**1. BACKGROUND**

The Helicobacter Eradication Aspirin Trial (HEAT) is a National Institute of Health Research (NIHR)-funded double-blind placebo-controlled randomised trial designed to investigate the hypothesis that *H. pylori* eradication will reduce the incidence of ulcer bleeding in patients taking aspirin [1]. In England in 2017/18 and in 2018/19, there were over 25,000 hospital admissions for gastric/duodenal ulcers [2], and in 2017 there were 1866 deaths [3]. If successful, the HEAT trial could improve health outcomes by increasing patient safety and reducing hospital admissions.

Although *H. pylori* infection is becoming less prevalent in the developed world, the level of infection is often higher in disadvantaged communities, some ethnic groups and migrants [4]. A study measuring active infection with *H. pylori* in the general population of England and Wales suggested that prevalence was related to decade of birth, and increased from 4.3% in people born in the 1980s to 30% in those born before 1940 [5]. The same authors also demonstrated regional differences in prevalence, which was highest in London and the North of England. They hypothesised that this may be related to household overcrowding and social deprivation.

The HEAT trial has three objectives:

1. To test the hypothesis that a one week course of *H. pylori* eradication therapy in patients taking aspirin ≤325mg daily reduces the incidence of subsequent peptic ulcer bleeding
2. To test the hypothesis that the intervention is cost effective
3. To establish an inexpensive methodology for performing large simple outcomes trials in primary care

Trial design was informed by an earlier pilot study in which 37% of those invited volunteered to take part, and of those 22% were *H. pylori* positive. Using these figures it was estimated that a full trial would need 6,600 randomised (*H. pylori* positive) participants from approximately 33,000 consented patients.

In order to achieve the required number of participants, the United Kingdom Clinical Research Network (UKCRN) was approached to aid recruitment of GP practices and patients. In each of the four UK nations, clinical research networks have been established whose aim is to provide the infrastructure to support clinical research studies [6]. In England, this infrastructure is organised through the NIHR CRN that is composed of 15 Local CRNs that cover all the Clinical Commissioning Groups (CCGs) and deliver research across 30 clinical specialities, one of which is primary care. The Scottish CRN covers 14 Local Health Boards (LHB) and has 7 topic-specific research networks including primary care. Wales has a clinical research infrastructure provided through Health and Care Research Wales covering 7 LHBs, and the Northern Ireland CRN covers nine areas of interest across 5 Health & Social Care Trusts (HSCT) with a coordinating centre based in Belfast.

Patient recruitment to HEAT has been solely from GP practices. Recruitment to clinical trials can be difficult, particularly in primary care, where factors related to the protocol, the clinical setting or the research setting can all contribute [7]. With this in mind, the trial was designed to provide the lowest workload possible for participating GP practices, and minimal face-to-face visits for patients. Practices were provided with a programmed search tool (HEAT Toolkit) that identified eligible patients, and all invitation letters were sent using a highly secure automated online mail management system (Docmail [8]).

One of the principal aims of the HEAT trial was to streamline the methodology of large-scale clinical trials performed in primary care, minimising impact on GP practices and their patients. This paper describes the methods used and assesses their success in recruitment across the UK.

**2. METHODS**

GP practices were recruited through local CRN research facilitators and from previous contacts who had taken part in other studies managed by the HEAT team.

Full details of the methodology have been previously published [1]. Briefly, eligible patients were identified by an electronic search tool (Morbidity Information Query and Export Syntax (MIQUEST) [9]) downloaded at participating GP practices (HEAT Toolkit). Using such a system ensured that all practices performed a detailed, identical search that provided an accurate list of patients, each with a unique screening number, which required minimal checking by the GP.

Eligible patients were ≥60 years old, on long-term aspirin (≤325mg daily for at least 4 months) and not on anti-ulcer therapy, oral non-steroidal anti-inflammatory drugs or any medication with a clinically significant interaction with the *H. pylori* eradication treatment. Patient invitations were sent out via Docmail [8], an online mailing system approved by Connecting for Health that uses the highest strength encryption for data transfer and the highest level of physical and IT security for mail processing. Practices were simply required to login to the HEAT account on the Docmail website and upload a spreadsheet of eligible patients. Having a dedicated HEAT Docmail account enabled complete version control of trial documents posted out to the patients.

Patient recruitment was performed principally by CRN research nurses, but also by research-active GP practice nurses and four dedicated trial research nurses based in the regional centres. Interested patients were seen once at their local GP practice for consent and a *H. pylori* breath test. During the consent visit, basic health information was collected that could be used by the practice for the National Health Service (NHS) Quality and Outcomes Framework (QOF) [10] if they wished.

