BMJ - Decision on
Manuscript ID
BMJ.2018.043530

Body: 31-Mar-2018

Dear Mr. Palmer,

Manuscript ID BMJ.2018.043530 entitled "Hip Arthroscopy compared with Physiotherapy and Activity Modification for the Treatment of Symptomatic Femoroacetabular Impingement: A Multi-Centre Randomised Controlled Trial"

Thank you for sending us your paper. We sent it for external peer review and discussed it at our manuscript committee meeting. We recognise its potential importance and relevance to general medical readers, but I am afraid that we have not yet been able to reach a final decision on it because several important aspects of the work still need clarifying. The most important of these have to do with the statistical analyses, as detailed in the report from our statistician Dr. Richard Riley.

We hope very much that you will be willing and able to revise your paper as explained below in the report from the manuscript meeting, so that we will be in a better position to understand your study and decide whether the BMJ is the right journal for it. We are looking forward to reading the revised version and, we hope, reaching a decision.

Please remember that the author list and order were finalised upon initial submission, and reviewers and editors judged the paper in light of this information, particularly regarding any competing interests. If authors are later added to a paper this process is subverted. In that case, we reserve the right to rescind any previous decision or return the paper to the review process. Please also remember that we reserve the right to require formation of an authorship group when there are a large number of authors.

Thanks!

Very truly yours,

Elizabeth Loder, MD, MPH
eloder@bmj.com

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Report from The BMJ's manuscript committee meeting

Present: John Fletcher (chair); Richard Riley (statistician); Elizabeth Loder; Jose Merino; Wim Weber; Georg Roeggla; Tiago Villanueva; Daoxin Yin

Decision: Put points after stats report from RR

* Thank you for registering the trial prospectively. In revising the paper please make certain that all outcomes listed in the trial registry are reported in the paper, using the same terminology and in the same order as they appear in the trial registry. If any outcomes have been changed in the trial registry, please explain when and why this happened and provide results for all outcomes so that readers can judge the effect of the changes. If you present any outcomes that were not listed in the trial

registry, please clearly flag them as post-hoc and please do not emphasise them in your interpretation of the trial results.

* The lower bound of the confidence interval is compatible with a smaller difference between groups than the 9 points said to be clinically significant, so we thought the interpretation of the study should be more nuanced.

* We were impressed with your careful attention to remote randomisation, with minimisation, after recruitment and baseline data input - this appears from table 1 to have worked well. High recruitment rate from those eligible reassures about generalisability as does the multicentre nature of the trial.

* Could you use the term "Arthroscopic surgery" rather than "arthroscopy"? Arthroscopy implies just a diagnostic look and see, at least in the minds of many of the editors who read the paper.

* Please see the separate comments of our statistician Professor Richard Riley.

* We do think that the comment of one of the reviewers needs far more attention than it currently receives: "The assessor blinded outcomes deliver no difference between the groups, while the self-reported (non-blinded) outcome (including the primary outcome) clearly are in favor of the arthroscopic intervention. I think this aspect absolutely needs more discussion" The MICD for the HOS-ADL is 9 (Arthroscopy. 2016 Sep;32(9):1877-86). Here you found an average difference of 10. This is not a big difference; can you say something about placebo effects of this type of surgery ?

* Another important outcome for this patient group is the PASS: Patient Acceptable Symptomatic State,
and for HOS-ADL it is 87 (The American Journal of Sports Medicine Vol 43, Issue 8, pp. 1844 - 1849). It is not a primary outcome, but can you give us the proportions of patients in each group that reached this threshold ?

* We would like more discussion of the physiotherapy intervention. Some editors thought this was a very weak comparison, and that the standard in clinical practice where they work is far more intensive and frequent physiotherapy.

PT more. It's a weak comparison. The standard is 12 sessions a month and then it gets renewed. Very relevant issue. Causes a lot of pain and distress. I am mildly in favor of this.

* Our patient editors say: "Thank you for the well written and thoughtful PPI declaration and dissemination plans."

