Evidence Assessment and Analysis Report commissioned by the NIHR HTA Programme on behalf of the National Institute for Health and Clinical Excellence - Protocol

1. Title of the project:

EOS 2D/3D X-ray Imaging System

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

CRD/CHE Technology Assessment Group (Centre for Reviews and Dissemination/Centre for Health Economics), University of York.

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3. Plain English Summary

The taking of images such as X-rays is very important to help guide the treatment of many orthopaedic conditions. There are some conditions where it can be beneficial to take an image that is weight-bearing, full body, or three-dimensional (3D). One example of such a condition is scoliosis.

Scoliosis is a 3D deformity of the spine. It is characterised by a curve from side to side. With this curve there is also a change in the normal front to back curves of the spine and some twisting. This distorts the rib cage and may give the patient a rib hump. The size, stiffness and cosmetic consequences of the curve change over time. Scoliosis usually develops during childhood and adolescence. When the condition has no clear underlying cause, it is referred to as 'idiopathic', which is the most common type of scoliosis. It has been estimated that adolescent idiopathic scoliosis occurs in 1-3% of children between 10 and 16 years of age. Scoliosis is also seen in adults.

Medical management aims to prevent the scoliosis from worsening or to straighten the spine in more severe cases. The treatment plan is often determined by the severity of the curvature and the patient's age. This necessitates periodic monitoring of curve progression. The repeated monitoring results in a high dose of radiation exposure with conventional X-ray imaging devices.

An alternative imaging device which can be used in conditions like scoliosis is the EOS 2D/3D X-ray imaging system, which is a new digital radiography system, capable of providing uninterrupted full-body, weight-bearing digital 2D and 3D imaging in a single scan with a low radiation dose.

The main purpose of this project is to assess the benefits, adverse effects and cost-effectiveness of the EOS 2D/3D X-ray imaging system compared with conventional X-ray devices for monitoring and evaluation of scoliosis and other relevant orthopaedic conditions.

4. Decision problem

- **Objectives**

The aim of the project is to determine the clinical and cost-effectiveness of the EOS 2D/3D X-ray imaging system for the evaluation and monitoring of scoliosis and other relevant orthopaedic conditions where there are potential benefits associated with imaging that is weight-bearing, full body, simultaneously posteroranterior (PA) and lateral, and/or 3D, and where radiation exposure is a concern. The relevant comparator imaging technologies are X-ray film, computed radiography (CR), and digital radiography (DR). The clinical outcomes to be considered will be the radiation-associated risk of cancer and other patient health benefits.

- **Background**

The management of many orthopaedic conditions involves the use of imaging for diagnosis, treatment planning and assessment and monitoring. For certain conditions and/or stages of management, certain features of the imaging are important, for example being weight-bearing, uninterrupted full body, the ability to scan PA and laterally simultaneously, or to produce a 3D image. One example of such a condition is scoliosis.

Scoliosis

Scoliosis is a 3D deformity of the spine. It is characterised by a curve from side to side. With this curve there is also a change in the normal front to back curves of the spine and some twisting. This distorts the rib cage and may give the patient a rib hump. The size, stiffness and cosmetic consequences of the curve change over time.[1] Progression of scoliosis leads to cosmetic deformity, which in turn can lead to poorer body image perception and problems in psychological and social development, loss of flexibility, cardiopulmonary problems and pain.

The causes of scoliosis include problems of nerve or muscle, infection, tumours, injuries or problems during development in the womb. However, the majority of spinal curves have no clear underlying cause and are therefore described as 'idiopathic'.[1] Most of these are of late onset (appearing during adolescence), which may occur due to an imbalance in the growth of the spine. It has been estimated that adolescent idiopathic scoliosis occurs in 1-3% of children between 10 and 16 years of age.[2] For the majority of patients, their back shape will change with growth and then stabilise when they are fully grown.

The management of children and adolescents with scoliosis primarily involves monitoring at intervals to assess disease progression and guide treatment decisions. Progression is measured in terms of the degree of the curvature, which is monitored using serial upright weight-bearing X-rays. The interval chosen between X-rays will be determined by the age of the patient, their rate of growth at the time and the nature of their curve. However, the interval between X-ray monitoring tends to range from four months to almost two years. Other techniques, such as body surface scans may also be used in conjunction with the weight-bearing X-rays to assess other characteristics of the patient's deformity.

