at the time of union and had not previously demonstrated early instability". (Mackenney et al., 2006).

Such definitions are descriptive rather than predictive, and so are not very useful in early decision making.

There have been many attempts to identify factors predictive of distal radius fracture instability in order to aid management (Lafontaine et al., 1989, Abbaszadegan et al., 1989, Hove et al., 1994, Leone et al., 2004, Mackenney et al., 2006). A summary of the main representative attempts is presented in Table 1.2. The heterogeneity of study populations could, in part, explain discrepancies between reports. These studies may have identified certain risk factors for instability, but whether any of the suggested algorithms are actually predictive is open to debate, as validating studies are lacking.

Table 1.2 Summary of main studies attempting to predict distal radial fracture instability

Reference	Number of fractures	Predictors identified
(Lafontaine et al., 1989)	112	Dorsal angulation Dorsal comminution Intra-articular involvement Ulna fracture Age >60 years
(Abbaszadegan et al., 1989)	267	Radial length Age Lidström classification
(Hove et al., 1994)	645	Dorsal angulation Radial length Age Older type
(Leone et al., 2004)	71	Radial length Volar tilt Dorsal comminution Age
(Mackenney et al., 2006)	4000	Metaphyseal comminution Ulnar variance Age

The most popular criteria were devised by Lafontaine (Lafontaine et al., 1989). He examined the correlation of radiographic criteria to risk of displacement using 112 fractures. Correlation, however, does not imply causality. The popularity of Lafontaine's criteria lies in the simplicity and applicability of his conclusions. He suggested five factors that indicate instability. The presence of three or more of these factors correlated with loss of position despite cast immobilisation.

Probably the most methodologically robust attempt was made by MacKenney et al., who looked at 4000 distal radius fractures (Mackenney et al., 2006). They concluded that patient age, metaphyseal comminution and ulnar variance where the most consistent predictors of radiographic outcome. However, the predictive formulas reported in this study are mathematically complex and remain non-validated.

There is currently no predictive, easy to use, validated algorithm.

In all attempts to predict instability, it is assumed that a correlation exists between the severity of the primary displacement and an expectant loss of reduction over a given time period when treating with cast immobilisation. This does not take into account that a small percentage of fractures, which present in acceptable alignment, still displace over time (Leone et al., 2004).

It can also be argued that the above attempts are inherently flawed, as predictive factors should, by definition, be independent. Radiographic determinants of a fracture are not. For example, magnitude of radial shortening, ulnar variance and dorsal tilt are descriptors of the same fracture, when measured from a different angle/perspective. They are also not independent of the degree of fracture comminution present.

Finally, all the referenced attempts rely on the definition of what is "unacceptable alignment" in terms of radiographic measurements. This definition varies greatly and is a matter of ongoing debate as … "the anatomic results of fracture treatment have no meaning unless they are considered in light of the functional outcome" (Slutsky, 2005). The relationship between radiographic malunion and function is considered in the following section.

In conclusion, fracture instability is multi-factorial and not solely dependent on radiographic parameters. Mechanism of injury (energy), quality of the bone, condition of the soft tissues, quality of the initial reduction and plaster and even patient compliance must also be taken into account. In the absence of definitive evidence, the decision for early fixation remains dependent on both surgeon judgement and patient choice.

1.1.4 Sequelae of distal radius fractures and the malunion debate

A further source of controversy in the management of distal radius fractures has been the effect on outcome of radiographic malunion.

Jupiter and Fernandez published the criteria most commonly used to describe the presence of extra-articular malunion: less than 20° of radial inclination, dorsal angulation past neutral and shortening of 2mm or more in comparison with the contra-lateral wrist (Fernandez and Jupiter, 2002). The presence of a visible intra-articular step is also considered an indication for intervention (Lichtman et al., 2011).

A number of biomechanical studies (Short, Palmer et al. 1987; Pogue, Viegas et al. 1990; Kazuki, Kusunoki et al. 1993) have shown parameters of malunion to affect distribution of forces across the wrist. Following on from these studies, is a common yet unsubstantiated belief that anatomical reduction of deformity, especially intra-articular, is a requirement for restoration of function (Diaz-Garcia and Chung, 2012). As percutaneous methods cannot always correct or maintain radiographic parameters to perfection, this belief has fuelled the increase of open reduction and internal fixation of fractures. Attempts to correlate radiographic parameters and clinical outcome (Stewart et al., 1985, Jenkins and Mintowt-Czyz, 1988, Kopylov et al., 1993, Young et

al., 2003, Goldfarb et al., 2006) suffer from methodological shortfalls, including small study numbers and lack of validated outcome data (Karantana and Davis, 2012).

The most cited paper in the relevant literature is by Knirk and Jupiter (Knirk and Jupiter, 1986), investigating the outcome of intra-articular distal radius fractures in young adults at an average 6.7 year follow-up. The authors found that 65% of their population developed radiographic evidence of osteoarthritis and 39% had a poor or fair result. They inferred that one was the result of the other. They concluded that accurate articular restoration was the most critical factor in achieving a successful result.

Despite being very influential and widely cited (Porrino et al., 2008), this study has important limitations. Due to a lack of validated instruments at the time of publication, the investigators failed to measure patient-rated functional outcomes. Conclusions were based on the Gartland and Werley score, an non-validated, physician-rated system which has not been found to correlate with patient-rated outcomes and function (MacDermid, Richards et al. 2000). Furthermore this scoring system incorporates radiographic measurements into what should be purely a clinical score, introducing bias. In addition there were methodological issues related to the use of correlation statistics, such as the use of

Pearson's correlation for categorical and non-parametric data and the assumption of causality.

Haus and Jupiter revisited their article in 2009, citing its flaws in methodology and limitations in its interpretations (Haus and Jupiter, 2009). The authors acknowledged their absence of controls and lack of assessment of observer reliability regarding radiologic analysis of arthritis and articular incongruity. They reviewed their original radiographs, showing that a substantial number of the patients had carpal instability that likely influenced function and promoted the progression to arthritis (Diaz-Garcia and Chung, 2012).

Although radiographic measurements of radial height, angulation, dorsal tilt and step-off reflect the accuracy of surgical reduction, the link between malunion and function is still under debate and acceptable values for reduction have not been established scientifically. While many studies have investigated the relationship between extra-articular malunion and outcome after fractures of the distal radius, there is little consensus on the amount of malunion that can be tolerated without loss of function (Karantana and Davis, 2012).

Of the studies that correlate radiographic parameters and outcome using a patient-centred functional outcome measure, Anzarut and Johnson (Anzarut et al., 2004) found no correlation between dorsal

angulation and function using the SF-12 (Brazier, Roberts et al. 2002) and Disabilities of the Arm, Shoulder and Hand Questionnaire (DASH) (Hudak et al., 1996) questionnaires. Barton found no association of moderate radial shortening with the Patient Rated Wrist Evaluation score at a mean of 29 months in a group of 60 patients over 55 years of age (Barton et al., 2007). Gliatis and Plessas (Gliatis et al., 2000) also found no association with radial shortening using the Patient Evaluation Measure for Hand Surgery (Macey et al., 1995), but found dorsal angulation greater than 10° from neutral to be associated with difficulty in activities of daily living.

There is lack of consistency in the findings of those studies that do report an effect of extra-articular malunion on clinical measurements and other, non-patient centred tests of function. Villar and colleagues (Villar et al., 1987) found range of motion was influenced by dorsal tilt and shortening, and grip strength correlated with shortening. McQueen and Caspers (McQueen and Caspers, 1988) found dorsal tilt and radial inclination affected function, activities of daily living, and grip strength. In contrast, Keating and colleagues (Keating et al., 1994) found dorsal tilt, but not loss of radial inclination or shortening, affected grip strength. Trumble and colleagues (Trumble et al., 1994) found radial inclination, but neither shortening nor dorsal tilt, affected function. Beumer et al. found post-traumatic ulna positive variance (>2mm)

to be the only radiographic factor associated with a poor outcome, however they used components of the Gartland and Werley score to assess outcome (Beumer et al., 2013).

The presence of an intra-articular step also has been associated with poor outcome (Knirk and Jupiter, 1986). But even this is now a topic of debate. Intra-articular malunion may predispose to the development of radiographic arthritic changes (Baratz, Des Jardins et al. 1996; Catalano, Cole et al. 1997; Kreder, Hanel et al. 2005), but this does not seem to correlate with a functional deficit. Forward et al. (Forward et al., 2008) published a study in which 106 young adults were retrospectively reviewed at a mean of 38 years post injury. They found that, while there was radiological evidence of post-traumatic osteoarthritis after an intra-articular fracture in 68% of patients, their DASH scores were no different from population norms, and function assessed by the Patient Evaluation measure was impaired by less than 10%. No radiographic parameter of extra-articular malunion affected outcome at a very long follow-up in this study (Forward et al., 2008). Two further studies examined the wrists of young adults functionally and via computed tomography after intra-articular fractures treated via open reduction and internal fixation. Catalano et al. examined a series of 21 young adults at an average of 7.1 years and found osteoarthritis in 76 per cent of the wrists. Despite this, all patients had a good or excellent functional outcome

(Catalano et al., 1997). Goldfarb et al. reported on the functional and radiographic outcomes of 21 young adults with treated intra-articular fractures 15 years after their injury. Despite joint space narrowing and evidence of advanced arthrosis, patients maintained a high level of function (Goldfarb et al., 2006).

Finally, there has been a distinction between low demand and predominately older patients and the younger high demand population (Young and Rayan, 2000), the assumption being prolonged high demand use would lead to accelerated wear in a less than perfect joint. It has yet to be proven that degenerative changes in the younger wrist are progressive and correlate with symptoms and functional impairment.

1.1.5 Treatment options

When first described, before even the advent of X-rays, distal radial fractures were considered rather uncomplicated. Abraham Colles in his 1814 paper famously stated that "the limb will at some remote period again enjoy perfect freedom in all its motions, and be completely exempt from pain" (Colles, 1814).

The understanding of these fractures, techniques of radiographic evaluation, as well as the options for intervention have since progressed. The goals of treatment, however, have remained constant: restoration of function, cosmesis and prevention of associated complications.

As with any orthopaedic injury, decisions on management should not be based solely on radiographic appearance and fracture pattern. Factors such as handedness (dominance), patient age and bone quality, functional demands, co-morbidity and other injuries are also taken into account. Fractures of the distal radius can be associated with open wounds, tendon rupture, neurological or vascular injury and the multiply injured patient. Treatment of those injuries must coincide with fracture care (Kreder, Hanel et al. 2005).

1.1.5.1 Closed treatment

Fractures that are undisplaced or reducible and stable are generally treated non-operatively, with protection in a plaster or splint. This avoids complications inherent to surgery, but is not without risks. Immobilisation in excessive wrist flexion has been associated with stiffness, complex regional pain and carpal tunnel syndrome (Cooney, Dobyns et al. 1980; Gelberman, Szabo et al. 1984).

Patients with fractures not fulfilling the above criteria are often selected for surgery. Options include percutaneous pinning, external fixation and open reduction internal fixation with a variety of implants.

1.1.5.2 Percutaneous pinning

Percutaneous trans-osseous pinning has traditionally been an effective way of maintaining acceptable reduction with mostly

minor complications such as skin irritation, superficial pin-site infection, and transient nerve palsies (Botte et al., 1992, Diaz-Garcia et al., 2011, Subramanian et al., 2012, Singh, 2005).

It is worth noting, although percutaneous pinning has been one of the most widespread methods of fixation over many years, only 13 randomised trials evaluating percutaneous pin fixation were included in a 2007 Cochrane review, most of these small and methodologically weak (Handoll, 2007b). This paucity of randomised studies has been a common feature of the distal radius literature. The Cochrane review concluded that, for dorsally displaced fractures, percutaneous pinning, compared with plaster cast immobilisation alone, helped to maintain reduction and reduce deformity. There was limited evidence, however, that its use improved function. However, most of the trials included in the review predated the development of validated patient functional assessment instruments. There was also lack of clear indications for fixation and evidence to support any particular wiring method.

1.1.5.3 External fixation

External fixation has been used extensively in the treatment of distal radial fractures and is also a well-established method. In a separate Cochrane review, it produced good results for unstable fractures when compared to non-operative treatment: external fixation reduced re-displacement, gave improved anatomical

results when compared to casting alone and most of the excess surgically-related complications were minor (Handoll 2007).

The advantages of external fixation are ease of application, minimal surgical exposure and reduced surgical trauma (Chung et al., 2006). The disadvantages include prolonged immobilisation of the radiocarpal joint, pin-related complications (Ahlborg and Josefsson 1999; Chung, Watt et al. 2006), loss of ligamentotaxis over time (Bartosh and Saldana, 1990) and stiffness caused by excessive distraction (Kaempffe et al., 1993).

The technique of external fixation uses ligamentotaxis to indirectly reduce fracture fragments. In bridging fixation, as longitudinal traction is applied to the carpus, tension is transmitted mostly through the radioscaphocapitate and long radiolunate ligaments to restore radial length (Slutsky, 2007). Because ligaments exhibit visco-elastic properties (Woo et al., 1981), there is gradual loss of the initial distraction applied to the fracture site through relaxation (Winemaker, Chinchalkar et al. 1998). This can result in partial loss of the initial reduction achieved (Sun et al., 2001). Ligamentotaxis also requires fracture fragments to have soft tissue attachment (capsule or ligament). Central or impacted articular fragments cannot be manipulated indirectly and this has been one of the limitations of using fixators in isolation. Lastly, traction in isolation cannot correct the dorsal tilt of the distal articular fragment past neutral. This is because the stout volar radiocarpal ligaments are

shorter and pulll out to length before the thinner dorsal radiocarpal ligaments (Bartosh and Saldana, 1990). A dorsally directed vector is still necessary to restore the normal volar tilt (Slutsky, 2007). As a result, external fixation has often been supplemented with other forms of fixation, most commonly percutaneous pinning and sometimes even open direct elevation and bone grafting of a free articular segment.

External fixation was the mainstay in the management of unstable fractures until the advent of volar locking plates (Wulf et al., 2007).

1.1.5.4 Dynamic and non-bridging external fixation

External fixation can be static or dynamic, bridging or non-bridging.

Dynamic constructs with joint spanning fixators attempting to mobilise the wrist have been largely unsuccessful (Slutsky, 2007). This was due to the complex kinematics of the carpus and the inability to maintain ligamentotaxis throughout the entire range of motion (Sommerkamp, Seeman et al. 1994; Kawaguchi, Sawada et al. 1998).

Non-bridging fixators have given good results in terms of range of motion and grip strength in extra-articular fractures, even superior to those of bridging fixators in some centres (McQueen 1998). But there have been concerns regarding rates of soft tissue

complications. Their use is contra-indicated when the distal fragment is too small for pin placement. At least 1cm of intact volar cortex is required for pin purchase (Slutsky, 2007). Non-bridging fixation can be used for intra-articular fractures in conjunction with intra-focal wires, but reports are sparse and the results unconvincing (Krishnan, Chipchase et al. 1998; Mehta, Slavotinek et al. 2002; Gradl, Jupiter et al. 2005). Prerequisites are good bone density, minimal comminution and a stable distal radio-ulnar joint (Slutsky, 2007).

A 2008 Cochrane systematic review attempting a comparison of methods of external fixation in the setting of randomised controlled trials concluded that there is not enough robust evidence to determine the relative effects of different methods (Handoll, 2008).

1.1.5.5 Plating

Plates have the advantage of providing fixation without protruding wires or pins, which transfix soft tissues. They can allow earlier rehabilitation. Disadvantages include more extensive operative trauma, risk of fragment devascularisation through dissection, tendon ruptures, added scar and subsequent stiffness and, in some cases, the need for removal. New designs and operative strategies have improved the results of plate fixation.

In 1973, Mathys designed metallic T-shaped small fragment plates (Synthes®), which were proportionate to the size of the distal

radius (Freeland and Luber, 2005). These were the first generation of plates fashioned specifically for distal radial fractures. Since then, plate design has evolved toward smaller, lower profile implants. The ∏-plate and the low profile T-plate (Synthes®) were amongst early low profile designs.

Early plates were applied through a dorsal approach. Placing fixation on the dorsal aspect of a dorsally angulated fracture allows the plate to act as a buttress, providing a biomechanical advantage. It is subcutaneous and easy to access surgically. It also allows direct visualisation of the joint surface for the reduction of intra-articular fractures. Studies showed excellent results of dorsal plating in terms of fracture reduction (Ring, 1997), but were less encouraging for range of motion (Green and O'Brien, 1978). Loss of palmar flexion due to dorsal scarring was a problem (Bassett, 1987). There was also a high rate of soft tissue complications attributed to extensor tendon irritation and attrition rupture (Schnur, 2000, Kambouroglou, 1998, Lowry et al., 2000). Early removal of metalwork did not necessarily prevent these complications (Fitoussi et al., 1997). Consequently, dorsal plating became less popular and design focused on fixed-angle constructs, which would be capable of supporting the metaphyseal bone through a volar approach.

Another concept in distal radial plating is that of fragment-specific fixation. This was developed by Medoff and Kopylov in 1991 and is

designed to independently stabilise each major fracture element using an implant designed for each fragment. Increased rigidity is provided by using implants placed in orthogonal planes (Martineau et al., 2007). Fragment-specific fixation has shown good results in published series (Konrath and Bahler 2002; Schnall, Kim et al. 2006), however it requires a two-incision surgical approach. It has increased potential for complications (Konrath and Bahler, 2002). In addition, though the construct is significantly more stable in four part fractures, it showed no biomechanical advantage over wiring and external-fixation in a three part fracture model (Dodds et al., 2002). A prospective longitudinal study compared outcomes of volar plating with fragment-specific fixation. While the radiographic parameters were superior with volar locked plating and the complication rate was higher with fragment-specific fixation, there was no clinical difference (Sammer et al., 2008).

While fragment-specific fixation is advocated by some for comminuted fractures not readily amenable to a standard approach, the technique requires expertise and experience and is not widespread outside specialist centres in the UK.

1.2 The volar locking plate for distal radial fractures

1.2.1 The concept of locking fixed-angle plates

Locking plates were initially developed to treat difficult fracture patterns in the distal femur, and later in response to the challenges of fixation in osteoporotic bone of an aging population. Their application in the management of distal radius fractures was a relatively new advance.

Conventional compression plating technique, as described by Arbeitsgemeinschaft für Osteosynthesefragen (AO), requires exposure of the fracture site, anatomic reduction of fragments and internal fixation with the goal of achieving absolute stability and primary bone healing (Perren, 2001). The plate in this setting functions as a load-sharing device, in direct contact with the bone and preventing movement through compression. The periosteum is locally compressed by the plate across the fracture site (Figure 1.3).

Locking plates function as load-bearing devices. The reduction is maintained by screw placement held at a fixed angle to the plate via threaded screw heads. The plate may not need to be in direct contact with the bone, avoiding periosteal ischemia and reducing the need for soft tissue stripping (Egol et al., 2004). The plate effectively functions as an "internal" fixator (Larson and Rizzo, 2007). Locking plates, however, have increased stability when

compared with external fixators, as the working length of the screw is 10 to 15 times shorter (Egol et al., 2004).

Locking plates are considered to be more compatible with the biological healing response (Freeland and Luber, 2005). When used to bridge the fracture site, they facilitate secondary bone healing (Egol et al., 2004), allowing strains of between 2% and 10%. Primary bone healing requires absolute stability and less than 2% strain (Perren, 2001) whereas strain more than 10% leads to fibrous union or non-union (Egol et al., 2004).

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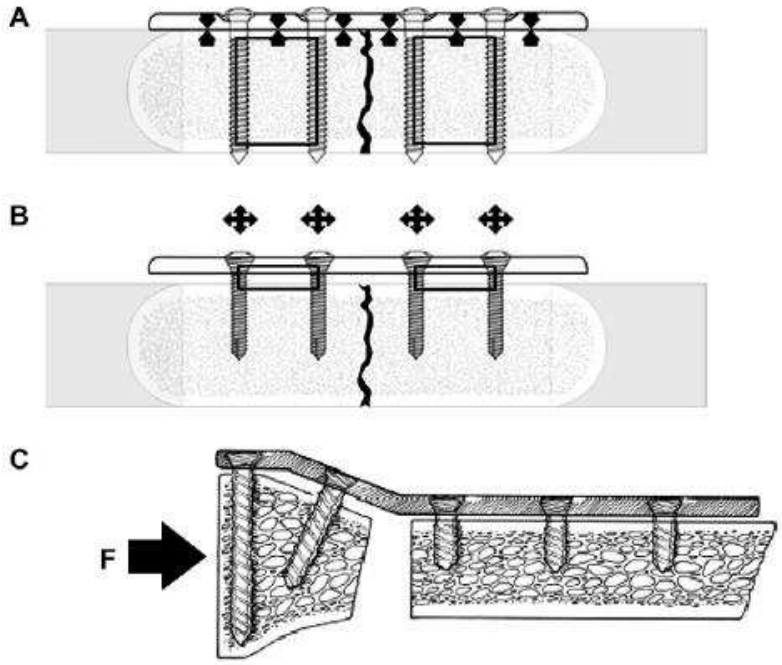
Figure 1.3 (A) Traditional compression plate. Normal force created between the plate and the screw prevents shearing of the plate-bone interface and thus stabilizes the fracture site. Soft tissues and periosteum are either stripped or compressed between the plate and cortical bone. **(B)** Locking plate. Stability is provided by threaded screw heads interfacing with the threaded holes. The plate acts as a second cortex. Soft tissues and periosteum may safely be left between the plate and bone. Unicortical fixation can obtain adequate stability. Locking screws will not compress the plate to the bone. **(C)** Even with comminution or gaps, a locking plate will maintain alignment, since screws cannot toggle in the plate. Axial forces will be transmitted along the length of the plate. (Nana et al., 2005)



1.2.2 Relevant anatomy of the distal radius

The anatomy of the distal radius lends itself to a volar approach for internal fixation. The articular surface of the radius is triangular, with the apex of the triangle at the radial styloid. It slopes in a volar and ulnar direction with a radial inclination of 23° (range 13-30°), a radial length of 12 mm (range 8-18 mm) and an average volar tilt of 12° (1-21°) (Feipel et al., 1998). The volar surface of the bone in the metaphyseal region is relatively flat in the transverse plane. The dorsal cortex is thin, which often results in comminution and subsequent dorsal tilt, while the volar cortex is thicker, stronger and typically less comminuted in dorsally angulated fractures. This makes restoration of rotational alignment easier (Orbay and Touhami, 2006) and provides an excellent surface to fix an implant.

There is also more space on the volar aspect of the wrist. Flexor tendons are located away from the surface of the bone, while extensor tendons on the dorsal surface run directly under the skin (Orbay and Touhami, 2006). There is a volar concavity in the sagittal plane making a smooth curve from proximal to distal (the pronator fossa), allowing plenty of space for an implant. The distal edge of the concave surface of the volar distal radius is marked by a transverse ridge or watershed line. Distal to this line the bone slopes dorsally and gives rise to the attachment of the volar wrist capsule and volar carpal ligaments. The plate must not project past

this line to avoid irritation of, and injury to, the flexor tendons (Imatani et al., 2012). Another theoretical advantage to volar fixation is that the blood supply to the distal fracture fragment occurs mainly through the dorsal vascular retinaculum (Sheetz, Bishop et al. 1995; Shin and Bishop 2001), which remains undisturbed in this approach.

1.2.3 Evolution of locking plate technology and its application to distal radial fractures

The success of locking plates in the distal femur came at a time when open reduction and internal fixation of complex distal radial fractures was fraught with difficulties. Gesensway (Gesensway et al., 1995) was the first to design fixed-angle dorsal plates for dorsally displaced fractures, advocating subchondral bone support. Low profile dorsal locking plates were subsequently introduced, but still characterised by the numerous complications associated with the approach (Ring 1997; Kambouroglou 1998; Lowry, Gainor et al. 2000; Schnur 2000). These complications were not seen with the approach used for buttress plating of volar fracture patterns. Noting the anatomical advantages of this surface of the distal radius, the development of a volar fixed-angle device for this was the next step (Orbay 2000; Henry, Griggs et al. 2001; Orbay, Badia et al. 2001). Further refinements on the concept came from

a better understanding of the anatomy and biomechanics of the distal radius.

Early fixed angle fixation for the wrist came in the form of non-modular, single unit tine or blade plates (Freeland and Luber, 2005). These were soon replaced by modular devices with separate, fixed-angle locking screws, initially in one and now in two transecting rows. The most recent advancement has been the introduction of multi directional fixed angle locking pegs and screws, which allow the surgeon more flexibility in positioning, but require significant expertise.

Over the years, research into the treatment of distal radial fractures has focused largely on the biomechanics of different constructs (Raia 2007). The subset of papers discussing locking plates is impressive when one considers the relative paucity of clinical literature. Taylor et al. compared volar locking plates to fragment specific fixation and found the two methods to have similar biomechanical characteristics (Taylor et al., 2006). Knox et al. more recently compared stability of a volar locking plate to percutaneous pin fixation in a cadaveric model (Knox et al., 2007). They found internal fixation to be more stable. Egol et al compared locking plates to external fixation and found plates to be more stable, as the working length of the screws is 10 to 15 times shorter than external fixator pins (Egol et al., 2004).

Osada et al. compared volar locking plates with conventional volar and dorsal plates and concluded that plates are superior in stability and ultimate strength when testing to failure under axial compression (Osada, Viegas et al. 2003; Osada, Fujita et al. 2004). A number of similar studies compared different designs of locking plate (though notably all with a single row of pegs) and found all to have comparable biomechanical characteristics (Chen, Dai et al. 2006; Liporace, Kubiak et al. 2006).

The clinical relevance of studies concentrating on the yield point of different internal fixation constructs is debatable since the forces which caused failure of the implants were many times over the estimated loads for active finger motion and thus an unlikely clinical scenario (McCall et al., 2007). The important message arising from these studies, however, is that volar fixed-angle plates for dorsally unstable radial fractures are strong enough to support the dorsal fragment and have sufficient stability to allow early active motion. This has been one of the main arguments for their exponentially increasing use.

1.2.4 Types of volar locking plates

The past decade has seen a shift away from percutaneous fixation to open reduction and internal fixation of distal; radius fractures. The only published quantitative data on recent trends of treatment originate from the United States. Chung et al. investigated the

treatment of distal radius fractures in patients over the age of 65 using Medicare data. In 2005, the last year examined, 70% of the Medicare claims were for closed treatment, with the remaining 30% representing operative management. Within the operative group, there was an increasing trend in the use of internal fixation (from 3% in 1996 to 16% in 2005), which corresponded to a decrease in the use of closed treatment (from 82% to 70%). Even though they could not specify the type of plating system used, they stipulated that the rapid increase in internal fixation from 2002 to 2005 is likely to represent fixation with the volar locking plating system (Chung et al., 2009). It is also suggested that plate fixation of distal radius fractures is even more widespread in younger populations and that the trend for volar locking plate fixation has been increasing (Koval et al., 2008).

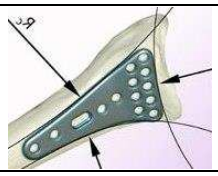
Implant manufacturers have shown great interest in developing and marketing volar locking plate technology. Many distal radius-specific designs are available (Table 1.3). The most popular implants in terms of publications in North America and the United Kingdom have been the Dorsal Volar Radial or DVR® (Biomet) and the LCP 2.4mm Distal Radius Plate (Synthes). These implants have been the subject of numerous biomechanical studies which compare plating options (Chen, Dai et al. 2006; Koh, Andersen et al. 2006; Liporace, Kubiak et al. 2006; Taylor, Parks et al. 2006; Willis, Kutsumi et al. 2006; Knox, Ambrose et al. 2007; McCall,

Conrad et al. 2007; Roberts, Grindel et al. 2007; Levin, Nelson et al. 2008). In terms of clinical data, the DVR® and the 2.4mm Synthes LCP are the most popular representatives of distal radial volar locking plates in the clinical literature. They feature in a number of longitudinal studies (Orbay and Fernandez 2002; Orbay 2004; Arora, Lutz et al. 2005; Musgrave 2005; Chung, Watt et al. 2006; Rozental and Blazar 2006; Murakami, Abe et al. 2007; Pichon and Saragaglia 2007) and comparative studies (Jubel 2005; Rein, Schikore et al. 2007; Egol, Walsh et al. 2008). In terms of volume of literature, the DVR appears to be the most widely used, especially in the more recent studies.

The DVR® was the first distal radial volar locking plate. It was developed and patented by Orbay who introduced the concept through his article in Hand Surgery entitled "The treatment of unstable distal radial fractures with volar fixation" (Orbay, 2000). He also developed the pre-defined fixed-angle intersecting proximal and distal rows of locking pegs and screws, which are designed to provide tangential support for subchondral bone. These rapidly took over as a feature of newer plate design. In 2001, Orbay followed his original paper by publishing his modification of the traditional FCR approach, which quickly became popular (Orbay et al., 2001).

It is worth mentioning the more recent emergence of multidirectional angularly stable volar locking plates for the distal radius, where the screw angle for each locking hole is selected by the surgeon, and is not dictated by the fixed-angle drill guide. There has been an increase in the availability of such implants from different manufacturers in recent years. Current versions include the Medartis Artus®, the VariAx®, the PERI-LOC◇, the Synthes Variable Angle LCP, the TriMed Volar Bearing Plate™ and the Precise SD™. These types of volar locking plates are gaining popularity amongst upper limb specialists because of their versatility. However, their use is also technically challenging and requires familiarity with the three dimensional anatomy of the distal radius, as the positioning of screws is freehand and can easily penetrate the articular surface.

Table 1.3 Examples of available distal radial volar fixed-angle and multidirectional locking plates

Company	**Plate**	
Biomet	DVR®	
Synthes	LCP Distal Radius Plates 2.4	
Stryker	VariAx®	
Smith & Nephew	PERI-LOC◇	
Wright Medical	LOCON™VLS Distal Radius System	
Medartis	APTUS®	
Small Bone Innovations	Precise SD™	
TriMed	Volar Bearing Plate™	

1.2.5 Literature on outcomes of volar locking plate fixation

Although distal radius fractures are the subject of many publications, the shortage of good quality, large prospective randomised studies is notable. In the Cochrane review on surgical management of distal radius fractures, Handoll states: "only a few and provisional conclusions relating to clinical management can be drawn from the available randomised trials, which do not provide robust nor sufficient evidence for most of the decisions necessary in the management of these fractures" (Handoll, 2003). In volar locking plate fixation, the evidence is scarcer still.

Many longitudinal studies have documented the advantages of, and shown good outcomes following volar plate fixation (Osada et al., 2008, Pichon et al., 2007, Arora et al., 2005, Orbay and Fernandez, 2002, Orbay et al., 2004, Musgrave, 2005, Musgrave and Idler, 2005, Chung et al., 2006, Rozental and Blazar, 2006, Murakami et al., 2007, Matschke et al., 2011, Jupiter and Marent-Huber, 2010). Early studies consist of case series, predominately retrospective, with small numbers and a wide case mix.

Nonetheless, comparative studies have not always shown that volar plate fixation provides better outcomes than treatment with potentially less expensive, less invasive implants such as percutaneous wires (Wright et al., 2005, Jubel, 2005, Hull et al.). It is important to note the potential for serious bias in uncontrolled

case series, retrospectively controlled studies, and prospective non-randomised controlled studies.

1.2.5.1 Randomised prospective studies

It has been over a decade since Orbay introduced the concept of the fixed angle device for volar fixation of dorsally displaced fractures of the distal radius (Orbay, 2000). The concept was rapidly embraced by the orthopaedic community. In sharp contrast was the lag in publication of randomised studies comparing this method of fixation with conventional established percutaneous techniques. When the current study started recruiting in February 2008, there were only two published prospective randomised studies examining volar locking plate fixation, and many unanswered questions (Downing and Karantana, 2008). Koshimune et al. compared the effectiveness of locking and non-locking volar plating for unstable Colles' type fractures in the elderly. No significant difference was found in radiographic parameters between the two groups or in range of motion apart from flexion, which was better by 10 º in the locking group (Koshimune, Kamano et al. 2005). Egol et al. compared volar locked plating with bridging external fixation and found no differences in outcomes after 3 months, 6 months and one year (Egol et al., 2008). Neither study provided strong evidence in favour of the new technique.

Currently there are five published randomised trials, excluding the current study, which compare volar locking plate with percutaneous fixation (Hollevoet et al., 2011, McFadyen et al., Marcheix et al., Rozental et al., 2009, Goehre et al.). This is not inclusive of trials of plating versus external fixation, which are discussed separately. A further unpublished study, presented at the American Orthopaedic Trauma Association Meeting in 2008, was included recently by its investigators in a German language systematic review (Meier et al., 2013). Details of these studies are presented in Table 1.4 and their results summarized in Table 1.5.

Table 1.4 Summary of randomised studies of volar locking plate versus percutnaeous wire fixation

Author Year	Plate	Control	Fracture Classification	No	Age	Outcomes measured	POM	Time points	Follow-up rate	Conclusions
Hollevoet 2011	LCP Distal Radius System 2.4mm (Synthes)	k-wires	Not stated	40	>50	DASH, ROM, grip, radiographic, complications	Ulnar variance	3 and >12 months (range 12-26)	85%	No difference in radiographic parameters , DASH, grip, ROM
McFayden 2011	DVR (Biomet) or LCP T-plate 3.5mm (Synthes)	k-wires	AO Type A	56	18-80	*Quick*DASH, Gartland and Werley, radiographic, complications	Not specified	3 weeks, 3 and 6 months	100%	Better *Quick*DASH at 3 and 6 months, Better radiographic parameters for plate at 6 months
Marcheix 2010	Not stated	k-wires	AO Type A2, A3, C2, C3	110	<50	DASH, Herzberg, radiographic, complications	30% loss of reduction	6, 12 and 26 weeks	94%	At 26 weeks, DASH, Herzberg scores and grip were better for plate. In both groups overall recovery was slower than has been reported in other studies.
Rozental 2009	VLS plate (Wright Medical) or DVR (Biomet)	k-wires ± bridging external fixation	AO Type A2, A3, C1, C2	45	19-79	DASH, ROM, grip and pinch, radiographic, complications	DASH	6,9,12 weeks , 1year	93%	DASH better for plate up to 12 weeks. No difference at 1 year. Better ROM and grip to 9 weeks. No radiographic differences.
Goehre 2013	LCP Distal Radius System 2.4mm (Synthes)	k-wires	AO Type A2, A3, C1	40	>65	DASH, PRWE, Castaing ROM, grip, radiographic, complications	Not stated	3, 6 12 months		No obvious differences , comparative statistics not reported
Probst (unpublished)	Aptus (Medartis)	K-wires	Not stated	103	18-80	DASH, ROM, grip, radiographic, complications	Not stated	1 year	91%	DASH better for wire group

ROM = range of motion

Table 1.5 Summary of outcome measures of randomised studies of volar locking plate versus percutnaeous wire fixation

Author Year	DASH	Other scores	Grip stength	ROM	Ulnar variance	Volar tilt	Radial inclination	Radial height	Complications (plate/wires)	Re-operation (plate/wires)
Hollevoet 2011	No difference		No difference	No difference	No difference	No difference	No difference	No difference	6/11	2/3
McFayden 2011	QuickDASH better for plate at 3 and 6 months	Gartland and Werley better for plate at 3 and 6 months				Better for plate	Better for plate	Better for plate	0/8	0/3
Marcheix 2010	DASH better for plate at 26 weeks, no difference at 12 weeks	Herzberg better for plate at 12 and 26 weeks	Better for plate at 26 weeks	No difference	No difference	No difference	Initially better for k-wires but no difference at 26 weeks	No difference	1/9	
Rozental 2009	DASH better for plate up to 12 weeks, no difference at 1 year.		Better for plate up to 9 weeks.	Better for plate up to 9 weeks.		No difference	No difference	No difference	1/6	0/1
Goehre 2013	No obvious differences , comparative statistics not done	PRWE, Castaign, same as DASH	No difference	Better flexion-extension arc for plate only at 12 months		Poorly reported, no great differences, some loss of volar tilt with k-wires at 6 months			3/3	1/0
Probst (unpublished)	DASH better for K-wire group		No difference	Better flexion-extension arc for plate		No difference	No difference	No difference	3/5	

ROM = range of motion

Difference = statistically significant difference as defined by the authors

Egol et al. compared volar plate fixation with bridging external fixation and found no differences in outcomes after 12 weeks (Egol et al., 2008). Marcheix et al. noted better functional results in the plate group when compared with k-wires at 26 weeks, but with a slower overall recovery for both treatment arms than those reported in other studies (Marcheix et al.). McFayden et al. reported better *Quick*Dash scores for the volar locking plate group at 3 and 6 months, but did not follow patients further (McFadyen et al., 2011). Hollevoet at al. found no functional or other difference between volar locking plate and percutaneous wire fixation at 3 and > 12 months (Hollevoet et al., 2011). Rozental et al. compared volar locking plate fixation to percutaneous wires ± external fixation in a well-designed trial and found better results for the plate group in the first post-operative 3 months, but no differences at 1 year (Rozental et al., 2009).

