



# Guidelines on autopsy practice

## Maternal death

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NICE has accredited the process used by the Royal College of Pathologists to produce its autopsy guidelines. Accreditation is valid for 5 years from 25 July 2017. More information on accreditation can be viewed at [www.nice.org.uk/accreditation](http://www.nice.org.uk/accreditation).

For full details on our accreditation visit: [www.nice.org.uk/accreditation](http://www.nice.org.uk/accreditation).

## Foreword

The autopsy guidelines published by the Royal College of Pathologists (RCPATH) are guidelines which enable pathologists to deal with non-forensic consented and medico-legal (coronial/procurator fiscal) post-mortem examinations in a consistent manner and to a high standard. The guidelines are systematically developed statements to assist the decisions of practitioners and are based on the best available evidence at the time the document was prepared. Given that much autopsy work is single observer and one-time only in reality, it has to be recognised that there is no reviewable standard that is mandated beyond that of the FRCPath Part 2 exam or the Certificate of Higher Autopsy Training (CHAT). However, maternal deaths will form part of mortality reviews by the involved healthcare agencies, when the autopsy report will be studied in the context of the clinical information and results of investigations, as well as being examined as part of the national triennial audit, by MBRRACE-UK (Mothers and Babies: Reducing Risk through Audits and Confidential Enquiries across the UK – see below). This guideline has been developed to cover most common circumstances. However, we recognise that guidelines cannot anticipate every clinical scenario or circumstance. Occasional variation from the practice recommended in this guideline may therefore be required to report a case in a way that maximises benefit to the coroner/procurator fiscal and the deceased's family.

There is a general requirement from the General Medical Council (GMC) to have continuing professional development (CPD) in all practice areas and this will naturally encompass autopsy practice. Those wishing to develop expertise/specialise in pathology are encouraged to seek appropriate educational opportunities.

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

The following stakeholders were contacted to consult on this document:

- the Human Tissue Authority (HTA)
- the Coroners' Society of England & Wales
- Coroners Service for Northern Ireland

- the Crown Office and Procurator Fiscal Service
- the Home Office Forensic Science Regulation Unit
- MBRRACE-UK
- Healthcare Safety Investigation Branch (HSIB).

The information used to develop this autopsy guideline was derived from current medical literature and a previous version of this guideline. A systematic search of PubMed and the Cochrane Database was undertaken using a variety of terms including 'maternal death', 'maternal mortality', 'pregnancy death', 'direct death', 'indirect death' and 'autopsy' or 'post mortem' and dates searched were between July 2022 and February 2023. Much of the content of the document represents custom and practice and is based on the substantial clinical experience of the authors. The modified SIGN guidance was used to assess the evidence (see Appendix A). Consensus of evidence in the guideline was achieved by expert review. Gaps in the evidence will be identified by College members via feedback received during consultation. The sections of this autopsy guideline that indicate compliance with each of the AGREE II standards are indicated in Appendix B.

No major organisational changes or cost implications have been identified that would hinder the implementation of the guidelines.

A formal revision cycle for all guidelines takes place on a 5-yearly cycle. The College will ask the authors of the guideline to consider whether it needs to be revised. A full consultation process will be undertaken if major revisions are required. If minor revisions or changes are required, a short note of the proposed changes will be placed on the College website for 2 weeks for members' attention. If members do not object to the changes, the changes will be incorporated into the guideline and the full revised version (incorporating the changes) will replace the existing version on the College website.

The guideline has been reviewed by the Professional Guidelines team, Death Investigation Committee, Forensic Pathology Specialty Advisory Committee and Lay Advisory Group. It was placed on the College website for consultation with the membership from 23 October to 20 November 2023. All comments received from the membership were addressed by the author to the satisfaction of the Clinical Lead for Guideline Review.

This guideline was developed without external funding to the writing group. The College requires the authors of guidelines to provide a list of potential conflicts of interest; these

are monitored by the Professional Guidelines team and are available on request. The authors of this document have declared that there are no conflicts of interest.

## 1 Introduction

Maternal mortality is relatively uncommon in the UK compared to many other countries,<sup>1</sup> with a maternal mortality rate of 10.9 women per 100,000 maternities in 2018–2020 (or on average 76 women per year).<sup>2</sup> The spectrum of causes of death seen is broad and full investigation is required at post mortem to obtain maximal information.

Whereas direct causes of maternal death (such as obstructed labour) predominate internationally, owing to factors such as poor infrastructure/access to medical care and the illegality of abortion, in the UK, indirect causes (particularly cardiac diseases, neurological diseases and psychiatric diseases) have dominated for the past 20 years (although less so more recently, with the classification of suicide as a direct cause within the World Health Organization's *International Classification of Diseases – Maternal Mortality*).<sup>3</sup>

### 1.1 Target users and health benefits of this guideline

These guidelines aim to assist pathologists undertaking coronial/procurator fiscal, Home Office and consented post-mortem examinations in such women to ensure a standard level of investigation is undertaken. The examination and subsequent interpretation of the findings in such cases can be challenging. Performing a good autopsy with appropriate clinicopathological correlation will enable families and the professionals who cared for the woman to have the best chance of understanding why she died. All maternal deaths are reviewed by MBRRACE-UK, which in its triennial reports makes specific recommendations to various professional groups and public health/medical bodies, with the aim of reducing severe acute maternal morbidity (SAMM) and maternal mortality.

### 1.2 Definitions

- Maternal death: death of woman while pregnant or within 42 days of end of pregnancy.
- Late maternal death: death of woman from 42 days to 1 year after abortion, miscarriage or delivery.
- Direct maternal death: death due to obstetric complications of pregnancy, labour or puerperium.

- Indirect maternal death: death due to pre-existing disease or disease which was aggravated by the physiological effect of pregnancy but not due to direct obstetric causes.
- Pregnancy related death: coincidental ('fortuitous') deaths, in which the pregnancy had no impact on the cause of death.
- Maternal mortality ratio (used internationally): direct and indirect deaths per 100,000 livebirths.
- Maternal mortality rate (used in the UK): direct and indirect deaths per 100,000 maternities.
- Maternities: women giving birth to a liveborn or stillborn baby at 24/40 weeks' or greater gestation
- SAMM: 'near-miss' maternal death.

A list of the abbreviations used in this guideline is given in Table 1.

