CROSSFIRE STUDY PROTOCOL

Contents

1. Study title

A Combined Randomised and Observational Study of Surgery for Fractures In the distal Radius in the Elderly (CROSSFIRE).

2. Project summary

Fractures of the distal radius are the most common fractures presenting to emergency departments and orthopaedic surgeons.(1) These fractures are more common in the elderly (due to osteoporosis and increased risk of falls) and the incidence in this age group is increasing.(1) Considerable practice variation exists in the management of distal radius fractures in the elderly in Australia,(2) ranging from closed reduction (manipulation of the arm to realign the fracture) with cast immobilisation, to open reduction (surgical exposure and realignment of the fracture) with plate fixation. Open reduction and (volar locking) plate fixation is currently the most common treatment provided. While there is evidence showing no significant advantage for some forms of surgical fixation over closed treatment, and no difference between different surgical techniques, [3-15] there is a lack of evidence comparing the two most common treatments used in Australia: volar locked plate fixation versus cast immobilisation. Surgical management of these fractures involves significant costs (implant costs, medical costs, hospital costs) and risks (infection, implant failure, general surgical risks) compared to non-operative management (closed reduction and cast immobilisation in the emergency department). Therefore, high level evidence comparing the current treatment alternatives (plate fixation versus casting) is required in order to address practice variation, justify or avoid costs, and to provide the best clinical outcome for patients with these common fractures.

This pragmatic, multicentre randomised comparative effectiveness trial aims to determine whether (volar locking) plate fixation leads to better pain and function and is more cost-effective than closed reduction with cast immobilisation in displaced distal radius fractures in adults aged 60 years and older. The trial will compare the two techniques, but will also follow patients that are unwilling to be randomised (but consent to follow up) in a separate, observational arm. Inclusion of non-randomised patients provides a more complete spectrum of fracture presentation, provides practice and outcome insights about standard care, and improves the generalisation of the results from the randomised arms.

Given that plate fixation requires hospital admission and surgery, and that closed reduction with cast immobilisation is usually performed in the emergency department without admission, the findings have important implications for use of resources (theatre time, bed days, staff and implant costs) and may also reduce harms associated with plate fixation (infection,

implant mal-positioning, tendon rupture and reoperation for implant removal). This trial will have significance in Australia, New Zealand and internationally, as it will address an important need for evidence supporting surgical practice.

3. Study identification

Registered with a World Health Organisation Universal Trial Number (WHO UTN).

Registered with ANZCTR (Australian and New Zealand Clinical Trials Registry).

WHO UTN:	U1111-1186-3557		
ANZCTR number:	ACTRN12616000969460		
Web address:	http://www.ANZCTR.org.au/ACTRN12616000969460.aspx		
Date submitted:	12	July	2016
Date registered:	22	July	2016
Registered by:	Ian Harris and Andrew Lawson		

4. Sponsor

Whitlam Orthopaedic Research Centre, Ingham Institute for Applied Medical Research, UNSW Australia.

Grant funding has been received from NHMRC Project Grant (2016, APP1098550), the Australian Orthopaedic Association Research Foundation, AO Trauma Asia Pacific and The Lincoln Foundation.

5. Administering institution

Whitlam Orthopaedic Research Centre, Ingham Institute for Applied Medical Research, UNSW Australia

Street address:	Level 2, 1 Campbell St, Liverpool, 2170, NSW, Australia
Postal address:	Locked Bag 7103, Liverpool BC 1871, NSW, Australia
Telephone:	+61 2 8738 9254
Facsimile:	+61 2 9602 7187
Website:	www.worc.org.au

6. Investigators and participating institutions

The following investigators comprise the CROSSFIRE Study Group

Prof Ian Harris	Liverpool Hospital / Whitlam Orthopaedic Research Centre
A/Prof Justine Naylor	Whitlam Orthopaedic Research Centre
Dr Rajat Mittal	Whitlam Orthopaedic Research Centre
Andrew Lawson	Whitlam Orthopaedic Research Centre (Project manager)
Prof Rachelle Buchbinder	Monash University
Prof Rebecca Ivers	The George Institute, University of Sydney
Dr Wei Xuan	Ingham Institute for Applied Medical Research
A/Prof Herwig Drobetz	Mackay Base Hospital
Prof Zsolt Balogh	John Hunter Hospital
Dr Bernard Schick	Prince of Wales Hospital
Dr Ian Incoll	Gosford and Wyong Hospitals
Dr Michael Kale	Gosford and Wyong Hospitals
Dr Geoff Smith	St George and Sutherland Hospitals
Mr Ilia Elkinson	Wellington Hospital
Dr Woosung Kim	Wellington Hospital
Prof Paul Smith	Canberra Hospital
Dr Sameer Viswanathan	Campbelltown Hospital
Dr Keith Landale	Campbelltown Hospital
Prof Mellick Chehade	Royal Adelaide Hospital
Mr Andrew Oppy	Royal Melbourne Hospital
Dr Kim Latendresse	Nambour Hospital and Sunshine Coast University Hospital
Mr Phong Tran	Western Health
Dr Jonathan Mulford	Launceston Hospital
Prof Richard Page	University Hospital Geelong/Barwon Health
Dr Stephen Hutchinson	Royal Hobart Hospital
Dr Kaushik Hazratwala	Townsville Hospital

Dr Jai Sungaran	Concord Hospital
Prof Pier Yates	Fiona Stanley Hospital
Dr Bertram Rieger	Fiona Stanley Hospital
Dr Kirsten Howard	University of Sydney
Dr James Wong	Westmead Hospital
Dr Andrew Higgs	St Vincent's Hospital- Sydney

