# Transdermal Oestradiol for Androgen Suppression in Prostate Cancer: Long-term Cardiovascular Outcomes from the Randomised Prostate Adenocarcinoma Transcutaneous Hormone (PATCH) Trials Programme


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**Short title:** Transdermal oestradiol for androgen deprivation


**Key words:** transdermal oestradiol, androgen deprivation, prostate cancer, cardiovascular outcomes

**Abstract**

**Background:**

Androgen suppression is a central component of prostate cancer management but causes significant long-term toxicity. Oestrogen produces castrate levels of testosterone in men and mitigates the oestrogen-depleting effects (osteoporosis, adverse metabolic profiles, hot flushes and impaired quality of life) of Luteinising Hormone Releasing Hormone agonists (LHRHa). Transdermal administration of oestradiol (tE2) circumvents first-pass hepatic metabolism and therefore should also avoid the cardiovascular (CV) toxicity seen with oral oestrogen.

**Methods:**

Men with locally advanced or metastatic prostate cancer were randomly allocated (1:2 and from 2011 1:1), within an adaptive phase II/III multi-centre trial to LHRHa according to local practice or tE2 patches (four 100 μg patches/24hrs changed twice weekly reducing to 3 patches twice weekly if castrate at 4 weeks.) CV events: heart failure; acute coronary syndrome; thromboembolic stroke and other thromboembolic events (confirmed using pre-defined criteria/source data), and CV risk factors after allocation to LHRHa and tE2 were compared.

**Findings:**

Between 2007-2019, 1,694 men (790 LHRHa, 904 tE2) were randomly allocated. Castration rates (testosterone $\leq$ 1.7nmol/L) at 1 and 3 months: LHRHa 65% and 93%, tE2 83% and 93%. 157 events from 145 men met pre-defined CV criteria with an additional 10 sudden deaths with no post-mortem. Twenty six (1.5%) of 1694 patients had fatal CV events, LHRHa 15/790

(1.9%) tE2 11/904 (1.2%). On intention-to-treat analysis, the CV event hazard ratio (HR) was 1.11 (95% confidence interval (CI) 0.80 to 1.53) including the no post-mortem deaths and 1.20 (CI 0.86 to1.68) for the confirmed group only. 34% of tE2 CV events occurred more than three months after tE2 was stopped/changed to LHRHa. At 12 months mean percentage change (95% CI) LHRHa v tE2: glucose +5.9% (3.7% to 8.1%) v -1.1% (-2.7% to 0.6%) p<0.0001, cholesterol +3.1% (1.4% to 4.8%) v -5.7% (-7.0%- to 4.5%) p<0.0001. Gynaecomastia (all grades) LHRHa 38% v tE2 86% p<0.001, hot flushes (all grades) LHRHa 86% v 35% tE2.

**Interpretation:** Long-term data show no evidence of a difference in CV mortality or morbidity and improved metabolic profiles comparing tE2 to LHRHa. Oestrogens administered transdermally should be reconsidered for androgen suppression in the management of prostate cancer.

## Research in Context

### Evidence before this Study

Oestrogen is not routinely used to produce androgen suppression in men with prostate cancer because previous studies using oral oestrogen (stilboestrol) reported increased rates of cardiovascular embolic events. Administering oestradiol parenterally (e.g. through a transdermal patch (tE2)) avoids first-pass hepatic metabolism and should avoid the cardiovascular toxicity.

### Added Value

This large (n=1694), long-term, randomised study shows no evidence of a difference in cardiovascular mortality or morbidity between men receiving tE2 compared to Luteinising Hormone Releasing Hormone agonists (LHRHa) for the management of locally advanced and metastatic prostate cancer.

### Implications

Oestrogens in men are derived from the aromatisation of androgens therefore most androgen suppression strategies used to treat prostate cancer, such as LHRHa, cause a dual set of toxicities related to both androgen and oestrogen depletion. Using tE2 to produce castrate levels of testosterone in men with prostate cancer mitigates the side effects of LHRHa caused by oestrogen depletion (e.g. hot flushes, osteoporosis and adverse metabolic profiles), as well as avoiding the cardiovascular toxicity seen with oral oestrogen. Oestrogens administered transdermally should be considered for androgen suppression in the management of prostate cancer.

## Introduction

Prostate cancer therapy has evolved significantly over the last 20 years resulting in improved outcomes, but as a result some men receive androgen depleting therapies for many years, if not decades (1). Androgen suppression is the cornerstone of management in metastatic disease and is also utilised in combination with radiotherapy, either adjuvantly or neo-adjuvantly, in the locally advanced setting. Currently, the most commonly employed method of achieving androgen suppression is Luteinising Hormone Releasing Hormone agonists (LHRHa). Toxicities from LHRHa include erectile dysfunction and loss of muscle mass as a result of testosterone suppression (2-4). Additionally, most androgen depleting strategies also lower oestrogen levels (as oestrogens in men are derived from the aromatization of testosterone), thought to be the primary driver of osteoporosis, osteoporotic fractures, hot flushes and adverse metabolic effects such as hyperlipidaemia and increased glucose levels (5-8).

Exogenous oestrogen, through a negative feedback loop on the hypothalamus and pituitary (9, 10), is a potential strategy for achieving castrate levels of testosterone and avoids the physiological effects of oestrogen depletion. This approach was first investigated using oral oestrogen (stilboestrol) but it was found to cause increased thromboembolic cardiovascular (CV) disease (11), and as a result the use of oestrogen in the management of prostate cancer was largely discontinued. However, as the embolic events seen with oral oestrogen are attributed to first-pass hepatic metabolism and associated activation of coagulation pathways they should be avoided by transdermal administration of oestrogen (tE2). In women the dose of oral oestrogen required to have the same therapeutic effect as transdermal administration

is approximately ten-fold higher highlighting the significant effect of intestinal and hepatic metabolism on the pharmacokinetics of exogenous oestrogen. Levels of several proteins involved in the coagulation pathway are altered by oral oestrogen including anti-thrombin III and coagulation factor VII (12).

PATCH (Prostate Adenocarcinoma TransCutaneous Hormones, MRC PR09 (ISRCTN:70406718)) is an adaptive randomised trials programme, designed to evaluate the safety and efficacy of tE2 compared to LHRHa for the treatment of advanced prostate cancer using a seamless phased approach (Supplementary Appendix Figure 1). The first stage, a phase IIa evaluation (n=254), previously published, assessed early toxicity and feasibility (13). Recruitment was then extended to a phase IIb evaluation to provide early data on efficacy. Following this recruitment continued within the PATCH trial network sites and was extended into the STAMPEDE (Systemic Therapy in Advancing or Metastatic Prostate cancer: Evaluation of Drug Efficacy ISRCTN:78818544) trial network to widen experience with the transdermal patches in the treatment of advanced prostate cancer (14). The aim of the analysis presented is to compare long-term CV outcomes between those randomly allocated to receive LHRHa and tE2.

**Study Design and Participants**

PATCH is a seamless phase II/III randomised, multi-centre trials programme. The stages of the development programme with number of men recruited are shown in the consort diagram (**Figure 1)**. The co-primary outcome measure for the phase III design is overall survival (OS) and progression-free survival (PFS). The original recruitment target was 2150 but due to a lower than anticipated event rate this has been extended to 2550. The non-inferiority margin

hazard ratio (HR) for OS is 1.16 (with tE2 assumed to be associated with an absolute improvement in OS of 1% at 5 years compared to LHRHa) with 88% power and a one-sided significance level of 0.03. The PFS analysis was planned with 88% power and one-sided significance level of 0.03 and a non-inferiority margin HR of 1.16.

This analysis was pre-defined to include all men recruited through the PATCH trial sites as these centres had agreed to provide additional supporting data to verify the CV events at the end of the original phase III recruitment. This included the phase IIa, (n=203), phase IIb (n=482) and the original phase III design (overall target accrual for PATCH and STAMPEDE sites 2150) (n=1009), in total 1694 men. The first 51 patients randomised in the PATCH trial were excluded from this analysis as they received an initial dosing schedule of the patches that produced lower than anticipated castration rates (15). Throughout the study phases men from participating UK centres were eligible if they had locally advanced (M0) or metastatic (M1) prostate cancer (newly diagnosed or relapsing after radical treatment) and were scheduled to start long-term ($\geq$ 3 years) continuous hormonal therapy.

Patients with a previous history of major CV disease were excluded. These exclusions were defined as: 1) cerebral ischaemia (e.g. stroke or transient ischaemic attack) within 2 years of randomisation; 2) history of deep vein thrombosis or pulmonary embolus confirmed radiologically or a known thrombophilic disorder; 3) history of myocardial infarction/acute coronary syndrome within the last 6 months or greater than 6 months with evidence of q-wave anterior infarct on electrocardiogram (ECG); 4) unstable angina within the last year; 5) angina that occurs on walking 100 metres on the level or after climbing one flight of stairs at a normal pace and in normal condition, or angina that causes marked limitation of ordinary physical activity or occurs at rest; 6) New York Heart Association grade III/IV heart failure; and

7) pulmonary oedema on CXR. Patients were also required to have evidence of a controlled blood pressure prior to randomisation (systolic BP <160 and diastolic <100 mmHg).

