HAEMOGLOBINOPATHIES - MANAGEMENT OF THALASSAEMIA (MAJOR) & AND SICKLE CELL DISEASE IN PREGNANCY - FULL CLINICAL GUIDELINE

Reference No.: Obs/07:17/H4

Contents

1. Introduction

Haemoglobinopathies are inherited blood disorders in which there is a haemoglobin defect resulting in an abnormal (eg sickle cell) or reduced globin formation (eg thalassaemia).

Sickle cell disease is more common in the local area. The main phenotypes which need special management are Homozygous sickle-cell disease (HbSS), Sickle-cell/HbC (HbSC) and Sickle-cell/thalassaemia (S βthal). Sickling of red cells occurs particularly to trigger factors like hypoxia, cold, acidosis, infection, dehydration and stress. Intravascular sickling leads to vaso-occlusive symptoms and tissue infarction with severe pain. They are chronically anaemic with an individual baseline haemoglobin not routinely requiring blood transfusion.

Thalassaemic disorders that matter in pregnancy are β-thalassaemia major(BTM), β-thalassaemia intermedia(BTI), HbEβ thalassaemia and Haemoglobin H disease (HbH). BTM will need life-long blood transfusions and they continue with it throughout their pregnancy. The clinical course in BTI and HbH is variable. These disorders are less common locally and should be managed on a case-by-case basis.

Pregnancy in a haemoglobinopathy is associated with increased morbidity and mortality. Hence it needs to be managed as a high-risk pregnancy in the hospital jointly by a specialist Consultant Haematologist and Consultant Obstetrician with an individual pregnancy management plan that includes antenatal management, labour and delivery, and postpartum care.

2. Purpose and Outcomes

The purpose of this guideline is to ensure women with a haemoglobinopathy disorder receive appropriate specialist management of their pregnancy, labour and post-partum period to improve co-ordination, communication and liaison between healthcare professionals

3. Abbreviations

BTI	-	β-thalassaemia intermedia
BTM	-	β-thalassaemia major
CMV	-	Cytomegalovirus
CNS	-	Clinical Nurse Specialist
CRP	-	C-Reactive Protein
CXR	-	Chest X-Ray
EMSTN	-	East Midlands Sickle cell and Thalassemia Network
EXT	-	Exchange Blood Transfusion
FASP	-	Fetal Anomaly Screening Programme
FBC	-	Full Blood Count
Hb	-	Haemoglobin
HbS	-	Haemoglobin S
HbSB	-	Haemoglobin SB
HbSS	-	Haemoglobin SS
HDU	-	High Dependency Unit
IOL	-	Induction of Labour
IUCD	-	Intrauterine Contraceptive Device
LFT	-	Liver Function Test
LMW	-	Low Molecular Weight
LW	-	Labour Ward
MDT	-	Multidisciplinary team
MSU	-	Midstream Urine
NSAID	-	Non-Steroid Anti-Inflammatory Drug
O2	-	Oxygen
PAU	-	Pregnancy Assessment Unit
PCA	-	Patient-Controlled Analgesia
PET	-	Pre-Eclamptic Toxemia
PRN	-	Pro Re Nata (as and when)
RBC	-	Red Blood Cells
SCD	-	Sickle cell disease
SOB	-	Shortness of Breath
U&E	-	Urea & Electrolytes
VTE	-	Venous Thromboembolism

4. Key Responsibilities and Duties

- Consultant Haematologist Clinical Lead for Haemoglobinopathy- Author, Clinical advice
- Consultant Obstetricians: Lead Obstetrician for Obstetric Haematology (preconceptual antenatal, intrapartum and postnatal care), Fetal medicine Obstetricians (prenatal diagnosis)
- Antenatal screening midwife (haemoglobinopathy screening)
- Midwife combined obstetric haematology clinic (antenatal care)
- Fetal medicine midwives (prenatal diagnosis)
- Clinical Nurse Specialist in Haemoglobinopathy (clinical advice, referral for preconceptual advice)

5. Management of Pregnant Women with Haemoglobinopathy

All women with known SCD, BTM and BTI, or other serious haemoglobinopathy, should be referred for urgent booking under the Lead Obstetrician for Obstetric Haematology and

managed antenatally in the joint obstetric-haematology service. Urgent requests for prenatal diagnosis by Chorionic villous sampling should be referred directly to fetal medicine.

