



Tissue pathway for histopathological examination of the placenta

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NICE has accredited the process used by the Royal College of Pathologists to produce its tissue pathways. Accreditation is valid for five years from 25 July 2017. More information on accreditation can be viewed at www.nice.org.uk/accreditation.
For full details on our accreditation visit: www.nice.org.uk/accreditation.

Foreword

The tissue pathways published by the Royal College of Pathologists (RCPATH) are guidelines that should assist pathologists in providing a high standard of care for patients. Guidelines are systematically developed statements to assist the decisions of practitioners and patients about appropriate healthcare for specific clinical circumstances and are based on the best available evidence at the time the document was prepared. This guideline has been developed to cover most common circumstances. However, we recognise that guidelines cannot anticipate every pathological specimen type and clinical scenario. Occasional variation from the practice recommended in this guideline may therefore be required to report a specimen in a way that maximises benefit to the patient.

The guidelines themselves constitute the tools for implementation and dissemination of good practice.

The following stakeholders were contacted to consult on this document:

- The British and Irish Paediatric Pathology Association (BRIPPA)
- The Royal College of Obstetrics and Gynaecology (RCOG)
- The Royal College of Midwives (RCM).

The information used to develop this tissue pathway was collected from electronic searching of the medical literature, previous recommendations of the RCPATH, RCOG and local guidelines, and protocols from perinatal pathology units in the UK. Published evidence was evaluated using modified SIGN guidance (see Appendix D). The level of evidence was either grade C or D, or met the Good Practice Point (GPP) criteria. Consensus of evidence in this tissue pathway was achieved by expert review. Gaps in the evidence will be identified by College Fellows via feedback received from consultation. The sections of this tissue pathway that indicate compliance with each of the AGREE II standards are indicated in Appendix E.

Implementation of the tissue pathway to its full extent may have some cost implications or require some local organisational changes, as the delivery of placental pathology services varies widely between hospitals and is not available to all obstetric units in the UK.

A formal revision cycle for all tissue pathways takes place on a five-yearly basis. Each year, the College will ask the author(s) of the tissue pathways, in conjunction with the relevant subspecialty adviser to the College, to consider whether or not the document needs to be updated or revised. A full consultation process will be undertaken if major revisions are required. If minor revisions are required, an abridged consultation process will be undertaken whereby a short note of the proposed changes will be placed on the College website for two weeks for members' attention. If members do not object to the changes, the changes will be incorporated into the pathway and the full revised version (incorporating the changes) will replace the existing version on the publications page of the College website. All changes will be documented in the data control section on the front page of the relevant pathway.

The pathway was reviewed by the Clinical Effectiveness department, Working Group on Cancer Services and Lay Governance Group. It was placed on the College website for an abridged consultation with the membership from 11 July to 25 July 2019. All comments received from the Working Group, Lay Governance Group and membership were addressed by the authors to the satisfaction of the Chair of the Working Group and Clinical Lead for Guideline Review (Cellular Pathology).

This pathway was developed without external funding to the writing group. The College requires the authors of tissue pathways to provide a list of potential conflicts of interest; these are monitored by the Clinical Effectiveness department and are available on request. The authors have declared no conflicts of interest.

1 General introduction

Histopathological examination of the placenta following a pregnancy affected by medical complications, pregnancy loss or neonatal death may provide an explanation of why this occurred. It may also provide information relevant to the management of the associated infant and/or subsequent pregnancies and be of use to serious incident reviews and other audits of patient care.^{1,2}

This document is intended as a guide to reasonable practice, rather than a policy statement. It also attempts to provide information that might be useful when dealing with different types of placenta. Where possible, references are provided, but it is inevitable that many of the suggestions are based on common UK practice rather than on published evidence, as the latter is often non-existent or sparse. Many laboratories have adopted approaches based on their own experience, evidence and resources, which may differ from these guidelines but which achieve the same outcome. This document does not aim to change such approaches. In addition, the document is not intended as a replacement for standard textbooks, but highlights the principles of handling and reporting placental specimens. For detailed guidance on examination of the placenta in specific circumstances, the reader is referred to the 'Further reading' list in section 9.