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**Randomisation and Masking**

Participants were randomly allocated to receive LHRHa or tE2 without blinding in 1:2 ratio before February 2011, and thereafter 1:1. The 1:2 ratio was used in the first phase of the evaluation to increase experience of using the patches. Randomisation was performed using a computer-based minimisation algorithm with a random element (80%) and stratification factors: disease stage; age (<70; and ≥70 years); smoking status; family history of cardiac disease; which LHRHa agent to be used; prostate specific antigen (PSA) level at baseline (<50, ≥50 to <500, ≥500 ng/mL); study centre and from 2013, intention to give radical radiotherapy; and from 2015 intention to give upfront docetaxel.

**Procedures**

The patches (tE2) were administered as four oestradiol 100 microgram/24hr patches (FemSeven or Progynova TS), self-administered and changed twice weekly during the first 4 weeks. Provided the testosterone concentration reached castrate levels (≤1.7 nmol/L) at 4 weeks, the dose was reduced to three patches changed twice weekly. Serum oestradiol and testosterone levels were monitored every 12 weeks up to six months and then every 6 months

during follow up to ensure appropriate testosterone suppression was maintained. LHRHa was administered intramuscularly or subcutaneously as per local practice. Prostate cancer radiotherapy was mandated (since January 2014) for all locally advanced (N0, M0) patients unless contraindicated, and the use of upfront docetaxel was permitted for all patients (since October 2015) reflecting evolving standard of care.

If there was evidence of cancer progression, subsequent therapy was at the discretion of the treating clinician. Men could remain on their allocated first-line hormonal therapy with the addition of other therapies (e.g. anti-androgen, corticosteroids, cytotoxic chemotherapy). A switch to LHRHa for patients progressing on tE2 was permitted. Until May 2019 the protocol mandated treatment with tE2 be discontinued if the patient experienced one of the pre-defined CV outcome events. Subsequently clinician discretion has been allowed when such an event occurred.

CV outcome events were defined as follows: 1) Heart failure: new symptoms or clinical signs consistent with a diagnosis of new or decompensated cardiac failure with supporting evidence from chest X-ray, echocardiogram or rise in serum brain natriuretic peptide (BNP). 2) Acute coronary syndrome (including unstable angina, ST-elevation and non-ST-elevation myocardial infarction (STEMI and NSTEMI): new onset cardiac chest pain, confirmed as ischaemic in origin by ECG and/or troponin rise +/- coronary angiography. 3) Thromboembolic stroke: new neurological symptoms and clinical signs with confirmatory evidence from brain CT or MRI. For transient ischaemic attacks, corroborative data from carotid duplex scanning was sought and evidence of pre-existing or new, persistent or paroxysmal, atrial fibrillation. 4) Other arterial embolic events: detected by new clinical symptoms and supporting radiological evidence. 5) Venous thromboembolism: thromboses confirmed radiologically

(Doppler ultrasound scan/cross sectional imaging) or pulmonary embolism confirmed by means of CT pulmonary angiogram (CTPA), ventilation/perfusion scans or angiography. 6) Death attributed to any of the above (where the event was not documented according to the definitions provided above). Cardiac events were reported by investigators on follow-up forms (at three and six months and six-monthly thereafter) or as notable events, or identified from reports of serious adverse events and routinely collected toxicity data. All potential events and requested supporting evidence (which included original investigation reports, clinic and hospital discharge letters) were reviewed not blind to treatment allocation by RL, DG or AM as they occurred and prior to this analysis reviewed again for consistency. Sudden/unexpected deaths were attributed to a CV category if a confirmatory post mortem report was available. Sudden/unexplained deaths where no post-mortem report were available were classified as other significant events recognising that the most likely causes would include myocardial infarction/arrhythmia, pulmonary embolism or a cerebrovascular event.

**Statistical analyses**

No formal sample size calculation was specified for this analysis but the nature and timing was pre-specified in the protocol and scheduled for the end of the original phase III recruitment period. A formal request was made to the Independent Data Monitoring Committee (IDMC) by the Trial Management Group to permit publication of this analysis without prior knowledge of the results. The aim was to potentially provide further supporting evidence for ongoing research and information for patients and their physicians. The primary outcome measure was CV morbidity and mortality. The proportion of patients with a confirmed CV event (as defined above) was summarised by original treatment allocation,

stratified by randomisation period before and after the change in randomisation allocation ratio (since those randomised under 1:2 allocation ratio had longer duration of follow-up). Kaplan-Meier methods were used to describe time to first CV event by treatment group, based on an intention-to-treat approach. Follow-up of each patient was considered up to the date of first CV event, or date of death or last follow-up for those without an event. The treatment effect on CV risk was estimated using Cox proportional-hazards models, adjusted for pre-selected stratification factors (age, smoking status, and family history of cardiac disease) and stratified by randomisation period (1:2 randomisation and 1:1 randomisation). Heterogeneity of the treatment effect over the two randomisation periods (2:1 and 1:1) was checked by assessing the interaction between randomisation period and treatment, with the overall treatment effect presented if no evidence interaction was found. To assess whether cardiovascular risk varied with cumulative exposure time on original allocated treatment, follow-up in a given patient was divided according to time on treatment from randomisation (<12, 12-23.99, 24-35.99, ≥36 months) and accounting for when treatment stopped, which was analysed as a time-varying covariate.

Castration rates were assessed at four weeks, then three, six and twelve months, with patients being deemed castrate if their testosterone levels were ≤1.7nmol/L. Patients were included if they were still on their allocated treatment without additional systemic anticancer therapy, and for tE2 patients with an oestradiol level of at least 250 pmol/L. Data were included if tests were conducted at four weeks ± two weeks, and at three, six, and 12 months ± six weeks. The percentage of castrate patients in each treatment arm are presented, but were not formally compared.

Toxicities experienced whilst patients were receiving their original allocated treatment are summarised overall and separately for each randomisation cohort (1:2 and 1:1). The percentage of patients experiencing any toxicity, and toxicity of CTCAEv3.0 grade three or worse, are presented. The percentage of patients experiencing any toxicity on each treatment arm are compared using a logistic regression model, with patients recruited in each randomisation cohort being combined using a fixed effects meta-analysis. Toxicities were assessed at each follow-up visit, and data from a particular visit excluded from summaries if the patient had stopped their allocated treatment prior to that visit. This is to ensure that only toxicities definitely attributed to their original allocated treatment are included.

Changes in cardiovascular risk factors (fasting blood glucose, fasting total cholesterol, and high-density lipoprotein (HDL) cholesterol concentrations, weight, and blood pressure) at 6 and 12 months were compared between treatment groups using analysis of covariance (ANCOVA) models, adjusting for baseline values and study cohorts. These analyses were based on patients still on original allocated treatment without additional systemic anticancer therapy who had a fasting blood sample at the relevant follow-up assessments. Men on tE2 with oestradiol levels <250 pmol/L were considered not to be adhering to the patch regimen and were therefore excluded. Statistical analyses were performed using Stata version 15 (Stata Corporation, College Station, TX, USA).

**RESULTS**

Between August 2007 and August 2019, a total of 1694 patients were recruited through the PATCH trial network (52 sites) in the UK. This includes 203 patients in the IIa phase (August 2007 – April 2010), 482 patients in the IIb (July 2010 – October 2013) and 1009 patients in

phase III (Feb 2014 – August 2019). In total, 790 were allocated to LHRHa and 904 to tE2, the initial randomization ratio was 1:2 and 1:1 from 2011 (**Figure 1**). The baseline characteristics were similar between treatment groups (**Table 1**). Median age of the overall cohort was 73 years (interquartile range [IQR] 68–78) with a median (IQR) body mass index (BMI) of 27.1 (24.6-30.0). WHO performance status 0, 1 and 2 respectively at randomisation was 1197/1694 (71%), 437/1694 (26%) and 60/1694 (4%). 1000/1694 (59%) were current or previous smokers, 375/1694 (22%) long-term regular aspirin users and 493/1676 (29%) reported heart disease in a first degree relative. From a prostate cancer perspective, 670/1694 (40%) had metastatic disease and median PSA level at randomisation was 35 (14.9–96.8) ng/ml. For 426/458 (93%) of M0 N0 patients radical radiotherapy to the prostate was planned since this was included in the protocol in 2013. Upfront docetaxel was planned in 171/319 (54%) M1 patients overall since 2015 (<70 yrs 84/110 (76%) and $\geq$ 70 yrs 87/209 (42%)). Overall median follow-up was 3.9 years (IQR 2.4-7.0 years), with 1657/1694 (98%) having at least three months' follow-up data.

Only 1 patient (in the tE2 group) did not commence allocated treatment (**Figure 1**). At four weeks post randomisation, for men still receiving their allocated treatment without additional anti-cancer therapy, with oestradiol levels of at least 250 pmol/L in the tE2 group and a blood test within the analysis window, the proportion with testosterone concentrations ≤1.7 nmol/L was 65% (415/640) LHRHa, and 83% (661/793) tE2. By three months the rates were very similar (643/693 (93%) LHRH, 721/776 (93%) tE2) and remained so over time (**Figure 2 and Appendix Table S1**). There was no evidence of an early testosterone surge with tE2. The median oestradiol level at four weeks post randomisation was 70 (5th–95th centile range 18-124) pmol/L in LHRHa group and 845 (376-2280) pmol/L in tE2 group (**Appendix Table S2**).

