2017 United Kingdom National Guideline for the Management of Pelvic Inflammatory Disease

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What is new in the 2017 update?

- the role of *Mycoplasma genitalium* as an important cause of PID has become clearer and testing is recommended for women presenting with possible PID and the male partners of women with confirmed *M. genitalium* infection
- recent evidence suggests that serious adverse events are uncommon when using moxifloxacin and its use is now recommended as a first line therapy, especially in those women with *M. genitalium* PID
- the potential utility of MRI scanning of the pelvis in excluding differential diagnoses has been highlighted
- doxycycline is now suggested as empirical treatment for male partners of women with PID to reduce exposure to macrolide antibiotics which has been associated with increased resistance in *M. genitalium*
- references have been updated
- the Grade system for reporting strength of evidence has been adopted

Introduction and methodology

Objectives

This guideline offers recommendations on the diagnostic tests, treatment regimens and health promotion principles needed for the effective management of pelvic inflammatory disease (PID) covering the management of the initial presentation, as well as how to reduce transmission, complications and future repeat infection.

It is aimed primarily at women aged 16 years or older (see specific guidelines for those under 16) presenting to health care professionals working in departments offering specialist care in STI management within the United Kingdom. However, the principles of the recommendations should be adopted across all providers – non-specialist providers may need to develop local care pathways where appropriate.

Included in the guideline is a patient information leaflet.

Search strategy

The following reference sources were used to provide a comprehensive basis for the guideline:

1. **Medline Search**

Medline was searched using the search terms: (oophoritis or salpingitis or endometritis or pelvic inflammatory disease or PID or adnexitis or parametritis or adnexal disease) NOT primary immunodeficiency; the search was limited to humans and English language papers. The search was from 1st January 2010 to 17th January 2016 and identified 20,399 titles. Article titles and abstracts were reviewed and if relevant the full text article obtained. Priority was given to randomised controlled trial and systematic review evidence.

2. **2015 CDC STD Treatment Guidelines (www.cdc.gov/std/tg2015/default.htm)**

3. **Cochrane Collaboration Databases (www.cochrane.org)**

A number of limitations were recognised in the evidence base:

- a gold standard for the accurate diagnosis of PID is not available therefore a pragmatic approach to diagnosis and treatment is applied in many clinical trials
- the evidence base for PID treatment mostly comes from studies from several years ago which may not reflect recent changes in antimicrobial sensitivity patterns or newer diagnostic

tests, particularly for gonorrhoea. The management recommendations have therefore been adapted to reflect this.

- there is relatively less data available on the long term effectiveness of therapy compared to short term resolution of symptoms

Methods

Article titles and abstracts were reviewed and if relevant the full text article obtained. Priority was given to randomised controlled trial and systematic review evidence, and recommendations made and graded on the basis of best available evidence. The evidence was compiled by an external information specialist and reviewed by the authors before being incorporated into the guideline using the BASHH framework for guideline development. Successive drafts of the guideline were informed by feedback from the guideline authors. The final draft guideline was used for piloting and external review as outlined below.

An Equality Impact Assessment was undertaken to assess the relevance of the guideline recommendations in relation to age, disability, gender, gender reassignment, pregnancy, race, religion/belief and sexual orientation (Appendix 1).

A lay representative reviewed the guideline and contributed to the development of a patient information leaflet, with the support of co-author CE. This resulted in a number of changes to improve the clarity of both documents. The guideline was also reviewed by the BASHH Public Panel.

Piloting and feedback

Health professional and patient views were further sought by piloting a draft of the guideline with a sample of target users. This was coordinated by the BASHH Clinical Effectiveness Group (CEG) using health care professionals independent from the writing committee who adopt the guideline into their clinical practice in a virtual fashion for a period of time and then provide an evaluation using a standard feedback form.

Aetiology

- pelvic inflammatory disease (PID) is usually the result of infection ascending from the endocervix causing endometritis, salpingitis, parametritis, oophoritis, tuboovarian abcess and/or pelvic peritonitis.
- *Neisseria gonorrhoeae* and *Chlamydia trachomatis* have been identified as causative agents [1-3] but account for only a quarter of cases in the UK, whilst *Gardnerella vaginalis*, anaerobes (including *Prevotella*, *Atopobium* and *Leptotrichia*) and other organisms commonly found in the vagina may also be implicated. *Mycoplasma genitalium* has also been associated with upper genital tract infection in women and is a very likely cause of PID[4,5].
- *Neisseria gonorrhoeae* and *Chlamydia trachomatis* are detected less commonly in older women presenting with PID
- the insertion of an intrauterine device increases the risk of developing PID but only for 4-6 weeks after insertion. This risk is probably highest in women with pre-existing gonorrhoea, chlamydia or bacterial vaginosis.

