What is a scoping report?
Scoping reports ascertain the quantity and quality of the published clinical and cost-effectiveness evidence on health technologies under consideration by decision makers within NHSScotland. They also serve to clarify definitions related to the research question(s) on that topic. They are intended to provide an overview of the evidence base, including gaps and uncertainties, and inform decisions on the feasibility of producing an evidence review product on the topic. Scoping reports are undertaken in an approximately 1-month period. They are based upon a high-level literature search and selection of the best evidence that Healthcare Improvement Scotland could identify within the time available. The reports are subject to peer review. Scoping reports do not make recommendations for NHSScotland, however the Scottish Health Technologies Group (SHTG) produce an Advice Statement to accompany all evidence reviews. Further information on scoping reports is available at www.healthcareimprovementscotland.org

Key definitions
FDG: 18F-Fluorodeoxyglucose – a radiotracer used in PET or PET/CT scanning.
Gallium scan: a nuclear imaging test that uses gallium as a radiotracer.
Negative predictive value (NPV): the probability that a person with a negative test is a true negative (ie does not have the disease)¹.
Positive predictive value (PPV): the probability that a person with a positive test is a true positive (ie does have the disease)¹.
PUO: a duration of illness of more than 3 weeks prior to diagnosis, a repeatedly documented body temperature exceeding 38.3°C, and failure to be diagnosed after multiple examinations as either an inpatient or outpatient.
Sensitivity: the probability that a person having a disease will be correctly identified by a clinical test, ie, the number of true positive results divided by the total number with the disease¹.
Specificity: the probability that a person not having a disease will be correctly identified by a clinical test, ie, the number of true negative results divided by the total number of those without the disease¹.

Background
Pyrexia of unknown origin (PUO)
Pyrexia of unknown origin was originally defined as a temperature higher than 38.3°C documented on several occasions and lasting at least 3 weeks, with a diagnosis that remains uncertain after at least 1 week of investigation in a hospital². Subsequently, this definition has been modified by removing the requirement for in-hospital evaluation and redefining the latter criterion to include at least inpatient or outpatient evaluation for a minimum of 3 days or three outpatient visits, along with exclusion of immune-compromised states².

Most cases of PUO are unusual presentations of common diseases. There are more than 200 clinical findings associated with PUO³. In adults, infections and cancer account for 25–40% cases of PUO, and autoimmune disorders account for 10–20%. In children, 30–50% of cases are due to infections, 5–10% to cancer, and 10–20% to autoimmune disorders⁴. Some patients remain undiagnosed despite extensive investigations (10–15%) and usually in these cases (75%) the fever resolves spontaneously⁴.

PUO is often cited as a ‘common problem’, but incidence or prevalence figures could not be found for this scoping report. Clinical experts from Tayside estimate 250–300 cases per year from a catchment population of 440,000.
(J Davidson, Consultant Physician in Nuclear Medicine and Positron Emission Tomography (PET)/Computed Tomography (CT). Personal communication, 24 April 2013). A similar estimate has been given for the west of Scotland (though the catchment population is much larger) (S Han, Consultant Nuclear Medicine Physician & Clinical Lead. Personal communication, 31 July 2013). For NHS Grampian, there are an estimated 30–50 referrals from the catchment population (approximately 525,000) (A Denison, NHS Grampian Clinical Lead, Nuclear Medicine/PET. Personal communication, 3 August 2013).

PUO can be investigated using a wide range of tests including: full blood count, blood films, urea and electrolytes, liver function tests, C-reactive protein, plasma viscosity, vasculitis screen, blood cultures, urine cultures, stool cultures, sputum cultures, chest x-ray, echocardiography, CT scan, liver biopsy and bone marrow aspiration. There is no gold standard for the diagnostic work-up of PUO (J Davidson, Consultant Physician in Nuclear Medicine and PET/CT. Personal communication, 20 March 2013).