7. Rationale & background information

Epidemiology. Distal radial fractures are the commonest fractures seen in a hospital setting. (1) They are particularly common in the elderly due to higher rates of falls and prevalence of osteoporosis. In Australia, it is estimated that the number of osteoporotic wrist fractures (in people aged 50 years and over) will increase over 25% from approximately 20,000 in 2013 to over 25,000 in 2022. [16] Direct costs from osteoporotic wrist fractures have been estimated to be over $130 million dollars per year in Australia. [16] With increasing use of surgical fixation, the cost is expected to increase disproportionately. [16]

Current practice. Historically, these fractures have been treated by closed reduction (manipulation of the fracture) and plaster cast immobilisation. Over the last 10-20 years, the use of internal fixation for these fractures has increased more than 5-fold[17] due to the frequent loss of alignment seen with plaster fixation, despite a lack of any clear association between alignment and function in this population.[6] In 2011, CIA and CID published the results of a survey of Australian orthopaedic surgeons showing that nearly half (47%) of surgeons preferred surgical (plate) fixation for the case example used (typical distal radius fracture in a 75 year old female).[2] Since that survey, open reduction and volar locked plating (a form of internal fixation) has continued to increase in popularity to the extent that it is now usual treatment for displaced distal radius fractures in many institutions.

Comparative trials. Comparative trials have not shown clear superiority of pain and function with plate fixation compared to plaster fixation, despite better radiographic appearance with operative (plate) fixation.

The improved radiographic and clinical alignment noted with surgical (plate) fixation is a driver of the preference for surgical fixation amongst surgeons, despite evidence that the residual alignment (or malalignment) is not correlated with pain or function in these fractures. [18]

In 2009, a Cochrane review involving 3,371 mainly elderly female patients concluded that there was a "lack of clear evidence for the surgical management of these fractures". [19] The

Cochrane review did not contain any studies comparing plate fixation to closed reduction and cast immobilisation. Surgery has also been associated with significant complications otherwise not seen with non-surgical approaches (Table 1). [20,21]

In 2011, a high quality randomised controlled trial (RCT) involving 73 participants aged 65 years and older found no difference in patient reported outcomes when volar plating was compared to plaster fixation for unstable distal radius fractures that had re-displaced after initial closed reduction. [4] However, this was a single centre study, limiting generalisability, and it did not report changes in quality of life. Furthermore, this study only included patients in whom the initial closed reduction had failed on first review, a practice not followed in Australia, where the decision to operate is made on initial presentation. In many countries, including Australia, a treatment decision is made on the initial radiographs (degree of displacement) with no trial of closed treatment first. Therefore, the current study reflects that practice by randomising based on the initial radiographs. It is the consideration of many (particularly in Australia and the US) that 'stability' is decided on the initial radiographs (displacement, comminution) and 'reducibility' decided on the post-reduction radiographs.

In 2014, a second randomised trial involving 185 participants aged 65 years and older also showed no significant benefit to volar locked plating over closed reduction for displaced distal radius fractures, but this paper had a high rate of crossover and only included the less common intra-articular fracture type, making interpretation and generalisation difficult. [22] These two studies are summarised in Table 2.

A third multicentre study investigating volar plate fixation of distal radius fractures in the elderly is currently recruiting in the US. [23] However, the study group decided not to have a cast-only group due to the "predictable loss of alignment", despite a lack of evidence supporting the popularity and perceived effectiveness of volar plate fixation, which drove the development of the study. Instead, volar plating is being compared to techniques that are (by their own admission) no longer in common practice (external fixation and percutaneous wiring). [24]

Table 1. Risks and costs of volar plate fixation (intervention) and cast immobilisation (control).

Risks	Volar locked plating	Cast immobilisation (ED)
1. Infection	Yes	No
2. Need for implant removal	Yes	No
3. Tendon rupture / irritation	Yes	No
4. Implant failure	Yes	No
5. Implant migration	Yes	No
6. Chronic regional pain syndrome	Yes	Yes
7. Wound breakdown	Yes (dehiscence)	Yes (pressure injury)
8. Loss of reduction	Yes (low)	Yes (high)
Costs		

1. Implant	Yes ($1,500)	No
2. Theatre costs	Yes	No
3. Surgeon / anaesthetists	Yes	No
4. Inpatient costs (bed)	Yes (one day)	No (discharge from ED)
5. Anaesthetic / sedation agents	Yes	Yes
6. Plaster	Yes	Yes

Justification. Given the increased resource utilisation and risks associated with surgery, a clear benefit is required to make this treatment cost-effective. No clear benefit to surgery has yet been established. Our aim is to definitively quantify the true benefit (if any) and harms of the current standard surgical treatment in Australia, and to determine its cost-effectiveness, in comparison to closed reduction and cast immobilisation. Our trial will address the methodological shortcomings of previous trials as outlined in Table 2.

Table 2. Comparison of previous RCTs and proposed study, comparing volar plate fixation to casting for distal radius fractures in the elderly.

	Arora et al, 2011	Bartl et al, 2014	Current study
All dorsally angulated distal radius fractures	Yes	No	Yes
Low crossover	Yes	No	N/A
Treatment assigned on initial presentation	No	Yes	Yes
Multicentre	No	Yes	Yes
Include general health outcome	No	Yes	Yes
Country	Austria	Germany	Australia / NZ

Given the ageing of the Australian population, there will be significant increases in presentations for distal radius fractures and costs will be significant if usual practice is surgery. Given the risk associated with surgery, particularly in older people, who are more prone to comorbidities that may lead to complications and longer hospital stays, there is an important need for a definitive trial to guide practice, reduce unwarranted practice variation, optimise health outcomes and justify use of valuable resources. The results of this trial will not only guide care in Australia and New Zealand but will also have major relevance internationally.