A total of 311 CV events were reviewed, of which 157 experienced by 145 patients fulfilled study endpoint definitions. A further ten events were classed as “other significant events”, these were sudden unexplained deaths with no post-mortem available to confirm the endpoint definition. They are presented with the main analysis as the most likely clinical causes are CV e.g. myocardial infarction/arrhythmia and thromboembolic events (pulmonary embolism). Of the 144 events deemed not to meet the primary outcome definitions these included: non-cardiac chest pain, stable angina or investigation for a silent myocardial infarction that was not confirmed (n=38); symptoms that might indicate congestive cardiac failure or venous thromboembolism, such as dyspnoea or leg swelling, but investigations did not confirm the diagnosis or symptoms were attributed to another cause (n=27); other cardiac events, including atrial fibrillation, hypotension, hypertension, collapse, valve disease and non-embolic peripheral vascular disease (n=54); possible intracerebral bleed, acute TIA or stroke that was not confirmed on imaging or associated history (n=13); death where on clinical review there was sufficient evidence for a non-CV cause e.g. progression of prostate cancer (n=10); other medical events (n=2).

Patients experiencing a CV event were more likely than those without an event to be current or former smokers (68% vs 58%), and were slightly older (median 75 vs 73 years). No other baseline factors were associated with having a CV event. The nature of the event is shown in **Table 2** with no consistent differences between the type of event across the 2 groups. Twenty six (1.5%) of 1694 patients had fatal CV events, LHRHa 15/790 (1.9%) versus tE2 11/904 (1.2%). The proportion of patients with at least one CV endpoint/sudden death was similar between treatment groups in the 1:2 cohort LHRHa 17.1% (14/82) versus tE2 19.8% (32/162)

306 and in the 1:1 cohort LHRHa 7.1% (50/708) and tE2 7.7% (57/742). The higher rate in the 1:2
307 cohort is accounted for by the longer follow-up. At the time of this intention-to-treat analysis
308 417 of those allocated to tE2 had changed therapy to LHRHa.
309
310 The overall HR for time to first CV endpoint in the intention to treat analysis, comparing tE2
311 versus LHRHa group was 1.11 (95% confidence interval (CI) 0.80 to 1.53), p=0.539 including
312 the patients with no post-mortem. This HR translates from an event rate of 7.2% at 3 years in
313 the LHRHa group (Table 3) to an estimate of the absolute difference at 3 years of 0.8% with
314 an upper (95%) bound to the absolute difference estimate of 3.6%. For the confirmed group
315 only the HR was1.20 (95% CI 0.86 to1.68, P = 0.283 **Figure 3**). The effect was similar in both
316 cohorts: 1:2 HR 1.10 (95% CI 0.59 to 2.06) including the patients with no post-mortem and HR
317 1.35 (95% CI 0.68 to 2.68) in the confirmed group and in the 1:1 cohort HR 1.11 (95% CI 0.76
318 to 1.62) including the patients with no post-mortem and HR 1.16 (95% CI 0.79 to 1.71) in the
319 confirmed group. Within the tE2 group, 30 of the 89 (34%) events occurred more than 3
320 months after the patient stopped tE2 treatment with 27/89 (30%) occurring more than 6
321 months after tE2 was stopped (Appendix **Table S3**).
322
323 The rate of a CV events over time remained constant (Appendix **Table S3**). The proportion of
324 patients experiencing a CV endpoint by 1 year was 2.8% (95% CI 1.8 to 4.2%) for LHRHa and
325 2.8% (1.9 to 4.2%) tE2 group; corresponding figures for 2 years were 5.3% (3.8 to7.3%) and
326 6.4% (4.8 to 8.4%), respectively. A potential cumulative effect was assessed by length of time
327 on therapy (Appendix **Table S3**) and again the effect remained constant for both drugs over
328 time. Inclusion of the treatment arm as a time-varying covariate also provided no evidence
329 that the treatment effect differed with increased time on treatment. By including oestradiol

level as a time varying covariate, there was no evidence that higher levels of oestradiol with patches was associated with an increased risk of a CV event. Similarly, among the 186 metastatic patients (90 LHRHa, 96 tE2) planned to receive upfront docetaxel treatment as part of first-line treatment, 7.0% LHRHa and 7.9% tE2 patients experienced a CV event by two years, compared to 7.8% LHRHa and 6.1% tE2 in metastatic patients not receiving docetaxel suggesting no evidence of increased CV toxicity with the patches when administered with docetaxel (**Appendix Table S4**).

At 6 and 12 months, changes in fasting glucose and total cholesterol concentrations differed significantly between treatment groups among men still on their original allocated treatment, with levels increasing from baseline in LHRHa group while decreasing in tE2 group (**Table 3**). At 12 months, mean percentage change in fasting glucose concentration was +5.9% (95%CI 3.7% to 8.1%) in LHRHa group and -1.1% (-2.7% to 0.6%, P<0.0001) in tE2 group; corresponding change in total fasting cholesterol concentration was LHRHa +3.1% (1.4% to 4.8%) versus tE2 -5.7% (-7.0% to -4.5%, P<0.0001). Both HDL cholesterol concentrations and weight increased by similar amounts in the two groups at 6 months and 12 months. Systolic and diastolic blood pressure increased between baseline and 6 months with LHRHa and decreased with tE2, though the changes were relatively small (relevant data not collected at 12 months).

Other adverse events experienced whilst patients were known to be receiving their allocated treatment were as expected and predominantly grade 1-2 (see **Table 4**). Gynaecomastia was significantly more common in tE2 patients (LHRHa 279/730 38% v tE2 690/807 86%, p<0.0001) and hot flushes more common in LHRHa (LHRHa 628/730 86% v tE2 280/807 35%,

p<0.0001). Sexual and reproductive toxicities were similar between the two groups as expected.

**Discussion**

For over 40 years, since the publication of the Veterans Administration Cooperative Urological Research Group (VACURG) studies, (11) oestrogens have been side-lined as a treatment for prostate cancer because of concerns about an increased risk of thromboembolic CV complications. Our data confirm that the administration of oestrogen transdermally via a patch, rather than orally as in the previous studies, abrogates this risk. Over a prolonged follow-up period there was no evidence of excess CV toxicity observed with tE2 compared to LHRHa, the current standard and widely used approach to achieving androgen suppression. These data are consistent with the hypothesis underpinning the PATCH programme: (i) with previous prostate cancer studies where oestrogens were administered intramuscularly (16); and (ii) with the data from hormone replacement studies in both cis-gender and transgender populations comparing oral and transdermal administration (17-19).

tE2 has three key pharmacological characteristics that make it particularly attractive as a method for producing androgen suppression in men with prostate cancer. Firstly, it avoids the oestrogen-depleting effects (loss of bone mineral density, adverse metabolic profiles and hot flushes) seen with other androgen-depleting strategies which cause significant long-term morbidity, secondly, transdermal administration avoids the embolic CV toxicity seen with oral oestrogen and thirdly the absence of an early testosterone flare negates the need for co-administration of anti-androgens that is usually required with LHRHa administration.

We have previously shown a significant difference in bone mineral density in the first 2 years of therapy with tE2 compared with LHRHa. For men who remained on allocated treatment, lumbar spine bone mineral density mean percentage change was −3.0% for LHRHa and +7.9% for tE2 $p < 0.001$ (20). The loss of bone mineral density with LHRHa is attributed to a reduction in circulating oestrogens. Additionally, we have previously published self-reported quality of life (QoL) data from 727 men within the PATCH programme. Overall higher global QoL scores were reported with tE2 compared to LHRHa (mean difference +4.2, 95% CI 1.2 to 7.1; P = 0.006), attributed to a reduction in hot flushes and fatigue (21). Our current data confirm the reduction in hot flushes with tE2 compared to LHRHa and also as anticipated the increase in gynaecomastia

Our current data demonstrate clear differences in fasting glucose and lipid levels over time between the two treatment approaches. The rise in fasting glucose levels/insulin resistance on LHRHa is consistent with the established literature (22) and may contribute to the increased CV mortality associated with LHRHa detected in epidemiological studies. The improvement in metabolic parameters with tE2 is consistent with previous studies: a) of post-menopausal women where it was shown that oestrogen improves lipid profiles (23) and b) in a previous study in men with prostate cancer where tE2 was administered with LHRHa to alleviate side effects (24). To date the improvement in metabolic parameters we observed with tE2 compared to LHRHa has not translated into a clinical benefit in terms of CV outcomes but further follow-up is required since the expected time from for such benefits would be of the order of 5-10 years. In comparison to LHRHa the only increased toxicity seen with tE2 was gynaecomastia (**Table 4**). Overall skin toxicity was reported at similar rates between the two groups, although this is likely to reflect different aetiologies, discomfort or irritation around

the injection site for LHRHa patients and erythema/pruritus and issues with adherence more common for the men receiving tE2.

