

TITLE: **THE SCOTTISH CLINICAL GUIDELINES AND INTEGRATED  
CARE PATHWAYS FOR MARFAN SYNDROME**

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SHORT TITLE: SCOTTISH MARFAN SYNDROME CLINICAL GUIDELINES

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## **ABSTRACT**

Marfan syndrome is an autosomal dominant multisystem disorder usually associated with mutation in the fibrillin gene on chromosome 15. Diagnosis remains clinical. Improvements in morbidity and mortality have been associated with improved prophylactic medical and surgical treatment. Important issues in Marfan syndrome include the correct identification of patients for medical surveillance and intervention, and the fragmentation of care which can occur in a multisystem disorder. A systematic literature review was undertaken, and clinical guidelines based on this review were drafted by expert groups. The guidelines were agreed at a Scottish clinical genetics meeting and integrated care pathways were devised. For genetic disorders where aspects of clinical practice may not have a secure evidence base, the use of guidelines based on multidisciplinary consensus agreement may have a useful role in providing a foundation for quality of care.

## **KEY WORDS**

Marfan syndrome, clinical guidelines, care pathway

## INTRODUCTION

Marfan syndrome is a variable, autosomal dominant connective tissue disorder, affecting mainly the cardiovascular system, eyes, and skeleton. Life expectancy is primarily determined by the severity of cardiovascular involvement, and has improved between 1972<sup>1</sup> and 1995<sup>2</sup>, partly attributable to prophylactic medical and surgical intervention. It is associated with mutation in the Fibrillin 1 gene on chromosome 15<sup>3</sup> except in one family linked to chromosome 3<sup>4</sup>. Accurate diagnosis is important to target prophylactic beta blockade<sup>5</sup> and aortic root surveillance. As nearly all cases have private fibrillin mutations, 27% are due to new mutation<sup>7</sup>, and because of locus heterogeneity<sup>4</sup>, molecular testing is of limited help unless the family is large enough for linkage analysis. Clinical evaluation remains fundamental to diagnosis, and is usually based on either the Berlin<sup>8</sup> or Gent<sup>9</sup> nosology. Like most genetic disorders, Marfan syndrome is relatively rare, affecting around 1 in 10000 live births<sup>7</sup>. The practise of evidence-based medicine depends on the integration of individual clinical expertise with the best external evidence<sup>10</sup>, yet the acquisition of such expertise and the generation of evidence through systematic research may be difficult in a rare disorder. As a result, family members attending different medical centres may be offered different medical advice, if clinical diagnostic criteria and management policies differ significantly between centres. In Scotland, clinical genetics services are based in four regional centres in Aberdeen, Dundee, Edinburgh and Glasgow. The Scottish Clinical Genetics Guidelines Group was established as part of a project to devise evidence-based clinical guidelines and integrated care pathways to address these issues for 5 genetic disorders including Marfan syndrome<sup>11</sup>. In this article, we describe clinical guidelines for the diagnosis and management of Marfan syndrome, and their development.

## METHODS

The guidelines were developed following the processes and criteria devised by the Scottish Intercollegiate Guidelines Network, which requires “systematic reviews to identify and synthesise evidence, development by multidisciplinary groups, including representatives from all key disciplines, and explicit links between evidence and recommendations”<sup>12</sup>. The recommendations were graded according to the level of evidence available from the literature and from expert opinion (Table 1). A systematic search for Marfan syndrome literature was performed using the MedLine, PubMed and OMIM databases. 2968 +34 articles were identified and abstracts reviewed by one of us (JD). Single case reports were mostly excluded, but 298 + 32 articles describing specific aspects of Marfan syndrome including trials of treatment, management topics, studies of series of patients, molecular testing, diagnostic criteria and the natural history of Marfan syndrome were selected for more detailed review by specialist subgroups. The subgroups reviewed assessment and diagnosis, cardiovascular system, ocular system, skeletal system, respiratory system, and pregnancy, although there was some overlap between subgroups. For example, thoracic surgery was reviewed by both the cardiovascular and respiratory subgroups. The guidelines drafted by the subgroups were discussed and amended at a Scottish meeting, and then reviewed by an international panel of Marfan syndrome experts. Based on these guidelines, integrated care pathways for diagnosis, management and pregnancy care were devised as part of the patient’s hospital case record. The guidelines shown below in bold print are the result of this process, and the letter in brackets refers to the grade of recommendation, depending on the level of evidence available (Table 1).