The main advantages of these studies are that they are prospective and randomised. They each have at least one functional patient-centred outcome measure (DASH or *Quick*DASH), but only one used a questionnaire which was joint specific (Goehre et al., 2013). All but one report an acceptable (>85%) rate of follow-up (Goehre et al.). There is variation in fracture patterns included. Fractures are described via the AO classification (Müller ME, 1990) in three studies, however Hollovoet and Probst give incomplete descriptions of fracture inclusion characteristics, which affects the ability to

interpret and generalise the results (Hollevoet et al., 2011, Meier et al., 2013). Awareness of the CONSORT reporting style, such as the inclusion of a participant flow diagram is evident in three studies (Rozental et al., 2009, Marcheix et al., Hollevoet et al., 2011). However, it is of great concern that all but two studies (Hollevoet et al., 2011, Rozental et al., 2009) fail to clearly state their primary outcome measure, and of those who do, only Rozental et al. chose a functional outcome measure of relevance to patients. Only three out of five studies have a follow-up of a year. None of the studies used quality-of-life or economic endpoints.

The overall conclusion of these studies, albeit their shortcomings, is that there may be a functional advantage to volar locking plate fixation, however this advantage is transient. There may be a statistical advantage in certain measurable clinical parameters, but this does not seem to correlate with the functional outcome measures used. Only one study reported evidence of improved radiographic outcomes for volar locking plate fixation (McFadyen et al., 2011), though two studies suggested that k-wire fixation may result in some collapse of the originally obtained reduction (Goehre et al., 2013, Marcheix et al., 2010). Finally, it is of interest to note that the only study reporting improved outcomes for the percutaneous fixation group remains unpublished.

1.2.5.2 External fixation versus open reduction and plate fixation

External fixation has been a long established method for treating unstable distal radial fractures. It is simple to apply with minimal surgical trauma. Advances in plate technology have made plating increasingly popular, however plating of complex fractures can be technically challenging. The debate as to which of the two methods is superior predates the advent of volar locking plate fixation and generated twelve randomised trials comparing external fixation and plating, published in the English literature since 2000 (Williksen et al., 2013, Gradl et al., 2005, Jeudy et al., 2012, Grewal et al., 2011, Wei et al., 2009, Landgren et al., 2011, Abramo et al., 2009, Xu et al., 2009, Egol et al., 2008, Kreder et al., 2005, Grewal et al., 2005, Kapoor et al., 2000).

Three separate meta-analyses of outcomes comparing external fixation and plating have been published so far in 2013 (Xie et al., 2013, Wang et al., Esposito et al.). Though showing some variation in the studies included, all concluded that internal fixation with plates provided better functional scores (DASH) and radiographic parameters of reduction and a lower incidence of minor complications, especially infection. All three meta-analyses attempted subgroup analysis of studies involving volar locking plates versus external fixation but their conclusions on this vary.

Six published randomised controlled studies compare volar locking plates with external fixation (with or without adjuvant wires) for distal radial fracture fixation (Williksen et al., 2013, Gradl et al., 2005, Jeudy et al., 2012, Grewal et al., 2011, Wei et al., 2009, Wilcke et al., 2011). These trials are not uniform in their design. Some combine volar locking and other plate fixation in the plating arm (Wei et al., 2009, Grewal et al., 2011). One utilises non-bridging external fixation (Gradl et al., 2005) as the comparator. As a result, these meta-analyses differ in their conclusions depending on the studies they included and the methods used to analyse them.

The most robust meta-analysis methodologically is by Xie et al. published in Acta Orthopeadica (Xie et al., 2013). This follows PRISMA guidelines (Moher et al., 2009). It is arguably the most inclusive of uniform studies and, unlike the other two meta-analyses discussed here, has not included data from the Rozental study. The later was effectively a study of percutaneous wiring, rather than external fixation, with only two (2/22) patients in the percutaneous fixation group requiring a supplemental external fixator (Rozental et al., 2009). Xie et al. is also the only meta-analysis which collated data for functional outcomes at separate time-points (3, 6 and 12 months), which is important given the hypothesis that plate fixation allows for earlier rehabilitation. Xie et al. concluded that patients who received internal fixation using

volar locking plates had improved functional scores (DASH) at the early stage after fixation, but that the difference diminished at one year. The techniques were associated with similar rates of complications (Xie et al., 2013).

The three most recently published trials have not yet been included in any meta-analyses, but are worthy of note. Williksen et al. originate from Norway and randomised 111 patients to external or volar locked plate fixation. They compared outcomes at 16, 26 and 52 weeks and found no differences in *Quick*DASH scores. Both treatment groups had similar high rates of complications (30% and 29%). Fifteen percent of plates had to be removed (Williksen et al., 2013). Jeudy et al. randomised 91 but analysed 75 patients (82%). Their maximum follow-up was six months and they found no differences in Patient Rated Wrist Evaluation (PRWE) at 3 and 6 months. Clinical measurements and radiographic reduction were better in the plating group throughout (Jeudy et al., 2012). It is interesting that, despite the lack of differences in functional outcome scores, both studies recommend the use of volar locking plates over external fixation. Finally, Gradl et al. compared non-bridging fixation for 102 dorsally displaced fractures (intra and extra articular) to volar locking plate fixation and found no differences, though they failed to use a patient-centred validated functional outcome measure (Gradl et al., 2005).

1.2.5.3 Ongoing studies

There are two large multicentre studies that are yet to complete or publish results.

The Wrist and Radius Injury Surgical Trial (WRIST) is a multi-centre international study, conceived in 2007 at the University of Michigan. Originally composed of 4 sites, the project has expanded over 5 years to include 21 sites in 3 countries, and is jointly funded by the National Institute of Arthritis and Musculoskeletal and Skin Diseases and the National Institute on Aging in the United States. The goal of WRIST is to randomize participants 60 years of age or older to one of three surgical procedures (percutaneous pinning, external fixation with or without pinning, and internal fixation with volar locking plates). The aim is to compare outcomes of these three surgical techniques in treating unstable distal radius fractures in the elderly. The secondary aim is to follow a cohort of elderly patients who choose not to have surgery to evaluate outcomes following treatment by closed reduction and casting alone, so participants who opted not to have surgical fixation will also be observed as a control group. The National Institute of Health (NIH) granted WRIST full approval in January 2012 and participant recruitment started in April 2012. The primary outcome measure is the Michigan Hand Outcomes questionnaire (Chung et al., 1998). Secondary outcome measures include a quality of life assessment,

functional and radiological measures. After enrolment, participants are to be observed for 2 years. This study has an estimated sample size of 623, aiming to complete data collection for the primary outcome measure in October 2014. The WRIST study group have recently published their reflections 1 year into the study, documenting their experiences of setting up and co-coordinating the trial. Recruitment has been a particular struggle with eligibility numbers lower than predicted and patients showing reluctance to be randomised. However, with the addition of study centres outside the US , the authors are confident of a successful completion of this highly ambitious study (WRIST_Study_Group, 2013, Chung and Song, 2010).

The DRAFFT study is a UK-based pragmatic, multi-centre, randomised clinical trial with parallel economic analysis. The primary aim of this trial is to determine if there is a functional difference 1 year following K-wire fixation versus locking-plate fixation for adult patients with a dorsally-displaced fracture of the distal radius. The primary outcome measure for this study is the Patient Rated Wrist Evaluation (MacDermid et al., 1998). Secondary outcome measures in this trial are: the DASH score, the EQ-5D quality of life score (EuroQol 1990), complications, radiographic parameters and resource use (Costa et al., 2011).The study recruited their target of 390 patients in trauma units across

the UK. The data collection completed in 2013 and publication of results is awaited.

1.2.6 Complications of volar locking plate fixation

Though the move from dorsal plating to the volar aspect of the wrist reduced the number of implant related complications, the use of volar locking plates is not without its own problems (Rozental and Blazar 2006; Arora, Lutz et al. 2007; Rampoldi and Marsico 2007).

A comparison of published complication rates, ranging from 4.9% to 32%, is presented in Table 1.6 (Johnson et al., 2013). There is a preponderance of tendon rupture and metalwork related complications, often leading to re-operation. Arora et al. is the most cited, reporting an overall complication rate of 27% in 114 consecutive patients treated from 2003 to 2005, in two centres with a single implant (Arora, Lutz et al. 2007). Johnson et al. is the most recent, reviewing 204 fractures in a teaching hospital from 2009 and 2010, and reporting a 7.9% complication rate and a 7.4% reoperation rate (Johnson et al., 2013).

The extensor tendons are not immune from injury with volar plates (Benson 2006) and irritation and rupture of the extensors form a significant proportion of the reported complications (20% of complications reported by Arora et al) (Arora et al., 2007). This is most likely the result of a failure to appreciate the three-

dimensional shape of the distal radius which is trapezoidal. Consequently, screws that appear to be within the bone on the lateral view may be penetrating the cortex dorsally with potential to harm the extensors (Downing and Karantana, 2008). Flexor tendons are also at risk (Al-Rashid et al., 2006) constituting 29% of complications reported by Arora et al.(Arora et al., 2007).The majority of flexor complications can be attributed to incorrect placement of the implant with failure to appreciate the 'watershed line'. However Klug et al. (Klug, 2007) also reported a case of flexor pollicis longus rupture in a patient with normal anatomy and a correctly positioned implant. It seems that in many cases tenosynovitis precedes rupture, which timely removal of the implant will reverse, so high levels of suspicion are warranted.

Because the distal radial articular surface cannot be inspected from the volar approach without disrupting the volar radio-carpal ligaments, placement of screws and pegs into the subchondral bone outside of the joint depends on a clear knowledge of the three-dimensional anatomy of the articular surface and careful intra-operative imaging using articular views. The use of fixed–angle locking plates increases the risk of inadvertent joint penetration, especially when the optimal position for subchondral bone support is just millimetres from the articular surface, such as for fractures involving the joint (Drobetz et al., 2006). When the plate is placed too distally or the fracture is not reduced

anatomically, the predetermined direction of the screws could inadvertently lead to joint penetration. Intra-articular screw placement after volar distal radius plating has been reported (Arora et al., 2007).

Sahu et al report an incidence of 10% for reoperation for metalwork complications following the use of volar locking plates for distal radius fractures in a study of 114 patients in two UK hospitals (Sahu et al., 2011). Gyuricza et al report on their experience of volar locking plate removal in 28 patients in the US (Gyuricza et al., 2011). Some, such as the inadvertent retention of angled drill guides (Bhattacharyya and Wadgaonkar, 2008) are implant specific.

Early complication can be attributed to the inevitable learning curve encountered with a new technique. However, reported rates remain high in later series. It is possible that complications of this technique remain under-reported, in part due to publication bias, and also because rates are more often than not reported from larger centres with research interests, where the more complex fractures are often addressed by surgeons with a subspecialist interest. With the number of distal radius fractures treated with a plate increasing exponentially in recent years, many are also now treated by surgeons with less experience, such as trainees. It is important to track and publish the incidence of complications from

all settings, as this will allow a realistic framework for evaluation of healthcare resources, which must be balanced against the perceived benefits of the technique.

Table 1.6 Complications in the published literature, modified from Johnson et al. (Johnson et al., 2013)

Study	N	Complication rate	CRPS	Wound	Nerve	Tendon (rupture)	Metalwork	Fracture
Johnson (2013)	206	7.9 %	1.9 %	0.5 %	0.5 %	3.4 % (1.9 %)	1.9 %	1.5 %
Phadnis (2012)	180	15 %	9 %	1.1 %	2.2 %	1.7 % (1.7 %)		
Lattmann (2011)	245	15 %	3.7 %	0.4 %	3.7 %	3.7 % (1.6 %)		0.8 %
Sahu (2011)	114	10.5 %				1.8 % (0.9 %)	10.5 %	
Arora (2007)	141	27 %	3.5 %	0	2.1 %	12 % (2.8 %)	2.1 %	2.1 %
Chung (2006)	161	4.9 %		3.1 %	0.6 %			
Rozental (2006)	41	22 %	0	2.4 %		7.3 %		9.8 %
Al-Rashid (2006)	35	8.6 %				8.6 % (8.6 %)		
Drobetz (2003)	50	32 %	6 %	4 %	2 %	16 % (14 %)	2 %	2 %

1.3 Summary

Distal radius fractures are common injuries that have a substantial impact on health care systems. There is no consensus view on their management (Karantana and Davis, 2012). This is partially because of the failure of clinical studies to demonstrate overall superiority of one treatment technique over the other (Handoll, 2007a, Handoll, 2007b, Handoll, 2003).

In the past few years, the rate of non-operative treatment of these injuries has declined, just as the rate of internal fixation, and particularly of volar locking plate fixation, has increased exponentially (Chung et al., 2009). Early studies documented a number of theoretical advantages of volar locking plate fixation (Larson and Rizzo, 2007) and many retrospective studies demonstrated good outcomes (Chung et al., 2006, Rozental and Blazar, 2006, Beaton et al., 2005, Orbay et al., 2004). However, the few published prospective randomized studies have failed to demonstrate a consistent and lasting benefit of volar plate fixation over percutaneous techniques (Hollevoet et al., 2011, McFadyen et al., 2011, Marcheix et al., 2010, Rozental et al., 2009, Goehre et al., 2013). These studies suffer from methodological shortfalls. In addition, there has been no attempt so far to establish the cost-effectiveness of volar locking plate fixation, which is considered to be a more expensive and more invasive technique (Shyamalan et al., 2009, Karantana and Davis, 2012).

1.4 Thesis Aims

The aim of this study was to perform a randomised controlled trial comparing the outcome of displaced distal radial fractures treated with a volar locking plate (the DVR®), to percutaneous fixation with wire fixation and/or supplemental stabilisation via bridging external fixator as required.

Primary objective

To determine whether the use of volar locking plates improved functional outcome, as experienced by the patient, at one year post intervention.

Secondary objectives

To ascertain whether the use of volar locking plates resulted in:

- improved measurable clinical outcomes, such as range of motion and grip strength,
- improved radiographic parameters or
- earlier return to normal activities and work

In addition, to determine the type and rate of complications associated with each fixation method.

Finally, to determine the additional costs of volar locking plate fixation compared with the potential additional benefits that this method

delivers over percutaneous fixation. This was achieved via a cost-effectiveness analysis of the interventions, from the perspective of the NHS.

Chapter 2 – Methods

2.1 Study design

This study was a single-centre, randomised controlled trial of pragmatic design with a parallel-group structure, accompanied by an economic evaluation. The conduct and reporting of the trial followed the CONSORT recommendations (Schulz et al.).

The current study was classified as a *parallel-group trial*, which is the most common RCT design. In this, patients are randomised to either the "new" or the standard treatment and followed-up to determine the effect of each in parallel groups (Grindel, 2007).

The study was designed to reflect routine surgical management of distal radius fractures in an NHS setting and so incorporates pragmatic features in the design. Exploratory trials generally measure *efficacy* – this is the benefit a treatment produces under ideal conditions, for example using carefully defined subjects in a research clinic. Pragmatic trials measure *effectiveness* – the benefit a treatment produces in routine clinical practice (Roland and Torgerson, 1998). The distinction between exploratory and pragmatic design is a continuum, not a binary system and most trials, like this one, have both exploratory and pragmatic aspects (Patsopoulos, 2011).

From an economic viewpoint, the study was primarily a cost-utility analysis of the interventions from the perspective of the NHS, modelled

around the RCT in line with NICE guidance on the methodology of technology appraisals (NICE, 2008). The preferred measure of health related utility in this approach is the EQ-5D. The NICE technology appraisal programme follows the QALY approach, so the units of effectiveness were expressed in QALYs.

A cost analysis of each treatment method was performed from the provider's perspective, the provider being the NHS. The analysis was based on a model pathway for each arm of the trial and was informed by real patient data collected, making it the most pragmatic and detailed estimation of real total cost for the described interventions available to date.

In addition to the EQ-5D, data were also collected via the SF-6D health state index (Brazier et al., 2002). The SF-6D represented a possible alternative to the EQ-5D, as utility weights generated from a UK population sample exist for both instruments. The rationale was to compare the two scores, and to explore whether the SF-6D could be a more sensitive utility measure in the setting of distal radius fracture.

Finally, the effectiveness of the interventions at reducing days off work was examined. The hypothesis was tested that volar locking plate fixation provides indirect economic benefit by returning people to work sooner. 'Time to return to driving' was also determined.

2.2 Study approval and registration

The study was approved by the regional Research Ethics Committee, the institutional Research and Development Unit and registered under Current Controlled Trials (ISRCTN27396017). The trial protocol, as approved by the local Research Ethics Committee and institutional Research and Development Unit, is presented in Chapter 6, along with evidence of board approval.

2.3 Participants and setting

All adult (skeletally mature) patients presenting to the orthopaedic trauma service were eligible for inclusion in the study. Participants had to satisfy the inclusion and exclusion criteria (Table 2.1), and be referred to the research team by their attending surgical team.

Table 2.1 Inclusion and Exclusion Criteria

Inclusion Criteria
Fractures which the referring physician considers require operative intervention
Adults (skeletally mature) with high demand requirements of their wrist in whom the radiological appearance of the bone suggests that it is robust enough to tolerate internal fixation
Fractures of the distal radius which are: • Dorsally displaced (≥20°) extra-articular fractures (with or without an undisplaced intra-articular component) with dorsal cortical comminution as seen on the lateral radiograph. • Displaced intra-articular fractures with an articular step or gap in the radio carpal joint surface.
Configuration is such that the fracture would be amenable to stabilisation via volar locking plate (not unreconstructable)
Exclusion Criteria
Patients with concomitant systemic diseases (diabetes with vascular or neurological complications, advanced cardiac, pulmonary or neurological disease)
Proximal metaphyseal fractures (more than 2.5 centimetres from the articular surface)
Open fractures
Smith's and volar Barton's configuration
Significant pre-existing radiological abnormality
Multiply injured
Bilateral injuries
Previous fractures of the distal radius of the same or contra-lateral limb
Patients who may have difficulties in adequate understanding of English
Patients who are unable to consent for themselves to treatment

The setting was an acute teaching urban NHS trust (Nottingham University Hospitals, Queen's Medical Centre Campus, Nottingham). Patients were recruited through fracture clinic and the acute orthopaedic take and treated on the orthopaedic wards and trauma theatres.

While distal radial fracture classification systems generally fall short in terms of repeatability and reliability, a description of the fracture distribution in our study was required. Fractures were classified according to the AO classification system (Müller ME, 1990). There is no gold standard classification with prognostic value. The AO system is commonly used in the literature and will allow for direct comparisons in future meta-analysis. The AO was also the classification requested by the target journal for this study.

There is no well justified precedent as to whether fracture severity should be treated as a nominal or ordinal variable. Categories of fracture classification in the study were treated as nominal.

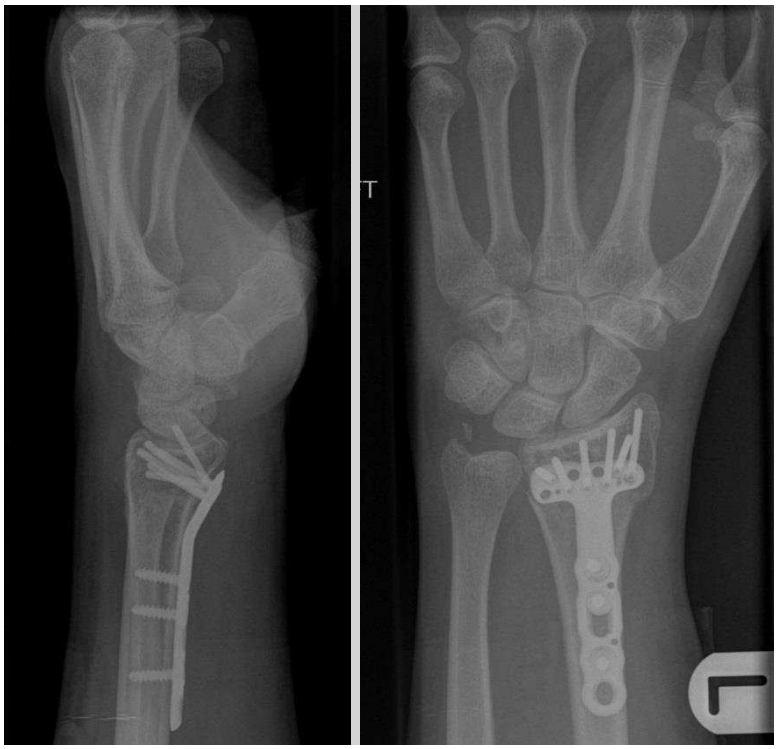
2.4 Methods: Clinical Trial

2.4.1 Clinical intervention

Open reduction and internal fixation with the volar locking plate was performed via a volar approach through the flexor carpi radialis flexor sheath, under fluoroscopic guidance. Fracture stabilisation was achieved with the use of the Distal Volar Radius (DVR®) plate (DePuy, Warsaw,

Indiana, USA), which was selected on the advice of our Hand Surgery and Trauma Units (Figure 2.1). It is in common use across the United Kingdom, widely represented in the published literature and is an implant with which our surgeons had significant prior experience. Bone grafting was not performed. The wrist was immobilised post-operatively in either a plaster splint or a removable Velcro splint. Patients were instructed in active and passive finger motion. Splints were removed 2 weeks after surgery when patients were seen by a physiotherapist and instructed on standard range-of-motion exercises.

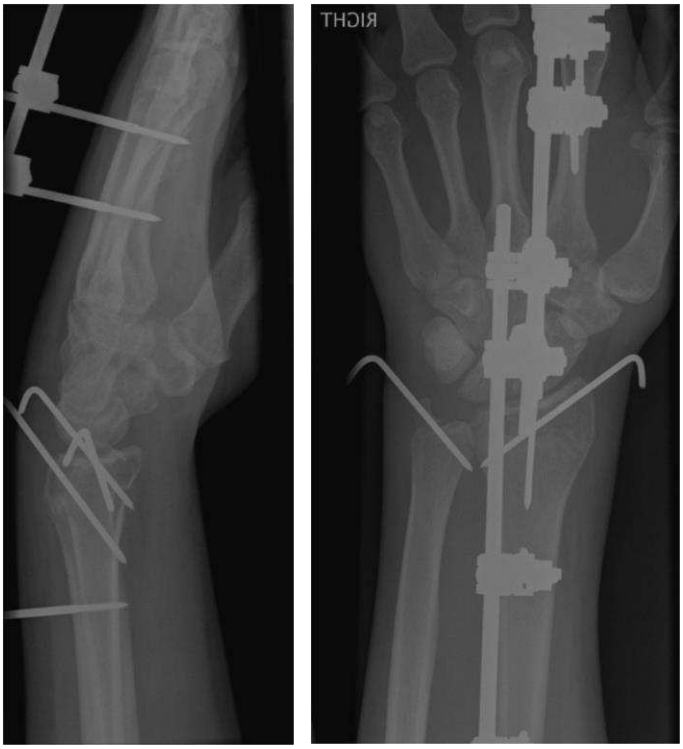
Figure 2.1 Example of a distal radius fracture treated via volar locking plate DVR® fixation



Instrumentation in the conventional arm of the trial included smooth 1.6mm Kirschner wires with a supplemental standard AO-ASIF external fixator (Synthes, Paoli, Pennsylvania, USA), if required. The surgical technique involved closed reduction with ligamentotaxis under fluoroscopic control and stabilisation with 1.6mm Kirschner wires passed through small stab incisions. Where additional stability, beyond that provided by k-wire fixation was necessary to maintain reduction, bridging external fixation was added to increase stability via ligamentotaxis (Figure 2.2). The decision was made based on the judgement of the operating surgeon at the time. Post-operatively the wrist was immobilised in a plaster splint for 6 weeks and patients were instructed in active and passive finger motion exercises. Patients with a supplemental external fixator did not require plaster cast support. The wires and external fixators were removed at 6 weeks. Patients were seen by a physiotherapist to be instructed on standard range-of-motion exercises.

All surgery was performed by one of six consultant surgeons, with a subspecialty interest in either hand and upper extremity or trauma surgery (N.D.D, D.P.F., M.H., C.G.M., A.M.T. and T.R.D).

Figure 2.2 Example of a distal radius fracture treated via Kirschner wires with a supplemental standard AO-ASIF external fixator



2.4.2 Outcome assessments

Outcome assessments were patient-reported, clinical and radiological and were performed at 6 weeks, 12 weeks and 1 year in a designated room in the Outpatient Fracture Clinic. Clinical assessments were performed by the main investigator and an independent research assistant, who had received extensive training on how to perform the range-of-motion and grip strength measurements.

2.4.2.1 Primary outcome measure

The primary endpoint of the current study was function of the limb following a surgically treated distal radius fracture. As an endpoint, function is clinically relevant and meaningful to the patient, more so than radiographic criteria of reduction or degeneration, which have not been shown to correlate with disability in the case of the radiocarpal joint (Karantana and Davis, 2012, Diaz-Garcia and Chung, 2012). Outcome assessment in the wrist has traditionally largely relied on measurements such as grip strength and range of motion. However, function of the upper limb is complex and these measurements do not always reflect the patient's experience. The importance of the patient's own assessment of outcome in this setting is now widely recognized (Amadio, 1994).

We selected the Hand Health Profile of the Patient Evaluation Measure (PEM) (Macey et al., 1995) as the primary measure of function. This is a standardized self- administered patient questionnaire proposed by the

first Derby consensus meeting for measuring outcomes of hand surgery as a practical means of recording outcomes in hand surgery (Hobby et al., 2005). It consists of ten questions relating to subjective hand function. They are rated by the patient on a scale of 1 to 7 and assess feeling, cold intolerance, pain, dexterity, movement, subjective grip strength, daily activities, work, appearance and a general assessment. The answers are expressed as a percentage disability ranging from zero to 100.

The PEM is short, uncluttered and easy to understand and score. Because of this, its use has gained ground in routine clinical practice. It has been shown to be comparable with other well established upper limb questionnaires such as the DASH and the Michigan Hand Outcome Questionnaire in terms of validity and reliability (Dias et al., 2008). It is a measure specifically assessed in the setting of distal radius fractures and shown to be valid in terms of content (Henry, 2007). Forward et al. assessed the internal consistency and validity of the PEM in the setting of medium and long term outcome (6 to 42 years) after distal radius fracture (Forward et al., 2007). We also know that, in a more general setting, the PEM has been shown to be reproducible and responsive (Sharma and Dias, 2000, Dias et al., 2001). It is also the only validated measure to have a question on cosmesis of the limb. As a final point, an additional benefit to choosing the PEM as the primary outcome measure for this study is the availability of comparable data which allowed a sample size calculation for the trial.

2.4.2.2 Secondary outcome measures

Our secondary endpoints consisted of objective measurements such as grip strength, range of motion and radiographic parameters, as well as two quality of life scores. The objective measures allowed comparisons to our functional measurements, in addition to producing data for future comparisons with other studies, which traditionally report these measures. The quality of life scores were required for determining health economic end-points. Patients were also asked at each attendance if they had returned to driving, if they drive, and to their work, if employed.

Range of motion of the wrist was assessed by recording flexion-extension and pronation-supination with a standard goniometer. Grip strength was measured with a calibrated dynamometer (Jamar®, Sammons Preston Rolyan, Bollingbrook, Illinois, USA). Values were compared with those of the contra lateral limb for each individual and expressed as the percentage values.

As part of what were defined as secondary endpoints in this trial, we also collected data in the form of the QuickDASH (Beaton et al., 2005) and Patient Rated Wrist Evaluation Questionnaires (PRWE) (MacDermid et al., 2003).

The *Quick*DASH is a shortened version of the Disability of the Arm, Shoulder and Hand (DASH) Outcome Measure. In a 2006 study, Gummesson et al determined that the QuickDASH can be used in place

of the DASH without sacrificing any precision for upper extremity disorders (Gummesson et al., 2006). It represents a regional evaluation of the whole upper limb and is not specific to the wrist, however has been widely used in the distal radius fracture literature. The DASH (Goehre et al., 2013, Hollevoet et al., 2011, Egol et al., 2008, Probst, 2008, Rozental et al., 2009, Marcheix et al., 2010, McFadyen et al., 2011) and *Quick*DASH (McFadyen et al., 2011) have been used in many RCTs of volar locking plates versus conventional fixation, allowing for a comparison of results across studies.

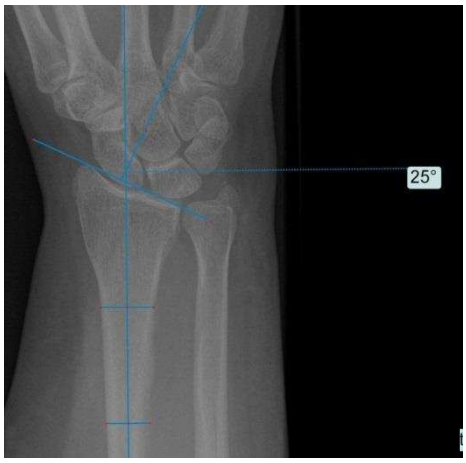
The PRWE was originally described by MacDermid et al. in 1998 (MacDermid et al., 1998). This score was used as it is specific for the outcome of one joint, the wrist. It is a 15-item questionnaire which allows patients to rate their levels of wrist pain and disability from 0 to 10 and a total score is computed on a scale of 100 (0 = no disability). Macdermid et al. (MacDermid et al., 2000) compared the responsiveness of the DASH, PRWE and SF-36 scores in evaluating recovery after distal radius fractures. The PRWE score was the most responsive of the three in this particular group of patients. There are however some concerns about the correlation of the score with objective clinical variables (Karnezis and Fragkiadakis, 2002).

Radiographic assessment included a standardised series comprising of dorsi-palmar, 45 degree pronated dorsi-palmar oblique and lateral views of the wrist, taken at presentation and at 6 weeks and 1 year

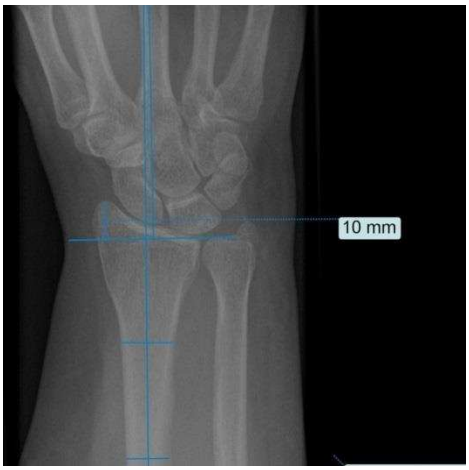
post injury. The contra lateral wrist was X-rayed at 6 weeks and acted as a standard for the assessment of palmar tilt, radial height, radial inclination and the presence of an intra-articular step or gap of 2mm or more. All radiographic measurements were performed by an independent assessor (S.C.), blinded to patient outcome. Measurement of radiographic angles was made using TraumaCad® software (Orthocrat Ltd, Israel), which was available as part of our Trust's software package. This allows users to perform measurements of digital images on-screen, using angle and length measurement tools. The software enables the import and export of all picture archiving communication system (PACS) files. An example of radiographic parameters measured using this system is presented in Figure 2.3.

Figure 2.3 Example of measurement of radiographic parameters using electronic measurement tools

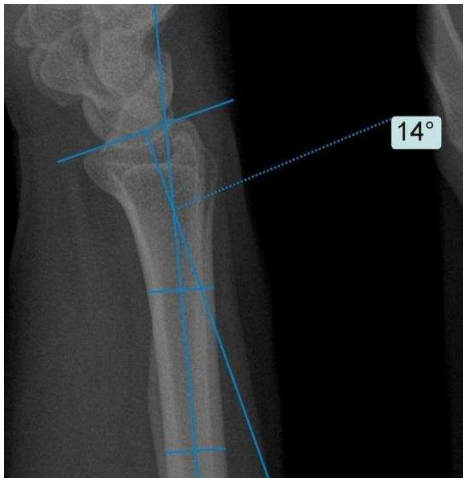
Radial inclination



Radial height



Palmar inclination



Reliability of the radiographic measurements was validated by a second observer (N.D.D). A sample, consisting of 45 anonymised and blinded radiographs, was selected at random from the trial x-ray database. Measurements of radial height, radial inclination and palmar inclination were made independently by the main independent assessor (S.C.) and a second observer (N.D.D), using the same approach and software. The second observer measurements were performed to assess inter-observer variation and to give an estimate of the accuracy of radiographic assessments. Data was analysed via the Bland-Altman method for comparing measurements of continuous variables using limits of agreement (Altman, 1999, Bland and Altman, 1986).

The number of complications was tabulated. Patients requiring additional interventions were identified and recorded.

2.4.3 Addressing sources of bias

In clinical research, bias is defined as systematic distortion of the estimated intervention effect away from the "truth", caused by inadequacies in the design, conduct or analysis of a trial (Altman et al., 2001). It is impossible to completely eliminate bias. However, bias can be reduced through careful study design.

2.4.3.1 Selection bias

Wide, pragmatic inclusion criteria were employed in an attempt to capture a representative study population.

There will always be an element of selection bias in enrolment of any study, even with adherence to carefully designed inclusion and exclusion criteria. First of all, this is because potential participants must somehow be identified and referred to the trial and this introduces bias from their original treating team. Second, because participation in any study is voluntary and this introduces an element of bias due to the personal beliefs of the potential recruit.

The personal belief of the referring surgeon that a certain fracture should be fixed by a certain method could prohibit referral to the trial. This is enhanced by the rules of research governance, which prohibit the study team from directly approaching suitable recruits. Participants must first be introduced to the investigators by their treating physician. In addition, non-trial personnel could express a biased personal opinion

to a potential patient, who subsequently refuses to enter the trial believing that they are likely not to get the "best" treatment.

In order to minimise this, we:

(1) disseminated detailed information of the study to all orthopaedic teams treating acute fractures prior to the onset;

(2) made every opportunity to discuss the published literature;

(3) obtained each team's opinion on study design.

We achieved the cooperation of the entire Orthopaedic unit at our hospital, with all consultants agreeing to refer their patients to the trial if they satisfied the inclusion criteria. In addition, we encouraged discussion with the junior staff as to the nature of the study question and the difference between personal preference and good quality published evidence.

2.4.3.2 Observer or ascertainment bias

Ascertainment bias is the systematic distortion of the results of a trial, which occurs when the person assessing outcome (whether an investigator or the participant) knows the group assignment (Altman et al., 2001). The best way of dealing with this is *blinding or masking.* This is the practice of keeping the trial participants, care providers, data collectors and sometimes those that analyze the data unaware of treatment allocation.

Blinding was not considered realistic due to the nature of the surgical procedures, differing hardware and their distinctive scars which are difficult to conceal during clinical examination of the area. Radiographic blinding was not feasible due to the presence of different hardware in the two arms of the study. Also, the principal investigator was at times both collecting and managing the data.

The choice of primary outcome measure reduced ascertainment bias. The Patient Evaluation Measure (PEM) (Macey et al., 1995) is a patient-centred validated functional assessment questionnaire, which is completed at each time point solely by the patient, prior to the encounter at which clinical data is collected, and with no input from study personnel.

2.4.4 Analysis

2.4.4.1 Intention-to-treat analysis

Analysis was intention-to-treat (ITT). This is a strategy in which all participants are analysed in the group to which they were originally assigned, regardless of whether they completed the intervention given to that group (Altman et al., 2001). It maintains the benefits of randomisation and prevents bias caused by non-adherence to protocol whether this is due to the patients or their clinicians. Intention-to-treat is the optimal way of analysing a pragmatic study. The benefit is that most types of deviation from protocol would continue to occur in routine

clinical practice and so should be included in the estimated benefit of a change in treatment policy (Hollis and Campbell, 1999)

However, intention-to-treat analysis assumes an equal "risk" of non-compliance in all treatment groups. If there is an imbalance in drop outs, this must be taken into account when interpreting results. It is noted in the literature that rarely, in 5% to 10% of cases, acceptable reduction of distal radius fractures cannot be achieved by closed reduction and percutaneous techniques and the surgeon must consider converting to open reduction and internal fixation (Kreder, Hanel et al. 2005; Wulf, Ackerman et al. 2007).