**Table 1. List of abbreviations.**

<b>BMI</b>	Body mass index
<b>COVID-19</b>	Coronavirus disease 2019
<b>DIC</b>	Disseminated intravascular coagulation
<b>HELLP</b>	Haemolysis, elevated liver enzymes, low platelets
<b>HSIB</b>	Healthcare Safety Investigation Branch
<b>MBRRACE-UK</b>	Mothers and Babies Reducing Risk through Audit and Confidential Enquiries across the UK
<b>MRSA</b>	Methicillin-resistant staphylococcus aureus
<b>ONS</b>	Office for National Statistics
<b>PET</b>	Pre-eclampsia toxaemia
<b>PMCT</b>	Post-mortem computed tomography
<b>SADS</b>	Sudden arrhythmic death syndrome
<b>SAMM</b>	Severe acute maternal morbidity
<b>SIRS</b>	Systemic inflammatory response syndrome
<b>TRALI</b>	Transfusion-associated lung injury
<b>TTP</b>	Thrombotic thrombocytopenic purpura
<b>VTE</b>	Venous thromboembolic disease/venous thromboembolism

## 2 The role of the autopsy

The role of the maternal death autopsy is to identify the pathologies in the patient and contribute critically to the clinicopathological evaluation of the death. As stated above, maternal death autopsy reports are integral to the rolling national audit of maternal deaths and its recommendations, so it is critical that the reports are of optimum quality and provide a clear opinion as to the cause of death. It is important that an autopsy is performed in the great majority of cases, particularly the suspected direct and indirect deaths.

These guidelines are intended to help the pathologist focus on the issues raised by a death related to pregnancy and thus optimise the autopsy procedure; they include nearly all the clinicopathological scenarios likely to be encountered. Pathologists are also encouraged to refer to other RCPATH autopsy practice guidelines where appropriate (e.g. where the deceased mother is a person with epilepsy the guideline for deaths in patients with epilepsy should also be consulted).<sup>4</sup>

It is evident that experience is required for these cases, as well as good mortuary and laboratory facilities. Given the relatively small number of maternal deaths in the UK, it is recommended that maternal death autopsies are performed by a pathologist with a special interest. If such a pathologist is not available, the local pathologist may consider asking for guidance or discuss the case with a pathologist with more maternal death experience before the autopsy and, if necessary, when interpreting the histology.

## 3 Pathology encountered at the autopsy

The major entities include the following.

### 3.1 Direct deaths

#### 3.1.1 Thrombosis and thromboembolism (venous thromboembolic disease, VTE) (see section 8.1)

Thrombosis and thromboembolism are the most common cause of direct death occurring within 42 days of the end of pregnancy,<sup>2</sup> including pulmonary embolism and cerebral venous sinus thrombosis. Risk factors for thromboembolism include obesity and pregnancy itself (during or up to 42 days after cessation of pregnancy) – these should be included in the cause of death.<sup>5</sup>

### **3.1.2 Suicide**

Increasing in incidence, suicide is currently the second most common cause of direct death up to 42 days of end of pregnancy. However, the rate of suicide is more frequent between 6 weeks and a year after the end of pregnancy (late maternal death). Violent forms of suicide are seen more often than in non-pregnant females, with hanging being the most commonly used method, although other methods include overdose, falling from a height or entering the path of a vehicle.<sup>2</sup> The cause of death should include the fact of pregnancy in part 2. Consideration of any clinical psychiatric diagnoses should be addressed by the investigating body, not by the pathologist.

### **3.1.3 Sepsis (see section 8.3)**

Genital tract sepsis is classed as a direct cause of death (for indirect causes of sepsis, see section 3.2).<sup>6</sup>

### **3.1.4 Obstetric haemorrhage (see section 8.4)**

Obstetric haemorrhage can be caused by uterine atony, uterine inversion, placental abruption, placenta praevia, morbidly adherent placenta (placenta accreta, increta, percreta), retained placenta, extensive decidualosis/decidualisation of the pelvis, tears or ruptures of the genital tract (either spontaneous or iatrogenic) and amniotic fluid embolism (see below for further on the latter).

Pathology due to supportive measures following an episode of obstetric haemorrhage, such as fluid overload or transfusion-associated lung injury (TRALI), may also be seen.

### **3.1.5 Early pregnancy deaths (see sections 8.3 and 8.4)**

Ectopic pregnancy remains the most common cause of early pregnancy death, with other causes including complications of termination of pregnancy, trophoblastic disease and miscarriage. Pathology encountered can include air embolism, uterine rupture (due to perforation due to trauma in surgical termination or from prostaglandin induction in medical termination) and genital tract sepsis.

### **3.1.6 Hypertensive diseases of pregnancy (see section 8.2)**

Chronic hypertension may be diagnosed pre-pregnancy, or may be present at the booking visit up to 20/40.

Hypertensive diseases of pregnancy include:<sup>7</sup>

- gestational hypertension: new hypertension presenting after 20/40 without proteinuria



- pre-eclampsia: new hypertension presenting after 20/40 with significant proteinuria
- severe pre-eclampsia: pre-eclampsia with severe hypertension +/-symptoms +/-biochemical +/-haematological impairment.
- eclampsia: pre-eclampsia and tonic-clonic seizures

The rates for maternal death due to hypertensive diseases of pregnancy are low in the UK, compared to a few decades ago, when, with VTE disease, it was a leading cause of maternal death.<sup>2</sup> Pre-eclampsia can manifest for the first time in the weeks following delivery. Deaths due to hypertensive disorders can be caused by haemorrhage associated with haemolysis, elevated liver enzymes, low platelets (HELLP) syndrome, intracranial haemorrhage, cerebral oedema with hypoxic damage and infarction of vasogenic origin, post-eclamptic seizure or flash pulmonary oedema in severe acute pre-eclampsia.