## THE MARFAN SYNDROME GUIDELINES

### 1 INITIAL ASSESSMENT AND DIAGNOSIS

Of the two major clinical assessment systems in use, the Berlin<sup>8</sup> and Gent nosologies<sup>9</sup>, the former is simpler to use in the clinic, but the latter is more precisely defined, and allows skeletal features and aspects of the family history and genetic testing to be taken more fully into consideration.

<b>1 (a)</b>	<b>The diagnosis of Marfan syndrome should be made on the basis</b>	<b>Grade B</b>
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	<b>of the Marfan nosology.</b>	
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Family history suggesting new mutation<sup>13</sup> or severe aortic involvement<sup>14</sup> predicts reduced life expectancy. Many Marfan features (echocardiographic findings<sup>5, 15-18</sup>, ectopia lentis<sup>19</sup>, scoliosis<sup>19-21</sup>, upper-lower segment ratio, protrusio acetabulae<sup>22</sup>) show age dependent penetrance<sup>23</sup> necessitating careful clinical evaluation. Aortic dimension measured by transthoracic echocardiogram at the sinus of valsalva and related to normal values based on age and body surface area (BSA)<sup>9, 24</sup>, is of prognostic value in an affected patient<sup>17, 24-26</sup>. Other imaging techniques such as transoesophageal echocardiography<sup>27</sup>, or MRI scanning<sup>16, 28</sup> may be considered.

<b>1 (b)</b>	<b>The initial assessment should include the following: personal history, detailed family history, clinical examination including ophthalmology examination, transthoracic echocardiogram.</b>	<b>Grade C</b>
<b>1 (c)</b>	<b>The echocardiogram should include measurement of the aortic diameter at the Sinus of Valsalva, and this dimension should be related to normal values based on age and body surface area.</b>	<b>Grade B</b>
<b>1 (d)</b>	<b>The development of scoliosis and protrusio acetabulae is age dependent, commonly occurring following periods of rapid growth. X-ray examination for these features should be considered in those of the appropriate age, if a positive finding would make the diagnosis of Marfan or if other clinically important decisions depend on the findings. Consideration may also be given to pelvic MRI scanning in adults to detect dural ectasia for similar reasons.</b>	<b>Grade B/C</b>

To address the related diagnostic dilemmas of younger patients with a family history of Marfan syndrome who do not fulfil the diagnostic criteria, and younger Marfan-like patients with no family history who do not fulfil the diagnostic criteria by one system, we suggest repeat evaluations until age 18, to avoid missing the evolving diagnosis, whilst not stigmatising children and adolescents who may be unaffected.

<p><b>1 (e)</b></p>	<p><b>Younger patients with a positive family history who do not manifest sufficient clinical features to fulfil the diagnostic criteria for affected status, and in whom DNA testing is not successful, and younger patients with no family history, who fall short of fulfilling the diagnostic criteria by one system only, should have further clinical evaluations pre-school, before puberty and at age 18 or more frequently, particularly around puberty, as the clinical situation dictates.</b></p>	<p><b>Grade C</b></p>
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### **Differential diagnosis**

Homocystinuria, (autosomal recessive) is characterised by raised urinary homocysteine excretion. Congenital Contractural Arachnodactyly or Beals Syndrome (autosomal dominant) includes joint contractures and ear anomalies, and is usually caused by mutation in fibrillin 2<sup>29</sup>. MASS phenotype (Mitral valve prolapse, Aortic dilatation, Skin involvement, Skeletal involvement) may be due to fibrillin-1 mutation<sup>3</sup>, yet the risk of aortic aneurysm rupture seems low. The Lujan-Fryns<sup>30</sup> syndrome is an X-linked mental handicap disorder with Marfanoid skeletal findings. In the Shprintzen-Goldberg syndrome<sup>31</sup>, (autosomal dominant) craniosynostosis occurs with Marfanoid skeletal features, sometimes with fibrillin 1 mutation<sup>32</sup>. The above disorders can be distinguished from Marfan syndrome by their clinical findings or biochemistry, even although some may be due to fibrillin 1 mutation. Autosomal dominant ectopia lentis with or without fibrillin 1 mutation<sup>33</sup> and hereditary aortic aneurysm, when not fulfilling either the Berlin or Gent nosologies, are not covered by these guidelines.

