

**Clinical Commissioning
Policy Proposition:
Balloon pulmonary
angioplasty for chronic
thromboembolic
pulmonary hypertension
(all ages)**



First published: **Month Year**

Prepared by NHS England Specialised Services Clinical Reference Group for Specialised Respiratory

Published by NHS England, in electronic format only.

Draft for public consultation

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1 Executive Summary

Equality Statement

Promoting equality and addressing health inequalities are at the heart of NHS England's values. Throughout the development of the policies and processes cited in this document, we have:

- Given due regard to the need to eliminate discrimination, harassment and victimisation, to advance equality of opportunity, and to foster good relations between people who share a relevant protected characteristic (as cited under the Equality Act 2010) and those who do not share it; and
- Given regard to the need to reduce inequalities between patients in access to, and outcomes from healthcare services and to ensure services are provided in an integrated way where this might reduce health inequalities

Plain Language Summary

About chronic thromboembolic pulmonary hypertension

Chronic thromboembolic pulmonary hypertension (CTEPH) is a form of lung disease where blood pressure in the lung is raised due to blood clots in the blood vessels in the lung. This causes right heart strain and may cause premature death. Normally if blood clots travel to the lungs (pulmonary emboli), they are broken down either by the body or by treatments e.g. anti-coagulation therapy. However, in CTEPH the blood clots damage the main artery (pulmonary arteries) and block the blood flow through the lungs. This causes breathlessness, fatigue, dizziness, chest pain, body swelling, coughing up of blood and an inability to exercise which all impact on patient's poor quality of life. Often patients cannot work and need to take oxygen all the time just to remain comfortable when resting. Usually the disease, if not treated, leads to heart failure and death.

About current treatments

The treatment of choice for CTEPH is surgery to remove the clots; this is called pulmonary endarterectomy (PEA). This is a very complex, high risk operation requiring a lowering of body temperature and stopping blood circulation for a

controlled period of time and is delivered at only one specialist centre in the UK. The average operative time is 8 hours, PEA has a mortality of 5%. The majority of patients improve after surgery and some are cured but 20-40% of patients are not suitable for surgery due to inaccessible disease or prohibitive risk. These patients are currently treated medically and they have a worse life expectancy and poorer quality of life than those successfully treated by surgery. Available medical treatments include blood thinners, water tablets, long term oxygen therapy, drugs that control heart palpitations and pulmonary vasodilators. The latter can have severe side effects and are very expensive. Medical therapy other than riociguat has not demonstrated long-term survival benefits in this condition when studied in clinical trials.

About the new treatment

Balloon pulmonary angioplasty (BPA) aims to treat CTEPH with the patient awake with a “keyhole” surgical technique. BPA treats narrowings in the scarred lung arteries with a balloon that is inflated to stretch open the lumen improving lung blood flow. To reduce the risk of complications, the procedure is performed in stages and several sessions (4-6 per patient) are usually required to achieve therapeutic benefit.

What we have decided

NHS England has carefully reviewed the evidence to treat CTEPH with BPA. We have concluded that there is enough evidence to consider making the treatment available.

2 Introduction

This document describes the evidence that has been considered by NHS England in formulating a proposal to routinely commission BPA.

This document also describes the proposed criteria for commissioning, proposed governance arrangements and proposed funding mechanisms.

For the purpose of consultation NHS England invites views on the evidence and other information that has been taken into account as described in this policy proposition.

A final decision as to whether BPA for CTEPH will be routinely commissioned is planned to be made by NHS England following a recommendation from the Clinical Priorities Advisory Group.

3 Proposed Intervention and Clinical Indication

Chronic thromboembolic pulmonary hypertension

CTEPH is a progressive disease caused by chronic occlusions of the pulmonary circulation leading to right heart failure and premature death. Currently approximately 40% of patients with CTEPH are inoperable and with the limited current alternative treatment options the 3 year survival rate is only 70% for this group (Delcroix 2016a). These patients are currently offered disease modifying therapies including endothelin receptor antagonists (ERAs) or novel soluble guanylate cyclase stimulators (sGCs) according to an agreed Clinical Reference Group Pulmonary Hypertension treatment policy (NHS England A11/P/c), which is continued lifelong. With current medical therapy survival is improved compared with historical controls but is inferior to PEA surgery.