8. Study hypothesis

Primary hypothesis:

Patients aged 60 years and older with displaced fractures of the distal radius managed operatively using volar locking plate fixation, will have superior patient rated pain and function

at 12 months post-injury compared to those managed non-operatively with closed reduction and plaster casting.

Secondary hypotheses

- There will be a significant difference in complication rates between the two groups
- There will be a significant difference in cost effectiveness between the two groups

9. Aims

Primary Aim: To determine the comparative effectiveness of operative treatment (volar locking plate fixation) versus non-operative treatment (closed reduction and cast immobilisation) for adults aged 60 years and older with displaced distal radius fractures in a multicentre randomised controlled trial.

Secondary Aims: To determine: comparative safety and cost-effectiveness of operative treatment versus non-operative treatment for adults aged 60 years and older with displaced distal radius fractures; comparative effectiveness and safety in a parallel prospective observational study.

10. Study design

We will conduct a multicentre randomised controlled trial with an accompanying economic evaluation, as well as a concurrent prospective observational study including all eligible patients who decline participation in the trial and will therefore receive standard care (either plate fixation or closed reduction according to patient preference and usual care for each institution) and consent to be followed up. All participants will be followed up at the same time using the same outcomes measures. Surgeons and participants will not be blinded. The primary outcome (patient reported outcome) will be collected by a blinded assessor.

The use of an observational 'preference' arm in addition to the core RCT addresses criticisms of selection bias in the RCT by following non-randomised patients, and increases generalisability by following a large cohort of patients receiving the same treatment options as the RCT, as part of usual care.(3) This study type has been used in surgical trials[26] and has been recommended as a model for trials of surgery versus non-operative treatment where recruitment rates are expected to be lower than for other RCTs. [27] Our experience from our recently completed, similar multicentre fracture trial [28] is that a third of patients accept randomisation with almost 100% of the remainder consenting to be part of the observational cohort.

11. Methods

Setting

The study will recruit from up to 32 institutions and use 30 site investigators (orthopaedic surgeons) that have contributed to the protocol and received departmental approval to recruit for this study, from all surgeons within each department.

Population

The study population will include non-institutionalised individuals aged 60 or older presenting to participating institutions with a displaced, dorsally angulated distal radius fracture, within one week of injury.

Inclusion criteria

- Age 60 years or older
- Displaced distal radius fracture (AO/OTA 23A or 23C with more than 10° dorsal angulation, referenced off a line perpendicular to the shaft of the radius or more than 3mm shortening or more than 2mm articular step) prior to reduction
- Medically fit for surgery
- Independent living (including hostel accommodation)
- Low energy injury (fall from less than 1m)
- Available for follow up for 12 months

Exclusion criteria

- Patient unable to provide consent (due to cognitive capacity or English proficiency)
- Volar angulation
- Diaphyseal extension
- Partial articular fractures eg chauffer, Barton's (AO/OTA 23B)
- Associated fracture or dislocation in any other body part that will affect the use of the involved wrist (ulna styloid fracture will be permitted, as these are usually associated with the fracture under investigation)
- Open injury
- Previous wrist fracture on the same side
- Medical condition precluding anaesthetic

Recruitment

Potential participants will be screened and those eligible will be approached by members of the orthopaedic team. Eligible patients will be provided with the Participant Information Sheet, invited to participate and given the opportunity to ask questions. Eligible patients who are

unwilling to be included in the randomised arm of the study will be invited to participate in the observational arm. Written consent will be obtained prior to inclusion in the either the randomised or observational arms of the study.

Randomisation and treatment allocation concealment

Randomisation will occur immediately after consent has been gained by the recruiting orthopaedic team, within one week of the date of the injury. This will occur by the orthopaedic team member contacting a central computer-based randomisation service by telephone. Participants will be randomized using the method of minimisation. Randomisation will be stratified by site, and minimisation, adjusting for gender and age (60-74 years and >74 years), will be employed as recommended by the NHMRC Clinical Trials Centre who will provide the randomisation service. Minimisation (adaptive stratified sampling) aims to reduce imbalance between the groups on prognostic factors which can occur despite random allocation of treatment. Here, age and gender will be included in the minimization algorithm for randomization.

Blinding

Due to the nature of the comparisons (surgery versus no surgery), it will not be possible to blind the surgeon (study) investigators or participants. While this may render the trial at risk of performance and detection bias, every effort will be made to ensure that treatment, other than the interventions under study is identical in both groups. The primary outcome (PRWE – patient rated wrist evaluation score at 12 months) will be collected from participants by blinded researchers, by telephone. The statistician will be blinded to the treatment group. Participating surgeons have equipoise regarding the two treatment alternatives.

Intervention group (plate group)

Surgical fixation using a volar locking plate will be performed within two weeks of initial injury according to usual care of the participating institution, with an orthopaedic surgeon in attendance. This is a commonly performed procedure. Surgical technique and type of plate (make and length) will be surgeon preference. A plaster cast may be applied post operatively but for no longer than two weeks. Active finger movement will be encouraged post operatively. Participants will be reviewed two weeks (10-17 days) after surgery; the wound will be reviewed and sutures removed where necessary. Participants will be provided with a home-exercise program (written information) post-operatively. Referral for outpatient rehabilitation will not be routinely provided but will be permitted. See section below (“Physiotherapy”) for more information on post-treatment rehabilitation.