These cases are discussed at the local haemoglobinopathy multidisciplinary team (MDT) and East Midlands Sickle cell and Thalassemia Network (EMSTN) MDT. The option of maternity care either at the specialist centre (Nottingham University Hospital) or locally in Derby should be discussed with the woman at Consultant Booking appointment. Neonatal Alert to be done by completion of the Sheffield 'Notification of Couples at Risk' form

In the local area the most common haemoglobin disorder is Sickle Cell Disease.

Management of pregnant women who are haemoglobinopathy carriers (Hb AS, HbAC, HbAβthal, Hb Aαthal)

- Care is similar as for any pregnant woman
- Clearly document in the notes to indicate haemoglobinopathy carrier (Ensure partner tested)
- Possible increased risk of urinary tract infections
- If partner is also a carrier, then neonatal testing should be performed before discharge
- If partner's status unknown, ensure neonatal diagnosis arranged

6. Management of Sickle Cell Disease in Pregnancy

Complications for women with SCD can occur during the antenatal period, labour and delivery, and the postpartum.

Maternal Complications:

• Worsening of anaemia
• Increased risk of infection particularly urinary tract infection and chest infection
• Increased sickle cell crises particularly in third trimester or associated with first trimester hyperemesis and dehydration
• Acute chest syndrome (Fever, tachypnoea, pleuritic chest pain)
• Pulmonary thromboembolism
• Increased incidence of preterm labour, pre-eclampsia, pregnancy induced hypertension, need for planned delivery, IOL or caesarean section
• Increased risk of maternal death (approx. 1%)

Fetal Complications:

• Increased risk of miscarriage
• Increased risk of fetal growth restriction
• Increased risk of prematurity
• Increased perinatal mortality 15% i.e.: 15x general population)
• Opiate addiction in the neonate

Antenatal Care

Preconceptual care

All women should have preconceptual planning and screening for chronic disease complications as part of their routine care under their Specialist Haematologist. This should include contraceptive advice, the importance of planned pregnancy, partner screening and advice on medications and vaccinations.

If identified as a 'high risk couple' they should be referred for specialist counselling as per National Screening Committee guidance to discuss the options of preimplantation genetic diagnosis or prenatal diagnosis

In addition all women should be offered a preconceptual appointment with an Obstetrician with a special interest in Haemoglobinopathy to discuss the implications for their pregnancy and their baby. They should be advised to take Folic Acid 5mg od for at least three months preconceptually and be aware of the importance of seeking advice early in pregnancy.

Early booking appointment

- Women should be referred for early booking under the Joint Obstetric Haematology Service
- Women should be booked for delivery in a consultant unit
- Early viability ultrasound 7-9 weeks
- Baseline booking bloods, renal function, liver function, ferritin and extended red cell phenotyping (including full Rh and Kell)
- Baseline MSU and urine protein- creatinine ratio
- Folic acid 5mg od and prophylactic penicillin V 250mg od (or alternative if allergic) to continue throughout pregnancy to prevent pneumococcal infection
- Review disease history and prepregnancy disease screening with Haematologist
- An individualised care plan should be made to include: partner testing or prenatal diagnosis as appropriate; medication review; schedule of antenatal care; PET and VTE prevention; fetal growth surveillance; advice on triggers for sickle cell crisis and self referral pathways; individual parameters to consider transfusion; anaesthetic referral
- Early involvement of Consultant Haematologist, Clinical Lead for Haemoglobinopathy

Antenatal care

- NT scan 11-14 weeks
- Aspirin for PET prevention from 12 weeks
- Monthly MSU and bloods
- Oral iron only if evidence of iron deficiency
- Blood transfusion to be discussed with Consultant Obstetrician or Haematologist
- 16 weeks MDT review
- 20 weeks detailed FASP anomaly scan
- Serial biometry from 24 weeks
- Monthly MDT review
- 2weekly Midwife review from 24 weeks for BP/urinalysis
- MDT intrapartum care planning: haematology, anaesthetic, obstetric, midwifery, neonatal 32-36 weeks
- Recommend planned delivery 38-40 weeks

