

# **Diagnostic Assessment Report commissioned by the NIHR HTA Programme on behalf of the National Institute for Health and Clinical Excellence – Protocol**

## **1. Title of project**

Computed tomography (CT) scanners for cardiac imaging – Somatom Definition Flash, Aquilion One, Brilliance iCT and Discovery CT750 HD.

## **2. Name of External Assessment Group (EAG) and project lead**

Kleijnen Systematic Reviews Ltd. Assessment Group.

Project lead:

Marie Westwood

Kleijnen Systematic Reviews Ltd

Unit 6, Escrick Business Park

Riccall Road

Escrick

York YO19 6FD

Tel: 01904 727983

Email: [marie@systematic-reviews.com](mailto:marie@systematic-reviews.com)

Second contact:

Jos Kleijnen

Kleijnen Systematic Reviews Ltd

Unit 6, Escrick Business Park

Riccall Road

Escrick

York YO19 6FD

Tel: 01904 727981

Email: [jos@systematic-reviews.com](mailto:jos@systematic-reviews.com)

Health economics lead:

Maiwenn Al

institute for Medical Technology Assessment (iMTA)

Erasmus University

P.O. Box 1738

3000 DR Rotterdam

The Netherlands

Tel: +31-10-4088565

Email: [al@bmg.eur.nl](mailto:al@bmg.eur.nl)

### 3. Plain English Summary

Medical imaging, including computed tomography (CT) scanning, is important in diagnosing and planning treatment for a wide range of conditions. It can also be used to follow patients' progress and to assess whether or not a treatment is working. However, there are some risks and potential disadvantages associated with particular imaging techniques; for example CT imaging uses x-rays and is therefore associated with exposure to potentially harmful radiation, and invasive coronary angiography (a technique used specifically to visualise the coronary arteries) is associated with an increased risk of stroke, heart attack and death).

Imaging technology has developed very rapidly in recent years and new generation high definition CT scanners may offer some advantages over CT scanners and other imaging methods currently in use (e.g. shorter imaging times, reduced radiation dose, better quality images in specific patient groups). The development of these scanners has particularly focussed on the assessment of patients with heart disease, specifically those with coronary artery disease (narrowing of the coronary arteries that may lead to angina or heart attack) and congenital heart disease (abnormalities of the heart present from birth).

The CT scanners currently in use can already diagnose very accurately coronary artery disease that needs treatment (either using stents to push open the affected artery, or one or more coronary artery bypass grafts) in most patients. Therefore, it is thought that new generation high definition CT scanners are most likely to be useful in patients who are difficult to image using current technologies (obese patients, patients with high or irregular heart rates, patients who cannot hold their breath during imaging, and patients who have high levels of coronary calcium or a stent).

High definition CT scanners may also be useful in assessing patients (babies, children and adults) who were born with heart disease. These patients can be diagnosed using existing imaging technologies (ultrasound and magnetic resonance imaging). However, it is thought that CT scanning may provide additional information to help with planning surgery in some patients who have complex abnormalities.

The purpose of this project is to assess the benefits, risks and cost-effectiveness of new generation high definition CT scanners in assessing patients with coronary artery disease who are otherwise difficult or impossible to image accurately, and in planning the treatment of patients with complex congenital heart conditions.

## 4. Decision problem

### 4.1. Objectives

- To determine the clinical and cost effectiveness of high definition CT imaging for the diagnosis of clinically significant coronary artery disease (CAD) in patients with suspected CAD (defined as those who have chest pain or have other symptoms suggestive of CAD) or known CAD (defined as those who have previously been diagnosed with CAD and whose symptoms are no longer controlled by drug treatment and/or are being considered for revascularisation), who are difficult or impossible to image accurately using 64-slice CT technology.
- To determine the clinical and cost effectiveness of high definition CT imaging for treatment planning in babies, infants, children and adults diagnosed with complex congenital heart defects.

### 4.2. Intervention technologies

High definition CT scanners can be used for all routine imaging procedures where earlier generations of CT technology are currently applied; this assessment focuses upon specialised cardiac applications, where high definition CT is claimed to offer potential advantages over current imaging modalities, e.g. decreased failure rates in difficult to image patients.<sup>1-4</sup>

The section below describes the relevant technical characteristics of the high definition CT devices included in this assessment.

#### *Somatom Definition Flash*

The Somatom Definition Flash is a second generation dual source 128-slice CT scanner designed to provide high resolution images at a fast scanning speed with low dose radiation. The scanner has two X-ray tubes and two detector arrays mounted at 95° to each other. There are 64 x 0.6 mm detector rows (total z-axis coverage 33.4 mm) and each detector row is double sampled to give 128 data channels. The maximum scan speed is 458 mm/s. Fast acquisition times may benefit uncooperative patients, such as young children, and patients for whom a breath hold is difficult.

Somatom Definition Flash also utilises a number of strategies to reduce the radiation load associated with imaging: 'Flash' mode scanning (is recommended for heart rates up to 65 beats per minute (bpm)) in which data projections of the entire heart can be captured in approximately 250 ms with a radiation dose of less than 1 mSv; selective photon shield which filters the high kilo voltage X-rays; Iterative Reconstruction in Image Space (IRIS) to reconstruct an image from raw data, which allows reduction in radiation dose with maintenance of image quality.

For heart patients with heart rates above 65 bpm, different scan modes are recommended which result in slightly higher acquisition times and radiation doses. These scan modes

provide the option of scanning patients with high heart rates without the need to use beta blockers to regulate the heart rate.

#### *Aquilion One*

The Toshiba Aquilion ONE is a 640-slice CT scanner with 320 x 0.5 mm detector rows giving z-axis coverage of 160 mm, or 80 mm from 160 x 0.5 mm detector rows in helical scanning mode. This technology offers reduced imaging time and reduced radiation and contrast doses.

#### *Brilliance iCT*

The Philips Brilliance iCT is a new generation 256-slice multi detector CT scanner. It has 128 x 0.625 mm detector rows providing a total z-axis coverage of 80 mm. Each detector row is double sampled which increases spatial resolution. It is claimed it can capture an image of the heart in two heart beats. Additional benefits claimed for the Brilliance iCT scanner are: A powerful X-ray tube for improved durability, image quality and spatial resolution, particularly in patients with high BMIs; Innovative NanoPanel detectors to reduce electronic noise, enabling fast, low-dose scans with better definition of small structures; Intelligent RapidView reconstruction to enable high resolution images with a high throughput.

#### *Discovery CT750*

The Discovery CT750 from GE Healthcare is a 2 x 64-slice dual energy CT scanner. It has a single X-ray source which switches between two energy levels, allowing two data sets – high energy and low energy – to be acquired simultaneously. It uses a Gemstone™ detector that contributes to high image quality, and an Adaptive Statistical Iterative Reconstruction algorithm to enhance low contrast detection at a reduced level of radiation.