### **3.1.7 Amniotic fluid embolism (see section 8.5)**

Amniotic fluid embolism is caused by amniotic fluid entering the circulation, usually during labour or during Caesarean section. There is usually a classical clinical picture, with sudden onset of shortness of breath and circulatory collapse in a previously well woman during or soon after delivery, which is almost always associated with a disseminated intravascular coagulation (DIC) picture.<sup>8-10</sup> The patient may seem agitated or describe a feeling of impending doom before collapse.<sup>10</sup>

### **3.1.8 Anaesthetic causes (see section 8.6)**

Anaesthetic maternal deaths are rare.<sup>2</sup> Causes of death include aspiration pneumonitis, difficulties in airway patency peri- and post-anaesthesia, therapeutic opiate toxicity when used for pain control, infection due to spinal or epidural anaesthesia, and venous air embolism. In the correct clinical context malignant hyperthermia and anaphylaxis should be considered and retention of tissue for genetic analysis may be appropriate (see also RCPATH autopsy guidelines *G147 Postoperative deaths*<sup>11</sup> and *G170 Autopsy for suspected acute anaphylaxis*).<sup>12</sup>

### **3.1.9 Peripartum (puerperal) cardiomyopathy (see section 8.9)**

Peripartum cardiomyopathy is a rare complication of pregnancy but can be difficult to diagnose. It is a clinical diagnosis of exclusion. The definition is development of cardiac failure between the last month of pregnancy and 5 months post-partum with no defined cause or previous cardiac disease before pregnancy.<sup>13</sup>

## 3.2 Indirect deaths

### 3.2.1 Cardiovascular disease (see sections 7 and 8)

Cardiovascular disease is the leading cause of indirect maternal death in the UK.<sup>2</sup>

Retention of material, such as frozen splenic tissue, for genetic investigation and familial screening should be considered, given the age group.

Causes include:

- coronary artery atherosclerosis
- spontaneous coronary artery dissection – rare, but the highest risk is in the 6 months immediately postpartum<sup>2</sup>
- valvular heart disease – includes endocarditis, bicuspid aortic valve, rheumatic heart disease, mitral valve prolapse
- myocardial disease/cardiomyopathy. The most common causes of cardiomegaly/left ventricular hypertrophy are hypertension, ischaemic heart disease, valve disease and obesity. Genetic cardiomyopathies are less common but warrant particular consideration in this young cohort. Peripartum cardiomyopathy is discussed above in the direct causes of death. The heart to body weight ratio can be a helpful indicator
- sudden arrhythmic death syndrome (SADS) with a morphologically normal heart
- vascular aneurysm/dissection. There is an increased risk of vascular aneurysm and dissection (in addition to the coronary arteries) during pregnancy, most often affecting the aorta or splenic artery. Aortic dissection can be associated with a bicuspid aortic valve
- pulmonary hypertension. This can manifest during pregnancy and can be overlooked clinically – symptoms include shortness of breath on exertion and can emerge as an acute pulmonary hypertensive crisis<sup>2</sup>
- pre-existing thrombophilia states (including antiphospholipid syndrome, thrombotic thrombocytopenic purpura).

### 3.2.2 Neurological causes

Neurological causes are the second most common aetiological group of indirect maternal death.<sup>2</sup> The majority of these deaths are epilepsy-related, although intracranial haemorrhage (subarachnoid or intracerebral) and thrombotic strokes do occur during or after pregnancy.<sup>6</sup> For deaths where there is a history of epilepsy, the RCPATH *Guidelines*

on autopsy practice G175: Deaths in patients with epilepsy including sudden deaths, should be consulted.<sup>4</sup> Ideally, in all cases, the brain should be examined by a specialist neuropathologist and appropriate samples should be obtained for toxicological assessment.<sup>6</sup>

### **3.2.3 Sepsis/systemic infections**

Indirect causes of sepsis are those where the focus of sepsis is extra-genital or unrelated to caesarean birth. In recent years in the UK, mothers have died as a result of influenza or COVID-19.<sup>14–15</sup>

### **3.2.4 Psychiatric causes**

Non-suicide psychiatric causes, including deaths as a result of drug or alcohol toxicity, are more often seen in late maternal deaths.

### **3.2.5 Pre-existing diseases where the pregnant state worsens the effect**

Examples of pre-existing diseases where pregnancy worsens the effect include breast or cervical malignancy, HIV/AIDS, tuberculosis, sickle cell disease, connective tissue diseases (e.g. systemic lupus erythematosus), diabetes mellitus or cirrhosis.

## **3.3 Coincidental**

This category includes deaths due to causes such as homicide, accidents (such as road traffic accidents) and malignancies not related to pregnancy or other underlying medical disorders, which have not been affected by the pregnancy.

Pregnancy-associated homicide accounts for a significant number of maternal deaths worldwide. As such, care should be taken to examine the body for any signs of physical injury and, when injuries are found that cannot be accounted for, the pathologist should cease their examination and inform the coroner/procurator fiscal, so that a forensic pathologist may take over at the earliest possible stage.

*[Level of evidence D – Evidence from case series.]*

## **4 Specific health and safety aspects**

There are no specific health and safety aspects, but universal precautions against blood-borne pathogens (e.g. HIV and hepatitis C virus) and respiratory pathogens (e.g. SARS-CoV-2, influenza A and tuberculosis) should be adopted.

*[Level of evidence – Good practice point (GPP).]*

## 5 Pre-autopsy preparation

### 5.1 Performance by specialist maternal death pathologist

If the pathologist is not a specialist in maternal death autopsies and transfer of the case to such a pathologist is not possible/practicable, the advice of such a pathologist should be sought.

### 5.2 Clinical information relevant to the autopsy

The clinical information that is relevant to the autopsy includes:

- all clinical information on the past pregnancy history and current pregnancy, including any delivery, is required. Information on the date and type of influenza and COVID-19 vaccinations is important in relevant cases. When drafting the final report, care needs to be taken over sensitive issues, such as previous terminations and pregnancies, if they may not be known to relatives
- detailed antenatal history, including BMI and gestation at booking, blood pressure readings and results of investigations
- information on the delivery process, e.g. Caesarean, forceps, transfusions, type of anaesthesia
- details of the events leading up to the death
- clinical and drug information on pre-existing medical conditions, including renal disease, cardiac disease, essential hypertension and haematological conditions, such as sickle disease
- relevant family history, including history of thrombosis and thromboembolism or sudden death at a young age
- fetal/neonatal information is also relevant, e.g. infected peripartum, small-for-dates, trauma, Apgar scores
- ideally and with the permission of the coroner/procurator fiscal, if relevant the case should be discussed with the appropriate obstetricians and other clinicians, to establish the major issues; in the case of suspected obstetric trauma, the attendance of the obstetrician at the autopsy may be beneficial.

