

## PEER REVIEW HISTORY

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### ARTICLE DETAILS

<b>TITLE (PROVISIONAL)</b>	Patient Specific Instrumentation (PSI) Referencing High Tibial Osteotomy Technological Transfer and Education: Protocol for a Double-blind, Randomized Controlled Trial (PROTECTED HTO Trial)
<b>AUTHORS</b>	Lau, Lawrence Chun Man; Chui, Elvis; Fan, Jason Chi Ho; Man, Gene Chi Wai; Hung, Yuk Wah; Ho, Kevin; Chung, Kwong Yin; Wan, Samuel; Chau, Jack; Yung, Patrick; Bhandari, Mohit

### VERSION 1 – REVIEW

<b>REVIEWER</b>	Nick Clement Royal Infirmary of Edinburgh Little France Edinburgh UK
<b>REVIEW RETURNED</b>	23-Jul-2020

<b>GENERAL COMMENTS</b>	<p>The authors set out a protocol to assess PSI with manual technique for the accuracy of HTO. It is a good study, but I am not sure of the clinical impact here. So, the authors show it is more accurate (likely outcome) what is the clinical impact on the patient? Is the increased cost of PSI worth it? How do the patient benefit? I do not feel this protocol has a clinical impact on practice. I realise this is a secondary outcome aspect of the study but the numbers are so small I suspect they will be under powered to show a deference.</p> <p>The authors need to be totally clear on their primary outcome which is in cm's in the power calculation but then they state Fujisawa point in the primary assessment section which is stated as a %.</p> <p>They should also clarify who will be performing the surgery - how many manual HTO have they performed previously?</p>
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<b>REVIEWER</b>	shu takagawa yokohama medical center, japan
<b>REVIEW RETURNED</b>	15-Aug-2020

<b>GENERAL COMMENTS</b>	significantly important study
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<b>REVIEWER</b>	Fabio A. Casari, M.D. Balgrist University Hospital, Zurich, Switzerland
<b>REVIEW RETURNED</b>	30-Aug-2020