These comments are an attempt to summarise the discussions at the manuscript meeting. They are not an exact transcript.

In your response please provide, point by point, your replies to the comments made by the reviewers and the editors, explaining how you have dealt with them in the paper. If several reviewers have made the same point, you can group the comments and respond only once. If you do not agree with a reviewer suggestion, please explain why - you should not feel you have to do everything that is recommended if you have good reasons not to.

As mentioned above, the comments from Professor Riley should take precedence as he will be reviewing the revision.

Comments from Reviewers

Reviewer: 1

Recommendation:

Comments:
Overall, this an important study that is worldwide waited for. The study is very well performed according to all quality criteria, and is written down very readable and clear. I only have a few comments.
1) In the trial register the clinical examination tests (ROM, and impingment test) are mentioned as secondary outcomes. I therefore do not understand why the authors only reported them descriptively. I recommend to assess and report the between group difference for this and its 95% CI.
2) The assessor blinded outcomes deliver no difference between the groups, while the self-reported (non-blinded) outcome (including the primary outcome) clearly are in favor of the arthroscopic intervention. I think this aspect absolutely needs more discussion.
3) Continuing, we have banned arthroscopic interventions in knee OA patients based on the fact that the effect of the real arthroscopic intervention did not surpass the effect of the placebo procedure. The placebo effect of such surgical interventions seems to be huge; at least higher than that of exercise. The same huge placebo effect most probably is true in the present arthroscopic intervention and could explain the difference in self-reported outcomes found between physical therapy and arthroscopic intervention. Like comment 2 this aspect needs more discussion.
4) For the same reason I also would like the authors to report on the patients' expectation of the intervention was measured beforehand (if measured), and what the impact of this could be on the outcomes, as well as what proportion of the patients already had received physical one year or more before the inclusion in the trial.
5) The authors talk about "to seed the minimisation system" (page 9, line 7); I recommend to use other words so that clinical readers can understand what is meant with this. The same is true for minimization factors (page 12, line7).
6) Apparently, the physical therapy in the UK does not exceed 8 sessions. To what extent were the goals achieved in the physical therapy group at the end of the sessions? Could it be that the physical therapy should be more extensive?

Additional Questions:
Please enter your name: Sita Bierma-Zeinstra

Job Title: Professor

Institution: Erasmus MC - University Medical Center Rotterdam

Reimbursement for attending a symposium?: No

A fee for speaking?: No

A fee for organising education?: No

Funds for research?: Yes

Funds for a member of staff?: No

Fees for consulting?: Yes

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Reviewer: 2

Recommendation:

Comments:
I appreciate the opportunity to review this manuscript.

This is a pragmatic multicenter two-armed randomized control trial comparing physiotherapy to hip arthroscopic surgery for the treatment of femoroacetabular impingement (FAI). There is a notable paucity of high-quality clinical trials comparing the outcomes between these two approaches. Several similar RCTs (e.g., the UK and Austrialian FASHIoN trials) are ongoing, but this study appears to be the first complete report. The analysis showed strong evidence of better outcomes (primary outcome: HOS ADL) achieved by hip arthroscopy, compared to physiotherapy, at eight months post-randomization. The study appears to be well designed and implemented, with a good adherence to CONSORT guidelines. The results provide very important knowledge to enhance the current understanding of the risks and benefits of these two mainstay approaches. Below are a few comments:

1. Discrepancy between the current study and the published protocol.
The primary outcome of this study was the HOS ADL measured eight months post-randomization. In the published protocol (Palmer et. al, 2014, Bone and Joint Research, 3-11), the primary outcome was the "change in the HOS ADL".

2. Radiographic inclusion criteria not clear
Inclusion was defined as "… have clinical and radiographic evidence of FAI" and "surgeons made a qualitative assessment of hip morphology to diagnose FAI". The qualitative assessment in the current study appears subjective. The consistency between centers in patient recruiting needs to be established. Although the authors argued that there is no consensus on a quantitative imaging measurement as inclusion criterion, more details should be described on how the qualitative assessment was performed. Currently it is unclear whether there is an effort to standardize this assessment among participating surgeons (If this is also part of the pre-trial meeting, please mention).

