PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (http://bmjopen.bmj.com/site/about/resources/checklist.pdf) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

| TITLE (PROVISIONAL) | Phase 2a randomised controlled feasibility trial of a new ‘Balanced Binocular Viewing’ treatment for unilateral amblyopia in children age 3-8 years: trial protocol |
|---------------------|----------------------------------------------------------------------------------------------------------------------------------|
| AUTHORS             | Dahlmann-Noor, Annegret; Greenwood, John; Skilton, Andrew; Baker, Daniel; Ludden, Siobhan; Davis, Amanda; Dehbi, Hakim-Moulay; Dakin, Steven C. |

VERSION 1 – REVIEW

| REVIEWER                | Zhang, Wei  
Tianjin Eye Hospital, Clinical College of Ophthalmology Tianjin Medical University, Tianjin Key Laboratory of Ophthalmology and Visual Science, Tianjin Eye Institute |
|-------------------------|---------------------------------------------------------------|
| REVIEW RETURNED         | 19-May-2021                                                  |
| GENERAL COMMENTS        | The paper presents a phase 2a feasibility RCT of a dichoptic treatment for amblyopia. It is a further study mainly to test the effect and safety of the new ‘Balanced Binocular Viewing’ treatment based on previous researches. However, the paper still needs significant improvement before acceptance for publication. My detailed comments are as follows: |
|                         | 1. The preliminary study [24] showed that BBV treatment engaged in high levels of compliance and led to substantial gains in visual function after a relatively short period of treatment. However, the study used on the measure of adherence, the treatment time, resulting in the conclusion is not accurate enough. In addition, adherence data is almost entirely subjective as it is reported by parents in the form of diaries or calendars. Subjective reports prefer to overestimate adherence rates comparing with objective measures. This paper directly quoted the previous results, which should be considered. |
|                         | 2. Poor adherence is the largest source of potential bias in the study. It should be considered that whether the true compliance of patients in two trials can affect the results. A recent systematic review and meta-analysis of randomize controlled trials (published in BMJ Open) also indicated a significant relationship between the effect size and the subjective adherence rate. But the study did not fully explain it, the relationship may be exaggerated. |
|                         | 3. The overall strength of evidence for the comparison is insufficient, which implies that further research is still required. |
| REVIEWER                | Osborne, Daniel                                              |

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| General Comments |
|------------------|
| Dear authors,    |
| Thank you for allowing me to review your manuscript. It is a very clearly presented protocol of a proposed study. The results will be interesting to all stakeholders in amblyopia therapy when considering the implementation of dichoptic therapy for amblyopia in childhood. |
| I have identified one point of clarity only in the manuscript: Line 32-33 says that children, parents/carers will be questioned about acceptability of the intervention. How will they be questioned (for example, through semi-structured interviews with children with or without their parent/carer) and how will data be interpreted and used? |
| The control group is representative of current clinical guidelines, which recommend offering children/carers the choice of atropine penalisation or occlusion therapy. It is still common practice to favour occlusion therapy as a first line treatment, reserving atropine penalisation for children that have struggled with adherence. Offering children/carers the choice of therapy, as is done in this study's control group, may encourage better adherence to their chosen therapy. In the study, participants randomised to the intervention group do not get a choice of intervention. This difference between control and intervention groups could introduce a low risk of bias in the study, which could affect adherence outcome measures. |
| The trial is designed to assess safety of the intervention and collect data to inform the phase 3 trial, and preliminary data about efficacy. This design (RCT) with this control group (that follows current best practice) is most appropriate to address the research question. Problems outlined above could be explored when children and parents/carers are questioned about the acceptability of the intervention (ie, "if you'd had a choice of the intervention, patching or atropine, would you be more likely to adhere to your chosen intervention?") |
| I recommend this manuscript is published and I look forward to the results and impact of this trial. |
| Yours |
| Daniel Osborne |
| Research Orthoptist |
| Southampton |
Reviewer 1

Comments to the Author:
1. The preliminary study [24] showed that BBV treatment engaged in high levels of compliance and led to substantial gains in visual function after a relatively short period of treatment. However, the study used on the measure of adherence, the treatment time, resulting in the conclusion is not accurate enough. In addition, adherence data is almost entirely subjective as it is reported by parents in the form of diaries or calendars. Subjective reports prefer to overestimate adherence rates comparing with objective measures. This paper directly quoted the previous results, which should be considered.

Thank you for this comment, and we agree measures of adherence/treatment-time are very important. The reviewer makes two points here: 1) diary-based adherence figures vs objectively measured usage, and 2) treatment time being insufficient as a measure of adherence.

With regard to the first point, our previous study (24) used an objective estimate of usage time recorded by the device, and did not use diaries to record usage. The proposed trial will use:
• (Patching arm) objective estimates of treatment time recorded by occlusion dose monitors
• (Dichoptic treatment arm) objective estimates of treatment time recorded by the device.
In short, we did not use diaries in the previous study, and will not use diaries in this pilot trial.