Give appropriate advice

- Ensure understanding of triggers for sickle cell crisis and increased frequency in pregnancy
- Ensure has simple analgesia available at home suitable for use in pregnancy. NSAIDs can only be used 12-28 weeks gestation.
- Self referral pathways: advise self referral via 24 hr PAU triage and immediate admission to LW, HDU if sickle painful episode or other concerns
- Contact information for CNS Haemoglobinopathy Nurse Specialist
- Self treatment of crisis at home is not appropriate during pregnancy because of the need to monitor the fetus.
- Individual parameters for transfusion and symptoms of anaemia. Blood transfusion is not routinely required if asymptomatic. CMV negative blood must be used for transfusion in pregnancy

In-patient care

- Women having crises need be admitted to High Dependancy unit on the labour ward as soon as possible
- Inform the Haemoglobinopathy Specialist Nurse(CNS), on call Consultant anaesthetist and obstetrician.
- There should be a low threshold for admission if women with sickle cell disease are unwell (e.g. malaise, fever, breathlessness or pain). Any deterioration in maternal health should be taken seriously.
- Discuss promptly with Consultant Haematologist or oncall Consultant Haematologist (if out of hours via switchboard)

Indications for admission include:

- Sickle cell painful crisis
- Increasing anaemia
- Chest pain or dyspnea
- Pre-eclampsia
- Infection

Precipitating factors: Infection, hypoxia, hypothermia, fever, dehydration, pain, pre-eclampsia, acidosis, prolonged labour, operative delivery

Management of Sickle cell painful crisis (Refer to the Full Clinical Guideline on Flo, Reference Number: CG-T/2013/170)

- Admit to HDU on Labour ward
- Keep warm
- Hydration: Encourage normal diet (eating and drinking if not in labour)
- Encourage oral fluids. If unable to maintain oral intake give i.v. fluids to reduce risk of dehydration.
- 60mls/kg/24 hours (risk of overload if pre-eclampsia)
- Maintain strict fluid balance chart.

Initial observations of temperature, pulse rate, BP and pulse oximetry every 20-30 mins reduced to hourly once pain has settled

• If febrile >37.50C take blood cultures, MSU and consider appropriate antibiotics.

• If O2 sats <95% on air – take Arterial Blood Gases and get urgent medical/haematology input. Early consideration of ITU if unable to maintain oxygen saturations
• If PO2 <9kPa on air – discuss need for urgent exchange transfusion with haematology team.
• Humidified O2 41/min to aim for oxygen saturations >95%

Pain relief

• Prompt control of pain is advised to prevent further complications. Aim to give initial analgesia within 30 mins and effective analgesia within 1 hour
• Morphine in addition to paracetamol as regular or PRN and oral, parenteral or PCA should be commenced early depending on the level of pain. If unsure contact Dr Sangam Hebballi or the oncall Consultant Haematologist
• Avoid pethidine due risk of toxicity and maternal seizures. NSAIDs can only be used 12-28 weeks
• Anticipate the need for laxatives and anti-emetics with opiate analgesia

- Investigations
  • Infection screen
  • FBC, CRP, U&E's, LFT's
  • Group and Save; cross match samples
  • Daily urinalysis, weight
- Thromboprophylaxis is crucial for all such admissions with painful crisis due to increased risk VTE
- All infections should be promptly investigated with CXR. Treated with appropriate antibiotics according to the Trust's antibiotic policy after blood cultures and MSU are taken
- Closely monitor for signs and symptoms of acute chest syndrome, a life-threatening sickling complication (tachypnoea, chest pain, SOB, cough, new infiltrate on CXR)- **Refer to the guidelines on Flo : Sickle Cell Disease - Acute Chest Syndrome - Clinical Guidelines Reference Number: CG-HAEM/2016/003**
- Monitor Fetal wellbeing during acute episode according to guidelines and Consultant Obstetric advice
- Physiotherapy if evidence of chest complications
- Blood transfusion may become necessary and should be discussed with Dr Sangam Hebbballi or oncall Consultant Haematologist(if out-of-hours) in view of specific blood requirements in SCD
- Acute stroke should be considered in any woman with acute neurological impairment

Blood transfusion

Blood transfusion is not routinely required if asymptomatic. A randomized trial comparing prophylactic transfusion versus need based transfusion showed no difference in fetal outcome. As multiple transfusion increases the risk of isoimmunisation, transfusion related infections and the need for hospital admissions, transfusion should be reserved for symptomatic patients.

Possible indications for transfusion include:

- Hb < 70g/dl
- Recurrent crisis
- Previous poor obstetric history
- Multiple pregnancy due to increased risk complications
- Patients on hydroxycarbamide pre-conception

ALL TRANSFUSIONS MUST BE DISCUSSED WITH THE HAEMATOLOGY TEAM.

