NICE National Institute for Health and Care Excellence

NICE Pathways

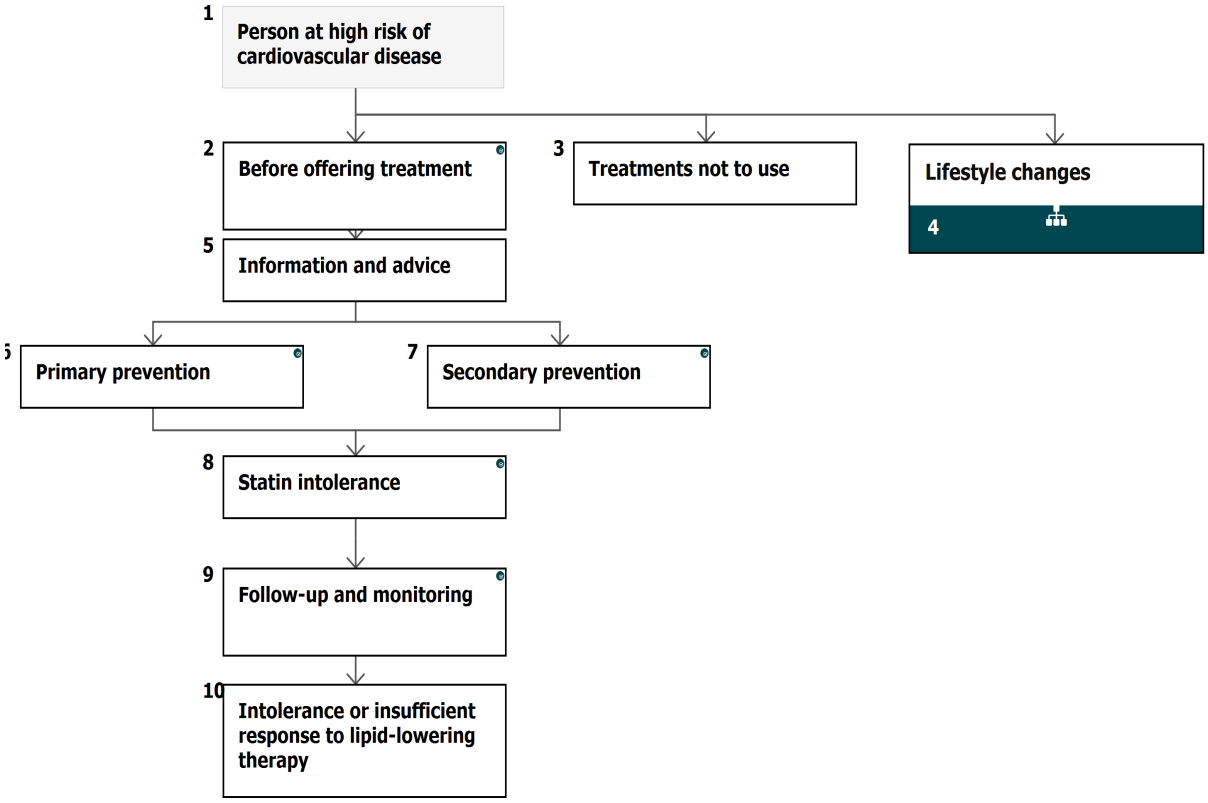
Lipid modification therapy for preventing cardiovascular disease

NICE Pathways bring together everything NICE says on a topic in an interactive flowchart. NICE Pathways are interactive and designed to be used online.

They are updated regularly as new NICE guidance is published. To view the latest version of this NICE Pathway see:

http://pathways.nice.org.uk/pathways/cardiovascular-disease-prevention
NICE Pathway last updated: 27 March 2018

This document contains a single flowchart and uses numbering to link the boxes to the associated recommendations.



1 Person at high risk of cardiovascular disease

No additional information

2 Before offering treatment

Be aware that when deciding on lipid modification therapy for the prevention of cardiovascular disease, drugs are preferred for which there is evidence in clinical trials of a beneficial effect on cardiovascular disease morbidity and mortality.

The decision whether to start statin therapy should be made after an informed discussion between the clinician and the person about the risks and benefits of statin treatment, taking into account additional factors such as potential benefits from lifestyle modifications, informed patient preference, comorbidities, polypharmacy, general frailty and life expectancy.

