Institution: University of Portsmouth
Unit of Assessment: UoA3 - Allied Health Professions, Dentistry, Nursing and Pharmacy
Title of case study: Earlier detection of oesophageal cancer saves lives
Period when the underpinning research was undertaken: July 2004 - 31 July 2020
Details of staff conducting the underpinning research from the submitting unit:

Name(s):	Role(s) (e.g. job title):	Period employed by submitting HEI:
Prof Pradeep Bhandari	Honorary Professor of Gastroenterology	Category C
Dr James Brown	Principal Lecturer	01/09/1997 - date
Dr Ann Dewey	Principal Lecturer	05/07/2006 - 30/03/2019
Dr Carole Fogg	Senior Lecturer	01/06/2009 - 30/09/2018
Mr Bernard Higgins	Senior Lecturer	01/09/1979 - 09/09/2018
Dr Gaius Longcroft-Wheaton	Honorary Reader	Category C

Period when the claimed impact occurred: 01 August 2013 - 31 July 2020
Is this case study continued from a case study submitted in 2014? N

1. Summary of the impact

Following diagnosis, fewer than 15% of patients with oesophageal cancer survive beyond five years. A team from the University of Portsmouth (UoP) and Portsmouth Hospitals University NHS Trust has developed a method that provides earlier and more accurate detection of precancer and cancer that significantly reduces the likelihood of cancer development. Recommended by professional bodies and in use worldwide, the early identification and minimally-invasive removal procedure has reduced the mortality risk to zero, compared to 20% mortality from open surgery at a later stage. The procedure can also be performed on previously untreatable patients who are older or who have underlying health conditions. Cost savings to healthcare systems over previous methods and reduced bed days for patients has been estimated at GBP1,600,000 per hospital over a five-year period.

2. Underpinning research

Barrett's oesophagus (BO), a condition associated with gastric reflux, is a significant risk factor for oesophageal adenocarcinoma; patients with BO are up to 125 times more likely to develop oesophageal cancer and, following diagnosis, five-year survival rates are less than 15%.

Progression to oesophageal adenocarcinoma can be prevented with detection and removal of precancerous cells. Detection itself centres on surveillance. Prior to adoption of the described innovation, surveillance comprised periodic inspection of the oesophagus with spaced biopsies taken for histology. Unfortunately, this approach fails to detect 40% of precancerous lesions.

As a collaborator with UoP since 2007, **Bhandari** (made Honorary Professor in 2011; Cat. C in this submission) has published extensively on the diagnosis of, and treatments for, gastrointestinal cancers, first publishing on BO in 2001. With **Longcroft-Wheaton** (made Honorary Reader in 2020; Cat. C in this submission), he undertook a study between July 2004 and November 2008, recruiting 190 BO patients, to determine whether acetic acid, used previously in detection of cervical cancer, might help to identify precancerous and cancerous cells during endoscopy of the oesophagus. The study described how the application of low concentration (<3%) acetic acid causes a whitening of the oesophagus apparent by endoscopic inspection and, in areas where there are precancerous or cancerous cells, a reddening which is revealed when the acetowhitening fades (**R1**). Importantly, the study demonstrated concordance in the diagnosis made by this **acetic acid chromoendoscopy (AAC)** method and spaced biopsies assessed by histology.

With promising outcomes, and envisaging the need to train endoscopists in AAC, **Brown** joined the team in 2009, bringing expertise of GI mucosa and in the development of methods for medical education. Together, **Bhandari**, **Longcroft-Wheaton** and **Brown** performed research (Nov. 2010-2013; ClinicalTrials.gov NCT01618643) on 132 BO patients, demonstrating that AAC could be used to differentiate cells at different stages of oesophageal cancer development and identify the extent to which cancer penetrated the oesophagus, thus indicating whether the cancer could be

treatable by a minimally-invasive procedure (**R2**).