Infections

- All infections should be promptly investigated with CXR
- Treated with appropriate antibiotics according to the Trust's antibiotic policy after blood cultures and MSU are taken
- Avoid hypoxia and dehydration to prevent sickle painful crisis
- Maintain oxygen saturations >95% with humidified O2 if needed
- Intravenous hydration given until infection is controlled
- SROM – discuss with Consultant Obstetrician as increased risk of SCD complications if develops chorioamnionitis. If term advise immediate rather than conservative management.

Labour and delivery

Refer to the Individual Pregnancy Management Plan for the case and inform the Co-ordinating midwife, Consultant Obstetrician, Anaesthetist and Haematologist when admitted
Planned induction of labour should not occur at a weekend unless for emergency indications – discuss with Consultant Obstetrician

General principles
• Keep warm, and well oxygenated and hydrated
Xmatch blood if atypical antibodies
• Half hourly pulse, BP and hourly temp and O2 saturations(if less than 95%, do ABGs, give O2 41/min
and get urgent medical/haematology opinion)
Continuous electronic fetal monitoring
• Prolonged labour should be avoided, with low threshold for assisted delivery/caesarean section as increased stress may trigger a crisis. **Please refer to the guidelines on Flo Sickle Cell Disease - Surgery - Clinical Guidelines Reference Number: CG-HAEM/2015/001**
• If painful crisis occurs give morphine/diamorphine. PCA may be considered
• Analgesia: low threshold for epidural recommended according to patient choice. Avoid pethidine.
Investigate temperature over 37.5
•Occasional Exchange Blood transfusion(EXT) would be needed to in Acute Chest Syndrome or high risk SCD to control sickling crisis. If clinically stable, the woman may need to be transferred to Nottingham HDU and if unstable manual EXT need to be undertaken locally after discussion with the Consultant Haematologist.
Paediatrician at delivery

Postnatal care (refer to individual care plan)

- Admit to LW HDU for immediate postpartum care and monitoring. Maintain maternal hydration and oxygen saturations above 94%
- Give thromboprophylaxis – see individual plan, 6 weeks duration if C/S or antenatal thromboprophylaxis.
- Remain vigilant for complications of SCD: acute crisis; acute chest syndrome; acute stroke; VTE; acute anaemia
- Neonatal samples where indicated need to be taken and sent to Oxford Reference Lab, in addition to the routine heel prick sample (Guthrie test for Universal Neonatal Screening) to the Regional Newborn Screening Lab at Sheffield)

On going care

• Contraception: No contraception is absolutely contra-indicated although the IUCD may be inappropriate because of the risk of infection .The Mirena coil may be highly recommended. The progestogen only pill (Cerazzette) is recommended in preference to the oral contraceptive pill.
• Continue on prophylactic penicillin V and folic acid
• Outpatient appointment for the joint antenatal sickle cell disease clinic in 6 weeks……..RH to add

7. Management of Thalassaemia in Pregnancy

Women with BMT will continue on their regular blood transfusion. There is an increased risk to the mother and baby especially if the mother has iron –overload associated cardiomyopathy. Close fetal monitoring is recommended due to the increased risk of fetal growth restriction.

Preconceptual

Prepregnancy planning with specialist haematologist

Referral for prepregnancy diabetic advice if diabetes, endocrine review if hypothyroid and cardiology review as appropriate

Offer partner screening and discuss preimplantation genetic diagnosis/ prenatal diagnosis as appropriate for high risk couples

Offer referral for prepregnancy obstetric counseling

Recommend prepregnancy folic acid 5mg od for three months prior to pregnancy

At booking
Advise urgent referral for booking under specialist obstetric haematology service

- Care may need to be delivered jointly with the diabetic obstetric team, cardiology and endocrinology team depending on maternal complications of thalassaemia
- Early viability scan 7-9 weeks
- Iron chelation should be stopped (if not stopped ideally 3 months prior to conception). Desferrioxamine should be avoided in the first trimester.
- Other potentially toxic medications (including bisphosphonates) are stopped
- Advise folic acid 5mg od to continue throughout pregnancy
- Review need for penicillin prophylaxis
- Check for presence of any red cell antibodies which may cause a problem with fetus
- Discuss prenatal diagnosis and options for pregnancy
- Anaesthetic referral