Positron Emission Tomography/Computed Tomography (PET/CT)

PET is a non-invasive imaging technique that is widely accepted in oncological practice. It involves introducing a radiotracer to the body (normally intravenously), such as fluorodeoxyglucose (FDG). FDG is similar to naturally occurring glucose, and the body treats it in a similar way. Metabolically active cells (including malignant and inflammatory) utilise and import more glucose than other tissues, and thus take up FDG more rapidly. A newer generation of PET scanners is now available, known as PET/CT scanners. These incorporate a CT scanner, to provide complementary anatomical images. There are currently five PET/CT scanners in Scotland (two in Glasgow, and one each in Edinburgh, Aberdeen and Dundee) (P McAuley, Scottish Government. Personal communication, May 2012). Although still in use, standalone PET scanners are no longer manufactured.

In Scotland, PET/CT scans tend to be used as a ‘final resort’ in patients with PUO who have been investigated using more conventional means, often over a significant period of time as both inpatients and outpatients. The majority of the PET/CT clinical workload tends to be based around oncology cases. The use of this technology in the investigation of non-oncology cases varies between the four centres in Scotland, and there is a need for evidence-based clarity on the role of PET/CT in PUO (J Davidson, Consultant Physician in Nuclear Medicine and PET/CT. Personal communication, March 2013).

Guidelines from the Royal College of Physicians (RCP) and Royal College of Radiologists (RCR) recommend that PET/CT be used ‘to identify the cause of a PUO where conventional investigations have not revealed a source’.

The purpose of this scoping report is two-fold:
- to evaluate the evidence supporting the recommendation in the RCP/RCR guidelines; and
- to search for, and evaluate, any additional evidence available.

The following questions were scoped:
1. What is the sensitivity and specificity of PET/CT compared with other diagnostic imaging modalities in determining the cause of PUO?
2. What is the clinical and cost effectiveness of PET/CT as a first-line investigation in patients with PUO?

Literature search

A systematic search of the secondary literature was carried out between 29 March 2013 and 11 April 2013 to identify systematic reviews, health technology assessments, meta-analyses and other evidence-based assessments. Medline, Medline in process, Embase, Cinahl and Web of Science databases were searched for systematic reviews and meta-analyses.

Key websites were searched for guidelines, policy documents, clinical summaries and economic studies.

Concepts used in all searches included: pyrexia of unknown origin, fever of unknown origin, fever without source, positron emission tomography (PET), fluorine-18 fluorodeoxyglucose positron emission tomography FDG PET/CT. A full list of resources searched and terms used are available on request.

Studies on either PET or PET/CT were included.
Evidence base

Table 1 Included evidence sources

<table>
<thead>
<tr>
<th>Publication type</th>
<th>Number of publications</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systematic review</td>
<td>1</td>
<td>7</td>
</tr>
<tr>
<td>Meta-analysis</td>
<td>1</td>
<td>7</td>
</tr>
<tr>
<td>Clinical guidelines</td>
<td>3</td>
<td>6, 8, 9</td>
</tr>
<tr>
<td>Diagnostic cohort studies</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>General review with comprehensive search</td>
<td>1</td>
<td>12</td>
</tr>
</tbody>
</table>

Full text not retrieved, details taken from Dynamed and Meller et al (2009) 10, 11

The two studies included in the RCP and RCR guidelines have not been included in this table3,13.

Findings

Clinical effectiveness

Calculation of parameters of accuracy (including sensitivity, specificity, NPV and PPV) is complex for PUO in that there is no gold standard for comparison, so studies use a range of, usually composite, reference standards for which follow-up time is an important criterion. In addition to this:

- a final diagnosis is typically missed in a substantial number of patients; and
- a negative scan is not generally helpful in the diagnostic work-up of PUO, even if the result is a true negative11.

Many studies report how often the scans helped in reaching the final diagnosis (for example, by directing further targeted investigations). Therefore, when available these data have also been extracted from the studies.