Clinical Features

Symptoms

The following features are suggestive of a diagnosis of PID[2,3,6,7]

- lower abdominal pain which is typically bilateral (but can be unilateral)
- abnormal vaginal or cervical discharge which is often purulent
- deep dyspareunia
- abnormal vaginal bleeding, including post coital bleeding, inter-menstrual bleeding and menorrhagia
- secondary dysmenorrhoea

Signs

- lower abdominal tenderness which is usually bilateral
- adnexal tenderness on bimanual vaginal examination – a tender mass is sometimes present
- cervical motion tenderness on bimanual vaginal examination
- fever (>38°C) in moderate to severe disease

A diagnosis of PID should be considered, and usually empirical antibiotic treatment offered, in any sexually active woman who has recent onset, bilateral lower abdominal pain associated with local tenderness on bimanual vaginal examination, in whom pregnancy has been excluded and no other cause for the pain has been identified. The risk of PID is highest in women aged under 25 not using barrier contraception and with a history of a new sexual partner.

Complications

- Women with HIV may have more severe symptoms associated with PID but respond well to standard antibiotic therapy[8]. No change in treatment recommendations compared to HIV uninfected patients is required[9-11]. (Grade 1B)
- The Fitz-Hugh Curtis syndrome comprises right upper quadrant pain associated with perihepatitis which occurs in some women with PID, especially when caused by chlamydia. Although laparoscopic division of hepatic adhesions has been performed, there is insufficient clinical trial evidence to make specific recommendations for additional treatment beyond that for uncomplicated PID.
- A tubo-ovarian abscess should be suspected in patients who are systemically unwell and/or have severe pelvic pain. The palpation of an adnexal mass, or lack of response to therapy, should prompt pelvic imaging with ultrasound, CT or MRI. Tubo-ovarian abscess is an indication for hospital admission for parenteral antimicrobial therapy, with appropriate anaerobic cover, and to monitor for signs of rupture or sepsis.
- The randomised controlled trial evidence for whether an intrauterine contraceptive device should be left in situ or removed in women presenting with PID is limited[12-14]. Removal of the IUD when the patient presents should be considered and may be associated with better short term clinical outcomes[12]. When antibiotic treatment is commenced and the IUD is left in situ a review should be performed after 48-72 hours and the IUD removed if significant clinical improvement has not occurred. The decision to remove the IUD needs to be balanced against the risk of pregnancy in those who have had otherwise unprotected intercourse in the preceding 7 days. Emergency hormonal contraception following removal of an IUD may be appropriate for some women in this situation.

Diagnosis

- PID may be symptomatic or asymptomatic. Even when present, clinical symptoms and signs lack sensitivity and specificity (the positive predictive value of a clinical diagnosis is 65-90% compared to laparoscopic diagnosis[3,6,7])
- Testing for gonorrhoea, chlamydia and *M. genitalium* in the lower genital tract is recommended since a positive result supports the diagnosis of PID and may alter subsequent therapy (Grade 1B). The absence of infection at this site does not exclude PID however[3,6,7].
    - Local availability of *M. genitalium* testing currently varies but implementation of testing is strongly recommended to guide the appropriate choice of therapy
- An elevated ESR or C reactive protein, or high blood white cell count, also supports the diagnosis but is non-specific[15] and usually only abnormal in moderate or severe PID.
- The **absence** of endocervical or vaginal pus cells has a good negative predictive value (95%) for a diagnosis of PID but their **presence** is non-specific (poor positive predictive value – 17%)[16].
- Ultrasound scanning is of limited value for uncomplicated PID but is helpful if an abscess or hydrosalpix is suspected[17]. Doppler ultrasound can detect increased blood flow associated with pelvic infection and may be useful, but it cannot differentiate between PID and other causes of increased vascularity such as endometriosis[18,19].
- Magnetic resonance imaging (MRI) or computed tomography (CT) scanning of the pelvis may be helpful in differentiating PID from alternative diagnoses[20-22]. MRI, when available, is preferable since it provides high resolution images and avoids ionising radiation in women of reproductive age.