This tissue pathway aims to provide guidance on the range of indications for referral of a placenta for histopathological examination and minimum standards for pathologists undertaking placental examinations. Variations to the standard pathway for singleton placentas, relating to pregnancies from multiple gestations, are also included. Please note that products of conception (1st trimester) have been included in the tissue pathways for gynaecological pathology.

1.1 Target users of this guideline

This pathway will be of use to consultants and trainees in general histopathology, subspecialist paediatric and perinatal pathologists, obstetricians and midwives, and those commissioning perinatal pathology services.

2 Generic considerations

2.1 Staffing and workload

Pathologists should:

- participate in audit
- participate in the RCPATH Continuing Professional Development scheme
- participate in relevant external quality assessment (EQA) schemes of a general or specialist nature. Although there is currently no EQA scheme solely for placental pathology, it does form part of the paediatric and perinatal pathology EQA scheme organised by the British and Irish Paediatric Pathology Association (BRIPPA) and is undertaken by all subspecialist paediatric and perinatal pathologists. General pathologists undertaking perinatal autopsies or paediatric surgical pathology, in addition to placental pathology, should participate in this scheme

- have access to specialist referral opinions on a local/regional network or national basis. For general pathologists, this will usually mean access to a subspecialist perinatal pathologist at a regional centre.

2.2 Laboratory facilities and generic laboratory requirements

Placental examination should be undertaken in an appropriate laboratory environment. Provision should be made for macroscopic and microscopic photography as placentas from pregnancy losses may be discussed at local perinatal mortality meetings and visual information may assist the discussion. If injection studies are to be undertaken on monochorionic twin placentas, appropriate equipment, solutions (agar) and dyes should be available.

The laboratory should:

- be equipped to allow the recommended technical procedures to be performed safely
- be enrolled with the UK Accreditation Service (UKAS)
- participate in the UK National External Quality Assurance Scheme for cellular pathology technique
- participate in the UK National External Quality Assurance Scheme for immunocytochemistry
- have access to light microscopy and common special stains
- have access to immunohistochemistry
- have access to genetics services
- have access to microbiology and virology services
- have access to photographic equipment.

Reports should be held on an electronic database that has facilities to search and retrieve specific data items and that is indexed according to SNOMED codes. It is acknowledged that existing laboratory information systems may not meet this standard; however, the ability to store data in this way is recommended when laboratory systems are replaced or upgraded.

Workload data should be recorded in a format that helps determine which resources should be used and which, if applicable, is suitable for mapping to healthcare resource groups.

3 General issues

3.1 Staffing and workload

In hospitals with specialist(s) in perinatal pathology, placental examination may be undertaken by the specialist. However, in many departments, placental examination is undertaken as part of a general rota. In either circumstance, there must be a sufficient number of pathologists to provide cover and to conform to the College's guidance on staffing and workload levels.^{3,4}

3.2 Specimen submission

The decision about the indications for referral of a placenta for histopathology should be agreed with local obstetricians and neonatologists. A suggested list of indications for referral is shown in Appendix A.⁵ As a minimum, all placentas from stillbirths,⁶ fetal growth restriction (FGR – below 10th centile with abnormal fetal growth curve during pregnancy),^{7,8} immaturity (less than 32+0 completed weeks gestation),^{7,8} and cases of severe fetal distress requiring admission to

a neonatal intensive care unit (NICU),⁵ maternal pyrexia (>38°C) and late miscarriages (20+0 to 23+6 completed weeks gestation) should be referred. Consideration may be given to providing an urgent placental examination service for infants in NICU. Submission of placentas following other pregnancy complications may depend on local resources and the value placed on placental examination in these situations by the local obstetricians.⁹

[Level of evidence – C, D and GPP].

Full details of the patient (mother), clinical consultant and date of delivery should be provided on the request form. As a minimum, the gestational age, birth weight and the indication for referral should be stated. Details of previous pregnancy complications and relevant maternal disease should also be provided. It may be appropriate to develop a simple placental referral proforma for use by clinicians, such as that shown in Appendix B.