### **4.3. Population**

This assessment will consider two distinct populations, patients with CAD who are difficult or impossible to image using current 64-slice CT technology, and patients with complex congenital heart disease requiring additional information for treatment planning.

CAD is a major cause of cardiovascular disability and death in the UK. It is caused by narrowing of the coronary arteries, most commonly by atherosclerotic deposits of fibrous and fatty tissue, leading to a reduction in the flow of blood to the heart, angina, and ultimately myocardial infarction.

The NICE clinical guideline CG95 (Chest pain of recent onset) defines significant CAD as  $\geq 70\%$  diameter stenosis of at least one major epicardial artery segment or  $\geq 50\%$  diameter stenosis in the left main coronary artery.<sup>5</sup> Some factors intensify ischaemia and allow less severe lesions (for example  $\geq 50\%$  diameter stenosis of one major epicardial artery segment) to produce angina, for example, reduced oxygen delivery, increased oxygen

demand, large mass of ischaemic myocardium, or longer lesion length. Similarly, some factors reduce ischaemia and may render lesions ( $\geq 70\%$  diameter stenosis of one major epicardial artery segment) asymptomatic, for example a well developed collateral supply or small mass of ischaemic myocardium.

Coronary angiography (CA) or CT coronary angiography (CTCA) is used to assess the state of the arteries and to identify significant narrowing (stenosis) as recommended by NICE clinical guideline CG95.<sup>5</sup> The guideline recommends use of a 64-slice (or above) CT scanner and the diagnostic performance of 64-slice CT is well established; recent systematic reviews have estimated the sensitivity and specificity of 64-slice CT, for the detection of  $\geq 50\%$  coronary artery stenosis, to be 92-99% and 89-92% respectively.<sup>6-8</sup> For most patients, it is therefore unlikely that the use of a high definition CT scanner would offer significant benefit over the use of a 64-slice CT scanner. However, high definition CT scanners may be beneficial in difficult to image groups of patients, for example, those who cannot hold their breath, have an irregular or fast heartbeat, are obese, or in whom artefacts produced by high levels of coronary calcium or existing stents may reduce image quality.<sup>3,4</sup> These patients are not currently candidates for CT imaging in routine practice, though some may be imaged in specialist centres. The impact of reducing the radiation exposure associated with scanning may be limited in this population as patients with known or suspected CAD tend to be older adults. However, consideration of radiation exposure outcomes may provide some insight into the potential benefits of high definition CT scanners.

High definition CT scanners may also be used to aid treatment planning in a small group of patients with complex congenital heart disease. Though there is some evidence that high definition CT may provide accurate diagnoses for a range of congenital heart conditions,<sup>9,10</sup> diagnostic accuracy is not considered a relevant outcome for this assessment, as existing imaging strategies provide accurate initial diagnoses, without the need for radiation exposure.

Congenital heart disease is a general term which describes birth defects that affect the heart. There are over 30 different types of heart defect, the most common being ventricular or atrial septal defects, pulmonary or aortic stenosis, patent ductus arteriosus, tetralogy of Fallot, and transposition of the great arteries. The incidence rate for congenital heart disease in the UK is estimated to be one in every 150 babies born and approximately 85% of children born with congenital heart disease respond well to treatment and will survive into adulthood.<sup>11</sup> It is likely that high definition CT would be applicable in only a small proportion of these patients, those with complex conditions. Expert input has indicated that these will primarily involve lesions with a major extra cardiac component that is not well imaged by echocardiography, e.g. Pulmonary atresia with Major Aorta Pulmonary Collaterals (MAPCA), variants of Anomalous Pulmonary Venous Drainage (TAPVD, Scimitar syndrome etc), aortic arch abnormalities (double aortic arch, vascular ring, etc), and lesions with both a vascular and an airway component (pulmonary artery sling, tracheal stenosis, right aortic arch with

aberrant subclavian artery, etc). Additionally, previously treated lesions where stents or pacemakers make MRI unsuitable will be of interest.

The potential advantage of high definition CT scanners over current CT technologies, in these patients, is the fast image acquisition time, which may allow babies and infants to be scanned without the need for a general anaesthetic. Reduced radiation dose also has the potential to decrease rates of radiation-induced cancer and infertility in later life. However, as CT scanning is likely to be used as a single instance for treatment planning, rather than for ongoing monitoring, this impact may be reduced.

#### **4.4. Relevant comparators**

##### *Evaluation of known or suspected CAD in patients who are difficult or impossible to image using 64-slice CT*

In these patients, where 64-slice CT is not a viable option, high definition CT may be used to rule out significant stenosis, or to confirm substantial stenosis requiring CABG and thus avoid invasive CA. The only relevant comparator is therefore:

- Invasive coronary angiography (CA) - an invasive imaging technique which uses a contrast dye and X-rays to provide anatomical information about the degree of stenosis in the coronary arteries. A catheter is generally inserted into an artery in the groin and is moved up the aorta and into the coronary arteries. Once in place, the dye is injected through the catheter, and a rapid series of X-ray images are taken to show how the dye moves through the branches of the coronary arteries. Any narrowing of the arteries will show up on the X-ray images. In babies and children a general anaesthetic would be required to perform the procedure.

Invasive CA is considered the 'gold standard' for providing anatomical information and defining the site and severity of coronary artery lesions despite the significant inter- and intra-reader variation in interpretation. However, there are serious complications associated with the technique, including death, non fatal myocardial infarction and stroke. In addition, it only provides a 2D image as oppose to the 3D image produced by other imaging techniques.

**Invasive CA will be the reference standard for diagnostic accuracy evaluations**

##### *Evaluation of congenital heart disease*

In these patients, CT scanning is likely to be used following initial diagnosis and as an add-on to imaging with echocardiography and magnetic resonance imaging (MRI). Therefore, 64-slice CT is the only relevant comparator; conventional imaging (echocardiography and/or MRI), without the addition of CT, may be included in the cost-effectiveness model, dependent upon the advice of paediatric cardiology experts.

- 64-slice CT - Multi-slice CT scanners combine the use of X-rays with computerised analysis of series of 2D X-ray images to create 3D images. The technology has been rapidly advancing, with 4-slice CT scanners first appearing in 1998, 16-slice scanners in

2001 and 64-slice scanners at the end of 2004. Multi-slice CTCA is a minimally-invasive investigation which uses a contrast dye injected through a cannula in the forearm and provides anatomical information about the degree of stenosis in the coronary arteries. Cardiac CT has particular challenges due to the continuous motion of the heart.

