**ARTICLE DETAILS**

| TITLE (PROVISIONAL) | LIMPER trials: Immediate mobilization versus two-week cast immobilization after distal radius fracture treated with volar locking plate: a study protocol for a prospective, randomized, controlled trial |
|---------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| AUTHORS             | Kärnä, Laura; Launonen, Antti; Karjalainen, Teemu; Luokkala, Toni; Ponkilainen, Ville; Halonen, Lauri; Helminen, Mika; Mattila, Ville; Reito, Aleksi |

**VERSION 1 – REVIEW**

| REVIEWER          | Belloti, João  
|-------------------| Federal University of São Paulo (UNIFESP/EPM), Orthopedics and Traumatology - Division of Hand Surgery and Upper Limb |
| REVIEW RETURNED   | 13-Jun-2022 |

**GENERAL COMMENTS**

The study aims at early functional assessment comparing patients with distal radius fractures who had immediate mobilization compared to those who used a splint for two weeks. The study has a good methodological design but there are some points that were not clear.  
1. What is the clinical relevance of the functional result at 2 months PO, in the treatment of fractures of the distal radius with volar plate?  
2. The exclusion criteria for patients with "Fracture will need prolonged casting (more than 2 weeks) after operation", is unclear and should be better explained  
3. The study protocol does not describe whether there will be use of drugs for pain, which criteria for prescribing and whether the use of these drugs will be computed to analyze the results, which will certainly influence the primary and secondary outcomes of the study

| REVIEWER          | Reijman, M  
|-------------------| Erasmus Medical Center |
| REVIEW RETURNED   | 29-Jun-2022 |

**GENERAL COMMENTS**

This is a interesting study protocol with clinical relevance. I have the following comments / remarks:  
- the study design is not clear: is it a non-inferiority or equivalence design? This should be added to the manuscript  
- working-aged patients will be eligible to participate. Why not include working patients?  
- date of birth will be collected at baseline. Is this allowed in Finland, with regard to the privacy regulations?  
- return to work will be measured with a yes/no question. Doe this also cover if a patient starts working part time, instead of fulltime?
- Pain will be evaluated with the VAS. Which question will be used: pain during rest / during activity / during night / mean pain during the last week / maximal pain?
- How will the activity level measured during the first two weeks be evaluated / compared between both groups?
- The primary outcome is the PRWE score at 2 months time point. Why do the authors use repeated measures to answer the primary research question?
- How many centers will participate in the study?

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**REVIEWER**
Hilden, Jørgen
University of Copenhagen, Biostatistics

**REVIEW RETURNED**
07-Aug-2022

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**GENERAL COMMENTS**
Review Aug 2022 of BMJ Open ms. 2022-064440, “LIMPER trials: Immediate mobilization versus two-week cast immobilization after distal radius fracture treated with volar locking plate: a study protocol for a prospective, randomized, controlled trial” by L. Kärnä & al.

This is a protocol paper describing a well-thought-out surgical multi-centre trial. I have no serious criticism, but several points for the authors to think about.

To introduce myself: After a career in biostatistics, it is now 57 years since I stood in an emergency department and delt with wrist injuries. And I am also totally ignorant of the social services in Finland.

References px/y = pdf page x, pdf line y.

Minor points
A1) ‘LIMPER’ in the title is never explained. A single sentence is needed, e.g. at p5/11, and probably in the Abstract as well.

A2) The editors want it to be made explicit when inclusion began, and I would then find it natural to have a brief remark concerning the rate of accrual, seen vs. expected. The participating centres may also have to be listed. (Cf. E1 below.)

A3) The Abstract refers to the SPIRIT guideline. The corresponding reference in the main text I could not find.

A4) Everybody appears to be granted sick leave in Finland, enabling the present researchers to record time off work. There must be exceptions, or how?

Completeness and clarification
B1) In the Abstract a primary and a ‘co-primary’ outcome are presented on p2/55; similarly on p8/15 and 14/13. At p5/20 their ranking disappears, and they seem to be on the same footing. Actually, later sections suggest that the PRWE is the targeted outcome, to govern the final conclusion UNLESS the sick leave data come out definitely contrary to expectations. This should be made clearer. A formal alpha-adjustment, however, is not required in my opinion.

B2) P5/56: 18-65 years, i.e., < 66th birthday. Here I want formal precision, sorry.
B3) P6, 6th exclusion bullet: please correct (fractures are operated on) and clarify, e.g. by writing “Fractures that are operated on 3 weeks or more after the injury.”