Participants with a positive breath test were randomised to eradication treatment (lansoprazole 30mg, clarithromycin 500mg and metronidazole 400mg twice daily for one week) or placebo.

A bespoke HEAT web-based database and trial management system was developed for the trial, housed within the secure NHS N3 Data Network, that communicated directly with the HEAT Toolkit at the GP practices. Once a participant consented to the trial and was recorded as such on the HEAT Toolkit, basic demographic and relevant healthcare information was uploaded from the participant’s medical record to the trial database.

The primary endpoint of the HEAT trial is the rate of hospitalisation due to definite or probable peptic ulcer bleeding, adjudicated by a blinded Adjudication Committee; the trial will end when 87 adjudicated primary events have occurred.

Randomised participants have been followed up by collecting information from:

1. MIQUEST queries (through the HEAT Toolkit) of GP practice databases, searching for clinical terms indicating a trial endpoint, as well as current relevant health and prescribing information. Results are communicated directly to the HEAT web-based trial management system
2. Regular requests to NHS Digital for Hospital Episode Statistics secondary care admission data [2] and mortality data from the Office of National Statistics [3], matched to the data provided by the MIQUEST searches of the GP practice records
3. Event forms given to all randomised participants for the purpose of reporting any hospital admissions or changes to GP/home address
4. Serious Adverse Event reporting by GPs. Because the trial is classified by the Medicines and Healthcare products Regulatory Agency as the lowest risk trial of an investigational medicinal product, and trial medication was only taken for one week, this was only collected for 4 weeks from the start of eradication treatment for each randomised participant

All follow-up data has been accumulated in the HEAT database from which anonymised reports can be downloaded for analysis. Success of recruitment of both GP practices and patients has been evaluated across the regions of the UK. Recruitment figures were also analysed with respect to area level deprivation based on postcode. The Index of Multiple Deprivation (IMD) is a measure of relative deprivation used to rank neighbourhoods across the UK. Small areas of the country are ranked from the most deprived to the least deprived, and these are then divided into 10 equally sized groups, or deciles, numbered 1 (10% most deprived) through to 10 (10% least deprived) [11, 12, 13, 14].

**3. RESULTS**

**3.1 GP Practice Recruitment**

Practice recruitment began in 2012 and completed in 2017. HEAT was managed from four regional centres based in Nottingham (Trial Sponsor), Southampton, Oxford/Birmingham and Durham. Each regional centre was responsible for recruiting GP practices in their area. Recruitment began in the CRN regions in England closest to the regional centres but ultimately HEAT recruited from practices across the whole of the UK (Figure 1, Table 1).