Antenatal care

- Monthly MDT review until 28 weeks then 2 weekly
- NT scan 11-14 weeks
- FASP anomaly scan 18-20+6 weeks
- Serial fetal biometry 4 weekly from 24 weeks
- Blood transfusion frequency is likely to remain the same but will increase in the later stages of pregnancy aiming for a pre-transfusion Hb of 100g/l is the aim. Specific requirements are fresh blood, CMV negative, Rh and Kell compatible red cells.
- Aspirin 75mg/day should be offered to those with a platelet count of >600 x10 9/l or have undergone splenectomy

- Thromboprophylaxis to be offered to women who have undergone splenectomy and have a platelet count > 600
- Thromboprophylaxis should be offered for other VTE risks as per unit guidelines
- In exceptional circumstances desferrioxamine chelation may be used from 20-24 weeks gestation. This will usually be in those with evidence of severe iron overload and who may be at risk of cardiac decompensation. This decision would be made by the consultant haematologist following extensive multidisciplinary consultation

*In women with BTI and HbH transfusion may be required in pregnancy if becomes more symptomatic or there is evidence of fetal growth restriction. In general the transfusion management would be similar to thalassaemia major patients in pregnancy. For asymptomatic cases, transfusion should be considered at 37-38 weeks gestation if haemoglobin is <70g/l

Labour and Delivery

Please refer to the Individual Pregnancy Management Plan for the case and contact the team and consultant Haematologist

- Spontaneous labour and delivery is possible unless specific complications, either due to thalassaemia or obstetric, arise.
- Timing of delivery should be dictated by obstetric indications
- Ensure haemoglobin >100g/l prior to delivery, if possible. Cross match will be required for labour if there are RBC antibodies
- *Continuous fetal monitoring*
- *Active management of the third stage to minimise blood loss*
- Postnatal thromboprophylaxis for 7-10 days after vaginal birth, extended to 6 weeks if antenatal clexane or C/S
- Maintain maternal haemoglobin >100g/l post delivery
- There is minimal safety data for breast feeding with deferasirox or deferiprone so these chelators should only be used if there is a decision not to breast feed or when breast feeding has stopped
- Desferrioxamine can be given peripartum and regular regimen commenced after initial 24 hour intravenous desferrioxamine is completed (desferrioxamine is excreted in breast milk but is not orally absorbed so is suitable for breast feeding).
- Post-natal follow-up should be booked as planned (or at 6 weeks if no plan) in the joint Obstetric Haematology clinic and follow-up in the Specialist Haemoglobinopathy Clinic .

8. Monitoring Compliance and Effectiveness

As per agreed business unit audit forward programme

9. References

a. RCOG, 2014: Management of Beta Thalassaemia in Pregnancy. Green top guideline no 66, March 2014

b. RCOG, 2011: Management of Sickle Cell Disease in Pregnancy. Green top guideline no 61, July 2011

c. NICE Sickle cell acute painful episode(CG143) June 2012

d. Standards for the Clinical Care of Adults with Sickle Cell Disease in the UK, 2008

e. Standards for the Clinical Care of Children and Adults with Thalassaemia in the UK, 2008

Communication of positive Haemoglobinopathy in Pregnancy Screening results pathway*

**Please use this flow chart in addition to the Antenatal Screening Tests guideline [OBS/03:16/H11]*

Lab

Haemoglobinopathy found on antenatal screening.

Lab will authorise report so results are available on ICM and enter patient details on shared spreadsheet.
S:\Gynae\Antenatal & Newborn Screening Management\NGH screening\HAEMOGLOBINOPATHY\ANTENATAL & NEONATAL & GENERAL HB'THY\ANTENATAL\Maternity HBE referral spreadsheet.xls

Woman is a carrier for a haemoglobinopathy

Woman has a haemoglobinopathy of uncertain significance.
Enter **Maybe** on Significant Maternal Hb'thy column on spread sheet.
Inform Consultant Haematologist by email.

Woman has a clinically significant haemoglobinopathy.
For example HbSS
Enter **YES** on Significant Maternal Hb'thy column on spread sheet.
Inform Consultant Haematologist by phone & email.

- **Phone result to Antenatal Screening Coordinator (ANSC) / cover midwife in order of preference:**
- Indicate clearly if the woman has a significant haemoglobinopathy or condition of uncertain significance.

