



The Royal College of Pathologists

Pathology: the science behind the cure

## Guidelines on autopsy practice: Post-mortem examination in patients with cerebrovascular disease

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## Contents

Foreword.....	3
1 Introduction.....	4
2 The role of the autopsy.....	4
3 Brain pathology encountered at autopsy.....	5
4 Specific health and safety aspects.....	7
5 Clinical information relevant to the post-mortem examination.....	7
6 The autopsy procedure.....	8
7 Specific organ systems to be considered.....	9
8 Organ retention.....	9
9 Histological examination.....	9
10 Toxicology.....	11
11 Other relevant samples to consider.....	11
12 Imaging.....	11
13 Clinicopathological summary.....	11
14 Example cause of death opinions/statements.....	12
15 Criteria for audit.....	12
16 References.....	13
Appendix A Summary table – explanation of grades of evidence.....	15
Appendix B AGREE II guideline monitoring sheet.....	16



NICE has accredited the process used by the Royal College of Pathologists to produce its autopsy guidelines. Accreditation is valid for five 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 consent and coroner's 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). Nevertheless, much of this can be reviewed against ante-mortem imaging and other data. 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 coroner 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 and participate in the relevant external quality assurance (EQA) scheme.

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 and Wales
- the Home Office Forensic Science Regulation Unit
- the Forensic Pathology Unit
- British Medical Association (BMA).

The information used to develop this autopsy guideline was obtained by undertaking a systematic search of PubMed with ongoing review of cerebrovascular neuropathology literature.<sup>1</sup> Much of the content of the document represents custom and practice and is based on the substantial clinical experience of the authors. Key terms searched included cerebrovascular disease, stroke, autopsy and post-mortem between January 2016 and January 2022. Published evidence was evaluated using modified SIGN guidance (see Appendix A). Consensus of evidence in the guideline was achieved by expert review. Gaps in the evidence were 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 five-yearly cycle. The College will ask the authors of the guideline, to consider whether the guideline 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 two 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 Clinical Effectiveness team, Death Investigation Committee, Neuropathology Specialty Advisory Committee and Lay Network. It was placed on the College

website for consultation with the membership from 20 July to 17 August 2022. All comments received from the membership were addressed by the authors 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 Clinical Effectiveness team and are available on request. The authors of this document have declared that there are no conflicts of interest.

## 1 Introduction

Cerebrovascular disease may present acutely with transient ischaemic attack (TIA) or stroke or as a chronic syndrome such as vascular dementia. The term 'stroke' describes a sudden focal loss of neurological function due to blockage or rupture of a blood vessel supplying the brain. TIA is reserved for cases in which the loss of neurological function resolves within 24 hours.

Cerebrovascular disease often has a direct bearing on the cause of death and clinical diagnosis does not always reliably predict the underlying pathology. Although much more common in the elderly, cerebrovascular disease may affect young people and, in such cases, establishing the underlying pathology may identify inherited, metabolic or toxicological causes.

Stroke is a major cause of morbidity and mortality. In the UK it is the fourth most common cause of death after dementia, cancer and heart disease.<sup>2</sup> Of those surviving a stroke, about 30% die within one year and over 50% within six years.

Cerebrovascular disease is an important cause of, and contribution to, dementia. Vascular dementia is not considered further in these guidelines (see the RCPATH guidelines *Neuropathology autopsy practice: Post-mortem examination in dementia*).<sup>3</sup>

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

The target primary users of this guideline are general pathologists, trainees, forensic pathologists and neuropathologists performing consented and coronial or fiscal post mortems in persons with cerebrovascular disease. The recommendations will also be of value to trainee pathologists, especially those considering the CHAT.

## 2 The role of the autopsy

In cases of death related to cerebrovascular disease, the post mortem may:

- establish whether cerebrovascular disease has caused or contributed to death
- provide correlation with clinical information and radiological studies
- allow for accurate pathological diagnosis
- obtain information relating to the effectiveness of a treatment
- obtain information relevant to the deceased relatives in cases of familial syndromes
- obtain accurate national statistics regarding the incidence of the various pathologies seen in cerebrovascular disease
- support consented research.