<b>GENERAL COMMENTS</b>	The here presented article is a protocol of a RCT to evaluate surgical accuracy and clinical outcome in patients suffering from
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	<p>symptomatic osteoarthritis of the medial knee compartment, treated with PSI navigated and conventional HTO. 36 patients are included to undergo PSI navigated procedure or the institutional conventional method (not further described). Plan to outcome accuracy is measured on radiologic imaging and compared between the two groups.</p> <p>Patients are followed up for 24 months with documentation of the clinical outcome based on the Knee Society Scores (Knee Scores and Functional Scores), Oxford Knee Scores and Pain Visual Analog Scale (VAS) score.</p> <p>The group conducts the first RCT to compare conventional to PSI guided medial opening wedge HTO to the conventionally performed procedure.</p> <p>The research question is clear. The group wants to assess plan to outcome accuracy of conventional and PSI navigated HTOs and report the clinical outcome followed up for 24 months.</p> <p>The manuscript does not report any results.</p> <p>Comments:</p> <p>Minor:</p> <ol style="list-style-type: none"> <li>1. P6 Line 7-12 is misleading as the WHO states osteoarthritis in general as a leading cause of disability, not OA of the knee.</li> <li>2. P6 Line 45 MEDIAL knee compartment.</li> <li>3. P6 Line 48 - 56 Please rephrase this section the message is not clear.</li> <li>4. P11 Line 31-35 An image or a reference of the design would help understanding.</li> <li>5. P16 Line 16-18 The use of PSI in orthopedic is relatively established, especially in the area of corrective osteotomies. Literature is available.</li> </ol> <p>Major:</p> <ol style="list-style-type: none"> <li>1. P7 Line 10 the 3D models for planning are not based on a 3D-scan, but segmented tomographic imaging to further generate a 3 model.</li> <li>2. P7 Line 33-37 the development of OA is accelerated by activity. The study would benefit to include a method to scale patients activity level. (Lysholm, Tegner score) Lane NE. Physical activity at leisure and risk of osteoarthritis. Ann Rheum Dis. 1996;55(9):682-684. doi:10.1136/ard.55.9.682</li> <li>3. P10 Line 8-12 Is this the error of the planned entry point of the saw blade or the error of opening the fragments? A recent article evaluated accuracy of PSI navigated HTO. Fucentese, S.F., Meier, P., Jud, L. et al. Accuracy of 3D-planned patient specific instrumentation in high tibial open wedge valgisation osteotomy. J EXP ORTOP 7, 7 (2020). <a href="https://doi.org/10.1186/s40634-020-00224-y">https://doi.org/10.1186/s40634-020-00224-y</a></li> <li>4. P11 Line 10 The used instruments might influence executional accuracy. Please include K-wire and sawblade thickness.</li> <li>5. P11 Line 12-14 Please describe the navigation used. Is it simply using a radiopaque line to connect hip joint to upper ankle joint center or an advanced computer-based navigation method?</li> <li>6. P11 Line 34 Please describe the image data processing and planning procedure. The PSI design with an accurate undersurface of the guide to fit the bone surface will highly influence accuracy of</li> </ol>
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	<p>the procedure. The quality of planning is dependent on good CT data therefore several protocols with slice thickness are used. Which manufacturer produced the PSI? Frnstahl et al. Computational Radiology for Orthopaedic Interventions. Cham: Springer International Publishing; 2016. p. 123-49.</p> <p>7. P11 Line 37 See comment 4</p> <p>8. P12 Line 8 This section is missing on how accuracy is measured and defined. Is it simply the blade entrance site, deviation of the osteotomy plane in angulation or translation? Is it a 2D angle in x ray or CT or is it a 3D angle or a 2D angle measured in a 3D coordinate system?</p> <p>9. P22 Line 24-25 Why is the CT recorded on the day of discharge? Would a CT scan at the 3 months visit when bone consolidation should be apparent make more sense as the surgical plan is aimed as definite anatomy?</p> <p>The protocol included collection of the relevant data that would allow revising the manuscript according to the here proposed comments. Activity levels would need retrospective assessment.</p>
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### VERSION 1 – AUTHOR RESPONSE

Comments from Reviewer #1	Responses
<p>1. The authors set out a protocol to assess PSI with manual technique for the accuracy of HTO. It is a good study, but I am not sure of the clinical impact here. So, the authors show it is more accurate (likely outcome) what is the clinical impact on the patient? Is the increased cost of PSI worth it? How does the patient benefit? I do not feel this protocol has a clinical impact on practice. I realise this is a secondary outcome aspect of the study but the numbers are so small I suspect they will be under powered to show a deference.</p>	<p>Thank you for the comments.</p> <p>The question is best answered by the article cited by another reviewer (Fucentese, S.F.et al. J EXP ORTOP, 2020). In that article which also evaluate the use of PSI in HTO, it mentioned that “One of the leading principles in HTO is to perform axis correction as precisely as possible because under- or overcorrection is known to be the main reason for clinical failure.”</p> <p>Herein, the rationale of using PSI is to allow us to perform HTO as precise as possible. In this regard, it is similar to the use of robotic in unicompartmental knee arthroplasty (UKA). In a randomised control trial of manual UKA versus robotic UKA, it found that the early clinical score are similar in both groups despite more accurate implant position/alignment. And we know the difference in accuracy may implies future risks of revision in the long run. (S.W. Bell et al. J Bone Joint Surg Am, 98 (2016), pp. 627-635) &amp; (Alisdair Gilmour et al. The Journal of Arthroplasty Vol 33, Issue 7, July 2018, Pages S109-S115.)</p> <p>In addition, our previous article have shown that inaccurate alignment correction (though performed by experienced surgeons) can obtain initial good clinical response but subsequent fail in ten years’ time (Lau LC et al., J Orthop Translat. 2020). Therefore, we aim to illustrate PSI can help HTO in obtaining more satisfactory alignment, osteotomy bone cut and correction consistently in form of RCT study when compared to manual HTO plus navigation system. The clinical impact of accurate alignment and hence better survival of HTO is enormous as it potentially renders HTO as a definitely surgery for knee OA instead of just a buy-time surgery before TKR.</p>

