Author's response to reviews

Title: Task-oriented training with computer gaming in people with rheumatoid arthritis (RA) or osteoarthritis (OA) of the hand: Study protocol of a randomized controlled pilot trial

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Author's response to reviews: see over
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Dear Professor Curt D. Furberg, Co-Editor in Chief

We appreciate the time taken to review this manuscript and for all the very good suggestions and questions. This has strengthened our manuscript.

We are re-submitting our revised manuscript titled, “Task-oriented training with computer gaming in people with rheumatoid arthritis (RA) or osteoarthritis (OA) of the hand: Study protocol of a randomized controlled pilot trial” for review. The revisions made in the manuscript are highlighted with ‘track changes’. We are also attaching herewith our point-by-point responses to the reviewer’s comments.

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If you have any questions please do not hesitate to contact me anytime.

Sincerely

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Responses to reviewer’s comments

Abstract:

1. Comment: Methods: change “double arm” to “parallel group”

Response: “double arm” changed to “parallel group” in the revised manuscript abstract.

2. Comment: “A mixed effect repeated measures analysis of variance,” can the authors comment why they chose this statistical analysis rather than another parametric tests such as a two sample t-test that measures change across the intervention groups at the end of the trial. Most interventions in rheumatology of RA and OA trials whether pharmacologic or device would use a simple t-test.

Response: For our study variables, we initially planned for the mixed effects repeated measures ANOVA method. In addition to estimation of the within group effects pre to post intervention, this method would allow an estimation of the between group effects and interaction. However, as mentioned that most published works use the t-statistic to estimate treatment effects within and between the groups, we have modified the statistical analysis plan in the revised manuscript as below,

‘Based on the data distribution of the study outcomes- grip strength, peg board dexterity, applied dexterity and applied strength (AHFT items), the DASH and number of exercise sessions completed in six weeks, changes over time (pre to post intervention) within each group will be assessed by paired student t test or Wilcoxon signed-rank test. Differences in study outcomes between groups (control versus experimental) post intervention will be analyzed using unpaired student t test or Mann-Whitney U test’.

3. Comment: Discussion: “initial estimation” - can the authors’ state that the results from this pilot be used to inform a ‘main trial’.

Response: The “Discussion” paragraph has been modified and added to the revised manuscript abstract as,

“The study findings will inform decisions on the feasibility, safety and completion rate and also provide preliminary data on the treatment effects of the task-oriented training compared to conventional hand exercises in people with RA or OA of the hand”.

4. Comment: Background: Second sentence: “The condition presents itself as acute symmetric polyarthritis developing over a few months or years especially in the small
joints of hand, wrists or feet.” This may not be the optimal description of RA. It may present as this but often does not. Most rheumatologists and RA cohort studies would find that rheumatoid arthritis has a sub acute onset or insidious onset that develops over a period of weeks to months. The 1987 ACR classification criteria weight hand MCPJ, PIPJ and wrist involvement. Many patients with RA have other joint such as predominantly shoulder or knee involvement at disease onset. However, over time the majority of patients may develop hand and wrist involvement.

Response: The sentence has been modified and added to the revised manuscript as,

“Rheumatoid Arthritis (RA) is a chronic symmetric polyarthritis which can affect most synovial joints but particularly the small joint of the hands, wrists and feet.”

5. Comment: Joint damage is inferred whereas joint deformity is the clinical sign.

Response: The word ‘joint damage’ is removed in the revised manuscript.

6. Comment: “Exercises play an integral part in the conservative management of the hand affected with arthritis.”

I do not understand what the authors mean by conservative. The management of OA differs considerably from that of RA. In RA rheumatologists use a variety of primarily pharmacologic treatments to limit patient pain, stiffness, swelling, and physical disability. Exercises do not play an integral role initially. Perhaps exercise treatment varies by geographical setting. Suppressing RA disease, inducing clinical remission and preventing irreversible joint deformity and limitation of range of motion are the long-term goal of treatment in RA. If this is successful then conservative management may not be needed unless there is evidence of ongoing RA disease activity despite DMARDs and biologic DMARDs or there is evidence of irreversible joint damage that is not amenable to DMARD treatment.