It was anticipated that, in a small number of cases, a trial participant could be randomised to percutaneous treatment but converted intra-operatively to volar locking plate fixation. Therefore, non-compliance (defined as the surgeon's intra-operative decision to convert from one method of fixation to the other) carried an inherent risk of imbalance which was not due to failure of randomisation, but due to unpredictably difficult fracture configurations. In the present study, per protocol (PP) analysis was planned, in addition to intention to treat analysis. This was in order to address the risk of potential imbalance between intention-to-treat randomisation arms, as a result of the number of cases of non-compliance being considerable. The combined results were interpreted with the aid of the grid demonstrated in Table 2.2.

Table 2.2 Interpretation of combined results from ITT and PP analysis. Derived from the interpretation of Chapter 22 of Wang's textbook entitled "A Practical Guide to Design, Analysis and Reporting of Clinical Trials"(Grindel, 2007)

Per Protocol (PP)	**Intention-to-treat (ITT)**	**Interpretation**
-	-	Non-compliant cases equally distributed or minimal
-	+	Presence of unidentified / unadjusted confounder
+	-	High crossover* in one direction
++	+	High rates of non-compliance

Key

"**+**" indicates the presence of a statistically significant difference in outcome between the two treatment groups.

"**++**" indicates a higher level of statistical significance. The

"–" indicates no statistically significant difference in outcome between treatment groups

"*" crossover is the rate of participants switching treatments.

2.4.4.2 Addressing sources of confounding

In the context of a surgical trial, a confounder is best described as a variable which we would expect to have a significant impact on outcome, but is not the result of allocation. The most effective way to prevent confounding is through randomisation. Randomisation of over 100 participants in a trial is usually able to balance the main confounders in a study.

Though statistical tests comparing baseline group characteristics are often reported in published trials, this is not the correct way to address potential imbalance. The 2010 CONSORT statement recommends avoiding such blanket comparisons, stating that such hypothesis testing is superfluous and can mislead investigators and their readers. Significance tests assess the probability that observed baseline differences could have occurred by chance. However, providing randomisation was adhered to, any potential differences are, by definition, caused by chance (Schulz et al., 2010).

The landmark paper on this topic is by Altman (Altman, 1985) which states:

"If significance tests are inappropriate for comparing baseline variables in randomised clinical trials, how should the comparability of the treatment groups be established? An initial comparison may be made non-statistically using a combination of clinical knowledge and common sense. In any trial most variables examined will either differ only very

slightly between groups or will be felt, on the basis of previous knowledge, to have no direct bearing upon the outcome of the trial, be it survival, cure, or whatever".

The alternative approach is to compare the results from analyses of the trial both with and without allowance being made for the variable(s) in question. If the two results are essentially the same, this indicates that the simple comparison of treatment groups is reasonable. If they differ then the imbalance was important and adjustment beneficial.

CONSORT recommends presenting baseline data in a table, with mean and standard deviation given for continuous variables, and proportions for categorical variables (Schulz et al., 2010).

Potential confounders in this study, as well as the strategy that can be employed to address each, if not balanced by randomisation, are shown in Table 2.3.

Table 2.3 Potential confounders in our study and the strategy which can be employed to address each, if not balanced by randomisation

Confounding factor	Strategy
Fracture classification	Nominal logistic regression
Employment category	
Age	Linear regression
Sex	Binary logistic regression
Hand Dominance	

Linear regression to control for age can only be used if values are normally distributed. If they are not, log transformation will be attempted to normalize the data. If the data remains non-parametric after transformation, then the option of non-parametric regression will be explored. The main disadvantage of non-parametric regression is that it is computationally intensive and requires a large number of observations, which surgical trials rarely achieve.

2.4.4.3 Dealing with missing data

There will inevitably be participants who are either lost to follow-up or miss a particular data entry point in a study. Dealing with missing data is a much more complex issue than non-compliance with protocol. No golden standard method exists and strategies vary from simply analysing only the completely observed data (complete-case analysis) to using complex statistics or ad hoc methods to arbitrarily replace missing data (multiple imputation).

Statistical software packages also deal with missing data in different ways. STATA uses "listwise deletion" by default. Listwise deletion means that only cases with available data on each variable are analysed and is another term for complete-case analysis. The main advantages of this approach are its simplicity and that it allows comparability across analyses. The disadvantages are that it may reduce statistical power (because it lowers n) and it does not use all information.

We examined the number of data entry points in the study. All missing data was tagged at the point of insertion in the data base. This allowed us to readily differentiate data that was "missing" rather than "not applicable" to a particular patient. We also examined absence from follow-up at each time point in the study.

Given the resources available, the decision was made that, unless the overall data missing at any time point in the study exceeded 10% of total values, a complete-case analysis would be performed. The sample

size was adjusted upwards accordingly to allow for potential loss to follow-up and improve power. If missing data was to exceed 10%, then specialist input would be sought for multiple imputation analysis.

If imputation analysis were required, analysis would be as follows:

1. First analyse only the completely observed data.
2. Then perform multiple imputation on the assumption that missing data is MAR (missing at random).
3. If the above two analyses give similar results (and there is no reason to believe that the missing values are not MAR) then it is reasonable to assume that these missing observations do not alter the conclusions of the trial.
4. If results of two analyses differ, then sensitivity analysis should be undertaken.

2.4.4.4 Randomisation

Randomisation is the process of assigning participants to groups such that each participant has a known probability of receiving each treatment before it is assigned, but the actual treatment is determined by a chance process and cannot be predicted (Altman et al., 2001). It should be determined by someone independent to the trial, ideally a statistician, using a computer-generated random sequence or random-number tables.

The size of the current study meant that simple randomisation was likely to produce imbalances in numbers between the two treatment groups. We therefore opted for restricted randomisation in the form of random permuted blocks of randomly varying size. This would ensure a good balance of numbers, even if the trial was to be stopped early or went on to recruit larger numbers than first anticipated. Furthermore, it made it impossible for anyone in the team to predict what treatment was coming up next in any particular block.

We also had to deal with the "surgical" aspect of our study. It is a known fact that varying levels of experience of a surgeon, as well as conscious or unconscious preference of a particular technique, are sources of bias in surgical RCTs (Lilford, 2004, McCulloch et al., 2002). It is not possible to completely eliminate this in a surgical trial. The bias is larger with smaller numbers of surgeons in a study, even more so in a single-surgeon trial. Conversely, the more surgeons involved, the larger the likely variation in technique.

We decided to address this, as well as practical issues to do with resources, through the inclusion of six surgeons, experienced in both treatment techniques. In order to ensure each individual performed a balanced number of both treatment methods (thus addressing surgeon bias) each participating surgeon had their own series. The randomisation is "stratified by surgeon".

To ensure indisputable pre-allocation concealment and avoid selection bias, we use a computer generated random code, created by the Nottingham Clinical Trials Support Unit (CTSU) and held on a secure server. Access to the sequence was confined to the CTSU Data Manager. The trial coordinator accessed the treatment allocation for each participant by means of a remote, internet-based randomisation system, which was developed and maintained by the CTSU.

2.4.4.5 Sample size calculation

In order to determine appropriate sample size the following must be considered:

- Whether treatment groups are to be of equal size
- The primary outcome measure and its form
- What are the values of the primary endpoint in previous studies of standard treatment?
- The standard deviation (SD) of these measurements.
- How large a difference in treatment outcome is considered clinically important?
- What is the acceptable Type I error rate (a)?
- What is the acceptable Type II error rate (β)?
- The rate of potential drop outs

The above information is entered into a mathematical equation or statistical software.

One of the most difficult tasks in the current study was identifying published outcome data for the primary outcome measure (PEM) at one year. Given that studies of distal radius fractures have only recently employed validated functional outcome measures such as the PEM or DASH, and these are almost exclusively studies of plates, such data for the conventional treatment of wires +/- ex-fix was not readily available at the onset of the current study in 2008. In addition, many studies failed to give the standard deviation or standard error of their means and had variable follow-up lengths.

Data was identified from a historical cohort of distal radial fractures examined in 2001, on average 3-9 years following distal radial fracture. This cohort received what was considered standard treatment (including manipulation, wiring, external fixator and plating) between 1989 and 1996. The cohort originated from the same geographic area as the current study sample (Forward et al., 2007).

These data were selected as a reference for our sample size calculation, as the patient group was deemed the most relevant and comparable. In terms of management, patients had what was considered conventional treatment of their wrist fracture at the time. They were of similar level of function as the patients we aimed to recruit. In addition, they were treated in the same institution, in some cases by the same surgical teams.

The PEM does not have a published minimally clinical important difference (MCID). An arbitrary 10% difference was used. This represents a minimum one point drop in score in each of the 10 items comprising the score.

It is also important to consider that the number of patients required for a clinical trial (sample size) refers to the number of patients who finish a trial rather than the number that enter. The expected drop out rate was considered at the recruitment stage. A frequently quoted estimate is 10%, but in some studies of certain conditions this can be higher. One would expect a higher dropout rate when treating trauma, such as distal radius fracture, which is acute and the result of opportunistic exposure. Patients typically fail to return for long term follow-up if they have good results and consider themselves "cured". A proportion of patients may be young, otherwise fit and more likely to be geographically mobile, making them difficult to track. We therefore assumed a maximum loss to follow-up of 20%, adjusting our sample size upwards accordingly.

The size of a trial is determined by the power needed to detect a difference in the primary endpoint. Calculating sample size on the basis of a single primary outcome measure is a well-established method which features in most surgical RCT publications. However, it does not guarantee that secondary outcome measures will not be underpowered, nor does it take into account loss of significance due to multiple testing.

The Bonferroni correction (Altman, 1999) was used to adjust the study sample size for multiple comparisons. This involved dividing the alpha level by the number of tested hypotheses. This gave an adjusted alpha value of 0.01 for the five main outcome categories: function, grip strength, range of movement, quality of life and quality of radiographic reduction.

STATA® 10.0 software and the "sampsi" command were used for a two sample test. Power (β) was set at 80%, as this is the level recommended by Cohen and it is the most common for non-critical studies (Cohen, 1988). Higher power of 90% is used predominately for critical studies with life-or-death outcomes. We set our alpha at an original 0.05, which was dropped to 0.01 following Bonferroni correction.

A sample size calculation for a two-sample comparison of the means was performed, based on the following:

Primary outcome measure: *PEM*

Test Ho: *m1 = m2, where m1 is the mean in population 1 and m2 is the mean in population 2*

Assumptions:

Minimum clinically important difference in PEM score: 10%

Standard deviation is the same in both groups

Alpha = 0.01 (two-sided)

Power = 0.8000

m1 = 21

m2 =31

sd1 = 15

sd2 = 15

n2/n1 = 1.00

Estimated required sample sizes

n1 = 53

n2 = 53

Assuming a maximum loss to follow-up of 20% (22 patients), the total sample size to reach significance in this study would be 106+22= 128 patients.

2.4.4.6 Statistical methods

STATA® 10.0 software was used. The characteristics of the groups were compared with use of the Pearson chi-square test for categorical variables and the Student t-test for continuous variables. For non-parametric data we used the Mann-Whitney test.

It is now recognised that post-hoc subgroup analysis in the form of significance testing should not be reported (Oxman and Guyatt, 1992, Pocock et al., 1987, Rothwell, 2005b). This is because rates of false positive and false negative results are extremely high. The accepted analysis is not the significance of the treatment effect in one group or

the other, but whether the effect differed significantly between the subgroups – the test of subgroup-treatment effect interaction (Rothwell, 2005b). This test can be applied to continuous data, such as age. In the current study, to answer the question whether the treatments behaved differently in patients of differing age, a two-way ANOVA test with effect modification was used in order to examine treatment interaction effect for age.

The overall level of significance for the study was set at $p<0.01$.

2.5 Methods: Economic Evaluation

2.5.1 Derivation of costs

To calculate the cost of interventions comprising the two arms of the randomised controlled trial, resource use was modelled and translated into monetary values using unit resource costs. All costs were expressed in UK pounds sterling (£). The base year for all cost figures was 2011/12.

In economic evaluation, the choice of perspective influences the range of costs to be identified, measured and valued (Brazier, 2007). The cost-utility study was performed from the perspective of the NHS. Therefore, direct healthcare costs were identified and estimated including implants, consumables, labour costs, investigations, pharmacy supplies and hospital resources. The sources of unit cost figures used to convert resource usage into costs are detailed in Table 2.4.

No protocol driven costs were incurred during the RCT. None of the costs incurred in the randomised control trial were associated with the trial *per se* rather than the costs of providing healthcare.

This analysis considered the trial period of 12 months follow-up. As the analysis used a one year time horizon over which cost and benefits were incurred, discounting was not required (Drummond, 2005).

According to NICE guidance, value added tax (VAT) should be excluded from all economic evaluations, but included in budget impact calculation when the resources in question all liable for this tax (NICE, 2008). Our costs are therefore exclusive of VAT.

Economists have generally advocated the mean average as the theoretically correct way to aggregate individual values, irrespective of the nature of the distribution. This is because the mean reflects people's intensity of preference and addresses whether the total benefit of those who gain are greater than the total benefits of those who lose form a policy change (Brazier, 2007). However, if you look at the issue from the public policy point of view, the median value seems to be a fairer choice as the median treats each person's valuation as equal in the voting context.

When calculating cost in a randomised controlled trial, the distribution is rarely normal. This is because:

- cost cannot be negative

- there is often a fraction of study participants that require more medical services than the norm
- there is usually a small number of participants among whom a catastrophic event occurs that is several standard deviations above the mean

As a result, cost distribution is usually right skewed with a long right tail, with a median smaller than the arithmetic mean. Though the median may be useful in describing the data, it does not provide information about the total cost that will be incurred by treating all patients, nor the amount saved by treating with one therapy versus another. For this reason Glick concludes that the arithmetic mean and the difference in the means of the treatments are the measures we should use for cost-effectiveness analysis in clinical trials (Glick, 2007). NICE guidelines to the methods of technology appraisals also state that, for continuous variables, mean (rather than median) values are used in the analysis (NICE, 2008).

Table 2.4 Cost data sources

Cost categories	Source
Implants and hardware	Manufacturer public list
Consumables (dressings, casting materials, splints and slings)	NHS Supply Chain National Catalogue 2011
Pharmacy items and medication	British National Formulary 2011
NHS staff costs	Unit Costs of Health and Social Care 2011
Local resource hospital costs (theatre, ward cost and investigations)	Finance Department Nottingham University Hospitals NHS Trust (NUH)
GP practice and A&E attendance costs	Unit Costs of Health and Social Care 2011
Productivity costs	Office of National Statistics (ONS) Bulletin Annual Survey of Hours and Earnings 2011
HRG4 Tariffs	NHS Payment by Results 2010-2011 National Tariff Information

2.5.1.1 Consumables

According to NICE guidance (NICE, 2008), costs should relate to resources that are under the control of the NHS and these resources should be valued using prices relevant to the NHS. When the acquisition price paid for a resource differs from the public list price (for example, pharmaceuticals and medical devices sold at reduced prices to NHS institutions), the public list price should be used. The exception to this are prices of consumables supplied via the NHS Purchasing and Supply Agency (PASA), in which case the reduced prices are transparent and can be consistently available across the NHS. In the absence of a published list price and price agreed by a national institution, the price submitted by the manufacturer may be used, provided that it is nationally and publicly available.

In the current study, the cost of consumables was calculated based on prices supplied by the NHS Purchasing and Supply Agency (PASA) (Appendix 6.5) and public list price for those items not available in the NHS supply chain catalogue. For the price of the implants, we contacted the manufacturers directly and were provided with the list price, excluding all hospital discounts. Net prices of drugs were sourced from the 2011 BNF (BNF, 2011) (Appendix 6.6).

Biomet UK Healthcare Limited, the company which at the time of the trial marketed and supplied the DVR® implant, provided legal permission for use of the price data provided by them for economic evaluation

purposes, provided that the following footnote was expressly contained in the evaluation paper as follows: “The prices quoted for the Biomet DVR trauma plate and accessories are an indicative price only and may vary depending on a hospital’s usage.” In addition, the principal investigator would have to provide Biomet with a copy of the evaluation paper after submission, to show compliance with this condition. Synthes, the company which markets the K-wire and external fixator implants, provided implant cost data without requiring a signed permission letter.

When undertaking economic evaluation, it is important to ensure transparency from the onset and the agreement of all parties concerned. This is especially important when aspects of pricing may be confidential and could vary between institutions. Lack of relevant permissions could preclude publication.

2.5.1.2 Costing of re-usable external fixator components

Costing of reusable components, such as the external fixator clamps and bars, is controversial. These devices are very expensive. The rationale used in this study is outlined below.

In the United States, external fixators are sold as single use devices. This creates liability issues with re-use. If not licensed as a re-usable component, the liability for failure of such a device lies with the doctor who applied it. As the use of external fixators in trauma grew, hospitals sought to rationalise their costs and a profitable new industry of

reprocessing components flourished. The Food and Drug Administration Agency responded by introducing regulations for third party processors and hospitals (Sikka et al., 2005). They defined the term "reprocessed single use device" as "an original device that has been previously used on a patient and has been subjected to additional reprocessing and manufacturing for the purpose of an additional single use on a patient" (2006). The regulations required re-processors to comply with a set of approved processes for the non-implantable components known as the 510(k) pathway, and an industry worth 1.4 billion dollars in 2003 (Sung et al., 2008) with huge potential for growth was born. Such refurbishment programmes can, on average, reduce the cost of non-implantable external fixator devices by 25% (Dirschl and Smith, 1998, Horwitz et al., 2007, Dirschl, 2006).

In the UK, many companies also market non implantable external-fixator and circular frame components as single use. This would make the use of these devices in the NHS impracticable. Hospitals and departments can - and do- get around this problem through local risk assessment processes.

Synthes, the company which manufactures the fixators used in this study, is a notable exception, licensing non implantable components as re-usable. However, they offer no specific recommendations regarding how many times and/or by what standards components can be safely re-used.

The evidence on the subject of safety is scarce and originates from the American literature. Although not all external fixator brands have been tested, available biomechanical data suggest that many external fixators are "over-engineered" (Dirschl, 2006) and can withstand at least 3 clinical uses (Horwitz et al., 2007), without compromise of their ability to stabilise.

While a cost reduction of 25% via the reprocessing industry is achievable in the American market, the current study is aimed at a UK audience, where such reprocessing facilities do not exist. In the current study, our approach was based on the biomechanical published data suggesting a minimum of three safe uses of each component. In practice records of use are not kept and most components are likely re-used many more than three times, until they fail or exhibit significant macroscopic wear. This was considered a rational approach. It was a generous estimate of price, however, in practice, would also cover the cost of any lost components.

2.5.1.3 Costing of resource use

According to the NICE guide to the methods of technology appraisal (NICE, 2008), national data based on Healthcare Resource Groups (HRG), such as the Payment by Results tariff, are a valuable source of information and should be considered for use when they are appropriate and available. However, data based on HRGs may not be appropriate in all circumstances, for example, when the definition of the HRG is broad

or the mean cost probably does not reflect resource use in relation to the technology under appraisal. This was the case in the current study, where the HRG code for inpatient operative treatment of an isolated distal radius fracture in an uncomplicated patient is identical for the two arms of the trial. As a result, it does not allow for differential costing. Consequently, a micro-costing study of the trial treatment pathway was performed, via a detailed 'bottom-up' approach.

Nevertheless, in the costing of complications requiring formal surgical intervention (such as carpal tunnel decompression, removal of metalwork in theatre and extensor pollicis longus reconstruction), certain HRG codes were used. These events were rare and data for micro-costing in this setting were not readily available. Market Force Factor Index adjustments were not applied to any HRG code.

In costing fracture clinic appointments, a combination approach was used. When an outpatient fracture clinic appointment involved no procedure, the HRG codes "WF01B First Attendance - Single Professional (£)" and "WF01A Follow Up Attendance - Single Professional (£)" were used (Table 2.5). A fracture clinic appointment differs from a standard hospital consultation, in that it is fast-paced and involves input from a great number of personnel of differing grades and professions, as well as periods of waiting, which are variable and extremely difficult to track. Therefore the standard HRG codes were considered to be the best approximation of this cost, including

overheads. However, when a procedure was performed during the course of fracture clinic appointment (either in the treatment or plaster room) the HRG code used for "outpatient procedures" was felt to be too broad and did not reflect the differences in aftercare of the technologies under review. For example, the cost of a wound check for the plate group is not expected to be the same as a K-wire wound check for the control group, the later requiring the additional removal and then re-application of a plaster cast. As a result, the cost of individual procedures was calculated via a detailed 'bottom-up' micro-costing technique, in an attempt to accurately reflect the two differing treatment pathways and minimise bias. The cost of the outpatient procedure was then added to the standard appointment cost.

In terms of physiotherapy input, all patients in the study had three physiotherapy contacts as part of the protocol: post-operatively whilst an inpatient, at the two week wound check and at the 6 week outpatient appointment. Any further physiotherapy input was classed as "extra" and cost £25, a figure provided by the physiotherapy department which reflected what the department charged the commissioning body per appointment contact.

Table 2.5 Payment by Results tariffs used (DOH, 2010)

HRG name	Code	Tariff (£)
Outpatient Attendance Trauma and Orthopaedics Consultant-led		
First Attendance - Single Professional	WF01B	143
Follow Up Attendance - Single Professional	WF01A	86

2.5.1.4 Tracking inpatient and outpatient resource use

Data regarding inpatient length of stay and any readmission were collected prospectively.

Data on operative times were obtained via the ORMIS theatre management system. ORMIS is the name of the Operating Room Management Information System supplied by EHR software vendor iSoft, used in the study institution.

Data on outpatient resource usage (fracture clinic, accident and emergency attendances relating to the treatment of the wrist fracture) were collected prospectively via review of the electronic patient health record on hospital attendances (PAS). All plaster room attendances at the study institution, as well as the reason for attendance and the intervention performed, are manually recorded in the plaster room log. Data on outpatient physiotherapy attendance was collected via review of the electronic patient records and physiotherapy notes.

This data was validated by confirming attendances with the patient. Patients were also asked to report their time to return to work, if they worked, and the time to return to driving, if they drove.

Data on complications, the management of such and the outcome were collected prospectively on the database, which was updated at each clinic attendance.

2.5.1.5 Health personnel labour costs

Health personnel labour costs were derived from national estimates which include salaries, insurance and pension contributions, labour related hospital overheads and capital development costs. Hourly costs for nursing time were based on patient contact time. Hourly rates for junior medical staff were based on a 48 hour week. Rates for consultants were calculated per contract hour (Curtis, 2011).

2.5.1.6 Overheads

Overhead costs were calculated based on adding 20% to direct costs, as advised by the financial directorate of the host Trust. This percentage has previously been published in economic evaluations from the same trust (Whynes et al., 2012) and it follows closely the proportion of expenditure devoted to areas other than personnel, clinical services and supplies in our own hospital (NUH, 2010).

2.5.1.7 Productivity loss

The rehabilitation days off work were calculated for each patient in gainful employment at the time of their injury. In valuing production gains and losses, the issue of what to include or exclude has been a source of debate, particularly when the role of the government is included. The most common means of valuation, and the means adopted in this study, is the human capital approach. According to this, the output lost if an individual is unable to work is generally estimated

by using the individual's gross earnings. The underlying justification assumes that employers go on hiring labour until the value of the marginal contribution to output by an additional worker is just matched by the cost of employing them (Fox-Rushby and Cairns, 2009).

Labour costs were sourced from the Office of National Statistics 2011 Bulletin Annual Survey of Hours and Earnings (ONS, 2011). Our randomisation groups were balanced for age, sex, and employment category. Therefore, for the calculation of labour costs, we used the figure of £400 per week representing median gross earning for all employee jobs in the United Kingdom, regardless of age, sex, and employment type (ONS, 2011)

Whether production gains should be used or not is controversial. One implication of taking them into account when informing health policy is that more productive groups could tend to be given more priority over less productive groups. The treatment of diseases which have a more marked impact on those of working age could receive more resources than those affecting the elderly. It has been argued that to the extent that these production gains result in increased private consumption rather than a contribution to the rest of society, they are of less significance (Fox-Rushby and Cairns, 2009).

It should be considered that not every person works, and of those who do, only part of their time is spent at work. It remains very difficult to measure time devoted to what is termed 'non-market activities'. The

standard approach is to use diary cards or interviews. The resources to do this were not available in this study. It is also likely that the compliance rate would be low due to the acute nature of the injury and the length of the study. Furthermore, it is generally proposed that changes in leisure time should be reflected in quality of life measurements, rather than measured in monetary terms (Drummond and McGuire, 2001).

Finally, a valuation of carer's time was not required, as the study population was selected to include active individuals with no significant medical co-morbidities. While restriction of the use of one's upper limb does impair self-care to a degree and impedes driving, the participants did not require formal care input as would be supplied by Personal Social Services. Informal care giving can only be estimated by the use of diary cards or interviews, resources not at the disposal of the study.

2.5.1.8 Cost of complications

Complications which required medical intervention and could be converted to NHS monetary and/or productivity costs, were itemised. Self-resolving complications, requiring no additional follow-up appointments and no intervention were not included as part of the costing exercise. The indirect cost of these complications, if any, was reflected via the condition-specific and HRQL scores.

Complications which were treated on an outpatient basis were costed via a micro-costing approach detailed in Appendix 6.7. Selected HRG

codes were used to cost complications which required formal surgical intervention, such as carpal tunnel decompression, removal of metalwork in theatre and extensor pollicis longus reconstruction. These events were rare and data for micro-costing in this setting were not readily available.

2.5.2 Health related quality of life outcome measures

The EuroQol health related-quality of life instrument (EuroQol, 1990) was used to quantify the effects of the compared technologies on HRQL.

The EQ-5D-3L version of the EQ-5D questionnaire was used. It has five domains, mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each domain is defined by three levels of function from good to poor. The three levels for each of the five domains can be used to define 243 (3^5) health states (Glick, 2007).

Responses were obtained directly from participants at baseline, 6 weeks, 12 weeks and 12 months.

The EQ-5D a widely used, standardised generic instrument, validated in many different patient populations (Brazier, 2008) and the preferred measure of health related utility used by NICE, in order to ensure consistency across their appraisals. The valuation of changes in HRQL reported by patients should be based on public preferences elicited using a choice-based method (the time trade-off method) (NICE, 2008). A set of preference values elicited from a large UK population study

using the time trade-off method is available for the EQ-5D classification system (Dolan, 1997). The Standard Gamble and the Visual Analogue Scale (VAS) approach were also presented.

The standard tariff values (Dolan, 1997) were applied to responses at each time point to provide EQ-5D-3L quality of life values. QALYs were calculated as an 'area under the curve' via a suitable algorithm.

In addition to the EQ-5D, the SF-6D health state index was calculated. This was derived from the SF-12 Health Survey, a 12-item short form self-administered health survey which measures functional health and well-being from the patient's point of view (Ware, 2007). The SF-12 was obtained via QualityMetric, who hold the licence for its use, for a charge. The SF-6D algorithms were provided by the University of Sheffield Health Economics and Decision Science Unit, free of charge for the purposes of the study.

The SF-12 generates eight dimension scores and two summary scores for each of physical and mental health. Whilst such scores provide an excellent means for judging the effectiveness of health care interventions, they cannot be applied directly in economic evaluation because they are not based on preferences. The SF-6D comes with a set of preference weights obtained from a sample of the general population using the valuation technique of standard gamble. The SF-6D provides a means for using SF-12 data in economic evaluation by estimating a preference-based single index measure for health from these data using

general population values, allowing us to obtain quality adjusted life years (QALYs) for use in the cost utility analysis. This technique is described by Brazier et al. (Brazier et al., 2002).

Validation of EQ-5D scores

In order to demonstrate that the study sample was also a good representation of the population as a whole, each participant was asked to complete the Quality of Life scores at the point of recruitment, as if they had not just injured their wrist. These measurements were collated with the purpose of acting as a baseline to which patients return when they have fully recovered from their injury. Given the potential of some bias due to recall (the period of recall was typically less than a week), compounded by the distress of just having sustained a painful injury, the measurements were validated. This was achieved by comparison with published population norms, which also served to confirm that the study sample was representative of the general population.

The EQ-5D recruitment TTO index and health state scores were compared with UK population norms published by the University of York Centre for Health Economics (Kind et al., 1999), after a survey of 3395 individuals selected using a strategy designed to generate a sample representative of the general population with respect to age, gender and social class. The survey collected data on health state evaluations using a time-trade-off procedure and reports on the TTO index and VAS health state scores in the form of tables providing population norms and

standard deviation. There are many ways of classifying the data. The current study participants were matched to their respective population norms by age/sex and standard region (East Midlands).

The comparisons were made using the methodology described in the discussion paper by Kind et al (Kind et al., 1999). Individual scores were compared to the group means presented in the tables by transforming the individual score to a *z* score (or standard score) which indicates where the score stands in relation to all other scores. A *z* score is a measure of how many standard deviations an individual score is from the mean of the distribution. The formula for calculating a z score is as follows:

$$z = \frac{X - \mu}{\sigma}$$

X = the individual score to be transformed

μ = population mean

σ = population standard deviation

A *z* score of ±2 is considered to be an extremely high or low score.

2.5.3 Analysis

2.5.3.1 Base-case analysis

Cost-effectiveness derives from the analysis of economic efficiency, where one alternative is preferred to another if it provides greater benefit at the same or lower cost, or lower cost for the same or greater benefit (Parkin, 2009).

In order to allow direct comparisons, an incremental cost-effectiveness ratio (ICER) was introduced between the intervention under investigation (volar locking plate) and the alternative (percutaneous methods of fixation) in the form of:

$$\frac{\text{Cost of new intervention} - \text{Cost of old intervention}}{\text{Outcome of new intervention} - \text{Outcome of old intervention}}$$

or

$$\text{ICER} = \frac{\text{Cost}_A - \text{Cost}_B}{\text{Effect}_A - \text{Effect}_B}$$

The ICER shows the cost of obtaining a unit of benefit. For the cost-utility analysis, benefit was expressed in QALYs.

The concept of the cost-effectiveness plane, including how it relates to the ICER of a new intervention and the NICE cost-effectiveness threshold are detailed in Appendix 6.8.

When the acquisition price paid for a resource differs from the public list price (for example, pharmaceuticals and medical devices sold at reduced prices to NHS institutions), the public list price should be used in the reference or base-case analysis. In the absence of a published list price and price agreed by a national institution, the price submitted by the manufacturer may be used, provided that it is nationally and publicly available (NICE, 2008).

The base-case scenario was constructed using public list price provided by the manufacturers of all implants used, with no hospital discounts applied. This price was sought directly from the companies involved for express use in the study. For re-usable implant components, as no formal guidelines exist, we calculated cost based on three safe uses of components, an approach based on published biomechanical data and detailed previously.

2.5.3.2 One-way sensitivity analysis

There are large uncertainties regarding much of the information required in order to estimate ICERs. These may pertain to the methodology, the data collected, the assumptions made and /or the generalisability of the results (Briggs, 2000b). In response to these uncertainties, economic evaluation must include some form of sensitivity analysis (NICE, 2008).

Sensitivity analysis is a set of techniques that analyse how sensitive the results are to changes in the model, for example in the data that are contained within it or the way that the data are combined.

One-way or univariate sensitivity analysis involves examining the impact on the ICER of changing one parameter at a time. After calculating the base-case scenario, the ICER is re-calculated holding all parameters constant, apart from the parameter selected to vary over a specified and justified range. NICE requires the uncertainly around the appropriate selection of data sources to be dealt with through sensitivity analysis. In particular, guidelines specify it should be performed when there is variability between hospitals in the acquisition price of a technology (NICE, 2008).

In the current study, we performed one-way sensitivity analysis based on possible differing costs of the volar locking plate construct. The base-case analysis used public list price for all implants, as per NICE guidance. The one-way sensitivity analysis included a 20% hospital discount.

Most, if not, all hospitals receive discounts on implants and other consumables, which are usually volume-based and vary depending on the particulars of a contract. The discounts are confidential and are not disclosed. Subsequently, the cost of implants will vary in different environments. 20% was chosen as a representative discount for a large

volume hospital environment, which is an indicative figure. It is not meant to represent the discount given to the host trust.

Threshold analysis allows us to determine the price range for the volar locking plate and its accessories, which would result in the technology becoming potentially cost effective.

2.5.3.3 Probabilistic sensitivity analysis

Simple sensitivity analysis deals predominately with issues of construct, such as the accuracy of the model selected and decisions around the origin of values for the key resources like cost and utilities. Probabilistic sensitivity analysis addresses the uncertainty arising from parameter imprecision, once the most appropriate sources of information have been identified. This reflects the uncertainty around mean health and cost values used in the calculation of the ICER.

NICE states in their Guidance for technology appraisal (NICE, 2008).

"All inputs used in the analysis will be estimated with a degree of imprecision. Probabilistic sensitivity analysis is preferred for translating the imprecision in all input variables into a measure of decision uncertainty in the cost effectiveness of the options being compared".

This translates to the need to present confidence intervals for the ICER. The mathematics used to generate confidence intervals when non-linear distributions are involved are extremely complicated. The statistical methodology was based on the use of non-parametric boot-strap. Boot-

strap methods are founded on the generation of multiple replications of the parameter of interest, by sampling with replacement from the original data (Glick, 2007).

Monte Carlo simulation was used to produce the cost–effectiveness plane and cost-effectiveness acceptability curve (CEAC). The statistical technique of calculating ICERs by simulation, including the generation and interpretation of the cost-effectiveness plane and CEAC are detailed in Appendix 6.9.

2.5.3.4 Comparison of EQ-5D TTO and SF-6D

As the SF-6D describes 18,000 health states, as opposed to 243 for the EQ-5D, and has a summary score specifically for physical health, we sought to investigate if the SF-6D could be a more responsive instrument, with the possibility of being better able to discriminate between small, particularly marginal, changes in randomised trials (Fox-Rushby and Cairns, 2009). The responsiveness of the EQ-5D and the SF-6D were assessed by use of effect size (ES) and the standardised response mean (SRM) (Kazis et al., 1989).

2.5.3.5 General statistical methods

Data were stored in Microsoft Access, coded in Excel, Windows 2000 (Microsoft Corp., Redmond, Washington, USA) and analysed using SPSS (IBM, Armonk, USA) and STATA version 10.1 software (StataCorp LP,

College Station, Texas, USA). Risk 4.5 software (Palisade, Ithaca, USA) was used for the probabilistic analysis.

The characteristics of the groups were compared with use of the Pearson chi-square test for categorical variables and the Student t-test for continuous variables. For non-parametric data we used the Mann-Whitney test. The level of significance was set at $p<0.01$.

Cost distributions and utility distributions were summarised by their mean, confidence intervals and standard deviation. All confidence intervals reported are at 95 per cent. Evidence suggests that it is the arithmetic mean cost that is most useful to NHS decision makers (Thompson and Barber, 2000).

All outcomes were analysed according to intention-to-treat principles, whereby patients are analysed in the group they were initially assigned.

Chapter 3 – Results

3.1 Participant flow

Between February 2008 and August 2009, 180 patients were referred to the research team and assessed for eligibility. Twenty-nine of these did not meet the inclusion criteria and 16 refused to participate. Thus 135 patients, aged 18 to 73 years met the inclusion criteria and were randomised to either Group One (open reduction and internal fixation using a volar locking plate) or Group Two (conventional treatment group consisting of closed reduction with percutaneous Kirschner wire fixation with/without external fixation). Eleven patients within the percutaneous fixation group required an external fixator for added stability (11/64, 17%).

Five participants were excluded. One patient withdrew from the trial after randomisation. In a further four cases, due to sickness and unforeseen scheduling issues, the operating surgeon was a not a participating trial senior surgeon. This resulted in deviation in the surgical device(s) used in one case, the treatment randomisation in two others, and the procedure being performed by a registrar in four cases. These five patients were therefore not included in the analysis.