For further information, see what NICE says on medicines optimisation and multimorbidity.

When a decision is made to prescribe a statin use a statin of high intensity (see information on grouping of statins in the table below) and low acquisition cost.

Before starting statin treatment perform baseline blood tests and clinical assessment, and treat comorbidities and secondary causes of dyslipidaemia. Include all of the following in the assessment:

- smoking status (see what NICE says on smoking)
- alcohol consumption (see what NICE says on alcohol-use disorders)
- blood pressure (see what NICE says on hypertension)
- body mass index or other measure of obesity (see what NICE says on obesity)
- total cholesterol, non-HDL cholesterol, HDL cholesterol and triglycerides
- HbA_{1c}
- renal function and estimated glomerular filtration rate
- transaminase level (alanine aminotransferase or aspartate aminotransferase)
- thyroid-stimulating hormone.

Before offering a statin, ask the person if they have had persistent generalised unexplained muscle pain, whether associated or not with previous lipid-lowering therapy. If they have, measure creatine kinase levels.

- If creatine kinase levels are more than 5 times the upper limit of normal, re-measure creatine kinase after 7 days. If creatine kinase levels are still 5 times the upper limit of normal, **do not start** statin treatment.
- If creatine kinase levels are raised but less than 5 times the upper limit of normal, start statin treatment at a lower dose.

Measure baseline liver transaminase enzymes (alanine aminotransferase or aspartate aminotransferase) before starting a statin.

Do not routinely exclude from statin therapy people who have liver transaminase levels that are raised but are less than 3 times the upper limit of normal.

Grouping of statins used in this interactive flowchart

	Reduction in low-density lipoprotein cholesterol				
Dose (mg/day)	**5**	**10**	**20**	**40**	**80**
Fluvastatin	–	–	21%[1]	27%	33%[2]
Pravastatin	–	20%	24%	29%	–
Simvastatin	–	27%	32%	37%	42%[3],[4]
Atorvastatin	–	37%	43%	49%	55%
Rosuvastatin	38%	43%	48%	53%	–

The information used to make the table is from Law MR, Wald NJ, Rudnicka AR (2003) Quantifying effect of statins on low density lipoprotein cholesterol, ischaemic heart disease, and stroke: systematic review and meta-analysis. BMJ 326: 1423.

Quality standards

The following quality statements are relevant to this part of the interactive flowchart.

[1] 20%–30%: low intensity

[2] 31%–40%: medium intensity

[3] Above 40%: high intensity

[4] Advice from the MHRA: there is an increased risk of myopathy associated with high-dose (80 mg) simvastatin. The 80-mg dose should be considered only in patients with severe hypercholesterolaemia and high risk of cardiovascular complications who have not achieved their treatment goals on lower doses, when the benefits are expected to outweigh the potential risks.

Cardiovascular risk assessment and lipid modification

2. Excluding secondary causes

3. Lifestyle advice for primary prevention

4. Discussing risks and benefits of statins for primary prevention

3 Treatments not to use

Do not routinely offer fibrates and **do not offer** nicotinic acid (niacin), a bile acid sequestrant (anion exchange resin) or omega-3 fatty acid compounds for the prevention of cardiovascular disease to any of the following:

- people who are being treated for primary prevention
- people who are being treated for secondary prevention
- people with chronic kidney disease
- people with type 1 diabetes
- people with type 2 diabetes.

Tell people that there is no evidence that omega-3 fatty acid compounds help to prevent cardiovascular disease.

Do not offer the combination of a bile acid sequestrant (anion exchange resin), fibrate, nicotinic acid or omega-3 fatty acid compound with a statin for the primary or secondary prevention of cardiovascular disease.

Do not offer coenzyme Q10 or vitamin D to increase adherence to statin treatment.

4 Lifestyle changes

See Cardiovascular disease prevention / Lifestyle changes for preventing cardiovascular disease

5 Information and advice

Advise people who are being treated with a statin:

- that other drugs, some foods (for example, grapefruit juice) and some supplements may interfere with statins **and**
- to always consult the patient information leaflet, a pharmacist or prescriber for advice when starting other drugs or thinking about taking supplements.

Remind the person to restart the statin if they stopped taking it because of drug interactions or to treat intercurrent illnesses.

