Six versus 12 months' adjuvant trastuzumab in patients with HER2-positive early breast cancer: the PERSEPHONE non-inferiority RCT

Helena Earl,[1,2,3*] Louise Hiller,[4] Anne-Laure Vallier,[5] Shrushma Loi,[4] Karen McAdam,[6,7] Luke Hughes-Davies,[1,7] Daniel Rea,[8] Donna Howe,[4] Kerry Raynes,[4] Helen B Higgins,[4] Maggie Wilcox,[9] Chris Plummer,[10,11] Betania Mahler-Araujo,[12,13] Elena Provenzano,[3,12] Anita Chhabra,[14] Sophie Gasson,[4] Claire Balmer,[4] Jean E Abraham,[1,2,3] Carlos Caldas,[1,2,3,15] Peter Hall,[16] Bethany Shinkins,[17] Christopher McCabe,[18] Claire Hulme,[17,19] David Miles,[20] Andrew M Wardley,[21,22] David A Cameron[16] and Janet A Dunn[4] on behalf of the PERSEPHONE Steering Committee and Trial Investigators

[1]Department of Oncology, University of Cambridge, Addenbrooke's Hospital, Cambridge, UK
[2]Cambridge Breast Cancer Research Unit, Cambridge University Hospitals NHS Foundation Trust, Cambridge, UK
[3]NIHR Cambridge Biomedical Research Centre, Cambridge, UK
[4]Warwick Clinical Trials Unit, University of Warwick, Coventry, UK
[5]Cambridge Clinical Trials Unit – Cancer Theme, Cambridge University Hospitals NHS Foundation Trust, Cambridge, UK
[6]Department of Oncology, North West Anglia NHS Foundation Trust, Peterborough City Hospital, Peterborough, UK
[7]Department of Oncology, Cambridge University Hospitals NHS Foundation Trust, Cambridge, UK
[8]Cancer Research UK Clinical Trials Unit (CRCTU), Institute of Cancer and Genomic Sciences, University of Birmingham, Birmingham, UK
[9]Independent Cancer Patients' Voice, London, UK
[10]Translational and Clinical Research Institute, Faculty of Medical Sciences, Newcastle University, Newcastle upon Tyne, UK
[11]Department of Cardiology, Freeman Hospital, Newcastle upon Tyne Hospitals NHS Foundation Trust, Newcastle upon Tyne, UK
[12]Department of Histopathology, Cambridge University Hospitals NHS Foundation Trust, Cambridge, UK
[13]Metabolic Research Laboratories, University of Cambridge, Cambridge, UK

[14]Pharmacy, Cambridge University Hospitals NHS Foundation Trust, Addenbrooke's Hospital, Cambridge, UK
[15]Cancer Research UK Cambridge Institute, University of Cambridge, Cambridge, UK
[16]Edinburgh University Cancer Research Centre, Institute of Genetics and Molecular Medicine, University of Edinburgh, Western General Hospital, Edinburgh, UK
[17]Academic Unit of Health Economics, University of Leeds, Leeds, UK
[18]Institute of Health Economics, Edmonton, AB, Canada
[19]Health Economics Group, University of Exeter Medical School, Exeter, UK
[20]Medical Oncology, Mount Vernon Cancer Centre, Northwood, UK
[21]NIHR Manchester Clinical Research Facility at The Christie NHS Foundation Trust, Manchester Academic Health Science Centre, Manchester, UK
[22]Division of Cancer Sciences, Faculty of Biology, Medicine and Health, University of Manchester, Manchester Academic Health Science Centre, Manchester, UK