Usual treatment for patients with CTEPH

PEA is the treatment of choice for CTEPH and can be curative for selected group of patients. PEA is a very complex, high risk operation with mortality of 5% (Mayer 2011). It requires deep hypothermia and total circulatory arrest with an average

operative duration of 8 hours. This highly specialised service is nationally commissioned at one national centre in England. 20-40% of patients with CTEPH have inoperable disease, due to comorbidities or inaccessible distal location of pulmonary vascular obstructions (Mayer 2011). Patients with inoperable CTEPH have an unmet clinical need. They have a worse life expectancy (70% mortality at 3-years) (Delcroix 2016a) and poorer quality of life compared to those patients who undergo surgery despite medical treatment with diuretics, digitalis, pulmonary vasodilator therapies and long term oxygen therapy.

Treatment options for patients with inoperable disease are limited:

- Exercise training has been found in small studies to improve exercise capacity and quality of life in patients with inoperable CTEPH who are stable on therapy with pulmonary arterial hypertension (PAH) targeted therapy (Nagel 2012, Fukui 2016). Concern about safety and tolerability has limited its use in routine care for patients with inoperable CTEPH (Fukui 2016).
- Conventional medical treatments to reduce pulmonary vascular resistance (diuretics, digitalis and chronic oxygen therapy) have little effect and do not affect the underlying disease processes in CTEPH (Pepke-Zaba 2016).
- Patients with CTEPH may be treated with medications used against PAH such as prostacyclin analogs (epoprostenol, beraprost, iloprost), endothelin receptor antagonists (bosentan, ambrisentan, macitentan) and phosphodiesterase-5 inhibitors (sildenafil, tadalafil). Small uncontrolled trials of these medications in CTEPH have had mixed results (Pepke-Zaba 2016). A randomized controlled trial of bosentan in 157 patients with CTEPH (BENEFIT) found improved pulmonary vascular resistance at 16 weeks among patients receiving bosentan compared to patients receiving placebo, but 6 minute walk distance (6MWD) was not significantly different (Mathai 2016).
- Riociguat, a soluble guanylate cyclase stimulator, is the first drug to be licensed for use in inoperable or persistent recurrent CTEPH. The main evidence of efficacy of riociguat against CTEPH is derived from one

randomized placebo-controlled trial of 261 patients, CHEST-1, which was followed by a 2-year extension, CHEST-2 (Ghofrani 2013, Simonneau 2016). The detailed results of these trials are described below.

The intervention: balloon pulmonary angioplasty

BPA aims to reduce pulmonary hypertension by dilating narrowings in the pulmonary arteries.

The procedure is done under local anaesthetic and light sedation, with the patient fully anticoagulated. A standard right heart catheterization is performed through the right internal jugular vein or right femoral vein. The narrowed or blocked vessels are identified using selective pulmonary angiography. A balloon catheter is then advanced over a guidewire, and the balloon is inflated to dilate the arteries and restore pulmonary blood flow. Several narrowings may be treated in one session. To reduce the risk of complications, a limited number of segments of lung are usually treated in one session and 4-6 sessions are usually required to complete therapy. These are performed at 2-8 week intervals.

4 Definitions

Pulmonary hypertension (PH) is a disorder of the blood vessels in the lung, characterised by raised pressure in the pulmonary artery, which results in a range of symptoms and may be life threatening.

Chronic thromboembolic pulmonary hypertension (CTEPH) is a rare form of PH, categorized by the World Health Organisation as Group IV PH (see below). It is defined as mean pulmonary arterial pressure ≥ 25 mmHg and pulmonary capillary wedge pressure ≤ 15 mmHg in the presence of multiple chronic/organized occlusive thromboemboli in the elastic pulmonary arteries (main, lobar, segmental, sub-segmental) after at least three months of effective anticoagulation.

Pulmonary endarterectomy (PEA) - surgical removal of accessible intravascular occlusive material, the first choice therapy for CTEPH.