Among the strengths of our study is the randomised nature, the detailed review of all potential CV events and the length of follow-up. In epidemiological studies LHRHa have been associated with an increased risk of developing the metabolic syndrome and CV disease (25, 26), although data from randomised trials primarily designed to evaluate oncological outcomes has been less consistent (27, 28). Endpoint review is common practice in CV trials as the symptoms associated with CV disease may be similar to, or subsequently attributed to, another disease process. We initially employed a broad and conservative approach for events to be included in our detailed CV review based on symptoms/initial reports and used the additional clinical information received to confirm or refute our defined CV event with only 167/311 (53%) subsequently meeting our criteria. The initial inclusive approach minimised the risk of under reporting CV events but provides confidence of accurate categorisation. In addition the intention-to-treat analysis (where a substantial proportion of tE2 patients had already changed to LHRHa) provides data on the CV effect of any exposure to tE2 over a prolonged period even when the medication has been stopped. The rates of CV disease that we observed are consistent with our original estimates based on previous literature (29).

A limitation of our study was that the review of CV events was not blind to treatment allocation but it was supported by additional/confirmatory source data from the sites. Agreement on cases was reached by consensus of the clinical reviewers. A further limitation may be perceived to be the length of follow up (median (IQR) 3.9 (2.4-7.0) years). However, in the original VACURG studies the increased CV toxicity became apparent within the first year

and the rate remained constant over time. There has been no evidence of an increased rate of CV events on the patches compared to LHRHa over time and with the planned extension of recruitment described below there will be ongoing follow-up.

The PATCH project has been an evolving programme over the course of 15 years. During that time outcomes and treatment paradigms for M0 and M1 patients have diverged with radiotherapy to the prostate becoming standard of care for M0 patients and upfront docetaxel (and more recently abiraterone and other androgen-receptor targeting agents such as enzalutamide) entering clinical practice for more advanced disease (1). Most clinical trials now consider M0 and M1 patients as two separate entities and for this reason we aim to continue recruiting to the PATCH programme to provide 2 separate cohorts for M0 and M1 patients with conventional statistical power to assess prostate cancer efficacy based on a non-inferiority design. This will include patients recruited from both the PATCH and STAMPEDE networks and it is anticipated that the efficacy results for the M0 cohort will be available in 2023 and those for the M1 cohort in 2024. These results on efficacy will be required for a full assessment of this therapeutic approach and its role in the treatment of both locally advanced and metastatic prostate cancer. In parallel, we have assessed the patches alongside other evolving standards of care (1) including radiotherapy and docetaxel as presented in this paper with ongoing work to assess the patches in combination with androgen receptor targeted agents such as abiraterone and enzalutamide. During the course of this development programme, all the accumulating data including efficacy data has been monitored by an Independent Data Monitoring Committee who have supported the continued recruitment at each phase.

To date this has been a re-purposing project utilising oestradiol patches manufactured for the relief of menopausal symptoms in women. A practical limitation of this approach is that the current patches need to be changed twice weekly, whilst this is a simple procedure, it contrasts with a single intramuscular injection given monthly or 3 monthly for LHRHa. In addition in a randomised trial comparing the LHRH antagonist relugolix with leuprolide castration rates were higher and fewer serious adverse cardiovascular events were reported with relugolix (30). The reason for the reduction in toxicity is unknown though it has been seen in other trials of LHRH antagonists (31).

Given the castration rate data, in particular that castration is achieved more quickly with tE2 compared to LHRHa and the extensive toxicity data, there is arguably already sufficient information to support the use of tE2 for short-term use (< 6 months) for example alongside radiotherapy in men with localised intermediate risk prostate cancer. Equally for patients who are significantly affected by the side effects of LHRHa (or for those where the cost of standard therapy is prohibitive) this data provides the basis for a more detailed and personalised discussion around the different approaches to androgen deprivation.

In summary in terms of toxicity, there is no evidence of a difference in CV events between tE2 and LHRHa. While treatment with tE2 results in higher rates of gynaecomastia importantly there are fewer hot flushes, increased bone health, improved metabolic profiles and higher overall QL scores.

## Author Contribution

Ruth E Langley, Mahesh Parmar (and Paul Abel) developed the trial and oversaw study conduct. The team at the coordinating trials unit was led by Ruth Langley with the support of Mahesh Parmar and Duncan Gilbert. Statistical analyses were performed by Trinh Duong and Matthew Nankivell who had direct access to the data and double programmed the primary outcome analysis. Silvia Forcat and Melanie Weiss were responsible for trial co-ordination.

Abdulla Al-Hasso, Noel Clarke, Roger Kockelbergh, Howard Kynaston, Stephen Mangar, Archie Macnair and Stuart D Rosen, were clinical members of the Trial Management Group with Stuart D Rosen providing cardiovascular expertise. Ruth Langley, Duncan Gilbert and Archie Macnair reviewed all cardiovascular events for consistency.

Subramanian Kanaga Sundaram/ Marc Laniado/ Sanjay Dixit/ Sanjeev Madaan/ Caroline Manetta/ Alvan Pope/ Christopher Scrase/ Stephen Mckay/ Iqtedar Muazzam/ Gerald Collins/ Jane Worlding/ Simon Williams/ Edgar Paez/ Angus Robinson/ Jonathan McFarlane recruited and treated patients.

John Marshall and John Deighan were patient and public involvement representatives for the study.

All authors reviewed and approved the final version.

## Declaration of interests

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: no support from any organisation for the submitted work, however, Dr. Langley reports grants from Cancer Research UK , grants from UK Medical Research Council, during the conduct of the study; personal fees from Aspirin Foundation, outside the submitted work; Dr. Muazzam reports in the last 3 years that he had received honoraria for advisory boards and chairing/speaking at educational/pharma meetings with the following companies: Ipsen, EUSA Pharma, Novartis and Pzfizer.

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## Data sharing statement

Data will be shared according to the Medical Research Council Clinical Trials Unit controlled access approach, based on the following principles: no data should be released that would compromise an ongoing trial or study; there must be a strong scientific or other legitimate rationale for the data to be used for the requested purpose; investigators who have invested time and effort into developing a trial or study should have a period of exclusivity in which to pursue their aims with the data, before key trial data are made available to other researchers; the resources required to process requests should not be underestimated, particularly successful requests that lead to preparing data for release, thus adequate resources must be available to comply in a timely manner or at all, and the scientific aims of the study must justify the use of such resources; and data exchange complies with Information Governance and Data Security Policies in all the relevant countries. Researchers wishing to access data from the PATCH study should contact mrcctu.pr09@ucl.ac.uk in the first instance.

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640 **Table 1: Patient characteristics at randomisation**
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| | Treatment allocated | | | | | |
|---|---|---|---|---|---|---|
| | LHRHa (N=790) | | Patches (N=904) | | Total (N=1694) | |
| | No. | % | No. | % | No. | % |
| **Age at randomisation (years)** | | | | | | |
| Median (IQR) | 73 (67-78) | | 73 (68-78) | | 73 (68-78) | |
| Min-Max | 52-96 | | 49-91 | | 49-96 | |
| | | | | | | |
| **Inclusion criteria** | | | | | | |
| Newly diagnosed locally advanced prostate cancer | 358 | 45% | 414 | 46% | 772 | 46% |
| Newly diagnosed node positive or metastatic prostate cancer | 312 | 39% | 352 | 39% | 664 | 39% |
| Newly diagnosed prostate cancer with bone mets & PSA ≥50ng/ml, without histology | 74 | 9% | 84 | 9% | 158 | 9% |
| Relapsing with PSA≥4ng/ml | 7 | 1% | 15 | 2% | 22 | 1% |
| Relapsing with PSA≥20ng/ml | 18 | 2% | 20 | 2% | 38 | 2% |
| Relapsing with documented metastases and PSA≥4ng/ml | 21 | 3% | 19 | 2% | 40 | 2% |
| | | | | | | |
| **Tumour status** | | | | | | |
| T0 | 5 | 1% | 3 | <1% | 8 | <1% |
| T1 | 5 | 1% | 4 | <1% | 9 | 1% |
| T2 | 30 | 4% | 43 | 5% | 73 | 4% |
| T3 | 567 | 72% | 660 | 73% | 1,227 | 72% |
| T4 | 124 | 16% | 128 | 14% | 252 | 15% |
| TX | 59 | 7% | 66 | 7% | 125 | 7% |
| | | | | | | |
| **Nodal status** | | | | | | |
| N0 | 396 | 50% | 416 | 46% | 812 | 48% |

| | Treatment allocated | | | | | |
|---|---|---|---|---|---|---|
| | LHRHa (N=790) | | Patches (N=904) | | Total (N=1694) | |
| | No. | % | No. | % | No. | % |
| N+ | 233 | 29% | 251 | 28% | 484 | 29% |
| NX | 161 | 20% | 237 | 26% | 398 | 23% |
| | | | | | | |
| **Does patient have metastases?** | | | | | | |
| No | 469 | 59% | 555 | 61% | 1,024 | 60% |
| Yes | 321 | 41% | 349 | 39% | 670 | 40% |
| | | | | | | |
| **Does M1 patient have bone metastases?** | | | | | | |
| No | 38 | 12% | 40 | 11% | 78 | 12% |
| Yes | 283 | 88% | 309 | 89% | 592 | 88% |
| | | | | | | |
| **PSA at randomisation (ng/ml)** | | | | | | |
| Median (IQR) | 35.0 (14.8-95.2) | | 34.9 (14.9-97.1) | | 35.0 (14.9-96.8) | |
| Min-Max | 0.7-6247.0 | | 0.6-6710.0 | | 0.6-6710.0 | |
| *Missing data* | 12 | 2% | 8 | 1% | 20 | 1% |
| | | | | | | |
| **Gleason sum score at diagnosis**[1] | | | | | | |
| 4-6 | 46 | 6% | 54 | 6% | 102 | 6% |
| 7 | 227 | 29% | 280 | 31% | 507 | 30% |
| 8-10 | 443 | 56% | 476 | 53% | 919 | 54% |
| Newly diagnosed, without histology | 54 | 7% | 74 | 8% | 128 | 8% |
| *Missing/not yet received* | 20 | 3% | 20 | 2% | 40 | 2% |
| | | | | | | |
| | | | | | | |
| **WHO Performance status** | | | | | | |