In 2010, **Higgins** joined the team as a statistician, whose role it was to ensure planned clinical trials were suitably powered, assess the accuracy (sensitivity and specificity) of diagnoses and perform health economic analyses. His first collaboration with **Bhandari** and **Longcroft-Wheaton** was the demonstration of an improved method for the detection of colon cancer. The study design and health economic analysis together provided a methodological framework for the subsequent evaluation of AAC.

In 2012, **Fogg** joined the team, providing expertise in the design, conduct and analysis of quantitative and mixed-methods clinical research studies. Together, the team undertook a study (July 2013 to March 2014) demonstrating that a simple intervention could improve the visibility of the mucosa for endoscopic assessment (**R3**). As an important foundation for what was to follow, they demonstrated the feasibility of a mixed methods study comprising imaging, randomisation and blinded assessment with statistical measures of intra-observer agreement.

In 2014, **Dewey** joined the team, whose expertise in qualitative methods would be used to understand perceptions of patients and clinicians as potential barriers to adoption. Between March and April 2015, a study was undertaken to develop and validate a training and assessment program for AAC. The study demonstrated that 13 naïve endoscopists could develop professional standards of competency following online training and a one-day interactive seminar (**R4**).

In 2015, the team sought to assess whether the combination of acetowhitening and surface patterns following AAC could be used as predictors of the abnormality of cells, determining the extent of cancer development. A refined protocol (PREDICT) was shown to be able to diagnose oesophageal cancer in BO with very high accuracy (**R5**). Crucial for wider adoption by endoscopists, this study included practitioners from Italy, Germany and the USA.

That same year, recruitment began on the ABBA (<u>A</u>cetic acid targeted <u>B</u>iopsies vs non-targeted quadrantic biopsies during <u>BA</u>rrett's surveillance) trial (**G1**). Involving 200 BO patients recruited from July 2015 to December 2016, this was the first randomised and multicentre assessment of AAC. ABBA was conducted over six sites:

- Portsmouth Hospitals University NHS Trust - lead site
- University Hospitals, Leicester
- Brighton and Sussex University Hospitals NHS Trust
- Western Sussex Hospitals NHS Trust
- Royal Bournemouth and Christchurch Hospitals NHS Foundation Trust
- Gloucestershire Hospitals NHS Foundation Trust

The study demonstrated the feasibility, safety and acceptance of AAC by both clinicians and patients (**R6**).

3. References to the research

3.1 Research outputs

R1. **Longcroft-Wheaton, G.**, Duku, M., Mead, R., Poller, D., & **Bhandari, P.** (2010). Acetic acid spray is an effective tool for the endoscopic detection of neoplasia in patients with Barrett's esophagus. *Clinical Gastroenterology and Hepatology*, *8*(10), 843-847. https://doi.org/10.1016/j.cgh.2010.06.016

R2. **Longcroft-Wheaton, G.**, **Brown, J.**, Basford, P., Cowlishaw, D., **Higgins, B.**, & **Bhandari, P.** (2013). Duration of acetowhitening as a novel objective tool for diagnosing high risk neoplasia in Barrett's esophagus: a prospective cohort trial. *Endoscopy*, *45*(6), 426-432. https://doi.org/10.1055/s-0032-1326630

R3. Basford, P., **Brown, J.**, Gadeke, L., **Fogg, C.**, Haysom-Newport, B., Ogollah, R., Bhattacharyya, R., **Longcroft-wheaton, G.**, Thursby-Pelham, F., Neale, J., & **Bhandari, P.** (2016). A randomized controlled trial of pre-procedure simethicone and N-acetylcysteine to improve mucosal visibility during gastroscopy – NICEVIS. *Endoscopy International Open*, *04*(11), E1197-E1202. https://doi.org/10.1055/s-0042-117631

R4. Chedgy, F., Kandiah, K., Barr, H., De Caestecker, J., Dwerryhouse, S., Eross, B., Gordon,

C., Green, S., Li, A., **Brown, J.**, **Longcroft-Wheaton, G.**, & **Bhandari, P.** (2017). Development and validation of a training module on the use of acetic acid for the detection of Barrett's neoplasia. *Endoscopy*, *49*(02), 121-129. https://doi.org/10.1055/s-0042-120179