## MANAGEMENT OF THE MARFAN SYNDROME PATIENT

### 2 CARDIOVASCULAR SYSTEM

Marfan syndrome mortality from complications of aortic root dilatation has decreased (70% in 1972, 48% in 1995) and life expectancy has increased (mean age at death  $41 \pm 18$  versus  $32 \pm 16$  years)<sup>2</sup>, associated with increased medical and surgical intervention. Risk factors for aortic dissection include increased aortic diameter<sup>2,24</sup>, rate of aortic dilatation, and family history of aortic dissection<sup>14</sup>. Studies in turkeys prone to aortic dissection showed improved survival when treated with propranolol<sup>34,35</sup>. Studies of  $\beta$  blocker treatment in Marfan patients have shown a reduced rate of aortic dilatation with propranolol<sup>5</sup> and with atenolol<sup>36</sup>. Analysis of other studies suggests the effect is greatest in younger patients with less dilated aortas<sup>5,37</sup>. The Marfan aorta has abnormal elastic properties, with relatively increased stiffness at all ages<sup>15</sup>, although this is less evident in children<sup>38</sup>. Reduced left ventricular ejection force after  $\beta$  blocker therapy is thought to be the mechanism of reduced aortic dilatation rate<sup>39</sup>.

<b>2 (a)</b>	<b>Beta blocker therapy should be considered in any Marfan patient with aortic dilatation at any age..</b>	<b>Grade A</b>
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Aortic root dilatation leading to aortic dissection and/or aortic valve dysfunction usually occurs first at the sinus of Valsalva<sup>24</sup>. Comparative studies suggest a better outcome with early aortic root surgery, than with later or emergency surgery<sup>40</sup>, and prophylactic surgery is considered in an adult when the diameter at the sinus of Valsalva exceeds 5.5 cm<sup>9,25,26</sup>. In childhood, prophylactic surgery is recommended when the aortic diameter exceeds 5cm<sup>41</sup>. Marfan syndrome may affect the function of any heart valve and give rise to symptoms, for which valve surgery may be indicated in children and adults<sup>9,25,41</sup>, but consideration of this is beyond the scope of this guideline.

<b>2 (b)</b>	<b>Marfan patients should be referred for consideration of prophylactic aortic root replacement when the aortic root at the Sinus of Valsalva exceeds 5 cm in an adult or child.</b>	<b>Grade B</b>
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### **Cardiovascular follow-up**

At least annual evaluation with clinical history and examination and trans-thoracic echocardiography<sup>24,25, 42</sup> is recommended, with additional assessments as clinically indicated (e.g. ECG, CXR, Holter, trans-oesophageal echo). The rate of change of the aortic diameter is also of prognostic significance<sup>17, 25, 43</sup> and should influence follow-up intervals<sup>43</sup>.

<b>2 (c)</b>	<b>Marfan patients of all ages should be offered at least annual evaluation with clinical history, examination and transthoracic echocardiography. In children, serial trans thoracic echocardiography at 6 -12 month intervals is recommended, the frequency depending on the actual aortic diameter (in relation to body surface area) and the rate of increase.</b>	<b>Grade B</b>
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### **3 SKELETAL SYSTEM**

60 % of patients have scoliosis<sup>43</sup>. Rapid progression during growth spurts<sup>19, 43</sup> is common, leading to marked deformity, pain and a restrictive ventilatory deficit. Occasionally scoliosis can be progressive in adult life especially if the angle of curvature is >40°.