**Figure 1: GP Practices taking part in HEAT**

*Each dot on the map represents individual GP practices taking part in HEAT*

**Table 1: GP practice recruitment in each region of the UK**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| REGION | Date recruitment started in region | Total number of CCGs / LHBs / HSCTs within each region | Total number of CCGs / LHBs / HSCTs recruiting to study | 1Total (approx.) number of GP practices in region | Total number of GP practices recruiting to study | Percent of total GP practices recruiting to study |
| **ENGLAND** |  |  |  |  |  |  |
| CRN E MIDLANDS | 14.09.2012 | 19 | 19 | 578 | 127 | 22.0 |
| CRN YORKS & HUMBER | 20.09.2012 | 21 | 18 | 736 | 119 | 16.2 |
| CRN WESSEX | 27.09.2012 | 9 | 9 | 292 | 101 | 34.6 |
| CRN THAMES VALLEY & S MIDS | 05.11.2012 | 5 | 5 | 249 | 57 | 22.9 |
| CRN SW PENINSULA | 21.11.2012 | 4 | 4 | 279 | 72 | 25.8 |
| CRN EASTERN | 03.12.2012 | 11 | 11 | 431 | 88 | 20.4 |
| CRN W OF ENGLAND | 13.12.2012 | 5 | 5 | 281 | 80 | 28.5 |
| CRN NE & N CUMBRIA | 02.01.2013 | 11 | 11 | 418 | 65 | 15.6 |
| CRN W MIDLANDS | 27.03.2013 | 20 | 20 | 886 | 202 | 22.8 |
| CRN KENT, SURREY, SUSSEX | 27.08.2013 | 20 | 16 | 550 | 63 | 11.5 |
| CRN NW COAST | 04.01.2014 | 19 | 14 | 619 | 64 | 10.3 |
| CRN S LONDON | 28.03.2014 | 12 | 11 | 454 | 43 | 9.5 |
| CRN N THAMES | 10.07.2014 | 20 | 12 | 837 | 43 | 5.1 |
| CRN NW LONDON | 05.11.2014 | 8 | 7 | 388 | 11 | 2.8 |
| CRN GTR MANCHESTER | 25.11.2014 | 11 | 7 | 502 | 17 | 3.4 |
| **TOTAL IN ENGLAND** |  | **195** | **169** | **7500** | **1152** | **15.4** |
| **WALES** |  |  |  |  |  |  |
| BETSI CADWALADR UNIVERSITY LHB | 03.02.2015 |  |  | 107 | 11 | 10.3 |
| CARDIFF AND VALE UNIVERSITY LHB | 05.02.2015 |  |  | 66 | 10 | 15.2 |
| ABERTAWE BRO MORGANNWG UNIVERSITY LHB | 10.02.2015 |  |  | 70 | 6 | 8.6 |
| POWYS TEACHING LHB | 13.03.2015 |  |  | 17 | 4 | 23.5 |
| ANEURIN BEVAN LHB | 20.07.2015 |  |  | 80 | 5 | 6.2 |
| CWM TAF LHB | 11.09.2015 |  |  | 42 | 5 | 11.9 |
| HYWEL DDA LHB | 06.11.2015 |  |  | 51 | 1 | 2.0 |
| **TOTAL IN WALES** |  | **7** | **7** | **433** | **42** | **9.7** |
| **NORTHERN IRELAND** |  |  |  |  |  |  |
| BELFAST HSCT | 15.05.2015 |  |  | 82 | 1 | 1.2 |
| SOUTHEASTERN HSCT | 10.11.2015 |  |  | 54 | 4 | 7.4 |
| NORTHERN HSCT | 04.05.2016 |  |  | 75 | 1 | 1.3 |
| **TOTAL IN NORTHERN IRELAND** |  | **5** | **3** | **211** | **6** | **2.8** |
| **SCOTLAND** |  |  |  |  |  |  |
| TAYSIDE LHB | 24.01.2017 |  |  | 64 | 3 | 4.7 |
| LANARKSHIRE LHB | 07.06.2017 |  |  | 104 | 5 | 4.8 |
| **TOTAL IN SCOTLAND** |  | **14** | **2** | **168** | **8** | **4.8** |
| **TOTAL IN UK** |  | **221** | **181** | **8312** | **1208** | **14.5** |

*1Total number of GP Practices in area obtained from:*

[*https://digital.nhs.uk/services/organisation-data-service/data-downloads/gp-and-gp-practice-related-data*](https://digital.nhs.uk/services/organisation-data-service/data-downloads/gp-and-gp-practice-related-data) *(as of 31 August 2018)*

[*https://data.england.nhs.uk/dataset/ods-northern-ireland*](https://data.england.nhs.uk/dataset/ods-northern-ireland) *(as of 31 August 2018)*

[*http://www.isdscotland.org/Health-Topics/General-Practice/Workforce-and-Practice-Populations/*](http://www.isdscotland.org/Health-Topics/General-Practice/Workforce-and-Practice-Populations/) *(as of October 2018)*

By CRN region, the percent of participating GP practices ranged from 1.2% - 34.2%. Altogether 1208 GP practices were recruited, from which a total of 188,875 invitation letters were posted to patients. Forty-six practices were enrolled into the trial but withdrew before sending out any invitation letters. Approximately one third of practices (386, 32.1%) recruited using their own practice nurses.

**3.2 Participant Recruitment**

Of the invited patients, 77,754 (41.2%) returned a reply slip (Table 2), of which 38,771 (20.5% of those invited, 49.9% of those responding) patients expressed an interest (EOI) in participating in the trial (Figure 2).