B4) P6 presents 4 elements that have a special temporal interdependence: P6/51 describes the very first steps in the process. Next, ‘(being) pragmatically chosen,’ p6/13, occurs before inclusion-exclusion becomes an agenda (a reflection of pragmatic surgical methodology). However, a tentative inclusion in this phase, with consent and assignment of a TIN (described on p13/19), may be overruled ‘by the operating surgeon’ (p6, 7th bullet) if the derangement is found – with the patient asleep! – to be more complicated than anticipated. If not, and only then, is randomization permissible (P6/56), because earlier randomization might influence the surgeon's judgment, leading to secretly unbalanced comparisons. – These interdependences are correctly handled in the text, but for the benefit of learners I would like to see the reasons explained why a simpler setup would lead to bias or to practical difficulties. In a new comment paragraph, possibly next to the presentation of Table 2, the 4 steps then have to be mentioned in temporal order.

B5) Once this is done, it is natural to modify the Allocation/Operation/X(for Randomization) column in Table 2 by shifting the word ‘Operation’ to the left in its field, and the ‘X’ to the right; it may be replaced with the words ‘decided at end of op.’

B6) Please here or on P13 make explicit when the patient receives his TIN, and stress that/whether TINs are consecutive and never reused.

B7) P6, penultimate bullet: I think ‘contralateral,’ not ‘ipsilateral,’ is meant.

B8) The time from injury to operation (which is probably mostly a few hours but may up to 3 weeks by P6, Bullet 6) might be a strong outcome predictor, partly because of purely statistical associations between healing ability and those features that lead to a delayed decision to operate, partly as a physical result of the healing attempts the wrist structures have undergone during the delay. – Note also that whether or not statistical adjustments are undertaken in this regard, the practical and economic consequences for the patient may involve up to three off-work weeks more than the planned statistics will show (because their Time Zero is the operation and not the injury).

Speculative points
C1) P10, heading Pain: the protocol shares a very frequent trouble issue with many physiurgical, surgical, or oncologic studies: what will count as ‘pain’? In particular, can one really conduct a semi-quantitative interview about ‘pain’ without making a distinction between spontaneous pains (resting pain, pain without recognizable triggers, …) and tenderness (pain provoked by a recognizable stimulus). To the extent that a patient’s ‘pain’ is tenderness, it becomes less relevant to measure its strength and more relevant to probe into avoidable and unavoidable triggers.

C2) Returning to the patients whose provisional inclusion is overruled during the operation, readers may be curious how often that turns out to happen. – Anyhow, we here have a class of
patients who have invested some effort to understand the situation and sign the consent form, etc. Now they probably feel disappointed or snubbed. Why not include them as a third arm that follows the usual procedure with necessary, probably minor, modifications? Perhaps some non-controlled but illustrative auxiliary insight can be gained from their follow-up data. Clearly, much here depends on how many they are.

C3) As regards immobilization time in the two arms, zero is chosen for the first arm because we are curious how absence of immobilization will work. I am less sure how 2 weeks was chosen for the other arm. If, unknown to surgeons, 3.5 weeks is the optimum, then the value of the study, whatever its conclusion, is dubious; or at least one could have had more value for one's efforts with a three-armed study, 0-2-4 weeks, for instance, or 0-1-2-4-8 weeks, perhaps. A point here is that the performance curve may be descending or inverted U-shaped, etc., and conventional wisdom is not a rock-solid as thought.

Language
D1) P4/18, 'eligible evidence': I would write 'evidence from controlled datasets.' In fact, here begins a passage with some language problems. For what they are worth, please study these suggestions: "The literature does not provide controlled clinical evidence as to how the 3-months functional outcome after volar locking depends on the length [and type??] of immobilization (refs.) … sufficiently evidence-based … function, rehabilitation efforts ['effort' added!] can … role in reducing deterioration and quickening recovery, as well as alleviating/dampening socio-economic costs, including an income drop during time off work.(ref.)" – My point is that rehabilitation is a goal; here we talk about rehabilitation efforts.

D2) P5/18, PRWE: the E is missing.
D3) P7/13: a technique is not performed; it is used//applied.

D4) P9/30, 'valid': this is an impossibly strong claim. You mean that the ‘instrument’ has been subjected to several validatory tests and has passed ('has been subjected to validation' as the psychologists say).