<b>3 (a)</b>	<b>Even if there is no clinical scoliosis children should have an erect A-P plain X-ray film of the spine with gonadal shielding before puberty (growth spurt) i.e. between the ages of 8 - 11 years of age.</b>	<b>Grade C</b>
<b>3 (b)</b>	<b>A child with a clinical scoliosis requires formal orthopaedic assessment, and 6 monthly orthopaedic follow-up until the growth spurt is completed is recommended<sup>19</sup>.</b>	<b>Grade B</b>

<b>3 (c)</b>	<b>Adults with angle of curvature is <math>&gt;40^{\circ}</math> (measured on X-ray) should be referred to the orthopaedic department for indefinite follow-up (minimum yearly).</b>	<b>Grade B</b>
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**Height**

Final adult height in girls may be reduced by prescribing oestrogens before puberty<sup>44</sup>. Only a very few Marfan patients have been treated in this way. Neither the psychological consequences of induced puberty nor the physical affects of oestrogens on the aortic root are fully known. This treatment is not recommended as a routine.

**Bone mineral density**

There is no strong evidence that women with Marfan Syndrome have low bone mineral density and therefore routine bone densitometry on the grounds of Marfan Syndrome alone is not recommended<sup>45</sup>.  
<sup>46</sup>.

**Joint laxity**

There have been no trials studying sports limitation in Marfan syndrome to limit joint damage. Studies in patients with joint laxity of undefined cause have failed to demonstrate an increased risk of premature osteoarthritis, although certain sports such as gymnastics are associated with an increased frequency of joint injury<sup>47</sup>. Patients should be advised that sports can be undertaken, but if any joints are more painful that would be expected the activity should not be repeated (see also respiratory system guideline (d)).

#### 4 OCULAR SYSTEM

Ocular features of Marfan syndrome include bilateral ectopia lentis (40.7%), myopia (28%) and retinal detachment (0.78%)<sup>48</sup>. Other studies suggest up to 80% of Marfan patients have bilateral lens subluxation and dislocation into the anterior chamber may occur<sup>19, 20, 49</sup>. Subluxation may occur in utero<sup>20</sup>, in childhood<sup>42</sup> or later in the second decade<sup>19</sup>. Myopia because of increased length of the globe is associated with an increased risk of retinal detachment. Early detection and correction of refractive errors before the age of 12 years helps prevent amblyopia,<sup>50</sup>. Marfan patients may have a flat cornea (keratometer reading <42)<sup>51</sup> which is also found in other connective tissue disorders such as Ehlers-Danlos Syndrome<sup>20</sup>.

<b>4 (a)</b>	<b>When there is a family history, initial examination by an ophthalmologist should take place at three to six months of age with cycloplegia to look for evidence of lens dislocation, anterior chamber problems and incipient retinal detachment.</b>	<b>Grade B</b>
<b>4 (b)</b>	<b>When there is no family history, examination by an ophthalmologist should form part of the initial clinical assessment of the patient.</b>	<b>Grade B</b>
<b>4 (c)</b>	<b>To detect later changes in refraction in Marfan patients, such as those caused by later childhood lens subluxation, and to prevent amblyopia, annual review by an orthoptist or optometrist until the age of 12 is recommended.</b>	<b>Grade B</b>
<b>4 (d)</b>	<b>Families should be informed about the risk of retinal detachment and glaucoma, to that they can seek appropriate advice promptly should symptoms develop.</b>	<b>Grade B</b>

#### CENTRAL NERVOUS SYSTEM

Dural ectasia of the lumbosacral region is a major criterion for the diagnosis of Marfan syndrome in both nosologies<sup>8, 9</sup> affecting around 63% of adults<sup>52</sup>, but is rarely symptomatic and requires MRI or CT investigation for evaluation. It may be less common in children. Anterior sacral meningocele has been described rarely in Marfan syndrome, and may lead to diagnostic confusion when presenting as a pelvic

or abdominal mass<sup>53,54</sup>. There is no increased frequency of intracranial aneurysm in Marfan syndrome. No specific guideline has been devised for this system.

## 5 RESPIRATORY SYSTEM

### **Pectus excavatum**

This affects approximately two thirds of patients<sup>55</sup>. Moderate to severe pectus excavatum can be associated with a restrictive ventilatory defect<sup>56</sup>. It can also hamper cardiac surgical procedures<sup>57</sup> but correction is most often requested for cosmetic reasons. Delayed wound healing is common<sup>58</sup>. Recurrence following surgical correction is associated with young age at initial surgery and lack of temporary internal stabilisation<sup>59</sup>.