Follow-up was for one year and completed in August 2010. Follow up at 1 year was 95% (124/130), with four patients lost to follow-up from Group One and two patients from Group Two. All outcomes were

analysed according to intention-to-treat principals, whereby patients are analysed in the group they were initially assigned to via randomisation, regardless of the final treatment received. This is demonstrated graphically in Figure 3.1. The Consort flow chart (Moher et al.) is summarized in Figure 3.2.

Figure 3.1 Diagram demonstrating allocation according to intention-to-treat principles

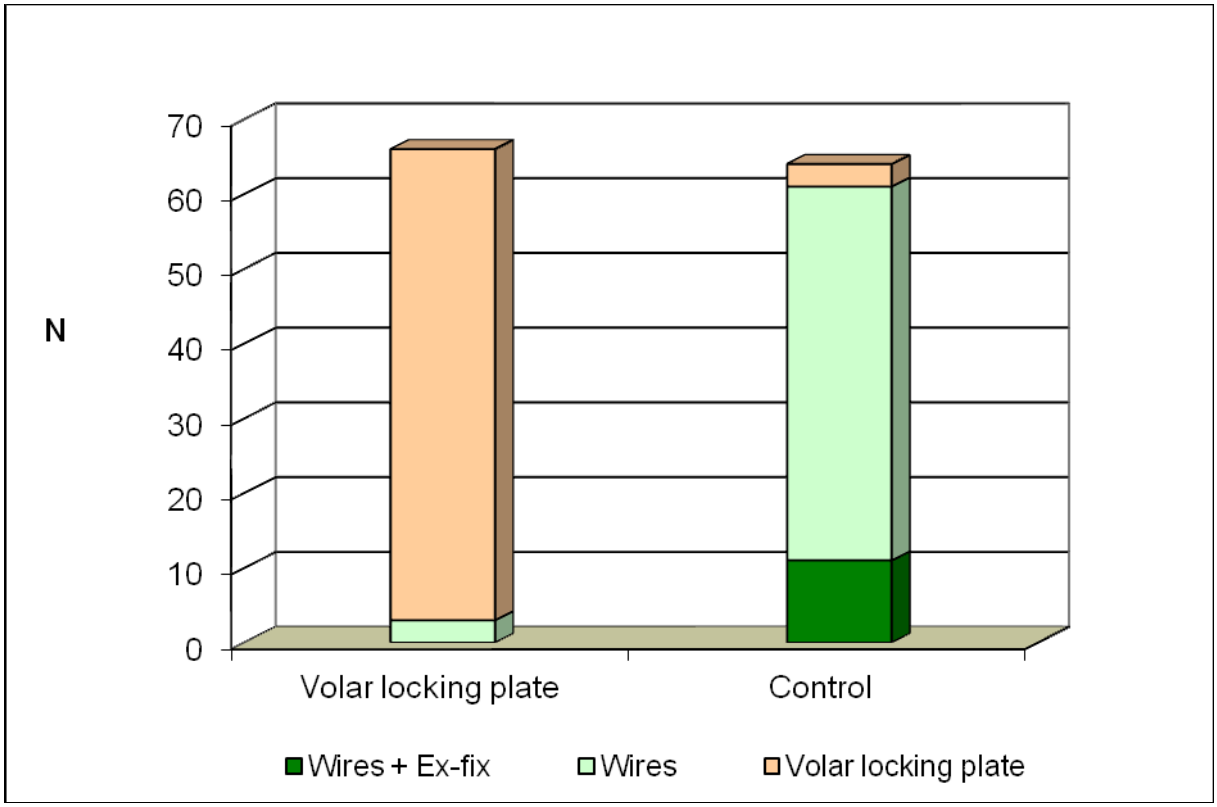
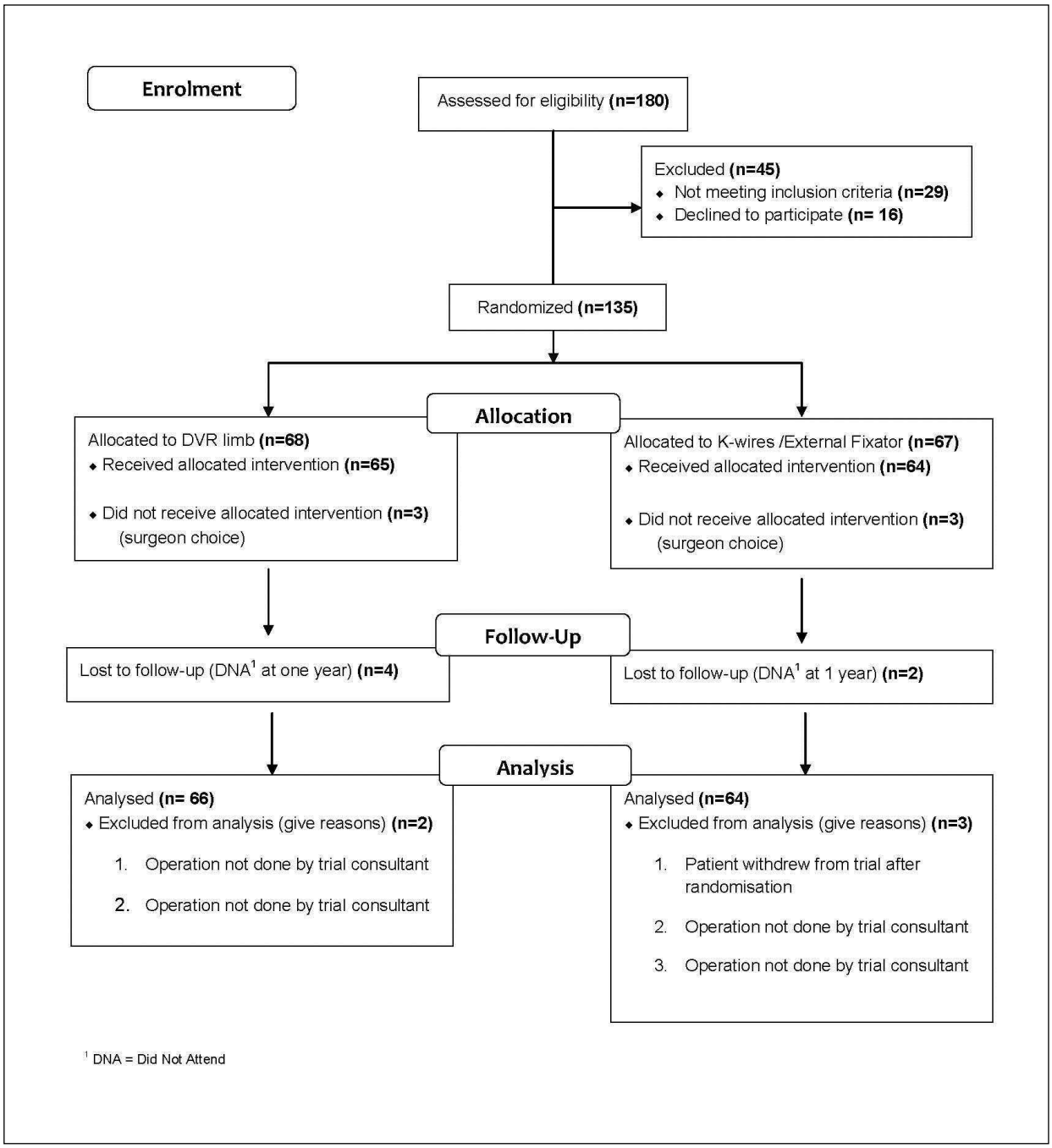


Figure 3.2 Consort flow chart for Enrolment and Analysis



3.2 Missing data

Absence from follow-up was examined at each time point in the study. This is presented in Table 3.1. The total number of data entry points in the study was also examined. All missing data was tagged at the point of insertion in the data base. This allowed data that was "missing", rather than "not applicable" to a particular patient, to be readily differentiated. The trial clinical database included 29,510 data entry points in total (100%). The rates of missing data points pertaining to each study time point are presented in Table 3.2. Given that the overall data missing at any time point in the study did not exceed 10% of total values, multiple imputation was not required.

Table 3.1 Participant numbers absent from follow-up at each study time point

	Volar Locking Plate (n)	Percutaneous (n)	Total per time point (n, %)
6 weeks	3	5	8 (6.2%)
12 weeks	7	3	10 (7.7%)
1 year	4	2	6 (4.6%)

Table 3.2 Rates of missing data points at each study time point

	Missing data points (n)	Total data points (N)	%
Recruitment	124	4550	2.7
6 weeks	828	12090	6.9
12 weeks	977	12090	8.1
1 year	740	12870	5.8
Total	**2669**	**41600**	**6.4**

3.3 Participant demographics

The demographic characteristics for the participant groups are summarized in Table 3.3. Characteristics of relevance to an economic viewpoint are presented in Table 3.4. All calculations on time to work and productivity pertain to those patients who were in employment at the time of their injury.

Randomisation groups were balanced for baseline characteristics. In addition, there was no difference in the age distribution between groups, which is demonstrated graphically in Figure 3.3 ($p=0.210$). Patients with a low energy mechanism of injury were older than those with a high energy mechanism (mean age 55, SD 13 versus 42, SD 15, $p<0.001$).

Table 3.3 Participant demographic characteristics

	VLP Group	Percutaneous Group
Age in years[†]	48 ± 15	51 ± 16
Gender		
Women	47 (71%)	50 (78%)
Men	19 (29%)	14 (22%)
Dominance		
Right	61 (92%)	60 (94%)
Side Injured		
Dominant	32 (49%)	28 (44%)
Mechanism		
Low energy	41 (62%)	41 (64%)
High energy	25 (38%)	23 (36%)
Smokers	15 (23%)	15 (23%)
Regular prescription medication	27 (41%)	25 (39%)

Low energy = fall from standing height

High energy = fall from above standing height, sport, road traffic accident

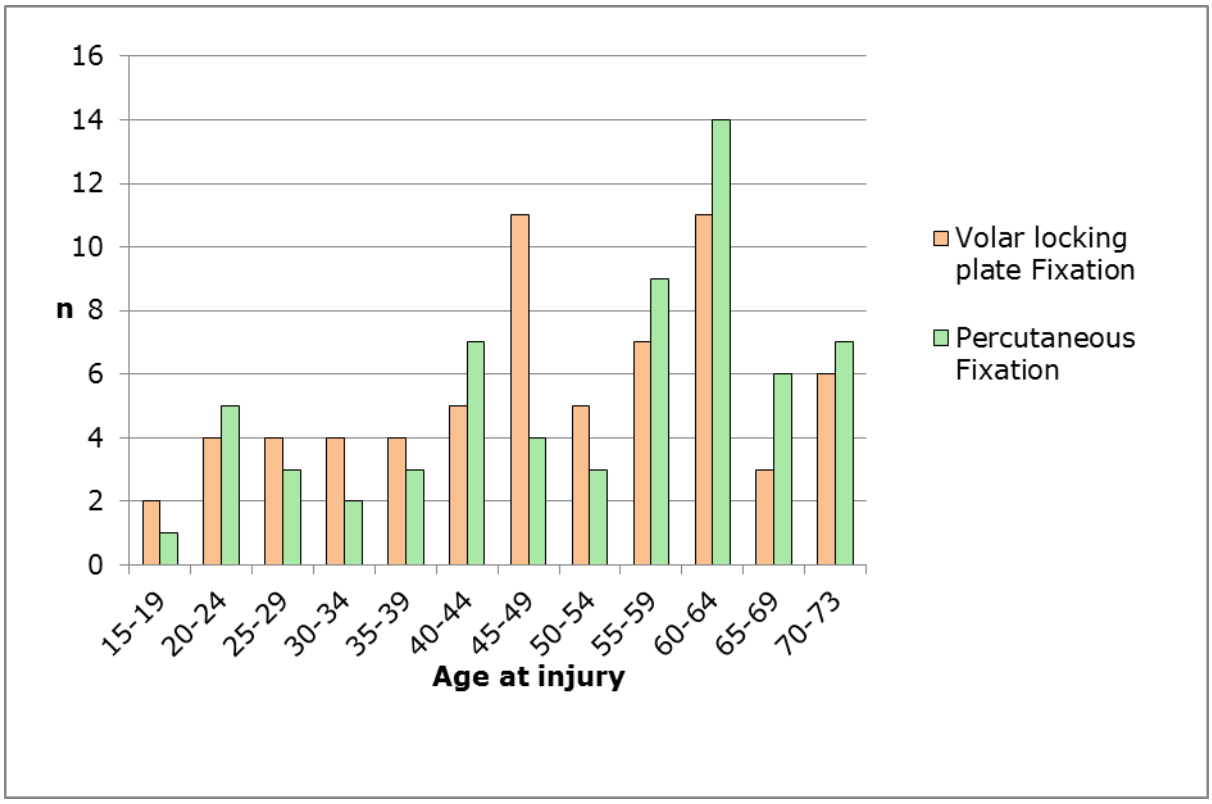
[†] The values are given as the mean and the standard deviation.

Taking regular prescription medication was used as an indicator of the presence or absence of significant past medical history.

Table 3.4 Participant employment characteristics

	VLP Group	Percutaneous Group
In employment	48 (73%)	35 (55%)
Self-employed	3 (6%)	2 (6%)
Occupation category		
Clerical	24 (36%)	20 (31%)
Light manual	13 (20%)	11 (18%)
Heavy manual	10 (15%)	4 (6%)
Fine skill	1 (1%)	0
Retired	11 (17%)	18 (28%)
Unemployed	3 (5%)	4 (6%)
Homemaker	4 (6%)	7 (11%)
Drives	40 (61%)	47 (73%)
Injured at work	5 (8%)	2 (3%)

Figure 3.3 Age distribution of participants within the two randomisation groups



3.4 Clinical results

3.4.1 Functional and measurable clinical outcomes

At 6 weeks PEM functional scores were significantly better in the volar locking plate group ($p<0.001$, 95% CI -15.44 to -6.28), but there was no significant difference at 12 weeks and 1 year. This was corroborated by significant differences in the *Quick*DASH ($p=0.002$, 95% CI -19.44 to -4.31) and PRWE ($p<0.001$, 95% CI -26.32 to -9.89) scores at 6 weeks, but no differences at 12 weeks and 1 year (Table 3.5). There was no significant functional treatment effect-interaction between age and method of fixation at 6, 12 weeks or 1 year for the PEM ($p=0.780$, $p=0.973$, $p=0.175$), *Quick* DASH ($p=0.475$, $p=0.827$, $p=0.662$) or PRWE ($p=0.06$, $p=0.145$, $p=0.399$).

The mean values for range of motion (ROM) and grip strength, expressed as percentage of the ROM and grip strength of the uninjured contra-lateral limb are summarized in Table 3.5. Patients in the volar locking plate group had greater ROM than the conventional group at 6 weeks ($p\leq0.001$), with no difference at 12 weeks and 1 year. Grip strength was greater for the plate group at 6 ($p<0.001$, 95% CI 0.64 to 1.13), 12 weeks ($p=0.002$, 95% CI 0.11 to 0.50) and 1 year ($p=0.005$, 95% CI 3.4 to 18.30).

Table 3.5 Functional and clinical outcomes

		Volar Locking Plate	Percutaneous	P value
PEM questionnaire				
	6 weeks†	34 ± 13	45 ± 12	0.000 *
	12 weeks†	24 ± 11	27 ± 12	0.116
	1 year†	17 ± 9	18 ± 10	0.703
*Quick*DASH questionnaire				
	6 weeks†	41 ± 21	52 ± 20	0.002 *
	12 weeks†	21 ± 17	27 ± 20	0.069
	1 year†	9 ± 12	12 ± 15	0.313
PRWE questionnaire				
	6 weeks†	43 ± 23	61 ± 22	0.000 *
	12 weeks†	23 ± 19	29 ± 22	0.150
	1 year†	13 ± 14	13 ± 16	0.412
Grip strength (as percentage % of grip strength of uninjured contra lateral limb)				
	6 weeks†	40 ± 23	10 ± 12	0.000 *
	12 weeks†	65 ± 26	45 ± 22	0.002 *
	1 year†	95 ± 22	84 ± 19	0.005 *
Range of movement (as percentage % of range of movement of uninjured contra lateral limb)				
6 weeks	Flexion†	59 ± 18	47 ± 22	0.001 *
	Extension†	57 ± 22	17 ± 30	0.000 *
	Pronation†	80 ± 17	65 ± 28	0.001 *
	Supination†	73 ± 23	37 ± 26	0.000 *
12 weeks	Flexion†	73 ± 19	72 ± 18	0.786
	Extension†	79 ± 17	78 ± 20	0.593
	Pronation†	91 ± 13	91 ± 14	0.971
	Supination†	91 ± 16	89 ± 15	0.394
1 year	Flexion†	88 ± 19	87 ± 16	0.893
	Extension†	93 ± 17	93 ± 18	0.885
	Pronation†	95 ± 8	98 ± 6	0.115
	Supination†	95 ± 10	96 ± 7	0.524

* Statistically significant values.
† The values are given as the mean and the standard deviation.

3.4.2 Per protocol analysis

In the present study, per protocol analysis (PP) of functional and clinical outcomes was undertaken, in addition to intention-to-treat analysis. The treatment groups compared included only those patients who completed the treatment originally allocated. This acted as a sensitivity analysis, and enabled the effect of cross-over between the groups to be investigated. A total of six participants cross over from their original randomisation groups, three each way, as demonstrated by the Consort Flow Chart (Figure 3.2).

The results of the per protocol analysis of clinical and functional outcomes are presented in Table 3.6 below. As demonstrated, the results of PP analysis were no different to intention-to-treat analysis.

Table 3.6 Functional and clinical results of per protocol analysis

		Volar Locking Plate	Percutaneous	P value
PEM questionnaire				
	6 weeks†	34 ± 13	46 ± 12	0.000 *
	12 weeks†	24 ± 11	28 ± 13	0.060
	1 year†	17± 9	18 ± 11	0.404
*Quick*DASH questionnaire				
	6 weeks†	40 ± 20	53 ± 20	0.000 *
	12 weeks†	21 ± 17	28 ± 20	0.036
	1 year†	9 ± 12	12 ± 15	0.180
PRWE questionnaire				
	6 weeks†	42 ± 23	63 ± 22	0.000 *
	12 weeks†	24 ± 19	30 ± 22	0.085
	1 year†	12 ± 14	13 ± 17	0.704
Grip strength (as percentage % of grip strength of uninjured contra lateral limb)				
	6 weeks†	42 ± 23	9 ± 12	0.000 *
	12 weeks†	65 ± 26	49 ± 22	0.003 *
	1 year†	95 ± 21	84 ± 19	0.006 *
Range of movement (as percentage % of range of movement of uninjured contra lateral limb)				
6 weeks	Flexion†	60 ± 18	46 ± 23	0.000 *
	Extension†	59 ± 21	15 ± 29	0.000 *
	Pronation†	80 ± 17	64 ± 28	0.000 *
	Supination†	76 ± 21	34 ± 24	0.000 *
12 weeks	Flexion†	73 ± 20	73 ± 18	0.838
	Extension†	80 ± 17	78 ± 20	0.567
	Pronation†	91 ± 14	91 ± 14	0.914
	Supination†	92 ± 15	89 ± 15	0.276
1 year	Flexion†	88 ± 19	87 ± 17	0.873
	Extension†	93 ± 17	93 ± 19	0.935
	Pronation†	95 ± 9	97 ± 6	0.161
	Supination†	96 ± 10	96 ± 7	0.713

* Statistically significant values.

† The values are given as the mean and the standard deviation.

3.4.3 Radiographic outcomes

The radiographic fracture characteristics are presented in Table 3.7. Positive values indicate a palmar angulation and negative values indicate angulation dorsally beyond neutral.

The randomisation groups at presentation were comparable in terms of fracture characteristics and anatomy of the contra-lateral uninjured wrist. Fractures in the study fell into one of three AO classification groups (23-A3 extra-articular multi-fragmentary, 23-C2 complete articular simple, metaphyseal multi-fragmentary or 23-C3 complete articular, multi-fragmentary). The randomisation groups were balanced in their distribution of fracture classification groups.

All fractures united radiographically. Reduction achieved via the fixation was expressed as the percentage of radiographic reduction, when compared to the contra-lateral normal limb for each patient at 1 year, with 100% reduction corresponding to full anatomical alignment.

The volar locking plate group achieved significantly better restoration of palmar tilt (8° versus 2°, $p<0.001$, 95%CI 4 to 9 at 6 weeks and 3 to 9 at 1 year). When expressed as percentage reduction, radial height was also better restored in the plate group ($p=0.004$, 95%CI 4 to 23) though the difference in absolute values did not reach statistical significance. There were no significant differences between the radiographic measurements at 6 weeks and 1 year within each

treatment group, which demonstrates that there was no significant loss of reduction with either treatment after week 6.

Table 3.7 Radiographic data and fracture classification

	Volar Locking Plate	**Percutaneous**	**p value**
AO classification			
A3	27/66 (41%)	28/64 (44%)	p=0.257
C2	37/66 (56%)	30/64 (47%)	
C3	2/66 (3%)	6/64 (9%)	
Injured wrist at presentation			
Palmar tilt (° from neutral) †	-27 ± 10	-25 ± 11	p=0.373
Radial height (mm) †	4 ± 5	4 ± 4	p=0.508
Radial inclination (°)†	15 ± 8	16 ± 8	p=0.336
Contra-lateral uninjured wrist			
Palmar tilt (° from neutral) †	12 ± 6	12 ± 5	p=0.815
Radial height (mm) †	11 ± 2	11 ± 2	p=0.280
Radial inclination (°)†	25 ± 2	25 ± 3	p=0.445
6 weeks post-operatively			
Palmar tilt (° from neutral) †	8 ± 6	2 ± 8	p<0.001*
Radial height (mm) †	10 ± 2	9 ± 3	p=0.010
Radial inclination (°)†	23 ± 4	23 ± 4	p=0.887
1 year post-operatively			
Palmar tilt (° from neutral) †	8 ± 6	2 ± 10	p<0.001*
Radial height (mm) †	10 ± 2	9 ± 3	p=0.029
Radial inclination (°)†	24 ± 4	23 ± 4	p=0.636
Reduction achieved at 1 year (as % of measurements of contra-lateral uninjured limb)			
Palmar tilt (° from neutral) †	71 ± 73	12 ± 86	p<0.001*
Radial height (mm) †	96 ± 20	82 ± 31	p=0.004*
Radial inclination (°)†	95 ± 15	89 ± 25	p=0.121

Significance set at p<0.01

* Statistically significant values

† The values are given as the mean and the standard deviation

Reliability of radiographic measurements

Three radiographic variables were compared between 45 sets of radiographs. Data were analysed via the Bland-Altman method for comparing measurements of continuous variables using limits of agreement (Altman, 1999, Bland and Altman, 1986).

In a Bland-Altman plot, the difference between the two measurements per observer is plotted against the mean of the two measurements. The lack of agreement can be summarised by calculating the relative *bias,* which is the mean difference ($\bar{a}$), and the standard deviation of the differences (s). If the observers tend to agree, the differences between the observers' observations will be near zero. If one observer is usually higher or lower than the other by a consistent amount, the relative *bias* (mean of differences) will be different from zero. The standard deviation (s) of the differences is the estimate of error. Differences within $\bar{a} \pm 1.96s$ are termed the "95% limits of agreement". Providing differences within the limits of agreement are not considered clinically important, then the observers show acceptable agreement.

Table 3.8 includes the indicators of reliability of the radiographic measurements. Positive values indicate a palmar angulation and negative values indicate angulation dorsally beyond neutral. The resulting Bland-Altman plots for radial height, radial inclination and palmar inclination are shown in Figure 3.4. The patterns of the plots

show no obvious relationship between the measurement differences and the absolute values.

Table 3.8 Indicators of reliability

	$\bar{a}$	Range	LA	95% tolerance limits (Kreder et al., 1996b)
Radial height	-0.7mm	0mm to 14.6mm	-2.4mm to 1.1mm	±10mm
Radial inclination	-0.4°	6° to 30°	-3.7° to 2.9°	±11°
Palmar inclination	0.4°	-40° to 19.5°	-6.7° to 7.4°	±15°

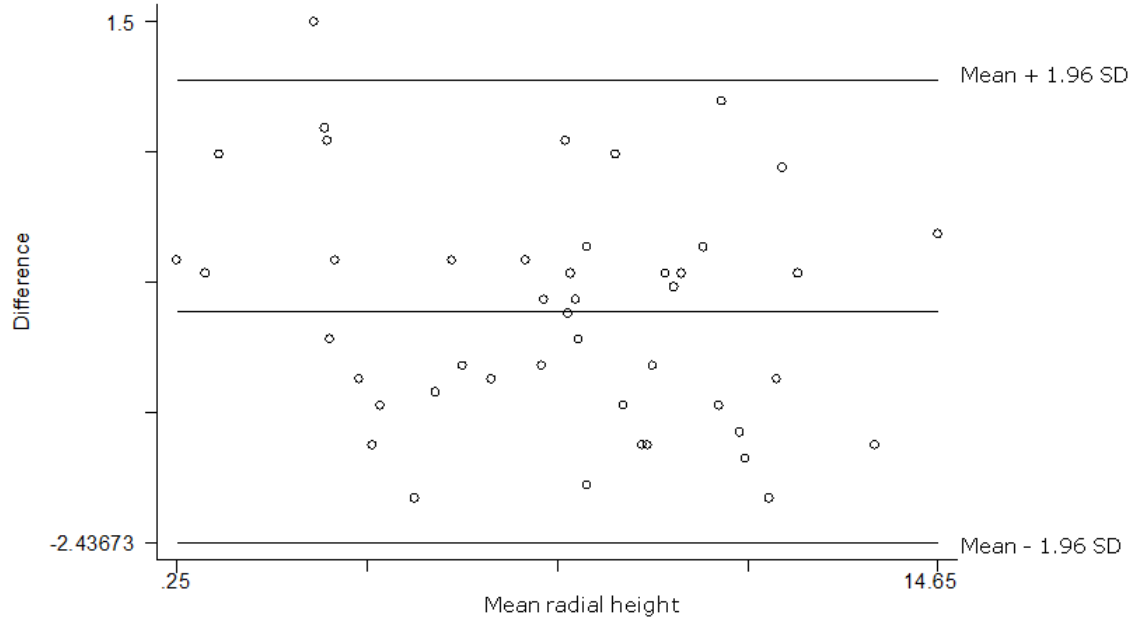
Key

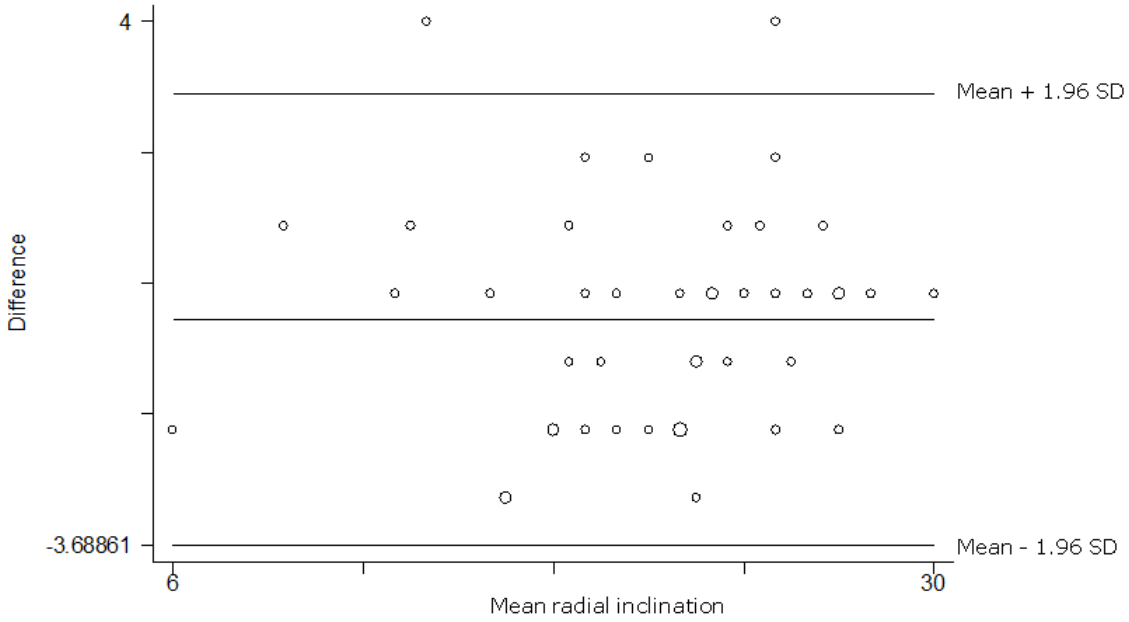
$\bar{a}$ mean difference (degrees)

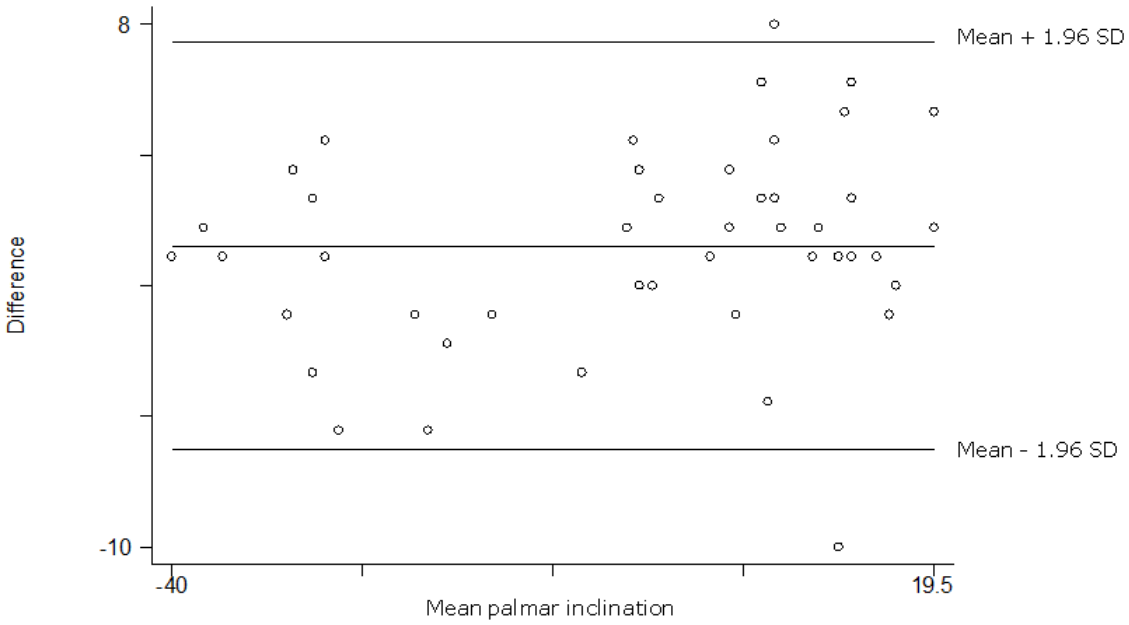
LA 95% limits of agreement

Range range of the observer measurements

Figure 3.4 Bland-Altman plots of radiographic parameters






8
-10
Difference
Mean + 1.96 SD
Mean - 1.96 SD
-40
19.5
Mean palmar inclination

3.4.4 Complications

Complications are summarized in Table 3.9. There were more complications in the percutaneous fixation group, but the difference was not statistically significant (p=0.047) for the level of significance set in this study. The participant complication rate was 15/66 (23%) for the volar locking plate group and 26/64 (39%) for the percutaneous fixation group (p=0.057).

In the percutaneous fixation group, transient nerve palsies consisted of superficial radial nerve palsies. The percutaneous k-wires became buried in six occasions, requiring removal under local anaesthetic on an outpatient basis. One patient, who developed carpal tunnel syndrome 3 months following her injury, required decompression. One patient suffered an extensor pollicis longus (EPL) rupture and proceeded to later reconstruction. This patient was randomised to the percutaneous group, but underwent volar locking plate fixation at his surgeon's discretion, after failure to achieve an acceptable intra-operative result with K-wires. This complication was analysed in the original randomisation group, according to intention to treat principles.

In the volar locking plate group, two plates required removal due to malposition. This presented as flexor pollicis longus crepitus in one case and restriction of wrist flexion in the second. Both recovered fully after removal of the plates. In one patient, it was

observed 4 months after the injury that some of the pegs appeared intra-articular at the border of the joint, whereas the intra-operative films showed them to be clearly outside the joint. A CT scan was obtained which confirmed that there had been some bone collapse and the pegs where prominent in the subchondral bone. The patient remained asymptomatic with no restriction and declined plate removal.

Table 3.9 Complications

Volar Locking Plate		**Percutaneous Fixation**		
N=16		**N=27**		**p=0.047**
Superficial infections	2	Superficial infections	5	
Transient nerve palsies	4	Transient nerve palsies	10	
Carpal tunnel syndrome	4	Carpal tunnel syndrome	2	
Plate impingement	2	Buried k-wires	6	
Migration of pegs into the joint	1	EPL rupture	1	
Ulnar styloid pain	2	Ulnar styloid pain	2	
Non-specific wrist pain	1	Non-specific wrist pain	1	
Further procedures		**Further procedures**		
n=2		**n=8**		**p=0.090**
Removal of plate	2	Carpal tunnel decompression	1	
		EPL reconstruction	1	
		Removal of buried k-wires	6	

N = Number of complications
EPL = Extensor Pollicis Longus

3.5 Economic evaluation results

3.5.1 Health related quality of life scores

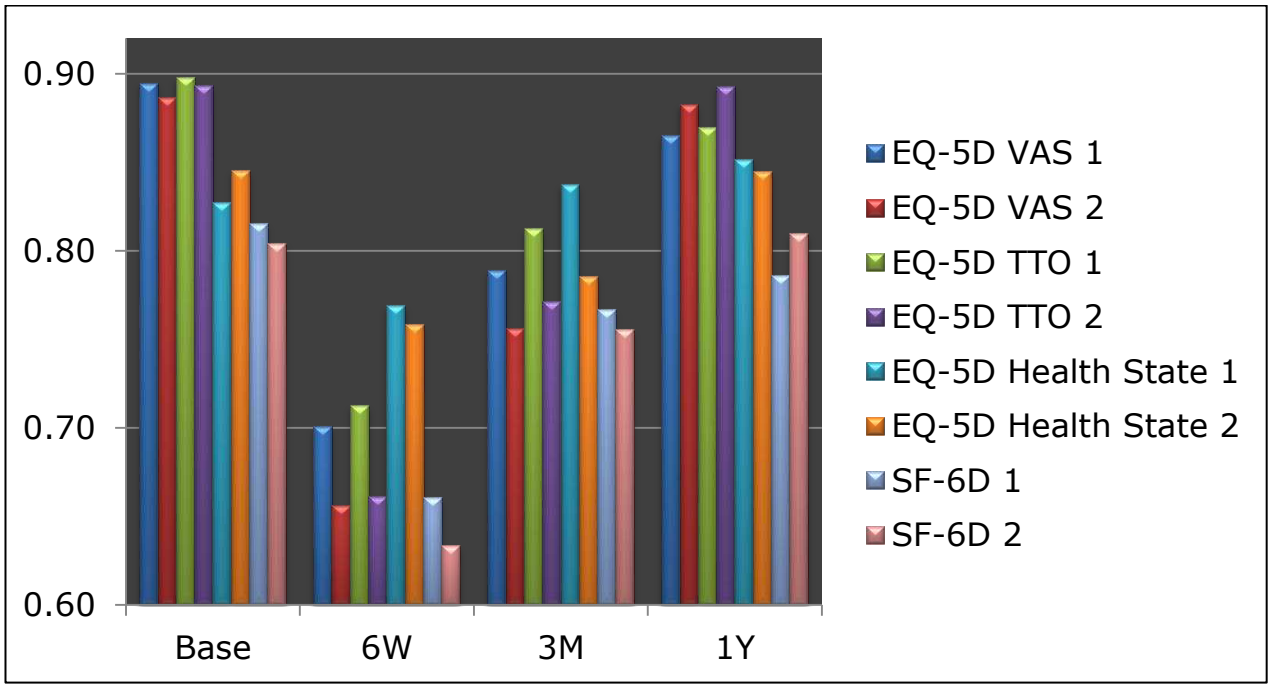
The health related quality of life (HRQL) scores achieved are presented in tabular (Table 3.10) and graphic form (Figure 3.5). Table 3.11 summarises comparative statistics at the time points of the study.