R5. Kandiah, K., Chedgy, F. J. Q., Subramaniam, S., **Longcroft-Wheaton, G.**, Bassett, P., Repici, A., Sharma, P., Pech, O., & **Bhandari, P.** (2018). International development and validation of a classification system for the identification of Barrett's neoplasia using acetic acid chromoendoscopy: the Portsmouth acetic acid classification (PREDICT). *Gut*, *67*(12), 2085-2091. https://doi.org/10.1136/gutjnl-2017-314512

R6. **Longcroft-Wheaton, G.**, **Fogg, C.**, Chedgy, F., Kandiah, K., Murray, L., **Dewey, A.**, Barr, H., **Higgins, B.**, Poller, D., Jankowski, J., DeCaestecker, J., & **Bhandari, P.** (2020). A feasibility trial of Acetic acid-targeted Biopsies versus nontargeted quadrantic biopsies during BArrett's surveillance: the ABBA trial. *Endoscopy*, *52*(01), 29-36. https://doi.org/10.1055/a-1015-6653

3.2 Evidence of the quality of the research

These outputs are a representative selection of a substantial body of work in this area. They are original research studies employing robust research design, relevant research techniques and appropriate data analysis and interpretation. All are published in respected peer-reviewed academic journals; combined, R1, R2, R4 and R5 have been cited 118 times (Scopus, range 6-78).

3.3 Related grants

G1. **Bhandari, P**. (PI), **Dewey, A**, Poller, D., **Longcroft-Wheaton, G**., de Caestecker, J., **Higgins, B**., McCord, M., **Fogg, C**. & Barr, H. *A feasibility study with a crossover design to assess the diagnostic accuracy of acetic acid guided biopsies versus non-targeted biopsies (current practice) for detection of dysplasia during Barrett's surveillance: The ABBA study*. Funded by the National Institute for Health Research, February 2015 - September 2017, (GBP247,632).

4. Details of the impact

Having demonstrated the improved accuracy of AAC for detection of precancer and cancer compared to existing methods through the ABBA trial (**R6**), the next step was to communicate benefits to other endoscopists. Key to this was the design of ABBA as a multicentre trial. Senior endoscopists working at the UK's major centres for gastrointestinal medicine were able to evaluate its efficacy first-hand (**R6**). Their junior colleagues were the naïve endoscopists that received training from **Bhandari** and his team (**R4**). Observing both the benefits of the technique, and the ease by which a naïve endoscopist could achieve professional standards of competency in just one day of training, were persuasive arguments. AAC for BO quickly became routine practice in the UK's major centres for gastrointestinal medicine, with trained Fellows now working at other UK sites and using AAC routinely. Outside of the UK, uptake was driven by the international endoscopists who assessed the PREDICT protocol (**R5**) and by significant efforts of **Bhandari** and colleagues to disseminate at major international conferences (ESGE Days Congresses; British Society of Gastroenterology Annual Meetings; International Digestive Disease Forum; Congreso de la Sociedad Española de Endoscopia Digestiva) and train virtually, with live streaming of cases (Endoport.org, Jan. 2020).

With improved accuracy of detection of oesophageal cancer compared to existing methods, the US and European professional bodies went on to recommend that AAC be used in BO surveillance, replacing the use of random surveillance biopsies (**S1**, **S2**). The American Society of Gastrointestinal Endoscopists has more than 15,000 members worldwide, provides the highest standards for endoscopic training and practice and is the foremost resource for endoscopic education. They endorse the method (**S1**), concluding: '*Our meta-analysis indicates that targeted biopsies with acetic acid chromoendoscopy... meet the thresholds set by the ASGE PIVI (Preservation and Incorporation of Valuable endoscopic Innovations), at least when performed by endoscopists with expertise in advanced imaging techniques. The ASGE Technology Committee therefore endorses using these advanced imaging modalities to guide targeted biopsies for the detection of dysplasia during surveillance of patients with previously nondysplastic BE [Barrett's oesophagus], thereby replacing the currently used random biopsy protocols*'.