*Corresponding author hme22@cam.ac.uk

Declared competing interests of authors: Helena Earl reports grants from Roche (Basel, Switzerland) and Sanofi-Aventis (Paris, France), personal fees and travel expenses from Daiichi Sankyo (Tokyo, Japan), AstraZeneca plc (Cambridge, UK) and Intas Pharmaceuticals (Ahmedabad, India), travel expenses from Pfizer Inc. (New York, NY, USA) and Amgen Inc. (Thousand Oaks, CA, USA) and personal fees from prIME Oncology (Atlanta, GA, USA), all outside the submitted work. Karen McAdam reports grants from Roche and personal fees from Roche, Novartis International AG (Basel, Switzerland), Pfizer and Eisai Co., Ltd (Tokyo, Japan), all outside the submitted work. Daniel Rea reports personal fees and grants from Roche during the conduct of the study, as well as personal fees from Novartis, Pfizer, Genomic Health (Redwood City, CA, USA) and Daiichi Sankyo, and grants from Celgene Corporation (Summit, NJ, USA), all outside the submitted work. Chris Plummer reports personal fees and non-financial support from Roche Products Limited, Novartis UK Limited, Pfizer UK Limited, Celgene and Incyte Corporation (Wilmington, DE, USA) for attending education meetings. He also reports personal fees and non-financial support from Amgen Limited for attending education meetings and advisory boards, all outside the submitted work. Jean Abraham reports fees to her institution, and accommodation and travel expenses from AstraZeneca for session boards and advisory chairs, as well as fees to her institution, and accommodation and travel expenses from Pfizer for a lecture, all outside the submitted work. Carlos Caldas reports grants from Genentech, Inc. (South San Francisco, CA, USA), Roche, Servier Laboratories (Suresnes, France) and AstraZeneca outside the submitted work, and that he is a member of the AstraZeneca iMED External Science Panel. Peter Hall reports grants from Roche, Pfizer, AstraZeneca, Novartis, Eisai and Daiichi Sankyo outside the submitted work. Christopher McCabe's institution holds research contracts with Roche and reports grants from Roche, all outside the submitted work. David Miles reports personal fees from Roche/Genetech, outside the submitted work. Claire Hulme reports that she is a member of the National Institute for Health Research (NIHR) Health Technology Assessment Commissioning Board. Andrew M Wardley reports personal fees from Roche, Napp Pharmaceuticals Ltd (Cambridge, UK), Amgen, Merck Sharp & Dohme (Hoddesdon, UK), Novartis, Pfizer, AstraZeneca, Laboratoires Pierre Fabre (Paris, France), Accord (Barnstaple, UK), Athenex (Buffalo, NY, USA), Gerson Lehrman Group (New York, NY, USA), Coleman Research Expert Network Group (New York, NY, USA) and Guidepoint Global (New York, NY, USA). He also reports personal fees and other from Eli Lilly and Company (Indianapolis, IN, USA) and Daiichi Sankyo, all outside the submitted work. He is leading the National Cancer Research Institute Breast Group Initiative to develop the next de-escalation trial for HER2-positive breast cancer. David A Cameron reports funds to his institution from Novartis, Astrazeneca, Pfizer, Roche, Eli Lilly and Company, Puma Biotechnology (Los Angeles, CA, USA), Daiichi Sankyo, Synthon (Nijmegen, the Netherlands), SeaGen International GmbH (Zug, Switzerland), Zymeworks (Vancouver, BC, Canada), Elsevier (Amsterdam, the Netherlands), European Cancer Organisation (Brussels, Belgium), Celgene Corporation, Succinct Medical Communications (Wilmington, DE, USA), Immutep (Sydney, NSW, Australia),

Oncolytics Biotech (U.S) Inc. (San Diego, CA, USA), Celldex Therapeutics Inc. (Hampton, NJ, USA), San Antonio Breast Cancer Consortium (TX, USA), Highfield Communication (Oxford, UK), Samsung Bioepis Co. Ltd (Incheon, South Korea), prIME Oncology, Merck Sharp & Dohme Ltd, Prima Biomed Ltd, RTI Health Solutions (Research Triangle, NC, USA) and Eisai, all outside the submitted work. Janet A Dunn reports that she is a member of the NIHR Efficacy and Mechanism Evaluation funding board and an NIHR senior investigator.