Medical therapy - pulmonary vasodilators can be used to control symptoms of pulmonary hypertension. These are only prescribed by designated Pulmonary Hypertension Centres.

Balloon pulmonary angioplasty (BPA) is the use of percutaneous catheter directed balloon dilation treatment in stenotic and sub-totally occluded sub-segmental pulmonary arteries.

WHO functional classes – a standard classification of disease severity in PH. Patients in class I have no symptoms; patients in class IV are symptomatic even at rest. Classes II and III are intermediate.

5 Aims and Objectives

This policy proposition considered BPA for the treatment of CTEPH.

The objectives are to:

- Define the eligibility criteria for BPA
- Define the commissioning arrangements required for BPA

6 Epidemiology and Needs Assessment

In the general population, the incidence of CTEPH is estimated to be approximately 5 cases per million people per year (Delcroix 2016b). Most patients have a known history of massive or recurrent acute pulmonary embolism. It is estimated that between 0.6 to 4.8 % of people who have an acute pulmonary embolism develop CTEPH within the next 2 years (Leopold 2016). This implies around 272 new cases of CTEPH per annum in England, of whom approximately 60% will be treated with PEA, remaining 40% will be very heterogeneous group of patients with:

1. Technically operable but not suitable for surgery due to severe co-morbidities (n~18 per annum) or physician/patient choice due to mild symptoms (n~18

per annum).

2. Distal distribution of disease not accessible by PEA and managed medically with PAH targeted therapies at present. There are two potential patient subgroups in this inoperable group:
 - a. Patients with lesions suitable for the BPA (main target are considered to be webs and slits lesions. Lesions with severe narrowing or complete obstruction by webs could also be treatable as long as distal run-off is confirmed on imaging), possibly enabling PAH medical therapy to be weaned (n~27 pa).
 - b. Patients with lesions inaccessible for BPA who will continue with medical management with targeted PAH therapy or lung transplantation (n~45pa).

These data have been confirmed by National Audit (Health and Social Care Information Centre 2014) provided by Pulmonary Hypertension Centres in the UK. Detailed triaging of inoperable CTEPH patients has determined that 20-30 patients per annum would be clinically eligible for BPA. There is expected to be a small amount of growth in the CTEPH population.

7 Evidence Base

NHS England has concluded that there is sufficient evidence to support a proposal for the routine commissioning of BPA for eligible patients with CTEPH.

Summary of evidence review

Eight studies from 7 centres were included in the review. All were observational case-series, including between 20 to 170 patients, which compared outcomes before and after BPA.

Clinical effectiveness

The best available estimate of survival was based on 68 patients, of whom 66

(97%) were alive at one year following BPA (Mizoguchi H 2012). No studies were found which directly described the effect of BPA for inoperable CTEPH on quality of life. Consistent evidence was found from all studies demonstrating an improved function (or reduced symptoms of heart failure) in the year following BPA compared to prior to BPA, and improved physiological markers of PH and right heart strain. The average improvement in the distance walked in 6 minutes ranged from 46 to 100 metres across the studies, and consistent improvements in functional classification and exercise testing were also reported. Reductions in average pulmonary vascular resistance ranged from 31% to 61% across the studies, while reduction in average brain natriuretic peptide ranged from 10% to 50%. These effects were large enough that they are expected to be clinically meaningful to patients, and were consistently observed. There is evidence to support associations of these functional and physical markers with quality of life and survival.

Additional data on long-term outcomes following BPA (Inami 2016) reports up to 7 years of follow up for 170 consecutive patients who had BPA for CTEPH between April 2009 and July 2016. The evidence from Inami et al (2016) is based on a different patient population than one described in the paper of Mizoguchi et al (Mizoguchi 2012)

- Survival: The authors report 1-, 3- and 5-year survival of 98.7% (95% CI 94.9–99.7), 98.0% (93.7–99.3), and 95.5% (85.9–98.6), respectively. Median follow up was 2.8 years (interquartile range 1.2–4.1 years); four patients died (one as a direct complication of BPA).
- Physiological long-term results: Pulmonary vascular resistance and mean pulmonary artery pressure improvements were maintained, but improvements in cardiac index were not maintained. Results were presented graphically and so precise results cannot be interpreted. Only 30 of 57 eligible patients had right heart catheterisation ≥ 3.5 years after BPA.
- Medication requirements: The proportion of patients who were medication free changed from 8.8% to 71.8% (95% CI 64.9 – 77.6) for PH medications and from 15.3% to 38.6% (95% CI 25.0 – 52.0) for home oxygen therapy,

over a period of ≥ 3.5 years after BPA.