Response: Limitations in activities of daily living (ADL) and participation restrictions are often presented in combination with structure/function changes such as joint swelling, joint damage, deformities, pain, and joint stiffness, reduced finger range of motion, reduced grip strength in both RA and OA populations. In spite of the advancements in pain or disease modifying medications and joint surgeries, many people affected with RA do experience varying levels of difficulties in ADL with reduced function and quality of life. Non-pharmacological management is recommended in both RA and OA as an adjunct which often includes splinting, assistive devices, exercises, self-management techniques, joint protection and therapeutic modalities. The role and therapeutic effects of exercises in RA and OA populations have been discussed in many reviews. Though no strong evidence is available
for the effectiveness of hand exercises (either range of motion or strength exercises), the theoretical basis and the purpose of prescribing exercises is to maximize function by reducing pain and stiffness, preventing joint deformities and improving joint movement and strength of the grip muscles. (This information is added in the revised manuscript)

7. Comment: The authors have provided 6 citations for systematic reviews that show evidence of modest treatment effects. Therefore there is no need to describe in greater detail the three specific trials that showed positive results. Rather, could the authors briefly describe the results of the systematic reviews?

Response: The paragraph has been modified and added to the revised manuscript as,

“A 2004 systematic review which included nine studies that evaluated any form of hand exercises on pain, stiffness, range of motion (ROM), grip and pinch strength, dexterity and function reported that there is no strong evidence for or against hand exercises in people with RA. Another review concluded that an optimal hand exercise program in RA is yet to be established.

With respect to OA, the EULAR (European League against Rheumatism) added that recommendations for finger range of motion exercises, grip and pinch strength exercises or thumb muscles strengthening in hand OA was limited to level 4 expert opinion. A 2010 review on RCT’s and cohort studies from 1986-2009 reported moderate evidence for exercises in improving grip strength, range of motion, hand function and pain relief. Another review with only three exercise treatment studies concluded exercises does improve grip strength and hand function but have no effect on pain and stiffness.

Thus with the limited number of studies with variability in the exercises prescribed, combination of additional therapeutic modalities, different outcome measures, exercise parameters (frequency, intensity, duration) and other methodological issues, it is difficult to arrive at definitive conclusions on the effects of ROM/ strength exercises on hand function in both populations”.

8. Comment: Specific training with manipulation of common objects should (this should be ‘could’) also be incorporated.

Response: ‘could’ used instead of ‘should’ in the revised manuscript

9. Comment: References to add.

Response: References are added in the revised manuscript
10. Comment: Grammatical error: provide ‘with’ interesting...

Response: The word ‘with’ removed. The paragraph has also been modified and added to the revised manuscript as:

“Several recent studies have described the use and benefits of interactive computer games and it has been reported that they provide interesting and challenging activities [17], and are enjoyable, engaging and intrinsically motivating” [17, 19, and 20].

11. Comment: Hypotheses “The task-oriented training will significantly improve performance based, self-reported hand function and reduce pain and stiffness levels.”

Is this RCT a pilot for a RCT that will attempt to show that task orientated training is superior to conventional therapy? For example
a) In patients with RA and OA, task-oriented training will significantly improve performance based, self-reported hand function and reduce pain and stiffness levels compared to a control group of RA and OA patients randomized to treatment with conventional exercise therapy.
b) In patients with RA and OA, task-oriented training will be feasible in terms of compliance, treatment safety and completion rate compared to a control group of RA and OA patients randomized to treatment with conventional exercise therapy. However, if change within the treatment arm is main outcome measure of interest rather comparing change across arms, why is a control group incorporated?

