# Study Protocol

**TITLE OF STUDY**  
Nutritional Rickets Presenting to Secondary Care in children under 16 years in the UK and Ireland

**SHORT TITLE**  
Nutritional Rickets Presenting to Secondary Care

**SPONSOR SITE**  
Royal College of Paediatrics and Child Health  
5-11 Theobalds Road  
Holborn  
London WC1X 8SH

**SPONSOR LEAD**  
RCPCH - Head of Research Governance – Helen Dodd

<table>
<thead>
<tr>
<th>Principal investigator: name and contact details</th>
<th>Job title and affiliation</th>
<th>Contribution to study</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Dr Priscilla Jules</td>
<td>Consultant Paediatrician Royal Free Hospital</td>
<td>Principle Investigator - Study design, data analysis &amp; interpretation – Write up</td>
</tr>
<tr>
<td>2 Prof Mitch Blair</td>
<td>Consultant Paediatrician Northwick Park Hospital, Reader in Paediatrics and Child Public Health, Imperial College London</td>
<td></td>
</tr>
<tr>
<td>3 Mr Richard Lynn Science and Research Department Royal College of Paediatrics and Child Health</td>
<td>BPSU Scientific coordinator</td>
<td>Study design, data analysis &amp; interpretation</td>
</tr>
<tr>
<td></td>
<td><a href="mailto:Richard.Lynn@rcpch.ac.uk">Richard.Lynn@rcpch.ac.uk</a></td>
<td>Co-Investigators</td>
</tr>
<tr>
<td>4</td>
<td>Karina Pall</td>
<td>Research and Policy Division Royal College of Paediatrics and Child Health</td>
</tr>
<tr>
<td>5</td>
<td>Dr Nicholas Shaw</td>
<td>Consultant Paediatric Endocrinologist, Birmingham Children's</td>
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PROTOCOL DETAILS
• Version 5 – 28/10/2014

Lay summary
Rickets is a condition of soft bones. Rickets is usually caused by not enough vitamin D in the body. It is rare, but seems to be an increasing problem as people spend less time outside. Rickets affects infants and children (ie those with growing bones).

Vitamin D lets the body absorb calcium and phosphorus (two minerals). Vitamin D, calcium and phosphorus all work together to help bones grow and keep them strong. Vitamin D is a fat soluble vitamin that our body can get in two ways:

1. From ultraviolet (UV) sunlight on the skin - most important source.
2. From the food we eat.

Signs and symptoms of rickets:
Sore arms, legs, back and hips; bone growth problems, like bowed legs; late teeth and problems with tooth enamel; swelling around the wrist and ankle joints; fractures (broken bones) for unknown reasons; the shape of the skull - 'a square head'

There are several causes of rickets:
Not enough vitamin D or calcium in the food your child eats; vegetarian, dairy-free or lactose-free diets that are not nutritionally balanced; less time spent in the sun; breast feeding babies whose mothers that have low vitamin D levels. (Breast milk is still the best food for babies); children with darker skin who absorb less sunlight than fairer skinned children; certain existing medical conditions.
Rickets has been reported in various geographic locations across the UK; however most of the data is presented as Vitamin D Deficiency, rather than rickets alone. This project aims to identify the number of rickets cases that present to secondary care in the UK.

As a disease that can be identified by specific clinical and radiological signs, the number of new cases (incidence) and treatment of rickets in the UK can be monitored and evaluated. In her recent Chief Medical Officer report Dame Sally Davies recommends investigation to be made into universal and targeted vitamin schemes and whether these approaches are cost effective. Vitamin D deficiency has an estimated prevalence (number of total children) of 12% and with as many as 40% of young children below the accepted threshold considered to be healthy. This project aims to estimate the annual incidence of Nutritional rickets, describe its presentation, previously reported risk factors and management and referral patterns.

Background

Rickets occurs when growing bones do not develop adequately, so is unique to growing children and adolescents. This results in pain and softening of their bones, which can then bend or break, leading to distressing short-term (e.g. pain, delayed walking) and sometimes long-term consequences (e.g. deformed limb needing surgical correction, difficulty with child-bearing). While it is defined histologically, it can be recognised by clinical signs and/or on bone X-rays usually under aged 2 years and in adolescents. It is vital to diagnose and treat it early to minimise morbidity.

It is caused by:
(i) lack of dietary calcium and/or a problem with the supply, metabolism or utilisation of vitamin D, so-called Nutritional rickets.
(ii) lack of phosphate, from loss from the kidneys, or genetic causes of deficient phosphate.
This study will be limited to nutritional causes of rickets.

Rickets is the commonest, but not the only childhood complication of Vitamin D Deficiency (VDD) It was a common Victorian disease, which in the UK, was wiped out (eradicated) by the 1950’s by food fortification, cod-liver oil supplementation and other environmental changes. However, worldwide, it has re-emerged as a major public health concern in recent years, particularly in immigrant, non-Caucasian children owing to a number of risk factors (pigmented skin, lack of sun exposure in high latitude areas, pollution, cultural and religious practices preventing sun exposure, exclusive prolonged breastfeeding, and vitamin D deficient mothers).

A Canadian Paediatric Surveillance Unit Study (2002-2004) identified 104 new cases of VDD presenting with significant morbidity including limb deformities (42%) and fractures (11%). The annual incidence was estimated at 2.9/100 000 children.

An Australian Surveillance Unit Study (January 2006 to July 2007) identified 398 children under 15 years, with Vitamin D deficiency, albeit with a wider definition of VDD rickets and milder clinical symptoms, identified mainly by routine biochemical screening. The annual incidence was 4.9/100 000.

A Glasgow Hospital retrospective cohort (2002 to 2006) identified 160 cases of symptomatic VDD, 40% with evidence of rickets. A Scottish surveillance study is in progress to determine the incidence of symptomatic VDD. The number of rickets cases seen has decreased thought to be due to a successful public health campaign (personal correspondence Professor F Ahmed, Lead Clinician).