There were no significant differences in any parameter of the EQ-5D or the SF-6D scores from recruitment to one year. All returned to baseline quality of life at the end of trial follow-up (Table 3.12a-b). EQ-5D and SF-6D index scores showed similar patterns of recovery.

Non-parametric distributions are identifiable. Non-parametric distributions (and those that cannot be log-transformed into parametric distributions), were compared via the Mann Whitney test. This is a test of shift in distribution and the confidence intervals are not easily calculated. SPSS does not provide confidence intervals, though STATA does. The method is based on jack-knifed estimates (similar to bootstrapping) and the command is "cendif" (Newson, 2002). Confidence intervals produced by this method represent the difference in the median and are used to summarize or estimate the shift of the distributions. They are

derived by a method which is different from the original test and are not a measure of significance.

Figure 3.5 Quality of Life Scores (EQ-5D and SF-6D)



KEY	
EQ-5D TTO	EQ-5D index score with UK time trade-off weightings
EQ-5D VAS	EQ-5D index score with UK VAS weightings
EQ-5D Health State	EQ-5D Health state thermometer score
SF-6D	SF-6D index score
1	Volar locking plate group
2	Percutaneous fixation group

Table 3.10 Quality of Life Utility Index Scores (EQ-5D and SF-6D)

	Randomisation group		N	Mean	SD
	Recr EQ-5D VAS score	1	63	0.89	0.17
		2	63	0.89	0.18
	Recr EQ-5D TTO score	1	63	0.90	0.20
		2	63	0.89	0.19
	Recr EQ-5D Health State	1	62	82.74	18.51
		2	61	84.54	12.98
	Recr SF-6D	1	62	0.82	0.09
		2	61	0.80	0.08
	6W EQ-5D VAS Score	1	64	0.70	0.18
		2	60	0.66	0.19
	6W EQ-5D TTO Score	1	64	0.71	0.22
		2	60	0.66	0.23
	6W EQ-5D Health State	1	64	76.89	16.59
		2	60	75.85	16.98
	6W SF-6D	1	63	0.66	0.13
		2	60	0.63	0.13
	3M EQ-5D VAS Score	1	58	0.79	0.13
		2	61	0.76	0.16
	3M EQ-5D TTO Score	1	58	0.81	0.12
		2	61	0.77	0.18
	3M EQ-5D Health State	1	58	83.76	13.41
		2	59	78.58	19.92
	3M SF-6D	1	58	0.77	0.12
		2	61	0.76	0.11
	1Y EQ-5D VAS Score	1	62	0.87	0.18
		2	60	0.88	0.16
	1Y EQ-5D TTO Score	1	62	0.87	0.20
		2	60	0.89	0.17
	1Y EQ-5D Health State	1	62	85.16	16.57
		2	59	84.49	11.93
	1Y SF-6D	1	62	0.79	0.11
		2	60	0.81	0.09

Recr = recruitment

6W = 6 week

3M = 3 month

1Y = 1 year

Table 3.11 Comparative statistics for HRQL measures at data collection time points

		Volar Locking Plate		Percutaneous Fixation				
		Mean	SD	Mean	SD	95% CI		Sig. (2-tailed)
						Upper	Lower	
EQ-5D questionnaire								
6 weeks	TTO score	0.71	0.22	0.66	0.23	0.15	0.38	0.04
	VAS score	0.70	0.18	0.66	0.19	-0.02	0.11	0.19
	Health State	77	17	76	17	-4.93	7.01	0.73
12 weeks	TTO score	0.81	0.12	0.77	0.18	-0.01	0.17	0.09
	VAS score	0.79	0.13	0.76	0.16	-0.02	0.09	0.23
	Health State†	84	13	79	20	0	9	0.22
1 year	TTO score†	0.87	0.20	0.89	0.16	0	0	0.73
	VAS score†	0.86	0.18	0.88	0.16	0	0	0.70
	Health State	85	17	84	12	-4.55	5.89	0.80
SF-6D utility index								
6 weeks		0.66	0.13	0.63	0.13	-0.02	0.07	0.24
12 weeks		0.77	0.12	0.76	0.11	-0.03	0.05	0.60
1 year		0.79	0.11	0.81	0.09	-0.06	0.01	0.19

Significance set at $p<0.01$

† Non-parametric distributions that could not be log-transformed to parametric.

Tables 3.12 a and b Paired sample t-tests comparing recruitment and one year HRQL scores for the two treatment groups, demonstrating return to baseline at one year

a. Volar locking plate group

Paired samples	Mean of diff	SD	95% Confidence Interval		Sig. (2-tailed)
			Upper	Lower	
1Y EQ-5D VAS - Recr EQ-5D VAS	-0.03	0.19	-0.08	0.02	0.30
1Y EQ-5D TTO - Recr EQ-5D TTO	-0.03	0.22	-0.08	0.03	0.36
1Y EQ-5D HS - Recr EQ-5D HS	2.20	15.94	-1.95	6.36	0.29
1Y SF-6D - RECR SF-6D	-0.03	0.12	-0.06	0.00	0.08

b. Percutaneous fixation group

Paired samples	Mean of diff	SD	95% Confidence Interval		Sig. (2-tailed)
			Upper	Lower	
1Y EQ-5D VAS - Recr EQ-5D VAS	0.00	0.18	-0.05	0.04	0.84
1Y EQ-5D TTO - Recr EQ-5D TTO	0.00	0.17	-0.05	0.04	0.98
1Y EQ-5D HS - Recr EQ-5D HS	-0.16	11.21	-3.16	2.84	0.92
1Y SF-6D - RECR SF-6D	0.00	0.08	-0.02	0.03	0.72

Significance set at $p<0.01$

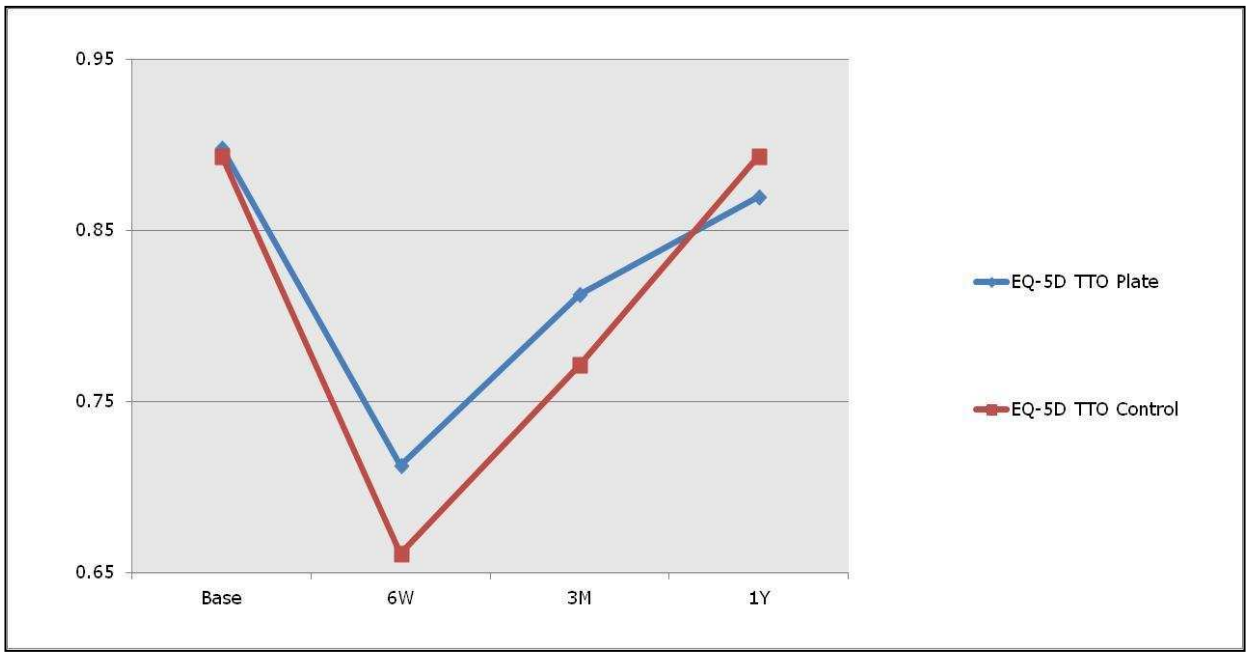
QALY Gain

A QALY is effectively the area under a curve, when plotting the selected HRQL measurements against time. An algorithm was created to calculate the QALYs reported by trial participants over the time period of the study and, subsequently by comparison, the differential QALY gain of volar locking plate fixation over conventional percutaneous methods. This is represented graphically as the surface area between the two curves or lines in Figure 3.6. This is a graphic representation of a more complex statistical algorithm which compared a distribution of values rather than the mean values between randomisation groups.

The QALY gain achieved by volar locking plate fixation over percutaneous methods in this study was $\Delta Q = 0.0178$ (SE 0.025). This represented the denominator of the ICER. The gain was not statistically significant ($p= 0.47$, 95% CI-0.03 to 0.07).

The results were similar for the EQ-5D VAS and Health State, scores, which are not used by NICE to inform cost-effectiveness.

Figure 3.6 EQ-5D TTO scores over time for the randomisation groups. The surface area between the lines graphically represents the QALY gain achieved by volar locking plate fixation over percutaneous methods. Note that the y axis represents the top range of the TTO scale and so the gain appears magnified.



Validation of EQ-5D scores

All trial patients questioned (126/130, 97%) had TTO recruitment index scores ranging from 0.53 to -1 standard deviation (SD) from their respective UK population norms, matched for age, sex and standard geographic region. There were 4 missing TTO recruitment index score values (4/130, 3%).

The vast majority of patients (115/123, 93.5%) had health state recruitment scores ranging from 1.63 to -1.96 SD of their respective UK population norm matched for age, sex and standard geographic region. Eight patients (8/123, 6.5%) had a health state recruitment score that was >2 or <-2 SD from their respective UK population norm. There were 7 missing recruitment health state score values (7/130, 5.4%).

Overall, the study population was comparable to the norm in terms of EQ-5D scores, with an average z score of -0.16 for TTO and -0.14 for health state and no discernable differences in matching between the randomisation groups.

3.5.2 Costs

3.5.2.1 Model cost analysis

A model cost analysis of each intervention from the perspective of the NHS was performed, based on individual patient data collected prospectively during the trial. The model, detailed in Table 3.13, identifies and lists incremental costs between treatment options. It was derived based on the management options:

- volar locking plate fixation
- k-wire fixation
- k-wires with supplemental external fixation

Resource use was translated into monetary values using unit costs as per the methodology described previously. The itemised cost per differential intervention is also detailed in Table 3.13. This was used to inform the main cost-utility analysis.

Table 3.13 Itemised model cost per intervention

Decision to enter trial												
Book for surgery												
DVR			**£**	**K-wire**			**£**	**Ex-fix**				**£**
Theatre and anaesthetic and recovery time and staff				**Theatre and anaesthetic and recovery time and staff**				**Theatre and anaesthetic and recovery time and staff**				
Average time in Recovery		82 min		Recovery time			76 min	Recovery time			105 min	
Cost of recovery including overheads	£0.43 per minute		35.26	Cost of recovery including overheads	£0.43 per minute		32.68	Cost of recovery including overheads	£0.43 per minute			45.15
Radiographer (CRIS code FPLULM)			111	Radiographer (CRIS code FPLULM)			111	Radiographer (CRIS code FPLULM)				111
Average time in theatre	80 min			Average time in theatre	43 min			Average time in theatre	83 min			
Pay element (Anaesthetics, trust funded element of Junior Doctors and Sterile Services) incl overheads	£6.2 per min		496	Pay element (Anaesthetics, trust funded element of Junior Doctors and Sterile Services) incl overheads	£6.2 per min		266.6	Pay element (Anaesthetics, trust funded element of Junior Doctors and Sterile Services) incl overheads	£6.2 per min			514.6
Consultant surgeon	£2.68 per min		214.4	Consultant surgeon	£2.68 per min		115.24	Consultant surgeon	£2.68 per min			222.44
Hardware DVR				**Hardware K-wire**				**Hardware K-wire + Ex Fix**				
Plate			417	1.6mm Kirschner wires (n=3)			16.8	1.6mm k wires (n=3)				16.80
Pegs (n=7)			336					Threaded 2.5mm Kirschner wires (n=4)				57.40
Cortical Screws 3.5mm (n=3)			87					Sterilisation of reusable components*				0
K-wire (n=2)			16									688.83
Drill bit 2.5mm			41									
Drill bit 2.0mm			33									
Consumables (non-incremental)				**Consumables (non-incremental)**				**Consumables (non-incremental)**				
Cost of anaesthetic drugs (ex gases)			7.1	Cost of anaesthetic drugs (ex gases)			7.1	Cost of anaesthetic drugs (ex gases)				7.1
Universal giving set			2.64	Universal giving set			2.64	Universal giving set				2.64
IV Cannula			0.67	IV Cannula			0.67	IV Cannula				0.67
Peripheral IV securement dressing			0.4	Peripheral IV securement dressing			0.4	Peripheral IV securement dressing				0.4
0.9% sodium chloride for infusion 1lt			1.17	0.9% sodium chloride for infusion 1lt			1.17	0.9% sodium chloride for infusion 1lt				1.17
Course of prophylactic antibiotics			26.5	Course of prophylactic antibiotics			26.5	Course of prophylactic antibiotics				26.5
20ml water for injection			0.68	20ml water for injection			0.68	20ml water for injection				0.68
10ml syringe (n=10)			0.6	10ml syringe (n=10)			0.6	10ml syringe (n=10)				0.6
Needle Green (n=10)			0.1	Needle Green (n=10)			0.1	Needle Green (n=10)				0.1
20 ml syringe (n=2)			0.18	20 ml syringe (n=2)			0.18	20 ml syringe (n=2)				0.18
Laryngeal mask			3.2	Laryngeal mask size 4			3.2	Laryngeal mask size 4				3.2
Light Handle (n=2)			1.01	Light Handle (n=2)			1.01	Light Handle (n=2)				1.01
Scrub brush (n=3)			0.6	Scrub brush (n=3)			0.6	Scrub brush (n=3)				0.6
Scalpel blade carbon steel (n=2)			0.12	Scalpel blade carbon steel (n=2)			0.12	Scalpel blade carbon steel (n=2)				0.12
Drape pack upper extremity			15.72	Drape pack upper extremity			15.72	Drape pack upper extremity				15.72
X-ray machine cover			2.15	X-ray machine cover			2.15	X-ray machine cover				2.15
Gown pack sterile disposable reinforced (n=3)			4.17	Gown pack sterile disposable reinforced (n=3)			4.17	Gown pack sterile disposable reinforced (n=3)				4.17
Face mask surgical (n=6)			0.24	Face mask surgical (n=6)			0.24	Face mask surgical (n=6)				0.24
Prep			0.06	Prep			0.06	Prep				0.06
Sterile gloves (n=6)			3.6	Sterile gloves (n=6)			3.6	Sterile gloves (n=6)				3.6
Padding for tourniquet			0.11	Padding for tourniquet			0.11	Padding for tourniquet				0.11
Sterile x-ray detectable gauze swabs (n=2)			0.9	Sterile x-ray detectable gauze swabs (n=2)			0.9	Sterile x-ray detectable gauze swabs (n=2)				0.9
Bradford type foam sling			10.38	Bradford type foam sling			10.38	Bradford type foam sling				10.38
Consumables incremental (dressings and sutures)				**Consumables incremental (dressings and sutures)**				**Consumables incremental (dressings and sutures)**				
Suture absorbable coated braided 4/0 3/8 circle needle			3.35	Dressing paraffin gauze sterile			0.29	Dressing paraffin gauze sterile				0.29
Suture non absorbable monofilament 4/0 3/8 circle needle			1.15	Swab non-woven in 5s sterile			0.03	Swab non-woven in 5s sterile				0.03
Hydrocolloid dressing 10x10cm			2.14	Undercast padding synthetic sterile 7.5cm			0.48	Undercast padding synthetic sterile 7.5cm				0.48
Dressing IV vapour premeable adhesive film			0.32	Crepe bandage sterile			0.93	Crepe bandage sterile				0.93
Wrist splint			3.67	Plaster of paris splint			0.49					
Theatre overheads (20%) based on hardware, consumable incermental and non-incremental costs			204.58	Theatre overheads (20%) based on hardware, consumable incermental and non-incremental costs			20.26	Theatre overheads (20%) based on hardware, consumable incermental and non-incremental costs				169.41
Inpatient stay				**Inpatient stay**				**Inpatient stay**				
One night on orthopaedic trauma ward including overheads			184	One night on orthopaedic trauma ward including overheads			184	One night on orthopaedic trauma ward including overheads				184
20ml syringe (n=3)			0.27	20ml syringe (n=3)			0.27	20ml syringe (n=3)				0.27
20 ml water for injections			0.68	20 ml water for injections			0.68	20 ml water for injections				0.68
Needle Green (n=3)			0.03	Needle Green (n=3)			0.03	Needle Green (n=3)				0.03
Post op analgesics			0.72	Post op analgesics			0.72	Post op analgesics				0.72
Discharge Analgesics			5.41	Discharge Analgesics			5.41	Discharge Analgesics				5.41
Two week wound check			86	**Two week wound check**			86	**Two week wound check**				86
Removal sutures in Treatment Room				**Treatment room and plaster room**				**Treatment room**				
Staff Nurse Band 5 (10 min)			16.2	Staff Nurse Band 5 (20 min)			32.4	Staff Nurse Band 5 (10 min)				16.2
Dressing pack sterile woundcare with forceps			0.28	Dressing pack sterile woundcare with forceps			0.28	Dressing pack sterile woundcare with forceps				0.28
Normal saline 20 mls (n=2)			0.92	Normal saline 20 mls (n=2)			0.92	Normal saline 20 mls (n=2)				0.92
Sterile gloves (n=1)			0.6	Sterile gloves (n=1)			0.6	Sterile gloves (n=1)				0.6
Dressing vapour permeable adhesive with absorbent sterile pad (medium)			0.21	**POP**				Dressing primary knitted polyester impregnated with neutral triglycerides (n=3)				0.39
Blade stitch cutting carbon steel			0.05	Swab non-woven in 5s sterile			0.03	Undercast padding synthetic non-sterile 7.5cm				0.32
				Dressing primary knitted polyester impregnated with neutral triglycerides (n=2)			0.26	Bandage crepe non-sterile				0.36
				Stockinette 7.5 x 40cms			0.09					
				Undercast padding synthetic non-sterile 7.5cm			0.32					
				Non fibreglass casting tape 7.5cm x 3.6m White (n=1.5)			5.97					
Overheads on procedure (20%)			0.41	Overheads on procedure (20%)			1.69	Overheads on procedure (20%)				0.57
Six week follow-up			86	**Six week follow-up**			86	**Six week follow-up**				86
				Plaster room POP off				**Wires and ex-fix out**				
				Wires out								
				Sterile gloves (n=2)			1.2	Sterile gloves (n=2)				1.2
				Dressing pack sterile woundcare with forceps			0.28	Dressing pack sterile woundcare with forceps				0.28
				Normal saline 20 mls (n=2)			0.92	Normal saline 20 mls (n=2)				0.92
				Sterile pliers			3.09	Sterile pliers				3.09
				Dressing vapour permeable adhesive with absorbent sterile pad (small) (n=2)			0.38	Dressing vapour permeable adhesive with absorbent sterile pad (small) (n=3)				0.57
				Staff Nurse Band 5 (15 min)			24.3	Staff Nurse Band 5 (15 min)				24.3
				Junior doctor (5 min)			6.1	Junior doctor (15 min)				18.3
				Overheads on procedure (20%)			1.17	Overheads on procedure (20%)				1.21
Three month follow-up			86	**Three month follow-up**			86	**Three month follow-up**				86
								Six month follow-up				86
One year follow-up			86	**One year follow-up**			86	**One year follow-up**				86
X-rays				**X-rays**				**X-rays**				
Post reduction			26	Post reduction			26	Post reduction				26
At one week			26	At one week			26	At one week				26
Post fixation			26	Post fixation			26	Post fixation				26
At six weeks			26	At six weeks			26	At six weeks				26
At three months			26	At three months			26	At three months				26
At one year			26	At one year			26	At one year				26
Physio (charged to PCT £25 per contact)				**Physio (charged to PCT £25 per contact)**				**Physio (charged to PCT £25 per contact)**				
Average contacts	n=6.3		157.5	Average contacts	5.9		147.5	Average contacs	n=9			225

With reference to Table 3.13, the following should be noted:

- New and follow-up fracture clinic attendance costs were based on the 2010-11 HRG tariffs for Trauma & Orthopaedic Outpatient Attendances (Market Forces Factor not applied)
- Consumable costs were exclusive of VAT, as per NICE guidelines (NICE, 2008).
- Operative time was calculated by subtracting the procedure start and end time, as recorded by theatre staff in ORMIS and included preparation, draping and the application of dressings, splints or plasters. Times reported in this model are not intention-to-treat.
- Different departments have different policies regarding disinfectant preparation solutions. We have estimated a minimum of one bottle used or discarded over 24 hours and average use of 125mls per patient.
- Consumable and implant prices were list prices. No hospital discounts were applied. The capital cost of purchasing equipment, such as re-usable operating sets and surgical instruments, was included in the non-pay element theatre overheads. Theatre Sterile Supply Unit (TSSU) costs were included in pay element and non-pay element overheads and were considered to be the same for each procedure.

- The costs of anaesthetic and resuscitation equipment which was not single use, as well as oxygen and other anaesthetic gases, were incorporated in overhead costs.
- Prophylactic antibiotics used were as per hospital protocol and are detailed in Appendix 6.6.1. Post op and discharge analgesics are also detailed in Appendix 6.6.2.
- The total cost figures do not include potential complications or above-average use of resources. Complication costs are presented separately in Appendix 6.7.

A model cost analysis, such as the one presented in Table 3.13, is a pre-requisite to, but separate from the main cost-utility analysis. Costing tables are itemised in great detail and consequently busy. The aim was to provide the greatest methodological transparency and allow reproducible use of the bottom-up costing methodology in this study for future economic evaluations.

3.5.2.2 Incremental treatment costs

Cost-utility analyses consider the incremental differences between two treatment alternatives. Incremental cost becomes the numerator of the ICER, which informs cost-effectiveness. In Table 3.13, the blue boxes highlight incremental costs i.e. costs that can differ between treatment interventions.

Figure 3.7 represents an "incremental cost flow chart" of a patient's journey through the study. When applied to each trial participant,

this allowed us to conceptually convert our data to columns in a workable excel spreadsheet.

Table 3.14 itemises the typical cost of a plaster room attendance. Tables 3.15 and 3.16 itemise the costs of a dressing change for the volar locking plate and a K-wire pin-site check as part of the percutaneous arm of the study.

The number of complications affecting cost per randomisation group is listed in Table 3.17. Details of cost per complication are presented in Table 3.18.

Figure 3.7 Incremental costs flow chart

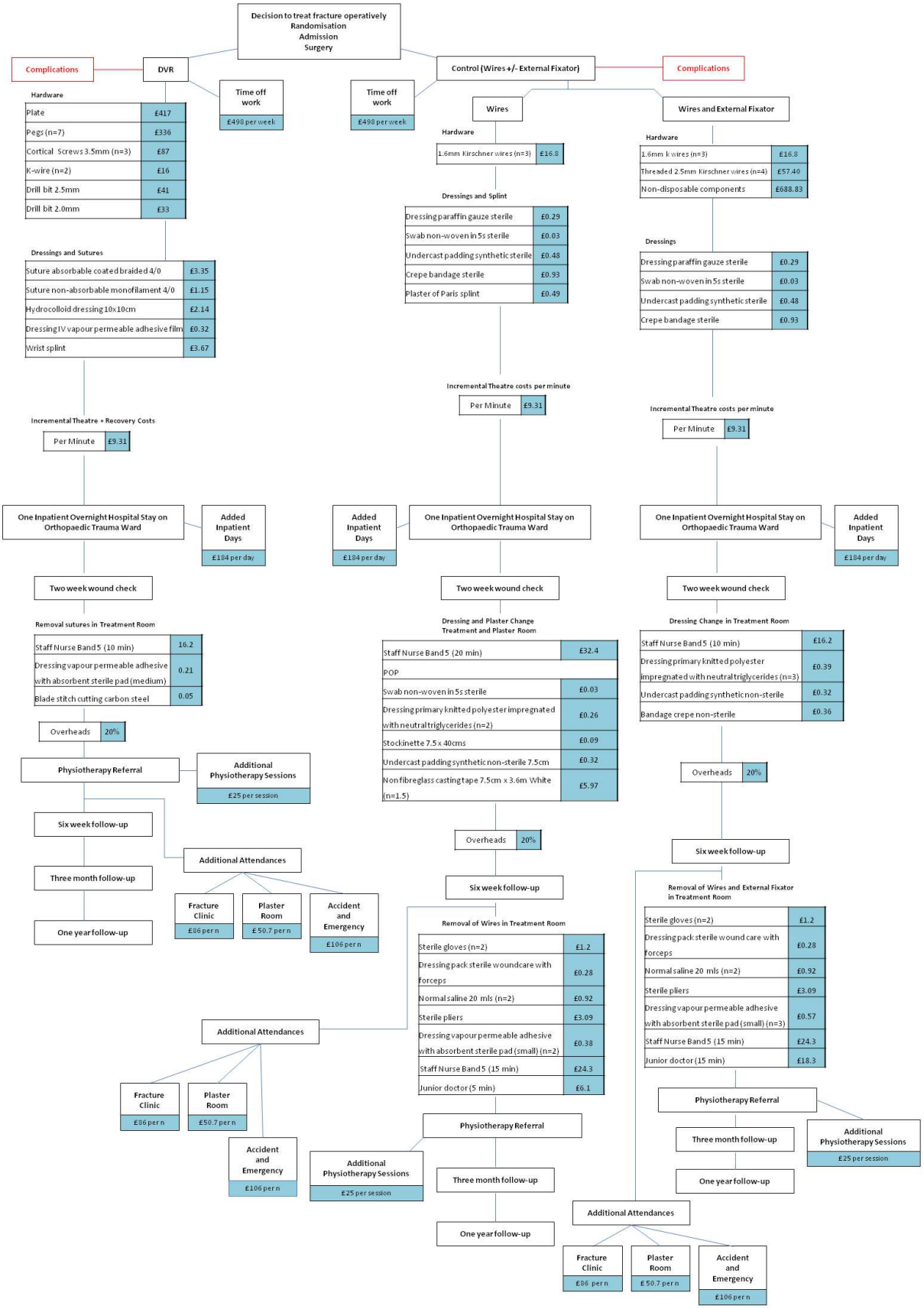


Table 3.14 Costing of plaster room attendance (removal and re-application of a below elbow cast with simple dressing change for k-wire inspection)

Cost category	Unit Cost (£)
Staff	
Staff Nurse Band 5 (25 min)	40.50
Change of dressing	
Dressing pack sterile wound care with forceps	0.28
20ml water for injection	0.68
Swab non-woven in 5s sterile	0.03
Dressing primary knitted polyester impregnated with neutral triglycerides (n=3)	0.39
Application of cast	
Stockinette 7.5 x 40cms	0.09
Under cast padding synthetic non-sterile 7.5cm	0.32
Non fibreglass casting tape 7.5cm x 3.6m White (n=1.5)	5.97
Overheads	1.55
Total	**49.81**

Table 3.15 Costing of dressing changes for the plate group

Dressing change plate	**Cost (£)**
Staff Nurse Band 5 (15 min)	24.30
Dressing pack sterile wound care with forceps	0.28
20ml water for injection	0.68
Sterile gloves (one pair)	0.60
Swab non-woven in 5s sterile	0.03
Dressing paraffin gauze sterile	0.29
Bandage crepe non-sterile	0.36
Overheads	0.45
Total	**26.99**

Table 3.16 Costing of dressing changes, which incorporate a cast exchange, for the K-wire patients

Dressing change wires	**Cost (£)**
Staff Nurse Band 5 (30 min)	48.60
Dressing pack sterile wound care with forceps	0.28
20ml water for injection	0.68
Sterile gloves (one pair)	0.60
Swab non-woven in 5s sterile	0.03
Dressing paraffin gauze sterile	0.29
Dressing primary knitted polyester impregnated with neutral triglycerides (n=2)	0.26
Cast change	
Stockinette 7.5 x 40cms	0.09
Undercast padding synthetic non-sterile 7.5cm	0.32
Non fibreglass casting tape 7.5cm x 3.6m White 9n=1.5)	5.97
Overheads	1.70
Total	**58.82**

[1] First dressing change at diagnosis, second at review.

[2] Based on an approximate amount; some institutions use other skin preparations; Hydrex® is the cheapest.

[3] This is the internal (in-house) charge. External charge to a different NHS provider is £11.55

Table 3.17 Complications requiring intervention per randomisation group

Locking Plate Group		Percutaneous Group	
	N		**N**
Superficial infection	2	Superficial infection	5
Removal of plate	2	EPL reconstruction	1
		Carpal tunnel decompression	1
		Removal of buried k-wires	6

EPL = Extensor Pollicis Longus

Table 3.18 Cost of complications

Complication	A (£)	B (£)
Removal of buried k-wires (outpatient procedure)	91.78	663.18
Removal of buried k-wires (day-case theatres)	934.2	1505.6
Superficial infection– plate	67.75	67.75
Superficial infection– control	135.33	135.33
Carpal tunnel decompression	934.2	2534.2
Removal of plate	1300	2900
EPL reconstruction	1310.2	3710.2

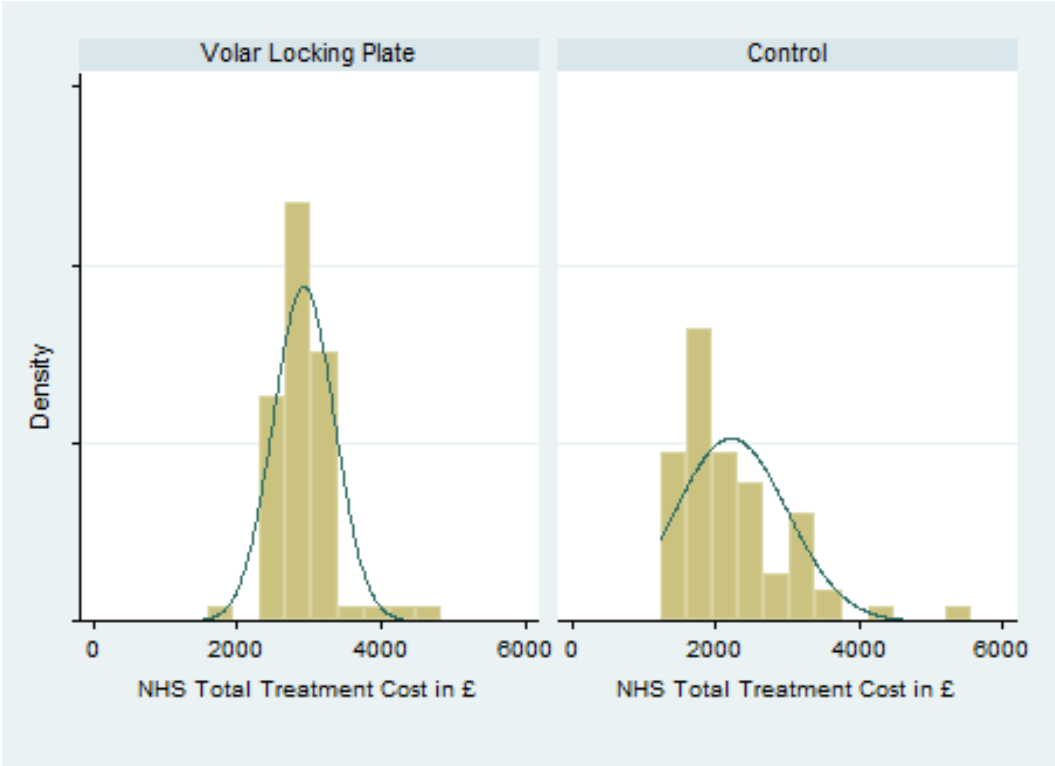
A = Cost from an NHS perspective

B = Cost from societal perspective (this also includes productivity loss)

3.5.2.3 True treatment costs

We present the total cost per treatment intervention, along with measures of spread and distribution. This cost is calculated from patient clinical data, taking into account the variability between individuals, potential complications, above or below average use of resources. The results are presented below as distributions (Figure 3.8). Total NHS cost, especially for the control group, is a positive skew.

Figure 3.8 Total NHS treatment cost per randomisation group



Descriptive statistics for NHS treatment costs in our study are summarized in Table 3.19. The volar locking plate option was significantly more expensive ($p<0.001$, 95% CI 496.9 to 929.5). The differential cost for the two arms of the trial was £713.42 (SE 109.3). This represents the numerator of the ICER.

Table 3.19 Total NHS treatment costs per randomisation group

Cost (£)	Mean	SD	Min	Max
Volar locking plate	2928.9	424.5	1912.6	4543.7
Percutaneous fixation	2215.7	776.5	1231.3	5212.5

This trial was not powered for subgroup comparative analysis. However, we can present the descriptive statistics of mean cost per non-intention to treat treatment category: £2995 (SD 486) for patients who underwent VPL fixation, £ 1915 (SD 426) for those who underwent simple K-wire fixation and £3169 (SD 550) for those who requiring supplemental external fixation. These figures are not used in the generation of the cost-effectiveness ratio.

There were no lost external fixation components.

3.5.3 Base-case analysis

The ICER for the base-case scenario, based on a differential treatment cost of £713.2 (SE 109.3) and the QALY gain achieved by volar locking plate fixation over percutaneous methods of 0.0178 (SE 0.025), was £40,080.

or

$$\text{ICER} = \frac{713.42}{0.0178} = 40{,}080$$

3.5.4 Resource use

As part of the trial protocol, each patient was allocated as standard one overnight inpatient stay and four follow-up fracture clinic appointments (two, six, twelve weeks and one year), incorporating dressing room or plaster room attendances according to the treatment arm. Any hospital contacts above this were considered extra. In addition, operative time in minutes and number of physiotherapy sessions are presented in Table 3.20.

There were significantly more extra plaster room visits, as well as overall number of extra hospital contacts for the percutaneous fixation arm. This represents the "hidden cost" of percutaneous fixation. Percutaneous fixation in this study was also no faster in terms of operative time.

Table 3.20 Resource use by randomisation group

	Locking Plate Group		**Control Group**		
	Mean	*SD*	***Mean***	*SD*	***p***
Operative time (min)	64	22	66	32	0.693
Extra inpatient days	0.39	0.74	0.61	1.50	0.265
Extra fracture clinic visits	0.42	0.88	0.72	1.23	0.117
Extra plaster room visits	0.07	0.32	0.48	0.89	**<0.001**
Extra emergency room visits	0.07	0.27	0.05	0.21	0.497
Extra overall hospital contacts*	0.52	1.07	1.56	2.22	**<0.001**
Extra physiotherapy sessions	3.90	4.75	3.47	4.88	0.643

* Extra overall hospital contacts = fracture clinic + plaster room + A&E visits

Descriptive statistics of the three subgroups are detailed in Table 3.21. Patients with supplemental external fixation required a longer inpatient stay, more fracture clinic follow-up visits and almost double the number of physiotherapy sessions. The study was not powered for subgroup analysis, so comparative analyses were not performed.

Table 3.21 Resource use by treatment subgroup (not intention-to-treat)

	Volar Locking Plate		**Percutaneous Wires**		**External fixator**	
	n=67		n=52		n=11	
	Mean	*SD*	***Mean***	*SD*	***Mean***	*SD*
Operative time (min)	66	26	63	29	69	28
Extra inpatient days	0.42	0.80	0.33	1.0	**1.72**	2.5
Extra fracture clinic visits	0.46	0.97	0.61	1.22	**1**	0.77
Extra plaster room visits	0.07	0.32	**0.58**	0.96	0.09	0.30
Extra emergency room visits	0.06	0.24	0.08	0.27	0	0
Extra overall hospital contacts*	0.62	1.21	1.33	1.91	**2.09**	3.33
Extra physiotherapy sessions	3.64	4.18	3.16	5.13	**6.3**	6.24

* Extra overall hospital contacts = fracture clinic + plaster room + A&E visits

Time taken to return to work and income lost (value in lost productivity) per randomisation group are reported in Tables 3.22a-b. The data distributions, as shown in Figures 3.9 and 3.10 were not normal and represented a positive skew. Though the median is useful in describing the data, for reasons described previously in the methods, it is broadly accepted that the arithmetic mean and the difference in the mean are the measures used for cost-effectiveness analysis (Glick, 2007). The results of the between-group comparisons are the same, either way.