- pre-mortem laboratory data includes blood cultures, high vaginal swabs, throat swabs for respiratory tract viruses, blood clotting and platelet counts, liver and renal function tests
- a good summary of the history provided should be included in the post-mortem report.

### **5.3 The placenta**

If the placenta was delivered and has not already been disposed of, the coroner's officer/procurator fiscal's office should be asked to obtain it (from the obstetric department or local histopathology department) for the pathologist performing the autopsy to examine macroscopically and microscopically. If the placenta was sent as a surgical specimen to histopathology, the tissue does not fall within the coroner's/procurator fiscal's legal remit, in relation to tissue retention.

### **5.4 The uterus post hysterectomy**

In cases of major obstetric haemorrhage, a peri-mortem hysterectomy may be performed and, as in section 5.3, the coroner's officer/procurator fiscal's office should be asked to obtain the specimen from the local histopathology department (with blocks and slides, if already processed) for the autopsy pathologist to examine, as above.

### **5.5 Ante-mortem blood samples**

In the scenario where a woman dies at home and peri-mortem blood samples are taken by paramedics or in hospital, it may be relevant to ask the coroner's officer/procurator fiscal's office to commandeer these blood samples from the hospital laboratories before they are routinely discarded.

*[Level of evidence – Good practice point (GPP).]*

## **6 The autopsy procedure**

- Full autopsy, including the examination of the cranial cavity, with the pathologist present at the evisceration; weight, height, BMI and ethnicity should be documented in the report. There is an increasing move towards non-invasive radiological post-mortem investigation (PMCT) but a full post mortem, with histology, is strongly advised in maternal death cases.
- Take aerobic and anaerobic blood cultures from an upper body site using sterile technique.

- Consider taking other samples for microbiology/virology: high vaginal swab, sample of the uterine content for microbiology (after sterilising the surface of the uterus), viral respiratory panel nasopharyngeal swab, lung viral swabs/pieces for microbiology and myocardium for the viral myocarditis panel.
- Reserve autopsy blood – untreated and spun – in case of later need for analysis.
- Consider toxicology samples (blood, urine and vitreous humour) if indicated by the history, including compliance with anti-epileptics and anaesthetic deaths.
- Take a sample of snap-frozen splenic tissue (or in suitable sample medium, or alternative material appropriate to your local genetics laboratory requirements) for potential genetic testing (this may be lawfully sensitively disposed of if no longer required, following the full investigation).
- Consider taking samples of renal cortex into glutaraldehyde for electron microscopy in suspected cases of pre-eclampsia/eclampsia.
- If obstetric trauma is suspected, consider retaining the female genital tract eviscerated en bloc (with its vasculature, and the bladder and rectum, if relevant) for optimal evaluation after fixation.
- Take digital photographs (under GMC standards of anonymity) of all relevant pathology.
- In some cases the fetus may be present, either in-situ, or delivered and accompanying the mother. Even if the baby was born alive and subsequently died, the medico-legal authority has potential jurisdiction. However, in the majority of cases, examination of the fetus does not contribute to understanding the cause of the mother's death. Exceptions are in possible sepsis where examination of the fetus may assist in typing, severity and timing of ascending infection, or very rare cases where a fetal malignant tumour has spread to the mother. While an external examination of the fetus may be of assistance to confirm gestation, it would be appropriate to consider seeking permission for this from the relevant authority before undertaking such due to the sensitivity regarding fetal tissue. If necessary, a perinatal pathologist should be asked to conduct an external examination.
- The placenta should be examined if available.

*[Level of evidence D – Evidence from case series.]*

## 7 Specific significant organ systems

- Heart
  - congenital heart disease; acquired disease, including hypertension and myocarditis. Include heart to body weight ratio in post-mortem report (normal ratio is less than 0.5%),<sup>16</sup> comment on number of aortic valve cusps and assess the fossa ovalis/presence of patent foramen ovale.
- Arterial system
  - coronary artery atherosclerosis (assessment of the lumina of the coronary arteries should use the Davies criteria)<sup>17</sup>
  - aneurysms/dissections of aorta, splenic and other arteries.
- Lungs
  - amniotic fluid embolism (see also above section), thromboembolism, fat embolism, pulmonary hypertension, acute lung injury/viral pneumonitis changes.
- Kidney
  - assess histology for hyaline arteriolopathy in systemic hypertension, glomerular endotheliosis in pre-eclampsia/eclampsia and thrombotic microangiopathy.
- Liver
  - fatty liver of pregnancy, pre-eclampsia/eclampsia, haemophagocytosis in sepsis.
- Brain
  - infarction, subarachnoid haemorrhage (with or without berry aneurysm), sagittal sinus thrombosis, meningitis, eclampsia.
- Uterus and genital tract
  - particular attention to possible trauma
  - infection.
- Fallopian tubes and ovaries in cases of ectopic pregnancy.
- Ovaries if ovarian hyperstimulation syndrome considered, or history of polycystic ovaries.
- Placenta

- standard examination, with measurements and weight, and histopathology for inflammation, infection and placental bed arterial lesions (see RCPATH guideline on placental examination).<sup>18</sup>
- Bone marrow
  - haemophagocytosis in sepsis, femoral long bone, and spleen if sickle cell disease (see RCPATH guideline *G159: Autopsy in sickle cell disease and persons with sickle trait*).<sup>19</sup>

[Level of evidence – Good practice point (GPP).]

## 8 Specific maternal death scenarios

### 8.1 VTE

In cases of pulmonary thromboembolism:

- search for the thrombus in the pelvic/lower limb veins
- if none is found, the diameter of the embolus will give a guide as to the calibre of the originating vein
- massive emboli cause sudden death (within a few hours) and are not adherent to the vessel walls
- microscopic examination is essential to attempt to date the thrombus/embolus and to rule out septic embolus and tumour embolus
- the bone marrow should be examined microscopically to exclude myeloproliferative and other disorders.

