PROTOCOL

Urinostics'

A study to test a sensor for giving early warning of urinary catheter blockage

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Protocol authorised by: Mr Edward Jefferies, Principal Investigator and Professor Toby Jenkins Laboratory Chief Investigator

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Signature:  **Prof. Toby Jenkins**

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Details of Sponsor:
The University of Bath is the research sponsor for this study.

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This protocol describes **Urinostics-Pilot** 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 trial. Problems relating to this trial should be referred, in the first instance, to the Principal Investigator.

This trial will adhere to the principles outlined in the NHS Research Governance Framework for Health and Social Care (2nd Edition). It will be conducted in compliance with the protocol, the Data Protection Act and other regulatory requirements as appropriate.

Abbreviations

RUH	The Royal United Hospital
UoB	University of Bath
PPI	Patient and public involvement
UTI	Urinary tract infection
AE	Adverse Event
AR	Adverse Reaction
SAE	Serious Adverse Event
SOP	Standard Operating Procedure

Keywords: Catheter, bladder, infection, diagnosis, point of care device, fluorescent dye

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1. Introduction

In the UK, approximately 15-25% of patients admitted to NHS hospitals each year will require urethral catheterisation. In the community, it is estimated that 3% of people living at home and up to 15% in care homes are catheterised.[1] Foley catheters are often used on a long-term (≥30 days) indwelling basis, as a common management technique for urinary incontinence or retention. These catheters exhibit an approximate 5% per day risk of developing bacterial infections, which can cause catheter blockages resulting in painful distention of the bladder and can lead to serious symptomatic episodes - such as acute pyelonephritis and septicaemia.

Catheter-associated urinary tract infections have been identified as a priority area for the NHS, with healthcare-associated infections costing some £1bn per year[2]. As well as the economic burden and a

[1] N. Acker, *J. Clin. Nursing*, **2014**, 28, 28-32.

[2] *researchbriefings.files.parliament.uk/documents/CDP-2018-0116/CDP-2018-0116.pdf*

concern for patient outcomes, the NHS has a commitment to reducing the burden of antimicrobial resistance (AMR), and infection-prevention is a key part of this.

Work to date

For the last five years, Scarlet Milo (MChem and Annett Trust-funded PhD student) and Toby Jenkins at the University of Bath have been working on technological solutions for improving the care of catheterised patients. These include coating of the catheter lumen to trigger the appropriate release of bacteriophage or a diagnostic dye (see publications list, below).

More recently, the Bath team have devised a very simple infection-detecting 'lozenge' – a small polymeric capsule which can be inserted into the leg bag of a catheterized patient. These will be low-cost to produce and give a 14-hour warning of impending blockage via the release of a bright green dye into the leg bag. See figure 1 below:

