Template Protocol for non-CTIMPs

CytoLUTs

Cytokines in the bladder: an investigation of inflammatory cytokine expression in the urine and bladder tissue of women with chronic lower urinary tract symptoms

Version 1, 27/11/2024

MAIN SPONSOR: Imperial College London/Imperial College Healthcare NHS Trust
FUNDERS: British Society of Urogynaecology
STUDY COORDINATION CENTRE:

IRAS Project ID: **351850**
REC reference: xxx

Protocol authorised by:

Name & Role	**Date**	**Signature**

Study Management Group

Chief Investigator: Professor Vik Khullar

MD student and principal investigator: Dr Bernadette Lemmon

Co-investigators and supervisors: Dr Edward Mullins, Professor Maria Kyrgiou

Study Management: Dr Bernadette Lemmon

For general queries, supply of study documentation, and collection of data, please contact:

Study Coordinator: Dr Bernadette Lemmon
Address: St Mary's urogynaecology department, Praed street, London, W2 1NY

Tel: 07961949624 E-mail: blemmon@nhs.net

Clinical Queries

Clinical queries should be directed to Dr Bernadette Lemmon who will answer directly or escalate queries to the appropriate person

Sponsor

Imperial College Healthcare NHS Trust is the main research Sponsor for this study. For further information regarding the sponsorship conditions, please contact the Head of Regulatory Compliance at:

Research Governance and Integrity Team
Imperial College London and Imperial College Healthcare NHS Trust
Room 215, Level 2, Medical School Building
Norfolk Place
London, W2 1PG

Tel: **0207 594 9480**
Imperial College - Research Governance and Integrity Team (RGIT) Website

Funder

British Society of Urogynaecology

This protocol describes the CytoLUTs study and provides information about procedures for entering participants. Every care was taken in its drafting, but corrections or amendments may be necessary. These will be circulated to investigators in the study. Problems relating to this study should be referred, in the first instance, to the Chief Investigator.

This study will adhere to the principles outlined in the UK Policy Frame Work for Health and Social Care Research. It will be conducted in compliance with the protocol, the Data Protection Act and other regulatory requirements as appropriate.

Table of Contents

GLOSSARY OF ABBREVIATIONS

LUTS	Lower urinary tract symptoms
BPS	Bladder pain syndrome
OAB	Overactive bladder
UTI	Urinary tract infection
rUTI	Recurrent urinary tract infection
KHQ	King's Health Questionnaire
ICIQ-fluts	International consultation on incontinence questionnaire-female lower urinary tract symptoms

KEYWORDS
Lower urinary tract symptoms
Bladder pain syndrome
Overactive bladder syndrome
Recurrent urinary tract infections
Inflammation
cytokines

STUDY SUMMARY

TITLE Cytokines in the bladder: an investigation of inflammatory cytokine expression in the urine and bladder tissue of women with chronic lower urinary tract symptoms

DESIGN Laboratory and Questionnaire based observational cohort study

AIMS To understand inflammatory cytokine expression in the urine and bladder tissue of women with different chronic urinary symptoms

OUTCOME MEASURES
1) Measurement of cytokine levels the urine and bladder tissue of women with lower urinary tract symptoms compared to healthy controls
2) Measurement of cytokine levels between women with different chronic lower urinary tract symptoms: bladder pain syndrome, overactive bladder syndrome, recurrent urinary tract infections
3) Comparison of cytokine levels in paired urine and bladder tissue samples

POPULATION Study group: 60, control group: 12

ELIGIBILITY Women equal or over the age of 18 years old, with lower urinary tract symptoms lasting for over three months who are already undergoing cystoscopy and bladder biopsy procedures as part of their routine NHS care.

DURATION 24 months

1. INTRODUCTION

1.1. BACKGROUND

Lower urinary tract symptoms (LUTS), including urinary incontinence (UI), urgency, nocturia and bladder pain are common problems affecting approximately half of the female population. Despite the widespread prevalence of LUTS the underlying aetiology is poorly defined. OAB as a symptom complex is likely the result of multiple underlying pathological processes [1]. It is widely acknowledged that an inflammatory process has a central role in BPS [2] but studies of bladder biopsies taken from patients with OAB have also found signs of inflammation [3] [4]. We will examine the presence of various inflammatory mediators in bladder biopsies and urine samples taken from women with OAB and BPS for comparison with normal controls. As there is often overlap and difficulty in diagnosis of women with recurrent urinary tract infections, we will also be studying women with recurrent urine infections. We will be aiming to look for groups of cytokines that exist together that main point toward inflammatory pathways that are triggered in patients with bladder pain and overactive bladder syndrome- but also look at the inflammatory pathways triggered in those with recurrent infection to see if these three groups show any distinct differences in the inflammatory pathways mediated.

Bladder pain syndrome (BPS) describes a collection of chronic urinary symptoms characterised by suprapubic pain or pressure, often accompanied by urinary frequency, urgency, and/or nocturia, in the absence of infection or other obvious pathology [5]. These symptoms preferentially affect women with an estimated prevalence in the US of 3-8 million women and 1-4 million men [6]. Due to its chronic and sometimes debilitating nature, BPS has a huge psychological and social impact on an affected individual as well as carrying a large economic burden. One study has shown that loss of productivity and cost of therapy for those with BPS reaches 500 million dollars annually in the US [7]. BPS is poorly understood with both the aetiology and pathophysiology being unknown. Symptoms overlap with other disorders, such as overactive bladder (OAB) and endometriosis, making a consensus on how to diagnosis and manage patients challenging. A survey of urogynaecologists in the UK has shown a large variation in how clinicians diagnose and treat women with BPS [8]. BPS, PBS (painful bladder syndrome), interstitial cystitis (IC), and IC/BPS are all terms used in the literature, highlighting some of the controversial changes in terminology over the years. To understand better we must look at the historical timeline of BPS or IC/BPS. An inflammatory condition of the bladder “tic douloureux” was first described by Dr Philip Physick and Dr Joseph Parish. The concept together with cystoscopic features was further developed and called interstitial cystitis (IC) in 1887 by Skene and more work was published in 1914 by Hunner, after whom “Hunner’s lesions” are named [9]. In 1987 the National Institute of Diabetes and Kidney Diseases (NIDDK) published criteria to standardise the diagnosis of IC for research. This definition required glomerulations (petechial haemorrhages) and/or Hunner’s lesions on cystoscopy for diagnosis. With only an estimated 5-7% of patients with BPS displaying these features on cystoscopy, a large group with chronic bladder pain were left without

