The Adler Genus Unicompartmental Knee Prosthesis Post-Marketing Surveillance Study

Study Sponsor
Adler Ortho

Study Co-ordinators
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1. SIGNATURES

1.1. PROTOCOL AUTHORS

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Name	Signature	Date
Richard Field Director of Research and Education, EOC		

1.3. CHIEF INVESTIGATOR'S SIGNATURE

Name	Signature	Date
Mr Mark Rickman MD FRCS Consultant Orthopaedic Surgeon		

2. CONTACT DETAILS OF SPONSOR'S KEY PERSONNEL

Edgardo Cremascoli

3. LIST OF ABBREVIATIONS AND KEY TERMS

Abbreviations	Description of abbreviations
CRF	Case Report Form
GP	General Practitioner
ODEP	Orthopaedic Data Evaluation Panel

4. SYNOPSIS

In 2000, the National Institute of Clinical Health and Excellence published a recommendation for the need of survivorship data on all hip prostheses sold to NHS trusts. Following these guidelines, the Orthopaedic Data Evaluation Panel (ODEP) was set up in order to review this data and grant implant ratings based upon the quality of the data and the implants' rate of revision. The purpose of this body was to ensure that NHS Trusts were knowingly purchasing high-quality implants with known survivorship figures.

While ODEP was established to review data on hip prostheses, the importance of long-term implant surveillance has spread to other sectors of the orthopaedic industry. In anticipation of an ODEP-style review of knee prostheses, many manufacturers are keen to obtain survivorship and functional data on knee implants using the ODEP data submission criteria. Additionally, surveillance studies can be used by both manufacturers and NHS Trusts to evaluate the safety and efficacy of implants that are new on the market.

ODEP has made recommendations of what submitted data should look like in order to ensure the highest, A-level rating. Data should be on an original cohort of at least 500 patients, studies should be multi-surgeon and multi-centre. Up to five independent centres can be involved, recruiting a minimum of 25 patients and a maximum of 250 at each site. All patients should be followed-up at 6 months, 3, 5, 7 and 10 years after their operation. The study will utilise a combination of patient-reported outcome assessments, clinical and radiological evaluations and comprehensive complications reporting.

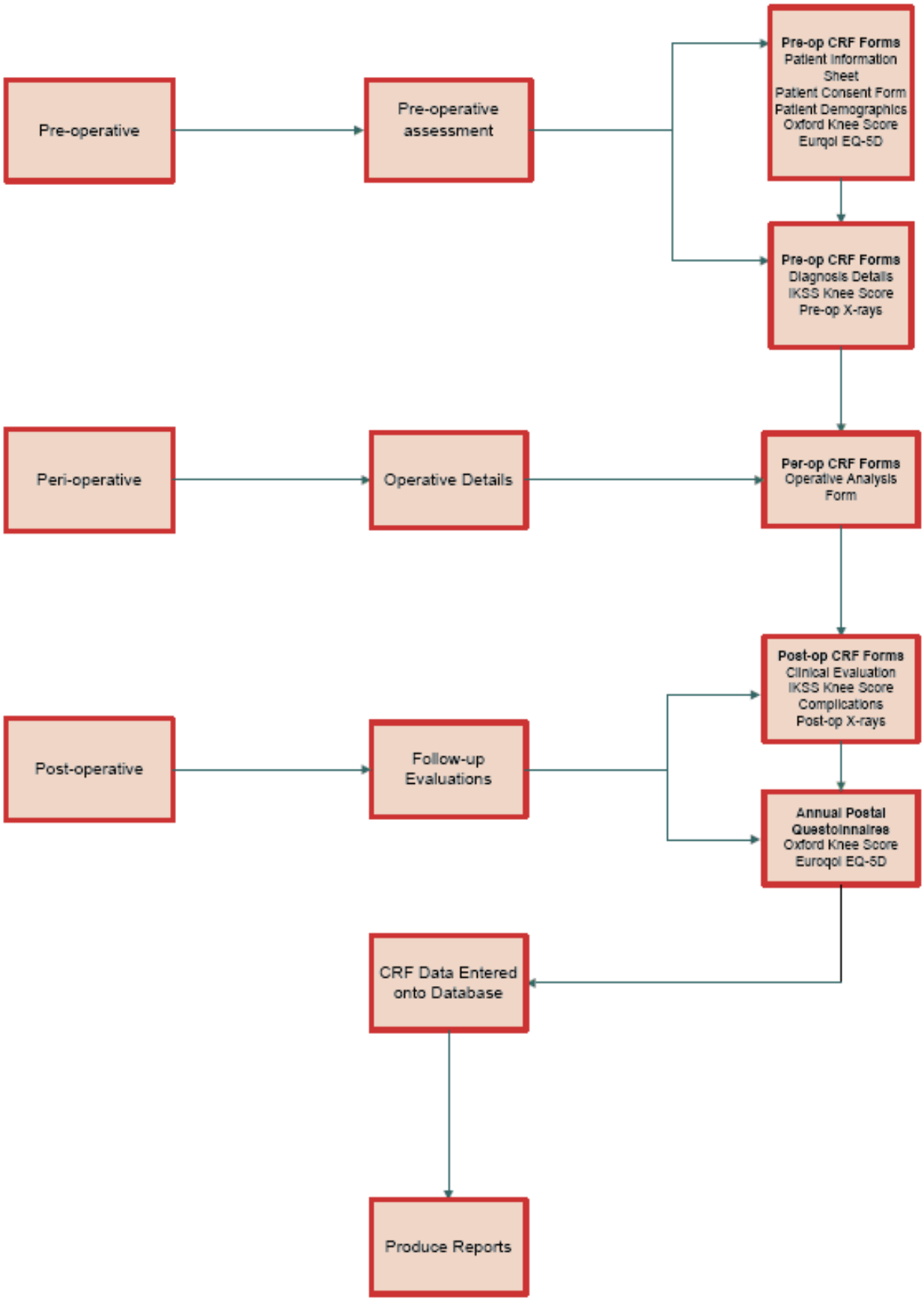
Publishable survivorship data is submitted for review at each of the time points. Data will be submitted to the ODEP in the form of journal publications, presentations or raw data that is available for peer-review.