The RCP and RCR recommendation is based on two studies3,13, which have been summarised below. The literature search for this report identified a further systematic review (with meta-analysis)7, two clinical guidelines8,9, two studies (summary taken from general reviews10,11) and a general review with a comprehensive search12.

All the studies used the radiotracer FDG for the PET or PET/CT scans. The studies also used the definition of PUO as described in key definitions.

No studies were identified that exactly addressed the questions scoped. While some studies report on sensitivity and specificity of PET/CT for detecting the cause of PUO, there was very little comparing it with other imaging modalities. Also, it was not clear from the literature where in the diagnostic work-up PET/CT would be most appropriate.

RCP and RCR guidelines (2012)6

Guidelines from the RCP and RCR recommend that PET/CT be used ‘to identify the cause of a PUO where conventional investigations have not revealed a source’6. The evidence supporting the recommendation comes from one retrospective and one prospective13 study. It is unclear how these particular studies were identified and selected.

The retrospective study investigated the diagnostic value of PET or PET/CT in the diagnostic work-up of children and young people presenting with PUO or unexplained signs of inflammation without fever3. The authors analysed 47 PET and 30 PET/CT scans in 69 patients.

Of all 77 scans, 35 (45%) were rated as helpful by either excluding the need for or directing further targeted investigations. Of the combined PET/CT scans, 53% were considered helpful, whereas PET without CT was helpful only in 40% of cases. Based on the findings, the authors of the study concluded that PET and PET/CT should not be suggested as a first-line diagnostic approach in children because of the radiation exposure, but could serve as a reliable non-invasive tool with satisfactory results if previous diagnostic approaches have been unsuccessful. However, as this is a retrospective study of a heterogenous patient group, it is prone to bias. Therefore, the results should be treated with caution. The authors noted that there is a need for large prospective multi-centre studies before firm conclusions can be drawn.

The prospective study included 48 adults with PUO (25 men, 23 women; age range 24–82 years)13. Previous clinical assessment included medical history, physical examination, and routine laboratory tests. All underwent PET/CT scans. Final diagnosis was based on histopathology, microbiologic assays, or clinical and imaging follow up.
Of the 48 PET/CT scans, 27 demonstrated foci of increased FDG uptake (ie were positive scans). In 22 of the 27, PET/CT diagnosed the aetiology of PUO. Nine patients had localised infection, ten had inflammation (including arteritis, idiopathic pericarditis and sarcoidosis/sarcoid-like disease), and three had a malignancy. The remaining five positive PET/CT scans were considered as noncontributory to the final diagnosis and defined as false positives.

PET/CT showed no abnormal uptake in 21 patients. None of these patients had a final diagnosis of focal infection, inflammation, or malignancy for a clinical follow-up period of 12 to 36 months. Thus, no false-negative studies were recorded. The authors reported that the performance of PET/CT for the diagnosis of a focal disease process representing the aetiology of PUO showed a sensitivity of 100%, specificity of 81%, PPV of 81%, NPV of 100%, and accuracy of 90%.

The authors note the good PPV and high NPV, and conclude that if proved by further studies, PET/CT may in the future be used as one of the initial diagnostic investigations in patients with PUO.

Other literature
A moderate quality meta-analysis from 2011 examined the overall diagnostic performance of PET and PET/CT in PUO. Nine studies representing 388 patients were included, of which five were PET studies and four were PET/CT studies (including the prospective study described in the previous section). The authors rated three of the studies as ‘high quality’, with the remaining six as ‘acceptable quality’ (although these assessments could be considered to be generous). All reference standards used in the individual studies were accepted.

A true positive result was defined as one where the pathological findings led to the direct determination of the correct diagnosis. An abnormal result (ie a positive scan) was defined as false positive when the detected abnormality was considered to be unrelated to the illness causing the fever or when no final diagnosis could be made. A scan with no suggestive foci was considered to be false negative when a focal disease process was identified by another method and was considered to be the cause of the fever. Finally, a result was defined as true negative when no localised focus was found and there was no evidence of disease after clinical follow up. The results are presented in table 2 (below).