| | Treatment allocated | | | | | |
|---|---|---|---|---|---|---|
| | LHRHa (N=790) | | Patches (N=904) | | Total (N=1694) | |
| | No. | % | No. | % | No. | % |
| Normal activity without restriction | 555 | 70% | 642 | 71% | 1,197 | 71% |
| Strenuous activity restricted, can do light work | 208 | 26% | 229 | 25% | 437 | 26% |
| Up and about >50% of waking hours, capable of self-care | 27 | 3% | 33 | 4% | 60 | 4% |
| | | | | | | |
| **Baseline BMI**[2] | | | | | | |
| Median (IQR) | 27.0 (24.4-30.0) | | 27.1 (24.8-30.1) | | 27.1 (24.6-30.0) | |
| Min-Max | 15.0-47.0 | | 17.7-45.8 | | 15.0-47.0 | |
| *Missing/not initially collected* | 134 | 17% | 164 | 18% | 298 | 18% |
| | | | | | | |
| **Is the patient a smoker?** | | | | | | |
| Never smoked | 322 | 41% | 372 | 41% | 694 | 41% |
| Previous smoker | 390 | 49% | 440 | 49% | 830 | 49% |
| Current smoker | 78 | 10% | 92 | 10% | 170 | 10% |
| | | | | | | |
| **History of heart disease in first degree relative**[3] | | | | | | |
| No | 551 | 70% | 632 | 71% | 1,183 | 71% |
| Yes | 234 | 30% | 259 | 29% | 493 | 29% |
| | | | | | | |
| **Is patient taking regular long-term aspirin?** | | | | | | |
| 0 No | 630 | 80% | 684 | 76% | 1,314 | 78% |
| 1 Yes | 157 | 20% | 219 | 24% | 376 | 22% |
| *Missing data* | 3 | <1% | 1 | <1% | 4 | <1% |
| | | | | | | |
| **If the patient is randomised to the control arm,** | | | | | | |

| | Treatment allocated | | | | | |
|---|---|---|---|---|---|---|
| | LHRHa (N=790) | | Patches (N=904) | | Total (N=1694) | |
| | No. | % | No. | % | No. | % |
| 1 Leuprorelin (Prostap) | 359 | 45% | 409 | 45% | 768 | 45% |
| 2 Goserelin (Zoladex) | 319 | 40% | 377 | 42% | 696 | 41% |
| 3 Other | 51 | 6% | 49 | 5% | 100 | 6% |
| 4 Triptorelin (Decapeptyl) | 61 | 8% | 69 | 8% | 130 | 8% |
| | | | | | | |
| **Intend to give the patient first-line docetaxel?** | | | | | | |
| No | 301 | 38% | 325 | 36% | 626 | 37% |
| Yes | 90 | 11% | 96 | 11% | 186 | 11% |
| *Missing/not initially relevant* | 399 | 51% | 483 | 53% | 882 | 52% |
| | | | | | | |
| **Intend to give the patient first-line docetaxel? M1 patients only** | | | | | | |
| No | 79 | 25% | 69 | 20% | 148 | 22% |
| Not available, pt randomised before October 2015 | 161 | 50% | 190 | 54% | 351 | 52% |
| Yes | 81 | 25% | 90 | 26% | 171 | 26% |
| | | | | | | |
| **Do you intend to give radiotherapy to the prostate?** | | | | | | |
| 0 No | 463 | 59% | 541 | 60% | 1,004 | 59% |
| 1 Yes | 318 | 40% | 347 | 38% | 665 | 39% |
| *Missing data* | 9 | 1% | 16 | 2% | 25 | 1% |
| | | | | | | |
| **Do you intend to give radiotherapy to the prostate? M0 patients only** | | | | | | |
| 0 No | 173 | 37% | 216 | 39% | 389 | 38% |
| 1 Yes | 290 | 62% | 328 | 59% | 618 | 60% |

| | Treatment allocated | | | | | |
|---|---|---|---|---|---|---|
| | LHRHa (N=790) | | Patches (N=904) | | Total (N=1694) | |
| | No. | % | No. | % | No. | % |
| *Missing data* | 6 | 1% | 11 | 2% | 17 | 2% |

[1]Of the patients missing gleason sum score, 20/40 (50%) are due to baseline CRF not yet received.

[2]Baseline BMI weight not initially reported

[3]The initial versions of the CRF asked about a personal history of cardiac disease, rather than a family history, and are not included in this table. 3/5 LHRHa, and 2/13 tE2 patients answered "yes" to a personal history of cardiac disease. Note that in analyses which include history of cardiac disease as a covariate, personal history is used in lieu of family history for these patients.

**Table 2: Number of CV events reviewed and classified as an cardiovascular endpoint**

| | 1:2 cohort | | 1:1 cohort | | |
|---|---|---|---|---|---|
| | **LHRHa (N=82)** | **tE2 (N=162)** | **LHRHa (N=708)** | **tE2 (N=742)** | **Total (N=1694)** |
| Number of events reviewed | 38 | 73 | 88 | 112 | **311** |
| Number of events fulfilling endpoint criteria (fatal)[1] | 16 (6) | 35 (5) | 56 (9) | 60 (6) | 167 (26) |
| | | | | | |
| **Type of event** | | | | | |
| Heart failure | 2 (0) | 4 (1) | 7 (2) | 12 (1) | 25 (4) |
| Acute coronary syndrome | 3 (1) | 12 (2) | 16 (2) | 18 (3) | 49 (8) |
| Thromboembolic stroke | 5 (1) | 6 (0) | 16 (1) | 15 (0) | 42 (2) |
| Other arterial embolic events | 0 (0) | 0 (0) | 0 (0) | 2 (0) | 2 (0) |
| Venous thromboembolism | 2 (0) | 12 (1) | 14 (1) | 11 (0) | 39 (2) |
| Other significant event[2] | 4 (4) | 1 (1) | 3 (3) | 2 (2) | 10 (10) |
| | | | | | |
| Number of patients with a CV endpoint event, including sudden death with no post-mortem (%) | 14(17.1%) | 32(19.8%) | 50(7.1%) | 57(7.7%) | 153(9.0%) |
| Number of patients with a confirmed CV endpoint event (%) | 11(13.4%) | 31(19.1%) | 47(6.6%) | 56(7.5%) | 145(8.6%) |

[1] Of the 95 events that occurred in patients initially randomised to tE2, 34 occurred when tE2 had been stopped and LHRHa started.

[2] Other significant events are unexpected death, but where no post-mortem took place and therefore the endpoint definition could not be verified.

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**Table 3: Six and 12 month changes from baseline in cardiovascular risk factors**

| | Arm | N[1] | Mean change (95% CI) | Mean % change (95% CI) | Treatment effect p-value[2] |
|---|---|---|---|---|---|
| **Fasting Glucose (mmol/L)** | | | | | |
| 6 month change | LHRHa<br>tE2 | 531<br>553 | 0.14 (0.04, 0.24)<br>-0.20 (-0.29, -0.12) | 3.1% (1.6%, 4.7%)<br>-2.4% (-3.7%, -1.0%) | **<0.0001** |
| 12 month change | LHRHa<br>tE2 | 433<br>473 | 0.31 (0.17, 0.46)<br>-0.11 (-0.22, -0.01) | 5.9% (3.7%, 8.1%)<br>-1.1% (-2.7%, 0.6%) | **<0.0001** |
| **Fasting Cholesterol (mmol/L)** | | | | | |
| 6 month change | LHRHa<br>tE2 | 551<br>575 | 0.19 (0.11, 0.26)<br>-0.32 (-0.38, -0.26) | 5.3% (3.7%, 6.9%)<br>-5.3% (-6.5%, -4.1%) | **<0.0001** |
| 12 month change | LHRHa<br>tE2 | 456<br>486 | 0.10 (0.01, 0.18)<br>-0.34 (-0.40, -0.28) | 3.1% (1.4%, 4.8%)<br>-5.7% (-7.0%, -4.5%) | **<0.0001** |
| **Fasting HDL (mmol/L)** | | | | | |
| 6 month change | LHRHa<br>tE2 | 528<br>554 | 0.05 (0.02, 0.09)<br>0.11 (0.08, 0.15) | 6.7% (4.3%, 9.0%)<br>11.6% (8.6%, 14.6%) | **0.023** |
| 12 month change | LHRHa<br>tE2 | 432<br>466 | 0.04 (-0.01, 0.08)<br>0.07 (0.04, 0.11) | 5.8% (2.4%, 9.2%)<br>8.5% (6.0%, 11.0%) | 0.188 |
| **Weight (Kg)** | | | | | |
| 6 month change | LHRHa<br>tE2 | 518<br>569 | 1.74 (1.17, 2.30)<br>1.43 (0.85, 2.01) | 2.3% (1.7%, 2.9%)<br>1.9% (1.3%, 2.5%) | 0.318 |
| 12 month change | LHRHa<br>tE2 | 421<br>452 | 2.16 (1.51, 2.80)<br>1.68 (1.09, 2.28) | 2.8% (2.0%, 3.5%)<br>2.2% (1.7%, 2.7%) | 0.161 |
| **Systolic blood pressure (mmHg)⁺** | | | | | |
| 6 month change | LHRHa<br>tE2 | 547<br>609 | 1.90 (0.50, 3.31)<br>-2.07 (-3.39, -0.75) | 1.9% (0.9%, 3.0%)<br>-0.8% (-1.8%, 0.1%) | **<0.0001** |
| **Diastolic blood pressure (mmHg)⁺** | | | | | |
| 6 month change | LHRHa | 547 | 1.27 (0.37, 2.18) | 2.6% (1.4%, 3.9%) | **<0.0001** |
| | tE2 | 608 | -1.77 (-2.60, -0.95) | -1.5% (-2.6%, -0.4%) | |