<b>5 (a)</b>	<b>Pulmonary function tests, with measurements related to sitting height, should form part of the assessment of pectus deformity.</b>	<b>Grade B</b>
<b>5 (b)</b>	<b>Surgical repair of pectus excavatum should be delayed, if possible, until late adolescence, and should include internal stabilisation to reduce the risk of recurrence.</b>	<b>Grade B</b>
<b>5 (c)</b>	<b>If cardiac and pectus surgery are required as elective procedures, surgical repair of pectus excavatum should precede cardiac surgery by several months for optimal functional and cosmetic results.</b>	<b>Grade C</b>

### **Pneumothorax**

Spontaneous pneumothorax occurs in 4 to 11%<sup>60,61</sup> of patients and may be associated with apical bullae. Recurrence is common, necessitating a low threshold for surgical intervention. Activities such as scuba diving should be avoided.

<b>5 (d)</b>	<b>Contact sports or those involving isometric exercise should be avoided, to protect the aorta, and diving should be avoided to reduce the risk of pneumothorax.</b>	<b>Grade C</b>
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### **Neonatal pulmonary emphysema**

Mechanical ventilation can exacerbate the respiratory difficulties in a Marfan neonate due to the increased risk of pneumothorax, bullae and emphysema.

**Sleep apnoea**

Patients with Marfan syndrome have an increased tendency to upper airway collapse during sleep, causing obstructive sleep apnoea. This may contribute to daytime somnolence, often attributed to beta-blocker therapy.<sup>62, 63</sup>

<b>5 (e)</b>	<b>Patients with nocturnal snoring or daytime somnolence should be considered for investigation of sleep apnoea.</b>	<b>Grade B</b>
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## 6 PREGNANCY

The two major issues in pregnancy are the risk of cardiovascular complications in an affected mother and of transmission of Marfan syndrome to the fetus.

### **Prenatal diagnosis**

The offspring of a Marfan parent have a 50% risk of inheriting the disorder. In one study, 18/23 affected individuals expressed an interest in prenatal diagnosis<sup>64</sup>. Mutation detection or linkage can be used for prenatal diagnosis in some families<sup>65</sup>. Ultrasound is unreliable.<sup>66</sup>

### **Assessment of the newborn**

Early diagnosis allows surveillance for complications but firm diagnosis may not be possible at birth.

### **Maternal complications of pregnancy**

The risk of aortic dissection in pregnancy is greatly increased, and may be due to inhibition of collagen and elastin deposition in the aorta by oestrogen, and the hyperdynamic hypervolaemic circulatory state of pregnancy<sup>67</sup>. Gestational hypertension and pre-eclampsia may increase the risk of aortic rupture<sup>68</sup>. Most complications occur in women with pre-existing cardiac disease<sup>69</sup>. In 32 cases reported prior to 1981, 16 pregnant women died of, and four survived, acute aortic dissection<sup>69</sup>. Combining data from three recent systematic studies, two retrospective<sup>69,70</sup> and one prospective<sup>71</sup>, nine women in 83 (11%) had severe complications, mostly aortic rupture. Endocarditis was also reported. Complications appear more likely if the aortic root is greater than 4 cm at the start of pregnancy, or dilates rapidly. In these circumstances, termination may be advisable. Aortic root replacement can be considered in pregnancy. Prophylactic beta blockers may prevent dilatation, although trial data is available only for non-pregnant patients. There is no increased risk of preterm labour, spontaneous miscarriage or postpartum haemorrhage in Marfan syndrome. The implications of dural ectasia for pregnancy and epidural anaesthesia is uncertain.