The specimen container must be labelled with the patient details. Placentas may be submitted to the laboratory fresh or formalin fixed as per local protocols. If submitted in formalin, the container should be of sufficient size to minimise distortion of the specimen and formalin should be of adequate volume to cover the specimen entirely to ensure proper fixation. Any samples for cytogenetic testing should be taken before fixation. The specimen should not otherwise be disrupted before receipt in the histopathology laboratory, unless this has been agreed on previously.

Submission of the unfixed placenta may be preferable for identification of macroscopic changes. However, formalin fixation may be preferred if there is likely to be a delay in undertaking the examination following submission or when refrigerated storage is not available. It may also be desirable to fix the placenta in potentially high-risk infective cases or where there is a risk of congenital infection being transmitted to a vulnerable member of staff. For adequate fixation, the placenta must be placed in a container of adequate size and containing at least three times the tissue volume of formalin.

3.3 Specimen dissection and block selection

Sampling of the placenta for histology should be undertaken from sufficient areas to provide a representation of the pathology present.^{5,9,10} Each cassette must have a unique identifying number or letter. A record of the number of pieces of tissue in each cassette is desirable for audit purposes. Specific details of dissection and block selection relating to singleton and multiple pregnancy placentas are detailed in sections 4, 5 and 6.

In a small number of clinical situations, it may be appropriate for the examination to be limited to a macroscopic description, without sampling for histology (Appendix C). In this case, the placenta should be retained for at least two weeks in case the baby or mother becomes ill and placental histology becomes necessary. Some centres may prefer in these cases to provide a macroscopic description and take tissue blocks for processing only. Block-only cases may then be formally reported as per clinical need.

In agreement with local clinicians, it may be appropriate in some clinical situations for the placenta to be referred to the pathology department for short-term storage only, in case the baby or mother develops significant complications that placental examination may help to explain or for which it may help to direct treatment. Suggested indications for short-term storage are given in Appendix C. In this situation, a report should be issued, notifying the clinician that the placenta has not been examined, stating the intended period of storage and providing the contact details to initiate examination if this becomes necessary.

3.4 Embedding options

Local procedures for processing and embedding tissue samples should be followed. There are no specific requirements for general placental tissue. Samples from the maternal surface, searching for spiral arteries in the decidua, may be embedded either 'on edge' or with the decidual face downwards, depending on local preference and experience.

3.5 Sectioning

Tissue sections should be produced as per local protocols.

3.6 Staining

In the vast majority of cases, a single haematoxylin and eosin-stained section of each tissue block is sufficient for diagnosis. It is essential that the sections produced include the fetal and maternal surface of the placenta and that sections of umbilical cord include the complete circumference of the cord.

3.7 Further investigations

Additional stains are usually not required. In individual cases, consideration may be given to the use of special stains, immunohistochemistry, genetic analysis, electron microscopy and microbiological samples. Commonly employed special stains include Gram-Twort for bacteria, PAS with diastase predigestion for fungi and Perls' stain for haemosiderin (to distinguish from meconium pigment in the fetal surface). Immunostaining for cytomegalovirus and parvovirus B19 may be useful in the appropriate context. Cytogenetic testing may be indicated if the placenta is being examined following fetal death, or where post mortem has been declined and there is a clinical indication (e.g. severe FGR or congenital malformations). Samples should only be sent for cytogenetic analysis if there is documented parental consent. Electron microscopy is rarely indicated, but may be considered in cases of death due to fetal hydrops, when post mortem is declined. Some authors suggest placental bacteriological swabs should be sent in cases of apparent chorioamnionitis. This is of questionable value except in specific circumstances (e.g. suspected listeriosis).

3.8 Report content

In general, the report should include as a minimum: the patient details, the clinical history (summarised or directly transposed from the request form), a macroscopic description of the umbilical cord, membranes, fetal, maternal and cut surfaces of the placenta, and a microscopic description of the umbilical cord, membranes, fetal placental surface, villous parenchyma and maternal decidua.^{10,11} The report should conclude with a diagnosis or list of pathological findings and, where appropriate, a clinicopathological comment to assist the clinician in interpreting the significance of the findings. Diagnostic coding of the findings is recommended.