Control group (cast group)

Participants in this group will be treated with a closed reduction and cast immobilisation, avoiding wrist flexion, within two weeks of the initial injury. This method of casting is consistent with standard casting practice in Australia. Immobilisation of a DRF in flexion has been associated with an increased risk of fracture displacement as well as finger and MCPJ stiffness [29]. Also, immobilisation in a cast that is too restrictive and excessively flexed has been associated with an increased risk of CRPS [30, 31]. The reduction may be performed in the Emergency Department under sedation and local anaesthetic infiltration into the fracture (haematoma block) where possible, but may also be performed in an operating room (according to availability and local practice). The procedure will be performed by an orthopaedic surgeon or registrar. Post reduction radiographs will be taken to assess the fracture alignment after the reduction. The best reduction achievable will be accepted.

The cast will be removed at six (+/-one) weeks from the initial reduction. Active finger movement and light use of the hand will be encouraged immediately. Participants will be provided with a home-exercise program (written information). Referral for outpatient rehabilitation will not be routinely provided but will be permitted (as above).

Observational arm

Patients who do not consent to be randomised will be offered participation in the observational arm of the study. Their treatment will consist of either closed reduction and cast immobilisation or operative fixation using a volar locking plate (the same two treatment options as the RCT arm). Treatment will be decided by patient preference as per usual practice at each institution. Post-operative treatment protocols, follow up and outcome measures will be the same as the randomised arms.

Physiotherapy

A home exercise program (written information) will be provided to all groups. Outpatient physiotherapy will be allowed according to local practice, but not controlled. This is based on RCTs and systematic reviews of RCTs that show no benefit, or no sustained (beyond 6 – 12 weeks) clinical benefit from outpatient physiotherapy compared to an unassisted home program (written information only). [32-36] Attendance at any physical therapy (physiotherapy, massage, osteopathy etc.) will be recorded at 3 month follow up.

Time points

Participants will have baseline data collected at the time of consent. Participants will be followed up in person at 1 week (cast group), 2 weeks (plate group), and 6 weeks by the study surgeons as part of usual care and assessed for complications and radiographic

documentation. Participants will be contacted by telephone by blinded researchers at 3 and 12 months and 2, 5 and 10 years post initial procedure for assessment of study outcomes.

Baseline measures

Baseline variables will include age, gender, pre-injury difficulty using arm (yes/no), fracture type (AO/OTA 23A or 23C), radiographic features (see above), diabetes (yes/no), smoking status (current smoker: yes/no), current glucocorticoid treatment: yes/no, osteoporosis treatment. Outcome scores (quality of life) and radiographic measures will be recorded at baseline. We will also collect treatment preference at baseline, as this may have an independent effect on outcome.

Primary outcome

Patient Rated Wrist Evaluation (PRWE) [37,38] at twelve (+/-one) months. The PRWE is a 15-item patient-reported measure of pain and function, specific to the wrist. It is a continuous score on a scale from 0 to 100 with higher scores being worse. It is commonly used, was developed with patient-input and has been validated for use in patients with distal radius fractures.

Secondary outcomes

- PRWE at 3 months and 2, 5 and 10 years
- Disability of the Arm Shoulder and Hand (DASH)[39] at 12 months
- EQ5D (5L) (Health related quality of life) at 3 and 12 months and 2, 5 and 10 years
- Pain (numerical rating scale NRS, 0-10) at 3 and 12 months and 2, 5 and 10 years
- Patient reported treatment success (at 12 month and 2, 5 and 10 years,5-point Likert scale)
- Patient rated bother with appearance (at 12 month and 2, 5 and 10 years, 5-point Likert scale)
- Complications (including deep infection, reoperation, neuropathy, tendon irritation requiring treatment, tendon rupture, fracture non-union at minimum 6 months, implant failure, complex regional pain syndrome, death) at 3 months, 12 months, 2, 5 and 10 years
- Radiographic measures (shortening [ulnar variance], dorsal angulation, radial tilt, articular step) measured at presentation, post reduction, and between 6 weeks and 12 months)
- Therapy utilisation up to and at 3 months

Sample size

The recent RCT by Arora [4] used a 1:1 allocation, 5% significance and 80% power to detect a difference of 10 points on the PRWE, calculating a sample size of 68 participants for both groups. Based on a standard deviation (SD) for the PRWE of 23 in the Arora study, a 10-point threshold would be less than the commonly used threshold of 0.5SD for a clinically important difference [40] and less than the MCID of 12 points determined by Walenkamp [41]. Using a 14 point cut off represents 0.6SD and is in line with another estimate of the minimum clinically important difference of the PRWE [42]. We consider 14 points to be the minimum clinical difference necessary to justify the additional costs of surgery compared to non-operative treatment.

A total of 128 patients (64 in each group) will provide 90% power to detect a difference of 14 points on the PRWE scale at a significance level of 0.05. We aim to recruit 160 patients to allow for 20% loss to follow up. The previous RCTs reported loss to follow up rates of 19% [4, 22].

The observational arm will be a convenience sample of patients not consenting to randomisation. In our experience, this group will comprise approximately 2 participants for every 1 randomised. We will therefore recruit 160 patients into the randomised trial and approximately 300 patients into the observational arm.

Data Collection

Primary data collection from site investigators will be paper-based but direct electronic data entry will also be allowed. Participant follow up will be by telephone, but the option of electronic data capture by participants (incorporating electronic reminders) will be available.

Analysis

The primary outcome is the PRWE score at 12 months. An analysis of covariance will be used to compare the mean PRWE between the two independent groups. Intention to treat analysis will be performed in the primary analysis. A per-protocol analysis (including participants according to treatment received) will be added as a secondary analysis. Analysis of secondary outcomes will include mixed model analyses, comparing secondary outcomes between timepoints. Non-operative treatment will be defined as a minimum of 28 days in the plaster splint for the purposes of the per-protocol analysis.