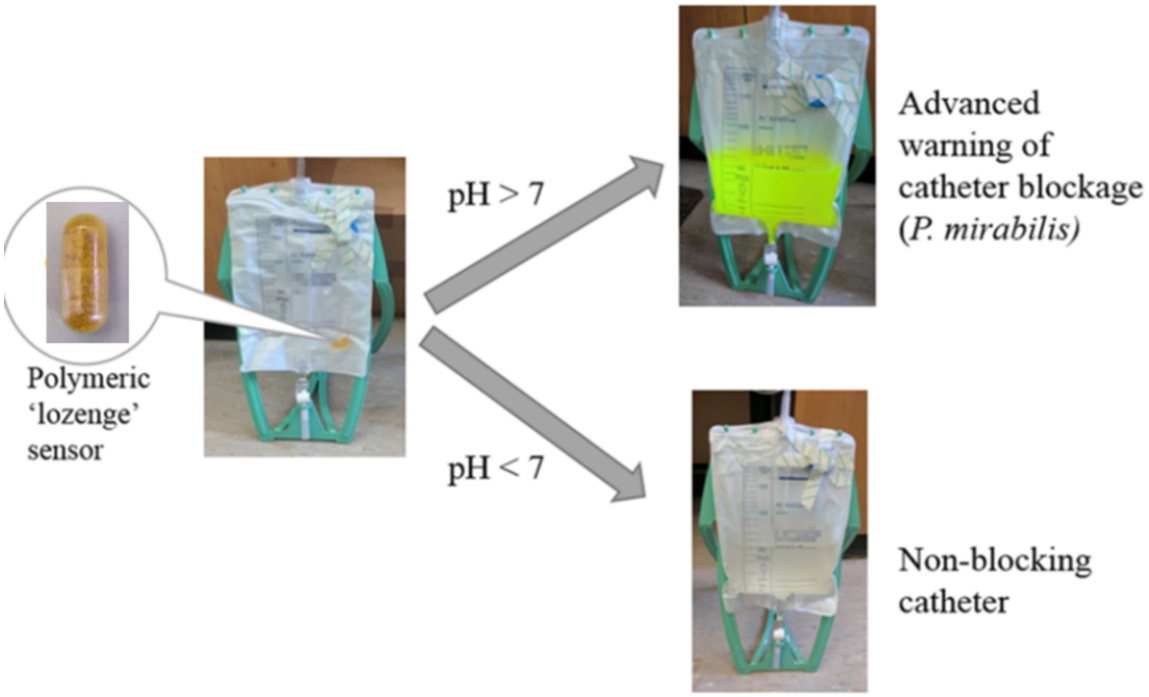

Figure 1: Diagnostic lozenge, detecting elevated pH due to *Proteus mirabilis* bladder infection, giving clear (14 h) advance warning of catheter blockage.

Our publications on the subject of diagnostics for catheterised patients include:

Milo, S., Acosta, F.B., Hathaway, H.J., Wallace, L.A., Thet, N.T., Jenkins, A.T.A., Development of an Infection-Responsive Fluorescent Sensor for the Early Detection of Urinary Catheter Blockage, *ACS Sensors* **2018**, 3, p. 612-617.

Milo, S., Nzakizwanayo, J., Hathaway, H.J., Jones, B.V., Jenkins, A.T.A., Emerging medical and engineering strategies for the prevention of long-term indwelling catheter blockage, *Proceedings of the Institution of Mechanical Engineers, Part H - Journal of Engineering in Medicine* **2018**, In press.

Milo, S., Hathaway, H., Nzakizwanayo, J., Alves, D., Pérez Esteban, P., Jones, B. V. & Jenkins, A.T.A., Prevention of Encrustation and Blockage of Urinary Catheters by Proteus mirabilis via pH-Triggered Release of Bacteriophage, *Journal of Materials Chemistry B* **2017** 5, 27, p. 5403-5411.

Milo, S., Thet, N.T., Liu, D., Nzakizwanayo, J., Jones, B. V. & Jenkins, A.T.A., An in-situ infection detection sensor coating for urinary catheters, *Biosensors and Bioelectronics*. **2016**, 81, p. 166-172.

2. Study aim and objectives

2.1 Study Aim

To test the correlation of colour change (arising from the lozenge technology), with the infection status of catheterised patients, measured by whether the patients are undergoing frequent catheter blockage (infected) or not (non-infected). Secondary aims will look at lozenge switch- on and more general patient condition, including patient-reported quality of life.

2.2 Study Objectives:

Feasibility of study design with a view to a larger trial:

- Practicalities of sample collection and viewing technology 'switch-on' / colour change in urine collection bags
- pH measure of all donated urine as soon as practicable.
- A microbiological test for the presence of *Proteus mirablis* in urine
- Correlation of technology result against retrospective clinical decision of patient infection condition (time to catheter blockage following urine donation)
- To correlate sensor switch-on with patient-reported quality of life factors
- To undertake PPI to assess understanding of the study concept and recruitment to a study assessing the technology.