There is currently no good evidence that either bracing or physiotherapy alter the long-term natural history of back shape in adolescent idiopathic scoliosis. The decision to offer surgical treatment will depend upon many factors including the degree of curvature of the spine (Cobb angle), rate of progression, cosmetic impact and the patient's age. Whilst only approximately 10% of children with adolescent scoliosis require surgical intervention,[3] nearly 95% of children with early onset scoliosis go on to require surgical treatment.[4] Surgery is often not performed until growth of the skeleton is complete or near complete and therefore monitoring can continue for many years. Patients are also monitored using weight-bearing X-ray post-operatively, for up to two years.

Scoliosis is also seen in adults, some of whom may go on to have surgical treatment. These may be patients who develop a new curve due to wear-and-tear changes in the spine. Alternatively, it may be patients who developed a curve as a child and then go on to develop additional wear-and-tear problems which cause some changes in the shape of the back.

A weight-bearing image is very important in the evaluation of patients with scoliosis due to the effect of gravity. The American College of Radiology Practice Guideline for the Performance of Radiography for Scoliosis in Children recommends PA and lateral radiography of the spine obtained in an upright position for initial or screening examination.[5] Non-weight-bearing images can lead to misinterpretation and misdiagnosis. Full body images can also help prevent misinterpretation of the spinal curvature by providing information about the position of the pelvis and legs.

Other potentially relevant orthopaedic conditions

Other orthopaedic conditions that may similarly benefit from the availability of reduced radiation dose, weight-bearing, full body, simultaneous PA and lateral imaging, and/or 3D imaging include: other spinal deformities in children and adolescents; leg length discrepancy and misalignment in children and adolescents; adult spinal deformities including degenerative scoliosis, progressive kyphosis and osteoporotic fractures; and loss of sagittal and coronal balance in adults, including hip and knee problems where a full body or full leg length image is required for treatment planning (e.g. joint replacement surgery).

Imaging technologies and the risks associated with radiation exposure

All exposure to radiation carries an increased risk of cancer. Where patient management involves a number of X-rays the increased risk has to be considered. This is of particular concern when X-ray monitoring is conducted throughout childhood and puberty.[6] Children are more sensitive to the harmful effects of radiation than adults. Studies have linked radiation exposure from the evaluation of scoliosis progression with harmful outcomes, such as breast cancer.[6, 7] Therefore radiation exposure, and subsequent detrimental health outcomes, is an important consideration in the selection of an imaging technology.

EOS 2D/3D X-ray imaging system

EOS is a biplane X-ray imaging system manufactured by BioSpace Med, Paris, France. It uses slot-scanning technology to produce a high quality image with less irradiation than standard imaging techniques. EOS allows the acquisition of images while the patient is in an upright weight-bearing (or seated or squatting) position, and can image the full length of the body (up to 175 cm), removing the need for digital stitching. The system takes approximately 20 seconds for an adult full body scan and 4-6 seconds to scan the spine, depending on the patient's height. As with the widely accepted standard position for all spine radiographs, the patient being scanned is also required to remain motionless, with their arms folded at 45°, and hold their breath during the scan.

EOS takes PA and lateral images simultaneously, and the digital image is available immediately on a 2D workstation. A 3D image can be reconstructed on the sterEOS workstation using the PA and lateral images and a statistical 3D spine model, generated from a database of scoliotic patients. The reconstruction of a 3D image takes 5 to 10 minutes for each part of the skeleton (e.g. spine or femur).[8]

The acquisition cost of the EOS system in the UK is in the region of £400,000, with an annual maintenance cost of £32,000. The maintenance contract covers all parts except X-ray tubes, which cost £25,000 to replace, including fitting.[9] In addition to the cost of purchasing and maintaining the equipment, there may be some building costs to provide a suitable location complying with radiation legislation requirements, if existing rooms are not available. EOS requires the same room planning and shielding as a general X-ray room and the same radiation protection protocols apply.