	<p>Hence, to better illustrate the concept the following statements have been added to the Discussion of this manuscript on page 13 line 25-26 and page 14 line 1-4</p> <p>Patient-specific instrumentation (PSI) is a development in orthopedic field made possible by the advancement in 3D scanning and 3D printing technology, in which an instrument that can couple closely to the targeting bony surface is virtually planned and later produced by 3D printing. The putative benefits of these PSI include increased surgical accuracy, decreased operation time, and elimination of the need for extra devices or reference trackers<sup>19,20</sup>. The application of PSI on HTO as a cutting jig is reported achieving precise osteotomy and accurate realignment of lower limb in case series<sup>19</sup>.</p> <p>Reference:</p>
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	<p>19. Yang JC, Chen CF, Luo CA, et al. Clinical Experience Using a 3D-Printed Patient-Specific Instrument for Medial Opening Wedge High Tibial Osteotomy. <i>Biomed Res Int</i> 2018;2018:9246529. doi: 10.1155/2018/9246529 [published Online First: 2018/06/02]</p> <p>20. Wong KC. 3D-printed patient-specific applications in orthopedics. <i>Orthop Res Rev</i> 2016;8:57-66. doi: 10.2147/ORR.S99614 [published Online First: 2016/10/14]</p>
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<p>2. The authors need to be totally clear on their primary outcome which is in cm's in the power calculation but then they state Fujisawa point in the primary assessment section which is stated as a %.</p>	<p>Thank you for the enquiry.</p> <p>The assessment are performed in several aspect and including: planned versus final position of: the blade entrance point (proximal/distal translation on CT images), osteotomy plane (towards PTFJ) angulation and osteotomy gap opening angle (2D angles in coronal and sagittal plane on CT images). Comparison with navigation on overall alignment correction is also measured on post-op full-length lower-limb radiographs.</p> <p>We assessed not only the overall lower-limb alignment correction, but also the local osteotomy cut in the proximal tibia which is directly related to the performance of PSI jig.</p> <p>Hence, the following statements have been amended “The primary outcome is obtained by post-operative radiological assessment of X-ray and computer tomography (CT) images to compare the accuracy of patient specific instrumentation (PSI) jig with freehand bone cut in achieving pre-operative planned bone cut. The planned bone cut is from 4 cm below the medial joint line towards proximal tibiofibular joint (PTFJ) near the lateral tibial cortex. Accuracy is measured by comparing the planned versus final position of: the blade entrance point (proximal/distal</p>
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	<p>translation on CT images), osteotomy plane (towards PTFJ) angulation and osteotomy gap opening angle (2D angles in coronal and sagittal plane on CT images) It also includes comparison with navigation on overall alignment correction. Anteroposterior fulllength lower-limb radiographs are taken with patients in the standing position to assess postoperative lower-limb alignment correction, which is compared with the preoperative planning, based on Miniaci method calculation to achieve target alignment passing through the Fujisawa point.” to the Primary Outcome in the methodology Section of this manuscript on page 10 line 14-23</p>
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<p>3. They should also clarify who will be performing the surgery - how many manual HTO have they performed previously?</p>	<p>Thank you for your enquiry.</p> <p>A group of experienced surgeons who have participated in our previous article’s HTO surgery (Lau LC et al., J Orthop Translat. 2020) will lead our team of knee surgeons with ≥ 5 year of experience in performing HTO. Our group currently performed the largest volume of HTO in Hong Kong.</p> <p>Hence, the following statements have been amended “Surgeon consent: the PI and co-investigators met with potential surgeons (with ≥ 5 year of experience in performing HTO) individually or as part of faculty meetings to discuss the study and to answer any questions. The surgeons were given a copy of the proposal detailing the assessments to review. Surgeons provided verbal and email consent to the PI to indicate their willingness to participate.” to the Ethics and dissemination Section of this manuscript on page 13 line 2-5</p>
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Comments from Reviewer #2