D5) Passim: Write ‘working-age patient,’ as on p14/17, not ‘...-aged patent.’

D6) P7/46, ‘similar in both groups’: one must write ‘the same in the two groups’ or ‘identical in the two groups’ or ‘the/one protocol was used in both groups.’ One writes ‘both’ when the alternative is ‘only one.’ And concepts like similarity, identity, or alternation make no sense with only one object. Here, English ‘both’ (like Danish ‘begge’) is different from German ‘beide’ – and in Finnish…?

Statistical matters
E1) The study size (2 times 120 patients) is said to have been ‘justified from different angles’ (p14/15), but only the test power angle is reported in detail. The selection of sample size is always a compromise between capacity (money, manpower, case flow, duration constraints) and desired statistical precision, and the arguments behind the compromise are the interesting part of the business. Here, capacity arguments, including the various surgical
centres’ willingness to participate, appear to underlie the 2X120 proposal, the power analysis being added as a safeguard against undersize. (Cf. A2 above.)

E2) The power analysis is o.k. – but is ‘equivalence margin’ (p14/28) a standard term? Anyhow, it is the smallest departure from the null hypothesis that is detectable with 90% probability or the largest departure that with probability at least 10% leads to an equivalence verdict (when the two-sided alpha is 0.05).

E3) The statistical analysis section (p14/37-) is succinct, so, naturally, many additional choices will have to be made during the analysis. The wording at p14/48 is confusing (it suggests that Time of assessment is a variable, and/or that the interaction is a group difference in a rate of change). So, I propose two small changes in the text: p14/44, ‘Time of assessment’ becomes ‘Level/Score at time of assessment,’ and p14/48, ‘interaction between group allocation/membership and level/score at time of assessment.’ This will do the job, at least for PSWE.

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VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Dr. João Belloti, Federal University of São Paulo (UNIFESP/EPM), Universidade Federal de Sao Paulo Escola Paulista de Medicina Comments to the Author:
The study aims at early functional assessment comparing patients with distal radius fractures who had immediate mobilization compared to those who used a splint for two weeks. The study has a good methodological design but there are some points that were not clear.

AR: We thank you for the positive comments and hope that the manuscript has improved.

1- What is the clinical relevance of the functional result at 2 months PO, in the treatment of fractures of the distal radius with volar plate?
AR: It is unlikely, that there will be difference between groups in working-aged patients. So the clinical relevance is to provide information that without casting the functional outcomes will be the same in both groups.

2- The exclusion criteria for patients with Fracture will need prolonged casting (more than 2 weeks) after operation, is unclear and should be better explained
AR: This is updated in the inclusion criteria section page 5: Fracture assessed to need casting after operation: for example, severely comminuted fracture where the fracture morphology is assessed to need both the volar locking plate and postoperative casting.

3- The study protocol does not describe whether there will be use of drugs for pain, which criteria for prescribing and whether the use of these drugs will be computed to analyze the results, which will certainly influence the primary and secondary outcomes of the study
AR: We will not monitor the use of medication as this is usually very hard to document and ambiguous for exact analysis. It is evident that use of medication has prognostic value for our co-primary outcomes. We assume that medication is used as needed and of course randomization will make sure that effect of medication used is random.

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Reviewer: 2
Dr. M Reijman, Erasmus Medical Center
Comments to the Author:
This is a interesting study protocol with clinical relevance.

AR: We thank you for the positive comment and hope that the manuscript has improved.

I have the following comments / remarks;
- the study design is not clear: is it a non-inferiority or equivalence design? This should be added to the manuscript
AR: This study is a equivalence study and it is updated in the manuscript in the trial design as well.

- working-aged patients will be eligible to participate. Why not include working patients?
AR: We decided to include patients under 65 year old, since most of the patients who work over 65 year old are retirement. Those who still work, are also getting their pension, so as our co primary outcome is the total length of the sick leave- it was clearer to rule patients over 65 out.

- date of birth will be collected at baseline. Is this allowed in Finland, with regard to the privacy regulations?
AR: It is allowed to collect date of birth in Finland.

- return to work will be measured with a yes/no question. Doe this also cover if a patient starts working part time, instead of fulltime?
AR: In our questionnaires, we ask by yes/no questions if the participant has returned to work. In the same questionnaire we also ask if participant has been returned to work as a part time job, or with modified work load. This is now updated in the outcome section, and the total length of sick leave is our primary outcome.