[1]N includes patients still receiving their randomly allocated treatment at the time of assessment. For tE2 patients, oestradiol levels needed to be at least 250 pmol/L. Among patients who reported any cardiovascular risk factors, at six months 54 LHRHa and 111 tE2 patients are excluded due to having stopped their allocated treatment, 25 tE2 patents are excluded due to having low oestradiol, and 13 are excluded due to not reporting an oestradiol value. At 12 months, 95 LHRHa and 158 tE2 patients were excluded due to having stopped allocated treatment, 19 tE2 patients for reporting low oestradiol, and 7 oestradiol patients for not reporting an oestradiol value.

[2]P-values are from ANCOVA models comparing mean change in each risk factor.

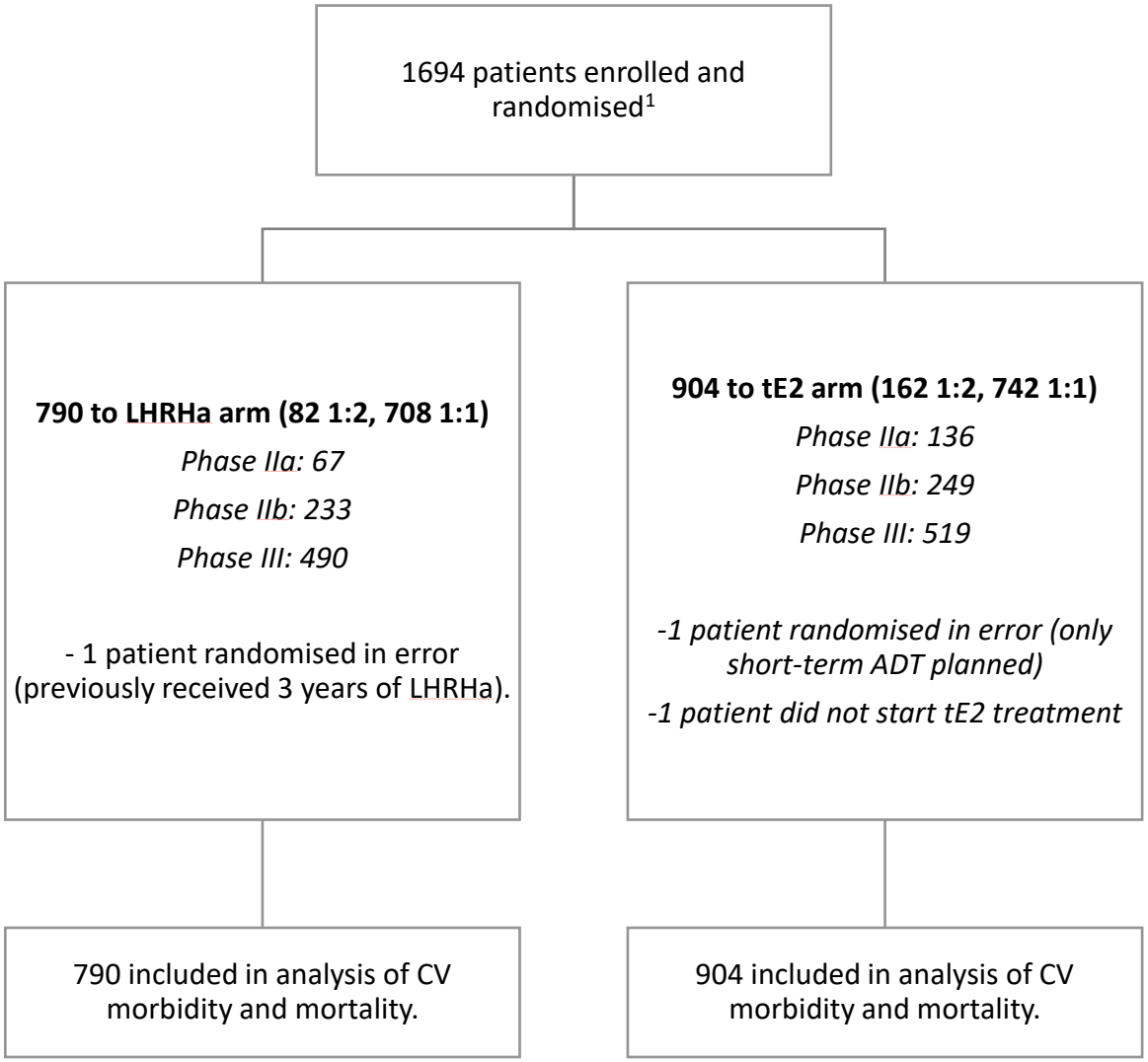
**Table 4: Adverse events**

| | | LHRHa | | | tE2 | | | |
|---|---|---|---|---|---|---|---|---|
| | **Cohort** | **Pts N** | **Any grade N (%)** | **Grade 3 N (%)** | **Pts N** | **Any grade N (%)** | **Grade 3 N (%)** | **P-value*** |
| **Gynaecomastia** | **Both cohorts** | 730 | 279 (38%) | 6 (1%) | 807 | 690 (86%) | 34 (4%) | <0.0001 |
| | 1:2 | 79 | 38 (48%) | 1 (1%) | 147 | 121 (82%) | 19 (13%) | |
| | 1:1 | 651 | 241 (37%) | 5 (1%) | 660 | 569 (86%) | 15 (2%) | |
| **Hot flushes** | **Both cohorts** | 730 | 628 (86%) | 23 (3%) | 807 | 280 (35%) | 1 (0%) | <0.0001 |
| | 1:2 | 79 | 66 (84%) | 5 (6%) | 147 | 52 (35%) | 1 (1%) | |
| | 1:1 | 651 | 562 (86%) | 18 (3%) | 660 | 228 (35%) | 0 (0%) | |
| **Skin/subcutaneous toxicity** | **Both cohorts** | 730 | 474 (65%) | 11 (2%) | 807 | 548 (68%) | 2 (0%) | 0.197 |
| | 1:2 | 79 | 56 (71%) | 3 (4%) | 147 | 92 (63%) | 0 (0%) | |
| | 1:1 | 651 | 418 (64%) | 8 (1%) | 660 | 456 (69%) | 2 (0%) | |
| **Sexual / reproductive toxicity** | **Both cohorts** | 730 | 671 (92%) | 48 (7%) | 807 | 732 (91%) | 56 (7%) | 0.583 |
| | 1:2 | 79 | 71 (90%) | 13 (16%) | 147 | 125 (85%) | 34 (23%) | |
| | 1:1 | 651 | 600 (92%) | 35 (5%) | 660 | 607 (92%) | 22 (3%) | |

Note: Toxicities experienced whilst patients are still known to be receiving allocated treatment are included.

*P-values compare the rate of toxicity at any grade, using a logistic regression model, and combining the two randomisation cohorts using a fixed effects meta-analysis.

**Figure 1. Patient flow diagram**

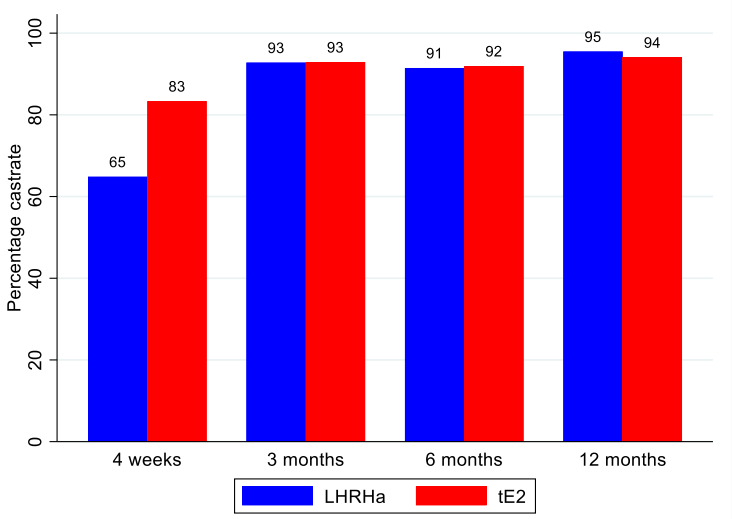



[1] 51 additional patients randomised as part of the initial cohort, treated using a different tE2 dose, are excluded from all analyses.