For further background on ODEP and to review their submission criteria, please visit the NHS Supplychain website:

http://www.supplychain.nhs.uk/portal/page/portal/Communities/Orthopaedics/ODEP%20database

5. FLOWCHART

5.1. STUDYFLOWCHART



6. SCHEDULE OF VISITS AND EVALUATIONS

6.1. SCHEDULE GRAPH

(Table 1)

Evaluation Type	Pre-op	Peri-op	Post-op	6 Wks.	3 Mon.	6 Mon.	12 Mon.	3 Yrs.	5 Yrs.	7 Yrs.	10 Yrs.
Medical History	✓										
Operative Details		✓									
Knee Society Score	✓						✓	✓	✓	✓	✓
Radiographic analysis	✓		✓				✓	✓	✓	✓	✓
Complication details		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Oxford Knee EuroQol EQ-5D scores	✓	**None**			✓	✓	✓	**Annually for 10 years**			

7. INTRODUCTION

7.1. STUDY DESIGN

The clinical performance of the Genus Unicompartmental Knee Prosthesis, manufactured by Adler Ortho srl, will be evaluated by a multicentre, prospective clinical surveillance study.

The Elective Orthopaedic Centre (EOC), in Epsom, Surrey, will be the study coordinating centre. Six (6) further centres will participate in the clinical study, for seven (7) total centres. Each participating centre will recruit approximately 50 patients. Patient recruitment will cease when a cohort of 350 Genus Unicompartmental knee prosthesis have been implanted.

7.2. IMPLANTS TO BE USED IN THE STUDY

For the purposes of this study, knee replacement surgery will be undertaken using the Genus Unicompartmental knee prosthesis.

7.3. STUDY OBJECTIVES

7.3.1. To verify the ten year clinical and radiographic performance of the Genus Unicompartmental knee prosthesis when used in patients under normal conditions of use.

7.3.2. To document the safety of the Genus Unicompartmental knee prosthesis over a period of 10 years by reporting any complications,

adverse events, adverse device events, serious adverse events and serious adverse device related events.

7.3.3. To evaluate patient-perceived implant functionality and quality of life following intervention with the Genus Unicompartmental knee prosthesis at each follow-up visit.

7.3.4. To determine the survivorship of the Genus Unicompartmental knee prosthesis at each follow-up visit.

7.4. METHODS

UK ethics committee approval will be obtained by the EOC from the National Research Ethics Committee (NRES). NRES approval will cover all participating sites in the UK. For sites outside of the UK, independent ethics approval will need to be obtained by the participating site in accordance with the country's guidelines for ethics approval.

Research & Development (R&D) approval will need to be independently sought at each participating UK site. The equivalent will need to be obtained by each participating site outside of the UK.