The differential diagnosis of lower abdominal pain in a young woman includes:

- ectopic pregnancy – pregnancy should be excluded in all women suspected of having PID
- acute appendicitis – nausea and vomiting occurs in most patients with appendicitis but only 50% of those with PID. Cervical movement pain will occur in about a quarter of women with appendicitis[23,24].
- endometriosis – the relationship between symptoms and the menstrual cycle may be helpful in establishing a diagnosis

- complications of an ovarian cyst e.g. torsion or rupture – symptoms are often of sudden onset
- urinary tract infection – often associated with dysuria and/or urinary frequency
- irritable bowel syndrome – disturbance in bowel habit and persistence of symptoms over a prolonged time period are common. Acute bowel infection or diverticular disease can also cause lower abdominal pain usually in association with other gastrointestinal symptoms.
- functional pain (pain of unknown aetiology) – may be associated with longstanding symptoms

Management

It is likely that delaying treatment increases the risk of long term sequelae such as ectopic pregnancy, infertility and pelvic pain[25,26]. Because of this, and the lack of definitive diagnostic criteria, a low threshold for empiric treatment of PID is recommended (Grade 1B). Broad spectrum antibiotic therapy is required to cover a broad spectrum of aerobic and anaerobic bacteria commonly isolated from the upper genital tract in women with PID[2,3].

Some of the best evidence for the effectiveness of antibiotic treatment in preventing the long term complications of PID comes from the PEACH study where women were treated with cefoxitin followed by doxycycline – pregnancy rates after 3 years were similar or higher than those in the general population[27,28].

The choice of an appropriate treatment regimen may be influenced by:

- robust evidence on local antimicrobial sensitivity patterns
- robust evidence on the local epidemiology of specific infections in this setting
- cost
- patient preference and compliance
- severity of disease

General Advice

Rest is advised for those with severe disease. (Grade 1D)

Appropriate analgesia should be provided. (Grade 1D)

Intravenous therapy is recommended for patients with more severe clinical disease (Grade 1D) e.g. pyrexia > 38^{o}C, clinical signs of tubo-ovarian abscess, signs of pelvic peritonitis.

Patients should be advised to avoid intercourse until they, and their partner(s), have completed treatment (Grade 1D).

A detailed explanation of their condition with particular emphasis on the long term implications for the health of themselves and their partner(s) should be provided, reinforced with clear and accurate written information (Grade 1D). A patient information leaflet is included in Appendix 2 of this guideline.

When giving information to patients, the clinician should consider the following:

- an explanation of what treatment is being given and its possible adverse effects
- that following treatment fertility is usually maintained but there remains a risk of future infertility, chronic pelvic pain or ectopic pregnancy
- clinically more severe disease is associated with a greater risk of sequelae
- repeat episodes of PID are associated with an exponential increase in the risk of infertility
- the earlier treatment is given the lower the risk of future fertility problems
- future use of barrier contraception will significantly reduce the risk of PID
- the need to screen sexual contacts for infection to prevent re-infection

Outpatient therapy is as effective as inpatient treatment for patients with clinically mild to moderate PID[27]. Admission for parenteral therapy, observation, further investigation and/or possible surgical intervention should be considered in the following situations (Grade 1D):

- a surgical emergency cannot be excluded
- lack of response to oral therapy
- clinically severe disease
- presence of a tuboovarian abscess
- intolerance to oral therapy
- pregnancy

Further Investigation

All sexually active women who are potentially fertile should be offered a pregnancy test to exclude ectopic pregnancy (Grade 1D).

Treatment

The following antibiotic regimens are evidence based.

Recommended Regimens

All the recommended regimens are of similar efficacy.