### 8.2 Hypertensive diseases of pregnancy

In pre-eclampsia (PET)/eclampsia:

- intracerebral haemorrhage
  - major or petechial
- cerebral oedema, hypoxic damage and infarction
  - vasogenic aetiology
- kidney



- glomerular endotheliosis (consider specialist renal histopathology opinion and electronic microscopy)
- liver
  - periportal necrosis and haemorrhage (HELLP syndrome)
- placenta/uterus
  - decidual vasculopathy, placental infarcts, syncytiotrophoblastic knots, etc (consider specialist perinatal histopathologist opinion)
- heart
  - may not show left ventricular hypertrophy, in the absence of pre-existing essential hypertension
- Note: PET/eclampsia deaths may occur in the community between antenatal visits; thus, brain, kidney, liver and placental/uterine histopathology can be critical in making the diagnosis at autopsy

### **8.3 Sepsis/systemic inflammatory response syndrome<sup>20</sup>**

Most genital tract sepsis related deaths occur either in the first trimester or third trimester/puerperium. A proportion of Group A streptococcal sepsis is community-acquired infection via the respiratory tract, with pregnancy possibly making the infection more virulent. The following are the main clinicopathological entities:

- early pregnancy ascending infection, usually by enteric bacteria, e.g. *E. coli*. In unwanted/ concealed pregnancies evidence for self-induced abortion should be sought from the history
- pre-term spontaneous rupture of membranes and ascending infection
- direct infection of the genital tract during or shortly after the delivery
- nasopharyngeal tract (community-acquired) infection, transfer of bacterium to vagina, ascending infection and bacteraemia
- necrotising fasciitis following a genital tract tear
- MRSA infection acquired in hospital
- retained products of conception

- sepsis from an organ not related directly to the genital tract, e.g. pneumonia/lower respiratory tract infection, especially due to influenza or COVID-19, breast (mastitis), Caesarean section skin wound infection, heart valve endocarditis.

## 8.4 Fatal haemorrhage

The commonest cause of persistent per vaginum blood loss post-delivery, associated with oozing from the vascular access lines, and usually associated with maternal collapse during delivery, is disseminated intravascular coagulation triggered by amniotic fluid embolism.

### 8.4.1 From the uterus and adnexae/its vasculature

- First trimester:
  - ectopic pregnancy (histological confirmation is essential, and sample background fallopian tube for chronic salpingitis).
- Second/third trimester:
  - spontaneous uterine rupture
  - placenta praevia
  - placental abruption
  - morbidly adherent placenta (placenta accreta/increta/percreta)
  - traumatic damage to pelvic or abdominal wall vessel during/after Caesarean section.
- From other organs/sites:
  - ruptured aortic aneurysm/dissection
  - ruptured splenic artery aneurysm
  - rupture of hepatic or splenic capsules
  - haemorrhage from liver in HELLP syndrome.

In a proportion of cases of vascular (usually arterial) aneurysm/dissection, an underlying connective tissue disorder is responsible, so material for genetic testing is important. In addition, histology of affected and unaffected vessels to assess structure is always required, including mucin/Alcian blue and EVG staining (assessing mucoid extracellular matrix accumulation, elastic fibre change including fragmentation, loss or thinning, loss of smooth muscle cell nuclei, laminar medial collapse and medial fibrosis).<sup>2</sup>

## 8.5 Amniotic fluid embolism<sup>8,9</sup>

- At post-mortem examination, the point of entry of the amniotic fluid/breach in the uterine lining is rarely identified.
- Amniotic fluid emboli are not visible macroscopically and the appearances are radiologically non-specific. Lung histology (at least 1 block per lobe if suspected) is essential to make the diagnosis.
- If the woman is kept alive on ICU for a prolonged period before death, it is possible that the amniotic fluid emboli may have resorbed by the time of autopsy.
- Fetal anucleate squamous cells, lanugo hairs and meconium (mucin with bile breakdown pigment) can be seen in pulmonary arterial branches on haematoxylin and eosin staining, usually numerous foci per section. The lanugo hairs will also polarise.
- To facilitate their identification, an Attwood's stain (Alcian blue/green phloxine tartrazine) will highlight the mucin, squames and hairs, and a high-molecular weight cytokeratin immunostain (e.g. 34BE12, LP34) will stain the squames (and bronchial epithelial cells, but not alveolar epithelium).
- Rare amniotic fluid emboli in the lungs may be seen in the maternal circulation as a consequence of a normal delivery. Conversely, florid amniotic fluid embolism in the lungs – particularly if also seen in large numbers in other organs, such as the myocardium – should raise suspicion of artefactual displacement of amniotic fluid, most often seen as a consequence of lay cardiac massage during attempted resuscitation. Therefore, the diagnosis of amniotic fluid embolism requires careful correlation with the clinical scenario (see section 3.1).

## 8.6 Deaths related to anaesthesia

- Aspiration pneumonitis.
- Difficulties in airway patency peri- and post-anaesthesia.
- Overdose of opiate drugs for pain.
- Misplacement of epidural anaesthetic.
- Infection introduced by spinal/epidural anaesthesia.
- Other anaesthetic complications such as anaphylaxis, malignant hyperthermia.

## 8.7 Termination of pregnancy

- Criminal or unsafe abortion
  - infection
  - air embolism
  - perforation of uterus.
- Medical or surgical termination
  - uterine rupture from prostaglandin induction
  - trauma to genital tract and perforation of uterus
  - infection
  - air embolism.

## 8.8 Sudden unexpected cardiac death

Cardiac related deaths are among the most common causes of maternal death and detailed macroscopic examination and microscopic examination of the heart is essential. See sections 3.2 and 7, also RCPATH autopsy guideline *G145 Sudden death with likely cardiac pathology*.<sup>21</sup>

## 8.9 Heart failure, peripartum cardiomyopathy and pulmonary flash oedema

The following causes of chronic heart failure developing during pregnancy or the peripartum period should be considered:

- pre-existing hypertensive heart disease
- pre-existing ischaemic heart disease
- pulmonary hypertension due to multiple, small pulmonary thrombo-emboli, or rarely lymphangiitis carcinomatosa
- obesity cardiomyopathy
  - proposed criteria for this are: four chamber dilation, excess cardiac weight, no valve or significant coronary artery disease, no history of diabetes mellitus or hypertension, BMI persistently elevated (over 35) and histological findings of myocyte hypertrophy and minor interstitial/perivascular fibrosis

- peripartum cardiomyopathy
  - this is a diagnosis of exclusion and the pathology findings are often non-specific and essentially those of a dilated cardiomyopathy, with four chamber dilation, myocyte hypertrophy, focal interstitial fibrosis and scattered inflammatory cells in the myocardium<sup>9,22</sup>

Pulmonary 'flash' oedema is rare, but the commonest causes are:

- cardiomyopathy + obesity
- hypertensive heart disease
- PET and acute lung injury
- fluid overload
- transfusion related acute lung injury (TRALI).