Patients who underwent volar locking plate fixation did not return to work earlier, and there was no significant productivity gain by using this treatment. However, they did return to driving sooner.

Figure 3.9 Days off work per randomisation group

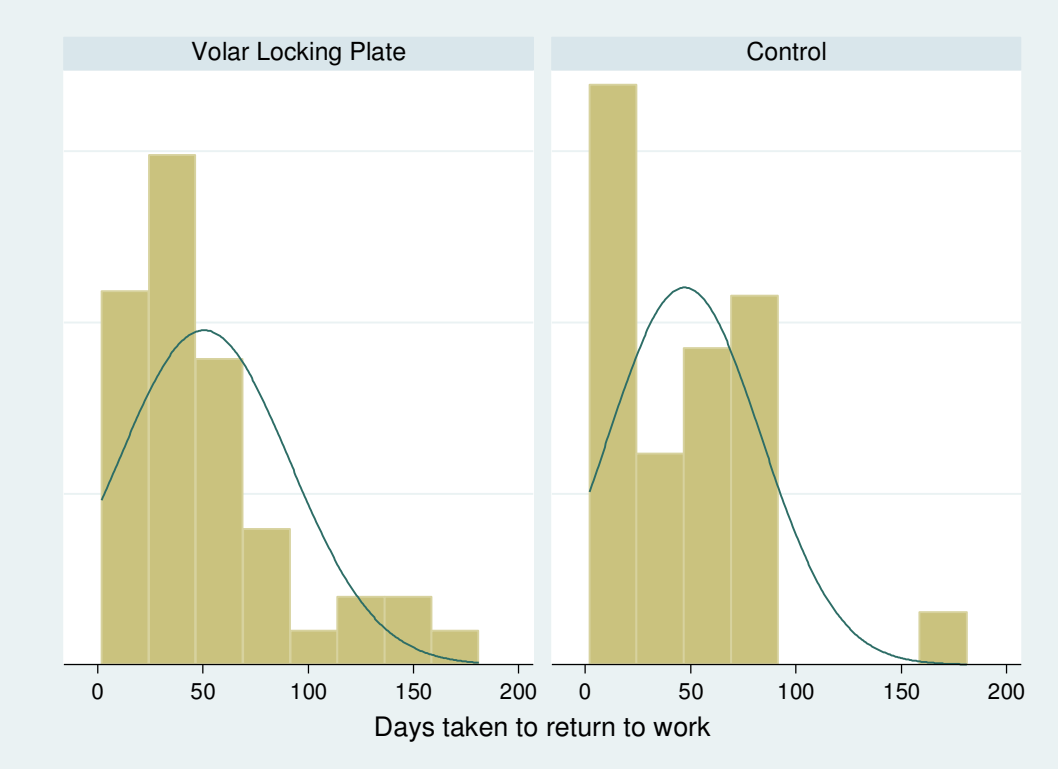


Figure 3.10 Lost productivity per randomisation group

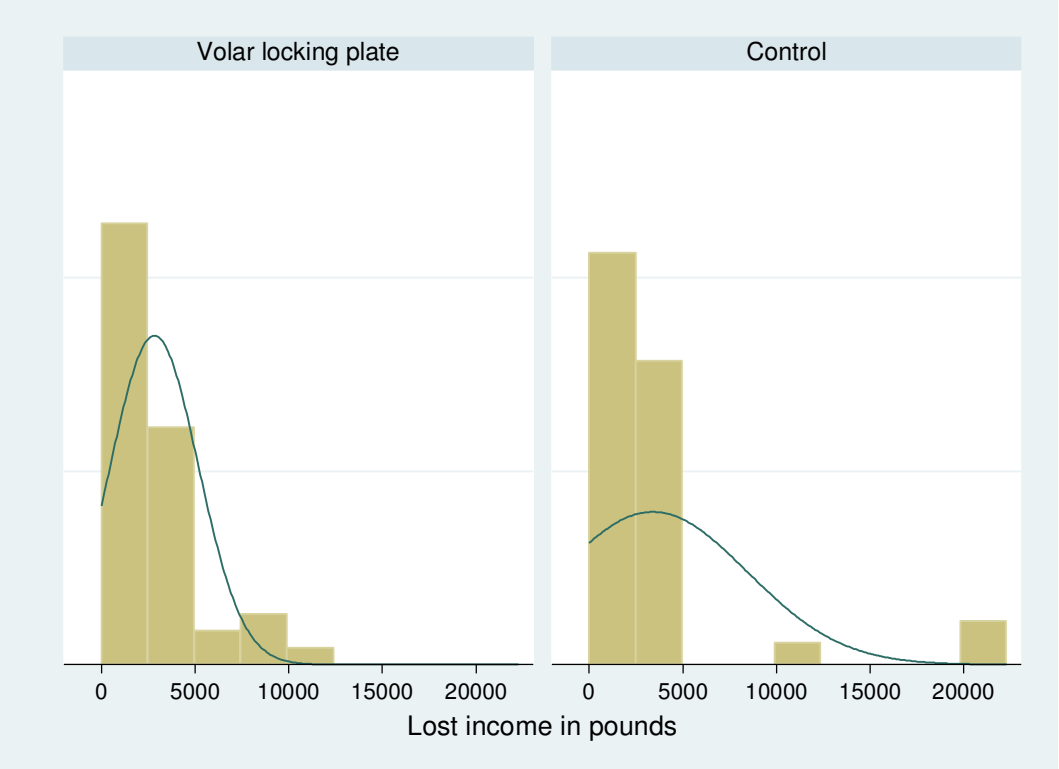


Table 3.22a and b Time of work, driving and value of lost productivity

	Locking Plate Group		**Control Group**		
	Median	*Range*	***Median***	*Range*	***p***
Days of work	43	3-181	63	2-174	0.877
Days off driving	37	6-242	46	8-272	<0.001
Value in lost productivity (£)	2086	0-10,343	2400	0-22,286	0.537

	Locking Plate Group		**Control Group**		
	Mean	*SD*	***Mean***	*SD*	***p***
Days of work	50.58	40.81	47.17	36.19	0.679
Days off driving	50.98	7.36	68.82	7.112	0.006
Value in lost productivity (£)	2827	2345	3400	5050	0.497

3.5.5 One-way sensitivity analysis

In this study, sensitivity analysis was performed to vary assumptions about the cost of implants. A 20% discount, before VAT, was applied to all orthopaedic implants (see methods). Given that the original cost of the volar locking plate implant was substantially higher (£930) compared to that of Kirschner wires (£16.8) and higher even to that of the components of supplemental external fixation (£763), the proportional savings were also larger. The ICER for this scenario was £31,898 (Table 3.23).

Threshold analysis allowed the indicative price to be determined for the volar locking plate implant, which would potentially bring the technology into the cost-effective range according to NICE thresholds. Assuming all other costs remain the same and an indicative hospital discount of 20% is applied to the control arm to simulate a realistic hospital environment, an implant cost of £621 for the volar locking plate would produce an ICER of £25,000 and an implant cost of £532 pounds an ICER of £20,000 (Table 4.18). The implications are debated in the discussion. Prices are exclusive of VAT and discount percentages are based on the public list price of the DVR® implant, which was the implant used in this study. There are a great number of volar locking plate implants, available from a variety of manufacturers, for differing prices.

Table 3.23 Results of one-way and threshold sensitivity analyses

	ICER	Cost of volar locking plate implant	Percentage discount on list price
Base-case analysis	£40,080	£930	0%
20% hospital discount	£31,898	£744	20%
ICER £25,000	£25,000	£621	33%
ICER £20,000	£20,000	£532	43%

3.5.6 Probabilistic sensitivity analysis

Cost and QALY data typically are not normally distributed. Cost data are often highly right skewed because of a few cases that incur extremely high costs, while QALY data are usually left skewed because of the ceiling effect (Willan and Briggs, 2006) (Thompson and Barber, 2000).

In the current study, probabilistic sensitivity analysis in the form of a Monte Carlo simulation was used to explore the calculated ICER. The results from the simulation were used to plot the cost-effectiveness plane (CEP) of the study (Figure 3.11) and the cost-effectiveness acceptability curve (CEAC) (Figure 3.12) to demonstrate decision uncertainty. The CEAC presents the

probability that fixation via volar locking plate is the preferred treatment option at different values for a decision maker's willingness-to-pay (WTP) (Fenwick et al., 2001)

The illustrations show that, on the majority of occasions, the volar locking plate was more costly than the control method of percutaneous fixation. The likelihood of it being cost-effective for any given threshold was 50% or less. On a small number of occasions, VLP fixation was more expensive and less effective compared with percutaneous fixation and vice versa.

At no point was the new treatment (plate) associated with 100% probability of being cost-effective. This was because there were a number of simulations that suggested it produces fewer QALYs at greater cost compared to the alternative. Note also that the average ICER was found at a willingness to pay threshold of approximately 50% (Fox-Rushby and Cairns, 2009).

The simulation also allowed the calculation of the confidence interval for the ICER (95% CI -100,123 to 95,833), which spanned zero, and similarly reflected the uncertainty associated with the results. The confidence interval was driven by HRQL accuracy rather than costs (there was much less variation in incremental cost rather than in incremental QALYs).

Figure 3.11 Cost-effectiveness plane showing bootstrapped replicates of the ICER

Each point represents an estimate of the ICER based on dual bootstrap of cost and efficacy. The diagonal red line represents a cost-effectiveness threshold of £25,000. Estimates of the ICER below this benchmark would be considered cost-effective.

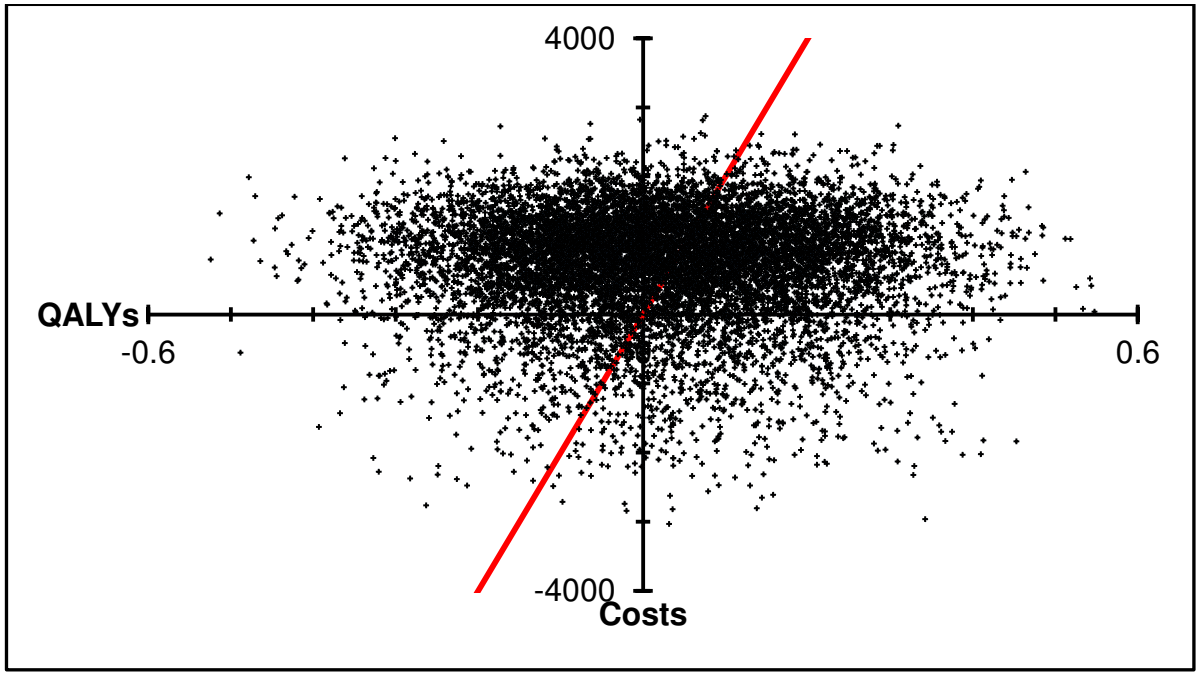
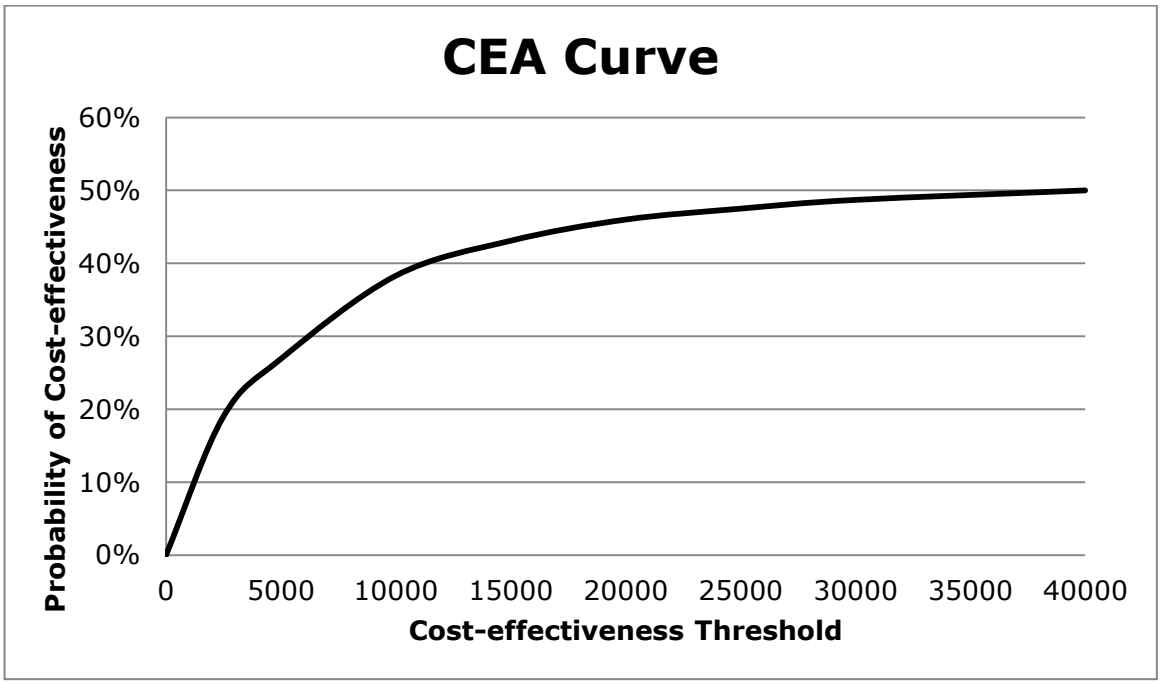


Figure 3.12 Cost-effectiveness acceptability curve showing the probability that the intervention is cost-effective at different willingness-to-pay thresholds



3.5.7 Comparison of the EQ-5D TTO and SF-6D

For the health states described in our study, the EQ-5D appears consistently to assign a higher utility score than the SF-6D (Table 3.10). Figure 3.13 graphically compares EQ-5D TTO and the SF-6D utility index scores for the randomisation groups at each time point in the study.

Table 3.24 demonstrates summary statistics for the QALY gain calculated using the SF-6D and the EQ-5D TTO index scores for each intervention.

Figure 3.13 EQ-5D and SF-6D utility index scores for the randomisation groups at each study time point.

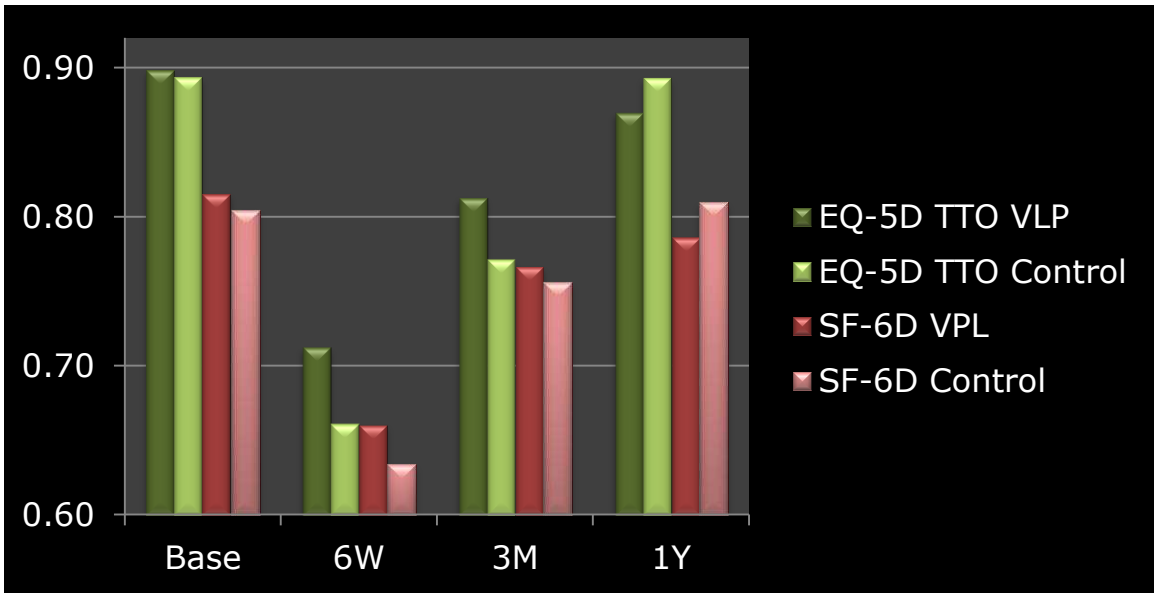


Table 3.24 QALYs calculated using the EQ-5D TTO and SF-6D utility measures

	Mean	Diff in means	SED	95% CI	Sign.
QALYs using EQ-5D TTO					
VPL	0.828	0.0178	0.025	-0.031 to 0.067	p=0.47
Control	0.811				
QALYs using SF-6D					
VPL	0.766	0.0032	0.016	-0.028 to 0.035	p=0.84
Control	0.763				

We found utility scores to be higher with the EQ-5D than with the SF-6D. Utility scores on the SF-6D have a narrower range (0.296 to 1.00) (Brazier et al., 2004), compared to the EQ-5D (-0.594 to 1.00) (Dolan, 1997). This is because both scales have 1.00 for perfect health, but the worst utility score for the EQ-5D is below zero, whereas the utility of the worst health state for the SF-6D is well above zero. In other words, the SF-6D and the EQ-5D are not perfect linear analogues of each other. Additionally, time trade-off valuation scores (the technique used with the EQ-5D) tend to be higher for milder states, but lower for more severe states, compared with standard gamble scores (which are used with the SF-6D) (Sach et al., 2009). As a result, it has been proposed that

estimated utility gains will tend to be higher according to the EQ-5D, compared with the SF-6D (Conner-Spady and Suarez-Almazor, 2003, Tsuchiya et al., 2006). This has been shown in different patient populations (Longworth and Bryan, 2003, Lamers et al., 2006, van Stel and Buskens, 2006). Our results support this conclusion, as the QALY gain was estimated to be higher according to the EQ-5D.

We examined whether the SF-6D could be a more sensitive utility score in our setting of the operative management of distal radius fractures. At 12 months the EQ-5D TTO standardised responses mean (SRM) 0.09 versus 0.03 for the SF-6D. It could therefore be considered the more *sensitive* measure in this population group.

Chapter 4 – Discussion

4.1 Statement of principal findings

This work compared the outcome of displaced distal radius fractures when treated with a volar locking plate or closed reduction and percutaneous wire fixation, with supplemental bridging external fixation when required. The study showed that the use of a volar locking resulted in better early post-operative function. However, there was no significant difference at, or after 12 weeks (Table 3.5). Despite the early functional advantage, participants did not return to work sooner (mean difference 3 days, SE 9 days, p=0.72). The volar locking plate achieved better radiographic reduction (Table 3.7) and grip strength throughout (Table 3.5). However this did not translate to a difference in function at 12 weeks and 1 year. There were more complications in the percutaneous fixation arm of the study (26/64, 39% vs 15/66, 23%, p = 0.057).

NHS costs for the volar locking plate group were significantly higher (£713.2, SE 109, p<0,001). Quality of life scores for this group were slightly, but not significantly better at early follow-up (ΔQ = 0.0178, SE 0.025, p=0.47). Both groups returned to baseline at one year (Table 3.12). Based on the results of cost-effectiveness analysis from the perspective of the NHS, volar

locking plate fixation for distal radius fractures in this study was not found to be cost-effective according to NICE threshold criteria (ICER = £40,080).

4.2 Discussion of results in the context of the literature

4.2.1 Discussion of clinical results

Distal radius fractures are common injuries that have a substantial impact on health care systems (Cummings et al., 1985). In recent years, the rate of non-operative treatment has declined, just as the rate of internal fixation and particularly of volar locking plate fixation, has increased exponentially (Chung et al., 2009).

Early biomechanical studies documented a number of theoretical advantages of volar locking plate fixation (Larson and Rizzo, 2007) and subsequent longitudinal clinical studies demonstrated good outcomes (Chung et al., 2006, Rozental and Blazar, 2006, Beaton et al., 2005, Orbay et al., 2004). More recently, prospective randomised studies have emerged, comparing treatment with volar locking plates and less invasive, percutaneous methods of fixation (Goehre et al., 2013, Egol et al., 2008, Rozental et al., 2009, Wei et al., 2009, Marcheix et al., 2010, McFadyen et al., 2011, Hollevoet et al., 2011). These studies are reported in detail in Chapter 1.2.5.1. Overall, they advocated the use of volar locking

plate fixation over percutaneous methods, despite failure to identify a long-lasting functional advantage of the new technique.

The benefit of volar locking plate fixation in terms of functional outcome in the short term has been challenged by the current study. Previously, it was suggested that the functional benefit of volar locked plating may last from 3 up to 6 months (Rozental et al., 2009, McFadyen et al., 2011, Marcheix et al., 2010). However, we found this short-term benefit was smaller and lasted for between six and twelve weeks after surgery. As such, and given the large prevalence of distal radial fractures (Wulf et al., 2007), the results of this and similar studies can be seen in a different light: if patients experience only an additional maximum six weeks of functional advantage from the use of the technique, it should be considered if these outcomes justify the cost of treatment with a volar plate.

Measured grip strength was significantly greater for the plate group at all study time points, in contrast to the functional patient-centred outcome measures, which showed no difference at, or beyond, 12 weeks (Table 3.5). This could be explained if the observed differences in grip strength were statistically, but not clinically important. There is no published Minimally Clinically Important Difference (MCID) for grip strength relevant to the population in this study. MCID for grip strength varies according to

the condition and the population studied. For example, in a study of stroke patients, the reported MCID was 22% for the non-dominant limb (Lang et al., 2008). In a health population differences between dominant and non-dominant hand are in the range of 10-15% for right handed people (Petersen et al., 1989, Nitschke et al., 1999).

Per protocol analysis (PP) of functional and clinical outcomes was undertaken, in addition to intention-to-treat analysis. The results of the PP analysis results were no different to the intention-to-treat analysis (Tables 3.5 and 3.6). The combined results were interpreted as per the grid demonstrated in Table 2.2 of the methods. This demonstrated that the effect of the equally distributed, non-compliant cases was minimal.

Radiographic outcomes demonstrated that better restoration of palmar tilt and radial height was achieved with plating (Table 3.7). This did not translate to a difference in function past 6 weeks. Radiographic parameters reflect the accuracy of surgical reduction, however the link between malunion and patient-related function has long been under debate (Downing and Karantana, 2008, Forward et al., 2008, Brogren et al., 2013, Finsen et al., 2013). While many studies have investigated the relationship between extra-articular malunion and outcome after fractures of the distal radius, there is little consensus on the amount of malunion that can be tolerated without loss of function (Karantana and Davis, 2012).

The uncertainty about the long term relevance of varying degrees of extra-articular malunion is unlikely to be resolved in the near future. Large prospective studies of long-term outcome, with appropriate outcome measures including cosmesis, and a clear, stratified and clinically relevant definition of malunion, are required.

Limits of agreement for radiographic parameters in this study (Table 3.8) were narrower than the intra-observer tolerance limits set by Kreder et al. in their paper on standardising x-ray film measurements for healed distal radius fractures (Kreder et al., 1996b). This is likely attributable to good quality, standardised radiographs obtained as part of the trial protocol, the experience of the observers in techniques of radiographic assessment and the accuracy of the electronic software measurement tools. Kreder et al. used the interclass correlation coefficient (ICC), a statistical method which according to Altman is inappropriate for the problem of judging agreement. This could have had an additional effect on the variance of their measurements (Bland and Altman, 1986) and is a commonly occurring error in the medical literature. The correlation coefficient is not a valid measure of agreement, as it is influenced not only by the measurement variation between observers, but also the values being measured. So, if the variation between individuals (i.e. patients, not observers) is high compared to the measurement error, the correlation will be high, whereas if

the variation between individuals is low the correlation will be low (Altman and Bland, 1983). The Bland-Altman method eliminates this problem.

Deciding what is good and poor agreement also depends on what is considered to be clinically important. Given the lack of correlation between radiographic parameters and function (as discussed in Chapter 2.1.4), this type of analysis can only show the level of precision of our measurements in relation to those made by others. It cannot help define what level of agreement is clinically relevant.

Though there were more complications in the percutaneous arm, the difference did not reach statistical significance (Table 3.9). Overall, most complications were transient. However, two plates required removal and a third patient, who received a plate but was analysed in the percutaneous group as per intention-to treat, required extensor pollicis longus tendon reconstruction. The number of implant specific complications for volar locking plate fixation (3/66, 4.5%) was lower than that reported by other studies (Table 1.6) (Johnson et al., 2013, Sahu et al., 2011, Arora et al., 2011, Rozental et al., 2009). This can be explained by the fact that surgery was consultant led, performed in a tertiary centre.

4.2.2 Discussion of economic evaluation results

There is, at present, no published evidence of the cost-effectiveness of volar locking plate fixation for distal radius

fractures. None of the existing trials have been accompanied by economic evaluations. Given that comparative studies have not proven a long-term benefit, one of the driving factors for the continued use of the technique has been the perception that it provides a fiscal advantage, with implant costs offset by a shorter period of immobilisation, a lower use of resources and an earlier return to work. The current study found no evidence to support these propositions.

Based on the results of the cost-effectiveness analysis, and according to NICE threshold criteria, volar locking plate fixation for distal radius fractures was not cost-effective at the current list price for the DVR® implant: the ICER for the base-case scenario was £40,080. However, as hospitals do not pay list price for implants, it is more realistic scenario to apply a hospital discount. With an indicative 20% hospital discount, the ICER was reduced to £31,898, which remained overly expensive.

This study used a specific implant, selected on the basis of surgeon preference, familiarly, popularity and widespread use. This plate is one of many implants available on the market, and at the more expensive end of the range. Though one would not want to select a particular implant based on price alone, the volume of volar locking plate implants utilised in the health service necessitates that pricing be, at least, a consideration. Sensitivity analysis showed

that, providing all other parameters remained the same, an implant cost of £621 plus VAT would generate an ICER of £25,000 and an implant cost of £532 plus VAT would generate an ICER of £20,000, within the approved cost effectiveness range. It should be emphasised that these figures are not absolute. They carry uncertainly and require specific assumptions. However, they provide a guide on what could be expected from a lower priced implant in the described context of use. This univariate sensitivity analysis based on price is fairly robust, as there are no assumptions made about resource use or patient preference-based scores, and only a single, constant parameter is altered in a transparent way.

The differential cost of the two treatments (ΔC=£713) was lower than the cost-difference of the implants involved (ΔC=£913). This reflected the higher use of certain resources by patients in the percutaneous treatment arm and the high cost of the infrequently used supplemental external-fixator components (£688.8). The study design focused on capturing what could be considered the "hidden" resource-use of the percutaneous fixation group, such as plaster changes, wound checks secondary to troublesome pin sites, inadvertently buried wires etc.

Unexpectedly, percutaneous fixation was no quicker than open reduction internal fixation in terms of operative time. This

remained the case, even when resource use was depicted separately for each subgroup: K-wire fixation was no quicker than plate fixation (Table 3.21). This could possibly be explained in part by delays in awaiting radiographers. However, the data to support this was not available as part of this study.

Patients with supplemental external fixation had high costs associated with expensive implants. They also required on average a longer inpatient stay, at least one additional fracture clinic visit and increased use of physiotherapy services. The study was not powered for subgroup analysis, so we cannot draw statistical conclusions. However, the figures suggest that the few patients with supplemental external fixation required more resources and a longer recovery period.

In terms of implant costing, published evidence was used to support the safe re-use of non-single use external fixator components three times. In practice, most re-usable external fixator components continue in use for longer, until they appear macroscopically worn or cease to function. This could represent a small potential bias in favour of the volar locking plate. Nevertheless, this would not alter the conclusion of the study.

The study showed that volar locking plate fixation was definitely a more expensive treatment (SED of costs was very narrow). Despite this, it was not more effective than percutaneous fixation, in terms

of quality of life scores. The SED of the QALY gain was very wide. As a result, the confidence interval for the ICER was also very wide and spanned zero. The confidence interval was calculated using stochastic probabilistic methods, a special type of modelling (Glick, 2007, Briggs, 2000b). This is a valid method which uses a computer algorithm and the data from the trial to carry out circa 25,000 calculations, in order to model what would happen if the trial had 25,000 participants. Confidence intervals cannot be produced with standard techniques, such as when comparing normal distributions. There are other methods of expressing uncertainty in cost-effectiveness analysis. In effect, calculating a confidence interval for the ICER in economic evaluation is, in itself, a subject of debate for health economists, as is the issue of power in economic evaluation (Polsky et al., 1997, Briggs, 2000a).

According to the analysis, there was no evidence to support volar locking plate fixation offering value-for-money in the setting of distal radius fractures. There was less than 50% chance of cost-effectiveness at current willingness-to-pay thresholds, as demonstrated by the cost-effectiveness curve (Figure 3.12). This probability represents less than the toss of a coin.

The study also examined the effectiveness of the interventions at reducing days taken off work. The expectation of a speedier recovery and potential earlier return to work has been one of the

driving forces for the increasing use of volar locking plate fixation in an active population (Diaz-Garcia and Chung, 2012). Patients who underwent volar locking plate fixation and were in employment at the time of injury, did not return to work significantly earlier in our study (mean difference 3 days, SE 9 days, p=0.72). There was therefore no significant productivity gain by using this treatment (Table 3.22). It is worth noting however, that only 6% (5/83) of working patients in the study were self-employed. It is conceivable that some patients returned to work later than they could physically have done so. To that end, we also examined as a soft surrogate outcome measure, the self-reported time from injury to return to driving. Patients who underwent volar locking plate fixation returned to driving earlier (mean difference 18 days, SE 10 days, p<0.01) than those undergoing percutaneous fixation. In a setting where compensation is offered, in the form of sick pay, for short term disability and illness, time taken off work reduces productivity, but not always personal income. Nevertheless, this does not alter the main study conclusion from a societal perspective. Finally, 5% (7/135) of injuries were sustained at work and, to our knowledge there was one compensation claim, which was in the volar locking plate group.

Baseline compatibility of the randomisation groups was very good. In addition the participants' age and sex distribution was consistent with published age and sex-specific incidence rates for distal radius

fractures (Larsen and Lauritsen, 1993), demonstrating that the study sample was representative of the demographics of the injury. The study population was also comparable, in term of baseline EQ-5D recruitment scores, with published UK population norms matched for age, sex and standard region (TTO z score = -0.16, HS TTO z score = -0.14), with no discernable differences in matching between the randomisation groups. Length of follow-up was adequate and appropriate. There were no significant differences in HRQL scores from recruitment to one year. Scores returned to baseline at the end of trial follow-up, and all showed similar patterns of recovery (Table 3.12).

Finally, we examined whether the SF-6D could be a more sensitive utility score in our setting of the operative management of distal radius fractures. A purported advantage of the SF-6D is its larger descriptive system (i.e. 18,000 unique health states can be described by SF-6D, compared to only 243 by EQ-5D). Therefore it potentially had greater ability to identify small health changes (Bryan and Longworth, 2005). Also, compared to the EQ-5D, the SF-6D has more dimensions and more levels. This leads to the suggestion that for patients with relatively high levels of health of baseline health, such as those in our study, the SF-6D could have been more sensitive to utility gain (Grieve et al., 2009). We found no evidence to support this in the current study (Table 3.24).

Even so, this does not prove that the EQ-5D is also the *preferred* measure, as this could represent an overestimation of the true gain in utility associated with the particular change in health. Due to the complexity of the methodology involved and the range of issues that need to be considered when choosing between HRQL measures, simple comparisons of data collected using the two instruments cannot effectively be used to uncover the main drivers of disagreement between utility measures (Bryan and Longworth, 2005). It was beyond the scope of the thesis to explore this complex and controversial issue. The main conclusion is that the SF-6D and the EQ-5D are not interchangeable in economic evaluation. In light of this, and to ensure a consistency in its approach, NICE developed its reference case, which includes use of the EQ-5D TTO score only, in order to estimate adult utility scores (NICE, 2008).

4.3 Study caveats

The present study has limitations.

Study time points

The postoperative immobilization period differed between the two surgical techniques. Patients in the volar locking plate group were allowed to start moving their wrist two weeks after surgery (though not everyone would mobilise to the same degree, and some

patients required longer periods of immobilisation), whereas patients in the percutaneous fixation group had the wrist immobilized in plaster for six weeks as standard. When the first functional outcome scores were determined at six weeks, the plate group demonstrated better results. It could be argued that the difference in outcomes at six weeks could be attributed to the longer immobilization period following percutaneous fixation, rather than the result of a difference in initial fixation techniques (Day et al., 2013). The implication would be that a slightly later follow-up time point, for example at seven or eight weeks, would have perhaps eliminated this potential advantage for the plate.

Perhaps in retrospect, an 8 week time point could have provided more precise information about the pattern of early functional recovery. However, the study was designed on pragmatic principles to reflect usual practice. Patients were routinely seen at six weeks as part of the treatment pathway. An additional follow-up appointment solely for the purpose of data collection would have increased cost and resources required to run the study. Furthermore, more follow-up points generally reflect a more exploratory approach, with implications on the external validity of other aspects of the study design, such as the economic evaluation.

Blinding and ascertainment bias

Blinding is very important in maintaining the integrity and validity of results. Failure to blind tends to influence results in favour of newer or more expensive treatments. In a review of 250 RCTs identified from 33 meta-analyses, researchers observed that lack of double-blinding led to a significant overestimate of treatment effect, with odds ratios being exaggerated by as much as 17% in un-blinded studies (Schulz et al., 1995).

The current study was not blinded. This is because the nature of the surgical procedures, the scars and the differences in the related post-operative care are difficult, if not impossible to realistically mask. Simply wearing a bandage or glove to cover scars during assessment was not judged adequate in our setting. Radiographic blinding was also not possible due to the presence of differing hardware.

In addition, organisational issues, lack of monetary and personnel resources, as well as time restraints introduced elements of ascertainment bias to the study. The chief investigator (CI) both designed and implemented the study. This included participation in recruitment, data collection, patient assessment, information management and analysis, but not operative management. As an assessor, she therefore could not be classed as fully "independent".

The choice of a patient-reported outcome measure as primary outcome measure, completed independently by the participants, reduced the risk of ascertainment bias. The PEM (Macey et al., 1995) is a patient-centred questionnaire, completed at each time point solely by the patient, with no input from study personnel, prior to the encounter at which clinical data was collected.

Age range

The study examined a large age range, with younger and older patients in each group. Based on their age, some of the older patients were more likely to be osteopaenic. While plain radiographs may suggest reduced bone stock, a 35-50% reduction in mineral density must occur before bone density appears decreased on x-ray (Jensen et al., 2004, Jergas et al., 1994). Furthermore plain X-rays are not quantitative and cannot be used for an objective measurement of bone mineral density. This would require Dual energy X-ray absorptiometry (DXA) scanning or computed tomography (CT), for which there was neither funding nor ethical approval.

However, the randomisation groups were balanced for age (no difference in age distributions between groups) with a sample size large enough to allow for this balance. If there had been a statistically significant difference in age between the groups, age as

a confounder would have been controlled for with regression analysis. This was not required.