diagnosis [10]. To address this, the International Continence Society (ICS) proposed a change in terminology from IC to BPS in 2002. The ICS categorised BPS patients as those experiencing bladder pain on filling with or without additional urinary symptoms, reserving the term IC only for those with typical cystoscopic features (Hunner's Lesions) [11]. There remains no agreement on nomenclature which has led to the development of IC/BPS as an umbrella term which describes a symptom complex that may encompass several distinct pathologies.
The aetiology of BPS remains unknown, however there are multiple proposed theories including: bladder epithelial dysfunction [12], mast cell activation [13], persistent infection, and pelvic floor hypertonicity [14]. It is likely that some or all of these play a part in the resultant presentation. One proposed pathway is that a primary insult causing uroepithelial dysfunction, leads to a dysregulated inflammatory response in susceptible individuals, and a "vicious cycle" of further epithelial damage and inflammation. Inflammatory mediators may go on to promote afferent nerve hyperexcitability leading to initially an acute and then a chronic pain response [15]. It may be that variation in the "dysregulated inflammatory" response leads to the heterogeneity seen in BPS. Individuals with BPS may have a variety of activated immune mediated pathways that leads to their symptoms, and greater understanding may allow us to subcategorise BPS patients and individualise treatment.

The development of a biomarker for BPS may be the key to understanding more about its pathophysiology, as well as aiding diagnosis, and discovering new drug targets for its management. As inflammation is widely understood to hold a central role in BPS, the evaluation of cytokines has gained interest.

Cytokines are a broad category of small 6-70kDa proteins involved in cell signalling [16]. They are known to support autocrine, paracrine, and endocrine functions, as well as being vital in immune responses, inflammation, and nociception. There are many types of cytokines including chemokines (chemotactic cytokines, cytokines that trigger movement of immune cells), interleukins (term derived from 'cytokines produced by white blood cells' but this is historical as since this terminology it's been found that interleukins are produced by a variety of immune cells), and tumour necrosis factors (type II transmembrane proteins that can be released from the cell membrane to function as a cytokine), as well as some growth factors (cytokines that stimulate cell proliferation), with overlapping terminology [17]. In immune responses a single cytokine can be produced by many immune cell types including macrophages, T-cells, B-cells, and mast cells, and one immune cell type may release several different cytokines. Cytokines act through cell surface receptors as they cannot cross the lipid bilayer into the cytoplasm. Expression of cytokines is needed for the infiltration of cells of the immune system and cell adhesion that is seen in tissue inflammation [18]. Whilst inflammation is a vital process for tissue healing and its initial role is protective, a prolonged inflammatory process becomes problematic, inducing tissue damage and pain. A single cytokine can have both anti-inflammatory and pro-inflammatory actions, be secreted by multiple cell types, and act on receptors of many cell types. Therefore, the activity of a cytokine depends on context [19].

Many cytokines are known to directly activate nociceptive sensory neurons causing pain [20]. The activation of inflammatory pathways also leads to inflammation-induced central sensitisation that can be seen in chronic pain syndromes like BPS.
Many cytokines have been found at higher levels in the serum, urine, and in bladder biopsies taken from patients with BPS. Furthermore, detrusor cells cultured from the human bladder have been shown to increase production of several cytokines when exposed to the inflammatory mediators Il-1β and TNF-α. Understanding which of these cytokines are key in the pathophysiology of BPS may result in the discovery of a clinically useful biomarker of disease.

In this study we will be collecting urine and bladder tissue samples from participants as paired samples taken at the time of cystoscopy and bladder biopsy under a general anaesthetic. Urine samples and bladder tissue will immediately be taken to our on-site laboratory where the bladder tissue is snap frozen at -80^{0}C and stored. Urine is first centrifuged at 1800 RPM at 4^{o}C for 10minutes and then 2x 500µl aliquots are pipetted into sterile eppendorf tubes for storage at -80^{o}C. All samples are only subjected to a single thawing process prior to cytokine analysis using a sandwich ELISA multiplex bead assay technique with plates being read by a Luminex machine.

Specific Aims: We hypothesise that different inflammatory proteins may drive the disease process of bladder inflammation in bladder pain syndrome, overactive bladder syndrome, and that there may be a completely different pattern triggered by infection in those suffering with recurrent urinary tract infections.
In previous research there has been an attempt to find a single inflammatory mediator as a biomarker of disease and this has failed. We believe that one single biomarker will not be found but that the pathway of inflammation is the key to better understanding.
Understanding the inflammatory proteins expressed in these separate clinical conditions may lead to better understanding of the underlying causes of bladder inflammation leading to possible targets of treatment.

1.2 RATIONALE FOR CURRENT STUDY

There have been multiple research projects and groups who have investigated urine expression of inflammatory cytokines in women with bladder pain syndrome in the search for a single biomarker of disease. This has failed so far as this is such a heterogenous condition with multiple phenotypes. Bladder pain syndrome remains poorly understood with the aetiology unknown. In this project we will not only look at bladder pain syndrome but women with a variety of chronic lower urinary tract symptoms as there are often overlapping symptoms and conditions. By looking at a panel of inflammatory cytokines in both urine and bladder tissue we aim to investigate whether there are particular inflammatory pathways triggered rather than looking for one single biomarker. We hope that by understanding patterns of inflammation better we may come to understand further some of the inflammatory processes that may be underlying some of these bladder conditions and the symptoms that women experiences.

The cytokines chosen for investigation have been chosen based on an extensive literature review of published articles investigating cytokine expression in women with bladder pain syndrome. This literature review has been published with the reference:

Lemmon B, Kyrgiou M, Mullins E, Khullar V. Cytokines in Bladder Pain Syndrome: A Review of the Literature. Int Urogynecol J. 2024 Jun;35(6):1119-1129. doi: 10.1007/s00192-024-05778-4. Epub 2024 May 21. PMID: 38771505.

2. STUDY OBJECTIVES

Primary objective:

1. Do women with chronic lower urinary tract symptoms have higher levels of inflammatory cytokines in their urine and bladder tissue versus controls?