## **8.10 Disseminated intravascular coagulation (DIC)**

There are many causes and differential diagnoses.

- Obtain the pre-mortem haematology laboratory results.
- Differentiate between DIC and thrombotic thrombocytopenic purpura (TTP) from the laboratory results and the histopathology (immunohistochemistry for fibrin and CD61 for platelets).
- Consider to prove or exclude as causes of DIC
  - severe sepsis/systemic inflammatory response syndrome (SIRS)
  - uterine atony and other causes of peripartum haemorrhage
  - amniotic fluid embolism
  - pre-eclampsia/eclampsia.

## **8.11 The negative maternal death autopsy<sup>23</sup>**

It is relatively common with maternal death autopsies for a cause of death not to be evident after the macroscopic examination of the organs. Reaching a final conclusion about the likely cause of death on the balance of probabilities requires careful evaluation/re-evaluation of:

- the clinical information, including results of ante-mortem tests; the assistance of an obstetric physician can be invaluable
- the macroscopic findings
- the autopsy histology (see section 10)
- results of other tests (see section 11).

Discussion with a/another maternal death autopsy specialist is highly recommended for complex/difficult cases.

A negative autopsy (including full histology and toxicology) in the correct clinical setting may allow the pathologist to conclude the death was due to SADS. Retention of genetic material for testing and familial screening is vital (see section 3.2).

Note that autopsies performed on patients who collapse from an undetermined event and are then on life support systems in intensive care for weeks or months are unlikely to identify the nature of that event, if pre-mortem investigations have not done so. However SADS (which includes cardiac arrest with resuscitation and ITU care without recovery of consciousness) remains a possibility in this scenario.

*[Level of evidence D – Evidence from case series.]*

## 9 Organ retention guidance to consider

- The genital tract en bloc in cases of suspected trauma.
- The heart in cases of suspected sudden cardiac death with a morphologically normal heart; consider referral for specialist cardiac opinion and taking an appropriate sample, such as snap-frozen splenic tissue, should genetic testing be required (see RCPATH *Guidelines on autopsy practice G145: Sudden death with likely cardiac pathology*).<sup>21</sup>
- The brain in cases of cerebral haemorrhage without specific preceding cause and epileptic deaths (see RCPATH *Guidelines on autopsy practice G175: Deaths in patients with epilepsy including sudden deaths*)<sup>4</sup> and if the clinical scenario is unclear but evidently involves brain death. Examination by a specialist neuropathologist is recommended.

*[Level of evidence – Good practice point (GPP).]*

## 10 Recommended blocks for histological examination – best practice

In addition to sampling of any significant macroscopic lesions/pathology, the following minimum histology blocks are recommended:

- lungs, both (at least upper and lower lobes)
- heart slice with circumferential sampling (see RCPATH guideline *G145: Sudden death with likely cardiac pathology*)<sup>21</sup>
- liver
- kidney
- brain with leptomeninges (at least cerebral cortex, deep grey matter, hippocampus, pons, cerebellum)
- uterus
- placenta (if available) (cord, membranes and placental disc) (see RCPATH guideline *G108: Histopathological examination of the placenta*)<sup>18</sup>
- bone marrow
- spleen
- aorta (in dissection)
- adrenal glands (in suspected sepsis)
- pituitary glands (in suspected Sheehan syndrome).

## 11 Other samples that may be considered

- Microbiology/virology samples (see sections 7 and 8.3).
- Renal cortex for electron microscopy in cases of suspected pre-eclampsia/eclampsia (see sections 7 and 8.2).
- Standard samples for toxicology if illicit drug intake or overdose of medical drugs is a possible factor or if no apparent cause of death is seen at the initial examination (see section 7).
- Blood samples for assessment of anti-epileptic drug compliance.

- Blood sample for mast cell tryptase analysis in suspected anaphylaxis (see RCPATH guideline *G170: Autopsy for suspected acute anaphylaxis*).<sup>12</sup>
- Blood sample and transfused blood sample (in the laboratory) if TRALI is suspected.
- Review of the pathology of any previous surgical resection specimens of relevance to the pregnancy, e.g. a hysterectomy specimen, products of conception, placenta. This may require liaison with other laboratories.
- Appropriate samples for genetic testing if no cause of death identified or if post-mortem findings may indicate a possible hereditary process – e.g. cardiomyopathy channelopathy, connective tissue disorder and for hereditary pro-thrombotic states.

*[Level of evidence – Good practice point (GPP).]*

## 12 The clinicopathological summary and cause of death

This must be comprehensive to assist the clinical team, the coroner/procurator fiscal (if a medico-legal autopsy), MBRRACE-UK, HSIB, local mortality reviews and the family (or their lawyers). The cause of death may be straightforward or complex; it may only be formulated finally at/after an inquest or following procurator fiscal investigation, or if there is to be no inquest and with the permission of the coroner/procurator fiscal, after a multidisciplinary meeting with, for example, the obstetrician, obstetric physician, cardiologist, intensivist, anaesthetist and midwife/nursing team.

The opinion of the pathologist as to the cause of death should be provided in the report in the standard Office for National Statistics (ONS) format (see section 13 for examples). In Scotland, the pathologist should also indicate on the death certificate this was a maternal death by ticking the appropriate box (M1 or M2).

State whether the death is direct, indirect or coincidental in relation to the pregnancy.

*[Level of evidence – Good practice point (GPP).]*

## 13 Example cause of death opinions/statements

- 1a. Massive uterine haemorrhage
- 1b. Uterine atony
- 1c. Recent vaginal delivery at 40 weeks' gestation



- 1a. Amniotic fluid embolism
- 1b. Third trimester vaginal delivery on DD/MM/YY

- 1a. Lung fibrosis
- 1b. Systemic lupus erythematosus
- 2. Pregnancy, delivered spontaneously at 28 weeks' gestation

- 1a. Sepsis due to Group A streptococcal infection
- 1b. Genital tract sepsis following delivery at term pregnancy

- 1a. Liver failure
- 1b. Fatty liver due to antiretroviral therapy for HIV disease, and third trimester pregnancy

- 1a. Pulmonary hypertension
- 1b. Congenital ventricular septal defect with reversed shunt
- 2. Caesarean section delivery at 34 weeks' gestation on DD/MM/YY

- 1a. Acute pulmonary hypertension
- 1b. Disseminated carcinoma of the lung
- 2. Recent delivery at term

- 1a. Acute lung injury and organising pneumonia
- 1b. Complications of general anaesthesia
- 1c. Placenta praevia (Caesarean section on DD/MM/YY), third trimester pregnancy

- 1a. Massive pulmonary arterial thromboembolism

1b. Morbid obesity and third trimester pregnancy.