All 3 countries have active health campaigns addressing Vitamin D deficiency, showing variable success in decreasing the incidence.

Nevertheless it remains a completely preventable disease by sensible sun exposure or vitamin D supplementation and must be eradicated.
**STUDY IMPORTANCE**

**Methodology**

**Research Objectives**

1) Estimate the annual Incidence of Nutritional Rickets in under 16-year olds in the UK and Republic of Ireland,

2) For identified cases of nutritional rickets, to
   a) Describe the Presentation of Nutritional Rickets
   b) Report the distribution of known risk factors (including latitude, age, ethnicity, vitamin
   c) Report the symptoms, clinical and radiological signs of nutritional rickets
   d) Associated Serum levels of 25OHD, calcium, phosphate, alkaline phosphatase and Parathyroid Hormone
   e) Management and referral patterns.

**Design**

Paediatric surveillance studies have an important public health function in collecting reliable and timely information regarding the distribution and determinants of disease in the population, and with facilitating effective healthcare responses to reduce morbidity and mortality and improve health (Nicoll et al 2000). Reporting rates for returning the BPSU orange card system are high, with a return compliance in 2013 of 95.0%. This return rate is higher than any equivalent UK scheme and has been ranked highly against other national paediatric surveillance units hence data validity and reliability are anticipated to be good. For a 13 month period consultant paediatricians will be asked to report whether they have or not seen a case in the past month.

The study will only ask for the minimum patient identifiers (NHS/CHI number, gender, month, date of birth and ethnicity) in order to be able to identify duplicate case reports. Once it has been established that this is a new case, the case will be assigned a unique study ID and all patient identifiers removed. In order to answer the research objectives we expect to survey for a one year period but would seek an extension if insufficient cases are identified to fulfill our objectives.

Following notification the clinicians will be sent an email asking for them to log onto a secure e-reporting website. We are using Document Capture Company (DCC), who have information technology toolkit approval, to develop an online questionnaire. The clinician can then complete the online questionnaire (via a weblink). Alternatively, they can complete a paper copy of the questionnaire, after which the investigators will input the data manually.

All questionnaires will be reviewed on receipt by the research team to ensure that the data are complete and unambiguous. Any outstanding queries will be addressed by direct contact between the researchers and the reporting paediatrician.

The electronic on line questionnaire will be completed to the reporting clinicians to collect clinical information about the demographics, known risk factors, presentation, (clinical, laboratory and radiological), referral and treatment options used for patients who meet the case definition. Our case definition has been developed as a result of examining other national and international surveillance systems and learning from their strengths and limitations. We are using clinical, biochemical and radiological preconditions to allow accurate ascertainment.

Information about some, but not all of the known risk factors for Rickets will be collected using the questionnaire. It will describe known risk factors of latitude, age, ethnicity, vitamin D deficient mother, exclusive breastfeeding, medical conditions (eg obesity) and drugs. See Data Analysis Plan for how the information will be collected and used to inform this.

Clinicians will be asked to review X-ray reports, and for this to be anonymised, and inserted into the questionnaire when available. The diagnosis does not depend solely on the x-ray report except when rickets was picked up incidentally on one. The X-ray reports will provide evidence for the clinical presentation of cases.
A project board meeting will be held every 3 months to review project progress. A project team meeting will be held every month to review case details and any methodology issues.

Once all the data has been collected there will be a final comparison to make sure all the confirmed cases have been identified and de-duplicated. Ones this occurs any identifiers will be removed from the data set. NB date of birth will be replaced with age in months

All data will be collected and retained in accordance with the Data Protection Act 1998.

See SLSP for further details

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<tr>
<th>Identifier</th>
<th>Yes/No</th>
<th>Justification</th>
</tr>
</thead>
<tbody>
<tr>
<td>NHS / CHI Number</td>
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<td>Unique identifier for matching cases and/or removing duplicates within single source and between sources and identifying cases to reporting clinicians, e.g. at follow-up.</td>
</tr>
<tr>
<td>Date of Birth</td>
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<td>Identifier for matching cases and/or removing duplicates within single source and between sources; identifying cases to reporting clinicians, e.g. at follow-up; clinical data for analysis</td>
</tr>
<tr>
<td>Gender</td>
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<td>Identifier for matching cases and/or removing duplicates within single source and between sources; clinical data for analysis</td>
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<tr>
<td>Ethnicity</td>
<td>Yes</td>
<td>To assess if the development of the condition has any ethnicity link</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Identifier for matching cases and/or removing duplicates within single source and between sources; clinical data for analysis</td>
</tr>
<tr>
<td>Partial Postcode</td>
<td>Yes</td>
<td>To inform analysis on regional variations</td>
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</table>
CASE DEFINITION / POPULATION

a) Surveillance case definition – a wider description to cover all possible cases

1. New Case of Clinical Rickets
   Any of the following: Leg deformity (bowing or knock-knees)/Swollen Wrists or Knees or Ankles or Ribs (Rachitic Rosary) AND 25OHVitamin D <25nmol/L with one or more abnormalities of serum calcium, alkaline phosphatase, phosphate, Parathyroid hormone

   Or

2. New Case of Radiological Rickets (new case)
   Widening, cupping, splaying of metaphysis (of any long bone) on X-ray AND 25OHVitamin D <25nmol/L

Exclusion Criteria:
Genetic Rickets
Rickets associated with other chronic diseases e.g. malabsorption, liver disease, chronic renal disease
Metabolic Bone Disease of Prematurity (infants whose corrected age at presentation is < 3 months, who were born < 36 weeks gestation and weighing <1.5kg)

b) Analytic case definition – a definition that maybe more aligned to DSM/ICD or requires specific tests to confirm – Sometimes this definition can be same as a) See guidance handbook for further advice

   Any of the following clinical signs: Leg deformity (bowing or knock-knees)/Swollen Wrists or Knees or Ankles or Ribs (Rachitic Rosary) AND 25OH< 25nmol/L AND one or more of the following: Raised Alkaline Phosphatase for age*, raised PTH*, low Calcium*, Low Phosphate* AND evidence of response to treatment, either clinical, biochemical or radiological (* using the local laboratory paediatric reference ranges)

   - Widening, cupping, splaying of metaphysis (of any long bone) on X-ray AND 25OH<25nmol/L

c) Age range for cases:
   <16 years

d) Reporting instructions

Please report any newly arising cases of rickets in children under the age of 16 seen in the past month fitting the surveillance case definition. Please report even if the case has now been referred to or from you paediatric/nurse colleagues.