Studies which compare treatment plan and/or patient outcome, in the same group of patients, with and without CT (high definition or 64-slice), or studies which randomise patients to receive treatment based on assessment with or without CT are relevant to this assessment. Diagnostic accuracy data are not considered relevant.

## **5. Report methods for assessing the outcomes arising from the use of the interventions**

A systematic review of the evidence on the clinical effectiveness of Somatom Definition Flash and equivalent high definition CT technologies, for the assessment of coronary artery stenosis in difficult or impossible to image patient groups with known or suspected CAD, and for treatment planning in patients with complex congenital heart disease. Systematic review methods will follow the principles outlined in the Centre for Reviews and Dissemination (CRD) guidance for undertaking reviews in health care<sup>12</sup> and NICE Diagnostic Assessment Programme interim methods statement.<sup>13</sup>

### **5.1. Inclusion and exclusion criteria**

#### *Participants*

Study populations eligible for inclusion will be:

- Adults ( $\geq 18$  years) with known (previously diagnosed who have symptoms that are no longer controlled by drug treatment and/or who are being considered for revascularisation) or suspected (chest pain or other suggestive symptoms) CAD, who are difficult to image (not currently candidates for CT imaging). Difficult or impossible to image patients may include, but are not limited to those with:
  - Obesity
  - High levels of coronary calcium
  - Arrhythmias
  - High heart rates ( $>70$  bpm)
  - Intolerance of beta-blockers
  - Stents
  - Bypass grafts
  
- Infants, children and adults diagnosed with complex congenital heart disease, including but not limited to:
  - Pulmonary atresia with Major Aorta Pulmonary Collaterals (MAPCA)

- variants of Anomalous Pulmonary Venous Drainage (TAPVD, Scimitar syndrome, etc)
- aortic arch abnormalities (double aortic arch, vascular ring, etc)
- lesions with both a vascular and airway component (pulmonary artery sling, tracheal stenosis, right aortic arch with aberrant subclavian artery, etc)
- previously treated lesions where stents or pacemakers make MRI unsuitable

This list may be expanded/refined with further expert paediatric cardiology input.

### *Setting*

Relevant settings are secondary or tertiary care.

### *Interventions*

Included interventions are high definition CT scanners:

- Somatom Definition Flash (Siemens AG, Healthcare)
- Aquilion One (Toshiba Medical systems)
- Brilliance iCT (Philips Healthcare)
- Discovery CT750 (GE Healthcare)

If any additional equivalent technologies are identified during the review process, these will also be considered for inclusion.

### *Comparators*

Relevant comparators are 64-slice CT, or conventional imaging (without CT) for the assessment of complex congenital heart disease, and CA only for difficult to image CAD patients.

### *Reference standard*

The reference standard, for diagnostic accuracy of CAD is invasive CA. Diagnostic accuracy is not a relevant outcome for congenital heart disease.

### *Outcomes*

The following outcomes will be considered for both clinical applications:

- Impact of testing on treatment plan (e.g. surgical or medical management), where information on the appropriateness of the final treatment plan is also reported
- Impact of testing on clinical outcome, (e.g. angina, myocardial infarction, cardiovascular mortality)
- Radiation exposure

Radiation dose data will be taken from audit sources rather than literature to avoid bias which may arise from patient selection in published studies.



The following outcomes will be considered for CAD only:

- Test accuracy
- Indeterminacy (test failure rate)

For included studies reporting any of the above outcome measures, the following outcomes will also be considered if reported:

- Acceptability of tests to patients
- Adverse events associated with testing

### *Study design*

The following types of studies will be included:

- Randomised or non-randomised controlled trials, where participants are assigned to the intervention or comparator tests, for treatment planning, and outcomes are compared at follow-up.
- Randomised or non-randomised controlled trials where participants are assigned to conventional imaging only, or conventional imaging plus high definition or 64-slice CT (congenital heart disease only).

Where there is insufficient evidence from trials, the following observational study types will be considered:

- Cross-sectional test accuracy studies, where the intervention is compared with the reference standard (CAD only).
- Observational studies reporting change to treatment plan or clinical outcome subsequent to high definition CT (CAD and congenital heart disease), or 64-slice CT (congenital heart disease only).

Where these 'secondary' study designs are considered, studies of comparator tests (64-slice CT) will only be sought separately for congenital heart disease once similar studies of intervention tests (high definition CT) have been identified. This approach will ensure that the number of studies to be screened remains manageable within the resources allocated to this assessment, and resources are focussed only upon those areas where evidence is available for the intervention technology.

Test accuracy studies, will be required to report the absolute numbers of true positive, false negative, false positive, and true negative test results, or sufficient information to allow their calculation. If data are incomplete, study authors will be contacted to seek clarification, where practical.

The following study/publication types will be excluded:

- Pre-clinical, animal and phantom studies
- Reviews, editorials, and opinion pieces
- Case reports
- Studies reporting only technical aspects of the test, or image quality
- Studies with <10 participants

## 5.2. Search strategy

Search strategies will be based on target condition and intervention, as recommended in the Centre for Reviews and Dissemination (CRD) guidance for undertaking reviews in health care and the Cochrane Handbook for Diagnostic Test Accuracy Reviews.<sup>12, 14</sup>

Additional supplementary searches will be carried out as necessary. Searches for studies for cost and quality of life will also be included, see Section 6 for further detail.

The following databases will be searched for relevant studies from 2000 to the present:

- MEDLINE (OvidSP)
- MEDLINE In-Process Citations and Daily Update (OvidSP)
- EMBASE (OvidSP)
- Cochrane Database of Systematic Reviews (CDSR ) (Internet)
- Cochrane Central Register of Controlled Trials (CENTRAL) (Internet)
- Database of Abstracts of Reviews of Effects (DARE) (CRD website)
- Health Technology Assessment Database (HTA) (CRD website)
- Science Citation Index (SCI) (Web of Science)

Completed and ongoing trials will be identified by searches of the following resources (2000-2010):

- ClinicalTrials.gov (<http://www.clinicaltrials.gov/>)
- Current Controlled Trials (<http://www.controlled-trials.com/>)
- International Clinical Trials Registry Platform (ICTRP) (<http://www.who.int/ictrp/en/>)

Key conference proceedings will be screened for the last five years. These may include Society of Cardiovascular Computed Tomography, British Institute of Radiology, Radiological Society of North America.

Identified references will be downloaded in Endnote X4 software for further assessment and handling.

References in retrieved articles and relevant systematic reviews will be checked.

Search strategies will be developed specifically for each database and the keywords associated with congenital heart defects shall be adapted according to the configuration of each database.

No restrictions on language or publication status will be applied. Limits will be applied to remove animal studies. Searches will take into account generic and other product names for the intervention. Examples of the search strategies to be used are presented in Appendix 1; terms for congenital heart disease will be refined following paediatric cardiology input. Separate search strategies will be constructed for 64-slice CT and congenital heart disease, as necessary.