Secondary objectives:

2. Do women with different lower urinary tract symptoms show a different expression of inflammatory cytokine expression in the conditions:
    a. Bladder pain syndrome
    b. Overactive bladder syndrome

3. Do women with acute or recurrent urinary tract infection display a distinct inflammatory pattern in their cytokine expression?

4. Is there a difference in measurable cytokine levels in paired urine and bladder tissue samples taken from our participants?

3. STUDY DESIGN

In this study women already undergoing cystoscopy and bladder biopsy procedures under a general anaesthetic will be invited for participation. Participants will be asked to fill out validated symptoms questionnaires about their symptoms and then urine and an extra bladder biopsy will be taken for cytokine analysis.

3.1. STUDY OUTCOME MEASURES

Primary study outcomes:

1) Do women with chronic lower urinary tract symptoms have high inflammatory cytokine expression in urine and bladder tissue versus healthy controls?

Secondary study outcomes:

2) Do women with different chronic lower urinary tract symptoms display different expression of inflammatory cytokines in urine and bladder tissue?
3) Do women with current or recurrent infection have a distinct inflammatory pattern expressed? Does this help differentiate between women with overlapping urinary symptoms?
4) Is there a difference in cytokine expression in paired urine and bladder tissue samples?

4. PARTICIPANT ENTRY

4.1. PRE-REGISTRATION EVALUATIONS

THERE IS NO PRE-REGISTRATION EVALUATION REQUIRED AS EXTRA FOR PARTICIPATION IN THIS STUDY

4.2. INCLUSION CRITERIA

- Women over or equal to 18 years old
- With a 3month history or more of troublesome lower urinary tract symptoms
- Who are already being investigated with a cystoscopy and bladder biopsy procedure as part of their routine NHS care
- Who understand the English language enough to be able to fill out three validated questionnaires about their urinary tract symptoms
- Who have the capacity to consent themselves for research
- Who are willing to sign a consent form for research participation

4.3. EXCLUSION CRITERIA

- Women under the age of 18 years old
- Women who are unable to consent for research themselves
- Women who do not understand English enough to fill out the validated questionnaires in English
- Women with a past history of urological malignancy
- Women with current urological malignancy
- Women who have had a previous procedure for stress urinary incontinence involving mesh such as a tension-free vaginal tape

4.4. WITHDRAWAL CRITERIA

As participation involves only one day the only criteria for withdrawal is if a participant wishes to withdraw from the study.

5. ADVERSE EVENTS

5.1. DEFINITIONS

Adverse Event (AE): any untoward medical occurrence in a patient or clinical study subject.

Serious Adverse Event (SAE): any untoward medical occurrence or effect that:

- **Results in death**
- **Is life-threatening** – *refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe*

- **Requires hospitalisation, or prolongation of existing inpatients' hospitalisation**
- **Results in persistent or significant disability or incapacity**
- **Is a congenital anomaly or birth defect**

Medical judgement should be exercised in deciding whether an AE is serious in other situations. Important AEs that are not immediately life-threatening or do not result in death or hospitalisation but may jeopardise the subject or may require intervention to prevent one of the other outcomes listed in the definition above, should also be considered serious.

5.2. REPORTING PROCEDURES

All adverse events will be reported. Depending on the nature of the event the reporting procedures below should be followed. Any questions concerning adverse event reporting should be directed to the Chief Investigator in the first instance.

5.3.1 Non serious AEs

All such events, whether expected or not, should be recorded- it should be specified if only some non-serious AEs will be recorded, any reporting should be consistent with the purpose of the trial end points.

5.3.2 Serious AEs

An SAE form should be completed and emailed to the Chief Investigator within 24 hours. However, relapse and death as a result of other health conditions, and hospitalisations for elective treatment of a pre-existing condition do not need reporting as SAEs.

All SAEs should be reported internally to ICHTB as per SOP-DOC-030 and to the Research and Ethics Council of England and Wales where in the opinion of the Chief Investigator, the event was:

- 'related', ie resulted from the administration of any of the research procedures; and
- 'unexpected', ie an event that is not listed in the protocol as an expected occurrence

Reports of related and unexpected SAEs should be submitted within 15 days of the Chief Investigator becoming aware of the event, using the NRES SAE form for non-IMP studies. The Chief Investigator must also notify the Sponsor of all related and unexpected SAEs.

Local investigators should report any SAEs as required by their Local Research Ethics Committee, Sponsor and/or Research & Development Office.

Contact details for reporting SAEs
RGIT@imperial.ac.uk
CI email (and contact details below)

Please send SAE forms to: blemmon@nhs.net

6. ASSESSMENT AND FOLLOW-UP

Women participating will all already be undergoing a cystoscopy and bladder biopsy procedure as part of their routine NHS care. Participation in this project does not alter any aspect of their NHS care. This means that their follow-up will be as planned by their direct NHS care team. This usually involves either a virtual or in-person clinic appointment to discuss the findings and results of their procedure. There is no scheduled or required follow-up of participants for this research project.

End of the study will be defined by successful recruitment of 60 study participants and 12 controls, with analysis of cytokine expression in samples obtained, analysis of data and write-up of an MD(res) thesis.

7. STATISTICS AND DATA ANALYSIS

Data and all appropriate documentation will be stored for a minimum of 5 years after the completion of the study, including the follow-up period.

8. REGULATORY ISSUES

8.1. ETHICS APPROVAL

The Study Coordination Centre has obtained approval from the Imperial College Healthcare Tissue and Biobank (ICHTB). The ethics under which the ICHTB operates is approved and is regularly reviewed by the Research Ethics Committee (REC) in Wales (Wales REC3) and Health Research Authority (HRA).
The study will be conducted in accordance with the recommendations for physicians involved in research on human subjects adopted by the 18th World Medical Assembly, Helsinki 1964 and later revisions.

8.2. CONSENT

Consent to enter the study must be sought from each participant only after a full explanation has been given, an information leaflet offered and time allowed for consideration. Signed participant consent will be obtained, entered onto each participants electronic hospital health record, and a hard copy offered to the particiants to keep, and stored by the research team for audit purposes. The right of the participant to refuse to participate without giving reasons will be respected. After the participant has entered the study the clinician remains free to give alternative treatment to that specified in the protocol at any stage if he/she feels it is in the participant's best interest, but the reasons for doing so should be recorded. In these cases the participants remain within the study for the purposes of follow-up and data analysis. All participants are free to withdraw at any time from the protocol treatment without giving reasons and without prejudicing further treatment.