Recruitment / Expected Numbers

100-300 cases per year; Estimated UK and Irish population of 12 million children

BPSU Hypocalcaemic Seizures secondary to VDD15 September 2011 to September 2012 -15-40 cases; Given that rickets is a commoner complication of hypocalcaemic seizures, (roughly twice as common), we would expect to see more than 50 cases per year.

Extrapolating from the Canadian (estimated incidence 2.9/100 000 children) and Australian studies (estimated incidence 4.9/100 000 children), we would expect to see roughly 300-500 cases of rickets in a population of 11 million UK children. However, we wish to highlight that the Australian surveillance study used a broader case definition of 25OHD levels <50nmol/L,
identifying large numbers of asymptomatic cases of VDD, incidentally picked up on routine screening.

We are using a stricter definition more similar to the Canadian study which used 25OHD levels <27nmol/L, but are excluding musculoskeletal features in our case definition, so we would expect lower numbers.

A Glasgow Hospital retrospective cohort (2002 to 2006), identified 160 cases of symptomatic VDD, 40% with evidence of rickets A Scottish surveillance study is in progress to determine the incidence of symptomatic VDD. The number of rickets cases seen has decreased thought to be due to a successful public health campaign (personal correspondence F Ahmed, Lead Clinician).

**DURATION OF THE PROJECT**

In accordance with the BPSU methodology, data collection will over a thirteen month period, anticipated to be 1st January 2015 – 31 January 2016. If however additional ascertainment is required to allow meaningful analysis, then there is the possibility of extending this further.

**STATISTICAL ANALYSIS AND DATA MANAGEMENT**

**Analysis**

Data will be analysed by using the Statistical Package for the Social Sciences (SPSS) and an epidemiological statistical software package such as ‘Epidemiological Graphics, Estimation and Testing’ (EGRET 1997). Primary analysis will focus on the presentation of descriptive statistics and measures of association.

**Data Management / Storage of Records**

Data management will adhere to the following processes:

The Security System comprises:

1. Patient identifiers consisting of initial, date of birth, sex, hospital reference number, NHS number or equivalent, will be stored separately to clinical research data and linked by a unique British Paediatric Surveillance Unit (BPSU) and study code.

2. Anonymised clinical research data which are entered onto the computer. A separate SLSP exists for the data collected on-line – see attached.

3. Patient identifiable information collected for the purposes of case verification and de-duplication only, and destroyed once this process has been completed.

4. Paper record consisting of the front and clinical data sheets of the questionnaire, will be stored separately in two locked cabinets and linked only by unique BPSU and study case codes.

The Physical Security System comprises:

1. Data will be entered in a secure setting at the offices of the data managers.

2. There is password protection on the desktop computer holding electronic research data (clinical data sheets of questionnaire).

3. Paper records consisting of the front and clinical data sheets of the questionnaire. Front and clinical data sheets will be stored separately in locked cabinets with restricted access and linked by a unique British Paediatric Surveillance Unit (BPSU) case code and unique study code.

4. All information (paper and electronic) will be stored in a locked office in the hospital, not accessible to the general public and within a restricted swipe access area.

5. See System Level Security Protocol (SLSP)
The system shall be risk assessed on an annual basis by the Data manager of the Royal College of Paediatrics and Child Health (RCPCH) using an audit checklist. Any deficiencies, including security or confidentiality matters, identified will be discussed with research team and solutions implemented.

The study will be monitored and audited in accordance with University Hospitals NHS Foundation Trust policy. All study related documents will be made available on request for monitoring and audit by RCPCH, Royal Free Hospital NHS Trust and the relevant Research Ethics Committee.

**RESEARCH GOVERNANCE, MONITORING AND ETHICS & R&D APPROVAL**

**Ethical Approval**

The study has received Research Ethics Committee (REC) XXXXXXX Ref: XX/XXX/XXX

Confidentiality Advisory Group approval is being sought as is local R&D office approval.

The study will be conducted in accordance with Research Governance Framework for Health and Social Care and Good Clinical Practice and will be monitored and audited in accordance with Trust policy. All study related documents will be made available on request for monitoring and audit by UH Bristol and the relevant Research Ethics Committee.

**Resource Requirements and Costs**

The study is being supported and administered by the Royal College of Paediatrics and Child Health (RCPCH) Research and Policy Division however additional advice is being supplied by the British Paediatric Surveillance Unit (BPSU)

Study Design; Database Development; Data Collection (DCC); Data Analysis and Interpretation.

The Royal College of Paediatrics and Child Health, Royal Free Hospital and the DCC – data collection systems are fully IG Toolkit compliant as of 2014.

**INDEMNITY**

This is an RCPCH sponsored research study. The RCPCH is a non-NHS site. The organisation is covered by indemnity insurance from CHUBB insurance of Europe.

**REPORTING AND DISSEMINATION OF THE RESULTS AND PUBLICATIONS**

Results from the study will be submitted and published through the BPSU. This organisation disseminates information to clinicians and the public through quarterly bulletins, an annual report and the BPSU website (http://www.rcpch.ac.uk/bpsu), where public access is being promoted. Additionally, similar reports will be submitted to ROYAL National Orthopaedic Hospital who are funding the study and through them to the Vitamin D Mission who are also supporting the dissemination of study results.

Paper(s) will submitted for publication to international peer review journal(s) that target health professionals who care for these children e.g. Archives of Disease in childhood. Submission of conference papers to appropriate national and international conferences would also be undertaken.