Advise people who are being treated with a statin to seek medical advice if they develop muscle symptoms (pain, tenderness or weakness). If this occurs, measure creatine kinase.

Statins are contraindicated in pregnancy:

- Advise women of childbearing potential of the potential teratogenic risk of statins and to stop taking them if pregnancy is a possibility.
- Advise women planning pregnancy to stop taking statins 3 months before they attempt to conceive and to not restart them until breastfeeding is finished.

6 Primary prevention

Statin treatment

Offer atorvastatin 20 mg for the primary prevention of cardiovascular disease to people who have a 10% or greater 10-year risk of developing cardiovascular disease. Estimate the level of risk using the QRISK2 assessment tool. (For help with implementation: getting started see the NICE guideline on cardiovascular disease: risk assessment and reduction, including lipid modification.)

For people 85 years or older consider atorvastatin 20 mg as statins may be of benefit in reducing the risk of non-fatal myocardial infarction. Be aware of factors that may make treatment inappropriate (see before offering treatment [See page 3]).

People with type 1 diabetes

Consider statin treatment for the primary prevention of cardiovascular disease in all adults with type 1 diabetes.

Offer statin treatment for the primary prevention of cardiovascular disease to adults with type 1 diabetes who:

- are older than 40 years **or**

- have had diabetes for more than 10 years **or**
- have established nephropathy **or**
- have other cardiovascular disease risk factors.

Start treatment for adults with type 1 diabetes with atorvastatin 20 mg.

People with type 2 diabetes

Offer atorvastatin 20 mg for the primary prevention of cardiovascular disease to people with type 2 diabetes who have a 10% or greater 10-year risk of developing cardiovascular disease. Estimate the level of risk using the QRISK2 assessment tool.

For more information, see what NICE says on diabetes.

People with chronic kidney disease

Offer atorvastatin 20 mg for the primary or secondary prevention of cardiovascular disease to people with chronic kidney disease.

- Increase the dose if a greater than 40% reduction in non-HDL cholesterol is not achieved (see follow-up and monitoring [See page 12]) and estimated glomerular filtration rate is 30 ml/min/1.73m^2 or more.
- Agree the use of higher doses with a renal specialist if estimated glomerular filtration rate is less than 30ml/min/1.73m^2.

For further information, see what NICE says on chronic kidney disease.

Ezetimibe for treating hypercholesterolaemia

The following recommendation is an extract from NICE technology appraisal guidance on ezetimibe for treating primary heterozygous-familial and non-familial hypercholesterolaemia.

Ezetimibe monotherapy is recommended as an option for treating primary (heterozygous-familial or non-familial) hypercholesterolaemia in adults in whom initial statin therapy is contraindicated.

NICE has written information for the public explaining its guidance on ezetimibe.

Quality standards

The following quality statements are relevant to this part of the interactive flowchart.

Cardiovascular risk assessment and lipid modification

3. Lifestyle advice for primary prevention

4. Discussing risks and benefits of statins for primary prevention

5. Statins for primary prevention

7 Secondary prevention

Statin treatment

Start statin treatment in people with cardiovascular disease with atorvastatin 80 mg[1]. Use a lower dose of atorvastatin if any of the following apply:

- potential drug interactions
- high risk of adverse effects
- patient preference.

(For help with implementation: getting started see the NICE guideline on cardiovascular disease: risk assessment and reduction, including lipid modification.)

People with chronic kidney disease

Offer atorvastatin 20 mg for the primary or secondary prevention of cardiovascular disease to people with chronic kidney disease.

- Increase the dose if a greater than 40% reduction in non-HDL cholesterol is not achieved (see follow-up and monitoring [See page 12]) and estimated glomerular filtration rate is 30 ml/min/1.73m^2 or more.
- Agree the use of higher doses with a renal specialist if estimated glomerular filtration rate is less than 30ml/min/1.73m^2.

For further information, see what NICE says on chronic kidney disease.

Ezetimibe for treating hypercholesterolaemia

The following recommendation is an extract from NICE technology appraisal guidance on ezetimibe for treating primary heterozygous-familial and non-familial hypercholesterolaemia.

[1] At the time of publication (July 2014), atorvastatin did not have a UK marketing authorisation for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Good practice in prescribing and managing medicines and devices for further information.