The observational arm will be analysed separately, comparing the same two treatment groups against the same outcomes using multivariable linear regression to adjust for potential confounders. Results from both arms of the study will be analysed, comparing the randomised groups with the observational groups.

Repeated measures analysis will be performed as a secondary analysis.

Attempts will be made to minimise missing data, such as obtaining multiple contact details at recruitment and using telephone follow up rather than mail. Missing data will be dealt with according to the instructions on the use of the outcome tools (PRWE, DASH and EQ-5D-5L). If greater than ten percent of data is missing from the randomised sample, then missing data will be imputed..

Cost-effectiveness

The costs of both treatment arms, and health service utilisation will be calculated for the cost-effectiveness analysis. A cost effectiveness analysis will be performed from the hospital perspective and a health care funder perspective, and limited to clearly defined, major costs. Costs will be calculated from: 1. Length of stay (if admitted), 2. Theatre costs (based on standard fees for public hospitals in each state), 3. Implant costs, and 4. Outpatient rehabilitation related costs. Using the mean costs and the mean health outcomes in each trial arm, the incremental cost per QALY of the plate group compared with cast group will be calculated; results will be plotted on a cost-effectiveness plane. Bootstrapping will be used to estimate a distribution around costs and health outcomes, and to calculate the confidence intervals around the incremental cost-effectiveness ratios. One-way sensitivity analysis will be conducted around key variables and a probabilistic sensitivity analysis to estimate the joint uncertainty in all parameters. A cost-effectiveness acceptability curve (CEAC) will be plotted to provide information about the probability that the intervention is cost-effective, given willingness to pay for each additional QALY gained.

Crossover

The cosmetic difference between non-operative treatment (which commonly results in a visible deformity) and plate fixation (which rarely results in a visible deformity) may be a reason for participants in the non-operative group to cross over. This was not reported to be an issue in the RCT by Arora et al, but was a significant issue in the RCT by Bartl et al, with nearly 50% crossover from non-operative to operative treatment prior to the primary endpoint. However, this was due to surgeon preference based on radiographic appearance. In order to minimise this, the importance of avoiding crossover prior to the primary endpoint will be emphasised with the participating surgeons, and participants will be informed of the likely residual deformity, but reassured (in the participant information sheet) that residual deformity is usually well tolerated and is not associated with functional loss or pain. The participating surgeons understand the importance of equipoise and have agreed to participate based on their equipoise and the understanding that cosmetic appearance is not an indication for crossover.

Stopping rules / interim analysis:

There will be no interim analysis due to the low risk of adverse events compared to usual care, as both treatment groups constitute reasonable and common practice. Adverse events will be reported to the administering institution and project manager. These will be defined as outlined below and are included in the reported complications listed above (secondary outcomes).

12. Safety Considerations

The study compares two treatments that comprise usual care. It is not anticipated that either treatment arm will be associated with adverse events above and beyond what is experienced normally with these therapies. An independent data safety monitoring board (DSMB) will be established, however, at the commencement of the trial. The board will convene four months after trial commencement to review study progress and, where appropriate, provide advice on issues regarding the scientific aspects of study conduct (eligibility, recruitment rates, compliance) and any emerging evidence as it relates to the trial. The DSMB will reconvene subsequently to review progress if any recommendations were made after the initial review. If not, the DSMB will only meet as required; that is, if any adverse event (defined below) occurs. The DSMB will be required to decide whether the adverse event is related to the trial interventions or not. If there appears to be an atypical trend in adverse events, trial suspension will be considered. This DSMB will comprise three members who are not investigators (an orthopedic surgeon, a physical therapist, and a statistician /epidemiologist), as well as one investigator.

Adverse events will be defined as:

- Symptomatic fracture non-union (3 of 4 cortices not united radiographically at minimum 6 months)
- infection (local infection requiring any treatment)
- neuropathy
- tendon irritation (requiring treatment)
- tendon rupture
- Complex regional pain syndrome (diagnosed on basis of presence of dysaesthetic pain, hyperaesthesia extending into the hand of the injured limb, vasomotor changes, skin atrophy, and diffuse osteopenia)

Site agreements include provisions for liability and insurance, requiring each site to maintain insurance for indemnity relating to activities in the conduct of the study. Participants are

informed in the patient information and consent form as to what they should do if they suffer any injuries or complications as a result of participation in the study.

13. Data management

Data will be collected by local site investigators and study documents will be submitted securely (scanned and emailed) to the project manager at the administering institution. Data will be stored in password protected computers and locked filing cabinets within the administering institution.

14. Ethical considerations

The study will be submitted to a lead ethics committee in NSW for initial ethical consideration. Relevant ethics approval from each site will also be necessary if not covered by the original NEAF, together with site-specific approvals.

The study will be registered prior to trial commencement at ANZ Clinical Trials Registry and the protocol will be published, in accordance with The SPIRIT Statement [46,47]. Reporting will be according to The CONSORT Statement [48].

The study satisfies the requirements of the National Statement on Ethical Conduct in Human Research (updated March 2014). No financial or other competing interests have been identified or declared.

The investigators consider randomised trials of operative versus non-operative treatment to be ethical, provided that the requirements of ethical research have been satisfied, and the potential benefits of the study to society outweigh the potential risks to individuals involved in the study. Two of the investigators have previously published on ethics in surgical research.[49,50] As operative treatment is currently the most common treatment, we see no increased harm from surgery than would exist without the presence of the study.

In this case, we consider the risks of continued operative treatment of distal radius fractures without supporting evidence of a clinical advantage over non-operative treatment to be unjustified. Risks associated with this study are the risks associated with each of the treatments.