Comparator imaging technologies

Currently available imaging technologies that can be used in an upright weight-bearing position include X-ray film, CR and DR. All of these technologies have higher radiation doses than EOS. X-ray film, CR and DR can only take images from one angle at a time, so simultaneous PA and lateral images are not possible and 3D reconstruction cannot be obtained. When a full body image is required, these conventional X-ray imaging technologies also require adjustment for distortion or digital stitching from multiple images.

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

To evaluate the clinical benefits of EOS 2D/3D X-ray imaging system relative to standard X-ray, a review of the evidence will be conducted. It is anticipated that much of the information required for this assessment will not be available in the published literature nor be retrievable using standard systematic review methods. However, the review will be conducted as far as possible following the general principles recommended in CRD's guidance[10] and the PRISMA statement[11] although not all searches will be exhaustive. In addition, where clinical study evidence is lacking for key parameters, formal elicitation of expert opinion may be undertaken.

- **Inclusion and exclusion criteria**

The titles and abstracts of records identified by the search strategy will be examined for relevance by two reviewers independently. Full papers of any potentially relevant records will be obtained where possible and screened by two reviewers independently. The relevance of each study to the review and the decision to include/exclude studies will be made according to the inclusion criteria detailed below. Any disagreements will be resolved by consensus.

Participants

Primarily, adolescents and children undergoing monitoring and evaluation of scoliosis will be eligible for inclusion.

The eligible patients will also include those with other relevant orthopaedic conditions where the benefits of reduced radiation dose, weight-bearing imaging, full body imaging, simultaneous PA and lateral imaging, and/or 3D imaging are likely to be clinically important for patient management. These additional conditions will include:

- children and adolescents with leg length discrepancy and misalignment;
- adults with spinal deformities (e.g. degenerative scoliosis, progressive kyphosis, and osteoporotic fractures);
- adults with loss of sagittal and coronal balance, including hip and knee problems where a full body or full leg length image is required for treatment planning (e.g. joint replacement surgery).

Interventions/Comparators

The EOS 2D/3D X-ray imaging system will be reviewed. The comparators will be conventional 2D PA/anteroposterior (AP) and lateral radiographs from X-ray film, CR or DR imaging.

Outcomes

The primary outcome will be cumulative radiation dose and its impact on the risk of cancer. Other outcomes will be condition specific, reflecting any beneficial effect on patient health, adverse effects and quality of life. For example, in scoliosis or other spinal deformity, outcomes may include improvement in patient health associated with the use of EOS, and for patients undergoing joint replacement surgery, outcomes may include the likelihood of success of the replacement.

Study designs

To evaluate the risk of cancer from the radiation exposure associated with the relevant interventions, controlled or uncontrolled studies that provide information relevant to current UK practice will be sought. This will include studies of radiation dose and cancer risk where available. Additionally, guidelines, studies or reviews that provide data on the number of images required for the clinical management of each relevant orthopaedic condition will be sought.

To evaluate the other outcomes (clinical benefits) of EOS studies that compare EOS with conventional 2D PA/AP and lateral radiographs will be included in the review, where available.

- **Literature searching**

Searches of the literature will be conducted in order to identify studies and other relevant information in the following key areas:

- Extensive searches of the EOS literature
- Standard practice and treatment pathways for scoliosis and other relevant orthopaedic conditions
- Information on radiation dose for all relevant indications
- Evidence on adverse effects of diagnostic x-ray radiation, such as cancer and infertility

Additional supplementary searches will be carried out as necessary. Searches for studies for cost and quality of life data will also be included, as outlined in Section 6.

Electronic sources will be searched for primary and secondary studies. These sources will include MEDLINE, EMBASE, CINAHL, HMIC, ISI Science Citation Index and the Cochrane Library (including the Cochrane Database of Systematic Reviews (CDSR), the Database of Abstracts of Reviews of Effects (DARE), the Health Technology Assessment (HTA) Database, the NHS Economic Evaluation Database (NHS EED) and the Cochrane Central Register of Controlled Trials).