**Lay Involvement**

Public patient involvement has been included throughout the development of the protocol and will continue through the project period and beyond.
Affected families were consulted about the proposal. They included parents (fathers and mothers) of children who had rickets in the past or current vitamin d deficiency in conjunction with other diagnoses. They were asked about Vitamin D and rickets awareness and our proposal using the BPSU approach during individual face-to-face clinic consultations.

Between August and December 2013, 2 fifth year Imperial College medical students conducted focus groups with members of the public from the Harrow Somali community supported by the Harrow Association of Somali Voluntary Organisation.

They conducted three information sessions and one discussion session. 45 participants, mainly women, completed questionnaires relating to basic Vitamin D knowledge, risk factors for deficiency and children and Vitamin D. The discussion sessions focused on their experience of Vitamin D deficiency, health beliefs and how to spread the message.

Both groups felt that rickets was an important issue to help clarify. They described a lack of or confusion about, health information and management they receive in terms of Vitamin D prevention and treatment. We echoed the confusion amongst health professionals in relation to Vitamin D and explained that our hope is that this project will help standardise public health information relating to rickets to decrease some of the confusion and anxiety.

All those we asked were not aware of the BPSU, but after describing its role, they agreed that it would a reliable way to collect information, given its longstanding history and reputation with Paediatricians throughout the UK.

The focus group gave valuable insights into the sources and dissemination of health information, and we agreed to use this information during the dissemination of results process.
COVERING LETTER

Re:

Case Reference RK/1501/01

Thank you for notifying a case(s) to this study, which is being undertaken by the British Paediatric Surveillance Unit.

We are writing to gather further information about this case. This can be done by completing the paper questionnaire enclosed.

Please fill in even if there are some sections you are unable to complete.

We will not be contacting your patient or his/her family at any time. Some patient identifiable data are needed to avoid duplication and to allow an estimation of the completeness of reporting. These will be removed once the case has been confirmed to be a unique case and all information you provide will be treated in strict confidence. The study has Health Research Authority approval to collect information in this way [Ref:XXXXXXXXX] and the appropriate ethics approvals. [Ref:XXXXXXXXX]

The study is funded via a grant through the Royal National Orthopaedic Hospital Research fund

Please do not hesitate to contact us if you have any queries about the questionnaire, or any aspect of the study. If you need any advice regarding the eligibility of a particular case for inclusion in the study please contact XXXXXXXXXXX (contact details below).

We are very grateful for your support of the BPSU. We would be delighted to provide you with a copy of the final study report if you wish

With many thanks,
Yours sincerely,
REMINDER LETTER

[Name]
[Address]
[Date]

Dear [Name],

Re:

You have previously notified a case(s) to this study. We note that we have yet to receive the data, it is important we do so as each case report is very important in maximising ascertainment and calculation of incidence.

Information can be supplied by completing the paper questionnaire enclosed.

Please fill in even if there are some sections you are unable to complete.

We will not be contacting your patient or his/her family at any time. Some patient identifiable data are needed to avoid duplication and to allow an estimation of the completeness of reporting. These will be removed once the case has been confirmed to be a unique case and all information you provide will be treated in strict confidence.

The study is funded via a grant through the Royal National Orthopaedic Hospital Research fund

Please do not hesitate to contact us if you have any queries about the questionnaire, or any aspect of the study. If you need any advice regarding the eligibility of a particular case for inclusion in the study please contact XXXXXXX (contact details below).

We are very grateful for your support of the BPSU. We would be delighted to provide you with a copy of the final study report if you wish.

With many thanks,

Yours sincerely,
Thank you letter

[Name]
[Address]
[Date]

Dear [Name],

Thank you for completing the questionnaire which we have received and processed. This questionnaire will help us to gain further information about rickets in children.

With many thanks for your help,

Yours sincerely,
Nutritional Rickets Presenting to Secondary Care

(Please contact Dr Priscilla Julies- 07942482894 or p.julies@nhs.net - with any questions)

The first page of the case notification form will be stored separately from the rest of the questionnaire and personal identifying information for the case will be used only for linkage of records.

Reporting Instructions:

Please report:

- any child under 16 years who has rickets secondary to vitamin D Deficiency in the last month
- all suspected cases, even if the results of investigations are pending

Case Definition:

1. Clinical Rickets

Any of the following: Leg deformity (bowing or knock-knees)/Swollen Wrists or Knees or Ankles or Ribs (Rachitic Rosary)  \textbf{AND}  25OHHitamin D <25nmol/L with one or more abnormalities of serum calcium, alkaline phosphatase, phosphate, Parathyroid hormone

Or

2. Radiological Rickets

Widening, cupping, splaying of metaphysis (of any long bone) \textbf{AND} 25OHHitamin D <25nmol/L

Exclusion Criteria:

Genetic Rickets

Rickets associated with other chronic diseases e.g. malabsorption, liver disease, chronic renal disease

Metabolic Bone Disease of Prematurity (infants whose corrected age is < 3 months at presentation, who were born < 36 weeks gestation and weighing <1.5kg)
Section A: Reporter Details

1.1 Date of completion of questionnaire: (Please note time of starting questionnaire)

1.2 Consultant responsible for case:

1.3 Hospital name:

1.4 Telephone number: Email:

1.5 Has the patient been referred to/from another centre? Yes ☐ No ☐ Not known ☐

If yes: 1) please name centre:

2) please name consultant:

Section B: Case Details

2.1 NHS/CHI No:

2.2 Hospital No:

2.3 Postcode: Town of Birth (if ROI)

2.4 Sex: M ☐ F ☐ Date of birth:

2.5 Ethnicity*: ☐ Specify if any “Other” background

*Please choose the correct ethnicity code from Appendix A overleaf
### Appendix A: Coding for Ethnic Group (ONS 2011 for UK wide data collection)