**Table 2: Participant recruitment in each region of the UK**

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| REGION | Total letters sent | Total  reply slips received | Total expressions of interest (EOI) | EOI as a percent of letters sent | 2Total consented patients | Consented as a percent of EOI | Total *H. pylori* positive participants | *H. pylori* positive as a percent of consented patients |
| **ENGLAND** |  |  |  |  |  |  |  |  |
| CRN E MIDLANDS | 20242 | 8333 | 4051 | 20.0 | 3531 | 87.2 | 664 | 18.8 |
| CRN YORKS & HUMBER | 20651 | 8306 | 4148 | 20.1 | 3023 | 72.9 | 606 | 20.0 |
| CRN WESSEX | 19070 | 8784 | 4250 | 22.3 | 3386 | 79.7 | 506 | 14.9 |
| CRN THAMES VALLEY & S MIDS | 9485 | 3946 | 2166 | 22.8 | 1698 | 78.4 | 249 | 14.7 |
| CRN SW PENINSULA | 14609 | 6511 | 3131 | 21.4 | 2631 | 84.0 | 418 | 15.9 |
| CRN EASTERN | 14732 | 6857 | 3728 | 25.3 | 2699 | 72.4 | 401 | 14.9 |
| CRN W OF ENGLAND | 13248 | 5899 | 2885 | 21.8 | 2384 | 82.6 | 321 | 13.5 |
| CRN NE & N CUMBRIA | 8030 | 3142 | 1486 | 18.5 | 1154 | 77.7 | 283 | 24.5 |
| CRN W MIDLANDS | 29953 | 11353 | 5046 | 16.8 | 4242 | 84.1 | 772 | 18.2 |
| CRN KENT, SURREY, SUSSEX | 9909 | 4723 | 2417 | 24.4 | 1653 | 68.4 | 256 | 15.5 |
| CRN NW COAST | 10697 | 3604 | 1932 | 18.1 | 1312 | 67.9 | 305 | 23.2 |
| CRN S LONDON | 3112 | 912 | 555 | 17.8 | 376 | 67.7 | 75 | 19.9 |
| CRN N THAMES | 4314 | 1453 | 793 | 18.4 | 573 | 72.3 | 123 | 21.5 |
| CRN NW LONDON | 974 | 252 | 134 | 13.8 | 80 | 59.7 | 26 | 32.5 |
| CRN GTR MANCHESTER | 1897 | 592 | 284 | 15.0 | 222 | 78.2 | 53 | 23.9 |
| **TOTAL IN ENGLAND** | **180923** | **74667** | **37006** | **20.5** | **28964** | **78.3** | **5058** | **17.5** |
| **WALES** |  |  |  |  |  |  |  |  |
| BETSI CADWALADR UNIVERSITY LHB | 1470 | 620 | 376 | 25.6 | 229 | 60.9 | 49 | 21.4 |
| CARDIFF AND VALE UNIVERSITY LHB | 1118 | 453 | 223 | 19.9 | 155 | 69.5 | 43 | 27.7 |
| ABERTAWE BRO MORGANNWG UNIVERSITY LHB | 1277 | 595 | 373 | 29.2 | 242 | 64.9 | 50 | 20.7 |
| POWYS TEACHING LHB | 427 | 214 | 134 | 31.4 | 83 | 61.9 | 17 | 20.5 |
| ANEURIN BEVAN LHB | 816 | 270 | 157 | 19.2 | 104 | 66.2 | 31 | 29.8 |
| CWM TAF LHB | 723 | 283 | 137 | 18.9 | 102 | 74.5 | 30 | 29.4 |
| HYWEL DDA LHB | 209 | 62 | 35 | 16.7 | 28 | 80.0 | 9 | 32.1 |
| **TOTAL IN WALES** | **6040** | **2497** | **1435** | **23.8** | **943** | **65.7** | **229** | **24.3** |
| **NORTHERN IRELAND** |  |  |  |  |  |  |  |  |
| BELFAST HSCT | 88 | 29 | 26 | 29.5 | 25 | 96.2 | 6 | 24.0 |
| SOUTHEASTERN HSCT | 609 | 181 | 119 | 19.5 | 107 | 89.9 | 28 | 26.2 |
| NORTHERN HSCT | 305 | 111 | 69 | 22.6 | 68 | 98.6 | 20 | 29.4 |
| **TOTAL IN NORTHERN IRELAND** | **1002** | **321** | **214** | **21.4** | **200** | **93.5** | **54** | **27.0** |
| **SCOTLAND** |  |  |  |  |  |  |  |  |
| 3TAYSIDE LHB | 261 | 71 | 23 | 8.8 | 6 | 26.1 | 0 | 0.0 |
| LANARKSHIRE LHB | 649 | 198 | 93 | 14.3 | 53 | 57.0 | 23 | 43.4 |
| **TOTAL IN SCOTLAND** | **910** | **269** | **116** | **12.7** | **59** | 50.9 | **23** | **39.0** |
| **TOTAL IN UK** | **188875** | **77754** | **38771** | **20.5** | **30166** | **77.8** | **5364** | **17.8** |

*2A consented patient was defined as one with a valid signed Informed Consent Form and a Data Capture Record form completed at screening and entered on the HEAT database*

*3Tayside LHB withdrew from the trial shortly after starting recruitment due to staffing problems*

**Figure 2: Total EOIs from patients invited to participate in HEAT**

*Bars represent recruitment in each English CRN (blue) / Welsh LHB (red) / Northern Irish HSCT (green) / Scottish LHB (dark blue) expressed as a percent of total invitation letters sent for each research network*

Sixteen GP practices did not receive any patient replies even though 6 of them sent out more than 40 invitation letters (455 total letters sent), and 8 practices received no EOIs. 31 GP practices did not consent any patients, despite sending out a total of 2457 invitation letters from which 632 responses were received (including 279 EOIs).