7.4.1. Suitable participants are identified when placed on the waiting list to undergo Unicompartmental knee replacement with Genus Unicompartmental knee prosthesis.

7.4.2. Each of these patients will receive written information about the study and an invitation to participate. The patient information sheet will explain the purpose of the study, study duration, the follow-up schedule.

7.4.3. The patient will also be informed that his/her medical records are subject to review by representatives of the sponsor as necessary and that data confidentiality of the patient will be maintained at all times. The patient will be told that he/she is free to refuse study participation or to withdraw from the study at any time without compromising future medical care.

7.4.4. Patient informed consent will be obtained for inclusion in the study prior to surgery. Informed written consent will be obtained from all patients who choose to take part in the study. Those who fulfil the inclusion criteria will be written to and sent the patient information sheets before their surgery. Those wishing to discuss the clinical study will be invited to attend an appointment with the participating surgeon or an appropriately trained member of the surgeon's team. Alternatively, the telephone numbers of the research office and surgeon's team will be provided to the patient in the event they would like to have the discussion over the phone as opposed to an appointment. Patients will be under no obligation to take part in the study and all of the benefits and risks will be explained. Patients who are deemed without capacity to consent will be excluded from the study. Consent will be taken before the patient's surgery by the surgeon or an appropriately trained member of his/her team.

7.4.5. The patients' GPs will receive notification of their participation in the study.

7.4.6. Data will be recorded on specially designed NCR CRFs.

7.4.7. The patient's pre-operative status and level of function will be evaluated using the Oxford Knee Score, the Knee Society Score, and the EuroQol-5D Health-State Assessment.

7.4.8. Pre-operative anterior-posterior and lateral will be taken.

7.4.9. Implant position, fixation and stability of the femoral, tibial and patellar components as well as their effect on surrounding bone will be monitored by review of the radiographs using established measurement criteria. An Anterior-posterior and lateral will be taken post-operative prior to discharge and at each clinical review (1, 3, 5, 7 and 10 years). X-rays from all participating centres will be sent to the EOC on burned CDs, indentifying the patient's study number and review time point. X-rays will be analysed by trained members of the EOC Research Department.

7.4.9.1. Post-operative x-rays will measure implant position and alignment and will be checked for signs of radiolucency and loosening.

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7.4.10. All complications will be documented in the appropriate CRF pages with specific details of the symptoms, their severity, duration and outcome will be collected and any actions taken to resolve the problem will be documented.

7.4.10.1. Any complications that are deemed to be adverse events or serious adverse events will be reported to the appropriate bodies.

7.4.11. The primary outcome measures for the study will be implant's survival, range of movement, pain, patient satisfaction, improvement in general knee function and quality of life. These will be assessed by the Knee Society Score, Oxford Knee Score and the Euroqol EQ-5D. Implant survivorship data of the study cohort will be analysed using the Kaplan-Meier technique.

7.4.12. The secondary outcome measure will be a radiographic evaluation checking for good fixation of the implant components to the bone. Antero-posterior and lateral will be analysed to measure this outcome.

7.4.13. Any medical device related adverse events or serious adverse events will be reported to the study sponsor and subsequently to all relevant competent authorities.

7.4.14. Recording of any pre-op, peri-op or post-op complications or medical device related adverse incidents will be the method by which the safety of the Genus Unicompartmental knee prosthesis is assessed.

7.4.15. Data will be collected at the time points detailed below:

Pre-op: Patient's demographic and radiological review; baseline questionnaire-EuroQol, Oxford Knee and Knee Society scores.

Peri-op: Operation details including peri-operative and early post-operative complications (complications that occur before patient discharge).

Post-op: Clinical Knee Society Score and radiological review at 1, 3, 5, 7 and 10 years and postal Oxford Knee and EuroQol scores annually.

7.4.16. A courtesy telephone call will be made to each study participant twice yearly, which will identify that the study participant's contact details remain correct. EOC Research will be responsible for the telephone calls in the UK.

7.4.17. Information held by the NHS and records maintained by The NHS Information Centre and the NHS Central Register may be used to help contact study participants and provide information about their health status.

7.5. SCHEDULE OF EVALUATIONS

The pre-operative and peri-operative data will be collected and entered into the CRFs and database. Post-operative annual questionnaires, clinical evaluations and radiographs will be gathered at the scheduled time points outlined in the table below.

See Table 1.