[Level of evidence – GPP.]

4 Specific considerations for singleton placenta

4.1 Dissection and macroscopic description^{5,9,10}

The following measurements should be made in all cases:

- maximum linear dimensions of the placental disc in two perpendicular planes (to nearest 10 mm)
- thickness of disc (to nearest 5 mm)

- length of umbilical cord (to nearest 10 mm) and approximate diameter (to nearest 1 mm)
- weight of placental disc following removal of cord and membranes (to nearest gram) and whether this is fresh or fixed.

There should be a systematic description of the umbilical cord, membranes, fetal and maternal surface, and parenchyma. The site of the cord insertion and number of umbilical cord vessels should be recorded. The degree of coiling of the umbilical cord may also be described, either qualitatively or numerically (e.g. *n* coils per 100 mm). The presence and site of true knots in the umbilical cord should be recorded and an assessment should be made about whether the knot appears to have occluded flow in the cord vessels. It may be helpful to record the appearance photographically. The appearance of the placental membranes (translucency, colour, insertion) and the fetal placental surface (colour, vascular congestion/thrombosis) should be described. The presence and extent of macroscopic pathology in the placental parenchyma should be described and an attempt should be made to assess whether the membranes and parenchyma have been received in their entirety or whether they are incomplete.

Major lesions, particularly in placentas from pregnancy losses, should be recorded photographically, if facilities exist. If the placenta is examined in the fresh state, consideration should be given to sampling the placenta for cytogenetic testing or virology, if clinically indicated. Cytogenetic analysis should only be undertaken if parental consent has been obtained.

4.2 Sampling for histology

Histological sampling is indicated in the majority of situations. It is recommended that the following samples are taken as a minimum:

- two transverse sections of umbilical cord
- one roll of membranes (to include the rupture site)
- two full thickness blocks of the placental parenchyma (away from the placental edge) to include the fetal and maternal surfaces
- additional blocks depending on the clinical indications for the examination and macroscopic findings.¹⁰

Representative samples of macroscopic lesions should be taken as necessary. In cases of severe FGR, maternal pre-eclampsia (PET) or a morbidly adherent placenta (MAP), additional small samples may be taken from the maternal surface to attempt to identify maternal vascular pathology (FGR, PET) or uterine smooth muscle (MAP).³ In cases of maternal pyrexia or prematurity, additional samples of umbilical cord and membranes and fetal placental surface may be necessary, since chorioamnionitis is often patchy in distribution.

In limited circumstances, with agreement from local obstetricians, macroscopic examination may be performed, without histology,⁵ or histology blocks may be taken but not examined unless further infant or maternal complications arise (see Appendix C).

When no histology is undertaken, it is advisable to issue a macroscopic report urgently, indicating that histology will only be undertaken if clinically indicated. The placenta should be retained for a short period (1–2 weeks) in case serious neonatal complications occur or further clinical information comes to light necessitating histological sampling.

4.3 Report content

See section 3.8 for general comments.

The histological report should be tailored to the specific clinical situation. Key elements to note include: the presence, severity and extent of acute inflammation in the cord, membranes and/or fetal surface; the villous development in relation to the stated gestation and evidence of villous ischaemia; and the presence of infarction, chronic inflammation and other parenchymal disease. In cases of FGR and maternal PET, the decidua should be examined for the presence of maternal vascular disease. In cases of MAP, the presence of uterine smooth muscle in the maternal surface should be sought.

[Level of evidence – GPP.]

5 Specific considerations for dichorionic twin placentas

5.1 Specimen submission

Dichorionic twin placentas are frequently referred to the pathology laboratory for examination. If the pregnancy and delivery have been uncomplicated, it may be appropriate to undertake macroscopic examination only, to confirm chorionicity. The examination may be of limited value in this situation and may equally be undertaken in the delivery suite by an appropriately trained midwife or doctor. If this approach is taken, the clinician should refer the placenta to the pathology for assessment if they are uncertain of the chorionicity in the delivery suite. If the pregnancy has been affected by medical complications, the approach to examination should be the same as for singleton placentas.⁵

5.2 Dissection and macroscopic description

The first aim of the examination is to confirm that the placenta is dichorionic, by examining the dividing membrane. A dividing membrane tethered to the placental surface indicates dichorionicity, while a mobile dividing membrane is characteristic of a monochorionic placenta. It is usual also to determine whether the placental discs are separate or joined. Otherwise examination assesses the same features as for a singleton pregnancy for each part of the placenta.