<p>significantly important study</p>	<p>The authors thanks the reviewer for the insightful comment and positive overall comment.</p>
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Comments from Reviewer #3

<p>Minor:</p> <p>1. P6 Line 7-12 is misleading as the WHO states osteoarthritis in general as a leading cause of disability, not OA of the knee.</p>	<p>Thank you for noting that.</p> <p>Based on the Lancet review, we have revised the wordings to focus on knee OA situation.</p> <p>Hence, the following statements “In recent Lancet review, osteoarthritis is expected to be the fourth leading cause of disability globally by 2020, with knee OA accounts for approximately 85% of the burden of OA worldwide <sup>1</sup>. The medical cost of osteoarthritis has been estimated to be around 1 - 2.5% of the gross domestic product in various high-income countries, with joint replacements representing the major proportion of the cost<sup>1</sup>.” have been amended to the Introduction Section of this manuscript on page 4 line 5-9</p>
<p>2. P6 Line 45 MEDIAL knee compartment.</p>	<p>Thank you for your meticulous review.</p>

	<p>We have made the correction accordingly.</p>
<p>3. P6 Line 48 - 56 Please rephrase this section the message is not clear.</p>	<p>Thank you for your suggestions and we have revised the message accordingly.</p> <p>Hence, the following statements have been amended to “In Asia, HTO is increasingly popular as treatment for knee OA with rising number of HTO performed in conjunction with the fell in number of TKA performed. For example, the annual number of HTO in Korea increased from 2649 cases in 2009 to 8207 cases in 2013, and the annual number of HTO in Japan increased from 261 cases in 2007 to 2152 cases in 2014<sup>5 6</sup>.” in the Introduction Section of this manuscript on page 4 line 24-26 and page 5 line 1</p>
<p>4. P11 Line 31-35 An image or a reference of the design would help understanding.</p>	<p>Thank you for your suggestion.</p> <p>Hence, we have included our PSI jig photo accordingly (Fig.2).</p>

<p>5. P16 Line 16-18 The use of PSI in orthopedic is relatively established, especially in the area of corrective osteotomies. Literature is available.</p>	<p>Thank you for your suggestions and we have added further reference of PSI on orthopedic field.</p> <p>The following reference has been added.</p> <p>Wong KC. 3D-printed patient-specific applications in orthopedics. Orthop Res Rev 2016;8:57-66. doi: 10.2147/ORR.S99614 [published Online First: 2016/10/14]</p>
<p>Major:</p> <p>1. P7 Line 10 the 3D models for planning are not based on a 3D-scan, but segmented tomographic imaging to further generate a 3 model.</p>	<p>Thank you for your meticulous review.</p> <p>We agreed on your point and deeply appreciated that.</p> <p>Hence, the following statements “PSI is a surgical advancement made possible by the advancement in computed tomographic imaging with 3D model reconstruction, virtual planning and 3D printing.” have been amended to the Introduction Section of this manuscript on page 5 line 2-4</p>
<p>2. P7 Line 33-37 the development of OA is accelerated by activity. The</p>	<p>Thank you for your suggestion.</p>