For each CCG/LHB/HSCT, the percentage of EOIs received from invited patients was analysed (Pearson correlation) against the IMD decile associated with the postcode of the GP practice and showed a moderate degree of positive correlation (r = 0.42, 95%CI 0.30-0.53, P <0.0001; Figure 3, Appendix Table 1). This suggested that patients registered with GP practices situated in less deprived areas were more likely to express an interest in the trial.

**Figure 3: Correlation of mean percent EOI with the mean IMD decile of the GP practice postcodes**

*For each GP practice the EOI was calculated as a percent of letters sent and a mean value calculated for each CCG, LHB or HSCT. These were plotted against the mean IMD decile associated with the practice postcode for each CCG, LHB or HSCT. Full data is shown in Appendix Table 1.*

Of those patients expressing an interest, 31,690 attended a screening visit and 30,166 were consented (16% of those invited, 77.8% of EOI). This represented a shortfall of 7,081 potential participants that had expressed an interest, who did not attend a screening visit. The percentage of patients consented across the UK research networks (excluding Tayside LHB) varied between 57.0% and 98.6% of the EOIs (Figure 4).

**Figure 4: Total consented patients expressed as a percent of total EOIs for each research network**

Tayside LHB consented only 26.1% of their EOIs, none of whom went on to be randomised because of its withdrawal from the trial owing to staffing problems. All three HSCTs in Northern Ireland consented 90% or more of their interested patients.

Of the consented participants, 29,894 had a recorded breath test result of which 118 were inconclusive and 5,364 positive. This represented a *H. pylori* positive rate of 17.9%, less than the 22% rate seen in the pilot study. Of those *H. pylori* positive participants 5,355 were randomised. Across the research networks, the percent of *H. pylori* positive participants varied between 13.5% and 43.4% of those consented (Figure 5; Table 2).

**Figure 5: Total H.pylori positive participants expressed as a percent of total consented patients for each research network**

For the three devolved nations, the percentage of *H. pylori* positive participants (24.3% in Wales, 27.0% in Northern Ireland, 39.0% in Scotland) appeared to be higher than that in England (17.5%). This difference was significant (1-way ANOVA, Sidak’s multiple comparisons test) for Wales (p=0.02) and Scotland (p=0.0004), but not for Northern Ireland (p=0.1)

The number of patients who consented to take part in the trial was more than 5-fold greater for those residing in areas of least deprivation (IMD decile = 10) than those residing in areas of the greatest deprivation (IMD decile = 1) (Figure 6).

**Figure 6: Patient consent in relation to IMD decile of their domiciliary postcodes**

In contrast, the proportion of those consented patients who were *H. pylori* positive decreased as the IMD decile increased (ie. in less deprived areas) (Figure 7).

**Figure 7: Proportion of H. pylori positive participants in relation to IMD decile of their domiciliary postcodes**

The number of patients consented at each practice was calculated as a percent of the number of invitation letters sent and mapped against the IMD decile associated with the postcode of each GP practice (Figure 8).

**Figure 8: Proportion of consented versus invited patients in relation to IMD decile of GP practice postcode**

The GP practice postcode was used to determine the IMD decile as the patient domiciliary postcodes were not available prior to consent, and were therefore not obtainable for all invited patients. Although this cannot give such an accurate representation as using domiciliary postcodes, it also showed an increased patient volunteering rate in practices located in less deprived areas.

Of the randomised (*H. pylori* positive) participants, 1271 (23.7% of randomised participants) have withdrawn from the trial to date (as of 12-Aug-2020), detailed in Table 3.

**Table 3: Randomised participant withdrawals (as of 12-Aug-2020)**

|  |  |  |
| --- | --- | --- |
| **Reason for withdrawal** | **Randomised patient withdrawals** | |
|  | n | % |
| Treatment sent but no response from patient | 224 | 4.18 |
| Incorrectly enrolled in the trial | 17 | 0.32 |
| Adverse reaction to trial treatment | 55 | 1.03 |
| Did not want to take medication/risk side effects | 18 | 0.34 |
|  |  |  |
| Consent to active follow-up contact withdrawn; continuing use of electronic data allowed | 457 | 8.52 |
| Consent to active contact and use of electronic data withdrawn | 72 | 1.34 |
| Patient died or terminally ill | 386 | 7.20 |
| At request of GP | 37 | 0.69 |
| Health reasons | 5 | 0.09 |

Two hundred and twenty-four randomised participants (4.18%) were sent a treatment pack but failed to return the treatment record form or respond to compliance calls. Seventy-three patients (1.36%) withdrew because of treatment related adverse events (55, 1.03%) or concern about taking the medication (18, 0.34%). During follow-up 529 patients (9.86%) withdrew consent to active follow-up, including receipt of the annual trial update letter, but 457 of these (8.52%) gave continuing consent to collection and use of their electronic data. A substantial number of this elderly population (386, 7.20%) died or became terminally ill and 37 (0.69%) were withdrawn at the request of their GP.