- Pain will be evaluated with the VAS. Which question will be used: pain during rest / during activity / during night / mean pain during the last week / maximal pain?
AR: We use VAS measurement and ask overall mean pain during last 7 days.

- how will the activity level measured during the first two weeks be evaluated / compared between both groups?
AR: We collect activity levels with axivity wrist bands. Both groups will keep these bands on from 2 to 4 weeks in both hands. This timeline will be our comparison time. We only measure activity level during the first two weeks with immediate mobilization group since with the cast on it is impossible to wear the wrist band in immobilization group. This analysis will be secondary data.

- the primary outcome is the PRWE score at 2 months time point. Why do the authors use repeated measures to answer the primary research question?
AR: We are also interested in the timepoints at 6 months and 12 months, assuming that there will be no difference.

- how many centers will participate in the study?
AR: There are 3 centers now in this study, these centers have been updated in the protocol. We also aim to have more centers participating in this study.

Reviewer: 3
Dr. Jørgen Hilden, University of Copenhagen Comments to the Author:
Review Aug 2022 of BMJ Open ms. 2022-064440, “LIMPER trials: Immediate mobilization versus two-week cast immobilization after distal radius fracture treated with volar locking plate: a study protocol for a prospective, randomized, controlled trial” by L. Kärnä & al.

This is a protocol paper describing a well-thought-out surgical multi-centre trial. I have no serious criticism, but several points for the authors to think about.

To introduce myself: After a career in biostatistics, it is now 57 years since I stood in an emergency department and delt with wrist injuries. And I am also totally ignorant of the social services in Finland.

AR: we thank you for the positive comments and hope that the manuscript has improved during this revision.

References px/y = pdf page x, pdf line y.

Minor points
A1) ‘LIMPER’ in the title is never explained. A single sentence is needed, e.g. at p5/11, and probably in the Abstract as well.
AR: LIMPER means: Lower and upper limb injuries, diseases and post-injury rehabilitation and treatment. This is updated in the manuscript.

A2) The editors want it to be made explicit when inclusion began, and I would then find it natural to have a brief remark concerning the rate of accrual, seen vs. expected. The participating centres may also have to be listed. (Cf. E1 below.)
AR: The participating study centers are Tampere University Hospital, Finland; Central Finland Central Hospital, Finland and South Carelia Central Hospital, Finland. We aim to have more centers participating this study. This is updated to manuscript.

A3) The Abstract refers to the SPIRIT guideline. The corresponding reference in the main text I could not find.
AR: The Spirit guideline is now filled and available in additional material.

A4) Everybody appears to be granted sick leave in Finland, enabling the present researchers to record time off work. There must be exceptions, or how?
AR: We also ask in our questionnaires to the patients in different time points weather they have returned as a part-time job- or if they haven’t used the sick leave at all. It is also possible to return to work with a modified work load- so this is also asked in the questionnaires.

Completeness and clarification
B1) In the Abstract a primary and a ‘co-primary’ outcome are presented on p2/55; similarly on p8/15 and 14/13. At p5/20 their ranking disappears, and they seem to be on the same footing. Actually, later sections suggest that the PRWE is the targeted outcome, to govern the final conclusion UNLESS the sick leave data come out definitely contrary to expectations. This should be made clearer. A formal alpha-adjustment, however, is not required in my opinion.
AR: PRWE and the total length of sick leave are both our co-primary outcomes. No alpha-adjustment is done. These are clarified in text as suggested.

B2) P5/56: 18-65 years, i.e., < 66th birthday. Here I want formal precision, sorry.
AR: This is updated in study setting pg 4, in the form of patients aged 18-65 (<65th birthday).

B3) P6, 6th exclusion bullet: please correct (fractures are operated on) and clarify, e.g. by writing “Fractures that are operated on 3 weeks or more after the injury.”
AR: This is updated in the inclusion criteria pg 5: Fractures that are operated on 3 weeks or more after the injury

B4) P6 presents 4 elements that have a special temporal interdependence: P6/51 describes the very first steps in the process. Next, ‘(being) pragmatically chosen,’ p6/13, occurs before inclusion-exclusion becomes an agenda (a reflection of pragmatic surgical methodology). However, a tentative inclusion in this phase, with consent and assignment of a TIN (described on p13/19), may be overruled ‘by the operating surgeon’ (p6, 7th bullet) if the derangement is found – with the patient asleep! – to be more complicated than anticipated. If not, and only then, is randomization permissible (P6/56), because earlier randomization might influence the surgeon’s judgment, leading to secretly unbalanced comparisons. – These interdependences are correctly handled in the text, but for the benefit of learners I would like to see the reasons explained why a simpler setup would lead to bias or to practical difficulties. In a new comment paragraph, possibly next to the presentation of Table 2, the 4 steps then have to be mentioned in temporal order.