8.3. CONFIDENTIALITY

The Chief Investigator will preserve the confidentiality of participants taking part in the study and is registered under the Data Protection Act.

Data will be pseudonymised with a unique research study code when entered onto the research database. There will not be any transference of data to third parties.

8.4. INDEMNITY

Imperial College Healthcare NHS Trust holds standard NHS Hospital Indemnity and insurance cover with NHS Resolution for NHS Trusts in England, which apply to this study.

8.5. SPONSOR

Imperial College Healthcare NHS Trust will act as the main Sponsor for this study. Delegated responsibilities will be assigned to the NHS trusts taking part in this study.

8.6. FUNDING

The British Society of Urogynaecology (BSUG) are funding this study. There are no per participants payments and no payments to investigators

8.7. AUDITS

The study may be subject to audit by Imperial College London/ Imperial College Healthcare NHS Trust under their remit as sponsor and other regulatory bodies to ensure adherence to GCP and the UK Policy Frame Work for Health and Social Care Research.

9. STUDY MANAGEMENT

The day-to-day management of the study will be co-ordinated through Dr Bernadette Lemmon.

10. PUBLICATION POLICY

This study has been submitted to the ISRCTN (International Standard Randomised Controlled Trial Number) registry. As part of this registration, results of this study will be published on this registry. Results will also be published in a peer reviewed journal following completion. Results will also be published internally with the ICHTB as part of the ICHTB ethical code.

11. REFERENCES

1) Blaivas, J. (2009). Overactive bladder: a new paradigm. Int Urogynaecol J Pelvic Floor Dysfunct, 1401-1402.
2) Sant, K. M. (2007). The mast cell in interstitial cystitis: role in pathophysiology and pathogenesis. Urology, supplement 4, 34-40.
3) Comperat E, R. A.-K. (2006). Histologic features in the urinary bladder wall affected from neurogenic overactivity- a comparison of inflammation, oedema and fibrosis with and without injection of Botulinum toxin type A. Eur Urol, 1058-64.
4) Apostolidis A, J. T. (2008). Histological changes in the urothelium and suburothelium of human overactive bladder following intra-detrusor injections of Botulinum neurotoxin type A for the treatment of neurogenic or idiopathic detrusor overactivity. Eur Urol, 1245-53.
5) Doggweiler R, Whitmore KE, Meijlink JM, Drake MJ, Frawley H, Nordling J, Hanno P, Fraser MO, Homma Y, Garrido G, Gomes MJ, Elneil S, van de Merwe JP, Lin ATL, Tomoe H. A standard for terminology in chronic pelvic pain syndromes: A report from the chronic pelvic pain working group of the international continence society. Neurourol Urodyn. 2017 Apr;36(4):984-1008. doi: 10.1002/nau.23072. Epub 2016 Aug 26.
6) Konkle KS, Berry SH, Elliot MN et al. Comparison of an interstitial cystitis/bladder pain syndrome clinical cohort with symptomatic community women from the RAND Interstitial Cystitis Epidemiology study. J. Urol. 187(2), 508-512. 2012
7) JT Anger, N Zabihi, JQ Clemens, CK Payne, CS Saigal, IV Rodriguez. Treatment choice, duration, and cost in patients with interstitial cystitis and painful bladder syndrome. International Urogynaecology Journal and Pelvic Floor Dysfunction, vol. 22, no. 4, pp 395-400, 2011.
8) Tirlapur SA, Khan KS. An assessment of clinicians' and patients' experiences in the management of bladder pain syndrome. J Obstet Gynaecol, 2016; 36:241–5
9) GL Hunner. A rare type of bladder ulcer in women, report of cases. The Boston Medical and Surgical Journal, vol 172, no 18, pp 660-664, 1915.
10) CA Jones, L Nyberg. Epidemiology of interstitial cystitis. Urology, vol 49, supplement 5, pp 2-9, 1997
11) Abrams PH, Cardozo L, Fall M, Griffiths D, Rosier P, Ulmsten U,et al.; Standardisation Sub-committee of the International Continence Society. The standardisation of terminology of lower urinary tract function: report from the Standardisation Sub-committee of the International Continence Society. Neurourol Urodyn 2002;21:167–78.
12) Dinis S, De Oliveira JT, Pinto R, Cruz F, Buffington CT, Dinis P. From bladder to systemic syndrome: concept and treatment evolution of interstitial cystitis. Int. J. Womens Health 7, 735-744, 2015
13) Gamper M, Regauer S, Welter J, Eberhard J, Viereck V. Are mast cells still good biomarkers for bladder pain syndrome/ interstitial cystitis? J. Urol. 193(6), 1994-2000, 2015.
14) Ackerman AL, Lee UJ, Jellison FC et al. MRI suggests increased tonicity of the levator ani in women with interstitial cystitis/ bladder pain syndrome. Int Urogynaecol. J. doi:10.1007/s00192-015-2794-6, 2015

15) GR Sant, D Kempuraj, JE Marchand, TC Theoharides. The mast cell in interstitial cystitis: role in pathophysiology and pathogenesis. Urology, vol. 69, supplement 4, pp. 34-40, 2007
16) J. J. Oshea, P. J. Murray, Cytokine signalling modules in inflammatory responses. Immunity 2008, 28, 477.
17) A. H. Sprague, R. A. Khalil. Inflammatory cytokines in vascular dysfunction and vascular disease. Biochem. Pharmacol. 2009, 78, 539.
18) M. F. Neurath. Cytokines in inflammatory bowel disease. Nat. Rev. Immunol. 2014, 14, 329.
19) Monastero, Pentyala. Cytokines as biomarkers and their respective cutoff levels. International Journal of Inflammation Volume 2017, Article ID 4309485.
20) Singh, Anshita, Ravichandiran. MCP-1: Function, regulation, and involvement in disease. International Immunopharmacology 101, 107598, 2021.

APPENDIX:

Appendix 1: Patient information sheets- about the study

NHS
Imperial College Healthcare
NHS Trust

Participant Information Sheet

Study Title: Bladder Cytokines and Inflammation

Information for patients, relative and carers
Version 1 27/11/2024

You are being invited to take part in a research study. Before you decide it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with others if you wish.