3. Study design

3.1 Recruitment

Consenting patients with long term catheters, at time of attending for their routine catheter change at the RUH weekly urology clinic. A Quality of Life survey will be undertaken by each recruited patient at this stage.

3.2 Study design

A pilot study to test the practicalities of undertaking a larger diagnostic accuracy study of the catheter blockage early warning lozenge. Feasibility issues will include: ability to recruit and patient acceptability; ability to warn of possible catheter blockage: correlation of 'switch on' with patients who experience catheter blockage at various time points post urine donation; correlation of lozenge non-switch on with patients not experiencing catheter blockage at various time points post urine donation; ability to take samples and clinician acceptance.

Consent to this study is voluntary; participants will be offered written information and the opportunity to ask any study-related questions before signing written consent.

Once the screening and consent process has been completed, volunteers will donate their (filled) urine drainage bags to the study. They will then proceed to have their catheter changed, as part of their standard care, in the catheter clinic. Bags will be marked with an anonymous reference number, which will blind the academic team from name / address / identification information about the patient. Bags will be stored in at room temperature in the clinic prior to collection by the UoB team (at ca. 16.00 on the day of the clinic taking place).

All participants will be invited to take part in PPI, with regards to study acceptability (section 3.5), during the consent process or follow-up period. All participants in the study will fill in the validated 'Quality of Life survey' on living with a catheter.

Demographic and any routinely-collected clinical data (including, but not limited to, patient and illness details, current or recent antibiotic use, date of last catheter change – routine or emergency – and clinical observations) will also be recorded.

Laboratory staff at UoB will be blinded to all clinical data; they will receive urine bags on a weekly basis. The study team at UoB will make the decision on using photographs to determine if the technology was activated (switch-on).

There will be no blinding at hospital sites, but treatment decisions will be made independently, and will be irrespective of any UoB test results. Patients will be followed-up, at 3 weeks, with a structured telephone interview.

Retrospective analysis of which patients have a blocking/blocked catheter, in the three-week period following urine donation, will be undertaken by the clinical team on an individual patient basis. The date on which catheter blockage occurred will be recorded.

3.3 Sample processing

All samples will be taken using a standard method:

- *Week 1* will be a pilot, where details of the laboratory SOP will be finalised and used in all subsequent weeks.
- *Weeks 2-12*, (subject to changes in SOP following the pilot) the urine pH will be measured within 2 hours of arrival at the UoB lab (bags not immediately analysed will be stored at 5 C), and three urine aliquots of 200 ml will be created in 100 ml sterile bottles. Two sensor lozenges will be added to each bottle. Urine pH will be measured and recorded. Presence of *Proteus mirablis* will be ascertained via culture and colour changing broth.

- The response of the sensor lozenge 30 minutes, 16 hours and 24 hours after addition to the urine will be photographed, next to a standardised colour scale using a camera set to fixed focus and aperture, by a member of the research team. Standard lighting conditions will be provided, at a distance of 10-30 cm from the sample, by the photo-capture box.

    - Once the response has been photographed, the urine and bag will be safely disposed of. Urine will be disposed of via the sewerage system; the collection bag via the autoclavable waste stream.

3.4 Clinical follow-up

The patient will be followed up via telephone by the research staff at the RUH through a 'patient notes review' at 3 weeks after the first sample has been collected for a:

- Any catheter attention required during the last 3 weeks (nursing, GP, hospital)
- Need for antibiotics due to UTI
- Any bypassing of catheter

3.5 PPI invitation

All patients recruited to the study will be asked if they would like to be involved in helping with their views on the research study, acceptability of diagnostic technology at home or community, the technology to be tested in the study and study concept. In an additional section of the consent form, participants will be asked if they would be happy to be contacted for further PPI at a later stage. This will involve being asked about their involvement in the study and future collaboration in designing the next stage of the study.

3.6 Data security

Screening logs will be kept at the RUH. Paper data collection forms (CRFs) will be stored in a locked cabinet at the research office. Source data will be stored in accordance with the NHS code of confidentiality.