AR: We modified the randomization chapter as follows: The randomization procedure will be set up in the research electronic data capture (REDCap) randomization tool. After recruitment and baseline measurements, a site principal investigator (PI) from each hospital will administer the online allocation procedure by entering patient data into the REDCap system, which will enable the randomization tool. Allocation concealment will be ensured, as randomization will not be performed and revealed before the patient has been included in the trial. Randomization will be performed by the researchers. Randomization will be performed after the wound has been sutured, because earlier randomization might influence the surgeon’s judgment, for example in longer operating time. Thereafter, the allocation group will be revealed to the patient and the operating surgeon. Participants will be included in the immediate mobilization group or the two-week cast group in a 1:1 allocation as per computer-generated randomization matrix with randomized block size and stratified by work physical exertion level (sedentary/light vs. medium/heavy/very heavy), fracture articulateness (intra- or extra-articular), and age (older or younger than 55 years).

B5) Once this is done, it is natural to modify the Allocation/Operation/X[for Randomization] column in Table 2 by shifting the word ‘Operation’ to the left in its field, and the ‘X’ to the right; it may be replaced with the words ‘decided at end of op.’

AR: This table is modified to the manuscript.

B6) Please here or on P13 make explicit when the patient receives his TIN, and stress that/whether TINs are consecutive and never reused.

AR: This is now updated in the data management section. Each patient will be assigned a unique trial identification number (TIN) matched with the patient’s personal identification number (ID). This is assigned when patient has signed informed consent, and TINs are consecutive and never reused. The research data will only be handled with a TIN throughout the trial.

B7) P6, penultimate bullet: I think ‘contralateral,’ not ‘ipsilateral,’ is meant.

AR: We wanted to exclude patients that may have another fracture in the same upper extremity. Next bullet polytrauma usually excludes these contralateral patients.

B8) The time from injury to operation (which is probably mostly a few hours but may up to 3 weeks by P6, Bullet 6) might be a strong outcome predictor, partly because of purely statistical associations between healing ability and those features that lead to a delayed decision to operate, partly as a physical result of the healing attempts the wrist structures have undergone during the delay. – Note also that whether or not statistical adjustments are undertaken in this regard, the practical and economic consequences for the patient may involve up to three off-work weeks more than the planned statistics will show (because their Time Zero is the operation and not the injury).
AR: We will have an exploratory analysis, where the result is adjusted with the delay from time from of the injury to the time to the operation. This is updated in the statistical analysis section.

Speculative points
C1) P10, heading Pain: the protocol shares a very frequent trouble issue with many physiurgical, surgical, or oncologic studies: what will count as ‘pain’? In particular, can one really conduct a semi-quantitative interview about ‘pain’ without making a distinction between spontaneous pains (resting pain, pain without recognizable triggers, …) and tenderness (pain provoked by a recognizable stimulus). To the extent that a patient’s ‘pain’ is tenderness, it becomes less relevant to measure its strength and more relevant to probe into avoidable and unavoidable triggers.
AR: We use VAS measurement and ask overall mean pain during last 7 days.

C2) Returning to the patients whose provisional inclusion is overruled during the operation, readers may be curious how often that turns out to happen. – Anyhow, we here have a class of patients who have invested some effort to understand the situation and sign the consent form, etc. Now they probably feel disappointed or snubbed. Why not include them as a third arm that follows the usual procedure with necessary, probably minor, modifications? Perhaps some non-controlled but illustrative auxiliary insight can be gained from their follow-up data. Clearly, much here depends on how many they are.
AR: This is an ongoing trial, and there are only few patients that have denied to take part. We have had only 2 patients that we have collected the baseline data, and they are having their own TIN- but then something happened in the surgery and the operating surgeon wants to put a cast on post-operatively. These patients will have questionnaires, and are analyzed as “third arm”. The patients that have denied to take part of this study will be marked to screening log. This is updated in the Recruitment section.