Initially it appears, from the abstract, that this pilot RCT is similar to a Phase IIb RCT in terms of evaluating safety, efficacy and feasibility. In many Phase IIb trials the interventions are directly compared. If it is not then could the manuscript state that a direct comparison will not be performed.

Response: We do agree with the reviewer. We have revised the study hypotheses as below and added to the revised manuscript:

a) It is hypothesized that the experimental group receiving task-oriented training will show greater improvements in performance based, self-reported hand function and reduction in pain and stiffness levels as compared to the control group receiving conventional hand exercises
b) It is hypothesized that the task-oriented training will be feasible in terms of compliance, treatment safety and demonstrate better completion rate as compared to the conventional hand exercises
12. Comment: Inclusion criteria

The inclusion criteria are unusual for RA and OA RCTs and not typical of the RA and OA population of patients seen in clinical practice. For example in the manuscripts Raven et al 2008 (ref 36) the average age of respondents was 57.5 years (range 22.6–86.4) and the average DASH was 39 (SD 22). Therefore irrespective of the RCT result there will be poor generalisability of the results to usual RA and OA populations. Why were these specific criteria chosen? It will also affect the imputation of the pilot RCT results to design of the ‘main’ study. Please justify

Response: The age limit of the study participants in the present study will be maintained between 30-60 years in order to minimize the presence of any co-morbid conditions associated with aging. We believe that this age range could be generalized to RA or OA population. A hypothetical DASH score range of 25 to 50 out of the maximum score of 100 was selected initially to include individuals presenting with moderate level of difficulty perceived in performing common activities of daily life. We chose to exclude individuals with mild difficulties or with severe limitations because the task-oriented training (experimental intervention) may either be easy or very demanding which may impact the treatment responses.

13. Comment: Exclusion criteria:

People will be excluded if they present with any of the following features:
1) Severely deformed finger joints
2) Neurological conditions of dominant side upper limb
3) Trauma in wrist or hand
4) Upper limb surgeries in previous six months
5) Co-existing hand conditions in the dominant hand
6) Problems with vision or hearing
7) Recent changes in drug regimen <3 months
8) Major diseases of heart or lungs or liver
9) DASH scores <25 or >50
Some of these are too vague, Impacts generalisability. Clinicians won’t know whether the results apply to their patients.

Response: Exclusion criteria have been rewritten and added in the revised manuscript as:
1) Recent surgeries (<6 months) in the dominant hand 2) problems with vision or hearing 3) Recent changes in drug regimen <3 months 4) Major diseases of heart or lungs or liver 5) fixed finger joint deformities and 6) DASH scores <25 or >50

Re 1) How deformed? How will this be determined? Some RA and OA patients have considerable joint deformity with good functional ability.
Response: It is quite difficult to accurately determine the degree of finger joint deformities. However, for the present study, any finger deformity that has become fixed without any joint motion possible is excluded. People presenting with passively correctable deformities or with limited joint motion will be included in the study, provided the other inclusion criteria are met.

Re 8) Why are major disease of heart and lung etc excluded. How is this determined?

Response: Patient history on diagnosis of any of the diseases of heart or lungs such as coronary heart disease, asthma, lung cancer, pneumonia will be collected during the initial screening. People diagnosed with any of the above will be excluded as we believe that such chronic diseases would functionally debilitate the individual in the normal day to day life and the home based hand exercise program may be even more demanding.

RE 9) why not DASH scores above 50? The average DASH in Raven 2008 was 39 (SD 22).

Response: Acknowledging that some patients with considerable joint deformity have good function, we decided to narrow the range of difficulty levels (DASH scores 25-50) perceived while performing the upper limb/ hand activities of the DASH questionnaire. This would allow homogenous baseline level of self-reported symptoms and function in all the participants.

What about measures of RA disease activity such as the Disease Activity Score (DAS) or ACR 20 which is generally collected in all RA RCTs? Are these patients in clinical remission? How would we know? It is difficult to interpret an intervention or RCT result in RA without a measure of disease activity at baseline. X-rays are another important baseline measure of disease damage. Please justify why measures of RA disease activity were not collected.