Research staff will ensure that the participants' anonymity is maintained through protective and secure handling and storage of patient information at the trial centre. The participants will be identified only by a patient ID number on the CRF and database. All documents will be stored securely and only accessible by trial staff and authorised personnel. Data will be collected and retained in accordance with the Data Protection Act 2018.

Data identified by the participant's unique study number will be entered directly into the database by the research staff.

Study documents (paper and electronic) will be retained in a secure location during, and after, the trial has finished. All essential documents, including patient records and other source documents will be retained for a period of 5 years following the end of the study. Where study-related

information is documented in the hard copy medical records – those records will be identified by a 'Do not destroy before dd/mm/yyyy' label where the date is 25 years after the last patient's last visit. Where electronic records are in use, trust policy will be followed.

4. Participant entry

4.1 Inclusion Criteria

- Patients with long term in-dwelling urinary catheters
- Adult >18yrs
- Attendance at weekly Urology clinic
- Consent gained for study

4.2 Exclusion Criteria

- Consent not gained for study
- Child < 18 yrs
- Adult without mental capacity to consent

5. Data collection and analysis, sample size, statistical analysis and results

5.1 Data collection and analysis

All data and samples will be anonymised and labelled with the allocated study number, along with storage details. Study data will be stored on paper CRF forms kept in a secure location in the RUH Urology Research Office, and investigators will only have access to their own site's data. No identifiable personal data will be sent to the laboratory site.

Correlation will be sought between *Urinostics* sensor switch on/off with clinical and patient-catheter blockage within three weeks of urine donation.

Demographics, clinical details and outcomes in addition to screening criteria will be collected. Data from the clinical record including temperature, urine, blood results and any other relevant results will be analysed using descriptive statistics; relationships between variables will be investigated using correlation matrices.

5.2 Sample size

The study will aim to recruit 48 patients

5.3 Results

Results will be publicly disseminated by publication in the medical-scientific literature and presentation at the British Urology Association annual conference.

6. Safety Reporting

6.1 Adverse events or reactions (AE/AR)

As the primary outcome is an *ex vivo* outcome – the patient is otherwise having standard care and the study has no effect on patient care.

An ***adverse event*** is any untoward medical occurrence in a subject to whom a medicinal product/medical device/intervention has been administered, including occurrences which are not necessarily caused by, or related to, that product.

6.2 Serious adverse events or reactions (SAE/SAR/SSAR/SUSAR)

An ***adverse event***, ***adverse reaction*** or ***unexpected adverse reaction*** is defined as serious if it:

(a) results in death,
(b) is life-threatening,
(c) requires hospitalisation or prolongation of existing hospitalisation,
(d) results in persistent or significant disability or incapacity, or
(e) consists of a congenital anomaly or birth defect.

6.3 Reporting Procedures

Adverse events will be recorded and reported in accordance with Royal United Hospital's (RUH) Research Safety Reporting SOP.

6.4 Non serious AEs

All such events, whether expected or not, should be recorded.

6.5 Serious AEs

An RUH Research Related SAE/SUSAR Initial Report form should be completed by the local investigators and submitted to the sponsor (UoB) within 24 hours of an SAE occurrence. However, relapse and death, and hospitalisations for elective treatment of a pre-existing condition, do not need reporting as SAEs.

All SAEs should be reported to the Research Ethics Committee where in the opinion of the Chief Investigator, the event was:
A non-IMP SUSAR- an SAE that occurs in a non-IMP trial and is:

- "Related" – that is, possibly, probably or definitely resulted from administration of any of the research procedures, and
- "Unexpected" – that is, the type of event is not listed in the protocol as an expected occurrence.

Within 24 hours of a member of the research team becoming aware of a *serious adverse event* the sponsor must be notified.

Reports of related and unexpected SAEs should be submitted as soon as possible, ideally within 24hours of the Chief Investigator becoming aware of the event, using the template provided in the RUH Research Safety Reporting SOP.