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<thead>
<tr>
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<tbody>
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<td>A</td>
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<td>B</td>
<td>White and Black Caribbean</td>
</tr>
<tr>
<td></td>
<td>English / Welsh / Scottish / Northern Irish / British</td>
<td>2</td>
<td>White and Black African</td>
<td>6</td>
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<tr>
<td></td>
<td>Irish</td>
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<td>White and Asian</td>
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<td>Any other Mixed / Multiple ethnic background, please describe</td>
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<td></td>
<td>Any other White background, please describe</td>
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<td></td>
<td></td>
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<tr>
<td>B</td>
<td>Mixed / Multiple Ethnic Groups</td>
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<td>Any other ethnic group, please describe</td>
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</table>
### Section C: Presentation/Clinical features

#### 3.1 Date of diagnosis of rickets by paediatrician

#### 3.2 At the time of your diagnosis, did the patient have any of the following conditions? *(Please tick Yes/No/Not Known)*

<table>
<thead>
<tr>
<th>Condition</th>
<th>Yes</th>
<th>No</th>
<th>Not Known</th>
<th>Date of Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Previous Rickets</td>
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<tr>
<td>First Degree Relatives with Nutritional Rickets</td>
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</tr>
<tr>
<td>Family History of Genetic Rickets <em>Eg</em> 1a-hydroxylase, 25α-hydroxylase deficiency; Vitamin D dependent rickets</td>
<td></td>
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<td></td>
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<tr>
<td>Mother with Vitamin D Deficiency</td>
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</tbody>
</table>

#### 3.3 At the time of your diagnosis, did the child have any other conditions?

- Yes [ ]
- No [ ]
- NK [ ]
- Not Recorded [ ]

If yes, please specify if the following:

- Chronic Liver Disease [ ]
- Chronic Renal Disease [ ]
- Gastrointestinal Disease with Fat Malabsorption [ ]
- Obesity [ ]
- Immobility (from any cause) [ ]
- Epilepsy [ ]
- Tuberculosis [ ]
- Cows Milk Allergy/Intolerance [ ]
- Other: [ ]

Please give details: ____________________________________________
Section C: Presentation/Clinical features

3.4 At the time of your diagnosis, was the child taking any vitamin D supplements

Yes ☐ No ☐ NK ☐ Not Recorded ☐

If yes, which preparation____________________________ and dose _______________________

3.5 At the time of your diagnosis, was the child taking any other medications? (including herbal/alternative medications)

Yes ☐ No ☐ NK ☐ Not Recorded ☐

If yes, please specify if the following:

Please specify Name and dosage if known

- Anticonvulsants
- Antituberculous drugs
- Antiretroviral drugs
- Glucocorticosteroids
- Antihypertensives
- Antibiotics
- Antineoplastic drugs
- Antioestrogen drugs
- Herbal Meds
- Other

3.6 At the time of your diagnosis, how was the child feeding?

☐ Exclusively Breastfed  Duration if known____________________________
☐ Exclusively formula fed
☐ Mixed breast and formula fed
☐ Solids  If known, is dairy included?
☐ Unknown
☐ Not recorded
Section D: Mode of Presentation

4.1 How did the child first present? (There may be more than one)

- **Bony Abnormalities**
  - Bone Pain
  - Bowed legs
  - Knock Knees
  - Swollen wrists
  - Craniotabes
  - Fracture
  - Rachitic Rosary

- **Neuromuscular Abnormalities**
  - Joint/Muscle Pain
  - Delayed Motor Development
  - Hypocalcaemic Siezures

- **Radiological Abnormalities**

- **Other**
  - Incidental Finding
    - (e.g. bloods or x-rays done for other reasons and found to have rickets)
  - Screening investigations
    - (e.g. as for Cerebral Palsy guidelines; before Bisphosphonate treatment)

Please describe:
**Section E: Diagnosis and Investigations**

Please indicate if any of the following tests were performed and their results:

**Please state units and local laboratory reference ranges.**

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<tr>
<th>Test Description</th>
<th>Yes</th>
<th>No</th>
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<th>Date</th>
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<td>Serum Alkaline Phosphatase (ALP)</td>
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Please include *anonymised* Xray report:
Section F: Management

6.1 Was the child treated prior to being seen by you?  
Yes ☐  No ☐  NK ☐

6.2 Was the child treated after being seen by you?  
Yes ☐  No ☐  NK ☐
If known, What was recommended and/or prescribed?

<table>
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<tr>
<th>Medication Recommended</th>
<th>Medication Prescribed</th>
<th>Dose in international units (IU) or micrograms (ug)</th>
<th>Frequency</th>
<th>Duration (days/weeks/months)</th>
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At the time of your diagnosis, who initiated the treatment?

6.3 Primary Care ☐ Secondary Care ☐ Tertiary Care ☐ NK ☐

Following your diagnosis, has follow-up been arranged?

Yes (GP) ☐ Yes (hospital) ☐ No ☐ NK ☐
Section G: Outcomes

7.1 What was the clinical outcome?

- Recovered
- Recovered with sequelae Specify: ____________________________
- Still under review
- Died Date of death: ____/____/____
- Not Known

7.2 What was the Management outcome?

- Discharged Date of discharge from clinician’s care: ____/____/____
- Transferred Date of transfer Name of Hospital
- Still Under Review
- Not Known

7.3 If the child died, was a post mortem done? Yes ☐ No ☐ N/A ☐

What were the findings?

Section H: Outcomes

8.1 What was the final outcome?

- Recovered Date of discharge: ____/____/____
- Recovered with sequelae Specify: ____________________________
- Transferred Name of hospital: ____________________________
- Still admitted Not Known
- Died Date of death: ____/____/____

8.2 Was a post mortem done? Yes ☐ No ☐ N/A ☐

What were the findings?
Thank you for taking the time to complete the Questionnaire

Please state, in minutes, how long it took you to complete this questionnaire

___________________ minutes

Please print and return the completed form in the SAE to:

RCPCH Research Project Team, 5-11 Theobalds Road, London, WC1X 8SH

If you have any questions about the study please do not hesitate to contact Dr Priscilla Julies by email or telephone:

Telephone: 07942482894       Email: p.julies@nhs.net
APPENDIX 3

BPSU required System Level Security Policy
Rickets in childhood

System Details

1. The System shall be known as Rickets in childhood
2. The responsible owners shall be Mr Richard Lynn, Dr Priscilla Jules
3. The system’s Data Guardian is Helen Dodd

System Security

4. Security of the system shall be governed by RCPCH Information Manager – Helen Dodd

5. The security manager duties shall include:
   ● overseeing the policies covering data protection at RCPCH
   ● connection to the network
   ● appointment of custodians of computer systems and network administrators
   ● computer security incident reporting procedures
   ● computer accounts
   ● disposal of equipment holding sensitive information and security of data and maintaining the firewall.