Participants will not be paid. Institutions will receive $250 reimbursement per participant for the randomised group and $100 per participant for patients declining randomisation (who will be offered inclusion in the observational cohort) to compensate for the time given by local research support staff in recruitment and data collection.

15. Peer review

The study has wide support from clinicians as evident from the participating centres; it was presented at the annual meeting of the Australasian Orthopaedic Trauma Society in Melbourne in October 2014 and drafts of the protocol were sent to members prior to the meeting. Further revisions have occurred after dissemination between study group members, including orthopaedic clinicians, statisticians and methodologists. The study protocol was presented at the 2016 ANZMUSC Scientific Meeting and received endorsement from the group. The investigators have published previous RCTs and surgical outcome studies, including studies of distal radius fractures. [2,40,41].

16. Feasibility

The administering institution and many of the included researchers performed the CROSSBAT multicentre ankle fracture trial (clinicaltrials.gov, NCT01134094) that has recently been completed, having recruiting approximately 450 patients from over 24 centres within 3 years, using funding from an Australian Orthopaedic Association grant. The administering institution and the CIs have extensive expertise and experience in performing and publishing multicentre randomised trials in orthopaedics. A Clinical Trials Coordinator housed at the Whitlam Orthopaedic Research Centre (WORC), within the Ingham Institute for Applied Medical Research will be assigned to this project.

17. Expected outcomes

The study will provide definitive evidence of the comparative effectiveness, safety and cost-effectiveness of two different but commonly used treatment options for this common fracture.

If the study finds that operative treatment (plating) is not superior to non-operative treatment (casting), it will strengthen the existing evidence for non-operative treatment for these fractures and therefore influence and change clinical practice.

If the study finds plating to be superior, and it is found to be cost-effective, it will provide high quality evidence to support the current practice of plate fixation.

Involvement of local surgeons is more likely to lead to acceptance of the results and facilitate early practice change within Australia and New Zealand. Inclusion of an observational arm will also increase the generalisability of the results by including non-randomised patients treated with the same interventions. Due to the frequency and impact of this fracture, and

continued contention over the treatment options internationally, the results of this trial will have impact on fracture treatment globally.

18. Dissemination of results and publication policy

The protocol will be published in an open access journal.

The results of the study will be presented at national and international orthopaedic scientific meetings such as the Australian Orthopaedic Association (AOA) Annual Scientific Meeting and the American Academy of Orthopaedic Surgeons Annual Scientific Meeting. Results will be published in a high impact general medical or surgical journal and will be disseminated via various forms of media. The results of the trial will be incorporated in clinical recommendations and practice guidelines produced by local professional bodies such as the AOA, and government bodies such as the Agency for Clinical Innovation (NSW) and similar interstate bodies. A medical education program will include direct feedback of the results to participating institutions, including orthopaedic departments, emergency departments, general practitioners and physiotherapists. Direct patient targeting will be performed by producing patient information sheets available in the emergency department.

Authorship will be under the name of “The CROSSFIRE Study Group”. This group will comprise all investigators, including at least one investigator from each contributing institution.

Aggregated, deidentified results will also be made available to participants and participating institutions via the study website, accessed via the WORC website.

The de-identified participant-level dataset and statistical code will be made available for collaborative research projects.

19. Duration of the project / timeline

Ethics approval and site preparation will take approximately 9 months. Recruitment is expected to take 12 months. Data cleaning, analysis and manuscript preparation will take 6 months. The study will take 4 years from initiation to manuscript submission. Table 3 provides a timeline for the study.

Table 3. Study timeline (periods in months [m])

	0-6m	7-12m	13-18m	19-24m	25-30m	31-36m	37-42m	43-48m
Ethics approval	X							
Site preparation	X	X						
Recruitment		X	X	X				
Follow up		X	X	X	X	X		
Analysis						X	X	
Dissemination							X	X

Data pertaining to 2, 5 and 10 year follow-up will be analysed and published in separate studies.

20. Anticipated problems

Slow recruitment due to local site issues, poor acceptance by potential participants, and greater than expected rates of exclusion criteria (e.g., cognitive state, language proficiency) may prolong the study. This can be addressed by the addition of more sites or prolonging the recruitment period. This is a common fracture, and we have previously achieved high participation rates. In a similar trial of operative versus non-operative treatment of ankle fractures (clinicaltrials.gov, NCT01134094) from a similar number of sites (24 versus 27 for this study) we were able to recruit 440 patients over 3 years, for a fracture that is less common that distal radius fractures in the elderly. With the sample size of 145 and 27 sites recruiting for six months, each site would need to recruit one patient per month. Each institution would treat 2-5 such cases per week.

Interest in the study will be maintained by regular contact from the administering institution through monthly newsletters and updates by email, and telephone contact and site visits as required.

21. Project management

A project manager will be assigned to oversee the day-to-day management of the study including liaising with local sites and ensuring complete data collection at each time point for each study participant.

Overall supervision of the project will be from the CROSSFIRE Study Group (all investigators listed above) who will maintain email contact and have regular teleconference meetings (bimonthly). Monthly progress emails will be distributed to all investigators. Members will also meet for face-to-face meetings twice per year.

Significance

The study will provide definitive evidence of the comparative effectiveness, safety and cost-effectiveness of two different but commonly used treatment options for this common fracture.

If the study finds that operative treatment (plating) is not superior to non-operative treatment (casting), it will strengthen the existing evidence for non-operative treatment for these fractures and therefore influence and change clinical practice. If the study finds plating to be superior, and it is found to be cost-effective, it will provide high quality evidence to support the current practice of plate fixation.