6.6 (Serious) Breaches

The Investigator and the research team have a responsibility to ensure that the research is conducted in accordance with the Protocol and Good Clinical Practice. Where there is a breach, this must be assessed by the Investigator and reported to the Sponsor within 24 hours of becoming aware of the event (unless it is the Sponsor that has identified the breach). Any non–serious breaches will be filed in the Investigator Site File and Trial Master File.

For serious breaches, the MHRA and Ethics committee **must be notified within 7 days of the breach being identified**. Where UoB are the Sponsor, the R&I department will liaise with the research team in order to make the required notification.

7. Regulatory issues

7.1 Authorisations and Research Governance Statement

The study will be performed subject to favourable opinion/ authorisation/permission from all necessary regulatory and other bodies. This includes, but is not limited to, REC, HRA, NHS trusts.

OTHER CENTRES/LABS will ensure all necessary approvals are in place for their site. The trial must be submitted for capacity and capability review at the RUH. The Chief Investigator will require a copy of the Trust R&D approval letter before accepting participants into the trial. The trial 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. This study will be conducted in accordance with: Good Clinical Practice and the Research Governance Framework for Health and Social Care.

7.2 Consent

Consent to this study is voluntary; participants will be offered appropriate written information and the opportunity to ask any study related questions before signing written consent.

7.3 Confidentiality

All data and samples will be anonymised and labeled with the allocated study number along with storage details. Once testing and photography is completed, the sample will be destroyed.

7.4 Indemnity

This is a. University of Bath-sponsored research study. The University of Bath has arranged Public Liability insurance to cover the legal liability of the University as Research Sponsor in the eventuality of harm to a research participant arising from management of the research by the University. This does not in any way affect an NHS Trust's responsibility for any clinical negligence on the part of its staff (including the Trust's responsibility for University of BATH employees acting in connection with their NHS honorary appointments).

The University of Bath holds Professional Indemnity insurance to cover the legal liability of the University as Research Sponsor and/or as the employer of staff engaged in the research, for harm

to participants arising from the design of the research, where the research protocol was designed by the University.

The University of Bath's Public Liability and Professional Indemnity insurance policies provide an indemnity to our employees for their potential liability for harm to participants during the conduct of the research.

7.5 Sponsor

The University of Bath will sponsor the study

7.6 Funding

The Urology Foundation and the Annett Trust are providing funding for this study, from 1 February 2019. The trial is expected to last for 3 months.

7.7 Monitoring and Audit

The study will be monitored in accordance with the RUH's Monitoring SOP. All trial-related documents will be made available, on request, for monitoring and audit by the RUH, the relevant Research Ethics Committee and for inspection by the Medicines and Healthcare products Regulatory Authority or other licensing bodies. The monitoring plan will be developed and agreed by the sponsor.

7.8 Trial Management

The day-to-day management of the trial will be coordinated by Dr June Mercer-Chalmers.

8. Publication policy

Peer-reviewed scientific journals, internal report and BAUS conference presentations.

9. References

1. N. Acker, *J. Clin. Nursing*, **2014**, 28, 28-32.
2. *researchbriefings.files.parliament.uk/documents/CDP-2018-0116/CDP-2018-0116.pdf*

10. Appendices

Appendix 1: Urinostics Study Pathway

Screening and consent

Patient attends urology clinic/ward -> identified to research team -> Screened for inclusion/exclusion criteria -> If eligible patient consent to study and given study ID

Taking the samples

Drainage bag changed as part of standard care.

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Drainage bag labelled with patient ID and reference number and date. Placed in external bag / container

Sample storage and transportation

All samples to be stored at 5 C when not being transported or analysed in laboratory at UoB

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Filled drainage bags to be collected on day of catheter clinic at RUH (Wednesdays) between 15.00-17.00 and transported directly to the University of Bath

Processing

Data collection and follow up