**3.3 Participant Demographics**

A summary of participant demographics available at this stage of the trial are detailed in Tables 4-8.

The mean age at consent for total consented participants was 73.1 ± 6.9 (SD) years and 72.1% were male. For those subsequently found to be *H. pylori* positive, mean age was 74.0 ± 7.0 (SD) years (73.8% male), and for those who were *H. pylori* negative, mean age was 72.9 ± 6.8 (SD) years (71.7% male).

**Table 4: Consented participant demographics**

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **INVITED**  188875 | **RESPONSE** | | **CONSENTED**  30166 | ***H. pylori* TEST RESULT** | | **IMD DECILE** | | |
| FEMALE  72644  38.5% of total invited  mean YOB 1938 | YES (EOI): 15.3% of females invited | 11146 | FEMALE  8373  27.8% of total consented  75.1% of female EOIs  mean YOB 1941 | POSITIVE | 1407  (16.8%)5 | 1-5 | 731  (8.7%)5 |
| 6-10 | 676  (8.1%) |
| NO | 14905 | NEGATIVE | 6822  (81.5%) | 1-5 | 3107  (37.1%) |
| 6-10 | 3715  (44.4%) |
| MAY IN FUTURE | 1886 | 4INCONCLUSIVE | 46  (0.5%) | 1-5 | 25  (0.3%) |
| 6-10 | 21  (0.2%) |
| NO RESPONSE | 44707 | 4NONE | 98  (1.2%) | 1-5 | 55  (0.7%) |
| 6-10 | 43  (0.5%) |
|  |  |  |  |  |  |  |  |
| MALE  116231  61.5% of total invited  mean YOB 1941 | YES (EOI): 23.8% of males invited | 27625 | MALE  21793  72.2% of total consented  78.9% of male EOIs  mean YOB 1942 | POSITIVE | 3957  (18.2%) | 1-5 | 2037  (9.3%) |
| 6-10 | 1920  (8.8%) |
| NO | 19274 | NEGATIVE | 17590  (80.7%) | 1-5 | 7695  (35.3%) |
| 6-10 | 9895  (45.4%) |
| MAY IN FUTURE | 2918 | INCONCLUSIVE | 72  (0.3%) | 1-5 | 35  (0.2%) |
| 6-10 | 37  (0.2%) |
| NO RESPONSE | 66414 | NONE | 174  (0.8%) | 1-5 | 96  (0.4%) |
| 6-10 | 78  (0.4%) |

*4Participants with an inconclusive or no breath test result were sent a repeat test in the post but these were not all returned for analysis*

*5figures in brackets show the percent of females / males consented*

For the *H. pylori* positive participants, 51.9% of females and 51.5% of males were living in areas with an IMD decile of 1-5, compared with 45.5% and 43.7% of *H.pylori* negative females and males respectively.

**Table 5: Consented participant demographics: smoking history and *H. pylori* status by sex**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **CONSENTED**  30166 | **SMOKING STATUS** | | **H pylori TEST RESULT** | |
| FEMALE  8373  (73 had no smoking history recorded) | SMOKER | 417  (5.0%)6 | POSITIVE | 90  (1.07%)6 |
| NEGATIVE | 319  (3.81%) |
| INCONCLUSIVE | 5  (0.06%) |
| NONE | 3  (0.04%) |
| EX-SMOKER | 3042  (36.3%) | POSITIVE | 563  (6.72%) |
| NEGATIVE | 2464  (29.43%) |
| INCONCLUSIVE | 14  (0.17%) |
| NONE | 12  (0.14%) |
| NEVER SMOKED | 4841  (57.8%) | POSITIVE | 752  (8.98 %) |
| NEGATIVE | 4032  (48.15%) |
| INCONCLUSIVE | 27  (0.32%) |
| NONE | 30  (0.36%) |
|  |  |  |  |  |
| MALE  21793  (117 had no smoking history recorded) | SMOKER | 1329  (6.1%) | POSITIVE | 297  (1.36%) |
| NEGATIVE | 1021  (4.68%) |
| INCONCLUSIVE | 7  (0.03%) |
| NONE | 4  (0.02%) |
| EX-SMOKER | 12558  (57.6%) | POSITIVE | 2270  (10.42%) |
| NEGATIVE | 10202  (46.81%) |
| INCONCLUSIVE | 38  (0.17%) |
| NONE | 48  (0.22%) |
| NEVER SMOKED | 7789  (35.7%) | POSITIVE | 1385  (6.36%) |
| NEGATIVE | 6343  (29.11%) |
| INCONCLUSIVE | 27  (0.12%) |
| NONE | 34  (0.16%) |

*6figures in brackets show the percent of females / males consented*

Only 5.8% of consented trial participants were current smokers, 51.7% were ex-smokers and 41.9% had never smoked. More males (63.7%) than females (41.3%) were smokers or ex-smokers whereas 57.8% of the females had never smoked compared with 35.7% of males.