Limitations: Most patient's assessment of the therapeutic benefit of BPA was too recent to permit long-term follow up; as a result five-year survival is estimated from fewer than 42 patients. Physiological outcomes were not standardised or mandated by protocol and therefore could be susceptible to selection bias.

Safety

Peri-procedural mortality was 5/281 (2%) among patients included in the 6 studies which reported complications. The main complications reported were: injury to the pulmonary artery with the guidewire during BPA, which may cause serious bleeding or death; and reperfusion pulmonary oedema, which may necessitate artificial ventilation.

Strengths

A number of case series studies were identified, some of which included moderate numbers of patients. Most stated that the patients were identified consecutively, and several had high or complete follow up, limiting the potential for selection bias. In all studies the intervention was described clearly and appeared to be implemented consistently. All studies reported at least one functional outcome of direct relevance to patients, and similar reporting of physiological outcomes allowed the consistency of results across studies to be identified.

Limitations

All studies were observational comparisons of patient outcomes after BPA compared to before BPA, which are more vulnerable to bias than randomised trials of treatment with a separate comparison group. Most were small studies and thus vulnerable to over-estimation of the size of effect from small numbers. Study quality varied and for several the reporting of design was unclear, limiting the extent to which bias could be assessed. Two particular limitations were worth further discussion:

Reliance on indirect (surrogate) outcomes

Evidence on the effect of BPA on outcomes which directly describe the patient's quality of life was limited. However, evidence consistently showed that patients have better function and indicators of physiology after BPA compared to before BPA. These would be expected to translate into better survival and quality of life for patients:

- Both the functional and the physiological outcomes described are associated with quality of life in CTEPH. Improvement in six minute walk distance (6MWD) has been found to be associated with higher quality of life among patients with CTEPH (Mathai 2016, Urushibara 2015). Among patients with CTEPH, reduced pulmonary vascular resistance (PVR) has been found to be associated with higher quality of life (Urushibara 2015)
- Both the functional and the physiological outcomes described are associated with survival among patients with CTEPH. Among 237 patients with inoperable CTEPH in the CHEST-2 trial, 6MWD was associated with 2 year survival ($p=0.02$) (Simonneau 2016). Patients in functional class IV (unable to carry out any physical activity without discomfort and has symptoms of cardiac insufficiency at rest) have a nearly five-fold increase in mortality among non-operated patients with CTEPH (HR 4.76, 95% CI 1.76 – 12.88, $P=0.0021$) (Delcroix 2016a). PVR predicts mortality of medically-treated patients with CTEPH (Saouti 2009). BNP was associated with 2 year survival of patients with inoperable CTEPH in the CHEST trial ($p=0.02$) (Simonneau 2016).
- This is consistent with the finding in large observational studies that post-surgical PVR predicts long-term survival among patients with CTEPH following surgery (Cannon 2016, Mayer 2011).

For this rare disease, recruiting patients to studies large enough to be powered to study rare outcomes such as mortality may be challenging, and surrogate outcomes with a strong clinical basis are a realistic and accepted alternative. Quality of life should be studied in future research wherever possible.

Comparison to medical treatment

The best medical treatment available for patients with inoperable CTEPH is riociguat. There is no direct evidence comparing BPA head-to-head against riociguat. This evidence gap is unsurprising as riociguat is recently licensed and so the comparison has only recently become relevant or possible. For the proportion of inoperable patients who cannot tolerate riociguat BPA may be the only evidence-based treatment option. However, for the majority of patients with inoperable CTEPH, riociguat represents the best alternative treatment to BPA. Riociguat has shown promising short-term results in one 16-week randomised placebo-controlled trial of 261 patients with a 2-year extension looking at safety and sustained effect. The effect of BPA on function and physiology compare well enough to these to suggest equipoise and encourage further study.