<b>1 (e)</b>	<b>Pre-pregnancy assessment by an obstetrician, physician and clinical geneticist including an echocardiogram is recommended. If the aortic root diameter is greater than 4 cm, the risk of maternal cardiovascular complications is increased. Beta blockers are recommended. Genetic counselling should include</b>	<b>Grade C</b>
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	discussion of prenatal diagnosis if DNA testing is possible in the family.	
<b>6 (b)</b>	<p><b>Antenatal care: If no pre-pregnancy assessment took place, it should be undertaken at first booking. Antenatal staff should be made aware that the pregnancy is high risk, management guidelines, and emergency contact numbers should be clearly recorded.</b></p> <p><b>Specialist review including a physician and/or clinical geneticist should occur regularly, with echocardiography at least 2 monthly. Beta blockers are recommended.</b></p> <p><b>A predelivery anaesthetic assessment is advised. MRI of the pelvis (to detect dural ectasia) may be useful to guide epidural anaesthetic catheter placement.</b></p>	<b>Grade C</b>
<b>6 (c)</b>	<p><b>Labour and Delivery:</b></p> <p><b>Delivery should occur in a teaching hospital, with consultant involvement. Prostaglandins should be used with caution.</b></p> <p><b>Prophylactic antibiotics are recommended for operative delivery if valvular heart disease is present.</b></p> <p><b>If there are no cardiac complications, and no obstetric risk factors, vaginal delivery should be considered.</b></p> <p><b>Epidural anaesthesia is recommended. Active pushing should be avoided, with early resort to instrumental delivery.</b></p> <p><b>If the aortic root is dilated, delivery by caesarean section is preferable.</b></p>	<b>Grade C</b>
<b>6 (d)</b>	<b>Syntocinon should be used in the active management of third stage. Ergometrine should be avoided is possible.</b>	<b>Grade A</b>
<b>6 (e)</b>	<b>Post-delivery: A neonatal examination should be performed, with parental consent for early diagnosis. Contraception and the risks of further pregnancy should be discussed. Surveillance should continue until 8 weeks postpartum, early discharge is not advised.</b>	<b>Grade C</b>

<b>6 (f)</b>	<b>Postnatal follow up: Postnatal review of mother and baby allows review of baby's diagnosis and discussion of the next pregnancy.</b>	<b>Grade C</b>
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## CONCLUSION

In developing the clinical guidelines for tuberous sclerosis<sup>10</sup>, it became evident that no randomised controlled trials of management of tuberous sclerosis had been published, and that therefore the majority (17/24 or 71%) of the guidelines were “expert opinion” (Grade C) with a minority (7/24 or 29%) based on clinical studies (Grade B). A similar problem exists for aspects of Marfan syndrome diagnosis and management. Randomised controlled trials have been carried out of cardiovascular management in Marfan syndrome, making this guideline Grade A. In addition, a substantial number of detailed clinical studies of Marfan syndrome have been published, perhaps because of the many possible medical interventions in the cardiac, ocular, skeletal and respiratory systems. A majority (14/26 or 54%) of the Marfan guidelines are therefore Grade B, and 10/26 (38%) Grade C. This suggests there may be less clinical reason for variations in medical care for Marfan syndrome than for some other genetic disorders. The general lack of randomised controlled trials of management of genetic disorders or even of large scale clinical studies is a challenge to clinical geneticists and others who provide medical care for genetic patients, and emphasizes the importance of stimulating both intra and multidisciplinary discussion and expert consensus agreement on these issues. To help implement these guidelines, local integrated care pathways have been devised. These are structured multidisciplinary care plans detailing essential steps in the care of patients with a particular medical problem<sup>72</sup> and are integrated into hospital case records. One pathway document prompts recording of relevant clinical features to simplify assessment using the Gent criteria, while further pathways prompt medical follow-up and obstetric care. In addition to acting as a clinical “aide memoire”, they also capture clinical details in a format which facilitates subsequent audit. They can therefore contribute towards future evidence based practice. Despite the preceding discussion, guidelines are not intended to be prescriptive, nor to act as a substitute for clinical judgement, and sections are included in the pathways to record deviations from the guidelines, and reasons for deviations. An audit of the use of these pathways will be undertaken after 1 year, to assess whether patient care has improved, and to allow for amendments in the light of the experience. We would be delighted to supply further details about the guidelines or care pathways on request.

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Marfan syndrome Guideline Development Group

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Plus Consensus Team

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**TABLE 1**

**GRADING OF RECOMMENDATIONS**

<b>GRADE</b>	<b>RECOMMENDATION</b>
A	Requires at least one randomised controlled trial as part of the body of literature of overall good quality and consistency addressing the specific recommendation
B	Requires availability of well conducted clinical studies but no randomised clinical trials on the topic of recommendation
C	Requires evidence from expert committee reports or opinions and/or clinical experience of respected authorities. Indicates absence of directly applicable studies of good quality