3. "Aim of this study" vs. "aim of this RCT"
In Introduction, the authors stated: "The aim of this study is to … and preventing the development or progression of osteoarthritis in patients …". However, there is no data on the prevention of OA development at this stage. To avoid confusion, please say: "the aim of FAIT is to …" or "the aim of this trial is to…", or something alike.

4. PROMs of the late treatment group
I am not sure if understand this correctly - It appears that "six months after intervention" was used interchangeably with "eight months post randomisation", e.g., in "what this study adds". But the primary outcome was set at eight months post randomisation. For patients who received treatment less than 12 weeks, these two time points were considered equal. But for patients who commenced their treatment more than 12 weeks post randomisation (page 12), "PROMs were collected at eight months post randomisation (primary outcome measure) and six months post intervention in this group." - isn't it better to use PROMs at six month post intervention as the primary outcome for analysis? The delay in treatment after randomisation will affect the time from the start of intervention to PROM collection and therefore make this time from intervention to PROM more variable.

Additional Questions:
Please enter your name: Yun Peng

Job Title: Research Staff

Institution: Massachusetts General Hospital

Reimbursement for attending a symposium?: No

A fee for speaking?: No

A fee for organising education?: No

Funds for research?: No

Funds for a member of staff?: No

Fees for consulting?: No

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Reviewer: 3

Recommendation:

Comments:
Originality
This study adds RCT data to support the decision between conservative physiotherapy and activity modification or arthroscopic treatment of femoroacetabular impingement. With physiotherapy revealing subjectively inferior outcomes in comparison to arthroscopy, currently holding a low priority in the NHS, these results adds relevant knowledge for general practitioners and policymakers.

Importance
Although arthroscopy presented beneficial and clinically significant outcomes in comparison to physiotherapy, the pragmatic approach, in this case, leaves some questions unanswered in order to fully answer the stated research questions. With 51% of included patients in arthroscopy group and 32% in the physiotherapy group achieving important symptomatic improvements, success-rates for both treatment groups are relatively low. Consequently, inclusion of planned long-term data regarding osteoarthritis and hip replacement surgery risk could potentially have contributed considerably to the decision towards arthroscopy if able to serve as tertiary prevention as hypothesized. Although adding data to the considerations of the general practitioner when referring patients and policymakers when prioritizing health care services, I am uncertain whether the condition and clinical implications are frequent and significant enough for a general journal.

Scientific reliability
- The introduction is well-written, well composed, and the research questions concisely stated. The feasibility study and thoroughly considered protocol are strengths of this study. It is unclear what is meant by "equipoise between surgeon and patient" in page 8, line 9.
- The methods section describes appropriate and convincing efforts to minimize bias with regards to power calculations, intention-to-treat, and robust questionnaire information. However the pragmatic and feasible approach to the physiotherapy intervention (non-specialized physiotherapist and eight sessions of physiotherapy over a period of five months) pose a problem when compared to a close to optimal arthroscopy intervention (performed by specialists and combined with exercises). More elaborate specifications of interventions could potentially alleviate this concern but is not reported. An intervention group receiving both arthroscopy and subsequent physiotherapy could possibly be interesting for future studies in order to further improve patient outcome from current treatments. Based on baseline characteristics of included participants, validity for mixed- and pincer-type hip impingement is questionable as the isolated Cam-type make up for 94% of the distribution of types. Exclusion criteria and baseline characteristics are clearly and adequately described and no checklist, ethical, or reporting issues were identified. The method section is very elaborate but would benefit from being more focused.
- Results were credibly reported. The extensive tables would benefit from containing lesser amounts of information, perhaps creating an online supplemental file for full table information and exclusively presenting essential and particularly interesting results in the main manuscript. The elaborate questionnaire data, radiography-measures and supporting analyses structure are strengths of this study but is not particularly clearly presented.
- Discussion and drawn conclusions are appropriate, but should be more explanatory of field-specific measures when targeting a general journal. As physiotherapy is still recommended as first-line treatment as a consequence of potential complications of surgery, a description of suggested place and/or conditions of arthroscopy is warranted to state the precise clinical implications of this study. A bullet point table or written summary, possibly in a Conclusion section, would enable readers to get a quick resume and authors to emphasize key messages. Abstract is well-written but needs to include the recommendation regarding preservation of physiotherapy as first-line treatment (on the basis of potential arthroscopy complications) to be representative of the discussion.
- No problems with references identified.