As coordinating centre, the EOC will run monthly reports to inform each participating centre of any upcoming clinical evaluations. These clinical evaluations will need to be scheduled for each patient at their base hospital at 1, 3, 5, 7 and 10 years.

7.6. INCLUSION/EXCLUSION CRITERIA

7.6.1. INCLUSION CRITERIA

- A primary osteoarthritis of one compartment (Medial or Lateral).
- Patients must be between the age of 18 and 80 at the time of consent
- Listed for unicompartmental knee arthroplasty.
- Patients who are willing to give informed written consent
- Absence of any degenerative disease of a progressive nature (e.g. Rheumatoid arthritis)

7.6.2. EXCLUSION CRITERIA

- Progressive local or systemic infection
- Muscular loss, neuromuscular disease or vascular deficiency of the affected limb, making the operation unjustifiable
- Severe instability secondary to advance destruction of chondral structures or loss of integrity of the medial, lateral or either cruciate ligament
- Any patient who cannot or will not provide informed consent for participation in the study
- Those whose prospects for a recovery to independent mobility would be compromised by known coexistent, medical problems
- Patient whose BMI exceeds 45
- Any case not described in the inclusion criteria

7.7. PRE-OPERATIVE EVALUATION

This will be obtained through analysis of patient hospital records and previous radiographs and will include.

- Clinical History
  - Date of visit
  - Date of birth, weight, height, Body Mass Index (BMI) and gender
  - Date informed consent for operation obtained
  - Side of knee to be operated
  - Primary indication for surgery
  - Primary diagnosis
  - Previous surgeries of involved knee
  - Concurrent joint involvement
  - History of sepsis

- Clinical Evaluation
  - Date of visit
  - Oxford Knee Score
  - Knee Society Score

- Radiographic evaluation
  - Date of X-ray
  - Review of the radiographs using established measurement criteria

- Quality of life evaluation
  - EuroQol-5D assessment

7.8. PERI-OPERATIVE EVALUATION

This will be obtained from analysis of the patients operation notes.

- Surgical details
- Date of surgery
- Side of operated knee
- Surgical technique
- Anaesthesia class and type
- Duration of surgery
- Estimated blood loss
- Systemic prophylactic therapy
- Angle of the tibial cuts
- Bone quality
- Bone defects and reconstruction techniques
- Intra-operative complications
- Components used (labels or identifying numbers from the labels Genus Unicompartmental Knee Prosthesis).

7.9. POST-OPERATIVE EVALUATION

Patients will be assessed prior to discharge and at 1, 3, 5, 7 and 10 years from the date of the operation using the evaluation methods defined below.

7.9.1. Clinical Evaluation
- Date of assessment
- Knee Society score
- Complications

7.9.2. Radiographic evaluation
- Date of x-rays
- Review of the x-ray using established measurement criteria

7.9.3. In addition to the above, Oxford Knee and EuroQol EQ-5D scores will also be collected through postal questionnaires at 3, 6 months, 1, 2, 3, 4, 5, 6, 7, 8, 9 and 10 years post-operatively

7.9.4 Data Analysis

Kaplan-Meier survivorship will be the method used to analyse the primary outcome measure of implant survivorship.

In addition, there will be summaries and comparisons presented according to:
- Demographic and pre-operative assessments
- Operative assessments
- Post-operative pain and function assessments: Knee Society, Oxford Knee and EuroQol scores.
- Radiographic images
- Adverse events
- General complications
- Local complications
- Device related complications
- Revisions/removals
- Patient Lost to Follow-up/ Deaths

Frequency and percent distributions will be presented in tabular form for categorical variables. The mean, standard deviation, minimum and maximum values will be presented for quantitative variables. Statistical significance will be measured using paired and un-paired student T tests and chi-squared tests.

7.10. CLINICAL AND DEVICE RELATED COMPLICATIONS

7.10.1. The investigator is required to document all surgical and medical complications and general medical complications, including date of occurrence, date diagnosed, type of complication and treatment.

7.10.2. When required, any complications deemed to be surgical or medical adverse or serious adverse events will be reported to the appropriate authorities.

7.11. MEDICAL DEVICE RELATED ADVERSE INCIDENTS

7.11.1. Definition

An adverse incident is an event that causes, or has the potential to cause, unexpected or unwanted effects involving the safety of device users (including patients) or other persons.