5.3 Sampling for histology

The pathologist may wish to include a roll of the dividing membrane or a T-block from the insertion of the dividing membrane into the placental surface as histological confirmation of chorionicity. Otherwise the rationale for sampling is the same as for two singleton placentas.

5.4 Report content

Apart from a description of the dividing membrane, the report should follow the same format as for two singleton placentas.

The conclusion or diagnosis should indicate the chorionicity of the placenta. Other relevant pathology should be listed and a clinicopathological comment added as necessary.

[Level of evidence – GPP.]

6 Specific considerations for monochorionic placentas

6.1 Specimen submission

Monochorionic pregnancies are subject to a number of additional pathological disorders not seen in singleton or dichorionic twin placentas.^{8,12} Rates of complications are also significantly higher. They may be subject to medical intervention during pregnancy to treat the complications. It is probably advisable for monochorionic twin placentas to be routinely referred for examination by a pathologist.

6.2 Dissection and macroscopic description

In general, it is necessary to approach the monochorionic twin placenta as a single entity in terms of weight, measurements and description – the obvious exception being the umbilical cords, which are described separately.

The fetal surface is of particular interest and usually carries connections between the two fetal circulations. The description of the fetal surface should include the site and distance between the insertion of the two umbilical cords and the relative shares of the placental disc. An assessment of the vasculature in the chorionic plate should be made and the presence, number and size of the three types of interfetal anastomoses – arterioarterial, venovenous and 'deep' arteriovenous – should be recorded.¹³ Identification of anastomoses may be facilitated by injection of the vasculature. A simple method involves injecting a 1% agar solution, coloured with four tissue-marking dyes, into an artery and the vein of each umbilical cord, after removal of excess blood from superficial vessels.¹³ The resulting preparation can be photographed and is suitable for histological examination. Injection studies are particularly helpful if the pregnancy has been complicated by growth discordance or twin-twin transfusion syndrome (TTTS). Other methods for placental injection to determine vascular anastomoses have been described.¹⁴ These methods are not suitable for formalin-fixed placentas.

If the placenta has been subject to laser coagulation for TTTS, the presence of laser sites and completeness of interruption of interfetal anastomoses should be recorded.

6.3 Sampling for histology

In cases where histological examination is undertaken, the approach to histological sampling is the same as for singleton placentas, except that in complicated monochorionic pregnancies, samples should be taken from the areas supplying each twin for comparison. A roll of the dividing membrane is also usually taken.

6.4 Report content

The description of the placenta should include a detailed description of its fetal surface, including the site and distance between the insertion of the umbilical cords, the sharing of the placental disc, the types, number and size of interfetal anastomoses and their direction (arteriovenous [deep] anastomoses only).

The histological report should include a description of the dividing membrane and compare the appearance of parenchymal samples from the areas supplying each twin. Otherwise the description follows the same lines as for singleton placentas.

A clinicopathological comment on the contribution of the placental findings to the observed clinical complications (if any) should be given.

Placentas from higher multiple pregnancies (e.g. triplets) should be processed according to the chorionicity of the placenta. Often this is a combination of monochorionic and dichorionic placentation.

[Level of evidence – GPP.]

7 Criteria for audit

Implementation of this tissue pathway may be monitored by audit of:

- completeness of adherence to referral criteria
 - standard: less than 10% of referred placentas fall outside the local referral criteria
- completeness of recording of standard measurements
 - standard: placental trimmed weight, measurements in three planes and umbilical cord length recorded in all cases
- adherence to minimum histological sampling guidance
 - standard: a minimum of one section of umbilical cord, one section of membranes and two full thickness samples of placenta taken in all cases submitted for histology
- turnaround time for reports
 - standard: 75% of placental histology reports issued within 42 days of receipt.