Based on these findings the authors conclude that PET appears to be a sensitive and promising tool for the detection of the causes of PUO. They also conclude that PET/CT should be considered among the first diagnostic tools for patients with PUO in whom conventional diagnostics have been unsuccessful, although this could be considered premature based on the evidence presented. For the PET studies (but not PET-CT), the meta-analysis for sensitivity and specificity revealed significant statistical heterogeneity.

Table 2 Summary of Dong et al meta-analysis

<table>
<thead>
<tr>
<th></th>
<th>PET</th>
<th>PET/CT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total number of studies</td>
<td>5 (3 retrospective and 2 prospective)</td>
<td>4 (3 retrospective and 1 prospective)</td>
</tr>
<tr>
<td>Total number of patients</td>
<td>214</td>
<td>174</td>
</tr>
<tr>
<td>Number of abnormal scans</td>
<td>123</td>
<td>117</td>
</tr>
<tr>
<td>Number in whom scan was helpful in obtaining final diagnosis</td>
<td>69/214 (32%)</td>
<td>108/174 (62%)</td>
</tr>
<tr>
<td>Pooled sensitivity for detecting cause of PUO</td>
<td>82.6% (95% confidence interval (CI) 72.9 to 89.9)</td>
<td>98.2% (95% CI 93.6 to 99.8)</td>
</tr>
<tr>
<td>Pooled specificity for detective cause of PUO</td>
<td>57.8% (95% CI 48.8 to 66.5)</td>
<td>85.9% (95% CI 75.0 to 93.4)</td>
</tr>
<tr>
<td>Sensitivity according to diagnostic category</td>
<td>Detection of neoplasm 86.7% (95% CI 59.5 to 98.3)</td>
<td>Detection of neoplasm 91.7% (95% CI 68.9 to 99.4)</td>
</tr>
<tr>
<td></td>
<td>Infection or inflammation 81.5% (95% CI 63.0 to 93.3)</td>
<td>Infection or inflammation 96.7% (95% CI 82.4 to 99.7)</td>
</tr>
<tr>
<td></td>
<td>Non-infectious inflammation 76.3% (95% CI 51.6 to 92.4)</td>
<td>Non-infectious inflammation 91.1% (95% CI 78.8 to 97.5)</td>
</tr>
</tbody>
</table>
Also, the authors rated three studies as ‘high quality’, but these were all retrospective and were likely to be prone to bias. Finally, a few inaccuracies in the reporting were noted. There is a need for larger prospective studies.

The literature search for this scope identified a further two general reviews\(^{10,11}\). These did not meet the inclusion criteria (as they were not systematic); however they highlighted two prospective studies (from 2000 and 2001) that were not included in the meta-analysis by Dong et al:\(^7\):

- A small study from 2000 (n=20) compared PET and gallium scans in patients with PUO. Follow up was 1 to 6 months. The authors reported a sensitivity of 84% and a specificity of 86% for PET in detecting the cause of the fever, and a sensitivity and specificity of 67% and 78%, respectively, for the gallium scans. Of the 20 PET scans, 11 showed abnormal uptake and contributed to the final diagnosis (55%). No focus of \(^{67}\)Ga-citrate uptake was missed on the PET-scans. A gallium scan was negative in one patient with pelvic abscess and non diagnostic in three patients with aortitis clearly visualised by PET\(^{10,11}\).

- The second study (2001) included 58 patients with PUO referred for a PET scan. Forty of these patients also had a gallium scan. The PET scans were abnormal in 46 patients (79%) and helped determine diagnosis in 24 (41%). Of the 40 people who had both PET and gallium scans, both suggested diagnosis in 10 patients (25%), and PET suggested diagnosis in an additional four patients (total 35% cases). In 20 patients, the cause of PUO was not diagnosed, and in all but six the fever resolved spontaneously. The remaining six were followed up as outpatients for ‘several years’ (exact length of follow up not clear)\(^{10,11}\).