What is the purpose of the study?

Currently there is a poor understanding of the underlying cause and the biological changes that occur to cause urinary symptoms such as: long-standing bladder pain, urinary urgency, and incontinence. Symptoms often overlap and change over time and recurrent infection in the bladder can also alter these.

We do often see that the bladder appears inflamed and previous research has shown that inflammation inside the bladder may cause many urinary symptoms. The purpose of this study is to understand what sort of inflammation may underlay which bladder symptoms. This could lead to new treatment targets in the future.

Why have I been chosen?

You are eligible to take part because you have: 1) urinary symptoms which have lasted for more than 3months and 2) you are already undergoing a cystoscopy and bladder biopsy procedure as part of your routine NHS care.

NHS
Imperial College Healthcare
NHS Trust

Do I have to take part?

No – participation is completely voluntary and whether you take part or not- will not affect your medical care in the NHS.

What will happen to me if I take part?

If you would like to take part:

- We ask you to sign a consent form for research participation
- You are asked to fill out three short questionnaires about your symptoms
- A urine sample is taken whilst you are asleep, and an extra bladder biopsy is taken (you are having two on the NHS – so this is an extra tissue sample for research)

What are the possible disadvantages and risks of taking part?

As an extra tissue sample is taken this very slightly increases the risk of bleeding or damage to the bladder. This risk is uncommon for a cystoscopy procedure.

What are the possible benefits of taking part?

There is a potential that taking part in this research could find new therapeutic targets for management of your symptoms- but this benefit would be in the longer term. In the short term there is likely no benefit to taking part.

Imperial College London holds insurance policies which apply to this study. If you experience harm or injury as a result of taking part in this study, you will be eligible to claim compensation without having to prove that Imperial College is at fault. This does not affect your legal rights to seek compensation.

If you are harmed due to someone's negligence, then you may have grounds for a legal action. Regardless of this, if you wish to complain, or have any concerns about any aspect of the way you have been treated during the course of this study, then you should immediately inform the Investigator (Insert name and contact details). The normal National Health Service mechanisms are also available to you. If you are still not satisfied with the response, you may contact the Imperial College, Research Governance and Integrity Team'.

How will we use information about you?

Imperial College Healthcare NHS Trust is the sponsor for this study and will act as the Data Controller for this study. This means that we are responsible for looking after your information and using it appropriately. Imperial College Healthcare NHS Trust will keep your personal data for:

- 5 years after the study has finished in relation to data subject consent forms

All other data kept is anonymised into the research database.

We will need to use information from your electronic medical records for this research project. This information will include:

- Your name
- Date of birth
- Hospital number and NHS number

These are included on your consent form for research. Following this any additional information is anonymised onto the research database.

People within the Trust and study team will use this information to do the research or to check your records to make sure that research is being done properly and the information held (such as contact details) is accurate.

We will keep all information about you safe and secure.

Once we have finished the study, we will keep some of the data so we can check the results. We will write our reports in a way that no-one can work out that you took part in the study.

As a university/NHS Trust we use personally-identifiable information to conduct research to improve health care and services. As a publicly-funded organisation, we have to ensure that it is in the public interest when we use personally-identifiable information from people who have agreed to take part in research. This means that when you agree to take part in a research study, we will use your data in the ways needed to conduct and analyse the research study. Our legal basis for using your information under the General Data Protection Regulation (GDPR) and the Data Protection Act 2018, is as follows:

Imperial College London/Imperial College Healthcare NHS Trust - "performance of a task carried out in the public interest"; Health and care research should serve the public interest, which means that we have to demonstrate that our research serves the interests of society as a whole. We do this by following the UK Policy Framework for Health and Social Care Research

Sharing your information with others:

We will only share your personal data with certain third parties for the purposes referred to in this participant information sheet and by relying on the legal basis for processing your data as set out above.

Other Imperial College Healthcare NHS Trust employees (including staff involved directly with the research study or as part of certain secondary activities which may include support functions, internal audits, ensuring accuracy of contact details etc.), Imperial College London/Imperial College Healthcare NHS Trust agents, contractors and service providers (for example, suppliers of printing and mailing services, email communication services or web services, or suppliers who help us carry out any of the activities described above). Our third party service providers are required to enter into

data processing agreements with us. We only permit them to process your personal data for specified purposes and in accordance with our policies.

You can stop being part of the study at any time, without giving a reason, but we will keep information about you that we already have. because some research using your data may have already taken place and this cannot be undone.

WHERE CAN YOU FIND OUT MORE ABOUT HOW YOUR INFORMATION IS USED

You can find out more about how we use your information

- at www.hra.nhs.uk/information-about-patients/
- or emailing the Data Protection Officer: imperial.dpo@nhs.net
- telephone: 020 3311 7344

Enquiries relating to Subject Access Requests (DPA) should be sent to: Imperial.accesshealthrecords@nhs.net

Complaints

If you wish to raise a complaint about any part of your participation in this research project, then please contact the research team first- by contacting the gynaecology department and then asking to the query to be taken to Dr Bernadette Lemmon.

Following our response, if you are not satisfied please contact Imperial College London's/Imperial College Healthcare NHS Trust's Data Protection Officer via email at dpo@imperial.ac.uk / imperial.dpo@nhs.net via telephone on 020 7594 3502 / 020331304001 and/or via post at Imperial College London, Data Protection Officer, Faculty Building Level 4, London SW7 2AZ./8th Floor of Salton House, ICT Division, St Mary's Hospital, Praed Street, London, W2 1NY

Imperial College Healthcare NHS Trust

If you remain unsatisfied with our response or believe we are processing your personal data in a way that is not lawful you can complain to the Information Commissioner's Office (ICO)- via www.ico.org.uk. Please note the ICO does recommend that you seek to resolve matters with the data controller (us) first before involving them.

What will happen to the results of the research study?

Results of this study will be submitted for publication in peer reviewed journals. Results may also be presented at International Conferences. This study has also been submitted to the ISRCTN registry which means that a summary of the project results will be available online. This project is part of a further research degree- and MD (res) which will be presented and submitted to Imperial College London.

There will never be any identifiable personal data ever published or presented from participation in this project.