### **5.3. Data extraction strategy**

Two reviewers will independently screen titles and abstracts of all reports identified by searches and discrepancies will be discussed. Full copies of all studies deemed potentially relevant, after discussion, will be obtained and two reviewers will independently assess these for inclusion; any disagreements will be resolved by consensus or discussion with a third reviewer.

Data relating to study details, participants, intervention and comparator tests, reference standard, and outcome measures will be extracted by one reviewer, using a piloted, standard data extraction form. A second reviewer will check data extraction and any disagreements will be resolved by consensus or discussion with a third reviewer.

### **5.4. Quality assessment strategy**

The methodological quality of included studies will be assessed using standard tools.<sup>12</sup> The QUADAS tool,<sup>15</sup> is recommended for assessing the methodological quality of test accuracy studies,<sup>12, 16</sup> but a revised version of QUADAS (QUADAS-2) is soon to be published (planned submission date March 2011). QUADAS-2 will more closely resemble the approach and structure of the Cochrane risk of bias tool. The QUADAS-2 tool will be used in this assessment, with the permission of the QUADAS steering group of which the DAR team lead is a member.

The results of the quality assessment will be used for descriptive purposes to provide an evaluation of the overall quality of the included studies and to provide a transparent method of recommendation for design of any future studies. In addition, if enough data are available from the included studies, quality components will be included as covariates in SROC models, to investigate their possible association with test performance. Based on the findings of the quality assessment, recommendations will be made for the conduct of future studies.

### **5.5. Methods of analysis/synthesis**

The results of initial scoping searches suggest that trial data are likely to be sparse or non-existent. This section therefore focuses on the synthesis of data from observational studies.

Where meta-analysis is considered unsuitable for some or all of the data identified (e.g. due to the heterogeneity and/or small numbers of studies), we will employ a narrative synthesis. Typically, this will involve the use of text and tables to summarise data. These will allow the reader to consider any outcomes in the light of differences in study designs and potential sources of bias for each of the studies being reviewed. Studies will be organised by clinical application (CAD or congenital heart disease), relevant patient sub-groups (e.g. type of congenital heart disease, specific 'difficult to image' CAD group), and the outcomes assessed.

Any data included on the following outcome measures: test failure rates; effects of testing on treatment planning and/or clinical outcome; radiation dose; adverse events associated with testing will be summarized according to the size and range of the outcomes reported. For test accuracy data, absolute numbers of true positive, false negative, false positive and true negative test results, as well as sensitivity and specificity values, with 95% confidence intervals will be presented for each study and patient group reported.

Where appropriate, and where sufficient accuracy data are available, summary receiver operating characteristic (SROC) curves will be calculated to summarise test accuracy data. SROC modelling will use the bivariate approach.<sup>17 18 19</sup> Potential sources of heterogeneity will be investigated by extending SROC models to include study level covariates, (e.g. participant age, risk category, CT instrument type, type of congenital heart disease); the bivariate approach to modelling allows investigation of the effects of covariates on sensitivity and specificity separately.

Where data are insufficient to support meta-analyses, the following graphical representations will be presented: plots in ROC space (without summary curves) for test accuracy data; forest plots for any trial data.

A detailed commentary on the major methodological problems or biases that affected the studies will also be included, together with a description of how this may have affected the individual study results. Recommendations for further research will be made based on any gaps in the evidence or methodological flaws.

## **6. Report methods for synthesising evidence of cost-effectiveness**

### **6.1 Identifying and reviewing published cost-effectiveness studies**

Exploration of the literature regarding published economic evaluations will be performed in the literature databases listed above. In addition, specific health economic databases will be searched (e.g. NHSEED (NHS Economic Evaluation Database), PEDE (Paediatric Economic Database Evaluation), and HEED (Health Economic Evaluation Database)); an example search strategy is included in Appendix 1. Searches will focus on original papers that report on cost, cost-accuracy, cost-effectiveness or cost-utility analyses, either studying the diagnostic phase, therapeutic phase or a combination, within both populations (CAD and congenital

heart disease). For our assessment only full economic evaluations, i.e. those that explicitly compare different decision options will be selected. Clinical trials as well as modelling studies and cohort studies will be relevant within the frame of our project. The intention is not to perform a systematic review, but to use the studies identified to support the development of an economic model that will aim to answer the research questions of this project.

The results and the methodological quality of the studies selected will be summarised. Assessment of methodological quality will follow the criteria for economic evaluations in health care as described in the NICE methodological guidance.<sup>13</sup> Data extraction will focus on technologies compared, indicated population, main results in terms of costs and consequences of the alternatives compared, and the incremental cost-effectiveness, but also on methods of modelling used (if applicable), analytical methods and robustness of the study findings.

## **6.2 Evaluation of costs, quality of life and cost-effectiveness**

Since this project aims to assess the value of the diagnostic technologies studied in two different patient populations, two separate economics models will be defined, constructed, analysed, and reported independently. Both models will evaluate the cost-effectiveness of new generation, high definition CT technologies compared to the currently available imaging methods, as described in section 5.1. The perspective will be that of the NHS and the timeframe used will be life time. Consequences will be expressed as number of correct diagnoses or treatment plans for the diagnostic phase, and (quality adjusted) life years to also include the therapeutic phase and the effects of reduced radiation exposure. Any assumption used in the models and any parameter value will be based primarily on literature and supplemented by clinical expert opinion as appropriate.

### *Known or suspected CAD in patients who are difficult or impossible to image using 64-slice CT*

The focus of the evaluation of high definition CT in this population will be in assessing the accuracy of imaging. As it is currently foreseen, the model for this patient group will be constructed to reflect the following assumptions: Without the option of high definition CT, patients are referred to invasive angiography without selection based on CT imaging. Estimates of the numbers of patients falling into this category will be provided by expert opinion/audit data from at least two centres, both specialist and more generalist (i.e. a range of estimates). The use of high definition CT will make it possible to assess the disease status of indicated patients and may allow clinically significant disease to be ruled out, in some patients, without the risks of invasive testing. The number of false negative imaging results is important in this scenario since, in principle, this will cause loss of benefit arising from missed treatment. Where imaging is positive the diagnosis will need to be confirmed by

angiography leading to a specific treatment decision. In addition, it may be possible to use high definition CT in some patients to confirm severe disease, requiring CABG, and thus avoid CA. The number of false positive imaging results is important in this scenario since these may result in unnecessarily aggressive treatment (CABG, where PCI may have been possible). As a short term result, the cost of the diagnostic phase will be related to the number of correct diagnoses. For a long term assessment of the cost-effectiveness of testing, the therapeutic benefits of treating a patient correctly (true positive diagnosis), unnecessary treatment of persons (false positive diagnosis), inappropriately withholding treatment in patients (false negative diagnosis), and preventing unnecessary treatment (true negative diagnosis) will be reflected within a cost per QALY framework.