Two additional reviews were identified. For the first, the authors appear to have conducted a comprehensive literature search, however the methodology was otherwise non-systematic. It did not identify any additional studies on PET or PET/CT in PUO\(^{12}\). The other review (which informed a guideline) largely supports the findings already presented, with the authors concluding that ‘there are promising data on the use of FDG-PET or FDG-PET/CT in evaluating adults with PUO, but the data regarding their use in paediatric patients are more limited’\(^8\). Finally, a guideline published in 2013 states that based on cumulated reported accuracy and expert opinion, PUO may be an indication for PET/CT\(^9\). However, they go on to say that the level of evidence available at this time remains insufficient to strongly advise the use of FDG PET/CT as a first-line diagnostic tool\(^9\).

Cost-effectiveness

No full economic evaluations were identified.

In Scotland, the average cost per FDG-PET/CT scan is £1,164 (G Dunn, Scottish Government. Personal communication, 17 January 2013).

Summary

1. What is the sensitivity and specificity of PET/CT compared with other diagnostic imaging modalities in determining the cause of PUO?

A moderate quality meta-analysis reported that PET/CT had a pooled sensitivity of 98.2% (95% CI 93.6 to 99.8) and specificity of 85.9% (95% CI 75.0 to 93.4%) for the detection of the cause of PUO\(^7\). PET/CT was helpful in obtaining a final diagnosis in 62% of patients. Further, PET/CT showed high sensitivity for the evaluation of infection or inflammation, neoplasm and non-infectious inflammation. This meta-analysis has some limitations, which should be noted. The data on the use of PET/CT in paediatric patients with PUO are very limited, and confident conclusions cannot be drawn.

Apart from one small study (from 2000) that compared PET with gallium scans, no literature was identified that compared the sensitivity and specificity of PET/CT with other diagnostic imaging modalities in determining the cause of PUO.

2. What is the clinical and cost effectiveness of PET/CT as a first-line investigation in patients with PUO?

In the studies identified, the patients had already had a thorough initial work-up. In this patient group (ie in those in whom other diagnostic measures had failed), the existing evidence suggests that PET/CT can help identify the cause of PUO. However, from this preliminary scope of the literature, it is not possible to confidently...
support or refute PET/CT as a first-line investigation in patients with PUO. It is also not possible to say, based on the evidence alone, where in the diagnostic work-up it is most appropriate.

No full economic evaluations were identified.

Immediately prior to publication of this report, a meta-analysis\(^1\) was published. It reported on the sensitivity (but not specificity) of FDG-PET/CT in detecting the cause of PUO. It included 15 studies, incorporating 595 patients, and reported a sensitivity of 85% (95% CI 81 to 88%). This does not change the conclusions of this report.

**Further work for Healthcare Improvement Scotland**

Given the lack of good quality clinical and economic evidence, no further work is anticipated.

**Equality and diversity**

Healthcare Improvement Scotland is committed to equality and diversity in respect of the nine equality groups defined by age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion, sex, and sexual orientation. As a scoping report summarises information and does not provide recommendations a full EQIA assessment is not deemed necessary.

The scoping report process has been assessed and no adverse impact across any of these groups is expected. The completed equality and diversity checklist is available on www.healthcareimprovementscotland.org

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Healthcare Improvement Scotland invited the following individuals and organisations to peer review the draft technologies scoping report:

- Dr Alan R Denison, Clinical Senior Lecturer, University of Aberdeen, Honorary Consultant Radiologist/Clinical Lead Nuclear Medicine/PET, NHS Grampian, independent clinical expert
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Declarations of interest were sought from the clinical advisor and all peer reviewers. All contributions from peer reviewers were considered by the group. However the peer reviewers had no role in authorship or editorial control and the views expressed are those of Healthcare Improvement Scotland.

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NICE has accredited the process used by Healthcare Improvement Scotland to produce its evidence review products. Accreditation is valid for 5 years from January 2013. More information on accreditation can be viewed at www.nice.org.uk/accreditation
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