Involvement of local surgeons is more likely to lead to acceptance of the results and facilitate early practice change within Australia and New Zealand. Inclusion of an observational arm will also increase the generalisability of the results by including non-randomised patients treated with the same interventions. Due to the frequency and impact of this fracture, and continued contention over the treatment options internationally, the results of this trial will have impact on fracture treatment globally.

22. References

1. Nellans, K.W., E. Kowalski, and K.C. Chung, The Epidemiology of Distal Radius Fractures. Hand clinics, 2012. 28(2): 113-125.

2. Ansari, U., et al., Practice variation in common fracture presentations: a survey of orthopaedic surgeons. Injury, 2011. 42(4): 403-7.

3. Chan, Y.H., et al., Comparison between cast immobilization versus volar locking plate fixation of distal radius fractures in active elderly patients, the Asian perspective. Hand Surg, 2014. 19: 19-23.

4. Arora, R., et al., A prospective randomized trial comparing nonoperative treatment with volar locking plate fixation for displaced and unstable distal radial fractures in patients sixty-five years of age and older. J Bone Jt Surg (Am), 2011. 93(23): 2146-53.

5. Belloti, J.C., et al., Treatment of reducible unstable fractures of the distal radius in adults: a randomised controlled trial of De Palma percutaneous pinning versus bridging external fixation. BMC Musculoskeletal Disorders, 2010. 11: 137.

6. Diaz-Garcia, R.J. and K.C. Chung, Common Myths and Evidence in the Management of Distal Radius Fractures. Hand Clinics, 2012. 28(2): 127-133.

7. Egol, K., et al., Bridging external fixation and supplementary Kirschner-wire fixation versus volar locked plating for unstable fractures of the distal radius: a randomised, prospective trial. J Bone Jt Surg (Br), 2008. 90(9): 1214-21.

8. Egol, K.A., et al. ORIF vs external fixation for distal radial fractures: a randomized prospective trial. in American Academy of Orthopaedic Surgeons Annual Meeting. 2007. San Diego, California.

9. Egol, K.A., et al., Distal radial fractures in the elderly: operative compared with nonoperative treatment. J Bone Jt Surg (Am), 2010. 92A(9): p. 1851-7.

10. Gradl, G., et al., Non-bridging external fixation employing multiplanar K-wires versus volar locked plating for dorsally displaced fractures of the distal radius. Arch Orthop Traum Su, 2013. 133(5): 595-602.

11. Grewal, R., et al., Open reduction internal fixation versus percutaneous pinning with external fixation of distal radius fractures: a prospective, randomized clinical trial. J Hand Surg (Am), 2011. 36(12): 1899-906.

12. Harley, B.J., et al., Augmented external fixation versus percutaneous pinning and casting for unstable fractures of the distal radius--a prospective randomized trial. J Hand Surg (Am), 2004. 29(5): 815-24.

13. Kreder, H.J., et al., A randomized, controlled trial of distal radius fractures with metaphyseal displacement but without joint incongruity: closed reduction and casting versus

closed reduction, spanning external fixation, and optional percutaneous K-wires. J Orthop Trauma, 2006. 20: 115-21.
14. Margaloit, Z., et al., A meta-analysis of outcomes of external fixation versus plate osteosynthesis for unstable distal radius fractures. J Hand Surg (Am), 2005. 30(6): 1185.e1-17.
15. Young, C.F., A.M. Nanu, and R.G. Checketts, Seven-year outcome following Colles' type distal radial fracture. A comparison of two treatment methods. J Hand Surg (Br), 2003. 28(5): 422-6.
16. Watts, J.J., J. Abimanyi-Ochom, and K.M. Sanders, Osteoporosis costing all Australians. A new burden of disease analysis - 2012 to 2022. 2013, Osteoporosis Australia: Sydney.
17. Chung, K.C., M.J. Shauver, and J.D. Birkmeyer, Trends in the United States in the treatment of distal radial fractures in the elderly. J Bone Joint Surg (Am), 2009. 91(8): 1868-73.
18. Synn, A.J., et al., Distal radius fractures in older patients: is anatomic reduction necessary? Clin Orthop Relat Res, 2009. 467(6): 1612-20.
19. Handoll, H.H. and R. Madhok, Surgical interventions for treating distal radial fractures in adults. Cochrane Database Syst Rev, 2009(3): CD003209.
20. Arora, R., et al., Complications following internal fixation of unstable distal radius fracture with a palmar locking-plate. J Orthop Trauma, 2007. 21(5): 316-22.
21. Berglund, L.M. and T.M. Messer, Complications of Volar Plate Fixation for Managing Distal Radius Fractures. J Am Acad Orthop Surg, 2009. 17(6): 369-377.
22. Bartl, C., Stengel, D., Bruckner, T., Gebhard, F., The Treatment of Displaced Intra-articular Distal Radius Fractures in Elderly Patients: A Randomized Multi-center Study (ORCHID) of Open Reduction and Volar Locking Plate Fixation Versus Closed Reduction and Cast Immobilization. Dtsch Arztebl International, 2014. 111(46): 779-87.
23. Chung, K.C., J.W. Song, and W.s. group, A Guide on Organizing a Multicenter Clinical Trial: the WRIST study group. Plast Reconstr Surg, 2010. 126(2): 515-523.
24. Wrist Radius Injury Surgical Trial Study Group Study, G., Reflections One Year into the 22 Center NIH-funded WRIST Study. A Primer on Conducting a Multicenter Clinical Trial. J Hand Surg, 2013. 38(6): 1194-1201.
25. Torgerson, D.J. and B. Sibbald, Understanding controlled trials. What is a patient preference trial? BMJ, 1998. 316(7128): 360.
26. Grant, A.M., et al., Minimal access surgery compared with medical management for chronic gastro-oesophageal reflux disease: UK collaborative randomised trial. BMJ, 2008. 337: a2664.
27. Blazeby, J.M., C.P. Barham, and J.L. Donovan, Commentary: Randomised trials of surgical and non-surgical treatment: a role model for the future. BMJ, 2008. 337: a2747.