Post-mortem examination in a patient with cerebrovascular disease may be performed with consent of the family or under the legal authority of the coroner or procurator fiscal. In either

case, the brain (and sometimes the spinal cord) may be examined by a general or forensic pathologist. Involving a neuropathologist will maximise the information obtained from the autopsy.

In a consented autopsy, examination may be limited to the brain. However, since examination of the heart and great vessels often provides important information, such examinations may limit interpretation.

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

### **3 Brain pathology encountered at autopsy**

Within the context of cerebrovascular disease, various different pathologies may be encountered.

#### **3.1 Atherosclerosis**

Atherosclerosis, affecting extracranial and intracranial arteries, is the most common pathology encountered in cerebrovascular disease. While it mainly affects older patients, it may also affect younger patients. It may cause local occlusion due to thrombus, or atherosclerotic emboli may cause distal obstruction.

#### **3.2 Embolism**

Cardioembolic strokes may be associated with previous myocardial infarction, left ventricular aneurysm, atrial fibrillation, valve disease or (rarely) cardiac tumours such as myxomas. It usually results in a large ischaemic stroke (infarct) in the territory of a large cerebral artery. Paradoxical embolism, in a patient with deep vein thrombosis and a patent foramen ovale, is a rare but important cause of stroke in younger patients. Other causes of embolic infarcts include fat (that may complicate bony fractures or cardiothoracic surgery), air and metastatic malignancy. Iatrogenic strokes caused by the embolisation of materials during neurosurgical or endovascular procedures may have medicolegal implications. In cases of spinal cord infarction after spinal surgery or trauma, fibrocartilaginous embolism should be suspected with appropriate histological sampling.

#### **3.3 Arteriosclerosis and lipohyalinosis**

This affects small arteries and arterioles supplying brain parenchyma. It can cause multiple small areas of (lacunar) infarction, typically around basal ganglia and central white matter. It can also result in diffuse white matter degeneration (Binswanger's disease) and can be associated with vascular dementia. It can result in vessel rupture and fatal intracerebral haemorrhage, typically in the region of the basal ganglia and, more rarely, the brainstem and cerebellum (hypertensive brain haemorrhage).

#### **3.4 Aneurysms and vascular malformations**

These are important causes of both subarachnoid and parenchymal haemorrhage, especially in younger patients. Examples include arteriovenous malformations (AVMs), cavernomas, arterial dural fistulas and saccular (berry) aneurysms. Infective (mycotic) aneurysms may be related to bacterial or fungal sepsis.

#### **3.5 Amyloid angiopathy**

Amyloid deposition within the walls of leptomeningeal and cerebral arteries can result in haemorrhage. The typical haemorrhagic manifestation of cerebral amyloid angiopathy (CAA) is lobar haemorrhage, a more superficial haematoma usually extending through the cortical

surface into the subarachnoid space. CAA is associated with Alzheimer's disease but can occur in the absence of Alzheimer's pathology. Rare familial cases can occur.

### **3.6 Hypoperfusion injury**

A reduction in cerebral perfusion due to systemic hypotension and/or raised intracranial pressure can result in watershed infarcts (often bilateral) and cortical laminar necrosis.

### **3.7 Herniation infarcts**

Uncal and cingulate herniation, in the context of critically raised intracranial pressure, can result in posterior and anterior cerebral artery infarcts respectively.

### **3.8 Arterial dissection and fibromuscular dysplasia**

Arterial dissection may be traumatic or spontaneous and usually occurs in the extracranial arteries (carotids and vertebrals). It presents as either an ischaemic stroke or, if intracranial arteries are involved, a subarachnoid haemorrhage. Fibromuscular dysplasia can predispose to arterial dissection.

### **3.9 Vasculitis**

Cerebral vessels may be involved in the context of systemic vasculitis such as Behcet's disease, or in primary angiitis of the central nervous system (PACNS). Leptomeningeal vasculitis can also be associated with CAA. Giant cell arteritis can rarely involve the anterior ophthalmic, posterior ciliary, central retinal arteries as well as the vertebral arteries, the latter resulting in posterior circulation strokes. Certain CNS infectious disease can cause vasculitis. These include bacterial and tuberculous meningitis, the latter classically associated with endarteritis obliterans, as well as viruses such as varicella zoster and HIV.<sup>4</sup>

### **3.10 Vasospasm**

This may lead to cerebral ischaemia. It can be a delayed complication of subarachnoid haemorrhage and has also been described in association with certain drugs, including cocaine and amphetamines.