<p>study would benefit to include a method to scale patients activity level. (Lysholm, Tegner score)</p> <p>Lane NE. Physical activity at leisure and risk of osteoarthritis. Ann Rheum Dis. 1996;55(9):682-684. doi:10.1136/ard.55.9.682</p>	<p>We totally agreed on your point and deeply appreciated that.</p> <p>Hence, we have revised the following statement accordingly to “The primary outcomes will be the radiological differences reflecting difference in surgical accuracy with or without PSI jig and the secondary outcomes will be the postoperative change in knee function from baseline using 4 questionnaires: Knee Society Scores (Knee Scores and Functional Scores), Oxford Knee Scores, Lysholm Knee Scoring Scale and Pain Visual Analog Scale (VAS) score7-10.” in the Introduction Section of this manuscript on page 5 line 12-16</p>
<p>3. P10 Line 8-12 Is this the error of the planned entry point of the saw blade or the error of opening the fragments? A recent article evaluated accuracy of PSI navigated HTO.</p> <p>Fucentese, S.F., Meier, P., Jud, L. et al. Accuracy of 3Dplanned patient specific instrumentation in high tibial</p>	<p>Thank you for your suggestion and comment.</p> <p>We assessed not only the overall lower-limb alignment correction, but also the local osteotomy cut accuracy in the proximal tibia which in our opinion is directly related to the performance/accuracy of the PSI jig. And therefore we choose parameters related to osteotomy cut for assessment. And based on our previous cases of high tibial osteotomy, we noted the average osteotomy plane entry point deviation from</p>

<p>open wedge valgisation osteotomy. J EXP ORTOP 7, 7 (2020). <a href="https://doi.org/10.1186/s40634020-00224-y">https://doi.org/10.1186/s40634020-00224-y</a></p>	<p>planning with PSI jig is 0 cm <math>\pm</math> 0.3 cm and without PSI jig is 0.76 cm <math>\pm</math> 1.2 cm.</p>
<p>4. P11 Line 10 The used instruments might influence executorial accuracy. Please include K-wire and sawblade thickness.</p>	<p>Thank you for your suggestion.</p> <p>We have revised the statement accordingly to the Introduction Section of this manuscript on page 9 line 4-6</p> <p>Two to three 2.5mm K-wires are placed 4 cm below the medial joint line toward the proximal tibiofibular joint over lateral tibial cortex under fluoroscopy and osteotomy is done below and parallel to the k-wires using an oscillating saw (blade thickness 0.9mm) leaving the lateral 5 mm intact.</p>
<p>5. P11 Line 12-14 Please describe the navigation used. Is it simply using a radiopaque line to connect hip joint to upper ankle joint center or an advanced computer-based navigation method?</p>	<p>Thank you for the comment.</p> <p>We use the the Orthomap ASM computer navigation supplied by Stryker for computer navigation. In brief, thin osteotomes are used to gradually open the osteotomy and finally the desired correction is achieved with the use of computer navigation (Orthomap ASM, Stryker, Michigan) checking overall lower limb alignment.</p>
<p>6. P11 Line 34 Please describe the image data processing and planning procedure. The PSI design with an accurate undersurface of the guide to fit the bone surface will highly influence accuracy of the procedure. The quality of planning is dependent on good CT data therefore several protocols with slice thickness are used. Which manufacturer produced the PSI? Frnstahl et al. Computational Radiology for Orthopaedic Interventions. Cham: Springer International Publishing; 2016. p. 123-49.</p>	<p>Thank you for the comment.</p> <p>The PSI jigs will be printed using a metal printing machine (LUMEX Avance-25, Matsuura, Japan) from a Hong Kong company that collaborate with our university. As for the detail on the image data processing and planning procedure, the have amended the following statement "3D printed patient specific jigs (PSI jig) are created based on the pre-operative CT image. Before operation, lower limb from hip to ankle center were scanned by CT with slice thickness <math>\leq</math>1 mm covering the proximal tibia and knee joint. CT image data were made available in Digital Imaging and Communications in Medicine (DICOM) format and transferred to a standard desktop computer and loaded to Mimics software (Materialise, Louvain, Belgium) for segmentation. Virtual planning of osteotomy plane and the associated jig was performed on Materialise 3-matic 13.0 (Materialise, Leuven, Belgium) according to TomoFix™ plate (Synthes Medical, Oberdorf, Switzerland) surgical technique manual. PSI jigs were printed in stainless steel by 3D metal printing machine (LUMEX Avance-25, Matsuura, Japan). Standard medial open wedge osteotomy similar as described previously is performed with modification." in the Intervention group section of this manuscript on page 9 line 1220</p>
<p>7. P11 Line 37 See comment 4</p>	<p>Thank you for your comment.</p> <p>The sawblade thickness used will be 0.9mm. This information has been added on page 9 line 25</p>