As for the second point - whether recorded use of treatment (treatment time) is a valid measure of adherence - observation of participants completing a prescribed activity is a standard measure of adherence in clinical trials. This is the approach we take here by measuring usage.

We have not changed the manuscript with respect to this point.

2. Poor adherence is the largest source of potential bias in the study. It should be considered that whether the true compliance of patients in two trials can affect the results. A recent systematic review and meta-analysis of randomized controlled trials (published in BMJ Open) also indicated a significant relationship between the effect size and the subjective adherence rate. But the study did not fully explain it, the relationship may be exaggerated.

The reviewer argues that compliance of patients with treatment could influence outcome. We agree. The reviewer’s comment that “the study did not fully explain it” seems to refer to the previous publication (reference 24), but it is true that (then and now) we are unable to entirely disentangle the effects of superior compliance of the efficacy of digital treatment (compared to traditional - patching/atropine – treatments) from other contributions to treatment-efficacy.

Establishing the contribution of compliance to outcomes is a general issue in clinical trials. Of note however, is what we would need to do for this NOT to be in issue, which would be to match compliance across interventions. While we endeavour to do this, a sizable body of research indicates that poor compliance is a huge and, many would argue, insurmountable issue with traditional treatments which fundamentally limits their effectiveness in the clinic. It is unreasonable then for us to be required to closely match compliance across treatment groups when (a) this is demonstrably not an achievable goal for traditional treatments in practice, and (b) the reviewer gives no indication as to
how we might do this. In a nutshell, we would argue that the superior adherence that digital
treatments enjoy is an intrinsic feature of these approaches that cannot be transferred to traditional
treatments.

What we are doing is carefully monitoring adherence using objective measures (see our response to
the last point) to go some way to estimating the impact of the (likely) differences in adherence across
treatments.

The present trial is a pilot study, and it does not seem appropriate to carry out sensitivity analyses to
explore the impact of adherence on effect size at this stage. However, we will bear this in mind when
designing the future phase 3 trial.

We have therefore not changed the manuscript on this point.

3. The overall strength of evidence for the comparison is insufficient, which implies that further
research is still required.

This manuscript describes the protocol for a pilot trial to evaluate the proposed methodology,
including the comparison of a dichoptic treatment with standard treatment. The pilot trial aims to
facilitate the design of a full trial. We believe this is what the reviewer means when stating that further
research is needed – we fully agree with this statement.
We have not changed the manuscript on this point.

Reviewer 2

R: I have identified one point of clarity only in the manuscript: Line 32-33 says that children,
parents/carers will be questioned about acceptability of the intervention. How will they be question
(for example, through semi-structured interviews with children with or without their parent/carer) and
how will data be interpreted and used?

Thank you – we have considered this point in depth when designing the study, and discussed it both
with parents and children in interviews and with the lay member of the Trial Steering Group.
Whilst we would have loved to conduct semi-structured interviews with children and
parents/guardians, the grant funding this work did not permit the inclusion of this level of qualitative
study and analysis with study participants and their parents/guardians. Together with the above
members of the public, we have therefore decided to condense work on acceptability into a series of
short questions for children and parents that will be asked at monitoring appointments (this has been
made clearer within our GRIPP2 reporting in the manuscript). We will use this pilot study to determine
the feasibility of this approach and to assess whether a more comprehensive qualitative research
component is required as part of a full trial.
We have changed the relevant section of the manuscript, and also section 4 of Table 1.

R: The control group is representative of current clinical guidelines, which recommend offering
children/carers the choice of atropine penalisation or occlusion therapy. It is still common practice to
favour occlusion therapy as a first line treatment, reserving atropine penalisation for children that have
struggled with adherence. Offering children/carers the choice of therapy, as is done in this study's
control group, may encourage better adherence to their chosen therapy. In the study, participants
randomised to the intervention group do not get a choice of intervention. This difference between
control and intervention groups could introduce a low risk of bias in the study, which could affect
adherence outcome measures.

Thank you for this thoughtful comment. Our intention is indeed to compare the new treatment,
dichoptic viewing, with the current standard of care. We foresee that offering choice in the control arm may require an increase in sample size in a future phase 3 trial, as the control group, as the reviewer correctly points out, effectively includes two subgroups. For the present trial, whose outcomes focus on feasibility and effect size of the new intervention, the bias created is not too relevant, but we plan to take it into account when designing the future trial. It might be more appropriate for a phase 3 trial to only use patching/occlusion as comparator.

We have not changed the manuscript on this point, as this only describes the methodology. We will include this thought in the manuscript reporting the outcomes of the pilot trial.

R: The trial is designed to assess safety of the intervention and collect data to inform the phase 3 trial, and preliminary data about efficacy. This design (RCT) with this control group (that follows current best practice) is most appropriate to address the research question. Problems outlined above could be explored when children and parents/carers are questioned about the acceptability of the intervention (ie, “if you’d had a choice of the intervention, patching or atropine, would you be more likely to adhere to your chosen intervention?”)

Thank you for this excellent suggestion. We have not changed the manuscript on this point, as this only describes the methodology. We will include this thought in the manuscript reporting the outcomes of the pilot trial.