It is a logical question to ask if one treatment fairs better in a particular age group. Despite the balanced nature of the randomisation groups, this trial was not set up to answer this question. A much larger sample size would be required. Even in a large multi-centre surgical study, one could not provide answers to cover individual decades. A limited number of age "groups" would have to be defined, for example a cut-off between "young" and "old", and a subgroup analysis so pre-defined. The point where this cut-off lies is debatable and depends on which factor one takes to be the confounder: is it the quality of the bone that is likely to affect outcome, or the level of activity, or even the ability to self-care? The DRAFFT study suggested tactic to tackle this issue (Costa et al., 2011). The investigators stratified on the basis of age, using age as a surrogate of bone mineral density and mechanism of injury. They chose to stratify by age above or below 50. This approach was based on a study from Norway that demonstrated that forearm bone mineral density remained stable until the age of 50 years, before declining steadily in males and more abruptly in females (Berntsen et al., 2001). This is a reasonably justified way to ensure balance across groups and eliminate a potential confounder, providing the sample size calculation a priori allows for such a comparison.

Supplemental external fixation

The choice to include supplemental external fixation in the percutaneous arm could also be questioned. Percutaneous Kirschner-wiring supplemented by external fixation is a recognised treatment modality and the established treatment prior to the introduction of angularly stable, volar locking plate devices. The decision for an external fixator to supplement k-wire fixation is generally made at the time of surgery and cannot always be predicted. It is based on the stability of the achieved wire fixation and the intra-operative images.

The option of supplemental external fixation was included, when the surgeon felt this was indicated, as it was considered unethical to assign additional external fixation to all patients in the percutaneous group, or alternatively to under-treat fractures for which an acceptable fixation was not achieved with k-wires alone. This represents a pragmatic aspect of study design and reflects clinical practice for percutaneous fixation.

It could be argued that patients with an external fixator were likely to have a slower recovery in the short term. Subgroup analysis in this setting would involve direct comparisons using the extremely small number of patients with external fixators. This comparison would be underpowered, non-randomised, and not predetermined, and therefore contra-indicated (Moher et al., 2010). In addition,

participants requiring supplemental external fixation would potentially be the patients with the most unstable fracture patters within the percutaneous fixation group. It could equally be argued that their potentially slower recovery was the result of the original injury, rather than the treatment modality.

Finally, excluding the patients with external fixation from the analysis would not have changed the results of the study. Such a practice of exclusion is methodologically flawed as it would introduce a different form of bias, namely "bias due to exclusions after randomisation". This is the same type of bias that intention-to-treat-analysis is aimed to address (Moher et al., 2010). Any potential bias introduced by the slower recovery in the small number of patients with external fixators would be in favour of the original hypothesis, which is that "the use of volar locking plates improves functional outcome". This would increase the possibility that the trial could have produced a spurious result in favour of the plate, which it did not. Hence, this does not compromise the conclusion.

Fracture types

There has been some discussion about the use of pragmatic trials with wide inclusion criteria to inform individual clinical practice (Rothwell, 2005a, Patsopoulos, 2011, Summerskill, 2005). In particular, there could be criticism regarding the inability to power

trials similar to this for subgroup analysis according to fracture type. The current study has dealt mostly with AO type A3 and C2 fractures, with these comprising over 90% of the fracture population (Table 3.7). Only a small number of AO C3 fractures were represented in each group. Though the current study provides answers for the most common fracture types treated via locking plate fixation, it is possible that a study of selected AO C3 fractures, performed by experts in the technique, and within a specific population, would give different results.

Power of economic evaluation

If the goal of a study is to show that the ICER is significantly below some upper limit on the maximum society is willing to pay for health gain, then it is very likely that sample size requirements for economic evaluation will be many times those required to show a clinical effect (Briggs, 2000a). As a result, cost-utility analyses alongside clinical trials are almost always underpowered, especially in surgery.

Some may argue that it is unethical to power a trial based on economic endpoints, as the numbers required are extremely high, many times those required to power a clinical outcome. In other words, this would require further randomisation of patients to a treatment which has already been proven to be clinically ineffective, merely to prove beyond doubt whether it is cost-

effective (Briggs, 2000a). On the other hand, most funding bodies now require economic evaluations to be performed alongside clinical trials. However, given finite budgets, the NHS is faced with funding either only a few very large trials based on economic endpoints or many more comparatively smaller ones powered for clinical endpoints, which can provide only estimates of cost-effectiveness.

Briggs et al. from Oxford have produced the main guidance to date on power and sample size calculations for stochastic cost-effectiveness analysis (Briggs and Gray, 1998). They explored the issues associated with sample size calculation for economic evaluation alongside RCTs and developed a formula for determining sample size that can be used for cost-effectiveness analysis. In their landmark paper, they give a numerical example. This suggests that in order to detect a 40% difference in outcome of a new surgical intervention compared to conventional treatment, for an ICER of circa £21,000-£25,000, with power of 90% at a 5% level of significance, a sample size of 750 is required. For a smaller difference in outcome, the number required is in the thousands. This is an unrealistic target for surgical trials, even for large multi-centre studies.

Confidence interval for the ICER

The ICER is accompanied by a very wide 95% confidence interval, due mostly to the large variation (SED) in EQ-5D scores. This is a common occurrence in economic evaluations which run alongside trials, and has to do predominately with the issues of power mentioned above. As a result, many cost-effectiveness studies do not present confidence intervals at all. When they do, very little can be inferred by a wide 95% CI for the ICER which spans zero in the context of an economic evaluation powered for the clinical trial it accompanies. This does not render a study valueless, it merely sets the context in which the results can be interpreted. As the ICER for an intervention increases within the acceptable NICE threshold cost-effectiveness range, the degree of uncertainty associated with it weighs more heavily in the decision-making process, making it less likely for an intervention to be approved (see Appendix 6.8).

We cannot prove with absolute certainty that the results are due to the volar locking plate being cost-ineffective, rather than the study being underpowered. However, when validated patient-centred functional outcome measures, for which the clinical study was sufficiently powered, fail to demonstrate improved outcomes for the plate over the year, there is, in our opinion, no reason to expect this from the more generic HRQL scores.

External validity

Single-centre studies are easier to organise and run, and allow for tighter quality control in both the intervention and the assessment. Multi-centre trials, however, may be a more efficient way of accruing sufficient participants over a shorter period of time, and also provide a better basis for generalisation of findings.

This was a single centre study performed in a United Kingdom centre, which may affect the external validity of findings. The structure of the treatment pathways represents practice within the NHS, where distal radius fractures are treated within a specific hospital environment and a particular specialty. Result of a similar comparison could be different in other healthcare settings, for example if presentation for treatment was regularly delayed making indirect reduction of fractures more challenging, availability of follow-up and access to fracture clinics was limited, or there were differing levels of resources and expertise with each technique.

Furthermore, it is a study reflecting practice in a tertiary centre, with surgery performed at the expert consultant level. It is plausible that, in a more generalist environment, volar locking plate fixation, as a more interventional technique, could be associated with a greater number of complications and revision surgery. For example, there was no flexor pollicis longus (FPL) tendon rupture

following plating in this study. This is an increasingly occurring complication, associated with plate mal-positioning and tendon attrition (Asadollahi and Keith). It requires subsequent plate removal and tendon reconstruction, which is major surgery with substantial costs and a long period of recovery. In addition, plate removal in the setting of malposition and/or poorly locked screws, is an increasingly reported problem (Sahu et al., 2011, Gyuricza et al., 2011), which was infrequent in the setting of the current study.

4.4 Study Strengths

This study also has several strengths.

It is currently the largest single-centre published RCT comparing volar locking plate fixation with percutaneous techniques for distal radius fractures. It is the also the first and only cost-effectiveness study of volar locking plate fixation. The economic evaluation was executed prospectively. The study design complied with NICE guidance on the methodology of technology appraisal criteria (NICE, 2008).

The conduct and reporting of the trial have followed the CONSORT recommendations (Schulz et al.).

The primary outcome measure was an appropriate validated patient-centred functional outcome measure. In addition, secondary outcomes measures could allow for direct comparison

with other published studies, making this trial suitable for inclusion in future meta-analyses.

The study was adequately powered and strictly executed. Significance criteria were stringent, and the sample size calculation transparent and based on a comparable population.

The follow-up rate achieved at one year was 95%. High retention rates throughout the duration of the study meant that there was no need to imputate missing data.

Costing for the economic study included detailed data collection based on a "bottom-up" micro-costing technique. This technique is particularly resource and time intensive. Most published economical evaluations are based on estimated costs referenced from the literature, department of health figures and national tariffs and do not attempt a bottom-up approach. Though large multi-centre trials have the benefits of larger patient numbers and potentially greater external validity, a single-centre study can be much more exacting in costing, and can provide useful reference for future studies. The costing model in this study was transparent and transferable and can be referenced in future distal radius fracture economic evaluation studies.

4.5 Future work

The next stage is for the ongoing, large UK multi-centre study comparing volar locking plate and Kirschner wire fixation (DRAFFT), to complete and publish results (Costa et al., 2011). This will enhance what we have learned from the current study, and add power to meta-analyses and systematic reviews.

The work in this thesis covers the short to medium term. Long term outcomes are also important. Though there is no funding in place, we hope to be able to approach this group of patients at 10 years and 20 years from their injury. Ideally both a functional and radiographic assessment would be sought, but this would depend on ethical and institutional approval, as well as the availability of funds. With such a long interval from the original intervention, we would expect a high drop-out with reduced rates of follow-up, as is often the case with trauma, higher even if patients remain asymptomatic and thus less incentivised to volunteer their time. One of the advantages of large, centrally funded studies is that long-term follow-up, when indicated, is typically planned for at the onset, making full use of the original resources.

Fractures of the distal radius are common and account for a considerable proportion of all attendances at fracture clinics. Although they have been the subject of much research, the paucity of large, prospective outcome trials of the different methods of

treatment is surprising, given the number of patients available for study. There remain unanswered questions regarding the optimal management of this very common fracture. These are mostly driven by the uncertainty about the long-term relevance of varying degrees of extra-articular malunion. Collating data on truly long term follow-up of younger patients will take decades.

In the meantime, the next step should perhaps be a return to basics: large randomised studies to compare operative and non-operative management of distal radius fractures. Given the increasing trend for operative intervention (Chung et al., 2009), there has been little interest in such studies in the recent past. However, the debate surrounding volar plate fixation has refuelled interest in outcomes of non-operative management.

Arora et al. in 2011 published a prospective randomised trial of 73 patients comparing non-operative cast treatment with volar locking plate fixation for displaced and unstable distal radial fractures in patients sixty-five years of age and older (Arora et al., 2011). At the twelve-month follow-up, the range of motion, the level of pain, and the PRWE and DASH scores were no different between the treatment groups. There were significantly more complications in the operative group. Improved radiographic reduction in the operative group did not convey any advantage in terms of the

range of motion or the ability to perform daily living activities, though cosmesis was not assessed when considering outcome.

An ambitious multi-centre trial (the ORCHID study) (Bartl et al., 2011) was attempted in Germany. ORCHID (Open reduction and internal fixation versus casting for highly comminuted intra-articular fractures of the distal radius) was funded by the German research council and planned to recruit 504 patients over a three year period. The primary objective was to determine differences in the Short Form 36 (SF-36) Physical Component Score (PCS) between volar locked plating and closed reduction and casting of intra-articular, comminuted (AO C3) distal radius fractures in patients over 65 years of age. Secondary outcomes included differences in other SF-36 dimensions, the EuroQol-5D questionnaire, the DASH score as well as clinical measurements and complications. Recruitment started in 2008 and unfortunately prematurely terminated in early 2012 due to low recruitment. Nevertheless, they report having randomised 183 patients up to that point, making it the largest study on the topic to date, and also the only study to randomise exclusively AO C3 fractures. The results have not so far been published, but would perhaps help provide answers to questions our the present and the DRAFFT multicentre studies were not designed to answer i.e. how far do we go in treating intra-articular comminuted fractures in the elderly?

Lastly, more focus on techniques of economic evaluation is required. Health practitioners are required to operate within a framework where budgets are limited and funds are allocated in ways not always under their control. Developments in the structure of health policy processes emphasise the importance of ensuring that the results of economic analyses are robust. Decision making therefore requires not only sound clinical evidence that treatments work, but also, good quality evidence that they provide value for money for the NHS and for society in general. More economic evaluations alongside prospective clinical studies in upper limb surgery are required.

The methodology that determines cost effectiveness through the guidance of bodies such as NICE is not without controversy. Topics relevant to the context of the current study are questions regarding the ability of HRQL measures to capture short-term benefits gained from the treatment of acute conditions and non-systemic conditions limited to the upper limb; also how the innovative nature of particular technologies adds distinctive benefits not adequately captured by the QALY measure.

A body of work is required which aims to map validated patient-centred functional outcome measures to generic quality-of-life scores. Or perhaps the development of a disease-specific measure of health related quality-of life (HRQL) for trauma. Disease-specific

measures of HRQL are increasingly being used to evaluate medical treatments, to make therapeutic decisions, and to allocate treatments (Bowling, 2001, Shumaker et al., 1994, Barber et al., 2001). In addition, we should invest in larger studies that can limit the degree of uncertainty associated with outcomes. Multi-centre collaborative long term studies are required. They are possible if a) adequate funds are allocated b) patients are willing to participate and c) individual practicing surgeons are willing to enter patients.

Chapter 5 – References

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Chapter 6 - Appendix

6.1 List of common abbreviations

- A&E Accident and Emergency
- CBA Cost Benefit Analysis
- CEAC Cost–effectiveness Acceptability Curve
- CI Confidence interval
- CQG Cost per QALY Gained
- CUA Cost Utility Analysis
- EPL Extensor Pollicis Longus
- GP General Practitioner
- HRG4 Health Resource Group Version 4
- HRQL Health Related Quality of Life
- ICER Incremental Cost Effectiveness Ratio
- MSD Minimally Significant Difference
- NHS National Health Service
- NICE National Institute for Health and Clinical Excellence
- NUH Nottingham University Hospitals NHS Trust
- ONS Office of National Statistics

- PASA NHS Purchasing and Supply Agency
- PP Per Protocol
- QALY Quality Adjusted Life Years
- RCT Randomised Controlled Trial
- SG Standard Gamble
- TSSU Theatre Sterile Supply Unit
- TTO Time Trade-Off
- VAS Visual Analogue Scale

6.2 Trial Protocol

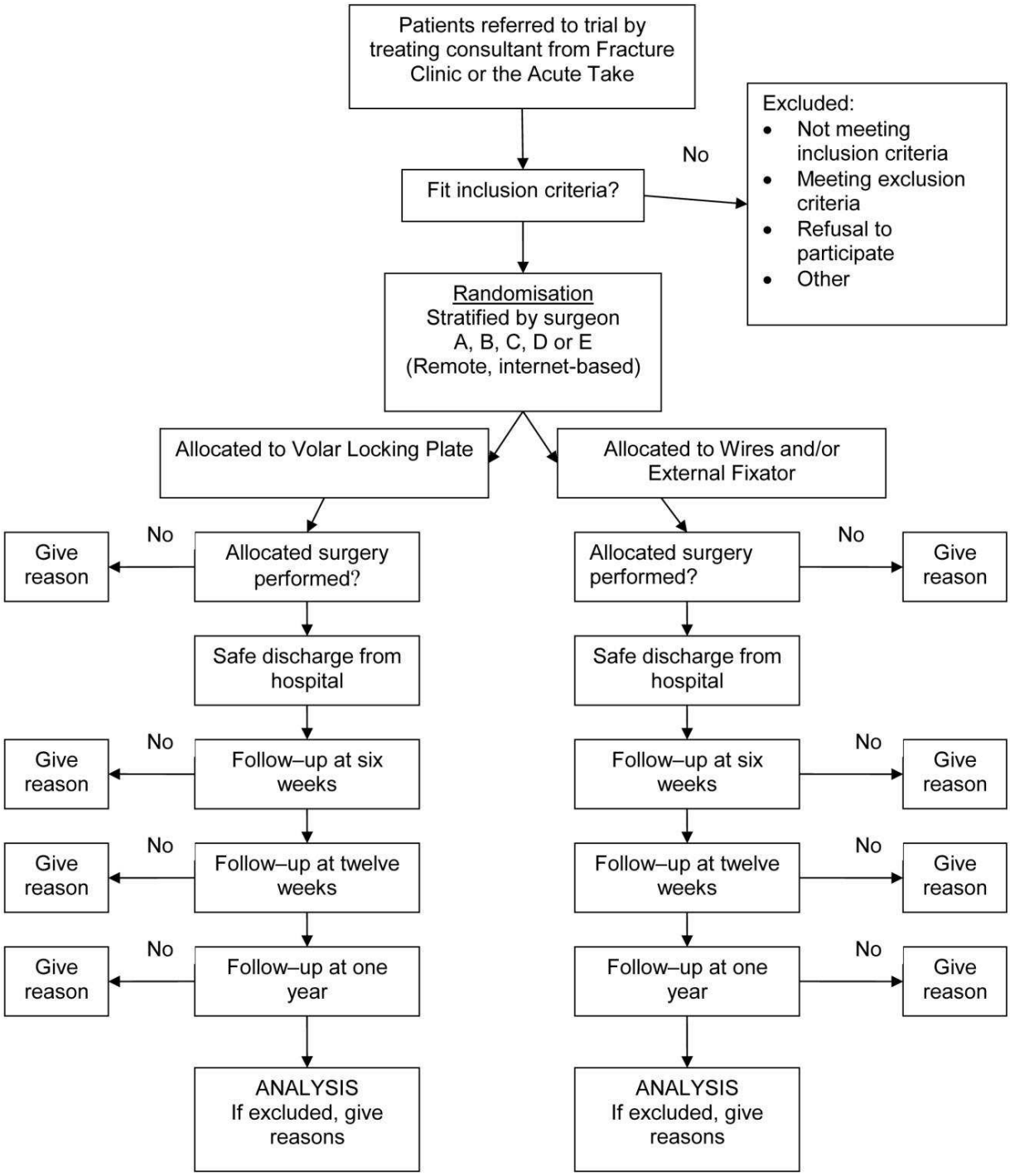
This is the trial protocol, in the form that was approved by the local Research Ethics Committee and institutional Research and Development Unit (September 2007).

Project Design

This study is a pragmatic surgical randomised controlled trial aiming to compare the outcome of fractures of the distal radius when treated with a volar plate with locking screws, or the established conventional method typically involving percutaneous wires and/or an external fixator.

A diagram demonstrating participant flow through each stage is demonstrated in Figure 6.1.

Figure 6.1 Diagram demonstrating participant flow



Objectives

Our research objectives are:

- To determine whether the use of volar locking plates improves clinical and functional outcome, and allows for an earlier return to normal activities and work.
- To undertake an Economical Evaluation from the point of view of the NHS and Personal Social Services as follows:
    - Cost Utility Analysis of the interventions, using the EQ-5D to calculate QALYs.
    - Clinical Effectiveness Analysis to determine effectiveness of the interventions at reducing the duration of rehabilitation. For this purpose we will calculate the incremental cost of rehabilitation days avoided for each intervention.

Setting

Acute teaching urban NHS trust (Nottingham University Hospitals, Queen's Medical Centre Campus, Nottingham). Patients are recruited through fracture clinic and the acute orthopaedic take and treated on the orthopaedic wards and trauma theatres.

Target Population

Adults (skeletally mature) with a fracture of the distal radius suitable for surgical treatment with a volar locking plate. Participants must satisfy the study inclusion and exclusion criteria and be referred to the research team by their treating consultant.

Recruitment and Consent

Potential participants will be identified as suitable for the study by their treating consultant through attendance at fracture clinic, which runs on a daily basis.

Suitable participants will be approached by their treating surgeon in fracture clinic and informed of the existence of the project. The chief investigator will be contacted, to ensure all inclusion criteria are met. Should the patient agree they will be introduced to the chief investigator who will discuss the nature of the study in more detail. Written information will be provided in the form of the Patient Information Sheet.

This will be done in the clinic room to ensure confidentiality. Patients will be allowed to ask questions and consider their decision in private. It will be reinforced that their decision will in no way affect the quality of their care.

It is aimed that recruitment occurs at this stage. This is due to the acute nature of the injury and the need to organise operative intervention as soon as possible by the appropriate surgical team

and in available theatre time, as would happen during routine clinical care.

Written consent will be obtained by the chief investigator. The investigator will retain the original consent form in the Trial Master File. A copy will be given to the participant and a copy will be placed in the medical notes. Patients will be admitted as appropriate. It will be reinforced that participants are free to withdraw at any point and consent is not binding. However, it is our aim whenever possible to allow at least 24 hours for the participant to decide if they wish to remain within the trial or withdraw. The participant will thus not be randomised at recruitment, but on the morning or afternoon of surgery. Should they decide to withdraw, surgery will take place as scheduled but the patient will not be randomised into the trial.

If a patient declines to participate, we will record the reason why. No other data will be collected. They will remain under the care of their admitting consultant team.

A patient can withdraw from the study at any time by informing a member of the medical team. Treatment will proceed as planned, but no further information will be collected nor retained for the purposes of the study.

Intervention

Patients will undergo their surgery on a dedicated orthopaedic trauma list, and the surgery performed by one of the five senior surgeon members of the study team, who are fully trained and experienced in the treatment of these fractures with both the DVR® plate and the alternative options. Each must perform a minimum of 16 fracture fixations.

The plate chosen for this trial is the Distal Volar Radius or DVR® plate, manufactured by Biomet. This has been selected on the advice of our Hand Surgery and Trauma Unit as representative of volar locking plates. It is in common use across the UK and widely represented in the published literature. It is an implant with which our surgeons already have significant prior experience. Instrumentation in the conventional arm of the trial will include smooth 1.6mm Kirschner wires and the standard AO external fixator, as appropriate. All the above devices are in current use within the NHS, CME licensed and will not require MHRA authorisation.

There is no expected difference in the type or the duration of the anaesthetic for the two techniques. Both treatments may involve spending a period of time in plaster.

Follow up

Expected duration of patient participation will be one year from injury.

Follow up and data collection will be performed at 6 weeks, 12 weeks and 1 year and will take place in orthopaedic outpatient fracture clinic.

Outcome measures consist of objective parameters, measured by the chief investigator and a trained research assistant with the relevant clinical aids. Also standard published valid questionnaires designed to be completed by the patient (see Outcome Measures).

Inclusion criteria

- Fractures which the referring physician considers require operative intervention.
- Configuration is such that the fracture would be amenable to stabilisation via volar locking plate (not unreconstructable).
- Adults (skeletally mature) with high demand requirements of their wrist in whom the radiological appearance of the bone suggests that it is robust enough to tolerate internal fixation and in whom the fracture pattern at presentation fulfils the criteria as described below.
- Fractures of the distal radius which are:

1. Dorsally displaced (≥20°) extra-articular fractures (with or without an undisplaced intra-articular component) with dorsal cortical comminution as seen on the lateral radiograph.
2. Displaced intra-articular fractures with an articular step or gap of in the radio carpal joint surface.

Exclusion criteria

- Patients with concomitant systemic diseases (diabetes with vascular or neurological complications, advanced cardiac, pulmonary or neurological disease)
- Proximal metaphyseal fractures (more than one inch or 2.5 centimetres from the articular surface)
- Open fractures
- Smith's and volar Barton's configuration
- Previous fractures of the distal radius of the same or contra-lateral limb
- Significant pre-existing radiological abnormality
- Multiply injured
- Bilateral injuries
- Patients who are unable to consent for themselves to treatment
- Patients who may have difficulties in adequate understanding of English

Outcome Assessments

These will be clinical and radiological, performed at 6 weeks, 12 weeks and 1 year.

Subjective assessments will include the following measures:

- Patient Rated Wrist Evaluation Measure
- *Quick*DASH
- PEM
- EUROQUOL EQ-5D
- SF-12
- Ten point visual analogue score for pain

Disease specific questionnaires are published and freely available for clinical use. The quality of life scores are available on an academic licence.

Objective measurements will include

- grip strength of the injured limb
- range of forearm and wrist motion

Radiographic assessment

Measurements obtained from radiographs as undertaken during the course of normal clinical management for this type of injury. Taken at the time of injury, post treatment and prior to discharge (check X-ray), at six, twelve weeks and one year post injury.

Established clinical practice for radiographic assessment includes a standardised series comprising of:

- standard PA

- 20 degree lateral
- 45 degree pronated oblique of the wrist

The contra lateral wrist is X-rayed at week 6 and acts as a standard for the assessment of shortening, loss of radial angle, palmar tilt and presence of intra-articular malunion.

- Radial length
- Palmar tilt
- Radial inclination

Demographic and other data

Written consent will be obtained for access to patient medical records by the chief investigator.

Demographic data will be collected from the patient and the clinical notes and will include:

- Hand dominance
- Date of birth
- Date of injury
- Occupation and relevant classification: office, office and manual, light manual, heavy manual), full time or part time employment.
- Date of return to work
- Length of hospital stay
- Number of outpatient and GP appointments
- Number of therapy appointments

- Number of plaster cast changes
- Attendance for fixator removal at six weeks
- Total number of post-operative hospital attendances
- Prescription of antibiotics
- Complication (loss of reduction, pin site infections, tendon rupture, finger stiffness, CRPS, CTS).
- Worker's compensation claims (as established at one year)
- A record of operative kit used
- Surgery time

Participant Safety

Participants are not expected to be exposed to additional harm as a result of their participation in the study. The only deviation from routine clinical care consists of collection of specific demographic data and completion of short questionnaires at routine clinical follow-up.

However, as part of routine clinical care participants will be undergoing surgical intervention which carries an inherent risk of complications. Patients will be informed of the risks of surgery as part of the process of surgical consent, by the treating surgical team as per standard clinical practice. This is a separate process to the research consent obtained at recruitment.

Should a complication of surgery arise, treatment and follow-up would be dictated by the nature of the complication, as per routine clinical care.

We aim to record all untoward medical events in study participants (such as complications of surgery, even if unrelated to the study, using the R&D Adverse Event or Serious Adverse Event Reporting Forms. These will be retained by the Chief Investigator and reported to the R& D department of the Trust.

Stopping Criteria

We will perform an interim analysis at the midpoint of recruitment for the study. Criteria for stopping the study would be

- 10% difference in the rate of catastrophic infection (septic arthritis) requiring operative intervention to treat or leading to significant joint damage as visible on X-ray

Method of allocation

Participants will be allocated with equal probability to the 2 treatment arms based on a computer generated random code using random permuted blocks of randomly varying size, created by the Nottingham Clinical Trials Support Unit (CTSU) in accordance with their standard operating procedure (SOP) and held on a secure server. In order to avoid surgeon bias each participating randomisation is stratified by surgeon.

Access to the sequence will be confined to the CTSU Data Manager. The trial coordinator will access the treatment allocation for each participant by means of a remote, internet-based randomisation system developed and maintained by the Nottingham CTSU. The sequence of treatment allocations will be concealed until interventions have all been assigned and recruitment, data collection, and all other trial-related assessments are complete.

Data Access, Management and Record Keeping

Data accessed by the principal investigator for the purpose of the study will include patients' medical health records and radiographs. Patient written consent will be sought.

Medical records of patients participating in the study will be identified by a sticker on the cover of the records denoting the patient is in the study and the date the notes will no longer be required for research purposes.

Information will be recorded using data collection proformas and via completion of standardised outcome questionnaires.

It is intended to use a unique trial number for each participant that is linked to their personal details so that all research data is anonymised. The encryption will happen at the point of randomisation.

All data relevant to the study will be transferred onto an Access database and held for ten years. This will be password protected, stored on Trust premises, in a password protected network area accessible through an NHS Trust computer. Files will be backed up to a hard copy CD- ROM disk on the first working day of each month and this back up will be kept with the Trial Master File in the Research Office, Level C, West Block, within the Academic Department of Orthopaedic and Accident Surgery on QMC premises. This is a locked, safe and secure location.

6.3 Ethics Committee confirmation of approval

North Nottinghamshire Local Research Ethics Committee
1 Standard Court
Park Row
Nottingham
NG16GN

Telephone: 01159123344 Ext: 39368
Facsimile: 01159123300

05 September 2007

Miss Alexia Karantana
Specialist Registrar Trauma and Orthopaedics Mid-Trent
C/0 Mr Holdsworth's Secretary
Level B, West Block,
Queens Medical Centre, Derby Road
Nottingham, NG7 2UH

Dear Miss Karantana

Full title of study: **Unstable Fractures of the Distal Radius: a Randomised Prospective Clinical Study Comparing their Treatment with Volar Locking Plate and Conventional Method**

REC reference number: **07/H0407/39**

Thank you for your letter of 18 August 2007, responding to the Committee's request for further information on the above research and submitting revised documentation.

The further information has been considered on behalf of the Committee by the Chair.

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation as revised.

Ethical review of research sites

The Committee has designated this study as exempt from site-specific assessment (SSA). There is no requirement for [other] Local Research Ethics Committees to be informed or for site-specific assessment to be carried out at each site.

Conditions of approval

The favourable opinion is given provided that you comply with the conditions set out in the attached document. You are advised to study the conditions carefully.

- Please note that there is a typographical error on page 2 of the Participant Information Sheet, last paragraph- the 3rd sentence "You will be to ensure there are no problems" should be removed

Approved documents

The final list of documents reviewed and approved by the Committee is as follows:

Document	*Version*	*Date*
Application		19 June 2007
Investigator CV- Educational Supervisor		01 June 2007
Investigator CV- Chief Investigator		13 June 2007
Protocol	3	08 August 2007
Peer Review		26 March 2007
Statistician Comments		06 March 2007
Questionnaire: Patient Rated Wrist Evaluation		
Questionnaire: EQ-50 Health Questionnaire		
Questionnaire: Quick Dash outcome measure		
Questionnaire: About The Wrist That You Broke		
GP/Consultant Information Sheets	2	08 August 2007
Participant Information Sheet	2	08 August 2007
Participant Consent Form	1	12 March 2007
Response to Request for Further Information		18 August 2007
Letter of clarification of follow period		09 August 2007

R&D approval

All researchers and research collaborators who will be participating in the research at NHS sites should apply for R&D approval from the relevant care organisation, if they have not yet done so. R&D approval is required, whether or not the study is exempt from SSA. You should advise researchers and local collaborators accordingly.

Guidance on applying for R&D approval is available from http://www.rdforum.nhs.uklrdform.htm.

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees (July 2001) and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

Feedback on the application process

Now that you have completed the application process you are invited to give your view of the service you received from the National Research Ethics Service. If you wish to make your views known please use the feedback form available on the NRES website at:

https://www.nresform.org.uk/AppForm/Modules/Feedback!EthicaiReview.aspx

We value your views and comments and will use them to inform the operational process and further improve our service.

07/H0407/39 Please quote this number on all correspondence

With the Committee's best wishes for the success of this project

Yours sincerely

Dr David Walsh
Chair

Email: trish.wheat@nottinghamshirecounty-tpct.nhs.uk

Enclosures: *Standard approval conditions*

Copy to: R&D office for NHS care organisation at lead site - NUH QMC Campus

6.4 Research and Development approval

Nottingham University Hospitals NHS Trust

Please reply to: Research and Development
E11 Curie Court
Queen's Medical Centre Campus
Derby Road
Nottingham
NG7 2UH

Telephone: 0115 970 9049
Fax: 0115 849 3295
E-mail: janet.boothroyd@nuh.nhs.uk

28 September 2007

Miss A Karantana
C/O Mr Holdsworth's Secretary
Level B, West Block
Queen's Medical Centre, Derby Road
Nottingham
NG7 2UH

Dear Miss Karantana

ID: 07OR003 Unstable Fractures of the Distal Radius: a Randomised Prospective Clinical Study Comparing their Treatment with Volar Locking Plate and Conventional Method.

The R&D Department have considered the following documents:

NHS REC Application form, version number 5.3
Protocol Version 3 dated 8 August 2007
GP/Consultant Information Sheets, Version 2 dated 8 August 2007
Participant Information Sheet, Version 2 dated 8 August 2007
Participant Consent Form, Version 1 dated 12 March 2007

Your study now has R&D approval, on the understanding and provision that you will follow the conditions set out below.

Conditions of Approval

That you:

1. Accept the responsibility of Chief/Principal Investigator as defined in the current Research Governance Framework.
2. Request written approval from the R&D department for any change to the approved protocol/study documents you wish to implement
3. Ensure all study personnel, not employed by the Queens Medical Centre, University Hospital NHS Trust Nottingham or the City Hospital NHS Trust Nottingham, hold honorary Contracts with this Trust, before they have access to any facilities, patients, staff, their data, tissue or organs.
4. Report any Serious Adverse Event involving the Trust to the R&D department, using the Trust 'policy for research safety reporting in human subjects'. Policy available from the R&D Department.
5. Complete the R&D Research Governance interim and final reports as requested.
6. Comply with the regulatory requirements and legislation relating to: Data Protection, Trust Caldicott Guidelines, Health and Safety and the use of Human Tissue for

research purposes.

7. Comply with the current Research Governance Framework, available at www.doh.gov.uk or via the R&D office or Research Governance Web-site.
8. Agree to conduct this research project in accordance with ICH Good Clinical Practice and/or the MRC Guidelines for Good Clinical Practice (as appropriate)
9. Must not start your project until you have received written approval from the relevant ethics committee.

Please note that the R&D department has a database containing study related information, and personal information about individual investigators e.g. name, address, contact details etc. This information will be managed according to the principles established in the Data Protection Act.

Yours sincerely

Dr Brian Thomson / Mrs Janet Boothroyd
Director of R&D / **Assistant Director of R&D**

cc Nottingham Research Ethics Committee

6.5 Reference costs of consumables

Figure 6.2 Reference cost of consumables. Sourced from NHS Supply Chain Catalogue 2011.