In addition, relevant reviews and guidelines will be identified through the following resources: Clinical Evidence, National Institute for Health and Clinical Evidence (NICE) website, NHS Evidence - National Library of Guidelines, SIGN Guidelines, the Guidelines International Network website and the Medicines and Healthcare products Regulatory Agency.

Search terms will be identified by scanning key papers identified during the review, through discussion with the review team and clinical experts, and by using database thesauri. Reference lists of included papers will be assessed for additional relevant studies and where necessary, authors of eligible studies will be contacted for further information. No limits relating to language, date of publication or study design will be applied to the searches.

- **Data extraction strategy**

Data relating to both study design and results will be extracted by one reviewer using a standardised data extraction form and independently checked by another. Discrepancies will be resolved by discussion, with involvement of a third reviewer when necessary. If time constraints allow, attempts will be made to contact authors for any missing data. Data from multiple publications of the same study will be extracted as a single study.

- **Quality assessment strategy**

The quality of included studies will be assessed using standard checklists[10] adapted as necessary to incorporate topic-specific quality issues. The assessment will be performed by one reviewer, and independently checked by another. Discrepancies will be resolved by discussion, with involvement of a third reviewer when necessary.

- **Methods of analysis/synthesis**

In the initial analysis/synthesis of data, the results of data extraction will be presented in structured tables and as a narrative summary, grouped by participant and intervention characteristics. Where sufficient clinically and statistically homogenous data are available, data will be pooled using appropriate meta-analytic techniques. Clinical, methodological and statistical heterogeneity will be investigated. If necessary, sensitivity analyses will be performed when permitted by sufficient data.

6. Report methods for synthesising evidence of cost-effectiveness

Identifying and systematically reviewing published cost-effectiveness studies

Searches for economic evaluations, as well as quality of life and cost data will be undertaken in the databases listed in Section 5. These sources will be used to identify any studies of the cost-effectiveness of EOS against its relevant comparators. A broad range of study designs will be considered in the assessment of cost-effectiveness including economic evaluations conducted alongside randomised or non-randomised comparator trials, modelling studies and analyses of administrative databases. The focus for the review will be full economic evaluations that compare two or more options and consider both costs and consequences (including cost-effectiveness, cost-utility and cost-benefit analyses). With a view to gaining insights into the modelling methods we might employ, we will also consider modelling studies for scoliosis monitoring and the other orthopaedic conditions where the interventions and comparators listed in Section 5 are assessed for cost-effectiveness; and cost analyses of EOS. These studies will not be subject to a formal

review (unless they complement the evaluation of the EOS 2D/3D X-ray imaging system) but will be used to assist in the overall development of a new decision analytic model, with the aim of identifying important structural assumptions, parameter estimates (including costs) and highlighting key areas of uncertainty.

The quality of the cost-effectiveness studies will be assessed according to the criteria for economic evaluation detailed in the methodological guidance developed by NICE.[12] This information will be tabulated and summarised within the report. In particular, information will be extracted on the comparators, study population, main analytic approaches, primary outcomes, quality of life estimates, costs, estimates of incremental cost-effectiveness and approaches to quantifying decision uncertainty (e.g. deterministic/probabilistic sensitivity analysis).

Evaluation of costs, quality of life and cost-effectiveness

A decision analytic model will be developed to estimate the cost-effectiveness of EOS and standard X-rays (film, CR, DR) for monitoring spinal deformity (principally scoliosis) and the other relevant orthopaedic conditions listed in Section 5 where full body or full leg length images are currently requested. The perspective will be that of the National Health Service and Personal Social Services, health benefits will be expressed in terms of quality-adjusted life years (QALYs) and both costs and quality-adjusted life years discounted at a rate of 3.5% per annum.

Since the primary benefit of EOS is to provide imaging at low dose radiation, the model will focus on evaluating the cost-effectiveness of EOS through reducing the amount of radiation exposure to patients, particularly to children and adolescents, over the monitoring period for scoliosis and the various conditions. The subsequent outcomes from radiation exposure on the risk of cancer, mortality and any other adverse effects will be explicitly modelled to determine the impact of radiation doses on quality-adjusted life years (QALYs). The robustness of the analysis will depend on the availability of evidence linking radiation exposure to cancer risk, as well as the effect of cancer on quality-adjusted life expectancy.