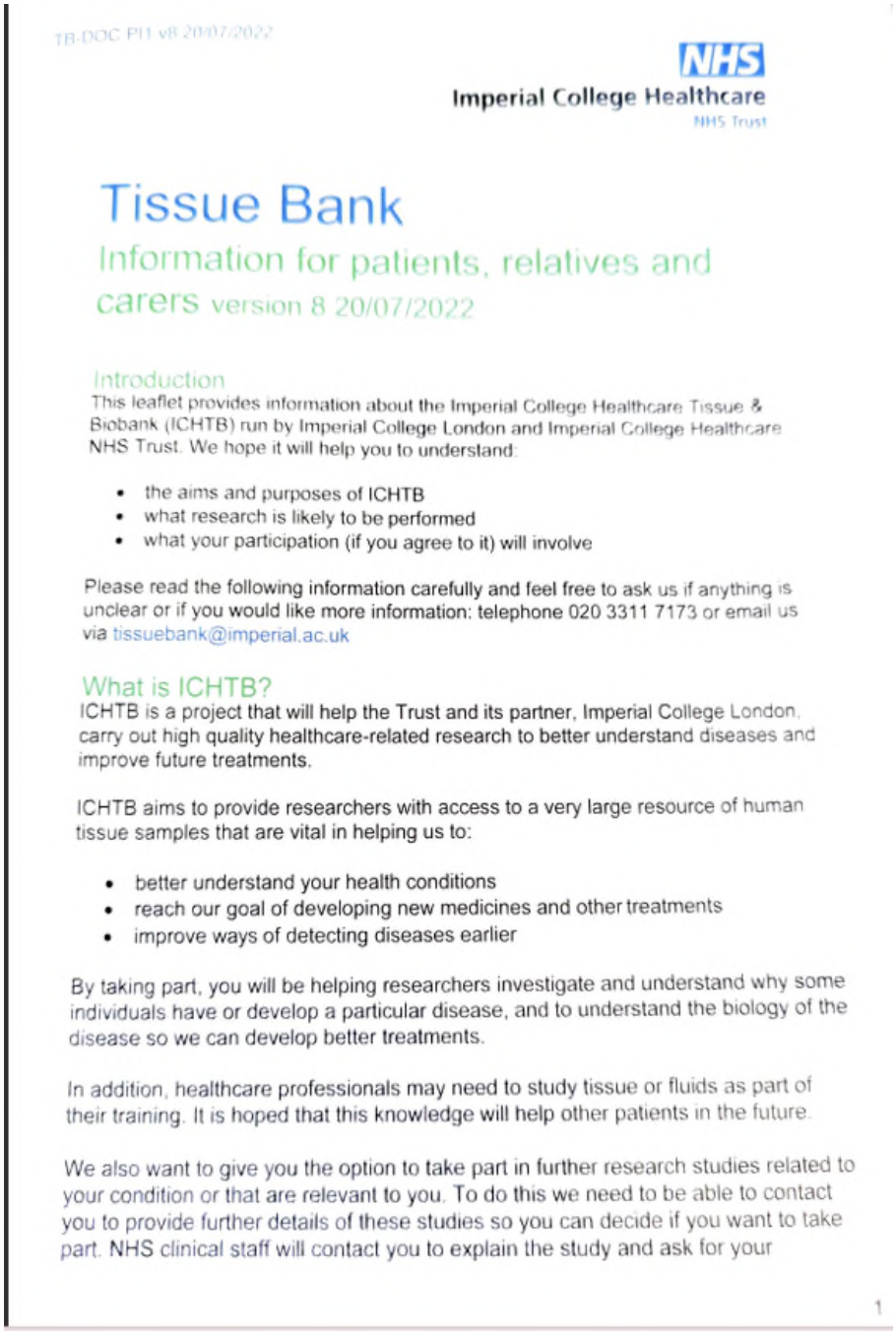
Who is organising and funding the research?

This research project has been designed, set-up, and conducted byyy the urogynaecology department at St Mary's Hospital, Imperial College Healthcare Trust under Professor Khullar. This project has been awarded a research grant by The British Society of Urogynaecology (BSUG).
No members of this research team are being paid for conducting this research.

Who has reviewed the study?

This study has been approved by the Imperial College Tissue and Biobank which is regularly reviewed by the Research and Ethics Authorities of England and Wales (REC Wales 3). This project has individually sought approval from the Health Research Authority and Research Ethics Committee review.

Appendix 2: Patient information sheet- Imperial College Healthcare Tissue and Biobank information sheet- TB-DOC-PI1 v8 20/07/2022



TB-DOC PI1 v8 20/07/2022

NHS
Imperial College Healthcare
NHS Trust

Tissue Bank

Information for patients, relatives and carers version 8 20/07/2022

Introduction

This leaflet provides information about the Imperial College Healthcare Tissue & Biobank (ICHTB) run by Imperial College London and Imperial College Healthcare NHS Trust. We hope it will help you to understand:

- the aims and purposes of ICHTB
- what research is likely to be performed
- what your participation (if you agree to it) will involve

Please read the following information carefully and feel free to ask us if anything is unclear or if you would like more information: telephone 020 3311 7173 or email us via tissuebank@imperial.ac.uk

What is ICHTB?

ICHTB is a project that will help the Trust and its partner, Imperial College London, carry out high quality healthcare-related research to better understand diseases and improve future treatments.

ICHTB aims to provide researchers with access to a very large resource of human tissue samples that are vital in helping us to:

- better understand your health conditions
- reach our goal of developing new medicines and other treatments
- improve ways of detecting diseases earlier

By taking part, you will be helping researchers investigate and understand why some individuals have or develop a particular disease, and to understand the biology of the disease so we can develop better treatments.

In addition, healthcare professionals may need to study tissue or fluids as part of their training. It is hoped that this knowledge will help other patients in the future.

We also want to give you the option to take part in further research studies related to your condition or that are relevant to you. To do this we need to be able to contact you to provide further details of these studies so you can decide if you want to take part. NHS clinical staff will contact you to explain the study and ask for your

1

permission to share your contact details with the researcher running it. You have the right to say no.

Do I have to join ICHTB?

No. It is completely up to you whether or not you wish to join. If you decide not to it will not affect the standard of care that you receive in any way. If you do decide to join, you will be free to withdraw at any time and without having to give a reason.

