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Hand Osteoarthritis: investigating Pain Effects in a randomised placebo-controlled feasibility study of estrogen-containing therapy (HOPE-e): report on the primary feasibility outcomes

Background: There is an unmet need for new treatments for hand osteoarthritis (OA). Symptomatic hand OA is more common in women and its incidence increases round the age of menopause. Pre-clinical, epidemiological and post hoc studies in Hormone Replacement Therapy (HRT) trials implicate estrogen deficiency as of likely importance in OA aetiopathogenesis. No clinical trials of HRT have been carried out in hand OA to date. The licensed HRT Duavive (conjugated estrogens + SERM bazedoxifene) was selected on its potential for efficacy and tolerability.

Objectives: We set out to determine the feasibility and acceptability of this form of HRT in post-menopausal women with hand OA, to generate proof of concept data and refine methods for a full study.

Methods: ISRCTN12196200. Females aged 40-65 yrs and 1-10yrs after final menstrual period with hand OA fulfilling ACR criteria and 2+ painful hand joints were recruited. Eligibility incorporated best practice for HRT prescription but did not require menopausal symptoms. Recruitment was at 3 sites in primary/secondary care, including directly from the community. Design was parallel group, double-blind 1:1 randomisation of Duavive or placebo, orally once daily for 24 weeks, then weaning for 4 weeks before stopping. Routes and rates of recruitment and the acceptability of randomisation, medication (compliance, retention), and proposed outcomes were measured, and the likelihood of unblinding. Measures related to hand pain and function, menopause symptoms and joint appearance. Patient and Public Involvement actively informed study rationale, design and materials. An end of study questionnaire and 2 participant focus groups provided further acceptability data.

Results: Recruitment was for 12/possible 18 months, interrupted due to COVID-19. Some study procedures were modified to allow reopening whilst collecting all primary outcomes. 434 enquiries/referrals were received, leading to 96 telephone pre-screens, of which 33 gave written informed consent and attended face to face screening. 28/33 screened (85%) were eligible and randomised. The highest number of randomisations was from study web presence (n=7) followed by SMS text from GP surgeries (n=5). Of 401 not proceeding, 250 (62%) were ineligible, most commonly due to contraindicated medication, followed by medical contraindication, whilst 55 (14%) decided not to take part, for reasons including not wanting to take a hormone-based drug or difficulty attending study visits. Retention and compliance were excellent. All 28 participants completed all study follow ups, with only 3 withdrawals from treatment due to AEs, 2 of these at week 24 and all in the placebo arm. There were no serious AEs. High levels of completeness of all study outcome measures were achieved. Bang's blinding index suggested that participants/investigators were well blinded. There were overall high/good levels of satisfaction with taking part in the study. 26/28

(92%) would recommend taking part to others with hand OA (irrespective of study arm). Many found the flexibility offered by a combination of remote and face to face visits (due to the pandemic) attractive. Additional insights from focus groups were to include hand stiffness as well as pain measures but to reduce the overall number of questions.

Conclusions: Despite COVID-19 and a reduced recruitment period, this study recruited sufficient numbers to assess feasibility outcomes. Randomisation of eligible people and retention rates were high. A mixture of remote and face to face visits due to COVID-19 probably improved recruitment and retention and was supported by participants, who were generally satisfied with the study design and medication. The study provided useful insight and improvements that would be incorporated into a future study. Overall, this feasibility study showed that with clear messaging on eligibility and a defined recruitment strategy, recruitment and retention to a study testing this treatment is possible.