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9 Further reading

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Appendix A Indications for referral of placentas for pathological examination (to be agreed with local clinicians)

Referral of placenta for examination is **essential** for:

- stillbirth (antepartum or intrapartum)
- late miscarriage
- severe fetal distress requiring admission to neonatal unit
- prematurity (less than 32+0 weeks' gestation)
- fetal growth restriction with birthweight below 10th centile and corresponding abnormal fetal growth curve
- fetal hydrops
- maternal pyrexia (>38°C).

Referral of placenta for examination may be **desirable** for:

- prematurity (32+0–36+6 weeks)
- placental abruption
- fetal congenital malformation
- rhesus (and other) isoimmunisation
- morbidly adherent placenta
- twins or other multiple pregnancy (uncomplicated)
- abnormal placental shape (if clinically relevant)
- two vessel cord, etc.
- prolonged rupture of the membranes (more than 36 hours)
- gestational diabetes
- maternal group B streptococcus
- pre-eclampsia/maternal hypertension
- maternal coagulopathy
- maternal substance abuse.

Referral is **not** indicated in the following conditions as pathological examination is unlikely to provide useful information:

- cholestasis of pregnancy
- pruritis of pregnancy
- hepatitis B, HIV, etc.
- other maternal disease with normal pregnancy outcome
- placenta praevia
- post-partum haemorrhage
- polyhydramnios
- normal pregnancy.

Appendix B Sample request form for placental examination

Registration no: NHS no: Surname: DOB: Forename(s): Ward: Address: Specialty: Consultant:	Clinical information:	
	Date of delivery	
	Live birth / stillbirth / TOP	
	Sex of baby (babies)	
	Gestation at birth (weeks)	
	Birth weight(s) (grams)	
<i>Alternatively attach patient label</i>		

Indication for referral (Please tick/delete all relevant)		*Delete as appropriate H Histology performed as routine R Histology on request M Macroscopic examination only S Will be stored for 2 weeks only and will only be examined if requested		
FGR (birth weight below 10th centile) R	Maternal pyrexia R	2 vessel cord, etc. (M)	PROM (more than 36 hours) (S)	
Abruption R	Fetal hydrops H	Abnormal placenta shape (M)	Gestational diabetes (S)	
Morbidly adherent placenta H	Isoimmunisation requiring fetal transfusion – Rh/ABO/Kell/Other*	Pre-eclampsia (uncomplicated) (S)	Maternal group B streptococcus (S)	
Prematurity (less than 34/40) (S unless <32/40 H)	Stillbirth – antepartum/intrapartum*; late miscarriage H	Fetal abnormality (specify) R		
Severe fetal distress (requiring admission to NNU) H Apgar scores: 1' 5' 10'		Other (must specify)		
Twins/other multiple pregnancy (specify)* M unless complications monochorionic/dichorionic/?*				
Complications/interventions (specify)				
Relevant previous medical/obstetric history (specify):				

Section to be completed by delivery suite staff		
Placenta request form and specimen checked by:		
Print name:	Signature:	Date:

Section to be completed by mortuary staff

Placenta received:

By (initials):

Date:

Time:

Examination type (pathologist to initial):

Full:

Macro:

Storage:

Appendix C Triage system for placental examination based on clinical situation (with agreement of local clinicians)

Full examination including histology

- Stillbirth (ante partum or intra partum).
- Late miscarriage.
- Severe fetal distress requiring admission to neonatal unit (pH <7.21, scalp lactate >4.8mmol/l or Apgar <7 at 5 mins).
- Prematurity (less than 32+0 weeks' gestation).
- Fetal hydrops.
- Morbidly adherent placenta.
- Fetal growth restriction (birth weight below 3rd centile).

Full examination – histology taken but only examined if further clinical indication/on request of clinician

- Fetal growth restriction (birth weight below 10th centile).
- Maternal pyrexia.
- Placental abruption.
- Fetal abnormality.
- Rhesus (and other) isoimmunisation requiring in utero transfusion.
- Maternal coagulopathy.
- Maternal substance abuse.