Allowing us to keep your biological samples for research

When you attend hospital your care team will often need to perform tests and procedures to diagnose and treat your condition. These procedures may involve the removal of fluids, pieces of tissue or sometimes a whole organ (known as biological samples). These biological samples are sent to a laboratory to be tested by doctors or scientists. This can help them diagnose your condition.

Not all of the biological samples may be needed for diagnosis. If you consent to join ICHTB, any leftover biological samples after diagnosis may be kept for research (under normal circumstances these would be thrown away).

If you are having a biopsy procedure, two or three extra samples may be taken for research which may mean the procedure would take a few extra minutes. If you have already had your operation you can still help us by consenting - we can then ask the pathologist for a small amount of tissue already used for your diagnosis.

After treatment, your doctor may invite you back for further visits and this may involve taking other biological samples. If, at a later stage, you have blood or tissues taken as part of your future care, we may wish to access these samples too. This will allow researchers to make potentially helpful comparisons with your original samples. If you do not wish to provide further samples, you do not have to.

Allowing us to take additional blood samples

As part of your regular hospital treatment, a doctor may need to take blood samples from you. If you consent to ICHTB, when you provide these blood samples, we may take up to an additional 45 millilitres (ml) - three tablespoons - of blood to be stored for research. You will not need to attend any extra appointments - we will only take this extra blood when you are required to provide blood samples as part of your regular clinical care. If you do not wish to provide further samples, you do not have to.

How will I benefit from joining ICHTB?

You may not benefit personally from any research carried out using your samples and data. However, the results of the research may benefit patients with your type of illness in the future. You will not receive a financial reward now or in the future for providing samples. The medical team involved in your treatment and care will receive no payment because of your donation.

Your sample will not be sold for profit to researchers, but the use of your samples may lead to the development of new drugs, treatments or tests by both academic and commercial organisations.

Will the samples be tested for (genetic) inherited disorders?

We want to know how genes influence disease. Genes are made out of DNA. We may, now or in the future, isolate, analyse and store a sample of your DNA from your donated biological samples. Using current advanced laboratory techniques or those developed in the future, we may determine your genetic make-up. This could include determining the sequence of all or part of your DNA code.

ICHTB will not disclose information about your genetic make-up in any way that could harm you or your family. Your personal identifiable information will never be shared without your permission.

Who will use the stored samples?

Your sample may be used by researchers based in academic institutions, the NHS or commercial companies worldwide. All research will be thoroughly reviewed by a tissue management committee before being allowed access to your samples and data. This committee will ensure that the research is scientifically valid, in the interests of human health and has appropriate security measures to protect your information. All of your information will be anonymised which means it will not contain details that could identify you. Your identity will never be shared without your permission.

What will happen to the results of the study?

Research studies usually take several years to complete. The results from these studies will be used to improve treatment and care of patients in the future. Results will be published as appropriate in scientific papers and magazines and regular updates of research in progress, research results and other relevant information will be published on the Imperial College London website at:
www.imperial.ac.uk/tissuebank.
You will not be identified in any publication or through any information on the website.

What if you find something new about my health?

Results for individual patients from particular research studies will not normally be given to you or your doctor. In very rare situations, some research projects could identify changes to your diagnosis or treatment or may indicate an inherited disease that could affect you or your family members. Your hospital doctor will be notified of this information.

When and how will I be contacted about research studies that I may wish to join?

Approved researchers will be able to search your anonymised health data, data obtained from your biological samples, and other data approved for use in research to find people who may be suitable to take part in research studies. For example, a search might be carried out to find people who are over the age of 40 and have diabetes. If your data matches the requirements for a research study that may be

research and teaching. If you withdraw sometime after joining, some of your samples may have already been used in research.

If you want to leave ICHTB please contact the team directly on 020 3311 7173 or via email at tissuebank@imperial.ac.uk

Who has approved/reviewed the collection of human tissue samples as part of ICHTB?

A Research Ethics Committee based in Wales (Wales REC3) has approved and will regularly review this project.

This project follows the UK Policy Framework for Health and Social Care Research which sets out principles of good practice in the management and conduct of health and social care research in the UK.

Contact details for the data protection officer

Post: Data protection officer, Information Governance, ICT Directorate, Charing Cross Hospital, London, W6 8RF
Email: Imperial.dpo@nhs.net
Telephone: 020 3311 7344

Enquiries relating to Subject Access Requests (DPA) should be sent to - imperial.accesstohealthrecords@nhs.net

Imperial College Healthcare NHS Trust is a registered data controller under the Information Commissioner's Office. Further information can be found at:
Information Commissioners Office, Wycliffe House, Water Lane, Wilmslow, Cheshire, SK9 5AF
Website: www.ico.org.uk/concerns
Phone: 0303 123 1113

If you are not satisfied with our response or believe we are processing your personal data not in accordance with the law you can complain to the Information Commissioner's Office