Response: Please see Response # 19.

14. Comment: Sample size calculation:
“This pilot trial is being conducted to enable a sample size calculation for a larger study, as there is insufficient data available from the previous studies [22, 23]. Thirty participants will be recruited and allocated into two groups throughout the data collection period.” This is a pilot for another ‘main’ trial. There is data regarding the effect size of the control group – here conventional exercise treatment in patients with RA and OA (as per literature reviews). If there are 15 patients for the new treatment of task-orientated training will 7 or so OA patients and 8 or so RA patients be enough to determine preliminary effect size estimates of this new intervention? RA patients can be very variable in the manifestations of their disease as reflected
by joint activity and joint damage measures and these measures of disease activity and damage will impact the effect of most RA interventions such as the one examined in this pilot RCT.

Response: Both RA and OA populations were included in the study for reasons related to limited time and recruitment issues. Effect size estimates or sample size calculation may not be determined from a small sample of 7 or 8 and at this point we would state that this pilot trial is being conducted to evaluate the feasibility and preliminary effects of the intervention (task-oriented training) received by the experimental group in comparison to the conventional hand exercises received by the control group.

We have also revised the original paragraph under ‘Sample size calculation’ in the manuscript as:

“In this pilot trial, a formal sample size calculation was not done. Thirty participants [22] will be recruited and allocated into two groups throughout the data collection period'.

15. Comment: A description of the intervention: “Task-oriented training program
In a study by Guzelkucuk et al, 2007[14] on ...” These three pages should be in the introduction.

Response: The three pages were added in the Introduction section in the revised manuscript.

16. Comment: Primary outcome measure: Can the authors provide the reliability of the Instrument (AHFT) for patients with RA and OA respectively?

Response: Test retest reliability of AHFT measured by Intraclass correlation coefficient in twenty individuals with RA who were evaluated in two sessions within two weeks ranged from 0.53 to 0.96; Inter rater reliability ranged from 0.89 to 1.0. Test retest reliability in twenty six individuals with OA evaluated in two sessions within two weeks ranged from 0.7 to 0.96; Inter rater reliability ranged from 0.99 to 1.0 (This information is added in the revised manuscript)

17. Comment: Secondary Outcomes. The DASH has been extensively validated. However, the computer based hand functional assessment tool has not. In Hammond 2009 it was evaluated in 20 healthy participants. The reliability metrics used a mean difference rather than standard (ICC and Bland/Altman) metrics of reliability. Has it been evaluated in patients with RA and OA? Is the computer based hand functional assessment tool influenced by visual processing ability as well as hand dexterity? There are three pages of the manuscript describing the outcome measure without providing objective metrics. Unless there is data regarding to its metric properties in RA and OA should the tool be designated an ‘exploratory’ outcome and not a secondary outcome to optimally differentiate treatment from measurement failure? Please comment. How long will all the assessments take to perform?
Response: For your information, we present the results of our unpublished work* on test retest reliability of the tool measure during three different object manipulation tasks done with predictable tracking in 40 individuals with arthritis affecting the hands (14 with RA, 26 with OA). The tool demonstrated moderate to high reliability, with ICCs ranging between 0.5 and 0.84. For the present study, the tool will be designated as an ‘exploratory’ outcome. (The tool is removed from secondary study outcomes initially listed in the manuscript). Evaluation of four object manipulation tasks using the computer based tool may take approximately 7-10 minutes. (This information is included in the revised manuscript)


Title: Test Re-test Reliability and Convergent Validity of a Computer Based Hand Function Assessment Tool in People with arthritis affecting the hands.

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19. Comment: No formal measure of RA or OA disease activity is included as a covariate. The authors should comment as to why it was not included and the impact on the internal validity and generalisability of the results of the intervention by their omission.