Published August 2020
DOI: 10.3310/hta24400

Scientific summary

The PERSEPHONE RCT

Health Technology Assessment 2020; Vol. 24: No. 40
DOI: 10.3310/hta24400

NIHR Journals Library www.journalslibrary.nihr.ac.uk

Scientific summary

Background

The incidence of breast cancer continues to rise in Western Europe and North America and breast cancer remains a major health problem, despite considerable improvements in the treatment of the disease. Trastuzumab (also known as Herceptin®; Roche, Basel, Switzerland) treatment in patients with human epidermal growth factor receptor 2 (HER2)-positive early breast cancer has proved a major advance. However, the choice of 12 months' adjuvant trastuzumab in the pivotal registration studies was arbitrary. As the beneficial effect of adjuvant trastuzumab was detected early in follow-up (median of 1 year), it was reasonable to hypothesise that the majority of the adjuvant benefit may result from the first months of therapy, rather than 12 months of treatment being required for the same effect. This hypothesis was supported by evidence from the FinHer trial, which randomised patients to chemotherapy with or chemotherapy without 9 weeks of trastuzumab. The trial demonstrated a significant benefit of 9 weeks' trastuzumab over no trastuzumab to a similar degree to that demonstrated in the registration trials of 12 months' trastuzumab.

Objectives

To compare 6 months of trastuzumab with 12 months of trastuzumab in terms of non-inferiority and safety. Mapping on to standard practice in the UK, the trial recruited patients with HER2-positive early breast cancer as determined by local diagnostic pathology tests and standard staging protocols.

End points

Primary end point

- To assess disease-free survival and non-inferiority of 6 months' (nine cycles) compared with 12 months' (18 cycles) trastuzumab in patients with HER2-positive early breast cancer.

Secondary end points

- To assess overall survival non-inferiority of 6 months' compared with 12 months' trastuzumab in patients with HER2-positive early breast cancer.
- To assess the expected incremental cost-effectiveness (cost per quality-adjusted life-year) for 6 months' compared with 12 months' trastuzumab.
- Cardiac function as assessed by left ventricular ejection fraction during trastuzumab therapy, and analysis of predictive factors for the development of cardiac damage.

Secondary objectives: substudies

- Trans-PERSEPHONE: tumour blocks (paraffin-embedded) were collected prospectively from patients in the study for molecular and candidate gene analysis as prognostic and predictive markers (separate protocol).
- Trans-PERSEPHONE-SNPs: blood samples were collected prospectively from patients in the study for single nucleotide polymorphism analysis to research genetic/pharmacogenetic determinants of inherited susceptibility to HER2-positive breast cancer, prognosis and trastuzumab response and toxicity (separate protocol).

Trial design and methodology

The trial was a prospective, randomised, multicentre, open-label, non-inferiority, Phase III clinical trial. Patients were randomised (1 : 1) to either 12 months of trastuzumab (standard) or 6 months of trastuzumab (experimental), with randomisation occurring at any time before the 10th cycle of trastuzumab. Randomisation was by telephone to the Warwick Clinical Trials Unit, where a central computerised minimisation procedure used stratification variables. These were (1) local diagnostic pathology-reported oestrogen receptor status (positive or negative), (2) chemotherapy type (anthracyclines without taxanes, anthracyclines with taxanes, taxanes without anthracyclines or neither anthracyclines nor taxanes), (3) chemotherapy timing (adjuvant or neoadjuvant) and (4) trastuzumab timing with reference to chemotherapy (concurrent or sequential).

Treatment and investigations

Experimental arm

Patients in the experimental arm received 6 months' trastuzumab intravenously every 3 weeks for nine cycles; this started in cycle 1 with a loading dose of 8 mg/kg and subsequent doses were 6 mg/kg. When the subcutaneous formulation of trastuzumab was licensed this was able to be used in the trial at a fixed dose of 600 mg from the start. Patients who commenced on intravenous trastuzumab could be switched to the subcutaneous formulation at the discretion of the treating clinician.