Additional Questions:
Please enter your name: Jeppe Bo Lauersen

Job Title: Medical doctor

Institution: Department of Orthopedic Surgery, Amager-Hvidovre Hospital, Hvidovre, Denmark

Reimbursement for attending a symposium?: No

A fee for speaking?: No

A fee for organising education?: No

Funds for research?: No

Funds for a member of staff?: No

Fees for consulting?: No

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Reviewer: 4

Recommendation:

Comments:
Thanks for inviting us to review this interesting study on the effect of hip arthroscopy versus physiotherapy. This review is performed by Gerjon Hannink, medical statistician and myself, Wim Schreurs. To perform a thorough review in a study with a set up like this I can not do this without experienced statistical advice.

Overall comments
This an impressive study by an extensive team of experts trying to study the effect of hip arthroscopy versus physical therapy in patients with femoro-acetabular impingement. There is a high demand for studies like these, given the enormous increase in hip arthroscopies worldwide for this indication, without a sound evidence of the effect of these arthroscopies.

They set up an RCT in 7 high volume arthroscopic centres, and surgeries are done by experts on hip arthroscopy. The control patients were referred for physical therapy, they had maximal 8 treatment of therapy, most had less, and were treated by physical therapist who had instructions on the training program.

There are many outcome parameters used and I was impressed by the number of tests used.

This is the first study based on this extensive study set up.

The conclusion at 8 months after randomisation, in practise around 6 months after the surgery, must be somewhat disappointing. They claim that after this period the mean HOS ADL was 10 points higher then in the physiotherapy group, however this

difference is clinically not very impressive. It is not expected that this benefit will increase after a longer follow up, the authors state in the paper that most gain will ne obtained in the first 6 months after the surgery.

It is worrisome that only half of the patients experiences a clinical benefit after this procedure, so that also means that 49 % of the patients will have a quite costly surgery without benefit.

In their conclusions the authors state that arthroscopy outcomes for this indication is superior to non-operative measures, and hence this study supports the provision of arthroscopy.

We are not sure that the authors can claim this. First, this is arthroscopy performed by excellent surgeons versus physical therapy. The level of surgery will be high and even in the excellent surgical hands the clinical difference is not impressive 6 months after surgery. And only 50 % of the patients has a minimal clinical benefit.

Of course, future better inclusion criteria can probably improve the outcome, however this is the state of the arthroscopy in the hands of experienced surgeons at the moment.

There is also a severe potential bias, there is very little information on the aftertreatment after the arthroscopy. They state that patients after arthroscopy got also physical therapy, but what was the protocol, how many treatments did they get and who trained them. This is compared to physical therapy in the conservative treated group who had a very low number of physical treatment session during their treatment, with a maximum of 8 session in 8 months. So, what is the effect of physiotherapy after the scopy on the outcome?

Although not part of this session, there is also a considerable cost aspect. As suggested by the authors in their paper, lateron they will focus on costs. However, one can not start promoting arthroscopy for an indication for which arthroscopy is widely used (FAI) and later come back on the costs.

It has to be acknowledged that in many patients the effect of this surgical treatment is limited, it is completely unclear if this surgery will really be effective in the longer follow up given the early results and it is at this stage also unclear if an arthroscopic early treatment will prevent the big problem on the long term, hip osteoarthrosis.