Dr Cesare Hassan, Head of the Guidelines' Committee for the European professional body (2013 – 2017), confirms that '*All major European centres providing specialist Barrett's service are now*

using acetic acid [AAC] *as an adjunct to help detect and delineate Barrett's neoplasia.'* (**S3**)

By providing earlier detection, at the precancer stage, achieving more accurate detection than previous methods, being easy to learn to professional standards and applicable to any endoscope, AAC has achieved the following impacts:

1. Patient Benefit

More accurate detection means fewer advanced cases of oesophageal cancer. The means to identify precancerous and cancerous cells based on the time it takes for acetowhitening to fade was a significant discovery (**R3**) by the team, benefiting patients through *'highlighting [precancerous or cancerous] areas that otherwise would be missed'* using standard endoscopy (**S4**) and significantly improving prognosis by early interventional surgery to remove the abnormal tissue. The consequences of failing to detect precancerous cells are catastrophic for the patient, with the annual progression from precancer to oesophageal adenocarcinoma up to 40% and, from diagnosis, there is a <15% five-year survival rate.

Early identification of precancerous cells allows removal by a minimally-invasive procedure, significantly reducing risks. Precancerous cells detected by AAC can be removed by a surgical intervention which is, in most cases, minimally-invasive and endoscopic-led. Previously, in the absence of a reliable means for the early detection of abnormal tissue, oesophageal adenocarcinoma was detected at a later stage in development and oesophagectomy was the only means to remove cancerous tissue. Oesophagectomy is significantly riskier, with up to 20% mortality and 30-50% of patients developing at least one serious postoperative complication such as pneumonia, arrhythmia, myocardial infarction or heart failure. In stark contrast, minimally-invasive endoscopic-led procedures have no mortality or major complications. Unlike oesophagectomy, which has an average hospital stay of 2 weeks, the majority of patients undergoing endoscopic-led procedures can return home the same day.

Treatment where it was not previously possible in older adults and those with underlying disease. A third of BO patients are 70 years old and above. As age increases above 70 years, oesophagectomy-associated risks of mortality and major complications rise steeply - a trend not observed for minimally-invasive, endoscopic-led procedures. A third patient benefit is therefore treatment where this was previously not possible, as the highly significant reduction in risk of an endoscopic-led procedure permits intervention in older adults with comorbidities where oesophagectomy would previously have been contraindicated.

Regular surveillance is painless and ensures patients can live their lives unaffected. Patients with BO have periodic surveillance, comprising endoscopic inspection of the oesophagus with AAC. Knowing that AAC is highly accurate in identifying precancerous and cancerous cells gives patients peace of mind. One patient described AAC as *'completely painless… [allowing] the clinician to correctly diagnose my condition at the time and remove the nodule via endoscope. Since that day and all the follow-up procedures, I always swallow this mixture just prior to having the scope. This is one of the main reasons I still have my oesophagus and have not had to have an esophagectomy, due to early diagnosis and of course the treatment I received via endoscope.'* (**S5**).

2. Cost savings to the healthcare system

As a more efficacious means of diagnosis, AAC has a number of benefits to the healthcare system:

● When compared to periodic monitoring of BO patients with endoscopic inspection and spaced biopsies for histological assessment, there are significant financial savings (of up to 97% or >GBP1,000 per patient) with an approach that biopsies only the abnormal regions identified by AAC (**S6**). Based on approximately 1,500 AAC procedures for BO from 2013 to 31 July 2020 at the Royal Bournemouth Hospital (**S4**), this equates to a GBP1,600,000 saving compared to spaced biopsies with histological assessment.

● The greater use of minimally-invasive, endoscopic-led procedures to remove precancerous cells - replacing more complex and risky oesophagectomy to remove cancer developed at a later stage in its development - was identified to save >GBP90,000 and 170 bed days a year at the Queen Alexandra Hospital, Portsmouth (**S7**).