Control arm

Patients in the control arm received 12 months' trastuzumab in the same dose and formulation as for 6 months' treatment.

All patients had HER2-positive breast cancers, reported in accordance with UK Royal College of Pathologists HER2 testing guidelines. All laboratories testing for HER2 were part of the National External Quality Assurance Scheme. Patients' breast cancers were either immunohistochemistry score 3+ or immunohistochemistry score 2+ with *HER2* gene amplification on in situ hydridisation. All patients received chemotherapy as adjuvant or neoadjuvant treatment and received trastuzumab either concurrently with or sequentially after chemotherapy. Trastuzumab was given concurrently with the non-anthracycline component of chemotherapy. For the first 2500 patients, left ventricular ejection fraction was measured at baseline and then 3-monthly for 12 months from the start of trastuzumab. For subsequent patients, left ventricular ejection fraction measurements were taken every 4 months, as had become standard in the UK. All chemotherapy regimens used routinely in standard practice were allowed in the trial.

Sample size determination

The trial was designed to allow demonstration of non-inferiority of the experimental arm (6 months' trastuzumab) in terms of the primary end point of disease-free survival compared with the control arm (12 months' trastuzumab). The power calculations assumed that the disease-free survival from the standard treatment of 12 months' trastuzumab would be 80% at 4 years. The margin for non-inferiority was set as a 3% level, implying that the 4-year disease-free survival of the experimental arm should not be below 77%, a difference equivalent to a hazard ratio of 1.17. On this basis, with 5% one-sided significance and 85% power, a trial randomising 4000 patients in total (2000 in each arm) would have the ability to prove non-inferiority of the experimental arm.

Follow-up

Follow-up was 6-monthly for 2 years and annually thereafter for a further 8 years to reach 10 years from the date of first trastuzumab treatment. A protocol amendment in 2018 allowed for annual follow-up by telephone call or e-mail, depending on standard practice at the site.

Inclusion criteria

- Histological diagnosis of invasive breast cancer.
- No evidence of metastatic disease.
- Known hormone receptor status.
- Overexpression of *HER2* receptor.
- Bilateral breast cancers were eligible provided that one of the tumours overexpressed the *HER2* receptor.
- Clear indication for neoadjuvant or adjuvant chemotherapy based on clinical and histopathological features.
- Patients were fit to receive neoadjuvant or adjuvant chemotherapy and trastuzumab in the opinion of the responsible physician.
- No previous diagnosis of malignancy unless:
    - managed by surgical treatment only, and disease free for 10 years.
    - previous basal cell carcinoma, cervical carcinoma in situ or ductal carcinoma in situ of the breast.
- Not pregnant and not lactating, with no intention of becoming pregnant during chemotherapy, and agreed to adopt adequate contraceptive measures if they were pre-menopausal and sexually active.
- No concurrent medical or psychiatric problems that might prevent completion of treatment or follow-up.
- Aged $\geq$ 18 years.
- Written informed consent for the study given at any time before the 10th cycle of trastuzumab.

Exclusion criteria

- Significant concurrent cardiac disease or significant concurrent comorbidity that, in the opinion of the responsible physician, would add to the risks associated with trastuzumab or cytotoxic chemotherapy.
- Inability to comply with protocol requirements.
- Received more than nine cycles of trastuzumab.
- Any other condition that, in the local investigator's opinion, would make the patient unsuitable to participate in the trial.