C3) As regards immobilization time in the two arms, zero is chosen for the first arm because we are curious how absence of immobilization will work. I am less sure how 2 weeks was chosen for the other arm. If, unknown to surgeons, 3.5 weeks is the optimum, then the value of the study, whatever its conclusion, is dubious; or at least one could have had more value for one’s efforts with a three-armed study, 0-2-4 weeks, for instance, or 0-1-2-4-8 weeks, perhaps. A point here is that the performance curve may be descending or inverted U-shaped, etc., and conventional wisdom is not a rock-solid as thought.
AR: Two week casting is the golden standard in Finland and nearly all patients who undergo volar plating of distal radius fractures get a 2 week cast after operation. We don’t use longer casting at all.

Language
D1) P4/18, ‘eligible evidence’: I would write ‘evidence from controlled datasets.’ In fact, here begins a passage with some language problems. For what they are worth, please study these suggestions: “The literature does not provide controlled clinical evidence as to how the 3-months functional outcome after volar locking depends on the length [and type??] of immobilization (refs.), … sufficiently evidence-based … … function, rehabilitation efforts ['effort' added!] can … role in reducing deterioration and quickening recovery, as well as alleviating/dampening socio-economical costs, including an income drop during time off work.(ref.)” – My point is that rehabilitation is a goal; here we talk about rehabilitation efforts.
AR: Thank you for your comment, this sentence is modified in page 3.

D2) P5/18, PRWE: the E is missing.
AR: This is updated.

D3) P7/13: a technique is not performed; it is used//applied.
AR: This is modified.
D4) P9/30, ‘valid’: this is an impossibly strong claim. You mean that the ‘instrument’ has been subjected to several validatory tests and has passed (‘has been subjected to validation’ as the psychologists say).
AR: PRWE is a 15-item questionnaire designed to measure wrist pain and disability in activities of daily living. It is a reliable upper extremity outcome instrument, and has passed to several validation tests. The questionnaire consists of two subscales (pain and function) and the score ranges from 0 (no disability) to 100 (severe disability).

D5) Passim: Write ‘working-age patient,’ as on p14/17, not ‘….aged patent.’
AR: This is updated.

D6) P7/46, ‘similar in both groups’: one must write ‘the same in the two groups’ or ‘identical in the two groups’ or ‘the/one protocol was used in both groups.’ One writes ‘both’ when the alternative is ‘only one.’ And concepts like similarity, identity, or alternation make no sense with only one object. Here, English ‘both’ (like Danish ‘begge’) is different from German ‘beide’ – and in Finnish…?
AR: This is updated.

Statistical matters
E1) The study size (2 times 120 patients) is said to have been ‘justified from different angles’ (p14/15), but only the test power angle is reported in detail. The selection of sample size is always a compromise between capacity (money, manpower, case flow, duration constraints) and desired statistical precision, and the arguments behind the compromise are the interesting part of the business. Here, capacity arguments, including the various surgical centres’ willingness to participate, appear to underlie the 2X120 proposal, the power analysis being added as a safeguard against undersize. (Cf. A2 above.)
AR: This sentence is removed.

E2) The power analysis is o.k. – but is ‘equivalence margin’ (p14/28) a standard term? Anyhow, it is the smallest departure from the null hypothesis that is detectable with 90% probability or the largest departure that with probability at least 10% leads to an equivalence verdict (when the two-sided alpha is 0.05).
AR: Equivalence margin as a term is based on previous literature.

E3) The statistical analysis section (p14/37-) is succinct, so, naturally, many additional choices will have to be made during the analysis. The wording at p14/48 is confusing (it suggests that Time of assessment is a variable, and/or that the interaction is a group difference in a rate of change). So, I propose two small changes in the text: p14/44, ‘Time of assessment’ becomes ‘Level//Score at time of assessment,’ and p14/48, ‘interaction between group allocation//membership and level//score at time of assessment.’ This will do the job, at least for PSWE.
AR: These are updated to manuscript as suggested.