### **3.11 Coagulopathies**

These can be iatrogenic (anti-coagulation, thrombolysis), thrombocytopenic complications of leukaemia and disseminated intravascular coagulation, etc. Thrombophilia syndromes (e.g. anti-phospholipid syndrome, protein S deficiency, protein C deficiency and Leiden mutation, etc.) as well as certain drugs (such as the oral contraceptive pill) can predispose to thrombosis and ischaemic stroke.<sup>5</sup>

### **3.12 Rarer causes of cerebrovascular disease**

A range of rare inherited disorders can predispose to cerebrovascular disease. These include cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy, autoimmune diseases such as Susac syndrome and mitochondrial disorders such as mitochondrial encephalopathy, lactic acidosis and stroke-like episodes. Sickle cell disease is a cause of both cerebral infarction and subarachnoid haemorrhage.<sup>6</sup> See the RCPATH *Guidelines on Autopsy practice: Autopsy in sickle cell disease and persons with sickle cell trait*.<sup>7</sup>

### **3.13 Potential mimics of cerebral infarction**

Potential mimics of cerebral infarction, both clinically and on macroscopic examination, should be considered and excluded with appropriate histological sampling.<sup>8</sup> Examples include infective pathologies such as herpes encephalitis, bacterial cerebritis, mycobacterial disease such as tuberculosis, fungal cerebritis and toxoplasmosis. Histological sampling around the edges of a necrotic lesion will help to rule out primary and metastatic neoplasia as a potential mimic of infarction and spontaneous haemorrhage. Vascular dementia has a broad differential that includes neurodegenerative conditions such as Alzheimer's disease, Lewy body disease, frontotemporal lobar degeneration and prion disease.

### **3.14 COVID-19**

COVID-19 has been linked with cerebral infarction and haemorrhage associated with microvascular thrombi and this may relate to the hyperinflammatory and hypercoagulable states seen in severe cases of COVID-19.<sup>9</sup> There is an emerging link between certain SARS-CoV-2 vaccines and vaccine-induced thrombotic thrombocytopenia, commonly including cerebral venous sinus thrombosis.<sup>10</sup>

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

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

No specific precautions beyond general protocols.

## **5 Clinical information relevant to the post-mortem examination**

As in any autopsy, it is important to review the clinical case notes and any relevant radiological imaging. It is useful to have details in relation to:

- specific neurological symptoms and signs to inform neuroanatomical examination and sampling
- any available neuroradiological imaging to inform neuroanatomical examination and sampling
- full details of treatment, especially where anticoagulation therapy, radiological or neurosurgical intervention has taken place
- family history – some rare cerebrovascular diseases have a genetic component, knowledge of this will allow planning for archiving fresh material for appropriately consented genetics
- social, drug and general medical history – systemic vasculopathies such as vasculitis, may affect the CNS. Abuse of certain drugs may be complicated by cerebral infarction
- cranial or craniocervical traumatic injury may be complicated by arterial dissection and ischaemic stroke
- neurosurgical and endovascular procedures can be complicated by cerebral haemorrhage or infarction.

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

## 6 The autopsy procedure

A full anatomical examination should be performed within the limits of the available consent or medicolegal authority. The brain and, when indicated, the spinal cord should be removed. If indicated and permitted, the brain should be fixed in formalin for later dissection after any necessary sampling of fresh tissue. If brain retention is not authorised/consented, dissection and examination in the fresh state should be achieved, with sampling if permitted.

### 6.1 External examination

Immobility may have predisposed the patient to pressure sores. Dysphagia may have been treated with nasal or percutaneous feeding tubes. Petechial skin rash may be encountered in cases of systemic vasculitis or fat embolism syndrome.

### 6.2 Internal examination

A full anatomical examination should be performed, within the limits of consent. There should be a standard dissection and macroscopic description of each organ system, including measurement of organ weights. A macroscopic cause of death should be sought, and where necessary, supported by histological examination. A common cause of death in stroke is the development of an aspiration or bronchopneumonia.