## 14 Criteria for audit

The following standards are suggested criteria that might be used in periodic reviews to ensure a post-mortem report for coronial autopsies conducted at an institution complies with the national recommendations provided by the 2006 National Confidential Enquiry into Patient Outcome and Death study:

- supporting documentation
  - standards: 95% of supporting documentation was available at the time of the autopsy
  - standards: 95% of autopsy reports documented are satisfactory, good or excellent.
- reporting internal examination:
  - standards: 100% of the autopsy report must explain the description of internal appearance
  - standards: 100% of autopsy reports documented are satisfactory, good or excellent.
- reporting external examination:
  - standards: 100% of the autopsy report must explain the description of external appearance
  - standards: 100% of autopsy reports documented are satisfactory, good or excellent.

A template for coronial autopsy audits can be found on the [RCPath website](#).

## 15 References

1. World Health Organization. *Maternal mortality country profiles*. Accessed May 2023. Available at: [www.who.int/data/gho/data/themes/maternal-and-reproductive-health/maternal-mortality-country-profiles](http://www.who.int/data/gho/data/themes/maternal-and-reproductive-health/maternal-mortality-country-profiles)
2. National Perinatal Epidemiology Unit, University of Oxford. *Saving lives, improving mothers' care core report – Lessons learned to inform maternity care from the UK and Ireland Confidential Enquiries into Maternal Deaths and Morbidity 2018-20, 2022*. Available at: [www.npeu.ox.ac.uk/assets/downloads/mbrance-uk/reports/maternal-report-2022/MBRRACE-UK\\_Maternal\\_MAIN\\_Report\\_2022\\_UPDATE.pdf](http://www.npeu.ox.ac.uk/assets/downloads/mbrance-uk/reports/maternal-report-2022/MBRRACE-UK_Maternal_MAIN_Report_2022_UPDATE.pdf)
3. World Health Organization. *The WHO application of ICD-10 to deaths during pregnancy, childbirth and puerperium: ICD-MM, 2012*. Available at: [https://apps.who.int/iris/bitstream/handle/10665/70929/9789241548458\\_eng.pdf](https://apps.who.int/iris/bitstream/handle/10665/70929/9789241548458_eng.pdf)
4. Thom M, Allinson K. *Guidelines on autopsy practice: Deaths in patients with epilepsy including sudden deaths*. London, UK: The Royal College of Pathologists, 2019. Available at: [www.rcpath.org/static/15a26420-ce7b-4858-ad538b210328d973/G175-Guidelines-on-autopsy-practice-Deaths-in-patients-with-epilepsy-including-sudden-deaths.pdf](http://www.rcpath.org/static/15a26420-ce7b-4858-ad538b210328d973/G175-Guidelines-on-autopsy-practice-Deaths-in-patients-with-epilepsy-including-sudden-deaths.pdf)
5. National Perinatal Epidemiology Unit, University of Oxford. *Saving lives, improving mothers' care – Lessons learned to inform maternity care from the UK and Ireland Confidential Enquiries into Maternal Deaths and Morbidity 2017-19*. Available at: [www.npeu.ox.ac.uk/assets/downloads/mbrance-uk/reports/maternal-report-2021/MBRRACE-UK\\_Maternal\\_Report\\_2021\\_FINAL\\_WEB\\_VERSION.pdf](http://www.npeu.ox.ac.uk/assets/downloads/mbrance-uk/reports/maternal-report-2021/MBRRACE-UK_Maternal_Report_2021_FINAL_WEB_VERSION.pdf)
6. National Perinatal Epidemiology Unit, University of Oxford. *MBRRACE-UK: Saving lives, improving mothers' care – Lessons learned to inform maternity care from the UK and Ireland Confidential Enquiries into Maternal Deaths and Morbidity 2016-18, 2020*. Available at: [www.npeu.ox.ac.uk/mbrance-uk/presentations/saving-lives-improving-mothers-care](http://www.npeu.ox.ac.uk/mbrance-uk/presentations/saving-lives-improving-mothers-care)
7. National Institute for Health and Care Excellence. *Hypertension in pregnancy: diagnosis and management*. Published 2019. Available at: [www.nice.org.uk/guidance/NG133](http://www.nice.org.uk/guidance/NG133)