Outpatient Regimens

i.m. ceftriaxone[*] 500mg single dose followed by oral doxycycline 100mg twice daily *plus* metronidazole 400mg twice daily for 14 days

Grade 1A[29-31]

[*]Clinical trial data support the use of cefoxitin for the treatment of PID but this agent is not easily available in the UK so ceftriaxone, which has a similar spectrum of activity, is recommended.

oral ofloxacin 400mg twice daily *plus* oral metronidazole 400mg twice daily for 14 days

Grade 1A[31-35]

oral moxifloxacin 400mg once daily for 14 days

Grade 1A[36-38]

Metronidazole is included in some regimens to improve coverage for anaerobic bacteria. Anaerobes are of relatively greater importance in patients with severe PID and metronidazole may be discontinued in those patients with mild or moderate PID who are unable to tolerate it.

Ofloxacin and moxifloxacin should be avoided in patients who are at high risk of gonococcal PID (e.g. when the patient's partner has gonorrhoea, in clinically severe disease, following sexual contact abroad) because of high levels of quinolone resistance [39]. *Neisseria gonorrhoeae* is, however, an uncommon cause of PID in the UK (< 3%) and in those not at high risk of gonorrhoea quinolones can be used as first line empirical treatment, with therapy being adjusted subsequently if testing reveals quinolone resistant *Neisseria gonorrhoeae*.

Levofloxacin is the L isomer of ofloxacin[40] and has the advantage of once daily dosing (500mg OD for 14 days). It may be used as a more convenient alternative to ofloxacin[36].

Three large RCTs support the efficacy of moxifloxacin for PID. There is a potential risk of serious liver reactions occurring with this agent but they are uncommon (12 cases reported in the UK from 2003-16 with no deaths) and moxifloxacin is generally well tolerated[41] (Grade 1D). Of the three recommended PID treatment regimens, moxifloxacin provides the highest microbiological activity against *M. genitalium*.

Quinilones (ofloxacin, moxifloxacin,levofloxacin) are not licensed for use in patients aged under 18.

Replacing intramuscular ceftriaxone with an oral cephalosporin (e.g. cefixime) is not recommended because there is no clinical trial evidence to support its use, and tissue levels are likely to be lower which might impact on efficacy. Reports of decreasing susceptibility of *Neisseria gonorrhoeae* to

cephalosporins also supports the use of parenteral based regimens when gonococcal PID is suspected (to maximise tissue levels and overcome low level resistance).

Azithromycin is recommended in some guidelines as additional treatment for uncomplicated gonorrhoea. It is not recommended for gonococcal PID for the following reasons:

- azithromycin is used to 'protect' cephalosporin therapy to try slow down the development of resistance
- the number of cases of gonococcal PID in the UK is very small (2-3% of all PID)
- use of the 'non-azithromycin containing' regimens listed above is clinically effective
- adherence rates for two weeks of current PID treatment are poor[42] and the addition of azithromycin may lead to early discontinuation of medication in a number of additional women

Alternative Regimens

intramuscular ceftriaxone 500 mg immediately, followed by azithromycin 1 g/week for 2 weeks

Grade 2B[43,44]

Clinical trial evidence for this regimen is limited but it may be used when the treatments above are not appropriate e.g. allergy, intolerance. Single doses of azithromycin have the potential to induce macrolide resistance in M*ycoplasma genitalium* and, if possible, use should be restricted to women who are known to be *M. genitalium* negative.

Inpatient Regimens

i.v. ceftriaxone 2g daily *plus* i.v. doxycycline 100mg twice daily (oral doxycycline may be used if tolerated) followed by oral doxycycline 100mg twice daily *plus* oral metronidazole 400mg twice daily for a total of 14 days

Grade 1A[30,31]

i.v. clindamycin 900mg 3 times daily *plus* i.v. gentamicin (2mg/kg loading dose) followed by 1.5mg/kg 3 times daily [a single daily dose of 7mg/kg may be substituted]) followed by either oral clindamycin 450mg 4 times daily or oral doxycycline 100mg twice daily plus oral metronidazole 400mg twice daily to complete 14 days

Grade 1A[30]

Gentamicin levels should be monitored if this regimen is used.

Intravenous therapy should be continued until 24 hours after clinical improvement and then switched to oral (Grade 2D). Intravenous doxycycline is not currently licensed in the UK but is available from IDIS world medicines (01932 824100).