6. The system shall incorporate the following security countermeasures:
   ● Paper records consisting of the front and clinical data sheets of the questionnaire will be stored separately in locked cabinets with restricted access and linked by a unique BPSU code and a unique study code.
   ● Electronically collected data will be downloaded and printed and stored in the same manner as the paper records.
   ● Only anonymised clinical research data will be held on a desktop computer.

System Processes
The system will process:

7. Patient identifiers consisting of date of birth, sex, ethnicity, NHS or equivalent number which are stored separately to clinical research data and linked by a unique case and study code.

8. Anonymised clinical research data collected via the paper questionnaire are entered onto the computer.

9. Patient identifiable information collected for the purposes of case verification and de-duplication, will be destroyed once this process has been completed.
10. Paper records consisting of the front and clinical data sheets of the questionnaire, stored separately in two locked cabinets and linked only by unique British Paediatric Surveillance Unit (BPSU) case number and study code.

Anonymised notifications are provided to the BPSU office by clinicians using BPSU methodology i.e. the orange card system http://www.rcpch.ac.uk/what-we-do/bpsu/what-bpsu/how-bpsu-system-works/how-bpsu-system-works. The BPSU informs the Rickets investigator, or their nominated staff, of the notifying clinician's details so the investigators can request further details. Clinicians notifying cases subsequently submit patient data to the investigator. Patient data are not held by the BPSU.

RCPCH Information Governance Policy has been developed using ISO 27002 as guidance. Specific security measures which comply with these standards include:
   a) Firewall
   b) Virus protection
   c) Password protection
   d) Locked rooms and cabinets
   e) Disposal of IT information

The system shall be risk assessed on an annual basis by Richard Lynn/Helen Dodd and the research coordinator using an audit checklist. Any deficiencies including security or confidentiality matters identified will be discussed with Helen Dodd and solutions implemented.

System Management

11. The System Level Security Policy (SLSP) for the Rickets study has been developed through a formal process of risk assessment by the study applicants. It covers security and management procedures in place throughout for data collection, data handling, data storage, data analysis and data destruction. It details the lines of accountability within.

12. The system shall be maintained by both Helen Dodd and the research coordinator at RCPCH

The system has the following resilience arrangements in place;
   a) Electronic research data are backed up daily on the network
   b) A back up copy of the research data that have been entered is held securely
   c) Paper records consisting of the front and clinical data sheets of the questionnaire are stored separately in two locked cabinets with restricted access and linked only by unique BPSU case number and study code.

The backup ensures that in the event of an electronic system failure the database system can be retrieved and re-loaded in an appropriately secure system.

When the study is complete the following methods will be adopted to dispose of all stored data
a) Patient identifiable information, essential only for the process of de-duplication and case verification will be permanently destroyed once this process has been completed.
b) Data entered on computer will be permanently wiped from the hard drive consistent with RCPCH Information Governance Policy and the Data Protection Policy.
c) Arrangements will be made with DCC on-line survey to delete the data at the earliest opportunity.

13. The system will not be shared or used by another organisation

System Design and Operational Process

14. The system shall comprise both paper based and electronic elements

- BPSU office receives an ‘orange card’ indicating that a case of rickets has been seen by a clinician
- BPSU office informs the study applicants – Research coordinator a that a case of rickets has been notified to them by a clinician
- The study applicants send a questionnaire to relevant clinician for completion or a link to the electronic data collecting site.
- On receipt of completed questionnaire the study applicants detach the front sheet of questionnaire (containing patient identifiable information) from the clinical data sheets of the questionnaire (containing research data)
- The front sheet and the clinical data sheets have a code assigned to the case it represents (BPSU case code) and a unique study code.
- Front sheet and clinical data sheets are stored separately in secure locked cabinets and accessed only by the nominated study applicants
- Clinical data sheets contain research data only – they are linked to the corresponding front sheet (which contains patient identifiable information essential for the identification of duplicates and case verification) by means of the unique BPSU case and study code
- Patient identifiable information essential for the identification of duplicates and case verification will be removed from the front sheet once the process of case verification and de-duplication has been completed.
- Research data held on the clinical information sheets, including that required for de-duplication, are entered on computer
- The electronically collected data will also be printed out and stored using the same protocol as above. We feel it is important to keep a complete anonymised paper record of the data for archiving purposes

The data will be held on the RCPCH server; whose system is IG toolkit approved. Only anonymised clinical research data will be held on computer systems. The network is firewall and virus protected. Access to the clinical research data will be password protected and the password changed weekly.
Appendix 4 summarises the paper data storage processes in the system

A Dell desktop computer will be used to access and process the electronic data which will be anonymised.

15. The system’s authorised users shall be Dr Priscilla Jules, Richard Lynn and the research coordinator Karina Pal.

In accordance with MRC arrangements
16. Paper records i.e. front and clinical data sheets will be held for a minimum of 15 years to allow adequate time for review or reappraisal and to allow any concerns about the conduct or consequences of the study to be resolved. Paper records will then be permanently destroyed by shredding. The exception to retention of paper records is patient identifiable information collected for the purposes of case verification and de-duplication. This will be shredded once this process has been completed (usually within 12 months). Anonymised electronic data will be permanently wiped from the hard drive consistent with RCPCH IT disposal policy.