For the diagnostic phase, we may use and adapt the model that was developed for the clinical guideline for stable chest pain.<sup>5</sup> We are not aware of any existing relevant diagnostic models which address the possibility that CA is not 100% accurate, but we will further investigate whether any methods have been published that would allow this issue to be addressed. If suitable methods cannot be identified, we will consider using sensitivity analyses, contingent upon availability of data. For the therapeutic phase we may use and adapt a model that was developed for treatment of stable coronary artery disease based on data from the EUROPA Study.<sup>20</sup> The EUROPA study included patients with previous MI, previous revascularisation or 70% narrowing of one or more major coronary arteries. Probability of a cardiovascular event was defined using a risk score formula that was derived from the trial data. This risk formula contains, for example, obesity, age, the presence of diabetes, the use of lipids lowering drugs as covariates. For our model, it is important to realize that those factors that cause patients to be difficult to image in the diagnostic phase may also impact the probability of a cardiovascular event. The EUROPA study shows this for obesity, but it is possible that also other factors such as high coronary calcium levels and irregular/fast heartbeat have similar impacts. Therefore, data need to be collected to adjust the relevant model input parameters for these factors. We will need to run the model separately for each factor listed in section 5.1, for which effectiveness/accuracy data are available, and combine the results into an overall ICER by weighting the separate costs and effects by the relative prevalence of these factors.

Additionally, because high definition CT is associated with lower radiation exposure than CA, the effects of decreasing radiation on the risk of cancer, mortality and adverse events and its associated costs will be assessed. For this, we will make use of a model that is currently being developed for the diagnostic assessment of the EOS 2D/3D X-ray Imaging System by the Centre for Health Economics, University of York.

### *Congenital heart disease*

The focus of the evaluation of high definition CT scanners in infants, children and adults with known complex congenital heart defects will be on assessing its potential impact upon

treatment planning. The costs and effects of high definition CT will be compared to current practice, i.e. 64-slice CT, and may also be compared to MRI and echocardiography alone (this is to be discussed with clinical experts). Since high definition CT is associated with lower radiation exposure than 64-slice CT, the effects of decreasing radiation on the risk of cancer, mortality and adverse events and its associated costs will be assessed. For this, we will make use of a model that is currently being developed for the diagnostic assessment of the EOS 2D/3D X-ray Imaging System by the Centre for Health Economics in York.

#### *Resource utilisation*

Resource utilisation and costs will be estimated for high definition CT scanners, 64-slice CT and CA. For high definition CT, these costs will include the capital cost of the equipment, including installation of workstation and software, consumables, annual maintenance costs and patient throughput. Particular attention will be paid to how per patient costs vary with total patient throughput for high definition CT and 64-slice CT in the indications listed in Section 5. The implication of this variation is likely to be explored using sensitivity and threshold analyses. Data for the cost analyses will be drawn from routine NHS sources (e.g. NHS reference costs, Personal Social Services Research Unit (PSSRU), British National Formulary (BNF)), discussions with individual hospitals and with the manufacturers of high definition CT scanners.

#### *Modeling issues*

Necessary choices and definitions regarding the structure of both models will depend on the findings from the literature review and consultation with clinical experts. In addition, the existence/availability of any other electronic models that reflect the cost-effectiveness of treatment pathways for these patients, and are representative of current care within the NHS, will be determined.

The objectives of modelling will be:

To assess the cost-effectiveness of high definition CT scanners in comparison to current diagnostic pathways. For CAD, the analysis will be done in terms of the consequences of diagnostic accuracy, treatment planning, and QALYs. For congenital heart disease, the analysis will be done in terms of treatment planning and, if available evidence allows, in terms of QALYs using a life expectancy time horizon.

Issues relevant to analyses:

- Longer term cost and consequences will be discounted using the UK discount rates of 3.5% of both costs and effects.
- One way sensitivity analyses will be performed for all key parameters, especially for parameters in the models based on expert opinion.

- Probabilistic sensitivity analyses will be performed using parameter distributions instead of fixed values.
- Decision uncertainty regarding mutually exclusive alternatives will be reflected using cost-effectiveness planes and cost-effectiveness acceptability curves.

### **7. Handling of information from the companies**

All data submitted by the manufacturers/sponsors will be considered if received by the EAG no later than 04/04/2011. Data arriving after this date will not be considered. If the data meet the inclusion criteria for the review they will be extracted and quality assessed in accordance with the procedures outlined in this protocol.

Any 'commercial in confidence' data provided by manufacturers, and specified as such, will be highlighted in blue and underlined in the assessment report (followed by company name in parentheses). Any 'academic in confidence' data provided by manufacturers, and specified as such, will be highlighted in yellow and underlined in the assessment report. Any confidential data used in the cost-effectiveness models will also be highlighted.

### **8. Competing interests of authors**

None



## 9. Timetable/milestones

<b>Milestones</b>	<b>Completion data</b>
Draft protocol	18/01/2011
Final protocol	09/02/2011
Progress report	w/c 04/04/2011
Draft assessment report	w/c 16/05/2011
Final assessment report	22/06/2011