Outcomes

The primary end point of disease-free survival was calculated from the date of diagnostic biopsy to the date of the first invasive breast cancer relapse (local or distant) or death, or to the date of censor in patients alive and relapse free. Overall survival was calculated from the date of diagnostic biopsy. As randomisation could occur at any time up to and including the ninth cycle of trastuzumab, a landmark analysis was carried out from 6 months after the start of trastuzumab. Additional analyses of invasive disease-free survival [to include invasive contralateral breast cancers and second primary invasive cancers (non-breast)], distant disease-free survival, and breast cancer-specific survival were carried out. The number of trastuzumab cycles received per patient was recorded, along with the route of administration and the reasons for any deviation from the protocol. Left ventricular ejection fraction was defined as low if $< 50\%$ or if reported as low without quantification. Incidence of clinical cardiac dysfunction, defined as symptoms or signs of congestive heart failure or prescription of new or altered

cardiac medication, was recorded every 3 months for 12 months. A cardiologist (CP) was a member of the trials group and reviewed the cardiac toxicity together with the chief investigator (HME) and other members of the Trial Management Group.

The cost-effectiveness of 6 months' trastuzumab compared with 12 months' trastuzumab was assessed 2 years after the start of trastuzumab, based on the landmark analysis, using a within-trial analysis. A secondary within-trial analysis was conducted adopting a societal perspective. A de novo decision-analytic model was also developed to assess cost-effectiveness over a lifetime horizon. Patients were also invited to regularly report their trial and treatment experiences in a free-text page in the quality-of-life booklet.

Results

Of 4088 patients, 2045 were randomly assigned to 12 months' trastuzumab and 2043 were randomly assigned to 6 months' trastuzumab. Sixty-nine per cent (2825/4088) had hormone-receptor-positive disease; 90% (3683/4088) received anthracyclines [41% (1696/4088) without taxanes and 49% (1987/4088) with taxanes)] and 10% (400/4088) received taxane combinations without anthracyclines; and 54% (2188/4088) received sequential trastuzumab and 46% (1900/4088) received concurrent trastuzumab. Eighty-five per cent (3462/4088) of patients received adjuvant chemotherapy and, of these, 41% (1419/3462) were axillary lymph node positive and 58% (2017/3462) were axillary lymph node negative; 47% (1626/3462) of tumours were ≤ 2 cm in diameter and 50% (1734/3462) were > 2 cm. At 6.1 years' median follow-up, there were 389 (10%) deaths [182 (9%) in the 12-month arm; 207 (10%) in the 6-month arm] and 566 (14%) disease-free survival events [270 (13%) in the 12-month arm; 296 (14%) in the 6-month arm]. The 4-year disease-free survival rate was 90.3% (95% confidence interval 88.9% to 91.5%) in the 12-month arm and 89.5% (95% confidence interval 88.1% to 90.8%) in the 6-month arm. The hazard ratio for 6 months compared with 12 months was 1.10 (90% confidence interval 0.96 to 1.26; non-inferiority $p = 0.01$), demonstrating non-inferiority of 6 months' trastuzumab. Congruent results were found for overall survival (4-year rates, 94.9% vs. 94.2% for 12 and 6 months, respectively; non-inferiority $p = 0.0003$), and also in a landmark analysis 6 months after starting trastuzumab, with 4-year disease-free survival 88.7% versus 88.4% (non-inferiority $p = 0.03$) and overall survival 93.2% versus 92.6% (non-inferiority $p = 0.006$). Survival curves of invasive disease-free survival, distant disease-free survival and breast cancer specific survival were comparable with those of the protocol-specified primary and secondary end points.