Ezetimibe monotherapy is recommended as an option for treating primary (heterozygous-familial or non-familial) hypercholesterolaemia in adults in whom initial statin therapy is contraindicated.

NICE has written information for the public explaining its guidance on ezetimibe.

Quality standards

The following quality statements are relevant to this part of the interactive flowchart.

Cardiovascular risk assessment and lipid modification

3. Lifestyle advice for primary prevention

6. Statins for secondary prevention

Chronic kidney disease in adults

3. Statins for people with CKD

8 Statin intolerance

If a person is not able to tolerate a high-intensity statin aim to treat with the maximum tolerated dose.

Tell the person that any statin at any dose reduces cardiovascular disease risk. If someone reports adverse effects when taking high-intensity statins discuss the following possible strategies with them:

- stopping the statin and trying again when the symptoms have resolved to check if the symptoms are related to the statin
- reducing the dose within the same intensity group
- changing the statin to a lower intensity group.

Seek specialist advice about options for treating people at high risk of cardiovascular disease such as those with chronic kidney disease, type 1 diabetes, type 2 diabetes or genetic dyslipidaemias, and those with cardiovascular disease, who are intolerant to 3 different statins. Advice can be sought for example, by telephone, virtual clinic or referral.

Quality standards

The following quality statement is relevant to this part of the interactive flowchart.

Cardiovascular risk assessment and lipid modification

7. Side effects of high-intensity statins

9 Follow-up and monitoring

Do not measure creatine kinase levels in asymptomatic people who are being treated with a statin.

Measure liver transaminase enzymes (alanine aminotransferase or aspartate aminotransferase) within 3 months of starting treatment and at 12 months, but not again unless clinically indicated.

Do not stop statins because of an increase in blood glucose level or HbA_{1c} (see the recommendations on assessing for risk of diabetes mellitus in preventing type 2 diabetes).

Provide annual medication reviews for people taking statins.

- Use these reviews to discuss medicines adherence and lifestyle modification and address cardiovascular disease risk factors.
- Consider an annual non-fasting blood test for non-HDL cholesterol to inform the discussion.

Discuss with people who are stable on a low- or middle-intensity statin the likely benefits and potential risks of changing to a high-intensity statin when they have a medication review and agree with the person whether a change is needed. (For help with implementation: getting started see the NICE guideline on cardiovascular disease: risk assessment and reduction, including lipid modification.)

Measure total cholesterol, HDL cholesterol and non-HDL cholesterol in all people who have been started on high-intensity statin treatment (both primary and secondary prevention, including atorvastatin 20 mg for primary prevention) at 3 months of treatment and aim for a greater than 40% reduction in non-HDL cholesterol. If a greater than 40% reduction in non-HDL cholesterol is not achieved:

- discuss adherence and timing of dose
- optimise adherence to diet and lifestyle measures

- consider increasing the dose if started on less than atorvastatin 80 mg and the person is judged to be at higher risk because of comorbidities, risk score or using clinical judgement.

If people report muscle pain or weakness while taking a statin, explore other possible causes of muscle pain or weakness and raised creatine kinase if they have previously tolerated statin therapy for more than 3 months.

Quality standards

The following quality statement is relevant to this part of the interactive flowchart.

Cardiovascular risk assessment and lipid modification

8. 3-month statin review

10 Intolerance or insufficient response to lipid-lowering therapy

Ezetimibe

The following recommendations are an extract from NICE technology appraisal guidance on ezetimibe for the treatment of primary (heterozygous-familial and non-familial) hypercholesterolaemia.

Ezetimibe monotherapy is recommended as an option for treating primary (heterozygous-familial or non-familial) hypercholesterolaemia in adults who cannot tolerate statin therapy (as defined below).

Ezetimibe, co-administered with initial statin therapy, is recommended as an option for treating primary (heterozygous-familial or non-familial) hypercholesterolaemia in adults who have started statin therapy when:

- serum total or LDL cholesterol concentration is not appropriately controlled (as defined below) either after appropriate dose titration of initial statin therapy or because dose titration is limited by intolerance to the initial statin therapy (as defined below) and
- a change from initial statin therapy to an alternative statin is being considered.

When prescribing ezetimibe co-administered with a statin, ezetimibe should be prescribed on the basis of lowest acquisition cost.