Prospects for future research

Observational studies from registries offer opportunities to improve the direct evidence of long term effectiveness and quality of life over time. One randomised trial of riociguat vs BPA is ongoing, [Riociguat Versus BPA in Non-operable Chronic thromboembolic Pulmonary Hypertension (RACE)]. This trial should improve the evidence base for treatment decisions among patients with inoperable CTEPH: the trial aims to complete recruitment in 2019 with estimated published data earliest in 2021, and the trial is a small study (aiming to recruit 124 patients) which may be under-powered to compare the effects on direct patient outcomes such as survival. It plans to evaluate an indirect primary outcome (pulmonary vascular resistance) over a short period (26 weeks). Several of these limitations are inherent in studies of such a highly specialized treatment of a rare disease, and a much stronger evidence base may be difficult to achieve.

8 Proposed Criteria for Commissioning

BPA will be commissioned for patients with symptomatic CTEPH who have disease not suitable for PEA and angiographic lesions amenable to BPA:

1. Distribution of thromboembolic disease too distal to be considered a suitable candidate for PEA.
2. Lesions suitable for BPA are considered to be webs and slits; lesions with severe narrowing or complete obstruction by webs could also be treatable as long as distal run-off is confirmed on imaging.
3. Symptomatic, haemodynamic and /or prognostic benefit for the patient expected. The service should have the expertise to determine whether or not a patient might benefit from PEA or whether BPA is a more appropriate intervention.

Criteria to determine which patients are inoperable :

Operability is decided by the National Pulmonary Endarterectomy Multi-Disciplinary Team meeting.

The place of medical treatment in the pathway :

Medical treatment is defined by NHS England's Clinical Commissioning Policy: "Targeted Therapies for use in Pulmonary Hypertension in Adults Commissioners PH targeted therapy policy" (NHS England A11/P/c).

Comorbidities that may be contraindications to the intervention (for example, those that increase the risk of the procedure):

Comorbidities that may be contraindications to the intervention in specific patients include left heart disease: systolic left heart failure, disease of the heart valves, significant parenchymal lung disease (such as interstitial lung fibrosing and severe emphysema).