Forest plots for disease-free survival showed heterogeneity in the treatment effect for the timing of trastuzumab (sequential and concurrent; $p < 0.001$). Patients receiving concurrent trastuzumab and chemotherapy appeared to do better with 12 months' treatment than with 6 months' treatment (hazard ratio 1.54, 95% confidence interval 1.19 to 1.99), whereas with sequential trastuzumab 6 months' treatment appeared non-inferior (hazard ratio 0.87, 95% confidence interval 0.70 to 1.07). It is important to note that the type of chemotherapy used and the scheduling of trastuzumab and chemotherapy were decided by the investigators and not randomised. Patients in whom concurrent rather than sequential scheduling was used were more likely to be node positive (53% vs. 32%; $p < 0.0001$) and had larger tumours (> 2 cm: 55% vs. 47%; $p < 0.0001$). The majority of patients given sequential treatment received six cycles of anthracycline-based chemotherapy and this group has the longest follow-up as this was the predominant chemotherapy in the early years of the trial. Heterogeneity was also found for chemotherapy type ($p = 0.01$), although this result should be interpreted with caution, as it is driven mainly by an apparent effect in the small taxane-only group. No heterogeneity was seen for oestrogen receptor status, timing of chemotherapy (adjuvant/neoadjuvant), age, tumour grade, menopausal status and immunohistochemistry score; and for adjuvant patients there was no heterogeneity for axillary nodal status, tumour size at surgery, and a composite of oestrogen receptor and axillary node status.

Clinical cardiac dysfunction was reported more commonly in 12-month than in 6-month patients [228/1987 (11%) vs. 156/2008 (8%) respectively; $p < 0.0001$]. A small absolute difference was observed in the first 6 months (8% of 12-month patients, 6% of 6-month patients, $p = 0.01$), with a larger difference during the 7- to 12-month period (8% vs. 5% respectively, $p = 0.0002$). Trastuzumab was stopped early because of cardiac toxicity in 146 out of 1941 (8%) 12-month patients and in 61 out of 1977 (3%) 6-month patients ($p < 0.0001$). Low left ventricular ejection fraction was recorded in 228 out of 2042 (11%) 12-month patients and in 175 out of 2038 (9%) 6-month patients. There was little difference in falls in left ventricular ejection fraction, with an absolute decrease of $\geq 10\%$ from baseline to $< 50\%$ seen in 164 out of 1964 (8%) 12-month patients and in 131 out of 1961 (7%) 6-month patients. Substantial falls in left ventricular ejection fraction to $< 50\%$ after a baseline of $\geq 59\%$ were seen in 109 out of 1964 (6%) 12-month patients and in 86 out of 1961 (4%) 6-month patients. In the first 6 months, this was similar in the 12-month arm (64/1955; 3%) and the 6-month arm (70/1957; 4%), but in the 7- to 12-month period it was higher for the 12-month group (71/1880; 4%) than for the 6-month group (33/1701; 2%) ($p = 0.0015$).

During the 12-month period from starting trastuzumab, a higher proportion of 12-month patients than of 6-month patients reported at least one adverse event of severe grade according to Common Terminology Criteria for Adverse Events version 3 (grade ≥ 3, or 2 for palpitations): 460 out of 1935 (24%) and 365 out of 1929 (19%), respectively ($p = 0.0003$). The toxicities that were reported in excess in the 12-month patients compared with the 6-month patients, in decreasing order of frequency, were fatigue (11.5% vs. 8.6%: $p = 0.003$), muscle/joint pains (11.3% vs. 8.8%: $p = 0.01$), pain (5.2% vs. 3.1%: $p = 0.001$), palpitations (4.8% vs. 2.8%: $p = 0.002$), cough (4.1% vs. 2.2%: $p = 0.0007$) and chills (3.6% vs. 2.0%: $p = 0.003$). The excess toxicities were seen predominantly during the 7- to 12-month period.

Health economic analyses demonstrated that 6 months' trastuzumab resulted in significantly lower lifetime costs than and similar lifetime quality-adjusted life-years to 12 months' trastuzumab, and there is a high probability that 6 months' trastuzumab is cost-effective compared with 12 months' trastuzumab. The cost-effectiveness of 6 months' trastuzumab is less certain in predefined subgroups. Further analysis is required to understand if there is a population of patients at sufficient clinical risk in whom 12 months' trastuzumab would be considered the more cost-effective option. Analysis of patient-reported experiences showed that side effects from trastuzumab had a significant impact on daily life; the most frequently reported were fatigue and aches/pains.