Of the smokers, 22.2% were *H.pylori* positive, 18.1% of ex-smokers were positive and 16.9% of those who had never smoked.

**Table 6: Participant demographics: alcohol consumption**

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| ALCOHOL UNITS PER WEEK | CONSENTED PARTICIPANTS | | | | RANDOMISED PARTICIPANTS | | | |
| Number of consented  participants | | Percent of consented participants | | Number of randomised  participants | | Percent of randomised participants | |
|  | F | M | F | M | F | M | F | M |
| 0 | 3158 | 4315 | 37.7 | 19.8 | 589 | 911 | 41.9 | 23.1 |
| 1-14 | 4232 | 11101 | 50.5 | 50.9 | 678 | 1956 | 48.3 | 49.5 |
| 15-50 | 553 | 5286 | 6.6 | 24.3 | 74 | 899 | 5.3 | 22.8 |
| 51+ | 10 | 256 | 0.1 | 1.2 | 0 | 44 | 0 | 1.1 |
| no record | 420 | 835 | 5.0 | 3.8 | 64 | 140 | 4.6 | 3.5 |

**Table 7: Participant demographics: body mass index (BMI)**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| BMI RANGE | TOTAL CONSENTED PARTICIPANTS | | RANDOMISED PARTICIPANTS | |
| 7Number of consented  participants | Percent of consented  participants | 7Number of randomised  participants | Percent of randomised participants |
| below 18.50 | 128 | 0.4 | 24 | 0.4 |
| 18.5 – 24.99 (Healthy weight) | 7360 | 24.6 | 1262 | 23.6 |
| 25 – 29.99 (Overweight) | 13436 | 44.9 | 2443 | 45.8 |
| 30 – 39.9 (Obese) | 8312 | 27.8 | 1495 | 28.0 |
| 40+ (Morbidly Obese) | 692 | 2.3 | 115 | 2.2 |

*7Not all participants provided appropriate information to calculate a BMI*

**Table 8: Participant demographics: statin prescribing**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| STATINS PRESCRIBED | TOTAL CONSENTED PARTICIPANTS | | RANDOMISED PARTICIPANTS | |
| Number of consented  participants | Percent of consented participants | Number of randomised  participants | Percent of randomised participants |
| Yes | 24018 | 79.99 | 4333 | 80.91 |
| No | 5990 | 19.95 | 1019 | 19.03 |
| No record | 158 | 0.07 | 3 | 0.06 |

For both the consented and randomised participant populations, approximately 90% of the female and 70% of the male populations consumed 14 units or less of alcohol per week, 45% were in the BMI range 25-30 (overweight) and 80% were prescribed statins.

**4. DISCUSSION**

HEAT has demonstrated that it is possible to recruit large numbers of patients into a clinical trial solely from primary care. One objective of the trial was to develop a methodology that would enable GP practices to take part with a minimal workload. To that end, several academic GPs were members of the Trial Management Group that developed the trial protocol and procedures [15,16]. Various processes were set up to make the practice’s role as simple as possible.

* GPs taking part in the study were given the position of Study Site Coordinators rather than Principal Investigators so that the burden of obtaining all regulatory approvals fell to the trial team rather than the practice
* The trial offered study-specific Good Clinical Practice training to non-consenting staff covering points specific to their role in the trial
* No targets for recruitment were set
* Practices were provided with a thorough electronic search tool that produced a list of eligible patients requiring minimal checking by the GP
* All invitation letters were sent by a secure electronic mailing system relieving work load on practice administrative staff
* All consent was performed by trained research nurses

The UKCRN have played a large role in facilitating HEAT. The figures shown in tables 1 & 2 demonstrate what high recruitment numbers are possible with the assistance of the research networks, enabling recruitment to take place across the whole of the UK whilst managing the trial from a few coordinating centres.

The percentage of GP practices taking part in the trial varied greatly across the regions, but this was constrained in some areas by local resource or budget restrictions. Some CRNs/CCGs experienced delayed recruitment due to IT issues; principally the presence of local firewalls preventing installation of the HEAT Toolkit at GP practices. In some instances, resolution was achieved only after long discussions between local IT teams and the designers of the HEAT Toolkit (TCR Nottingham Ltd.). The recent introduction of the General Data Protection Regulation (GDPR) [17] has increased sensitivity to introduction of external software onto GP practice computers and external data transfer, as well as the collection of follow-up data from NHS Digital and the Office of National Statistics. The design of a large-scale clinical trial such as HEAT depends heavily on electronic methods of data collection both for its results and for time- and cost-saving, and future trials could be severely hindered if such data were not readily available.