For the purposes of this guidance, intolerance to initial statin therapy is defined as the presence of clinically significant adverse effects that represent an unacceptable risk to the patient or that may reduce compliance with therapy.

For the purposes of this guidance, appropriate control of cholesterol concentrations should be based on individual risk assessment according to national guidance on managing cardiovascular disease in the relevant populations.

NICE has written information for the public explaining its guidance on ezetimibe.

Evolocumab

The following recommendations are from NICE technology appraisal guidance on evolocumab for treating primary hypercholesterolaemia and mixed dyslipidaemia.

Evolocumab is recommended as an option for treating primary hypercholesterolaemia or mixed dyslipidaemia, only if:

- The dosage is 140 mg every 2 weeks.
- Low-density lipoprotein concentrations are persistently above the thresholds specified in low-density lipoprotein cholesterol concentrations above which evolocumab is recommended [See page 16] despite maximal tolerated lipid-lowering therapy. That is, either the maximum dose has been reached, or further titration is limited by intolerance (the presence of clinically significant adverse effects that represent an unacceptable risk to the patient or that may reduce compliance with therapy).
- The company provides evolocumab with the discount agreed in the patient access scheme.

This guidance is not intended to affect the position of patients whose treatment with evolocumab was started within the NHS before this guidance was published. Treatment of those patients may continue without change to whatever funding arrangements were in place for them before this guidance was published until they and their NHS clinician consider it appropriate to stop.

NICE has written information for the public explaining its guidance on evolocumab.

Alirocumab

The following recommendations are from NICE technology appraisal guidance on alirocumab for treating primary hypercholesterolaemia and mixed dyslipidaemia.

Alirocumab is recommended as an option for treating primary hypercholesterolaemia or mixed dyslipidaemia, only if:

- Low-density lipoprotein concentrations are persistently above the thresholds specified in low-density lipoprotein cholesterol concentrations above which alirocumab is recommended [See page 16] despite maximal tolerated lipid-lowering therapy. That is, either the maximum dose has been reached or further titration is limited by intolerance (the presence of clinically significant adverse effects that represent an unacceptable risk to the patient or that may reduce compliance with therapy).
- The company provides alirocumab with the discount agreed in the patient access scheme.

This guidance is not intended to affect the position of patients whose treatment with alirocumab was started within the NHS before this guidance was published. Treatment of those patients may continue without change to whatever funding arrangements were in place for them before this guidance was published until they and their NHS clinician consider it appropriate to stop.

NICE has written information for the public explaining its guidance on alirocumab.

Low-density lipoprotein cholesterol concentrations above which alirocumab is recommended

	Without CVD	With CVD	
		High risk of CVD[1]	Very high risk of CVD[2]
Primary non-familial hypercholesterolaemia or mixed dyslipidaemia	Not recommended at any LDL-C concentration	Recommended only if LDL-C concentration is persistently above 4.0 mmol/litre	Recommended only if LDL-C concentration is persistently above 3.5 mmol/litre
Primary heterozygous-familial hypercholesterolaemia	Recommended only if LDL-C concentration is persistently above 5.0 mmol/litre	Recommended only if LDL-C concentration is persistently above 3.5 mmol/litre	

Low-density lipoprotein cholesterol concentrations above which evolocumab is recommended

	Without CVD	With CVD	
		High risk of CVD[3]	Very high risk of CVD[4]
Primary non-familial hypercholesterolaemia or mixed dyslipidaemia	Not recommended at any LDL-C concentration	Recommended only if LDL-C concentration is persistently above 4.0 mmol/litre	Recommended only if LDL-C concentration is persistently above 3.5 mmol/litre

[1] High risk of cardiovascular disease is defined as a history of any of the following: acute coronary syndrome (such as myocardial infarction or unstable angina requiring hospitalisation), coronary or other arterial revascularisation procedures, coronary heart disease, ischaemic stroke, peripheral arterial disease.

[2] Very high risk of cardiovascular disease is defined as recurrent cardiovascular events or cardiovascular events in more than 1 vascular bed (that is, polyvascular disease).

[3] High risk of cardiovascular disease is defined as a history of any of the following: acute coronary syndrome (such as myocardial infarction or unstable angina requiring hospitalisation), coronary or other arterial revascularisation procedures, coronary heart disease, ischaemic stroke, peripheral arterial disease.