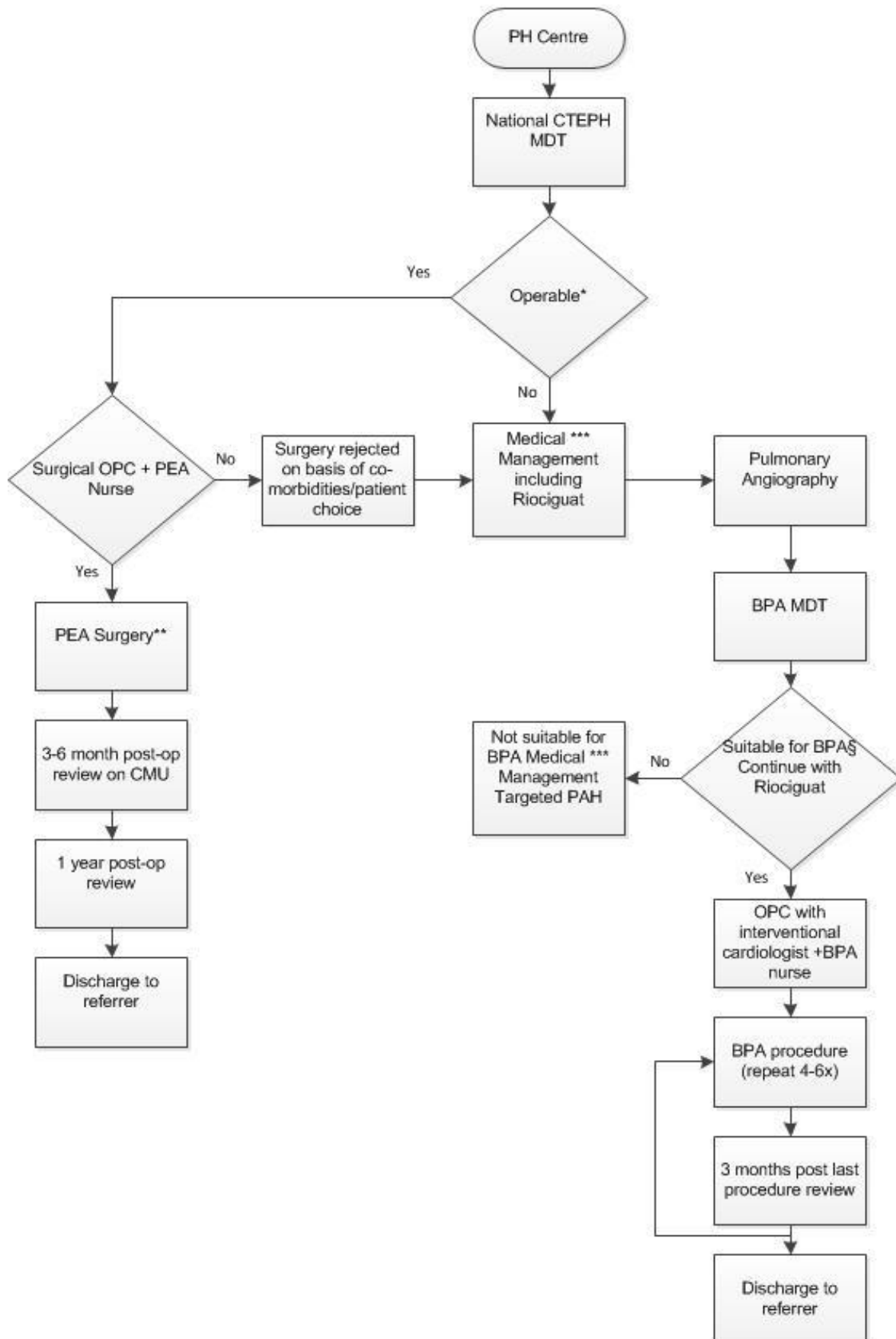
Comorbidities that reduce the likely ability of the patient to benefit, including where life expectancy is likely to be reduced:

Comorbidities that reduce the likely ability of the patient to benefit include active malignancy, and extreme fragility of the patient.

The potential use of concomitant medical therapy:

Additionally to PAH targeted therapy, the patient might be on conventional or supportive therapy with long term oxygen, diuretics, heart rate control medications.

CTEPH –Pathway



Pathway Legend

***Operable:**

Distribution of the disease with predominant proximal component suitable for the surgery with PEA (including those with co-morbid conditions which might exclude surgery, and those who might not accept management with the PEA).

**** Criteria for PEA surgery:**

1. Presence of chronic thromboembolic disease on imaging; and
2. Haemodynamic impairment in proportion to operable (clearable) disease on imaging; and
3. Symptomatic and/or prognostic benefit for the patient (balancing benefits from the surgery against risks from co-morbidities).

***** Medical management:**

Distal distribution of disease not considered suitable for PEA or BPA. Patients will require treatment with PAH targeted therapies with riociguat as first line treatment. Referral for lung transplantation should be considered.