## 10. References

- [1] Achenbach S, Marwan M, Ropers D, Schepis T, Pflederer T, Anders K, et al. Coronary computed tomography angiography with a consistent dose below 1 mSv using prospectively electrocardiogram-triggered high-pitch spiral acquisition. *Eur Heart J* 2010;31(3):340-6.
- [2] Ben Saad M, Rohnean A, Sigal-Cinqualbre A, Adler G, Paul JF. Evaluation of image quality and radiation dose of thoracic and coronary dual-source CT in 110 infants with congenital heart disease. *Pediatr Radiol* 2009;39(7):668-76.
- [3] Marwan M, Pflederer T, Schepis T, Lang A, Muschiol G, Ropers D, et al. Accuracy of dual-source computed tomography to identify significant coronary artery disease in patients with atrial fibrillation: comparison with coronary angiography. *Eur Heart J* 2010;31(18):2230-7.
- [4] Wang Y, Zhang Z, Kong L, Song L, Merges RD, Chen J, et al. Dual-source CT coronary angiography in patients with atrial fibrillation: comparison with single-source CT. *Eur J Radiol* 2008;68(3):434-41.
- [5] Cooper A, Calvert N, Skinner J, Sawyer L, Sparrow K, Timmis A, et al. *Chest pain of recent onset: assessment and diagnosis of recent onset chest pain or discomfort of suspected cardiac origin. Full guideline 95*. London: National Clinical Guideline Centre for Acute and Chronic Conditions, 2010 [cited 12.1.11]. 393p. Available from: <http://guidance.nice.org.uk/CG95>
- [6] Mowatt G, Cummins E, Waugh N, Walker S, Cook J, Jia X, et al. Systematic review of the clinical effectiveness and cost-effectiveness of 64-slice or higher computed tomography angiography as an alternative to invasive coronary angiography in the investigation of coronary artery disease. *Health Technol Assess* 2008;12(17):iii-iv, ix-143.
- [7] Schuetz GM, Zacharopoulou NM, Schlattmann P, Dewey M. Meta-analysis: noninvasive coronary angiography using computed tomography versus magnetic resonance imaging. *Ann Intern Med* 2010;152(3):167-77.
- [8] Khan R, Rawal S, Eisenberg MJ. Transitioning from 16-slice to 64-slice multidetector computed tomography for the assessment of coronary artery disease: are we really making progress? *Can J Cardiol* 2009;25(9):533-42.
- [9] Cheng Z, Wang X, Duan Y, Wu L, Wu D, Chao B, et al. Low-dose prospective ECG-triggering dual-source CT angiography in infants and children with complex congenital heart disease: first experience. *Eur Radiol* 2010;20(10):2503-11.
- [10] Hope SA, Crossett M, Nasis A, Seneviratne S. Early experience with Aquilion One 320 slice computerised tomography scanner in paediatric and congenital heart disease. *Fifth World Congress of Paediatric Cardiology and Cardiac Surgery*. Cairns, Australia, 2010.

[11] British Heart Foundation. *Incidence of congenital heart disease [internet]*, 2005 [cited 12.1.11] Available from: <http://www.heartstats.org/datapage.asp?id=3395>

[12] Centre for Reviews and Dissemination. *Systematic reviews: CRD's guidance for undertaking reviews in health care [internet]*. York: University of York, 2009 [cited 12.1.10] Available from: [http://www.york.ac.uk/inst/crd/systematic\\_reviews\\_book.htm](http://www.york.ac.uk/inst/crd/systematic_reviews_book.htm)

[13] National Institute for Health and Clinical Excellence. *Diagnostics Assessment Programme: interim methods statement (version 2) [Internet]*. London: NICE, 2010 [cited 12.1.11]. 46p. Available from: <http://www.nice.org.uk/media/164/3C/DAPInterimMethodsStatementProgramme.pdf>

[14] Whiting P, Westwood M, Beynon R, Burke M, Sterne JA, Glanville J. Inclusion of methodological filters in searches for diagnostic test accuracy studies misses relevant studies. *J Clin Epidemiol* 2010.

[15] Whiting P, Rutjes AW, Reitsma JB, Bossuyt PM, Kleijnen J. The development of QUADAS: a tool for the quality assessment of studies of diagnostic accuracy included in systematic reviews. *BMC Med Res Methodol* 2003;3:25.

[16] Cochrane Diagnostic Test Accuracy Working Group. *Handbook for DTA Reviews [internet]*: Cochrane Collaboration, 2011 [cited 12.1.11] Available from: <http://srdta.cochrane.org/handbook-dta-reviews>

[17] Reitsma JB, Glas AS, Rutjes AW, Scholten RJ, Bossuyt PM, Zwinderman AH. Bivariate analysis of sensitivity and specificity produces informative summary measures in diagnostic reviews. *J Clin Epidemiol* 2005;58(10):982-90.

[18] Harbord RM, Deeks JJ, Egger M, Whiting P, Sterne JA. Unification of models for meta-analysis of diagnostic accuracy studies. *Biostatistics* 2006;1:1-21.

[19] Chu H, Nie L, Cole S, Poole C. Meta-analysis of diagnostic accuracy studies accounting for disease prevalence: alternative parameterizations and model selection. *Statistics in Medicine*. 2009;28(18):2384-99.

[20] Briggs A, Mihaylova B, Sculpher M, Hall A, Wolstenholme J, Simoons M, et al. Cost effectiveness of perindopril in reducing cardiovascular events in patients with stable coronary artery disease using data from the EUROPA study. *Heart* 2007;93(9):1081-6.

## Appendix 1

### Clinical effectiveness search (high definition CT only)

Medline: 2000-2011/1/wk 1

Searched 17.1.11

- 1 Somatom definition flash.ti,ab,ot,hw. (4)
- 2 DSCT.ti,ab,ot,hw. (237)
- 3 (Aquilion-1 or Aquilion-one).ti,ab,ot,hw. (7)
- 4 Brilliance ict.ti,ab,ot,hw. (1)
- 5 (Discovery ct750 or Discovery ct-750).ti,ab,ot,hw. (0)
- 6 (640slice\$ or 640 slice\$).ti,ab,ot,hw. (0)
- 7 (256slice\$ or 256 slice\$).ti,ab,ot,hw. (44)
- 8 (128slice\$ or 128 slice\$).ti,ab,ot,hw. (30)
- 9 ('2' adj2 (energy or source\$)).ti,ab,ot,hw. (2361)
- 10 (Dual\$ adj2 (energy or source\$) adj3 (CT or scan\$ or DSCT or imag\$ or multidetect\$ or multi-detect\$ or computed or tomography\$)).ti,ab,ot,hw. (1101)
- 11 (High definition adj3 (CT or scan\$ or DSCT or imag\$ or multidetect\$ or multi-detect\$ or computer or tomography\$)).ti,ab,ot,hw. (156)
- 12 modern cone-beam dual-source spiral.ti,ab,ot,hw. (1)
- 13 (high pitch dual spiral adj3 (CT or scan\$ or imag\$ or technique\$ or protocol\$ or DSCT or multidetect\$ or multi-detect\$ or computer or tomography\$)).ti,ab,ot,hw. (1)
- 14 or/1-13 (3790)
- 15 exp Heart Defects, Congenital/ (103198)
- 16 exp Coronary Disease/ or myocardial ischemia/ or exp myocardial infarction/ (285046)
- 17 ((pulmonary or mitral or aortic or aorta or Tricuspid or coronary or cardiac or valve) adj2 (stenosis or atresia)).ti,ab,ot,hw. (50167)
- 18 (congenital\$ adj2 arter\$ adj2 (defect\$ or deform\$ or malform\$ or anomal\$ or abnormal\$ or disease\$)).ti,ab,ot,hw. (449)
- 19 (congenital\$ adj2 heart adj2 (defect\$ or deform\$ or malform\$ or anomal\$ or abnormal\$ or disease\$)).ti,ab,ot,hw. (42499)
- 20 (CAD or ASD or AVSD or CAVSD or HLHS or HLH or HRH or HRHS or IAA or PDA or VSD or CHD or LVOT or PVOD or TGA or UVH or TAPVD or TAPVR or PAPVD or PAPVR).ti,ab,ot. (45488)
- 21 (TOF or TAPVC or TGV or D-TGA or DTGA or ITGA or I-TGA or DILV or DORV or COA or IAA or SS or PAPVC).ti,ab,ot. (63488)
- 22 (Dextrocardia\$ or Dextro-cardia\$).ti,ab,ot,hw. (1335)
- 23 (dextro-Transpos\$ adj3 great arteries).ti,ab,ot,hw. (33)
- 24 (dextroTranspos\$ adj3 great arteries).ti,ab,ot,hw. (29)
- 25 ((cardium or cardio\$ or cardiac\$ or heart) adj3 (dextrover\$ or dextro-ver\$ or dextro-rotat\$ or dextroposition\$ or dextrorotat\$ or dextro-position\$)).ti,ab,ot,hw. (101)
- 26 ((interauricular or inter-auricular or inter-atrial or interatrial or atrial or atrium) adj2 (septal or septum) adj2 (shunt\$ or defect\$)).ti,ab,ot,hw. (11938)
- 27 (Lutembacher\$ adj2 (syndrome or complex)).ti,ab,ot,hw. (152)
- 28 ((persisten\$ or Patent\$) adj2 ostium secundum).ti,ab,ot,hw. (5)
- 29 (trilogy adj2 fallot).ti,ab,ot,hw. (54)
- 30 ((ventricul\$ or Atrioventricul\$) adj2 (septal or septum) adj2 (shunt\$ or defect\$)).ti,ab,ot,hw. (13819)
- 31 ((Hypo-plastic or Hypoplastic) adj3 left heart).ti,ab,ot,hw. (1819)