Establishing a direct link between diagnostic test accuracy, or the quality of the imaging, and final health outcomes is unlikely to be possible due to limited or no formal evidence. Should the review of clinical effectiveness allow us to establish the impact of the alternative interventions on image quality/accuracy, the longer-term impact (including any therapeutic implications) and subsequent prognosis of patients for the various conditions will be included. In the likely absence

of formal evidence linking image quality/accuracy with patients' health outcomes, formal elicitation of clinical opinions[13, 14] on these parameters may be undertaken.

Resource utilisation and costs will be estimated for EOS and standard X-rays. For EOS, these costs will include the capital cost of the equipment, including installation of workstation and software, consumables, annual maintenance costs and patient throughput. Consideration will also be given to building costs where a suitable location complying with radiation legislation requirements may be required if existing rooms are not available. Similar cost considerations apply to standard film, CR and DR imaging but these systems are probably in place and will not require special implementation. Particular attention will be paid to how per patient costs vary with total patient throughput for EOS, standard X-rays and the indications listed in Section 5. The implication of this variation is likely to be explored using sensitivity and threshold analysis. Data for the cost analysis will be drawn from routine NHS sources, discussions with individual hospitals and with the EOS and comparator manufacturers.

Further details of the model structure and data to be used to populate the model will have to await the findings from the systematic searches of the literature. However, we expect to give particular consideration to the following key variables:

- Amount of radiation dose exposed to the body and possibly to specific organs/parts of the body from the different types of imaging.
- The frequency of follow-up and monitoring for the various conditions.
- The link between radiation exposure and cancer risk and mortality.
- The duration of examination assessment time.
- Therapeutic implications and change in quality of life resulting from the alternative interventions.
- Resource utilisation and costs for EOS and standard X-rays.
- Patient throughput for the various conditions.

The specific objectives of the cost-effectiveness analysis are:

- To use an economic model to estimate the amount of radiation received over the entire monitoring period for the evaluation of scoliosis and the other conditions and use it to establish the impact of that radiation on overall QALYs by examining cancer risk and mortality.

- Subject to the availability of suitable data on image quality/accuracy and with the potential of using formal elicitation of expert judgements, to use the model to characterise patients' subsequent prognosis for the various conditions and alternative interventions in a way that is clinically appropriate.
- To populate the model using the most appropriate data identified systematically from published literature and routine sources. If feasible, formal methods of expert elicitation of clinical opinion will be used to help inform key model parameters.
- To relate intermediate outcomes to final health outcomes, expressed in terms of QALYs. This is necessary in order to provide decision makers with an indication of the health gain achieved by each intervention, relative to its additional cost, in units which permit comparison with other uses of health service resources.
- To estimate the mean cost-effectiveness of EOS and standard X-rays based on an assessment of long-term NHS costs and quality-adjusted survival.
- To use threshold analysis in the absence of formal evidence on specific parameters to establish the threshold of benefit required to achieve good value for money within the NHS.
- To characterise the uncertainty in the data used to populate the model and to present the uncertainty in these results to decision makers. A probabilistic model will be developed which requires that each input in the model is entered as an uncertain, rather than a fixed parameter. Using Monte Carlo simulation, this parameter uncertainty will be translated into uncertainty in the overall results. This will be presented graphically using cost-effectiveness acceptability curves which show the probability that each intervention is cost-effective conditional on a range of possible threshold values which NHS decision makers attach to an additional QALY.
- To use sensitivity analysis to examine alternative assumptions in the data and to see how sensitive the cost-effectiveness threshold is to uncertainty in the assumed base case parameters.

7. Handling information from the companies

Any 'commercial in confidence' data provided by the manufacturer (BioSpace Med) and specified as such will be highlighted in blue and underlined in the assessment report. Any 'academic in confidence' data provided by the manufacturer will be highlighted in yellow and underlined in the assessment report.

8. Competing interests of authors

None of the authors has any conflicts of interest.

9. Timetable/milestones

Milestone	Date to be completed
Submission of final protocol	28/10/10
Diagnostics Assessment Report (DAR) due (protocol sign off + 20 weeks)	09/03/11

10. References

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