System Audit

17. The system shall benefit from an internal audit checklist developed by Helen Dodd and the research coordinator.

18. The system shall be risk assessed on an annual basis by research coordinator using an audit checklist. Any deficiencies, including security or confidentiality matters identified will be discussed with Helen Dodd and solutions implemented.

System Protection

19. The system has the following resilience arrangements in place:
   - Electronic research data are backed up daily on the RCPCH Trust IT system. Paper records consisting of the front and clinical data sheets of the questionnaire are stored separately in two locked cabinets with restricted access and linked by unique BPSU and study case codes.

20. The back-up ensures that in the event of an electronic system failure the database system can be retrieved and re-loaded in an appropriately secure system.

21. All staff working on the project will sign a standard RCPCH and or NHS code of conduct. Any security or confidentiality breach shall result in disciplinary proceedings. In addition all staff signs BPSU guidance for researchers on confidentiality policy.
System Level Security Policy Ownership

22. This SLSP shall be the responsibility of Helen Dodd and it will be reviewed on an annual basis for its completeness and update.

23. A hard copy of the SLSP shall be made available to all staff working on the project.

24. Separate SLSP’s exist for the on-line data capture system run by DCC and RCPCH. Both are attached.
APPENDIX 4

Data storage in BPSU Surveillance of Rickets in children in UK and Republic of Ireland – Paper Records

**Front sheet**
Patient identifiable information collected for the purposes of case verification and de-duplication is immediately removed once this process has been completed.

**Front sheet**
Stored in locked cabinets with restricted access.

**Front sheet containing patient identifiable information is separated from clinical data sheets**

**Clinical Data Sheets**
Clinical data sheets contain research data only.

**Front Sheet & Clinical Data sheets are linked by a unique BPSU Case Code**

**Clinical data sheets**
Stored in locked cabinets with restricted access.
Electronic Data storage in BPSU Surveillance of Rickets in children in UK and Republic of Ireland
How the Surveillance System Works

Selection of studies for inclusion in the scheme

A study is eligible for participation in the scheme if the subject is a rare childhood disorder or a rare complication of a commoner disease of such low incidence as to require cases to be ascertained nationally in order to generate sufficient numbers for study.

The number of conditions under surveillance is usually limited to 12. The BPSU application procedure consists of two phases: a screening phase based on an outline of the study and a detailed consideration of the full application. Details about the BPSU application procedure can be downloaded from the website at http://bpsu.ionespuc.com/methodology.htm or are available on request from the BPSU office.

Factors that increase the likelihood of a study being accepted include scientific importance, clear objectives, a workable case definition and proposals with outcomes of clear importance to public health. Once approved by the BPSU Executive, studies require approval from the Research Ethics Committee (REC) and Ethics and Confidentiality Committee of the National Governance Information Board, formerly Patient Information Advisory Group (PIAG), before commencement.

The reporting system

Those participating in the reporting system include consultant paediatricians who are either members of the RCPCH or the Faculty of Paediatrics of the Royal College of Physicians of Ireland.

Surveillance is active in that the BPSU office actively sends out cards to clinicians asking for cases to be reported on the BPSU orange card (Figure 14). Each month, all clinicians participating in the surveillance scheme are sent the orange card listing the conditions currently under surveillance. Follow-up reminders are sent to those who have not returned their card for two consecutive months. A set of instructions for completing the card, including case definition of the condition listed on the card is also circulated. When a new study begins, the mailing also includes a specially produced study protocol card and other information about the study.

When reporting a case, respondents are also asked to make a note of the case (Figure 15) and keep the details for future reference as they will later be contacted by the study team with a questionnaire about each case.

Participants are also expected to return cards even if they have no cases to report - there being ‘nothing to report’ box on the card for them to tick. This is an important feature of the surveillance scheme as it allows us to measure compliance to the system. The compliance rates are continually monitored, thus ensuring good coverage of the paediatric surveillance scheme across the whole of the UK and Ireland.

Follow-up and confirmation of case reports

On receiving a case report the BPSU informs the relevant study team. To gather further information the study team sends a short questionnaire to the reporting clinician. Particular care is taken to ensure that questionnaires are as short as possible, clear, straightforward and not excessive.
in their demands. As the questionnaire cannot be fully anonymised, the amount of patient-identifiable data collected is strictly limited to preserve patient confidentiality. The study investigators report back to the BPSU, indicating when cases have been confirmed or are duplicate case reports (Figure 16). Duplication of reporting is most likely to occur when the condition requires referral to another clinician, but this is encouraged, as it is better to receive duplicate reports than to miss a case.

Table 8 (page 47) shows the number of cases reported to the BPSU from its inception until the end of year 2008 for conditions under surveillance at November 2008. The extent to which investigators receive survey data, identifying incorrect reports and duplicates and the speed in which this is done is known as the ‘completion rate’. The number of cases which have so far been subsequently confirmed as meeting the case definition are also shown.

The time taken to follow-up a case report varies greatly between conditions and may be longer if microbiological or pathological details are required to confirm a case. The completion rate is high. For example, as of May 2009, only 587 (5%) of the 11,424 case reports had yet to be followed-up. The final completion rate normally averages between 95-96% for a study undertaken through the BPSU.

Table 9 (page 48) summarises the outcome of the follow-up of all cases reported to the BPSU by the end of year 2008 and provides evidence for the level of accuracy of reporting by participating clinicians.