Item	Brand	Catalogue code	Page	Unit of issue	Price	Per unit	Exc VAT
Peripheral IV Advanced securement dressing	Tegaderm	ELW357	1625	case of 400	193.1	0.48	0.40
Green IV cannula	BD Venflon	FS610	143	500		0.8	0.67
Universal giving set	Flocare infinity universal giving set	FSC091	403	1		3.17	2.64
Swab non-woven in 5s sterile	Premier	ENK007	1642	Pack of 25	0.68	0.03	0.03
20 ml syringe	Codan	FWC065	929	Pack of 50	5.13	0.102	0.09
10 ml syringe	Codan	FWC063	929	Pack of 100	7.33	0.073	0.06
Green needle hypodermic 21 gauge sterile	B Braun Sterican	FTR167	912	Pack of 100	1.57	0.015	0.01
Sterile gloves	Ansell Gammex PF	FTE027	687	Box of 40	28.92	0.723	0.60
Stockinette cotton plain	Easiban Sallis	EGJ170	1586	7.5cm x 20m	4.28		0.09
Undercast padding synthetic sterile 7.5cm	Formflex synthetic lantor	EVN102	525	Case of 70	40.52	0.579	0.48
Undercast padding synthetic non-sterile 7.5cm	Undercast Padding Synthetic 7.5cm x 2.7m bandage Cellona	EPA036	Online	Case of 72	27.44	0.381	0.32
Crepe bandage sterile	Crepe bandages sterile 7.5cm x 4m	EVN158	Online	Case of 64	71.1	1.111	0.93
Bandage plaster of Paris 10cm roll	Bandage plaster of paris 10cm x 3m	EAA029	Online	Pack of 40	23.62	0.59	0.49
Non fibreglass casting tape 7.5cm x 3.6m White	Delta Cast Conformable	EAF401	Online	Pack of 10	47.74	4.774	3.98
Simple triangular sling	Bandage triangular calico, CREST	EED018	1585	1		0.2	0.17
Laryngeal mask size 4	Sure seal lm 100% silicon su standard	FDD1611	59	Pack of 10	38.24	3.84	3.20
Light handle	Delta universal handle cover single pack	FBM107	1107	Box of 50	30.65	0.613	0.51
Scrub brush	Integral sponge dry with nail pick	FSL727	582	Box of 25	5.9	0.236	0.20
Scalpel blade carbon steel	Swann Morton indicative size 11	FSF230	1158	Box of 100	6.75	0.0675	0.06
X-ray machine cover	Delta dome shape polybag for C arm	FBE295	1104	Box of 10	25.81	2.581	2.15
Drape pack upper extremity	Steripharm	VJD2448	1080	Box of 6	113.16	18.86	15.72
Gown pack sterile disposable reinforced	365 healthcare -sms-large- 2 hand towels	BWK430	1094	Case of 30	50.13	1.671	1.39
Face mask surgical	3M pleated 4 ties with noseband blue	BWM016	1221	Box of 50	7.21	0.042	0.04
Sterile x-ray detectable gauze swabs	5x5cm 32 ply Detex	EMI005	1232	Box of 96	51.81	0.54	0.45
Bradford type foam sling	Sling foam padded adult with velcro fastening Adult	EKM000	12.45	Each	12.45	12.45	10.38
Suture absorbable coated braided 4/0 3/8 circle needle	Suture vicryl Jv1014 75cm vicryl absorbable coated braided violet 4/0 13mm 3/8 circle needle	FVS1055	Online	Pack of 36	176.97	4.016	3.35
Suture non absorbable monofilament 4/0 3/8 circle needle	Sutures Non Absorbable W319 45cm ethilon non-absorbable monofilament blue 4/0 19mm 3/8 circle needle	FVQ501	Online	Pack of 12	16.5	1.375	1.15
Hydrocolloid dressing 10x10cm	10x10 cm Aquacel Convatec	ELY012	1604	Pack of 10	25.67	2.57	2.14
Dressing paraffin gauze sterile	Jelonet S+N	EKA011	1608	Pack of 100	35.02	0.35	0.29
Dressing primary knitted polyester impregnated with neutral triglycerides	Atrauman Hartmann 5x5cm	EKA024	1612	Pack of 50	7.98	0.16	0.13
Dressing IV vapour premeable adhesive film	IV3000 S+N	ELW039	1622	Pack of 100	38.14	0.3814	0.32
Wrist splint	Wrist/hand orthoses for immobilisation manipulation or protection splint Futura	GRZ2372	Online	Each	4.4	4.4	3.67
Dressing pack sterile woundcare with forceps	Vernaid	EHC110	869	Each	0.34	0.34	0.28
Dressing vapour permeable adhesive with absorbent sterile pad (small)	Mepore Fim & Pad 4x5cm	EIJ048	1625	Pack of 85	18.98	0.223	0.19
Dressing vapour permeable adhesive with absorbent sterile pad (medium)	Mepore Fim & Pad 5x7cm	EIJ055	1625	Pack of 85	21.71	0.255	0.21
Blade stitch cutting carbon steel	Swann Morton	FSX057	1160	Box of 100	6.49	0.0649	0.05
Disposable scalpel sterile plastic handle	Swann Morton	FGP142	1162	Box of 10	2.06	0.206	0.17
Bandage crepe non-sterile	Hospicrepe 239 7.5cm	ECA089	1584	Pack of 12	5.22	0.435	0.36
Sterile pack single use instrument suture	Rochialle	EVX207	866	Case of 25	87.87	3.51	2.93

6.6 Reference of drugs used and costs

6.6.1 Prophylactic antibiotics

Induction

- Flucloxacillin 2gr IV
- Gentamycin 2mg/kgr IV (average patient 80 kgr) so 160mg

  Followed by

- Three more doses Flucloxacillin 1gr IV

If mild allergy to penicillin (rash)

- Single dose of Cefuroxime 1.5gr IV on induction

If severe allergy to penicillin

- Single dose of Vancomycin 1gr IV before induction

6.6.2 Analgesics

Post-op analgesics

Paracetamol 1gr	qds x 24hrs
Ibuprofen 400mg	tds x 24hrs
Codeine Phosphate 60mgs	qds x 24hrs

Oramorph® oral solution 10 mg/5 mL 20 mgs

Discharge analgesics

Paracetamol 500mg	1 pack	100-tab pack
Ibuprofen 200 mg	1 pack	84-tab pack
Codeine Phosphate 30 mg,	2 packs	28-tab pack

6.6.3 Anaesthetic drugs

General anaesthetic

1 amp fentanyl (2ml amp)

1 amp propofol (20ml amp)

1 amp midazolam (2 mg/mL, 5-mL amp)

20mg morphine (2 x 1ml amp 1mg/ml)

1gr paracetamol IV

Axillary Block

30mls of levobupivocaine

1 amp clonidine (20mcgs used)

1 amp midazolam

Sonoplex stimulation cannula 22 gauge x 50mm

6.6.4 Pricing from BNF 2011

- **Atracurium (Non-proprietary)** Injection, atracurium besilate 10 mg/mL, net price 5-mL amp = £3.19
- **Catapres® (Boehringer Ingelheim)** Injection, clonidine hydrochloride 150 micrograms/mL, net price 1-mL amp = 28p
- **Cefuroxime (Non-proprietary)** Injection, powder for reconstitution, cefuroxime (as sodium salt), net price 1.5-g vial = £5.05
- **Chirocaine® (Abbot) Injection**, levobupivacaine (as hydrochloride) 5 mg/mL, net 10-mL amp = £1.62
- **Codeine Phosphate (Non-proprietary)** Tablets, codeine phosphate 30mg, net price, 28-tab pack = £1.18
- **Fentanyl (Non-proprietary)** Injection, fentanyl (as citrate) 50 micrograms/mL, net price 2-mL amp = 30p,
- **Flucloxacillin** Injection, powder for reconstitution, flucloxacillin (as sodium salt), net price 1-g vial = £4.90
- **Gentamicin (Non-proprietary)** Injection, gentamicin (as sulfate), net price 40 mg/mL,2-mL amp = £1.00
- **Ibuprofen (Non-proprietary)** Tablets, coated, ibuprofen 200 mg, net price 84-tab pack = £1.44

- **Midazolam (Non-proprietary)** Injection, midazolam (as hydrochloride) 2 mg/mL, net price 5-mL amp = 65p
- **Morphine Sulfate (Non-proprietary)** Injection, morphine sulfate 10, net price 1mL amp = 72p
- **Oramorph® oral solution**, morphine sulfate 10 mg/5 mL, 500-mL pack = £7.47
- **Paracetamol** Tablets (and caplets), paracetamol 500 mg, net price 100-tab pack = £1.61.
- **Perfalgan® (Bristol-Myers Squibb)** Intravenous infusion, paracetamol 10 mg/mL, net price 100-mL vial = £1.25
- **Propofol (Non-proprietary)** 0.5% injection (emulsion), propofol 5 mg/mL, net price 20-mL amp = £3.46
- **Ropivacaine (Non-proprietary)** Infusion, ropivacaine hydrochloride 2 mg/mL, net price 200 mL = £14.45
- **Sodium Chloride Intravenous Infusion (Non-proprietary)** Intravenous infusion, usual strength sodium chloride 0.9% (9 g, 150 mmol each of Na+ and Cl-/litre), this strength being supplied when normal saline for injection is requested. Net price 10-mL amp = 46p

- **Vancomycin Injection**, powder for reconstitution, vancomycin (as hydrochloride), for use as an infusion, net price 1-g vial = £12.99
- **Water for Injections** Net price 10-mL amp = 34p

6.7 Derivation of complication costs

This section details the approach in costing of complications, which is in line with the methodology, as detailed in Chapter 2.

In costing the complications we have not included the cost of additional fracture clinic, plaster room and/or Accident and Emergency and physiotherapy attendances. These are incorporated in the patient-specific data, as they differ per patient, according to presentation and rate of recovery. This ensures use of outpatient resources is not counted twice. This approach was chosen due to the way data is recorded in hospital systems and subsequently in our database. Though we have the total number of attendances for each patient, it is very difficult to distinguish with confidence whether, for example, an extra plaster change performed in plaster room, was due to the plaster rubbing (not a complication) or a superficial infection (complication). As a result, if one wishes to use this data to model complication costs for a different study, they should collate and add the cost of any outpatient attendances to these figures.

Tables 6.1. to 6.7 detail the costing for each complication. Lost wages were considered nil in the case of superficial infection. All cases of infection were early (within 3 weeks of surgery for the plate and six weeks of surgery for the control group) and patients

were already off work, recovering from the index procedure. The infection did not result in additional productivity loss.

All infections in the study were superficial and treated on an outpatient basis. No implants (plate, wires, fixator pins) had to be removed because of infection.

Tables 3.15 and 3.16 represent the detailed costing of dressing changes for each randomisation group, which are incorporated in Tables 6.3 and 6.4.

Table 6.1 Costing of removal of buried k-wires as an outpatient procedure

Removal of buried k-wires (outpatient procedure)	**Cost (£)**
Staff (nurse) 30 min	48.6
Staff (doctor) 20 min	24.4
Lidocaine 1% (10ml ampoule)	0.42
Dressing pack sterile wound care with forceps	0.28
Sterile gloves (one pair)	0.6
Skin preparation	0.06
20ml water for injection	0.68
Blade stitch cutting carbon steel	0.05
Sterile pack single use instrument suture	2.93
Suture non absorbable monofilament 4/0	1.15
Dressing vapour permeable adhesive with absorbent sterile pad (small) (n=2)	0.38
Overheads	1.31
Lost wages (10 days)*	571.4
GP nurse removal of sutures (12 min)	10.2
Total	**662.46**

Table 6.2 Costing of removal of buried k-wires as a day-case procedure

Removal of buried k-wires (day-case theatres)	**Cost (£)**
HRG code HB55C	924
Lost wages (10 days)	571.4
GP nurse removal of sutures (12 min)	10.2
Total	**1505.6**

Table 6.3 Costing of superficial infection (volar locking plate)

Superficial infection (not requiring admission) Volar Locking Plate	**Cost (£)**
Flucloxacillin 1gr qds 7 days	6.94
Analgesics	6.49
Culture swab	0.17
Processing of swab by microbiology (culture and sensitivity)	1.39
Overheads	3.00
Dressing Changes (n=2)	53.98
Lost wages*	0
Total	**71.97**

Table 6.4 Costing of superficial infection (control)

Superficial infection (not requiring admission) Wires and Fixator	**Cost (£)**
Flucloxacillin 1gr qds 7 days	6.94
Analgesics	6.49
Culture swab	0.17
Processing of swab by microbiology (culture and sensitivity)[3]	1.39
Overheads	3.00
Dressing Changes (n=2)	117.64
Lost wages*	0
Total	**135.63**

Table 6.5 Costing of carpal tunnel decompression

Carpal tunnel decompression	**Cost (£)**
HRG4 code HB55C	924
Lost wages (4 weeks)	1600
GP nurse removal of sutures (12 min)	10.2
Total	**2534.2**

Table 6.6 Costing of plate removal

Removal of plate	**Cost (£)**
HRG4 code HB54C	1300
Lost wages (4 weeks)	1600
Total	**2900**

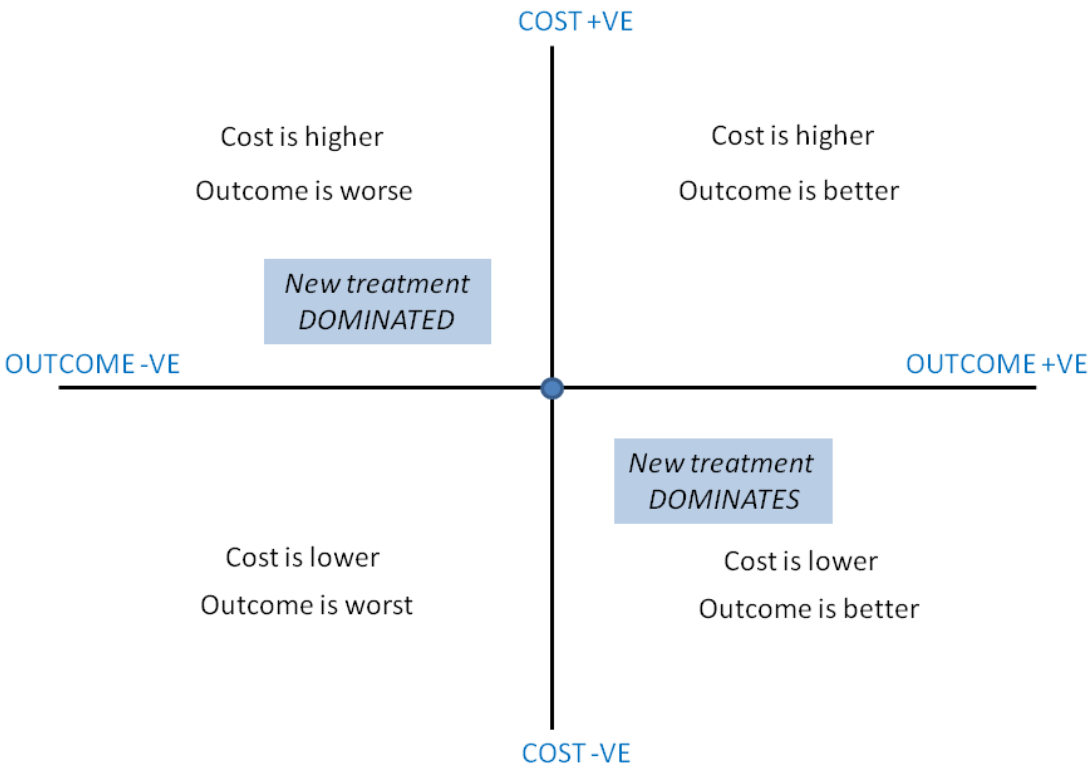
Table 6.7 Costing of extensor pollicis longus (EPL) reconstruction

EPL reconstruction	**Cost (£)**
HRG4 code HB54C	1300
Lost wages (6 weeks)	2400
GP nurse removal of sutures (12 min)	10.2
Total	**3710.2**

6.8 The concept of the cost-effectiveness plane

A cost-effectiveness plane is a useful way of diagrammatically comparing two or more interventions (Figure 6.3) (Black, 1990). The horizontal axis measures differences in effectiveness and the vertical axis measures differences in cost. When comparing a new and an old treatment, there are four possibilities. The four quadrants are by convention identified as in a map.

Figure 6.3 Cost-effectiveness plane



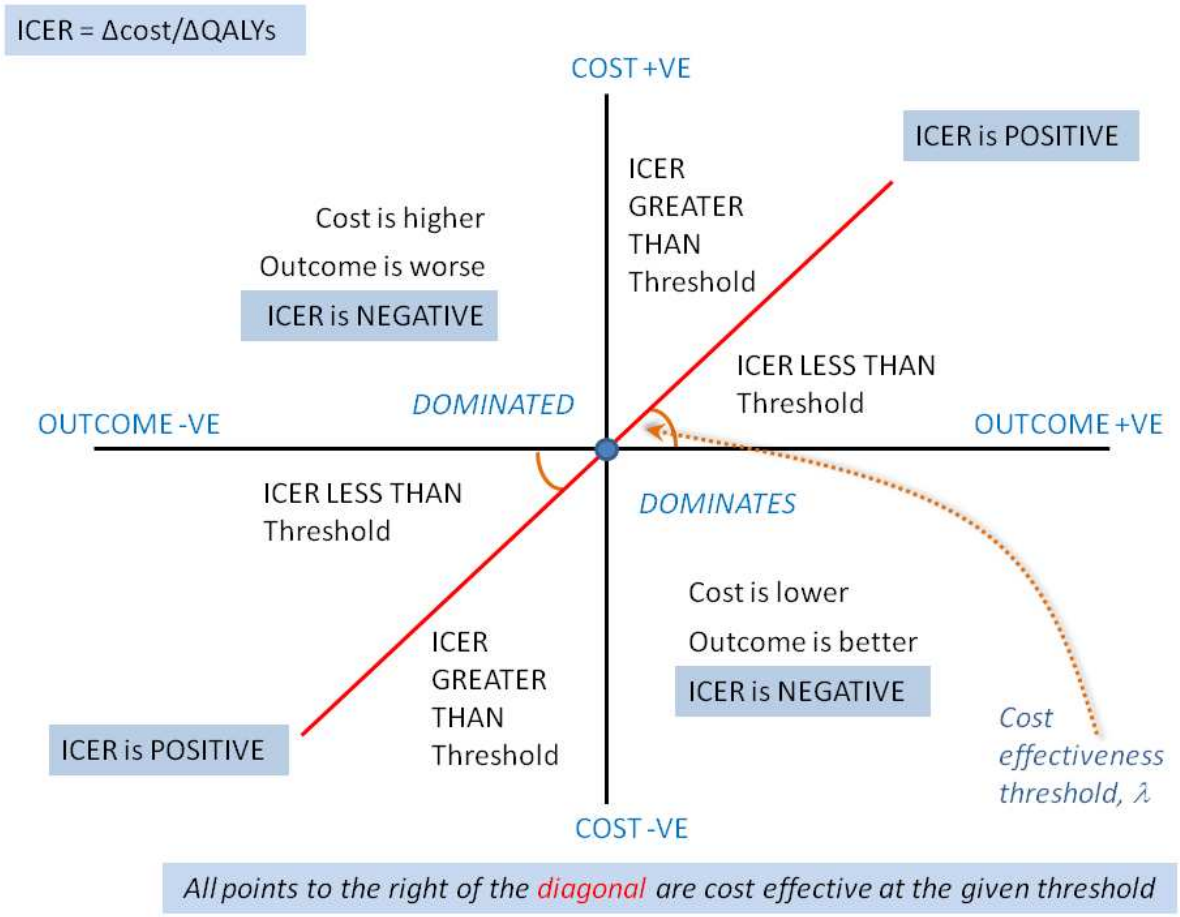
In the north-east quadrant the new treatment is more effective but also costs more. In the south-east quadrant the new treatment dominates the old treatment (Fox-Rushby and Cairns, 2009).

The north-east quadrant is where attention is more often focused. Here the issue is how the additional effect compares to the additional cost. The ICER allows such assessments to be made.

Cost-effectiveness threshold

We should reject any alternatives that are dominated, where the dominated alternative has a greater cost with no greater benefits or lower benefits without lower costs. The choice amongst non-dominated alternatives is more complex. Where only one alternative can be chosen, that with the lowest ICER should be chosen, but only if it is below a ceiling ratio, which is a level of the ICER which any alternative must meet if it is to be regarded as cost-effective (Parkin, 2009). This is the "cost effectiveness threshold", below which, within a pre-specified budget, an intervention will be regarded as cost-effective (Figure 6.4).

Figure 6.4 The cost effectiveness threshold and how it relates to the ICER of a new intervention



Courtesy of Prof DK Whynes, University of Nottingham

But how do you determine the level at which to set the threshold? When there is no set budget, the outcome of cost-utility analysis (CUA) can be expressed in terms of the extra "cost per QALY gained" (CQG). This is the amount we think it is reasonable to pay to gain a QALY and is sometimes referred to as the CQG threshold, because it is the dividing line between health care that is regarded to be cost-effective, and that which is not.

The concept and reality of the NICE cost-effectiveness threshold

Estimated cost-effectiveness for any intervention depends on the selected comparator (Fox-Rushby and Cairns, 2009). But how do you decide at what level to set the threshold?

If there is a fixed annual budget and a list of mutually exclusive interventions for each medical condition, then decisions are straightforward, the irrefutable result of mathematical ranking according to cost and QALYs, with the aim of maximising health gain for a given level of spending. In this setting, a precise threshold can be calculated which determines which interventions "dominate" and which are going to be "displaced" by comparison. In real life, decision-making is much more complex. Budgets are not precisely set, not all decisions are made at the beginning of a financial year, there is significant cross-over of resource use and, above all, most health interventions are not mutually exclusive.

When cost-effectiveness thresholds are used as an aid to decision-making by national bodies such as NICE in England and Wales, the budget of the NHS may be considered fixed, however the Institute does not have complete information about the cost and QALYs for all existing and competing health care programmes. Therefore, any cost-effectiveness threshold is necessarily less explicit because of greater uncertainty about the opportunity cost of the programmes that would be displaced as a result of an adoption decision (Fox-Rushby and Cairns, 2009). As a result, NICE does not use a fixed ICER threshold above which a technology would be automatically defined as not cost-effective or below which it would. It does, however, make reference to a cost-effectiveness range (NICE, 2008).

The National Institute for Clinical Excellence (NICE) was established in 1999 to address geographic variations in prescribing ("post-code lottery") by providing national-level guidance on the clinical and cost-effectiveness of new health technologies in the NHS. The role of NICE was strengthened by making implementation of its decisions mandatory in the NHS from 2002 (Devlin and Parkin, 2004).

When a new technology is more costly than existing technologies, the role of NICE is to decide whether the health expected to be gained by the use of this technology exceeds the health expected

to be foregone elsewhere as other NHS activities are displaced. When NICE issues positive guidance on a technology which imposes additional costs on the NHS, the resources required to deliver it must be found by disinvesting from services elsewhere. So the threshold represents the additional cost that has to be imposed on the system to forgo one QALY of health through displacement (Claxton 2013).

NICE does not accept or reject healthcare technologies on cost-effectiveness grounds alone, although it is undoubtedly a major deciding factor (Appleby et al., 2007).

Current NICE guidelines state that, below a most plausible ICER of £20,000 per QALY gained, the decision to recommend the use of a technology is normally based on cost-effectiveness. Above an ICER of £20,000 per QALY, judgements about the acceptability of the technology as an effective use of NHS resources take account of the following factors:

- The degree of certainty around the ICER
- Whether there are strong reasons to indicate that the assessment of the change in HRQL has not been adequately captured, and may therefore misrepresent the health utility gained
- The innovative nature of the technology, specifically if the innovation adds demonstrable and distinctive benefits of a

substantial nature which may not have been adequately captured in the QALY measure

Technologies are considered in relation to the threshold range, such that the influence of these factors is greater as the ICER increases from £20,000 to £30,000. Above an ICER of £30,000, an increasingly stronger case for supporting the technology as an effective use of NHS resources is required, with regard to the factors listed above (NICE, 2008).

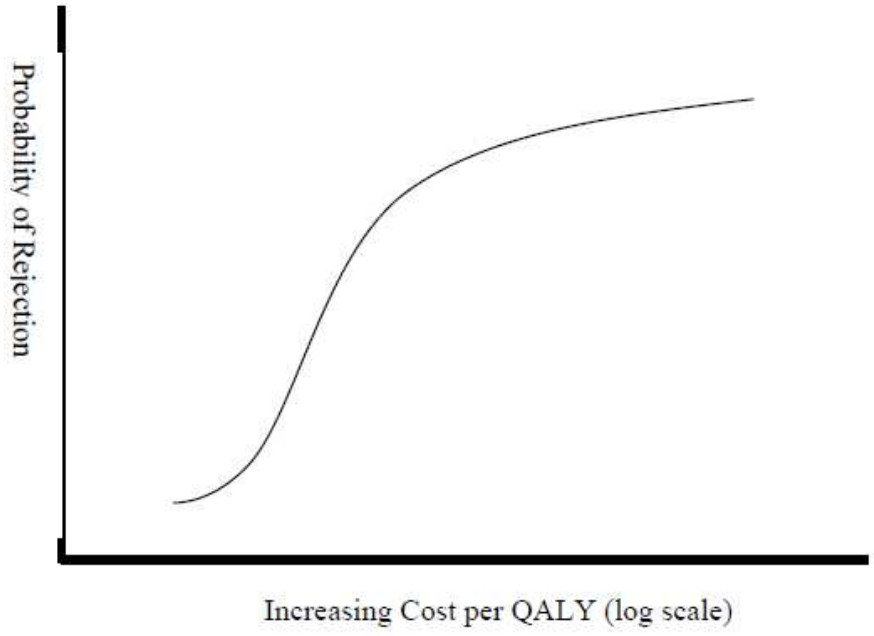
There is therefore, no red line which determines approval or rejection, and no logarithm that can predict the outcome of a decision. In fact, the way decisions are made is the subject of both research and controversy.

Rawlins and Culyer (Rawlins and Culyer, 2004) studied past decisions and identified an increasing likelihood of rejection as the ICER increased beyond £15,000, with few interventions being approved with an ICER >£30,000. This is reflected in Figure 6.5, which illustrates the relationship between cost-effectiveness and the probability of rejection. Devlin and Parkin (Devlin and Parkin, 2004), in contrast, estimated the true threshold to be even higher than the £20,000-£30,000 which NICE has publicly identified.

Outside the doors of the Institute, there is evidence to suggest a mismatch between NICE's threshold range and that apparent elsewhere in the NHS (Appleby et al., 2007). Figures from 2007

suggest that the average primary care trust is willing to spend even less than NICE thresholds, i.e. £12,000 to gain an extra QALY in circulatory disease and £19,000 in cancer (Martin S., 2007).

Figure 6.5 Relationship between cost effectiveness and probability of rejection. Reproduced Rawlins and Culyer (Rawlins and Culyer, 2004).



It has been widely recognised for many years that the NICE threshold range of £20,000 to £30,000 per QALY is not based on evidence. The most recent and major project aiming to provide an evidence-based threshold was completed by the University of York Centre for Health Economics in January 2013 (Claxton 2013, Claxton K., 2013). The project was commissioned by the Medical Research Council Methodology Research Programme. The health economists at York estimated a more accurate threshold to be £18,317 per QALY (based on 2008 expenditure). The research found no evidence that the threshold had increased with the NHS budget (2007 to 2008) and found some evidence that the threshold is likely to fall as the NHS comes under greater financial pressure. So we are unlikely to see increased spending on new technologies adopted in the near future.

6.9 Calculating ICERs by simulation

Assume our two randomised interventions, 1 & 2, with average costs C1 and C2 and average outcomes Q1 and Q2. The base model of the ICER is:

$$ICER = (C1 - C2) / (Q1 - Q2)$$

This is a point estimate and would only represent the true state of affairs if every patient were identical (zero variation between patients). This we know to be untrue, because we have data on each individual which shows that they are all different. Using this data, we can associate a variance or deviation within each of the four parameters. Consequently, there are confidence intervals (CIs) around each parameter which will, in turn, determine the CI around the ICER. Intuitively, the wider the CIs around each parameter, the wider the variation in the ICER will be.

In principle, the ICER is a ratio of two means and there is a standard formula for calculating this, known as Fieller's theorem (Chaudhary and Stearns, 1996, Willan and O'Brien, 1996, Polsky et al., 1997). However, the assumptions required for the theorem to work are restrictive (e.g. normal distributions and zero correlation between variables). These assumptions are sometimes met in randomised controlled trials and sometimes not. In our case, the

distributions are skewed (non-parametric) so the assumptions are not met. The alternative is to estimate the CIs by simulation.

In cost-utility analysis based on economic modelling, distributions for costs and outcomes for a model population are often assumptive, estimated from data from the literature or from a sample population. This is partly why this type of analysis is called "probabilistic" or "stochastic".

In economic analyses based on RCTs, the same process is used as in probabilistic sensitivity analysis. However, instead of assuming our distributions, we can calculate them from actual patient data and their parameters are known.

We have four distributions, one each for C1, C2, Q1 and Q2. In effect, the simulation instructs the computer to choose one value from each of the four distributions at random and use them to calculate the base model. It repeats the calculation for four new values again...and again...thousands of times. The "random choice" of values at each iteration is not entirely random, but governed by the distributions. For example if 55% of C1 values in the actual data exceed 100, then around 55% of values above 100 will be chosen in the simulation. This is called a Monte Carlo method simulation.

In this way, we derive thousands of estimates for the ICER (25,000 in our case) which we use to create a scatter plot. These estimates

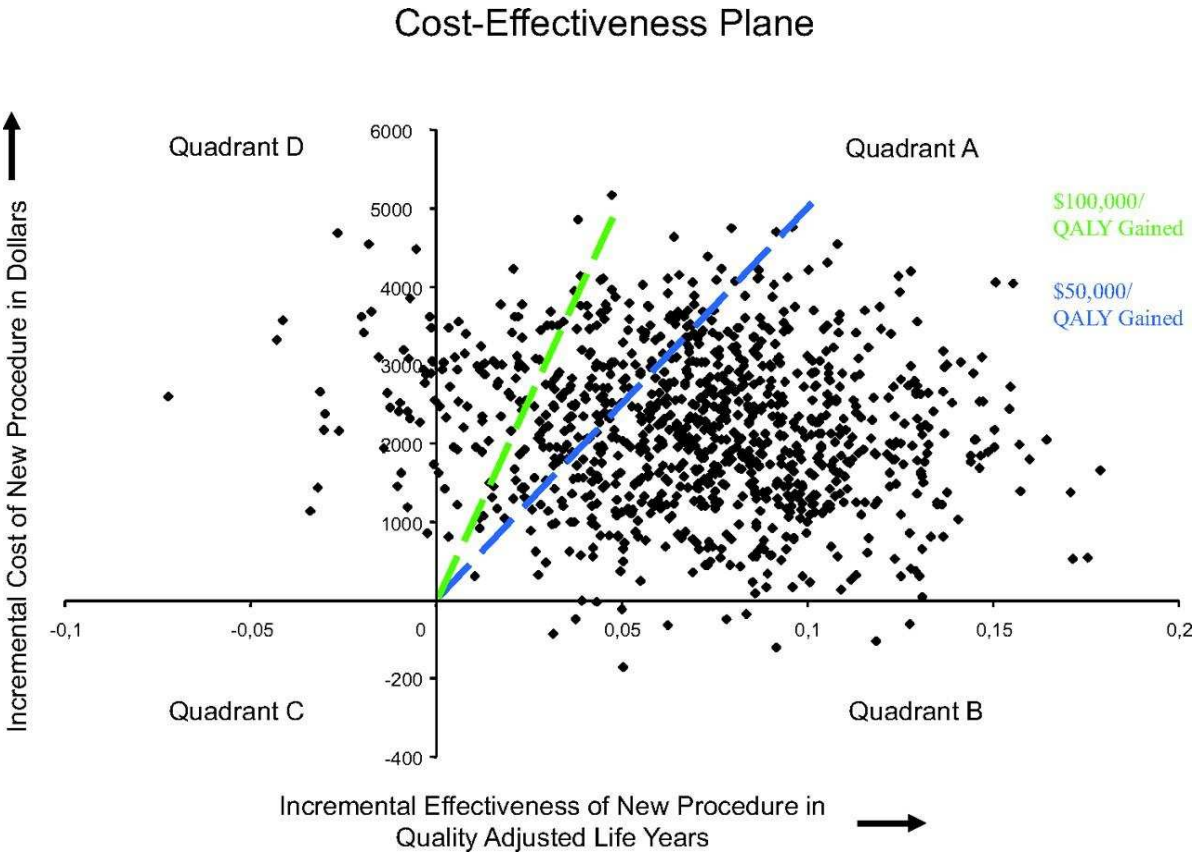
are presented as a distribution, from which, in principle, a variance can be calculated, and therefore a confidence interval around the ICER. An example of a scatter plot produced in this was is given in Figure 6.6 borrowed from Weintraub et al. (Weintraub et al.).

This approach is especially useful when costs and outcomes are correlated, e.g. where more expensive interventions tend to produce better outcomes. Here the formal maths for the CIs would be even more complicated. Correlation can be incorporated into the "random" selection of values that form the simulation. So the computer will be more likely to pick higher values of outcome when it picks high values of cost. The greater the correlation, the greater will be the association between the choices.

Figure 6.6 The distribution of cost-effectiveness in the cost-effectiveness plane

Each point represents an estimate of the ICER based on dual bootstrap of cost and efficacy. Potential $50 000 and $100 000 per QALY gained threshold lines are noted. Estimates of the incremental cost-effectiveness ratio below those benchmarks would be considered cost-effective.

In quadrant A, the new therapy is more effective but more costly than the previous standard. In quadrant B, the new therapy dominates the standard, being more effective and less expensive, whereas in quadrant D, the new therapy is dominated by the standard, being less effective and more expensive (Weintraub et al.).



Cost-effectiveness acceptability curve (CEAC)

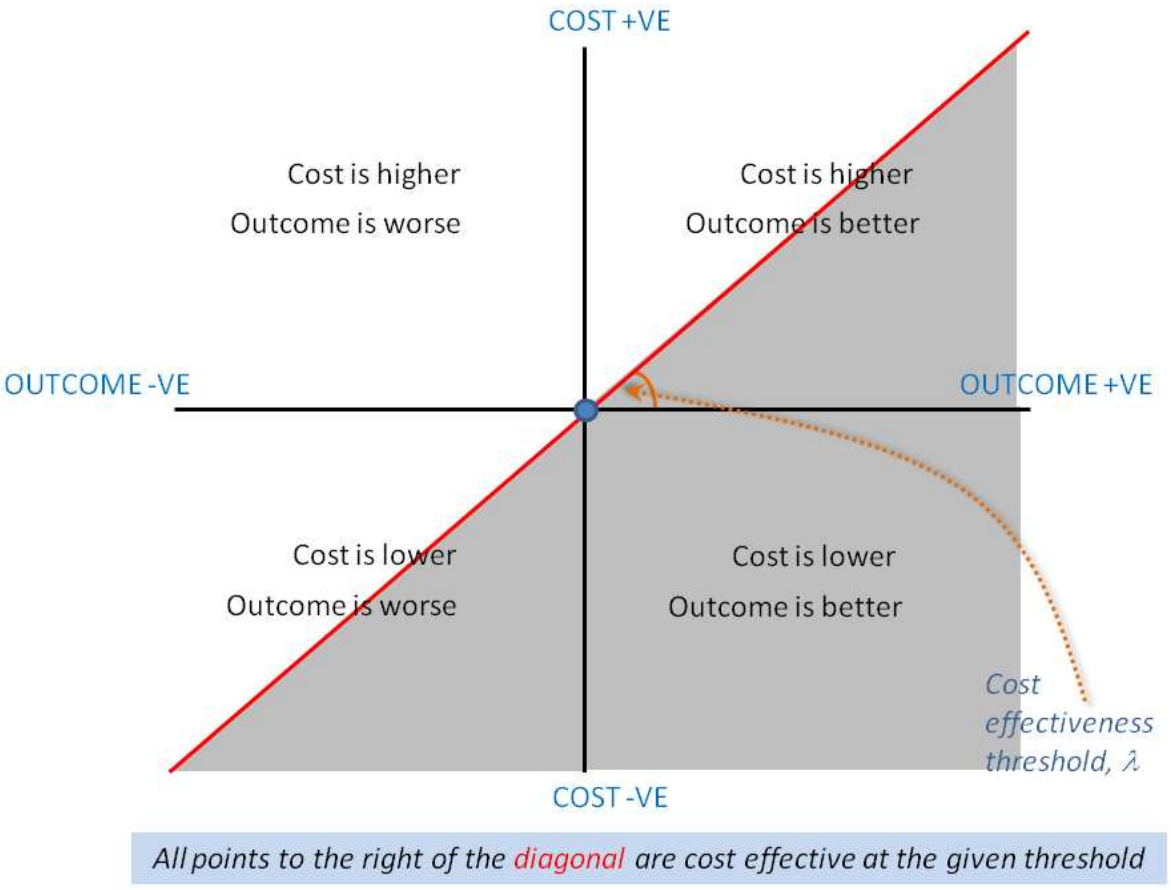
Cost–effectiveness acceptability curves (CEACs) are widely adopted as a method of quantifying and graphically representing uncertainty in economic evaluation studies of health care technologies. They are useful for two main reasons (Fox-Rushby and Cairns, 2009):

- They show how the decision to adopt a technology changes as the threshold value of health gain changes
- They provide a way of combining information on the uncertainties associated with the variables

They are also often used as an alternative to providing confidence intervals around the ICER, which as seen above, can be a statistical challenge

A CEAC is constructed by calculating the probability that the estimated ICER falls below specified values of willingness-to-pay. In Figure 6.7, the diagonal line intersecting the axes indicates the maximum willingness-to-pay, a threshold value of λ per additional QALY, where λ can be any figure and the diagonal can have any slope. The proportion of the distribution that falls below and to the right of this line is "acceptable" (has positive net monetary benefit). The proportion above and to the left of this line is "unacceptable" (Glick, 2007).

Figure 6.7 Cost-effectiveness plane demonstrating the acceptability criterion



The CEAC (Figure 6.8) is constructed by counting the number of ICERs that fall within this area of acceptability and plotting the results. This is repeated for all threshold values (λ) of interest, starting at 0 and increasing to a maximum threshold value of choice. The X axis of this curve represents potential values for the willingness to pay and the Y axis represents the proportion of the distribution that is "acceptable". In CEAC interpretation, this proportion is labelled "the probability that the intervention is cost-effective".

Figure 6.8 Example of a typical cost-effectiveness acceptability curve for resurfacing hip arthroplasty from Edlin et al. (Edlin et al., 2012)