3. The simplicity of AAC means that naïve endoscopists can be trained to professional standards in single day

Naïve endoscopists with experience of endoscopy of BO patients but with no formal training in AAC are able to develop professional standards of competency following online training and a one-day interactive seminar (**S8**). Once trained, endoscopists miss just 2% of cancer using AAC, compared to a 41-66% miss rate with the standard practice of random sampling. For a medium-sized hospital such as Leicester General Hospital which performs around 150 AAC procedures on BO patients a year, this equates to up to 96 patients a year in which early stage oesophageal cancer would simply have been missed. An endoscopist based in Hungary commented *'It can help clinicians to identify precancerous lesions and early cancer with great confidence.'* (**S9**)

4. AAC for detection of precancer and cancer in BO has changed endoscopy practice and policy

The final impact comes from the ease with which this technique can be integrated into standard endoscopic practice in gastroenterology. Acetic acid is inexpensive and, at a concentration of <3%, safe to patients and practitioners. It is non-proprietary and compatible for use with any endoscopy system. Given evidenced benefits - to the health of patients, in cost savings to healthcare systems, in ease of use and ease of integration into healthcare systems - AAC is recommended in BO by American (**S1**) and European (**S2**) professional bodies.

In summary, AAC allows earlier detection, at the precancer stage; it allows more accurate detection, compared to previous methods; it is easy to learn to professional standards and applicable to any endoscope. These characteristics produce significant benefits to the health of patients, in cost savings to healthcare systems, in ease of use and ease of integration into healthcare systems; and have resulted in changes in practice and policy.

5. Sources to corroborate the impact

S1. Thosani, N., Dayyeh, B. K. A., Sharma, P., Aslanian, H. R., Enestvedt, B. K., Komanduri, S., ... & ASGE Technology Committee. (2016). ASGE Technology Committee systematic review and meta-analysis assessing the ASGE Preservation and Incorporation of Valuable Endoscopic Innovations thresholds for adopting real-time imaging–assisted endoscopic targeted biopsy during endoscopic surveillance of Barrett's esophagus. Gastrointestinal endoscopy, *83*(4), 684-698. https://doi.org/10.1016/j.gie.2016.01.007

S2. Dekker, E., Houwen, B. B., Puig, I., Bustamante-Balén, M., Coron, E., Dobru, D. E., ... & Bisschops, R. (2020). Curriculum for optical diagnosis training in Europe: European Society of Gastrointestinal Endoscopy (ESGE) Position Statement. *Endoscopy*. *52*(10), 899-923. https://doi.org/10.1055/a-1231-5123

S3. Testimonial - Head of ESGE Guidelines Committee (2013-2017), 26/11/2020.

S4. Testimonial - Consultant Gastroenterologist, Royal Bournemouth and Christchurch Hospitals, 28/09/2020.

S5. Testimonial - Patient, 06/11/2020.

S6. Chedgy, F. J., Subramaniam, S., Kandiah, K., Thayalasekaran, S., & **Bhandari, P.** (2016). Acetic acid chromoendoscopy: Improving neoplasia detection in Barrett's esophagus. *World journal of gastroenterology*, *22*(25), 5753. https://doi.org/10.3748/wjg.v22.i25.5753

S7. Basford, P. J., Mead, R. J., Duku, M. D., **Longcroft-Wheaton, G. R.**, Somers, S., Toh, S., ... & **Bhandari, P.** (2011). Upper gastrointestinal EMR service: long-term feasibility, safety, efficacy and cost effectiveness from a large UK centre. *Gut*, *60*(Suppl 1), A48-A49. https://doi.org/10.1136/gut.2011.239301.95

S8. Chedgy, F., Kandiah, K., Barr, H., De Caestecker, J., Dwerryhouse, S., Eross, B., Gordon, C., Green, S., Li, A., **Brown, J.**, **Longcroft-Wheaton, G.**, & **Bhandari, P.** (2017). Development and validation of a training module on the use of acetic acid for the detection of Barrett's neoplasia. *Endoscopy*, *49*(02), 121-129. https://doi.org/10.1055/s-0042-120179

S9. Testimonial - Lead for Upper Gastrointestinal Research, University of Pécs, Hungary, 12/10/2020.