#### 6.2.1 Head and neck

- The scalp should be examined for any bruises or other injury.
- The skull should be examined for any fractures.
- The dura should be examined for any evidence of acute or old haemorrhage.
- The dural venous sinuses should be opened and examined for thrombosis or other pathologies.

#### 6.2.2 Cardiovascular system

- The carotid arteries should be examined for atheroma, thrombus or dissection with a particular focus on the carotid bifurcation.
- The heart should be carefully examined for a cardioembolic source of stroke. This includes mural thrombus (in association with left ventricular aneurysm, old myocardial infarction etc.), atrial thrombus (often in association with atrial fibrillation), endocarditis, patent foramen ovale (in cases of paradoxical embolism).
- In cases of posterior circulation stroke, the vertebral arteries should be examined throughout their entire length.<sup>5,11,12</sup> The temporal arteries can be examined in cases of suspected temporal arteritis.

#### 6.2.3 Respiratory system

Bronchopneumonia is a common cause of death in patients with cerebrovascular disease. Aspiration pneumonia is predisposed in cases of bulbar palsy.

#### 6.2.4 Bone marrow

In haemorrhagic lesions with no obvious explanation, the possibility of a blood dyscrasia should be investigated with bone marrow examination.<sup>13</sup>

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



## 7 Specific organ systems to be considered

- Central nervous system.
- Cardiovascular system.
- Respiratory system.
- Haematological system.
- Renal system.

## 8 Organ retention

In some cases of cerebrovascular disease, such as hypertensive haemorrhages and aneurysmal subarachnoid haemorrhage, a reliable cause of death can often be established by macroscopic examination alone. In cases of aneurysmal subarachnoid haemorrhage, for example, examination in the fresh state is preferable as formalin fixation will harden the blood making later examination much more difficult. In other cases of cerebrovascular disease, with the appropriate consent or coronial, fiscal or other relevant legal authority, it may be necessary to retain the brain for fixation to establish an accurate diagnosis.<sup>8,10</sup> It should be noted that very acute cerebral infarction can often only be appreciated as subtle softening in well-fixed white matter.

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

### 8.1 Recommended practice

A case should be made for whole brain retention with fixation for two to three weeks and referral to a neuropathologist.<sup>5,11</sup>

In cases where there is no consent or coronial authority to retain the brain, the following options should be considered:

- macroscopic examination of the fresh brain. This is often sufficiently informative to allow for a confident cause of death statement. When this is not the case, the limitations should be explained to those authorising the procedure.
- the brain may be retained in formalin for a period of 24 to 48 hours and then sectioned in the standard way. This will allow for a more detailed examination and relevant sections can be taken for histological examination. The brain can then be returned to the body for burial or cremation.
- retention of relevant blocks sampled in the fresh state. It should be explained that no material will be retained outside the paraffin blocks. The potential limitations should be explained to those authorising the procedure.<sup>8,10</sup>

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

## 9 Histological examination

### 9.1 Brain cut

The brainstem and cerebellum should be removed by an axial slice through the midbrain. The cerebellum should be removed from the brainstem by cutting through the three pairs of cerebellar peduncles. The brainstem can now be sliced in the axial plane. The cerebral

hemispheres should be sliced in the coronal or horizontal plane at approximately 0.5–1 cm intervals. The following key elements should be assessed:

- leptomeninges
  - subarachnoid blood – distribution (diffuse or localised; basal or supratentorial)
- basal arteries
  - anatomically complete circle of Willis and anatomical variations (which may affect infarct distribution)
  - involvement by atherosclerosis or thrombosis – specify degree of narrowing
  - aneurysms – ruptured or unruptured? Berry or fusiform? Atherosclerotic?
- brain herniation (raised intracranial pressure)
  - uncal (transtentorial) herniation
  - tonsillar herniation
  - cingulate (subfalcine) herniation
  - midline shift
- brain swelling
  - gyral flattening/sulci narrowing – regional or generalised
- cerebral infarcts
  - site
  - size
  - acute or old
  - arterial territory
- cerebral haematoma
  - site – deep (ganglionic) or lobar (frontal, temporal, etc.); haematomas associated with systemic hypertension are usually ganglionic but can be pontine or cerebellar
  - size
  - secondary involvement – e.g. of ventricles, subarachnoid space
  - associated vascular malformations, tumours, etc.