8. Rath WH, Hofer S, Sinicina I. Amniotic fluid embolism: an interdisciplinary challenge: epidemiology, diagnosis and treatment. *Dtsch Arztebl Int* 2014;21:126–132.
9. Garland J, Little D. Maternal death and Its Investigation. *Acad Forensic Pathol* 2018;8:894–911.
10. Haftel A, Chowdhury YS. *Amniotic Fluid Embolism*. Treasure Island, USA: StatPearls Publishing LLC, 2023.
11. Burton J, Survarna SK. *Guidelines on autopsy practice: Postoperative deaths*. London, UK: The Royal College of Pathologists, 2019. Available at: [www.rcpath.org/static/4b6fdd98-eeaa-4f94-bb8ee9fc10217250/G174-Guidelines-on-autopsy-practice-Postoperative-deaths.pdf](http://www.rcpath.org/static/4b6fdd98-eeaa-4f94-bb8ee9fc10217250/G174-Guidelines-on-autopsy-practice-Postoperative-deaths.pdf)
12. Chambers D, du Parcq J, Sheldon J. The Royal College of Pathologists. *Guidelines on autopsy practice: Autopsy for suspected acute anaphylaxis (includes anaphylactic shock and anaphylactic asthma)*. London, UK: The Royal College of Pathologists, 2018. Available at: [www.rcpath.org/static/47841b6b-891f-450a-b968889ff3e0a7d1/G170-DRAFT-Guidelines-on-autopsy-practice-autopsy-for-suspected-acute-anaphalaxis-For-Consultation.pdf](http://www.rcpath.org/static/47841b6b-891f-450a-b968889ff3e0a7d1/G170-DRAFT-Guidelines-on-autopsy-practice-autopsy-for-suspected-acute-anaphalaxis-For-Consultation.pdf)
13. Okeke TC, Ezenyeaku CCT, Ikeako LC. Peripartum cardiomyopathy. *Ann Medical Health Sci Res* 2013;3:313–319.
14. National Perinatal Epidemiology Unit, University of Oxford. *saving lives, improving mothers' care. Rapid report: Learning from SARS-CoV-2-related and associated maternal deaths in the UK March–May 2020*, 2020. Available at: [www.npeu.ox.ac.uk/assets/downloads/mbrrace-uk/reports/MBRRACE-UK\\_Maternal\\_Report\\_2020\\_v10\\_FINAL.pdf](http://www.npeu.ox.ac.uk/assets/downloads/mbrrace-uk/reports/MBRRACE-UK_Maternal_Report_2020_v10_FINAL.pdf)
15. National Perinatal Epidemiology Unit, University of Oxford. *Saving lives, improving mothers' care: Rapid report 2021: Learning from SARS-CoV-2-related and associated maternal deaths in the UK June 2020–March 2021*, 2021. Available at: [www.npeu.ox.ac.uk/assets/downloads/mbrrace-uk/reports/MBRRACE-UK\\_Maternal\\_Report\\_June\\_2021\\_-\\_FINAL\\_v10.pdf](http://www.npeu.ox.ac.uk/assets/downloads/mbrrace-uk/reports/MBRRACE-UK_Maternal_Report_June_2021_-_FINAL_v10.pdf)
16. Gaitsell K, Perera R, Soilleux EJ. Derivation of new reference tables for human heart weights in light of increasing body mass index. *J Clin Pathol* 2011;4:358–362.
17. Davies MJ. The investigation of sudden cardiac death. *Histopathology* 1999;34:93–98.

18. Evans C, Goodings L, Hargitai B, Heazell A, Jessop F, Marton T *et al.* *Tissue pathway for histopathological examination of the placenta*. London, UK: The Royal College of Pathologists, 2022. Available at: [www.rcpath.org/static/ec614dfa-007c-4a93-8173cb202a071a72/a8b51280-edf3-4414-9197ab58d641bafd/G108-Tissue-pathway-for-histopathological-examination-of-the-placenta.pdf](http://www.rcpath.org/static/ec614dfa-007c-4a93-8173cb202a071a72/a8b51280-edf3-4414-9197ab58d641bafd/G108-Tissue-pathway-for-histopathological-examination-of-the-placenta.pdf)
19. Lucas S, Raine J. *Guidelines on autopsy practice: Autopsy in sickle cell disease and persons with sickle cell trait*. London, UK: The Royal College of Pathologists, 2017 Available at: [www.rcpath.org/static/27824659-5adc-4641-9824e08d6980443f/2d09e2f4-8392-4d54-93adc5f0828001c3/Guidelines-on-autopsy-practice-Autopsy-in-sickle-cell-disease-and-sickle-trait.pdf](http://www.rcpath.org/static/27824659-5adc-4641-9824e08d6980443f/2d09e2f4-8392-4d54-93adc5f0828001c3/Guidelines-on-autopsy-practice-Autopsy-in-sickle-cell-disease-and-sickle-trait.pdf)
20. Wilkinson H. Saving mothers' lives: Reviewing maternal deaths to make motherhood safer: 2006–2008. *BJOG* 2011;118:1402–1403.
21. Sheppard MN, Suvarna SK. *Guidelines on autopsy practice: Sudden death with likely cardiac pathology*. London, UK: The Royal College of Pathologists, 2022. Available at: [www.rcpath.org/static/823dfcf4-8eba-40f7-81b7e174675ecdd9/482ebe54-91c8-4961-bff76b1c01f642cc/Guidelines-on-autopsy-practice-Sudden-death-with-likely-cardiac-pathology.pdf](http://www.rcpath.org/static/823dfcf4-8eba-40f7-81b7e174675ecdd9/482ebe54-91c8-4961-bff76b1c01f642cc/Guidelines-on-autopsy-practice-Sudden-death-with-likely-cardiac-pathology.pdf)
22. Byard R. Maternal, fetal, and neonatal conditions. *In*: Byard R (ed). *Sudden Death in the Young (3rd edition)*. Cambridge, UK. Cambridge University Press, 2010.
23. Lucas S. Difficult diagnoses in maternal death: The negative maternal autopsy. *Medical Research Archives* 2020;8:1–24.

## Appendix A 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	<p>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</p> <p>or</p> <p>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 cancer type.</p>
Grade B	<p>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</p> <p>or</p> <p>Extrapolation evidence from studies described in A.</p>
Grade C	<p>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</p> <p>or</p> <p>Extrapolation evidence from studies described in B.</p>
Grade D	<p>Non-analytic studies such as case reports, case series or expert opinion</p> <p>or</p> <p>Extrapolation evidence from studies described in C.</p>
Good practice point (GPP)	<p>Recommended best practice based on the clinical experience of the authors of the writing group.</p>

## Appendix B AGREE II guideline monitoring sheet

The autopsy guidelines of The Royal College of Pathologists comply with the AGREE II standards for good quality clinical guidelines. The sections of this autopsy guideline that indicate compliance with each of the AGREE II standards are indicated in the table.

AGREE standard	Section of guideline
<b>Scope and purpose</b>	
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
<b>Stakeholder involvement</b>	
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
<b>Rigour of development</b>	
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	All sections
13 The guideline has been externally reviewed by experts prior to its publication	Foreword
14 A procedure for updating the guideline is provided	Foreword
<b>Clarity of presentation</b>	
15 The recommendations are specific and unambiguous	All sections
16 The different options for management of the condition or health issue are clearly presented	All sections
17 Key recommendations are easily identifiable	All sections
<b>Applicability</b>	
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	All sections
20 The potential resource implications of applying the recommendations have been considered	Foreword
21 The guideline presents monitoring and/or auditing criteria	14
<b>Editorial independence</b>	
22 The views of the funding body have not influenced the content of the guideline	Foreword
23 Competing interest of guideline development group members have been recorded and addressed	Foreword