32 ((Hypo-plastic or Hypoplastic) adj3 left heart).ti,ab,ot,hw. (1819)  
33 (Interrupt\$ adj3 aortic arch).ti,ab,ot,hw. (912)  
34 ((persisten\$ or Patent\$ or closure or closed or ligation or ligated or obliterate\$) adj2 ductus arteriosus).ti,ab,ot,hw. (8591)  
35 ((persisten\$ or Patent) adj2 truncus arteriosus).ti,ab,ot,hw. (762)  
36 (tetralogy adj2 fallot).ti,ab,ot,hw. (8220)  
37 total\$ anomalous pulmonary venous connection\$.ti,ab,ot,hw. (491)  
38 (Transpos\$ adj3 great vessels).ti,ab,ot,hw. (5823)  
39 (Transpos\$ adj3 great arteries).ti,ab,ot,hw. (3205)  
40 (levoTranspos\$ adj3 great arteries).ti,ab,ot,hw. (7)  
41 Bicuspid aortic valve\$.ti,ab,ot,hw. (1150)  
42 Double inlet left ventricle\$.ti,ab,ot,hw. (163)  
43 (Ebstein\$ adj1 anomal\$).ti,ab,ot,hw. (1704)  
44 (Coarctat\$ adj3 aorta).ti,ab,ot,hw. (3506)  
45 (Co-arctat\$ adj3 aorta).ti,ab,ot,hw. (3)  
46 Interrupt\$ aort\$.ti,ab,ot,hw. (611)  
47 (Scimitar adj2 (syndrome or complex)).ti,ab,ot,hw. (445)  
48 Partial\$ anomalous pulmonary venous connect\$.ti,ab,ot,hw. (224)  
49 Total\$ anomalous pulmonary venous connect\$.ti,ab,ot,hw. (491)  
50 (Shone\$ adj2 (syndrome or complex or anomaly or defect\$ or deform\$ or malform\$ or abnormal\$)).ti,ab,ot,hw. (66)  
51 (Marfan\$ adj2 (syndrome or complex)).ti,ab,ot,hw. (5176)  
52 Marfans.ti,ab,ot,hw. (1904)  
53 (eisenmenger\$ adj2 (syndrome or complex)).ti,ab,ot,hw. (971)  
54 univentric\$ heart\$.ti,ab,ot,hw. (499)  
55 uni-ventric\$ heart\$.ti,ab,ot,hw. (3)  
56 ((coronary or heart) adj2 disease).ti,ab,ot,hw. (237067)  
57 (MI or IHD).ti,ab,ot,ab. (25570)  
58 (isch?emic heart disease\$ or myocardi\$ isch?em\$ or angina\$).ti,ab,ot,hw. (104587)  
59 or/15-58 (590875)  
60 animals/ not (animals/ and humans/) (3394409)  
61 59 not 60 (530061)  
62 14 and 61 (323)  
63 **limit 62 to yr="2000 -Current" (294)**

**Economic evaluations search (high definition CT only)**

**Medline: 2000-2011/1/wk 1**

**Econ filter + Somatom + CHD/CAD**

**Searched 17.1.11**

- 1 economics/ (25782)
- 2 exp "costs and cost analysis"/ (151394)
- 3 economics, dental/ (1783)
- 4 exp "economics, hospital"/ (16667)
- 5 economics, medical/ (8226)
- 6 economics, nursing/ (3784)
- 7 economics, pharmaceutical/ (2150)
- 8 (economic\$ or cost or costs or costly or costing or price or prices or pricing or pharmaco-economic\$.ti,ab. (319366)
- 9 (expenditure\$ not energy).ti,ab. (13589)
- 10 (value adj1 money).ti,ab. (16)
- 11 budget\$.ti,ab. (13872)
- 12 or/1-11 (428922)
- 13 ((energy or oxygen) adj cost).ti,ab. (2195)
- 14 (metabolic adj cost).ti,ab. (566)
- 15 ((energy or oxygen) adj expenditure).ti,ab. (12453)
- 16 or/13-15 (14627)
- 17 12 not 16 (425575)
- 18 letter.pt. (690072)
- 19 editorial.pt. (263844)
- 20 historical article.pt. (266040)
- 21 or/18-20 (1207825)
- 22 17 not 21 (402171)
- 23 Somatom definition flash.ti,ab,ot,hw. (4)
- 24 DSCT.ti,ab,ot,hw. (237)
- 25 (Aquilion-1 or Aquilion-one).ti,ab,ot,hw. (7)
- 26 Brilliance ict.ti,ab,ot,hw. (1)
- 27 (Discovery ct750 or Discovery ct-750).ti,ab,ot,hw. (0)
- 28 (640slice\$ or 640 slice\$.ti,ab,ot,hw. (0)
- 29 (256slice\$ or 256 slice\$.ti,ab,ot,hw. (44)
- 30 (128slice\$ or 128 slice\$.ti,ab,ot,hw. (30)
- 31 ('2' adj2 (energy or source\$)).ti,ab,ot,hw. (2361)
- 32 (Dual\$ adj2 (energy or source\$) adj3 (CT or scan\$ or DSCT or imag\$ or multidetect\$ or multi-detect\$ or computed or tomography\$)).ti,ab,ot,hw. (1101)
- 33 (High definition adj3 (CT or scan\$ or DSCT or imag\$ or multidetect\$ or multi-detect\$ or computer or tomography\$)).ti,ab,ot,hw. (156)
- 34 modern cone-beam dual-source spiral.ti,ab,ot,hw. (1)
- 35 (high pitch dual spiral adj3 (CT or scan\$ or imag\$ or technique\$ or protocol\$ or DSCT or multidetect\$ or multi-detect\$ or computer or tomography\$)).ti,ab,ot,hw. (1)
- 36 or/23-35 (3790)
- 37 exp Heart Defects, Congenital/ (103198)
- 38 exp Coronary Disease/ or myocardial ischemia/ or exp myocardial infarction/ (285046)
- 39 ((pulmonary or mitral or aortic or aorta or Tricuspid or coronary or cardiac or valve) adj2 (stenosis or atresia)).ti,ab,ot,hw. (50167)