Conclusions

We have demonstrated that 6 months' trastuzumab is non-inferior to 12 months' trastuzumab in the treatment of HER2-positive early breast cancer, with less cardiotoxicity and fewer severe adverse events. The trial accepted all patients who were HER2 positive and were receiving or planned to receive chemotherapy and trastuzumab treatment, and for the whole trial population we have demonstrated non-inferiority. This is the only reduced duration study to demonstrate clear non-inferiority, and these results support the consideration of reduced duration trastuzumab for patients at a similar risk of recurrence to patients included in the trial.

Trial registration

This trial is registered as ISRCTN52968807, EudraCT 2006-007018-39 and ClinicalTrials.gov NCT00712140.

Funding

This project was funded by the National Institute for Health Research (NIHR) Health Technology Assessment programme and will be published in full in *Health Technology Assessment*; Vol. 24, No. 40. See the NIHR Journals Library website for further project information.

Health Technology Assessment

HTA/HTA TAR

ISSN 1366-5278 (Print)

ISSN 2046-4924 (Online)

Impact factor: 3.370

Health Technology Assessment is indexed in MEDLINE, CINAHL, EMBASE, the Cochrane Library and Clarivate Analytics Science Citation Index.

This journal is a member of and subscribes to the principles of the Committee on Publication Ethics (COPE) (www.publicationethics.org/).

Editorial contact: journals.library@nihr.ac.uk

The full HTA archive is freely available to view online at www.journalslibrary.nihr.ac.uk/hta. Print-on-demand copies can be purchased from the report pages of the NIHR Journals Library website: www.journalslibrary.nihr.ac.uk

Criteria for inclusion in the *Health Technology Assessment* journal

Reports are published in *Health Technology Assessment* (HTA) if (1) they have resulted from work for the HTA programme, and (2) they are of a sufficiently high scientific quality as assessed by the reviewers and editors.

Reviews in *Health Technology Assessment* are termed 'systematic' when the account of the search appraisal and synthesis methods (to minimise biases and random errors) would, in theory, permit the replication of the review by others.

HTA programme

Health Technology Assessment (HTA) research is undertaken where some evidence already exists to show that a technology can be effective and this needs to be compared to the current standard intervention to see which works best. Research can evaluate any intervention used in the treatment, prevention or diagnosis of disease, provided the study outcomes lead to findings that have the potential to be of direct benefit to NHS patients. Technologies in this context mean any method used to promote health; prevent and treat disease; and improve rehabilitation or long-term care. They are not confined to new drugs and include any intervention used in the treatment, prevention or diagnosis of disease.

The journal is indexed in NHS Evidence via its abstracts included in MEDLINE and its Technology Assessment Reports inform National Institute for Health and Care Excellence (NICE) guidance. HTA research is also an important source of evidence for National Screening Committee (NSC) policy decisions.

This report

The research reported in this issue of the journal was funded by the HTA programme as project number 06/303/98. The contractual start date was in April 2007. The draft report began editorial review in July 2019 and was accepted for publication in January 2020. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The HTA editors and publisher have tried to ensure the accuracy of the authors' report and would like to thank the reviewers for their constructive comments on the draft document. However, they do not accept liability for damages or losses arising from material published in this report.

This report presents independent research funded by the National Institute for Health Research (NIHR). The views and opinions expressed by authors in this publication are those of the authors and do not necessarily reflect those of the NHS, the NIHR, NETSCC, the HTA programme or the Department of Health and Social Care. If there are verbatim quotations included in this publication the views and opinions expressed by the interviewees are those of the interviewees and do not necessarily reflect those of the authors, those of the NHS, the NIHR, NETSCC, the HTA programme or the Department of Health and Social Care.

Published by the NIHR Journals Library (www.journalslibrary.nihr.ac.uk), produced by Prepress Projects Ltd, Perth, Scotland (www.prepress-projects.co.uk).