28. Mittal R, Harris IA, Adie S for the CROSSBAT Study Group, et al Surgery for Type B Ankle Fracture Treatment: a Combined Randomised and Observational Study (CROSSBAT) BMJ Open 2017;7:e013298. doi: 10.1136/bmjopen-2016-013298
29. Gupta A. The treatment of Colles' fracture. Immobilisation with the wrist dorsiflexed. J Bone Joint Surg Br. 1991 Mar; 73(2): 312-5.
30. Raskin K and Weinstok T. Management of fractures of the distal radius. J Hand Ther 1999; April–June: 93–103.
31. Gillespie, S., Cowell, F., Cheung, G., Brown, D., Can we reduce the incidence of complex regional pain syndrome type I in distal radius fractures? The Liverpool experience. Hand Therapy, Vol 21, Issue 4, 2016
32. Handoll, H.H., R. madhock, and T.E. Howe, Rehabilitation for distal radial fractures in adults. Cochrane Database of Systematic Reviews, 2006. 3.
33. Lozano-Calderón, S.A., et al., Wrist Mobilization Following Volar Plate Fixation of Fractures of the Distal Part of the Radius. J Bone Jt Surge (Am), 2008. 90: 1297-1304.
34. Wakefield, A.E. and M.M. McQueen, The role of physiotherapy and clinical predictors of outcome after fracture of the distal radius. J Bone Joint Surg Br, 2000. 82(7): 972-6.
35. Krischak, G.D., et al., Physiotherapy after volar plating of wrist fractures is effective using a home exercise program. Arch Phys Med Rehabil, 2009. 90(4): 537-44.
36. Watt, C.F., N.F. Taylor, and K. Baskus, Do Colles' fracture patients benefit from routine referral to physiotherapy following cast removal? Arch Orthop Trauma Surg, 2000. 120(7):413-5.
37. MacDermid, J.C., et al., Responsiveness of the short form-36, disability of the arm, shoulder, and hand questionnaire, patient-rated wrist evaluation, and physical impairment measurements in evaluating recovery after a distal radius fracture. J Hand Surg Am, 2000. 25(2): 330-40.
38. MacDermid, J.C., et al., Patient rating of wrist pain and disability: a reliable and valid measurement tool. J Orthop Trauma, 1998. 12(8): 577-86.
39. Hudak, P.L., P.C. Amadio, and C. Bombardier, Development of an upper extremity outcome measure: the DASH (disabilities of the arm, shoulder and hand) [corrected]. The Upper Extremity Collaborative Group (UECG). Am J Ind Med, 1996. 29(6): 602-8.
40. Norman, G.R., J.A. Sloan, and K.W. Wyrwich, Interpretation of changes in health-related quality of life: the remarkable universality of half a standard deviation. Med Care, 2003. 41(5): 582-92.
41. Walenkamp, M.M.J., et al., The Minimum Clinically Important Difference of the Patient-rated Wrist Evaluation Score for Patients With Distal Radius Fractures. Clin Orthop Relat Res (2015) 473:3235–3241.

42. Sorensen, A.A., et al., Minimal clinically important differences of 3 patient-rated outcomes instruments. J Hand Surg Am, 2013. 38(4): 641-9.
43. Schmitt, J.S. and R.P. Di Fabio, Reliable change and minimum important difference (MID) proportions facilitated group responsiveness comparisons using individual threshold criteria. J Clin Epidemiol, 2004. 57(10): 1008-18.
44. Jupiter, J.B., M. Marent-Huber, and L.C.P.S. Group, Operative management of distal radial fractures with 2.4-millimeter locking plates. A multicenter prospective case series. J Bone Joint Surg Am, 2009. 91(1): 55-65.
45. Drobetz, H. and E. Kutscha-Lissberg, Osteosynthesis of distal radial fractures with a volar locking screw plate system. Int Orthop, 2003. 27(1): 1-6.
46. Chan A-W, Tetzlaff JM, Altman DG, Laupacis A, Gøtzsche PC, Krleža-Jerić K, Hróbjartsson A, Mann H, Dickersin K, Berlin J, Doré C, Parulekar W, Summerskill W, Groves T, Schulz K, Sox H, Rockhold FW, Rennie D, Moher D. SPIRIT 2013 Statement: Defining standard protocol items for clinical trials. Ann Intern Med 2013;158:200-207.
47. Chan A-W, Tetzlaff JM, Gøtzsche PC, Altman DG, Mann H, Berlin J, Dickersin K, Hróbjartsson A, Schulz KF, Parulekar WR, Krleža-Jerić K, Laupacis A, Moher D. SPIRIT 2013 Explanation and Elaboration: Guidance for protocols of clinical trials. BMJ 2013;346:e7586.
48. Schulz KF, Altman DG, Moher D, for the CONSORT Group. CONSORT 2010 Statement: updated guidelines for reporting parallel group randomised trials. BMJ 2010;340:c332.
49. Harris, I.A. and J.M. Naylor, Double standards in clinical practice ethics. Med J Aust, 2014. 200(2): 76.
50. Kishen, T.J., I.A. Harris, and A.D. Diwan, Primum non nocere and randomised placebo-controlled surgical trials: a dilemma? ANZ J Surg, 2009. 79(7-8): 508-9.