Patient participation in the trial was also made as convenient as possible. Only one appointment at their local GP practice was required and any travel costs were reimbursed. Trial medication was posted to the participant’s home and pre-paid envelopes were provided for the return of any trial documents. Members of patient participation groups were also incorporated in the Trial Management Group to advise on patient documentation and procedures.

Despite these measures, overall recruitment figures (30,166 patients consented, 5,355 randomised) were a little less than the target figures of 33,000 patients consented and 6,600 randomised. Recruitment was halted in October 2017 due to expiry of the eradication treatment and prohibitive costs of supplying further medication. Nevertheless, at this point, the target posting of invitation letters had been exceeded, while 91% of the consented participant target had been achieved and 81% of the randomised participant target.

The *H. pylori* positive rate was less than that seen in the pilot study, on which the original target participant numbers were based. Some regions (i.e. North-West London, Wales, Northern Ireland and Scotland) appeared to have higher rates of *H pylori* positive patients than others (Figure 5). Unfortunately, these regions did not start recruiting into the trial until it had already been up and running for two years, and so represent a missed opportunity to increase the numbers of randomised participants.

Of the patients expressing an interest in the trial, there were over 7,000 who did not attend a consent clinic. There could have been several reasons for this. Patients may perhaps have changed their mind, or other events may have intervened in the period between expressing an interest and being contacted to attend a consent clinic. For some practices, there was a significant delay between inviting patients and setting up the clinics, oftentimes due to lack of availability of clinic rooms. Likewise, the consent clinics were scheduled during daytime working hours and although eligible participants were over 60 years old, some were in full time employment and evening clinics might have been more convenient.

Some of the larger practices had a very high response rate and the CRN nurses who work across multiple studies may not have had capacity to see all of the patients. Similarly, practice nurses consenting patients also have many other demands on their time, and research can be a lower priority. Almost a third of the practices recruiting to HEAT did so using their own practice nurse. Perhaps if GP practices were incentivised to participate in research, for example by utilising QOF [10], they might be more willing to get involved and put aside practice staff time to run research projects.

Strategy for GP practice recruitment in different CRN regions varied. Some recruited a lot of practices in a short time, possibly due to pressures from interested GPs, whereas others staggered practice recruitment to match nurse (and financial) capacity. In these regions fewer practices were recruited, but the percent of consented patients relative to number of EOIs was greater.

The number of patients expressing an interest in the trial represented a 20.5% volunteering rate, which was less than that seen in the pilot study (37% volunteering rate). This may have been due to the presence of a placebo. All of the participants in the pilot study found to be positive for *H pylori* were treated with eradication therapy, whereas participants in the main study were blinded to the treatment they received. Participants who withdrew and returned their tablets post randomisation generally gave a reason related to size and number of tablets or concern about side-effects, but some also stated that they would prefer to get treatment from their GP rather than be given placebo, despite the risk-benefit discussion during their consent visit.

With such a large trial recruiting older participants, it is inevitable that some were lost to the study through death (7.2% of randomised participants). Of the remaining participants, HEAT did not require follow up visits and used routinely collected electronic clinical data. This affects the significance of withdrawal data. Although 1271 participants were recorded as withdrawals, full continuing data collection was possible in all but the 72 randomised participants (1.3%) who actively withdrew their consent to all follow-up.

Many of the participants who withdrew without specifying a reason did so in response to the annual letter sent out to randomised participants and the letter sent out to explain GDPR. The annual letters give participants an update on trial progress, but also contain text reminding them that they are free to withdraw from the trial at any time. Participants in the HEAT trial attended for only one visit, took medication for only one week, and were subsequently followed up electronically with no personal contact, and hence may have forgotten that they were taking part in a trial. Trial participation is voluntary and a very important part of informed consent is the freedom to withdraw at any time. In the development of trial correspondence it may be beneficial that all letters, both invitation and follow-up, are reassuring to the participant in terms of current and future commitment.

The HEAT trial has provided much useful information for the design and planning of future trials of this size. With a large study involving many practices and personnel it can be difficult to keep oversight of individual recruitment sites. Recruiting GP practices to maintain pace with capacity, completing recruitment at one practice before starting a new one, and making clinic times more flexible could contribute to better recruitment for future studies. Nevertheless, this large ongoing trial has developed methodology showing that recruitment of large numbers of patients from primary care is attainable and could be applied to other clinical outcomes studies.