Funding

The BPSU continues to be in receipt of a grant from the Department of Health to cover the majority of the running costs of the unit. In addition, the BPSU asks surveillance teams to contribute a sum to cover the administrative costs of coordinating their study. These funds also permit us to undertake additional activities such as holding workshops to support current and potential investigators and conferences most recently in March 2009. The BPSU is also grateful for the ongoing support that it receives from the Royal College of Paediatrics and Child Health, the UCL Institute of Child Health and the Health Protection Agency.
### TIMELINE FOR RESEARCH

**Proposed Time Period for Research (in months) – January 2015 – April 2016 (28 mths)**

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**Key:**
- **Completed Work**
- **Anticipated Work**

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REFERENCES


Data Analysis Plan:

Nutritional Rickets Presenting to Secondary Care

Objectives for the surveillance are:

1. Estimate the annual Incidence of nutritional rickets in under 16-year olds in the UK.
2. Describe the Presentation and clinical management of nutritional rickets
   a. Known risk factors for nutritional rickets - including latitude, age, ethnicity, vitamin D deficient mother, exclusive breastfeeding, not taking supplements, medical conditions (eg obesity), drugs
   b. Description of Symptoms, clinical and radiological signs of nutritional rickets
   c. Serum levels of 25OHD, calcium, phosphate, alkaline phosphatase and Parathyroid Hormone associated with nutritional rickets
   d. Management and Referral patterns for nutritional rickets

A. For Objective 1:

Annual incidence will be calculated using the number of confirmed cases over the length of the study period and estimates of the population by age group obtained from the UK Office of National Statistics.

B. For Objective 2:

Descriptive data analysis will be used to interpret the study questionnaire as follows:
<table>
<thead>
<tr>
<th>Section</th>
<th>Survey Questions</th>
<th>Analysis</th>
<th>Purpose/Question To Be Answered</th>
<th>Objective Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. Reporter Details</td>
<td>Date of Completion</td>
<td>Confirm case numbers during study period</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Consultant Responsible; Hospital Name; Telephone Number; Email</td>
<td>N/A</td>
<td>For correspondence purposes only</td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td>Referred from another centre; hospital name; consultant name</td>
<td>Link hospital postcode to geographic area</td>
<td>To identify duplicate cases; use hospital postcode as marker of geographic distribution of cases</td>
<td>1 + 2a</td>
</tr>
<tr>
<td>B. Case Details</td>
<td>NHS Number/Hospital Number</td>
<td>N/A</td>
<td>To identify duplicate cases</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Postcode</td>
<td>Link to geographical line of latitude</td>
<td>Describe geographical latitude as a risk factor; identify geographic areas with higher incidence including social disadvantage</td>
<td>2a</td>
</tr>
<tr>
<td></td>
<td>Sex, age</td>
<td>Frequency Distribution, Mean, Mode and Percentage Analysis</td>
<td>Describe sex and age presentation of rickets; Age is eligibility criteria</td>
<td>1 + 2a,b</td>
</tr>
<tr>
<td></td>
<td>date of birth</td>
<td>N/A</td>
<td>identify duplicate cases if no NHS or hospital number; eligibility criteria</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>ethnicity</td>
<td>Frequency Distribution, Mean, Mode and Percentage Analysis</td>
<td>Describe ethnicity as a risk factor and identify groups with higher incidence</td>
<td>2a</td>
</tr>
<tr>
<td>C. Presentation/Clinical Features</td>
<td>Date of diagnosis</td>
<td>Content Analysis</td>
<td>Confirm case numbers during study period; calculate seasonal variability of cases</td>
<td>1+2a</td>
</tr>
<tr>
<td>-----------------------------------</td>
<td>------------------</td>
<td>-----------------</td>
<td>--------------------------------------------------------------------------------</td>
<td>------</td>
</tr>
<tr>
<td>Family History</td>
<td>Content Analysis</td>
<td>Identify disease risk factors for rickets in patient and family; identify possible cases to be excluded</td>
<td>1 + 2a</td>
<td></td>
</tr>
<tr>
<td>Concurrent diseases</td>
<td>Content Analysis</td>
<td>Identify disease risk factors for rickets; identify possible cases to be excluded</td>
<td>1 + 2a</td>
<td></td>
</tr>
<tr>
<td>Vitamin D supplements</td>
<td>Content analysis</td>
<td>Identify risk factors and treatment of rickets</td>
<td>2a</td>
<td></td>
</tr>
<tr>
<td>Concurrent medications</td>
<td>Content Analysis</td>
<td>Identify drug risk factors and treatment for rickets</td>
<td>2a</td>
<td></td>
</tr>
<tr>
<td>Feeding Patterns</td>
<td>Content Analysis</td>
<td>Identify exclusive breastfeeding as risk factor for rickets;</td>
<td>2a</td>
<td></td>
</tr>
<tr>
<td>D. Mode of Presentation</td>
<td>Clinical Presentation</td>
<td>Frequency and Percentage Analysis</td>
<td>Describe clinical presentation; relation to age groups</td>
<td>2b</td>
</tr>
<tr>
<td>E. Investigations</td>
<td>Biochemical Parameters; X-ray findings</td>
<td>Frequency; Percentage and Content Analysis</td>
<td>Vitamin D level to confirm case; Describe biochemical and radiological features; incidence of associated clinical and radiological features</td>
<td>2c</td>
</tr>
<tr>
<td>F. Management</td>
<td>Treatment recommendations and prescriptions</td>
<td>Content Analysis</td>
<td>Describe current patterns for recommendations and treatment</td>
<td>2d</td>
</tr>
<tr>
<td>---------------</td>
<td>--------------------------------------------</td>
<td>-----------------</td>
<td>-----------------------------------------------------------</td>
<td>----</td>
</tr>
<tr>
<td></td>
<td>Treatment initiation</td>
<td>Content Percentage Analysis</td>
<td>Describe treatment initiation patterns; identify target groups for future education</td>
<td>2d</td>
</tr>
<tr>
<td></td>
<td>Follow-up Arrangements</td>
<td>Content Analysis</td>
<td>Describe follow-up patterns to identify target groups for future education</td>
<td>2d</td>
</tr>
<tr>
<td>G. Outcome</td>
<td>Clinical outcomes</td>
<td>Percentage and Content Analysis</td>
<td>Describe clinical outcome data</td>
<td>2d</td>
</tr>
<tr>
<td></td>
<td>Management outcome</td>
<td>Percentage and Content Analysis</td>
<td>Describe management outcome to identify target groups for future education</td>
<td>2d</td>
</tr>
</tbody>
</table>

C: Other Information to be recorded:

Number of participants

Number of replies

Mean response rate per month

Time taken to complete questionnaire (minutes)