Alternative Regimens

Clinical trial evidence for the following regimens is more limited but they may be used when the treatments above are not appropriate e.g. allergy, intolerance:

i.v. ofloxacin 400mg BD *plus* i.v. metronidazole 500mg TID for 14 days

Grade 1B[31-33]

i.v. ciprofloxacin 200mg BD plus i.v. (or oral) doxycycline 100mg BD plus i.v. metronidazole 500mg TID for 14 days

Grade 1B[32,45]

Allergy

There is no clear evidence of the superiority of any one of the suggested first line regimens over the others. Therefore patients known to be allergic to one of the suggested regimens should be treated with an alternative.

Pregnancy and Breastfeeding

- PID in pregnancy is uncommon but associated with an increase in both maternal and fetal morbidity, therefore parenteral therapy is advised although none of the suggested evidence based regimens are of proven safety in this situation.
- There are insufficient data from clinical trials to recommend a specific regimen and empirical therapy with agents effective against gonorrhoea, chlamydia and anaerobic infections should be considered taking into account local antibiotic sensitivity patterns (e.g. i.m. ceftriaxone plus

oral or i.v. erythromycin, with the addition of oral or i.v. metronidazole in clinically severe disease) (Grade 2D).

- The risk of giving any of the recommended antibiotic regimens (listed above for non pregnant women) in very early pregnancy (prior to a pregnancy test becoming positive) is justified by the need to provide effective therapy and the low risk to the foetus (personal communication, UK National Teratology Information Service – 11.2.10).

Surgical Management

- Laparoscopy may help early resolution of severe disease by dividing adhesions and draining pelvic abscesses[46] but ultrasound guided aspiration of pelvic fluid collections is less invasive and may be equally effective[47,48]
- Laparotomy may be required to assess and treat clinically severe pelvic infection
- It is possible to perform adhesiolysis in cases of perihepatitis but there is no evidence on whether this is superior to only using antibiotic therapy

Follow Up

Review at 72 hours is recommended[7] for those with a moderate or severe clinical presentation, or if the patient has not had a substantial improvement in clinical symptoms and signs (Grade 2D). Failure to improve suggests the need for further investigation, parenteral therapy and/or surgical intervention.

Further review, either in clinic or by phone, 2-4 weeks after therapy is recommended (Grade 1D) to ensure:

- adequate clinical response to treatment
- compliance with oral antibiotics
- screening and treatment of sexual contacts
- awareness of the significance of PID and its sequelae
- repeat pregnancy test, if clinically indicated

If initial testing for gonorrhoea was positive, repeat testing should be performed after 2 to 4 weeks. If initial testing for chlamydia was positive, repeat testing after 2 to 4 weeks is appropriate for women

who have persisting symptoms,or where compliance with antibiotics and/or tracing of sexual contacts indicate the possibility of persisting or recurrent infection.

The following are recommended if the initial test for *M. genitalium* is positive:

- treatment with moxifloxacin. This agent currently has good microbiological activity against *M. genitalium* (Grade 1D)
- repeat testing for *M. genitalium* to ensure microbiological clearance. Treatment failure following use of any of the recommended regimens has been reported but is least likely following treatment with moxifloxacin. The optimal time for testing after starting treatment is not known but 4 weeks is recommended based on expert opinion[49,50] (Grade 1D).

Partner Notification and Treatment of Sexual Partners

- Current male partners of women with PID should be contacted and offered health advice and screening for gonorrhoea and chlamydia (Grade 1D). Other recent sexual partners may also be offered screening - tracing of contacts within a 6 month period of onset of symptoms is recommended but this time period may be influenced by the sexual history (Grade 2D).
- Gonorrhoea or chlamydia diagnosed in the male partner should be treated appropriately and concurrently with the index patient according to the relevant BASHH guideline at www.bashh.org (Grade 1D).
- In women with confirmed *M. genitalium* infection, their male partner(s) should be offered testing for *M. genitalium* and, if positive, treated appropriately and concurrently with the index case (for appropriate treatment regimens see the BASHH Non-specific Urethritis Guideline – www.bashh.org)
- Because many cases of PID are not associated with gonorrhoea, chlamydia or *M. genitalium*, broad spectrum empirical therapy should also be offered to male partners e.g. doxycycline 100mg twice daily for 1 week (Grade 2D).
- Partners should be advised to avoid intercourse until they and the index patient have completed the treatment course (Grade 1D).