FAI is a pathology seen in many individuals in the population, about 20 %. Of these 20 % also around 20 % is symptomatic at a relative young age. So the number of patients with symptomatic FAI who can be considered as a candidate for arthroscopy is high. For communities, they cannot afford an enormous increase in arthroscopies without a sound scientific and clinical back and do we really prevent later problems like osteoarthritis.

We certainly would recommend this impressive study for publication in BMJ, this is the first study based on this trial and hopefully many new insights will be presented in future studies. However, for now, the interpretation of the data and the conclusion should be more balanced.

Comments Gerjon Hannink
Well conducted and reported study given the challenges associated with surgical trials.

Throughout the manuscript, the terminology ‘8 months post-randomization’ and ‘6 months post-operative’ is somewhat confusing.

How generalisable are the results since the surgery was performed in/by experienced high volume surgeons/centers? This could have overestimated the effect of surgery.

What are the authors comparing? Please be more precise / specific.
In the abstract it is stated that hip arthroscopy (followed by routine post-operative care) was compared with goal based physiotherapy. In the methods section it reads that arthroscopy patients received post-operative physiotherapy (routine NHS care). In what was this post-operative physiotherapy different from the goal based physiotherapy in the control group? This could be clarified.
Up to eight physiotherapy sessions in five months is rather limited in my opinion (although it is NHS current practice). How does this compare to the post-operative physiotherapy in the intervention group?

Analysis was performed as per modified intention (mITT) to treat including those patients with available outcomes data based on their randomized treatment allocation (regardless of compliance).
ITT analysis reflects the practical clinical scenario as it admits noncompliance and protocol deviations. The mITT analysis allows a subjective approach in entry criteria, which may lead to confusion, inaccurate results and bias (Gupta, Perspect Clin Res. 2011).
I am slightly worried that the mITT might have influenced the results. If noncompliant subjects and dropouts (no outcome available) are excluded from the final analysis, it might create important prognostic differences among treatment groups. Moreover, subjects may be noncompliant or may drop out from the study due to their response of treatment. This should be discussed.

The conclusion (and discussion) should be more balanced. I find it misleading shorthand to conclude that hip arthroscopy is superior to physiotherapy based on an MCID. Although the MCID is a useful tool to define general guidelines to determine whether a treatment produces clinically meaningful effects, the MCID value is impacted by the method used to calculate it (anchor, distribution), by the type of anchor chosen and by the definition (threshold) of improvement. The MCID is also dependent on the population characteristics such as disease type and severity, sex, age, etc.

The authors showed a statistically significant difference of 10 points/percent in HOSADL score between surgery and physiotherapy. This difference exceeds the MCID of 9 points reported by Martin & Phillipon (Arthroscopy 2008) and was therefore concluded to be clinically relevant. However, comparing the finding with the reported 6 months MCID in HOSADL of 15 points by Chahal et al. (Orthop J Sports Med 2014) would make the difference less relevant...
This said, most importantly, for appropriate use, the MCID should be applied to changes in individual subjects, not to group changes (Katz, J Orthop Surg Res. 2015).

Additional Questions:
Please enter your name: Wim Schreurs and Gerjon Hannink

Job Title: Orthopedic surgeon and Medical statistician

Institution: Radboudumc Nijmegen The Netherlands

Reimbursement for attending a symposium?: No

A fee for speaking?: No

A fee for organising education?: No

Funds for research?: No

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President of the European Hip Sociey 2016-2018
(Schreurs)

Reviewer: 5

Recommendation:

Comments:
Thank you for the opportunity to review this interesting trial. I have reviewed from a statistics viewpoint, and many analyses are well done (e.g. adjusting for baseline values and site, in a mixed effects model). However, I have some comments to be addressed before the BMJ can make a proper evaluation of the paper.