§ Criteria for BPA

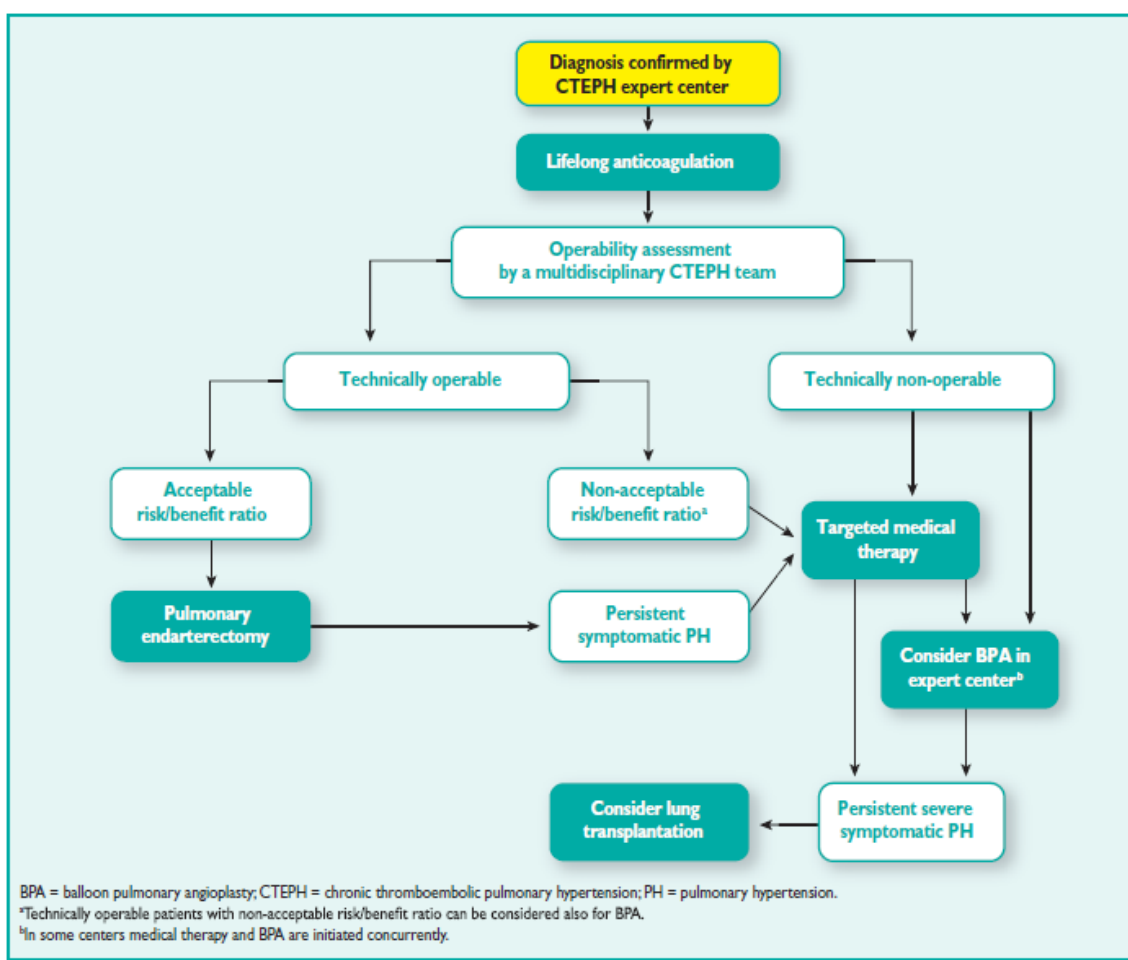
1. Mean Pulmonary arterial pressure greater than 25 mmHg at right heart catheterisation; and
2. Patient is symptomatic in WHO functional class III or IV; and
3. The pulmonary vascular obstructions (i.e. the disease distribution) is distal, not suitable for pulmonary endarterectomy; and
4. The presence of narrowed or blocked vessels (occluded sub-segmental pulmonary arteries) identified using conventional pulmonary angiography; and
5. There is a Balloon Pulmonary Angioplasty MDT meeting decision that there are sufficient, accessible, vascular lesion for BPA treatment to improve patient symptoms and haemodynamics. The MDT meeting will be attended by:
 - Consultant Interventional cardiologist performing BPA,

- Consultant Radiologist with interest into pulmonary vascular diseases,
 - Consultant Respiratory Physician,
 - BPA coordinator nurse and minute taker; and
6. The patient has already been discussed by the PEA MDT meeting and assessed as not suitable for PEA.

The documentation will be captured in the data base and patient case notes.

9 Proposed Patient Pathway

Patients with suspected CTEPH will be diagnosed and managed by a specialist PH centre. Patients will be referred from one of these centres (6 in England) to a provider of PEA, where the patient's suitability for PEA will be assessed. If disease distribution is unsuitable for PEA, the patient will be referred to the BPA provider team. Proposed patient pathway is consistent with current European Society of Cardiology/ European Respiratory Society guidelines (2015 ESC/ERS Guidelines) on the management of CTEPH which is illustrated below.