Response: We agree that formal measures of disease activity need to be incorporated to interpret the effects of an intervention. However, measures of RA or OA disease activity were not planned for the present study which is primarily designed to test the feasibility and obtain preliminary data on the effectiveness of the task-oriented training. We believe that the DASH inclusion criterion score between 25 and 50 will help to include people presenting with same level of self-reported symptoms and level of difficulty in activities and participation, irrespective of the type of arthritis. We also agree that the findings from this pilot trial cannot be generalized without documenting the baseline disease activity state of the study participants and this issue will be considered as one of the study limitations.

20. Comment: “The independent assessor who will perform the randomization and evaluate the study outcomes will be blinded to the group allocations.” This sentence is unclear.

Response: The sentence is rewritten and added to the manuscript as follows, “An independent assessor blinded to the group allocations will evaluate the study outcomes at baseline and at the end of the sixth week”.

21. Comment: “Both groups will be provided with software for use on their home computer to record and store pain and stiffness levels using separate 0-10 numerical verbal rating scales,
before and after each exercise session.” This indicates that the participants must be reasonably computer literate. Is there a reason why it has to be computerized? It will also limit generalisability.

Response: Knowledge on very basic functions of computer is indeed an inclusion criterion for the present study. In spite of it, participants from both groups will be sufficiently trained to use the computer based hand function assessment tool for pain and stiffness recording. Before and after each exercise session, the experimental group will be asked to play the paddle game of the computer based tool with one of their personalized objects for approximately ten seconds and record their pain and stiffness levels. On the other hand, the control group participants will be asked to simply run the software and record their pain and stiffness levels. The reasons for using computerized scores are, to allow fair and equal treatment set up for both groups and to check if the participants are able to manage recording the scores using the computer based tool. We believe that the three training sessions, the study staff visit to the participant’s home in the first week of the home program, and weekly emails/phone calls will help the participants’ in self-managing their home program. In rare cases, if any participant experience difficulties with the computer based tool, he/she will be provided with paper printouts of the pain and stiffness scales. Their scores could then be manually entered in the exercise log diary.

22. Comment: Can "HP" be changes to home program throughout (Hewlett Packard first comes to mind on every read).

Response: HP changed to ‘home program’ in the revised manuscript.

23. Comment: “If symptoms continue … the intervention will be discontinued…” How are these dropouts handled in the analysis? Are they treatment failures? How is this incorporated into the primary and secondary outcome measures? Is it treatment efficacy failure or an adverse event?

Response: The sentence, ‘If symptoms continue … the intervention will be discontinued…would be considered as an ‘adverse event’ rather than ‘treatment efficacy failure’. Each occurrence of increased pain or stiffness (>5 in the scales) continued over a week would be recorded as an adverse event and the intervention will be discontinued.

The paragraph is rewritten as, ‘When no increased symptoms (assuming a bench mark score > 5 in the pain and the stiffness scales) are reported during or after exercises, progression will be followed as in Table 3. In case of any symptoms being reported, the treatment parameters will be modified by reducing the number of repetitions or minutes of play. Any occurrence of increased pain or stiffness continued over a week would be recorded as an adverse event. The
intervention will be discontinued and the participant will be referred to his/her general practitioner.”

24. Comment: Statistical analysis plan “mixed effect repeated measures analysis of variance pre to post treatment will be used to test the significant differences in each of the outcome measures”. Can the authors’ comment why they chose this statistical analysis rather than other parametric tests such as a two sample t-test that measures change across the intervention groups at the end of the trial. Most interventions in rheumatology of RA and OA trials whether pharmacologic or device would use a simple t-test. How are dropouts analyzed?

Response: See response # 2 for the revised statistical analysis plan. Regarding the drop outs, all the participants will be included in the analyses regardless of adherence to the study protocol. The ‘last observation carried forward’ method will be utilized to minimize the number of missing values due to dropouts.