## 9.2 Block selection

Histological sampling of grossly abnormal areas should be undertaken. The following blocks should be considered:

- middle frontal gyrus to look at perfusion boundary zone
- putamen and globus pallidus to look at deep small vessels
- hippocampus and parahippocampal gyrus (vulnerable in hypoxia/ischaemia)
- occipital cortex to look at perfusion boundary zone
- midbrain to look at changes due to mass effect
- pons to look at changes due to mass effect as well as small vessel disease
- medulla to look at changes due to mass effect
- cerebellar hemisphere to look at perfusion boundary zone

- samples of a haematoma or infarct to look for a possible cause and provide evidence of timing
- local vessels supplying pathological area to look for a possible cause.

The spinal cord should be examined in cases where it is suspected clinically to be involved in vascular disease.

All blocks should be stained with haematoxylin and eosin (H&E). A myelin stain might be useful for neuroanatomical assessment. Elastic Van Gieson or similar will demonstrate abnormal vascular structures such as AVMs and berry aneurysms. Staining with Congo red or immunohistochemistry for beta-amyloid will be helpful in cases of suspected amyloid angiopathy.<sup>5,11</sup>

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

## **10 Toxicology**

Appropriate samples should be taken for toxicology where a stroke may be linked to recreational drug use (see RCPATH *Guidelines on autopsy practice: Autopsy when drugs or poisoning may be involved*).<sup>12</sup>

## **11 Other relevant samples to consider**

Fresh tissue such as spleen should be preserved in the context of a suspected genetic cause.

## **12 Imaging**

Radiological imaging can be a useful adjunct in the post-mortem examination of cerebrovascular diseases. Post-mortem magnetic resonance imaging may highlight areas of white matter change secondary to vascular disease that cannot be easily appreciated macroscopically. Microinfarcts and microhaemorrhages may also be evident which allow a more accurate quantification of the extent of cerebrovascular disease and target any histological sampling.<sup>5,13,14</sup>

## **13 Clinicopathological summary**

The clinicopathological summary should be clear and concise. Only statements of fact should be provided. The macroscopic and microscopic findings should be clearly outlined and considered in the context of the clinical history provided. It is important to consider the mechanism of death in cerebrovascular disease. Large cerebral haemorrhages and infarcts may precipitate death acutely by a mechanism of raised intracranial pressure. In most cerebrovascular disease-related deaths, immobility and or dysphagia will predispose to hypostatic and aspiration pneumonia or other infective process. In such cases, the stroke may precede death by a long-time interval while still being a necessary antecedent in the cause of death sequence.

Strokes may predispose to seizures and therefore epilepsy-related deaths including sudden unexpected death in epilepsy (see the RCPATH *Guidelines on autopsy practice: Deaths in patients with epilepsy including sudden deaths*).<sup>15</sup> In these cases, the stroke may precede death by a long-time interval while still being a necessary antecedent in the cause of death

sequence. Old, subacute and even acute cerebral infarcts that have no direct bearing on the cause of death can be encountered at autopsy.

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

## 14 Example cause of death opinions/statements

- 1a. Aspiration pneumonia
- 1b. Left frontal lobar haematoma
- 1c. Cerebral amyloid angiopathy
  
- 1a. Subarachnoid haemorrhage
- 1b. Ruptured right middle cerebral artery aneurysm
  
- 1a. Bronchopneumonia
- 1b. Cerebral infarct
- 1c. Right middle cerebral artery thrombosis
  
- 1a. Sudden unexpected death in epilepsy
- 1b. Previous right middle cerebral artery infarct

## 15 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 \(NCEPOD\) study](#):

- supporting documentations:
  - 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 Royal College of Pathologists' website.

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## 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 population.</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.

<b>AGREE standard</b>	<b>Section of guideline</b>
<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	2–14
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	2–14
16 The different options for management of the condition or health issue are clearly presented	2–14
17 Key recommendations are easily identifiable	2–14
<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	2–14
20 The potential resource implications of applying the recommendations have been considered	Foreword
21 The guideline presents monitoring and/or auditing criteria	15
<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