- 40 (congenital\$ adj2 arter\$ adj2 (defect\$ or deform\$ or malform\$ or anomal\$ or abnormal\$ or disease\$)).ti,ab,ot,hw. (449)
- 41 (congenital\$ adj2 heart adj2 (defect\$ or deform\$ or malform\$ or anomal\$ or abnormal\$ or disease\$)).ti,ab,ot,hw. (42499)
- 42 (CAD or ASD or AVSD or CAVSD or HLHS or HLH or HRH or HRHS or IAA or PDA or VSD or CHD or LVOT or PVOD or TGA or UVH or TAPVD or TAPVR or PAPVD or PAPVR).ti,ab,ot. (45488)
- 43 (TOF or TAPVC or TGV or D-TGA or DTGA or ITGA or I-TGA or DILV or DORV or COA or IAA or SS or PAPVC).ti,ab,ot. (63488)
- 44 (Dextrocardia\$ or Dextro-cardia\$).ti,ab,ot,hw. (1335)
- 45 (dextro-Transpos\$ adj3 great arteries).ti,ab,ot,hw. (33)
- 46 (dextroTranspos\$ adj3 great arteries).ti,ab,ot,hw. (29)
- 47 ((cardium or cardio\$ or cardiac\$ or heart) adj3 (dextrover\$ or dextro-ver\$ or dextro-rotat\$ or dextroposition\$ or dextrorotat\$ or dextro-position\$)).ti,ab,ot,hw. (101)
- 48 ((interauricular or inter-auricular or inter-atrial or interatrial or atrial or atrium) adj2 (septal or septum) adj2 (shunt\$ or defect\$)).ti,ab,ot,hw. (11938)
- 49 (Lutembacher\$ adj2 (syndrome or complex)).ti,ab,ot,hw. (152)
- 50 ((persisten\$ or Patent\$) adj2 ostium secundum).ti,ab,ot,hw. (5)
- 51 (trilogy adj2 fallot).ti,ab,ot,hw. (54)
- 52 ((ventricul\$ or Atrioventricul\$) adj2 (septal or septum) adj2 (shunt\$ or defect\$)).ti,ab,ot,hw. (13819)
- 53 ((Hypo-plastic or Hypoplastic) adj3 left heart).ti,ab,ot,hw. (1819)
- 54 ((Hypo-plastic or Hypoplastic) adj3 left heart).ti,ab,ot,hw. (1819)
- 55 (Interrupt\$ adj3 aortic arch).ti,ab,ot,hw. (912)
- 56 ((persisten\$ or Patent\$ or closure or closed or ligation or ligated or obliterate\$) adj2 ductus arteriosus).ti,ab,ot,hw. (8591)
- 57 ((persisten\$ or Patent) adj2 truncus arteriosus).ti,ab,ot,hw. (762)
- 58 (tetralogy adj2 fallot).ti,ab,ot,hw. (8220)
- 59 total\$ anomalous pulmonary venous connection\$.ti,ab,ot,hw. (491)
- 60 (Transpos\$ adj3 great vessels).ti,ab,ot,hw. (5823)
- 61 (Transpos\$ adj3 great arteries).ti,ab,ot,hw. (3205)
- 62 (levoTranspos\$ adj3 great arteries).ti,ab,ot,hw. (7)
- 63 Bicuspid aortic valve\$.ti,ab,ot,hw. (1150)
- 64 Double inlet left ventricle\$.ti,ab,ot,hw. (163)
- 65 (Ebstein\$ adj1 anomal\$).ti,ab,ot,hw. (1704)
- 66 (Coarctat\$ adj3 aorta).ti,ab,ot,hw. (3506)
- 67 (Co-arctat\$ adj3 aorta).ti,ab,ot,hw. (3)
- 68 Interrupt\$ aort\$.ti,ab,ot,hw. (611)
- 69 (Scimitar adj2 (syndrome or complex)).ti,ab,ot,hw. (445)
- 70 Partial\$ anomalous pulmonary venous connect\$.ti,ab,ot,hw. (224)
- 71 Total\$ anomalous pulmonary venous connect\$.ti,ab,ot,hw. (491)
- 72 (Shone\$ adj2 (syndrome or complex or anomaly or defect\$ or deform\$ or malform\$ or abnormal\$)).ti,ab,ot,hw. (66)
- 73 (Marfan\$ adj2 (syndrome or complex)).ti,ab,ot,hw. (5176)
- 74 Marfans.ti,ab,ot,hw. (1904)
- 75 (eisenmenger\$ adj2 (syndrome or complex)).ti,ab,ot,hw. (971)
- 76 univentric\$ heart\$.ti,ab,ot,hw. (499)
- 77 uni-ventric\$ heart\$.ti,ab,ot,hw. (3)
- 78 ((coronary or heart) adj2 disease).ti,ab,ot,hw. (237067)

- 79 (MI or IHD).ti,ab,ot,ab. (25570)
- 80 (isch?emic heart disease\$ or myocardi\$ isch?em\$ or angina\$).ti,ab,ot,hw. (104587)
- 81 or/37-80 (590875)
- 82 animals/ not (animals/ and humans/) (3394409)
- 83 81 not 82 (530061)
- 84 22 and 36 and 83 (7)
- 85 limit 84 to yr="2000 -Current" (7)**

Costs filter:

Centre for Reviews and Dissemination. NHS EED Economics Filter: Medline (Ovid) monthly search [Internet]. York: Centre for Reviews and Dissemination; 2010 [cited 13.1.11]. Available from:

[http://www.crd.york.ac.uk/crdweb/html/helpdoc.htm#MEDLINE\\_NHSEED](http://www.crd.york.ac.uk/crdweb/html/helpdoc.htm#MEDLINE_NHSEED)