Source: 2015 ESC/ERS Guidelines

NHS England is only commissioning this service from the current single national PEA provider in the first instance because this is the team that has the expertise to determine whether or not a patient might benefit from PEA or whether BPA is a more appropriate intervention. Once further evidence is gathered, NHS England may decide that it is appropriate to commission a BPA service from additional providers.

NHS England has a published policy on the use of Riociguat for the treatment of PAH and CTEPH [Reference: NHS England: 16055/P].

Current ESC/ERS guidelines (2015 ESC/ERS Guidelines) suggest starting Riociguat as the first line therapy and then proceeding to the BPA if indicated.

Rationale to treat patient first with Riociguat and then proceed then to BPA is:

1. There may be a significant delay between presentation to the PH centre and ability to offer BPA.
2. Adjuvant therapy with PAH targeted therapy may make BPA safer and facilitate BPA treatment (allowing more segments to be treated and therefore fewer procedures).
3. Successful BPA may allow patients to function without targeted pulmonary hypertension therapies, e.g. Riociguat. (See flowchart below for further detail on the patient pathway with the legend further describing clinical criteria at each point in the pathway).

10 Proposed Governance Arrangements

BPA will be commissioned from a single provider with experience of PEA.

11 Proposed Mechanism for Funding

The funding and commissioning will be managed through the relevant local NHS England Specialised Commissioning Team.

12 Proposed Audit Requirements

All patients with CTEPH are already included in the national arrangements for audit of PH. The following information will be collected for all patients treated with BPA as recommended by NICE in its Interventional Procedures Guidance 554, and uploaded to the NHS England QGIS portal:

Summary of data for BPA for chronic thromboembolic PH.

<https://www.nice.org.uk/guidance/ipg554/resources>

This tool helps clinicians using BPA for CTEPH to review clinical outcomes. Data should be reviewed at appropriate intervals and practice should be changed if the

results suggest the need to do so.

The tool contains a data collection sheet containing drop down options and free text boxes. A summary of the data is shown in the tables below:

Consent
A discussion has taken place about the uncertainties surrounding the procedure's safety and efficacy
The patient has received written information explaining that there are uncertainties about the procedure's safety and efficacy
Written consent to treatment has been obtained

Outcome measures of benefit
Improved functional activity (WHO-functional class / NYHA class)
Improved exercise tolerance (6 minute walk test)
Improved pulmonary haemodynamics (pulmonary vascular resistance)
Reduction in the use of oral medication
Other outcome measure of benefit

Adverse outcomes
Mortality resulting from procedure
Perforation
Aneurysm
Reperfusion pulmonary oedema
Haemotysis / haemosputum
Desaturation
Acute kidney injury
Other adverse outcome

To ensure that any valuable insight regarding the consequences of this procedure is shared among clinicians, serious or previously unrecognised patient safety incidents should be documented and information submitted to the National Reporting and Learning System (NRLS), operated by the National Patient Safety Agency.

13 Documents That Have Informed This Policy Proposition

National Institute for Health and Care Excellence (NICE) (2015) Interventional procedures programme. Interventional procedure overview BPA for chronic thromboembolic pulmonary hypertension. IPG554.

NHS England Commissioning Policy: “Targeted Therapies for use in Pulmonary Hypertension in Adults Commissioners PH targeted therapy policy” (NHS England A11/P/c).

14 Date of Review

This document will lapse upon publication by NHS England of a clinical commissioning policy for the proposed intervention that confirms whether it is routinely or non-routinely commissioned.

A routinely commissioned policy should be subject to formal review on publication of the RACE study.

15 References

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Riociguat Versus Balloon Pulmonary Angioplasty in Non-operable Chronic thromboEmbolic Pulmonary Hypertension (RACE), Available at:

<https://clinicaltrials.gov/ct2/show/study/NCT02634203>

Clinical Commissioning Policy: Riociguat for pulmonary arterial hypertension

Reference: NHS England: 16055/P 22 February 2017

<https://www.england.nhs.uk/commissioning/spec-services/npc-crg/group-a/a01/>

END