Note: Patients are included for analysis of CV risk factors if they have data at baseline and at six months, with tests performed whilst still receiving allocated treatment.

Note: Patients are included in analysis of adverse events if they return any toxicity data whilst still receiving allocated treatment

Figure 2: Castration rate (≤1.7nmol/L) by treatment arm, up to 12 months

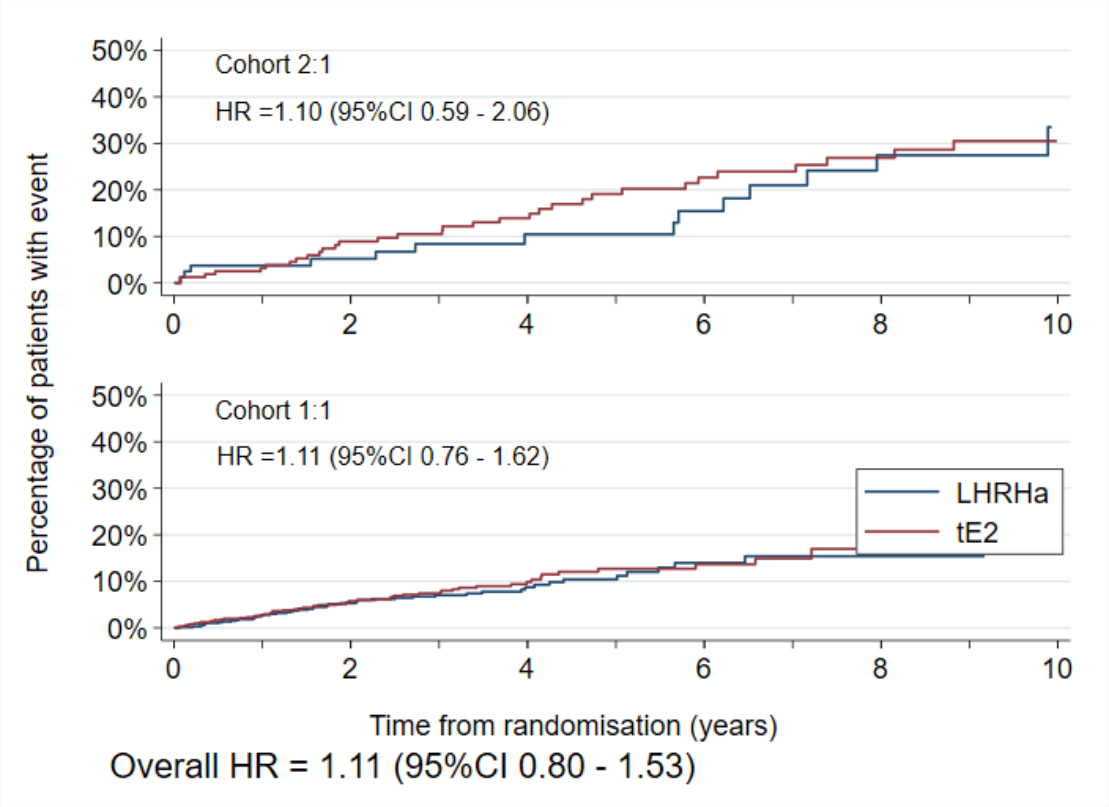



1. Patients included in analysis at 4 weeks (LHRHa 640, tE2 793); 3 months (693 LHRHa, 776 tE2); 6 months (633 LHRHa, 683 tE2); 12 months (511 LHRHa, 540 tE2).

2. Data are included if tests are conducted at 4 weeks ± 2 weeks, and at 3, 6 and 12 months ± 6 weeks and patient still on allocated treatment

**Figure 3: Time to first CV endpoint event, intention-to-treat analysis**

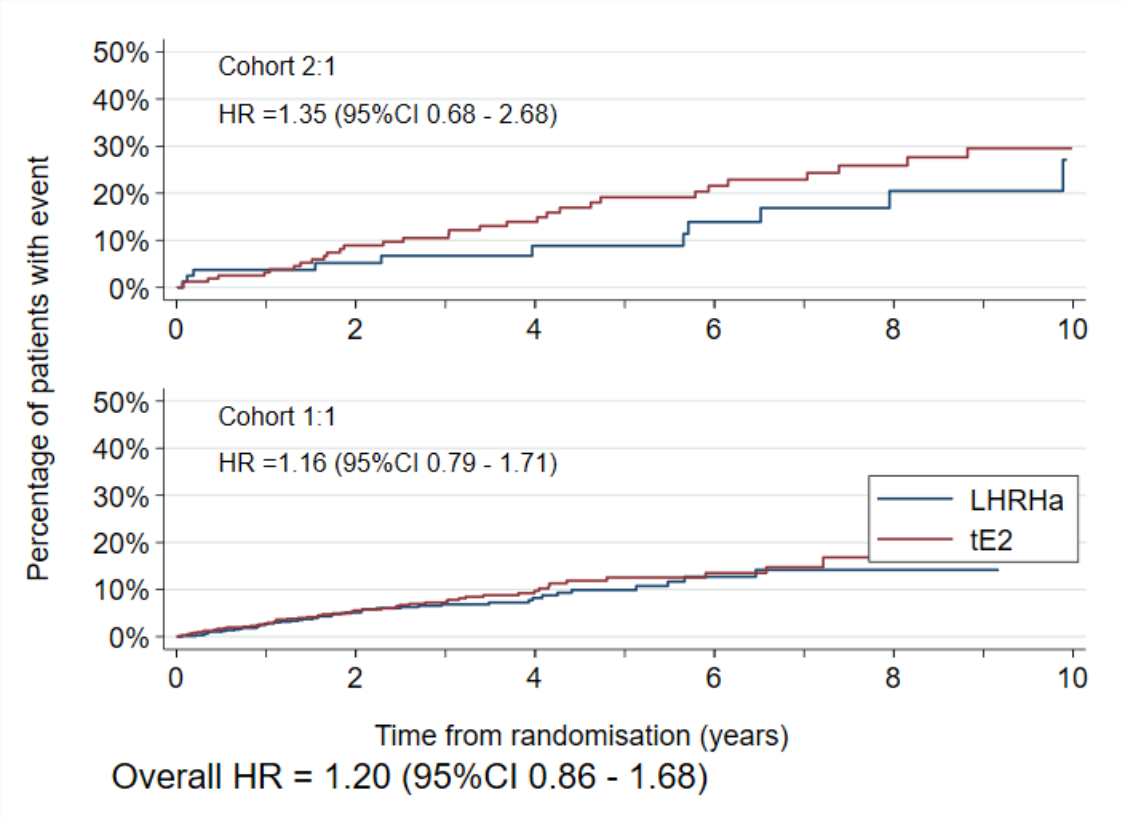
**Figure 3a**




Numbers at risk (and events, over time from randomisation

| Cohort | Arm | Time from randomisation (years) 0- | 2- | 4- | 6- | 8- | Total |
|---|---|---|---|---|---|---|---|
| 2:1 | LHRHa | 82 (4) | 64 (3) | 43 (2) | 34 (4) | 21 (1) | 82 (14) |
| | tE2 | 162 (13) | 119 (6) | 88 (8) | 64 (3) | 42 (2) | 162 (32) |
| 1:1 | LHRHa | 708 (31) | 430 (11) | 184 (7) | 73 (1) | 13 (0) | 708 (50) |
| | tE2 | 742 (35) | 446 (14) | 189 (6) | 87 (2) | 18 (0) | 742 (57) |

**Figure 3b**




Numbers at risk (and events, over time from randomisation

| Cohort | Arm | Time from randomisation (years) 0- | 2- | 4- | 6- | 8- | Total |
|---|---|---|---|---|---|---|---|
| 1:2 | LHRHa | 82 (4) | 64 (2) | 43 (2) | 33 (2) | 21 (1) | 82 (11) |
| | tE2 | 162 (13) | 119 (6) | 88 (7) | 64 (3) | 42 (2) | 162 (31) |
| 1:1 | LHRHa | 708 (30) | 430 (10) | 184 (6) | 73 (1) | 13 (0) | 708 (47) |
| | tE2 | 742 (34) | 446 (14) | 189 (6) | 87 (2) | 18 (0) | 742 (56) |

Figure 3a Time to first CV endpoint event, includes patients with sudden/unexplained death and no post-mortem.