[4] Very high risk of cardiovascular disease is defined as recurrent cardiovascular events or cardiovascular events in more than 1 vascular bed (that is, polyvascular disease).

Primary heterozygous-familial hypercholesterolaemia	Recommended only if LDL-C concentration is persistently above 5.0 mmol/litre	Recommended only if LDL-C concentration is persistently above 3.5 mmol/litre

Glossary

CVD

cardiovascular disease

disadvantaged

adults who are disadvantaged include (but are not limited to) those on a low income (or who are members of a low-income family), those on benefits, those living in public or social housing, some members of black and minority ethnic groups, those with a mental health problem, those with a learning disability, those who are institutionalised (including those serving a custodial sentence) and those who are homeless

HbA1c

glycated haemoglobin

HDL

high-density lipoprotein

high-intensity

the following doses for statins are high intensity, based on the percentage reduction in low density lipoprotein (LDL) cholesterol they can produce: atorvastatin 20–80 mg; rosuvastatin 10–40 mg; simvastatin 80 mg

high risk

if someone has a 20% or higher risk of a first cardiovascular event in the next 10 years they are deemed at high risk of cardiovascular disease

Intensity

for the purpose of this interactive flowchart, statins are grouped into 3 different intensity categories according to the percentage reduction in low-density lipoprotein cholesterol: low intensity if the reduction is from 20% to 30%; medium intensity if the reduction is from 31% to 40%; and high intensity if the reduction is above 40%

LDL

low-density lipoprotein

LDL-C

low-density lipoprotein cholesterol

Sources

Cardiovascular disease: risk assessment and reduction, including lipid modification (2014 updated 2016) NICE guideline CG181

Evolocumab for treating primary hypercholesterolaemia and mixed dyslipidaemia (2016) NICE technology appraisal guidance 394

Alirocumab for treating primary hypercholesterolaemia and mixed dyslipidaemia (2016) NICE technology appraisal guidance 393

Ezetimibe for treating primary heterozygous-familial and non-familial hypercholesterolaemia (2016) NICE technology appraisal guidance 385

Your responsibility

Guidelines

The recommendations in this guideline represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, professionals and practitioners are expected to take this guideline fully into account, alongside the individual needs, preferences and values of their patients or the people using their service. It is not

mandatory to apply the recommendations, and the guideline does not override the responsibility to make decisions appropriate to the circumstances of the individual, in consultation with them and their families and carers or guardian.

Local commissioners and providers of healthcare have a responsibility to enable the guideline to be applied when individual professionals and people using services wish to use it. They should do so in the context of local and national priorities for funding and developing services, and in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities. Nothing in this guideline should be interpreted in a way that would be inconsistent with complying with those duties.

Commissioners and providers have a responsibility to promote an environmentally sustainable health and care system and should assess and reduce the environmental impact of implementing NICE recommendations wherever possible.

Technology appraisals

The recommendations in this interactive flowchart represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, health professionals are expected to take these recommendations fully into account, alongside the individual needs, preferences and values of their patients. The application of the recommendations in this interactive flowchart is at the discretion of health professionals and their individual patients and do not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian.

Commissioners and/or providers have a responsibility to provide the funding required to enable the recommendations to be applied when individual health professionals and their patients wish to use it, in accordance with the NHS Constitution. They should do so in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities.

Commissioners and providers have a responsibility to promote an environmentally sustainable health and care system and should assess and reduce the environmental impact of implementing NICE recommendations wherever possible.

Medical technologies guidance, diagnostics guidance and interventional procedures guidance

The recommendations in this interactive flowchart represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, healthcare professionals are expected to take these recommendations fully into account. However, the interactive flowchart does not override the individual responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.

Commissioners and/or providers have a responsibility to implement the recommendations, in their local context, in light of their duties to have due regard to the need to eliminate unlawful discrimination, advance equality of opportunity, and foster good relations. Nothing in this interactive flowchart should be interpreted in a way that would be inconsistent with compliance with those duties.

Commissioners and providers have a responsibility to promote an environmentally sustainable health and care system and should assess and reduce the environmental impact of implementing NICE recommendations wherever possible.