Auditable Outcome Measures

Appropriate short term audit outcomes include:

- proportion of women receiving treatment with a recommended regimen – target 95%
- number of named male contacts screened for infection and/or treated – target 0.4 (verified by a health care worker) or 0.6 (reported by patient) per index case[51]

Recommendations for future research

- assessment of the utility of metronidazole as an adjunctive therapy for patients with mild to moderate PID
- development of sensitive and specific diagnostic tests
- assessment of efficacy of a single dose of ceftriaxone therapy in the treatment of gonococcal PID

Qualifying statement

The recommendations in this guideline may not be appropriate for use in all clinical situations. Decisions to follow these recommendations must be based on the professional judgement of the clinician and consideration of individual patient circumstances and available resources.

All possible care has been undertaken to ensure the publication of the correct dosage of medication and route of administration. However, it remains the responsibility of the prescribing physician to ensure the accuracy and appropriateness of the medication they prescribe.

Editorial independence

This guideline was commissioned, edited and endorsed by the BASHH CEG. The group receives funding from BASHH for external researcher support which was used in the production of this guideline.

Declarations of interest

All members of the guideline writing committee completed the BASHH conflict of interest declaration detailed below at the time the guideline's final draft was submitted to the CEG. JR has received consultancy fees from BD Diagnostics.

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Timescale for next revision

An author group will be invited by the BASHH CEG to review and revise the guideline in 2022 using the BASHH framework for guideline development.

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Appendix 1: Equality Impact Assessment

Topic suggestion: impact assessment				
Guidance title: BASHH Guidelines for the Management of Pelvic Inflammatory Disease 2017 Completed by Dr. Darren Cousins				
How relevant is the topic to equality?	Inequalities in health impact of the condition or public health issue	Potential of guidance to add value	Priority for NHS or other government department	Topic relevance: conclusions and outcome

	- Prevalence and impact of condition or public health problem - Prevalence of risk factors	- Inequalities in access, uptake or impact - Timeliness - Equality issues identified by proposers of this topic - Equality issues identified by patient or lay organisations	- Department of Health - DCLG, DCSF. DoT, Home Office, etc. - Other agency or ALB - Agencies in devolved nations	- High/medium/low/ none - Not known/inconclusive - Reasons for rating - Recommendation
Gender - Women - Men	This disease does not present in men	Clear guidance on treatment of male contact of patients with this condition	Society of Sexual Health Advisers (SSHA)	Low
Race - Asian or Asian British - Black or Black British - People of mixed race - Irish - White British - Chinese - Other minority groups not listed	The highest rates of STI diagnoses at sexual health clinics are found among people of black ethnicity in deprived areas. This is most likely seen as a consequence of a complex interplay of cultural, economic and behavioural factors.	Accurate diagnosis and better tolerated treatments should improve the burden of disease in the community	Dept of Health	Medium
Disability - Sensory - Learning disability - Mental health - Cognitive - Mobility - Other impairment	There is no data to suggest any link between this condition and disability status, although people with mental health problems are at disproportionate risk of STIs in general	None identified although use of clinical tests in guideline may improve diagnostic accuracy in non verbalising patients	Dept of Health	Low
Age - Older people - Children and young people - Young adults	Young woman are disproportionately at greater risk of this condition in common with other sexually transmitted infections	Accurate diagnosis and better tolerated treatments should improve the burden of disease in the community	Dept of Health	Medium

Sexual orientation and gender identity - Lesbians - Gay men - Bisexual people - Transgender people	This disease does not present in men. There is little data on the prevalence of this condition in gay or bisexual women	None identified	Dept of Health Commissioners of local sexual health services	Low
Religion / belief	There is no data to suggest any link between religion or belief and this condition	None identified	None identified	Low
Socioeconomic status	There is no specific data to suggest any link between this condition and socioeconomic status, although people of low socioeconomic status are disproportionately higher risk of STIs in general	Accurate diagnosis and better tolerated treatments should improve the burden of disease in the community	Commissioners of local sexual health services National public health agencies that consider data collection in sexual health (e.g. Public Health England)	Medium
Other categories - Gypsy travellers - Refugees and asylum seekers - Migrant workers - Looked after children - Homeless people	There is no data to suggest any link between this condition and these categories although some people in these categories may not be identified by sexual health services	None identified	Commissioners of local sexual health services National public health agencies that consider data collection in sexual health (e.g. Public Health England)	Low

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Appendix 2: Patient information leaflet on PID

To follow

References

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