Macroscopic examination – no histology (placenta retained for 2 weeks after examination)

- Twins or other multiple pregnancy (uncomplicated).
- Abnormal placental shape (if clinically relevant).
- Two vessel cord, etc.

Storage for 2 weeks (no examination)

A report indicating that the placenta has been received and is being stored without examination may be sent to the referring clinician depending on local agreement/policy.

- Prolonged rupture of the membranes (more than 36 hours).
- Prematurity (32+0–36+6 weeks).
- Gestational diabetes.
- Rhesus negative mother (no fetal anaemia).
- Maternal group B streptococcus.
- Uncomplicated pre-eclampsia/maternal hypertension.

Appendix D**Summary table – explanation of grades of evidence**

(modified from Palmer K *et al. BMJ* 2008;337:1832)

Grade (level) of evidence	Nature of evidence
Grade A	At least one high-quality meta-analysis, systematic review of randomised controlled trials or a randomised controlled trial with a very low risk of bias and directly attributable to the target population or A body of evidence demonstrating consistency of results and comprising mainly well-conducted meta-analyses, systematic reviews of randomised controlled trials or randomised controlled trials with a low risk of bias, directly applicable to the target population.
Grade B	A body of evidence demonstrating consistency of results and comprising mainly high-quality systematic reviews of case-control or cohort studies and high-quality case-control or cohort studies with a very low risk of confounding or bias and a high probability that the relation is causal and which are directly applicable to the target population or Extrapolation evidence from studies described in A.
Grade C	A body of evidence demonstrating consistency of results and including well-conducted case-control or cohort studies and high-quality case-control or cohort studies with a low risk of confounding or bias and a moderate probability that the relation is causal and which are directly applicable to the target population or Extrapolation evidence from studies described in B.
Grade D	Non-analytic studies such as case reports, case series or expert opinion or Extrapolation evidence from studies described in C.
Good practice point (GPP)	Recommended best practice based on the clinical experience of the authors of the writing group.

Appendix E AGREE II guideline monitoring sheet

The tissue pathways of the Royal College of Pathologists comply with the AGREE II standards for good quality clinical guidelines (www.agreetrust.org). The sections of this tissue pathway that indicate compliance with each of the AGREE II standards are indicated in the table.

AGREE II standard	Section of guideline
Scope and purpose	
1 The overall objective(s) of the guideline is (are) specifically described	Introduction
2 The health question(s) covered by the guideline is (are) specifically described	Introduction
3 The population (patients, public, etc.) to whom the guideline is meant to apply is specifically described	Foreword
Stakeholder involvement	
4 The guideline development group includes individuals from all the relevant professional groups	Foreword
5 The views and preferences of the target population (patients, public, etc.) have been sought	Foreword
6 The target users of the guideline are clearly defined	Introduction
Rigour of development	
7 Systematic methods were used to search for evidence	Foreword
8 The criteria for selecting the evidence are clearly described	Foreword
9 The strengths and limitations of the body of evidence are clearly described	Foreword
10 The methods for formulating the recommendations are clearly described	Foreword
11 The health benefits, side effects and risks have been considered in formulating the recommendations	Foreword and Introduction
12 There is an explicit link between the recommendations and the supporting evidence	2–6
13 The guideline has been externally reviewed by experts prior to its publication	Foreword
14 A procedure for updating the guideline is provided	Foreword
Clarity of presentation	
15 The recommendations are specific and unambiguous	2–6
16 The different options for management of the condition or health issue are clearly presented	2–6
17 Key recommendations are easily identifiable	2–6
Applicability	
18 The guideline describes facilitators and barriers to its application	Foreword
19 The guideline provides advice and/or tools on how the recommendations can be put into practice	Appendices A–C
20 The potential resource implications of applying the recommendations have been considered	Foreword
21 The guideline presents monitoring and/or auditing criteria	7
Editorial independence	
22 The views of the funding body have not influenced the content of the guideline	Foreword
23 Competing interests of guideline development group members have been recorded and addressed	Foreword