<p>8. P12 Line 8 This section is missing on how accuracy is measured and defined. Is it simply the blade entrance site, deviation of the osteotomy plane in angulation or translation? Is it a 2D angle in x ray or CT or is it a 3D angle or a 2D angle measured in a 3D coordinate system?</p>	<p>Thank you for pointing this out.</p> <p>In our study, accuracy is measured by comparing the planned versus final position of: the blade entrance point (proximal/distal translation on CT images), osteotomy plane (towards PTFJ) angulation and osteotomy gap opening angle (2D angles in coronal and sagittal plane on CT images).</p> <p>To avoid confusion, we have added the following statement “Accuracy is measured by comparing the planned versus final position of: the blade entrance point (proximal/distal translation on CT images), osteotomy plane (towards PTFJ) angulation and osteotomy gap opening angle (2D angles in coronal and sagittal plane on CT images)” to the Primary Outcome section on page 10 line 17-20.</p>
<p>9. P22 Line 24-25 Why is the CT recorded on the day of discharge? Would a CT scan at the 3 months visit when bone consolidation should be apparent make more sense as the surgical plan is aimed as definite anatomy?</p>	<p>Thank you for your suggestion.</p> <p>The purpose for the CT recorded on the day of discharge is our intention to pick up hinge fracture due to suboptimal osteotomy. However, we agreed with the reviewer’s suggestion that an additional CT scan at 3 months would be more favorable for this protocol.</p> <p>Hence, in addition to the day of discharge, an addition CT scan assessment at the 3 months visit was added to this protocol</p>
<p>The protocol included collection of the relevant data that would allow revising the manuscript according to the here proposed comments. Activity levels would need retrospective assessment.</p>	<p>Thank you for your suggestion.</p> <p>The assessment for activity level in the current protocol will be assessed by self-reported questionnaire on knee function and pain.</p> <p>Overall, we hope the above revision can help optimize the current protocol.</p>

**VERSION 2 – REVIEW**

<b>REVIEWER</b>	Nicholas Clement Royal Infirmary of Edinburgh, Edinburgh, UK
<b>REVIEW RETURNED</b>	13-Nov-2020
<b>GENERAL COMMENTS</b>	The authors have addressed my original comments. Please change X-rays to radiographs throughout the manuscript. P-values for the secondary outcomes should be adjusted for multiple testing.

## VERSION 2 – AUTHOR RESPONSE

Reviewer 1

General Comment:

The authors have addressed my original comments.

Author's Reply:

The authors would like to thank the reviewer for the kind comment.

Reviewer's Comment Author's Reply

1. Please change X-rays to radiographs throughout the manuscript.

Answers:

Thank you for the suggestion.

The word "X-rays" has been changed to "radiographs" throughout the revised manuscript. The changes include Page 10 Line 11 and Page 19 Table 1.

2. P-values for the secondary outcomes should be adjusted for multiple testing.

Thank you for the suggestion.

Answers:

The statistical analysis for the secondary outcomes was amended to be adjusted for multiple testing. Hence, the following statistical analysis was added: "Analysis of variance tests with Bonferroni correction are used for multiple testing of continuous variables" on Page 12 Line 13-14.