VERSION 2 – REVIEW

| REVIEWER | Belloti, João  
| Federal University of São Paulo (UNIFESP/EPM), Orthopedics and Traumatology - Division of Hand Surgery and Upper Limb |
| REVIEW RETURNED | 26-Sep-2022 |
| GENERAL COMMENTS | I consider that the observations and questions were answered and corrected adequately |
Introduction

Distal radius fractures (DRFs) are one of the most common fractures in adults. The incidence of DRFs is increasing in the older population, but also among individuals of a working age (18-65 years).\(^1\)\(^-\)\(^3\) In young adults with good bone quality, these injuries typically occur/arise from high-energy trauma, whereas older patients have/have low-energy accidents, such as falls from standing height. //As Displaced DRFs have been considered fractures with a dorsal tilt of more than 15 degrees, radial shortening, or an intra-articular step of more than 2 mm after closed reduction. (4–7) If any of the above criteria are met after closed reduction and casting, primary open reduction internal fixation with volar locking plate is usually performed in working/age patients with the aim of avoiding malunion and thereby(ADDING THIS WORD REMOVES AN AMBIGUITY) decreasing disability. A volar locking plate provides enough stability to allow early mobilization, thereby omitting/avoiding the need for prolonged cast immobilization. While postoperative immobilization is standard practice, there is no consensus on whether or for how long //[(LOGICALLY UNNECESSARY: , if at all,)]\) a wrist should be immobilized after operatively treated DRF//the operation. \(^8,9\) Previous studies have reported that post-operative immobilization varies widely from 0 to 6 weeks after the volar plating of DRF. \(^8,10–13\) However, relatively few studies specifically evaluate the impact of postoperative...
splinting/casting versus immediate mobilization. The main problem with previous studies has been the relatively small sample sizes, which makes the comparison of these studies difficult. (10,11,14). Moreover, the literature does not provide evidence from controlled datasets of the differences in functional outcomes after three months from DRF operation with volar locking plate between the varying postoperative immobilization periods. (12,13) Moreover, Systematic reviews on rehabilitation efforts after DRF in adults have confirmed//shown that the effectiveness in various rehabilitation protocols is not sufficiently evidence-based. (15,16) Since DRF can potentially lead to impaired physical function, rehabilitation can play a vital role in reducing deterioration and recovery time as well as socio-economical costs, such as (limiting the) time off work. (17) Any permanent loss of function can even lead to the inability to work/affecting personal coping. After primary intervention, DRFs (are associated with) involve the use of multiple resources, including operative interventions, outpatient visits, and rehabilitation. Post-operative casting (also uses expensive resources) (is similarly resource demanding,) (such as) (by virtue of) time spent in the OR and visits to outpatient clinics for cast fixing or removal. (18) Moreover, the restoration of wrist function and the reduction of impairment is important because (considering that) more than 50% of DRF patients are still of working age. A mean sick leave duration of 4-12 weeks has been reported, which means sick leave after DRF has an important socioeconomical role. (19–22) Further, a recent study has suggested that self-reported disability, pain, and Disabilities of the Arm, Shoulder, and Hand (DASH) outcome measure as early as 1-week post-fracture are the strongest predictors of length of sick leave, regardless of whether the treatment is operative or non-operative. (21)

To our knowledge, only a few studies exist that have compared standard post-operative casting to/immediate mobilization. (8, 10-12) The aim of this trial is to compare outcomes between working-age patients allocated to either immediate post-operative mobilization or two-week post-operative cast immobilization after volar locking plate fixation of DRF. We expect patients in the immediate mobilization group will have at least as rapid a return to work and function as those patients in the post-operative immobilization group, meaning that there will be no need for post-operative casting. Immediate mobilization will then allow for the effective use of scarce resources without compromising the results of volar plating in DRF (with no differences in as assessed by) the numbers of complications 1 year after surgery. ---18SEP2022---
Reviewer: 2
Dr. M Reijman, Erasmus Medical Center
Comments to the Author:
In my opinion is the design of the study to answer the primary research question a non-inferiority design.

AR: We thank you for the comment. We discussed of the design with our research team and concluded to be equivalence desing.

Reviewer: 3
Dr. Jørgen Hilden, University of Copenhagen
Comments to the Author:
BETTER TYPOGRAPHY IN THE ATTACHED VERSION OF THIS TEXT
===================================================================
The authors have been added the various items that were (felt to be) missing. I shall not argue for further revision – with one exception: to me the Introduction is linguistically still a bit bumpy. Below I suggest a number of (what I believe are) improvements; clearly, a native English-speaker might do a still better job.

AR: We thank you for the comments. Introduction has now been updated with some modifications. Native English-speaker proofread the protocol and protocol is modified according to those comments.

Reviewer: 1
Dr. João Belloti, Federal University of São Paulo (UNIFESP/EPM), Universidade Federal de São Paulo Escola Paulista de Medicina
Comments to the Author:
I consider that the observations and questions were answered and corrected adequately

AR: We thank you for your positive comments.