1) The drop out in the groups is a concern, but the authors do investigate this through imputation and missing not at random analyses. Also, drop out is perhaps expected in these field. Therefore, I do not think this is a fatal flaw, but it should be discussed in more detail as a limitation in the Discussion.

2) Baseline characteristics for each group should also be given for the subset of patients who actually gave follow up results toward the final analysis. Indeed, this is more important, as the large drop out of patients may well have caused baseline imbalances, and we can’t see this at the moment.

3) This is a major point:
The subgroup analyses are rather sub-standard. The authors dichotomise variables at arbitrary values, such as age at 40. Also, there is no estimate of the interaction (difference in effect between subgroups). Therefore, the authors state that there is a subgroup effect for age, but do not actually quantify this properly. The authors therefore need to address these things, by analysing covariates on their continuous

scale (or at least use 4-5 categories), and the potential for non-linear trends / interactions, and by quantifying interactions (differences between subgroups).

Also, there are a number of paragraphs hyping the subgroup effects (despite the note from the authors that the study was not powered for this), and this should be removed or toned down.

Here is an example of discussion that adds nothing new and is based on data dredging and speculation: "Patients with more severe symptoms pre-operatively have been shown to have a greater likelihood of achieving a clinically important improvement in HOS ADL after hip arthroscopy33,35. Using a threshold score of 65 on the HOS ADL, we did not detect a difference in treatment effect, although this may reflect the threshold selected or inadequate power."

4) There are multiple centres. Of interest, therefore, is whether there is heterogeneity in the treatment effect across centres? Was this accounted for in the analysis? Can the authors provide a forest plot of the centre-specific results? It was add credence to the overall results, if the direction of effect is similar in all the centres, with little heterogeneity.

5) Interesting reviewer point that "The assessor blinded outcomes deliver no difference between the groups, while the self-reported (non-blinded) outcome (including the primary outcome) clearly are in favour of the arthroscopic intervention. I think this aspect absolutely needs more discussion"

However, actually I do not find that the clinically defined outcomes are presented clearly, with effect estimates and CIs missing from Table 6. Is there actually evidence of a treatment effect or not for these outcomes?

6) The discussion says: "The greatest improvement in symptoms was seen within the first five months post randomisation in the hip arthroscopy group, with continued improvement between five and eight months." – where are the results at 5 months?
Perhaps I have missed them, but I cannot see them in the paper. Is there actually a decreasing trend over time, as implied? This comes out of the blue. Indeed, the 5 months is confusing, as in the results the authors actually say: "outcomes were measured eight months post randomisation and six months post intervention" – no mention of 5 months.

7) The CI for the treatment effect for the main outcome is wide and lower values within it may not be clinically important (based on the authors stating that 9 points is a clinically meaningful change). This needs discussion.

8) At the manuscript meeting, it was also noted that the control group is perhaps sub-optimal, with: physio therapy not very intensive (8 sessions over 5 months). It would be interesting to understand the authors' view on this.

9) Table 2, the groups should be in separate columns to allow an easier comparison

10) "Eight month post randomisation HOS ADL scores were higher than baseline in 70% patients who received arthroscopy compared with 50% patients who received physiotherapy. Clinically significant improvement, defined as a HOS ADL score greater than 9 points, was reported in 51% of patients who received arthroscopy and 32% of patients who received physiotherapy."
- can we have some CIs please for the differences?

11) Why is the CI for the treatment effect WIDER after multiple imputation? Surely, the additional patients will add more information to the analysis, and therefore narrow the CI. Can the authors explain more about how their imputation was done in the methods and why this finding occurs.

I hope my comments are helpful to the authors going forward, and allow the BMJ to make a fuller evaluation of the article.
With best wishes, Richard Riley

Additional Questions:
Please enter your name: Richard Riley

Job Title: Professor of Biostatistics

Institution: Keele University

Reimbursement for attending a symposium?: No

A fee for speaking?: No

A fee for organising education?: No

Funds for research?: No

Funds for a member of staff?: No

Fees for consulting?: No

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