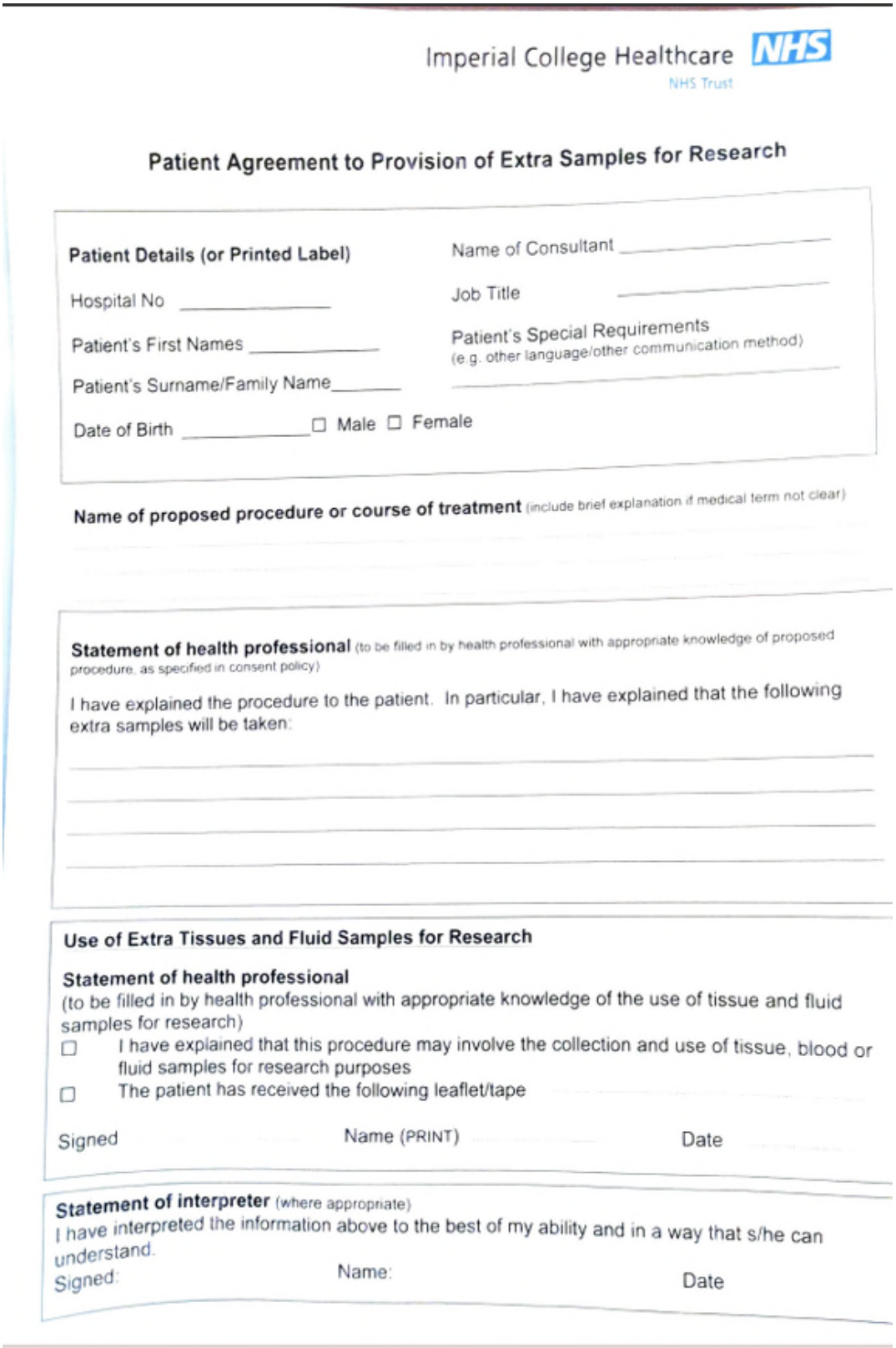
Contact details for Imperial College Healthcare's patient advice and liaison service (PALS)

If you have any questions or comments about your care, please contact PALS on **020 3313 0088** (Charing Cross, Hammersmith and Queen Charlotte's & Chelsea hospitals), or **020 3312 7777** (St Mary's and Western Eye hospitals). You can also email PALS at pals@imperial.nhs.uk The PALS team will listen to your concerns, suggestions or queries and is often able to help solve problems on your behalf.

Alternative formats

This leaflet can be provided on request in large print, as a sound recording, in Braille, or in alternative languages. Please contact the communications team on **020 3312 5592**.

Appendix 3: Consent forms for research



Imperial College Healthcare NHS
NHS Trust

Patient Agreement to Provision of Extra Samples for Research

Patient Details (or Printed Label)

Hospital No _____

Patient's First Names _____

Patient's Surname/Family Name _____

Date of Birth _____ ☐ Male ☐ Female

Name of Consultant _____

Job Title _____

Patient's Special Requirements
(e.g. other language/other communication method)

Name of proposed procedure or course of treatment (include brief explanation if medical term not clear)

Statement of health professional (to be filled in by health professional with appropriate knowledge of proposed procedure, as specified in consent policy)

I have explained the procedure to the patient. In particular, I have explained that the following extra samples will be taken:

Use of Extra Tissues and Fluid Samples for Research

Statement of health professional
(to be filled in by health professional with appropriate knowledge of the use of tissue and fluid samples for research)

☐ I have explained that this procedure may involve the collection and use of tissue, blood or fluid samples for research purposes

☐ The patient has received the following leaflet/tape

Signed Name (PRINT) Date

Statement of interpreter (where appropriate)
I have interpreted the information above to the best of my ability and in a way that s/he can understand.
Signed: Name: Date

Statement of patient

I have confirmed that I have read and understood the patient information leaflet "Tissue Bank Information for patients, relatives and carers".

I understand that my participation is voluntary and will not affect my treatment in any way.

I understand that sections of my medical notes may be accessed by healthcare professionals from the Tissue Bank. I give permission for these individuals to access my medical notes.

I understand that parts of my medical information may be passed to other organisations involved in the research on the understanding that my personal patient confidentiality will be maintained.

I understand, and agree to, data relating to my donated samples being stored electronically.

☐ I **AGREE** to the collection and use of my tissue blood or fluid samples for approved research

☐ I **DISAGREE** to the collection and use of my tissue, blood or fluid samples for approved research

Signed ..... Date .....

Name (PRINT) _____

A witness should sign below if the patient is unable to sign but has indicated his or her consent. Young people/children may also like a parent to sign here

Signed ..... Date .....

Name (PRINT) _____

Confirmation of consent (to be completed by the health professional following signature by the patient)

Signed ..... Date .....

Name (PRINT) _____ Job Title _____

Please note:
Top copy (gold) in health records, white copy to patient, green copy to research staff with specimen

Copy accepted by patient? Yes/No (please ring)

Appendix 4: Consent forms for research:

IRAS ID: **351850**

Study Number: URO_VK_16_041

Participant Identification Number for this trial:

CONSENT FORM

Title of Project: Cytokines in the Bladder: an investigation of inflammatory cytokine expression in the urine and bladder tissue of women with chronic lower urinary tract symptoms

Name of Researcher: Dr Bernadette Lemmon

Please initial box

1. I confirm that I have read the information sheet dated 27th Nov 2024 (version 1) for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily. ☐
2. I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason, without my medical care or legal rights being affected. ☐
3. I understand that relevant sections of my medical notes and data collected during the study, may be looked at by individuals from regulatory authorities or from the NHS Trust, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records. ☐
4. I understand that the information collected about me will be used to support other research in the future and may be shared anonymously with other researchers. ☐
5. I agree to take part in the above study. ☐

_____	_____	_____
Name of Participant	Date	Signature
_____	_____	_____
Name of Person seeking consent	Date	Signature