1. Phone ANSC office **89924** &/or mobile phone **07585 966169** if no answer leave voicemail
2. Phone cover ANSC (SpMW HIV) mobile phone **07799 337621** if no answer leave voicemail
3. Phone Fetal Medicine **89796 / 85409 / 89797** if no answer email as below:
4. Email to dhft.antenatalandnewbornscreeningRDH@nhs.net **& Flag as ! Urgent**.

- Leave a note to check Haem spread sheet next day to ensure message has been picked up
- Contact ANSC again about any patient not actioned after 3 working days & check daily thereafter
- If results have not been picked up via Haem spread sheet after 5 working days or there are any other issues, please contact Matron for Community & Antenatal Services on **89570 &/or 07788 388437**

Maternity – ANSC or cover midwife

1. Woman is a carrier of a haemoglobin-opathy

2. Woman has a haemoglobinopathy of uncertain significance:
- Enter **Maybe** on Significant Maternal Hb'thy column on spread sheet
- Inform Consultant Haematologist by email.

3. Woman has a clinically significant haemoglobinopathy: For example HbSS, HbS/beta thal or beta thal intermediary
- Enter **YES** on Significant Maternal Hb'thy column on spread sheet.
- Inform Consultant Haematologist by phone & email, plus inform Consultant Obstetrician (FMMC)

- Check result on ICM, review Lorenzo Maternity & Obstetric notes – complete pink SC&T record sheet
- Phone woman to book ANCHM counselling apt to inform woman of result within 3 working days, ask her to bring father of baby
- Offer & (if consents) undertake screening of baby's father ASAP – chase result next day (if declined / unavailable discuss options)
- If normal phone result out OR if abnormal – recall couple for further counselling & discuss / offer PND with FMMC

Refer to NHS SC&T flow chart & table regarding risk assessment for couples

Contact Consultant Haematologist for advice & guidance on how this haemoglobinopathy is likely to behave in pregnancy

Suitab pa t ri

No significant risk to woman during pregnancy.
No further action required.

Potential risk to woman during pregnancy

Refer URGENTLY for Consultant Obstetrician-led care (with Fetal Medicine Specialism) & to Combined Obstetric Haematology Clinic

Documentation Control

<table>
<tr><td>Reference Number:

OBS/07:17/H4</td><td colspan="2">Version: 2</td><td>Status: FINAL</td><td></td></tr>
<tr><td rowspan="3">Version / Amendment</td><td>Version</td><td>Date</td><td>Author</td><td>Reason</td></tr>
<tr><td>1</td><td>August 2003</td><td>Miss A Fowlie
Clinical Director
Dr S Mayne – Consultant Haematologist
Mrs Shamin Khan – Nurse Specialist</td><td>New</td></tr>
<tr><td>2</td><td>January 2017</td><td>Miss Hamilton - Consultant Obstetrician
Dr Hebali –Consultant Haematologist</td><td>Review</td></tr>
<tr><td colspan="5">Intended Recipients: All staff with responsibility for caring for women in the Antenatal period</td></tr>
<tr><td colspan="5">Training and Dissemination:
Cascaded through lead sisters/midwives/doctors; Published on Intranet; NHS Mail circulation list. Article in business newsletter</td></tr>
<tr><td colspan="5">To be read in conjunction with:</td></tr>
<tr><td colspan="2">Development / review of Guideline:</td><td colspan="3">Miss Hamilton - Consultant Obstetrician
Dr Hebali –Consultant Haematologist</td></tr>
<tr><td colspan="2">Consultation with:</td><td colspan="3">Obstetricians, Haematologists</td></tr>
<tr><td colspan="2">Approved By:</td><td colspan="3">10/01/2017 Maternity Guidelines Group: Miss S Rajendran – Chair

12/01/2017 Maternity Development & Governance Committee/ACD - Dr Janet Ashworth

Head of Midwifery / Divisional Nurse Director: Mrs. J Haslam

16/01/2017 Divisional Governance: Dr B Pearson - Chair</td></tr>
<tr><td colspan="2">Approval date CGG:</td><td colspan="3">11/01/2017</td></tr>
<tr><td colspan="2">Implementation date:</td><td colspan="3">10/08/2017</td></tr>
<tr><td colspan="2">Review Date:</td><td colspan="3">July 2020</td></tr>
<tr><td colspan="2">Key Contact:</td><td colspan="3">Cindy Meijer</td></tr>
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