A serious adverse event (SAE) is any untoward medical occurrence or effect that meets one of the following criteria/outcome:

- death
- is life threatening
- requires hospitalisation or prolongation of existing hospitalisation
- results in persistent or significant disability or incapacity
- results in a congenital anomaly or birth defect
- is otherwise considered medically significant by the investigator

7.11.2. Possible causes and outcomes:

Causes of adverse incidents involving devices may include:

- Design or manufacturing problems
- Inadequate servicing and maintenance
- Inappropriate local modifications
- Unsuitable storage and use conditions
- Selection of the incorrect device for the purpose
- Inappropriate management procedures
- Poor user instructions or training (which may result in incorrect user practice).

Conditions of use may also give rise to adverse incidents:

- Environmental conditions (e.g. electromagnetic interference)
- Location (e.g. devices designed for hospitals may not be suitable for a community or ambulance setting).

7.11.3. Investigator's responsibility

Incidents should be reported to the study sponsor immediately after the investigator first learns of the event. This should be to the study project manager defined in this protocol. SAEs that are both **unexpected and related to the procedure** should be reported to the main research ethics committee (REC) within 15 days of knowledge of the incident.

7.11.4. Sponsor's responsibility

Suspected unexpected serious adverse reactions should be reported as soon as possible, usually within 24 hours reported to the relevant competent authority [MHRA in the UK] by the fastest means available, preferably online, or by fax or email and should be confirmed with a telephone call. Where the first report is by telephone, a written report (email or fax – but preferably online) should follow as soon as possible. The initial report of an incident should contain as much relevant detail as is immediately available, but should not be delayed for the sake of gathering additional information.

7.11.5. The emergency contact details are:

Richard E. Field
The EOC Research Dept.
Epsom General Hospital
Dorking Road
Epsom, Surrey.
KT18 7EG

Tel: +44 (0)1372 735 425
Fax: +44 (0) 1372 735 422
Email: richard.field@eoc.nhs.uk

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7.12. PATIENT WITHDRAWALS

7.12.1. Every attempt must be made to ensure that all the patients return for all of the post-operative assessments. However, patients are free to withdraw from the study at any time and are under no obligation to provide a reason for doing so.

7.12.2. The reason for a patient's withdrawal from the study should be recorded in the CRF and the database if possible, although a patient is under no obligation to provide a reason if they choose to withdraw.

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7.12.3. Attempts should be made to determine whether patients lost to follow up are alive.

7.12.4. A patient will be considered for withdrawal from the study if he/she:

- Fails to attend three consecutive clinical reviews without explanation
- Fails to respond to three consecutive postal questionnaires without explanation

7.12.5. Criteria for review timeframes

- Acceptable timeframes for clinical reviews
  - Twelve months +/- two months
  - Three years +/- four months
  - Five years +/- four months
  - Seven years +/- four months
  - Ten years +/- four months

- Acceptable timeframe for postal questionnaires
  - Three months +/- two weeks
  - Six months +/- two months
  - Yearly +/- four months

Clinical reviews should always be scheduled within the acceptable timeframes; however, early or late reviews will be accepted along with a file note indicating a protocol deviation.

7.13. STUDY END-POINTS

- Definitive end points in this study are:
  - Completion of 10 year follow-up
  - Revision of implant
  - Patient withdrawal

- Medical withdrawal
- Lost to follow-up
- Death

7.14. REPORTS & PUBLICATIONS

Quarterly and annual reports will be issued by the EOC to study sponsor and participating sites to update status of study. The EOC will assist with preparing for ODEP submissions and will submit survivorship publications for the ODEP time points. Additional reports can be run for the sponsor company or participating sites upon request.

Any paper, derived from the Genus Unicompartmental Knee Prosthesis System ODEP study data, will be copied to Adler Ortho srl prior to publication. Adler Ortho srl will be granted a non-exclusive copyright license (subject to journal restrictions) and may use the text or results in product literature.

8. APPENDICES

Reporting adverse events definitions reference
http://www.mhra.gov.uk/Publications/Safetyguidance/DeviceBulletins/CON068594
http://www.mhra.gov.uk/Publications/Regulatoryguidance/Devices/DirectivesBulletins/CON2033888

Reporting serious adverse events to National Research Ethics Committees
http://www.nres.npsa.nhs.uk/applications/after-ethical-review/safetyreports/safety-reports-for-all-other-research/#safetynonCTIMPrepotingSAEs

Orthopaedic Data Evaluation Panel guidelines can be found on the NHS Supply Chain website
http://www.supplychain.nhs.uk/portal/page/portal/Communities/Orthopaedics/ODEP%20database