Figure 3b Time to first CV endpoint event – confirmed event only

# Appendix tables.

**Table S1:** Castration rates

| | | 1 month | | 3 months | | 6 months | | 12 months | |
|---|---|---|---|---|---|---|---|---|---|
| | | **LHRHa** | **tE2** | **LHRHa** | **tE2** | **LHRHa** | **tE2** | **LHRHa** | **tE2** |
| No testosterone data | Total | 129 | 57 | 66 | 45 | 106 | 88 | 193 | 201 |
| Reason for no data | Died | 0 | 0 | 3 | 2 | 10 | 7 | 26 | 35 |
| | Censored | 14 | 8 | 15 | 10 | 21 | 25 | 58 | 59 |
| | Test outside analysis window | 54 | 31 | 6 | 6 | 22 | 31 | 47 | 58 |
| | No data | 61 | 18 | 42 | 27 | 53 | 25 | 62 | 49 |
| | | | | | | | | | |
| Testosterone data | Total | 661 | 847 | 724 | 859 | 684 | 816 | 597 | 703 |
| Reason to exclude data | Off treatment | 21 | 16 | 31 | 50 | 51 | 104 | 86 | 141 |
| | Low oestradiol | - | 32 | - | 28 | - | 22 | - | 18 |
| | No oestradiol | - | 6 | - | 5 | - | 7 | - | 4 |
| | | | | | | | | | |
| Eligible data | Total | 640 | 793 | 693 | 776 | 633 | 683 | 511 | 540 |
| Is patient castrate? | No | 225 (35%) | 132 (17%) | 50 (7%) | 55 (7%) | 54 (9%) | 55 (8%) | 23 (5%) | 32 (6%) |
| | Yes | 415 (65%) | 661 (83%) | 643 (93%) | 721 (93%) | 579 (91%) | 628 (92%) | 488 (95%) | 508 (94%) |
| | | | | | | | | | |

Note: “Censored” means a patient has provided no trial data at or beyond this point in the trial.

Note: For data to be included in analysis, tests need to have been conducted at 1 month ± 2 weeks, and at 3, 6 and 12 months ± 6 weeks.

**Table S2:** Oestradiol levels (pmol/L) over time.

| | LHRH | | | | tE2 | | | |
|---|---|---|---|---|---|---|---|---|
| Month | N* | Median | 5% - 95% | Min - Max | N* | Median | 5% - 95% | Min - Max |
| 1 | 675 | 70 | 18 - 124 | 0.4 - 578 | 823 | 845 | 376 - 2280 | 251 - 5424 |
| 3 | 690 | 70 | 18 - 100 | 0.4 - 503 | 789 | 723 | 334 - 1996 | 250 - 5627 |
| 6 | 628 | 70 | 18 - 100 | 2 - 496 | 692 | 776.5 | 356 - 2080 | 252 - 5299 |
| 12 | 526 | 70 | 18 - 100 | 1 - 440 | 570 | 820.5 | 397 - 2239 | 261 - 6200 |
| 18 | 394 | 70 | 18 - 100 | 3 - 1416 | 434 | 795.5 | 372 - 2087 | 267 - 4753 |
| 24 | 345 | 70 | 18 - 100 | 18 - 306 | 360 | 819 | 371 - 2183 | 261 - 3908 |
| 30 | 120 | 70 | 18 - 100 | 18 - 167 | 279 | 802 | 369 - 2001 | 250 - 3245 |
| 36 | 80 | 70 | 18 - 104 | 18 - 117 | 204 | 812 | 381 - 1677 | 252 - 3458 |

*N includes patients still receiving their randomly allocated treatment at the time of assessment. For tE2 patients, oestradiol levels needed to be at least 250 pmol/L.

**Table $3: Proportion of patients experiencing CV event/sudden death**

| | **LHRH (N=790)** | **Patches (N=904)** |
|---|---|---|
| **Overall rate** | | |
| By 12 months | 2.8% (1.8%, 4.2%) | 2.8% (1.9%, 4.2%) |
| By 24 months | 5.3% (3.8%, 7.3%) | 6.4% (4.8%, 8.4%) |
| By 36 months | 7.2% (5.4%, 9.6%) | 8.0% (6.2%, 10.4%) |
| | | |
| **Rate by previous exposure to treatment (months)** | | |
| <6 | 3.5% (2.1%, 6.0%) | 3.5 (2.3%, 5.2%) |
| 6-11.99 | 2.5% (1.3%, 4.7%) | 2.7 (1.6%, 4.7%) |
| ≥12 | 2.4% (1.8%, 3.2%) | 2.8 (2.1%, 3.7%) |
| | | |

| | | |
|---|---|---|
| **Treatment status at time of event.** | | |
| **Number with event** | 64 | 89 |
| Patient still on tE2 | | 42 (47%) |
| Patient off tE2 treatment | | 47 (53%) |
| <3 months after stopping tE2 | | 17 |
| 3-5.99 months | | 3 |
| 6-11.99 months | | 6 |
| 12-23.99 months | | 9 |
| ≥24 months | | 12 |

**Table S4:** Overall CV event/sudden deaths over time, by metastatic status and docetaxel use

| | LHRH (N=790) | Patches (N=904) |
|---|---|---|
| **Overall rate** | | |
| By 12 months | 2.8% (1.8%, 4.2%) | 2.8% (1.9%, 4.2%) |
| By 24 months | 5.3% (3.8%, 7.3%) | 6.4% (4.8%, 8.4%) |
| By 36 months | 7.2% (5.4%, 9.6%) | 8.0% (6.2%, 10.4%) |
| | | |
| **All M0 patients** | | |
| By 12 months | 2.3% (1.2%, 4.2%) | 2.5% (1.4%, 4.2%) |
| By 24 months | 3.6% (2.2%, 5.9%) | 5.2% (3.6%, 7.7%) |
| By 36 months | 5.9% (3.9%, 8.9%) | 6.6% (4.6%, 9.3%) |
| | | |
| **All M1 patients** | | |
| By 12 months | 3.4% (1.9%, 6.3%) | 3.4% (1.9%, 6.1%) |
| By 24 months | 8.0% (5.2%, 12.2%) | 8.5% (5.7%, 12.6%) |
| By 36 months | 9.3% (6.1%, 13.9%) | 10.8% (7.4%, 15.5%) |
| | | |
| **M1 patients, no Docetaxel** | | |
| By 12 months | 4.4% (1.5%, 13.2%) | 6.1% (2.3%, 15.4%) |
| By 24 months | 7.8% (3.3%, 17.8%) | 6.1% (2.3%, 15.4%) |
| By 36 months | 7.8% (3.3%, 17.8%) | 12.7% (5.5%, 27.8%) |
| | | |
| **M1 patients, Docetaxel** | | |
| By 12 months | 1.4% (0.2%, 9.3%) | 0.0% (NA) |
| By 24 months | 7.0% (2.2%, 21.1%) | 7.9% (3.0%, 20.0%) |
| By 36 months | 7.0% (2.2%, 21.1%) | 7.9% (3.0%, 20.0%) |

**Table S5: PATCH committee members**

| Committee | Current/former member | Name | Institution |
|---|---|---|---|
| Trial management group | Current | Ruth Langley | MRC Clinical Trials Unit at UCL |
| | | Duncan Gilbert | MRC Clinical Trials Unit at UCL |
| | | Matthew Nankivell | MRC Clinical Trials Unit at UCL |
| | | Archie Macnair | MRC Clinical Trials Unit at UCL |
| | | Silvia Forcat | MRC Clinical Trials Unit at UCL |
| | | Melanie Weiss | MRC Clinical Trials Unit at UCL |
| | | Cindy Goldstein | MRC Clinical Trials Unit at UCL |
| | | Will Hudson | MRC Clinical Trials Unit at UCL |
| | | Abdulla Alhasso | Beatson West of Scotland Cancer Centre |
| | | Noel Clarke | The Christie and Salford Royal, Manchester |
| | | Roger Kockelbergh | Leicester General Hospital |
| | | Howard Kynaston | Cardiff University Medical School |
| | | Stuart D Rosen | National Heart and Lung Institute, Imperial College |
| | | Stephen Mangar | Charing Cross Hospital |
| | | Mahesh Parmar | MRC Clinical Trials Unit at UCL |
| | | John Marshall | Patient and Public Representative |
| | | John V Deighan | Patient and Public Representative |
| | Former | Paul Abel | Hammersmith Hospital, London |
| | | Trinh Duong | MRC Clinical Trials Unit at UCL |
| | | | |
| Trial Steering Committee | Current | Jeremy Whelan | University College London Hospitals Trust |
| | | John Chester | University of Cardiff |
| | | Emma Crosbie | University of Manchester |
| | | Ann Thomas | University of Leicester |
| | | Lucy Kilburn | Institute of Cancer Research |
| | | Anne Russell | Patient and Public Representative |
| | | | |
| Independent Data Monitoring Committee | Current | Laurence Collette | European Organisation for Research and Treatment of Cancer (EORTC) |
| | | Richard Adams | Velindre Cancer Centre |
| | | Philip Smith | Retired urologist |
| | | | |
| MRC CTU at UCL staff | Former | Trinh Duong | Project Lead |
| | | Fay Cafferty | Project Lead |
| | | Charlotte Tyson | Trial Manager |
| | | Andy Welland | Trial Manager |
| | | Ben Spittle | Trial Manager |

| | | | |
|---|---|---|---|
| | | Phil Pollock | Trial Manager |
| | | Lisa McDonald | Trial Manager |
| | | Montse Wells | Trial Manager |
| | | Gordana Jovic | Statistician |
| | | Suzanne Freeman | Statistician |
| | | Rachel Morgan/Jinks | Statistician |
| | | Katherine Beaney | Data Manager |
| | | Robin Carpenter | Data Manager |
| | | Vicky Tsipouri | Data Manager |
| | | Mark Hall | Data Manager |
| | | Katharina Waneck | Data Manager |
| | | Hassan Khan | Data Manager |
| | | James Pickering | Data Manager |
| | | Phil Pollock | Data Manager |

Supplementary Figure 1 PATCH Development Programme