AN EVALUATION OF THE QUALITY IMPROVEMENT POTENTIAL OF COMPUTER ASSISTED SCREENING TECHNOLOGY WITHIN A CERVICAL CANCER SCREENING PROGRAMME

Histopathology

School of Medicine

Trinity College Dublin
Coláiste na Tríonóide, Baile Átha Cliath
The University of Dublin

A Thesis submitted to Trinity College Dublin for the degree of Doctor of Philosophy (Ph.D.)
2018

David Samuel Nuttall M.Phil.; C.Sci.; FIBMS

Declaration

I declare that this thesis has not been submitted as an exercise for a degree at this or any other university and it is entirely my own work.

I agree to deposit this thesis in the University's open access institutional repository or allow the library to do so on my behalf, subject to Irish Copyright Legislation and Trinity College Library conditions of use and acknowledgement.

David Samuel Nuttall

Student Number 09125345

Date

Abstract

Between 2006 and 2011, three studies - known as **CAESAR** (**C**omputer **A**ssisted **E**valuation, **S**creening **A**nd **R**eporting) were carried out to evaluate Computer Assisted Screening (CAS) with manual primary screening to current procedures and protocols operated by the Welsh cervical screening programme – Cervical Screening Wales (CSW). A total of 45,317 SurePath™ liquid based cytology (LBC) cervical screening samples were submitted for CAS within four Welsh Cytology laboratories as part of a multi-centre randomised controlled trial.

The CAS technology chosen was the Becton-Dickinson FocalPoint™ GS Slide Imaging System (FocalPoint™) technology and a comparative assessment was carried out between the slides scanned and categorised using this technology (n=45,317) and those primary screened (n=137,806) over the same period and reported using established Cervical Screening Wales protocols, with a histological outcome where appropriate.

This thesis investigated several potential areas where this technology can be applied, in an effort to identify the overall benefits of the technology to the cervical screening programme.

These areas include:

- Rapid quality assurance screening
- Comparison of manual to automated primary screening
- No further review (NFR) reporting category
- Evaluation of the automated detection of endocervical cells
- Screener acceptance of the technology
- The relationship of the FocalPoint™ quintile ranking facility to sample Human Papillomavirus (HrHPV) status.

In addition, an economic analysis was carried out to identify any benefits and potential savings that might be realised by Cervical Screening Wales. The results of the study areas that have been analysed indicate that:

- The timings for carrying out a rapid QA screen via FocalPoint™ are comparable to a manual rapid pre-screen/re-screen and the sensitivity of the technology was determined to be at least equivalent to the rapid QA screens currently employed in cervical cytology.

- FocalPoint™ as a primary screening tool is not as sensitive for high grade or all grades dyskaryosis as manual primary screening as evidenced by not meeting the current minimum NHS Cervical Screening Programme (CSP) standards. Furthermore, the interval outcome rates for FocalPoint™ primary screened samples were greater than those for manually screened samples, both at 2 and at 3-year intervals.

- The 3-year interval outcome rates for CIN 2+ and cervical pre-cancer are significantly lower for the FocalPoint™ NFR category than those for manual screening. Interval cancer rates were similar, indicating that the FocalPoint NFR™ was demonstrably superior to manual primary screening in terms of fewer false negative results.

- System calibration and operational monitoring of the FocalPoint™ technology is vital for correct operation and optimised performance of the technology. **This study highlighted on a hitherto unprecedented behaviour of the NFR reporting technology and brought about a significant revision of the manufacturer's operating, calibration and monitoring procedures. The revised protocol was communicated to the NHS CSP task and finish group producing the NFR guidance document and the updated LPCA calibration procedure incorporated into the guidance (Denton *et al*., 2013). Therefore, as a direct result of this study, a major change in practice benefited a very large population of women (mainly outside the UK and Ireland) who received an improved screening outcome as a consequence.**

- The inter-laboratory detection rates of endocervical cells by FocalPoint™ are more consistent from laboratory to laboratory than those for manual screening and yet those detection rates are equivalent to those of manual screening. The technology is therefore equivalent to manual screening for the detection of endocervical cells and may be used for the quality assurance of sample takers in the same way as manual primary cytology screening.

- Screener perceptions and acceptance of the FocalPoint™ technology were positive with participating individuals mainly appreciative of the diversion offered by FocalPoint™ from manual primary screening. Respondent numbers were small, however, and further, more structured investigation and analysis should be undertaken to qualify these findings.

The outcome of the economic analysis initially indicated that FocalPoint™ was expensive to implement and therefore offered little advantage to manual screening in a working laboratory. Further analysis, considering insufficient staffing levels and the resultant requirement for backlog management indicated that FocalPoint™ NFR and rapid QA screening offered a viable alternative to overtime working at enhanced pay rates for staff and would be of use in situations where screening staff were difficult to recruit.

- Comparison of FocalPoint™ quintile ranking rates with HrHPV results on LBC samples provided unexpected results, however, the samples compared were from a specific cohort of women that had received recent treatment for high grade CIN and this might account for the results of the comparison. Numbers of samples compared were low (n = 124) and this is a factor for consideration, indicating that further work is required to evaluate the FocalPoint™ technology in conjunction with HPV primary screening.

- In conclusion, the BD FocalPoint™ GS imaging system offers several advantages that are worthy of consideration and implementation by laboratories offering a cervical screening service.

Keywords: computer assisted screening, quality assurance, quality control, quality improvement, cervical cytology, cervical cancer, cervical screening, false-negative

Contents

Page

List of Figures

Page

List of Tables

Page

List of Abbreviations

A4C	Agenda for Change
Adeno Ca	Adenocarcinoma
ASCUS	Atypical Squamous Cells of Uncertain Significance
ASM	Annual Scientific Meeting
BD	Becton Dickinson
BMS	Biomedical Scientist
CAESAR	Computer Assisted Evaluation, Screening and Reporting
Ca	Carcinoma
CAS	Computer Assisted Screening
CEA	Cost Evaluation Analysis
CI	Confidence Interval
CIN	Cervical Intraepithelial Neoplasia
CIN1	Cervical Intraepithelial Neoplasia Grade I
CIN1-	Any Lesion of CIN Grade I or Less – Cases Not Requiring Treatment
CIN2	Cervical Intraepithelial Neoplasia Grade II
CIN2+	Any Lesion of CIN2 or worse
CIN2–	Any Lesion of CIN Grade II or Less
CIN3	Cervical Intraepithelial Neoplasia Grade III
CIN3+	Any Lesion of CIN3 or Worse
CONSORT	Consolidated Standards of Reporting Trials
CSP	Cervical Screening Programme
CSW	Cervical Screening Wales
DNA	Deoxyribonucleic Acid
EASR	European Age Standardised Incidence Rate
FDA	United States Food and Drug Administration
FEG	FocalPoint™ Executive Group
FOG	FocalPoint™ Operational Group
FOV	Fields of View
FP	Becton-Dickinson FocalPoint™ GS Imaging System
GLP	Good Laboratory Practice
GSW	Guided Screener Workstation

GUM	Genito Urinary Medicine
HB	Health Board
HC2	Qiagen™ High-risk HPV Hybrid Capture 2
HG	High Grade (as in High Grade Dyskaryosis)
HSIL	High Grade Squamous Intraepithelial Lesion
HSIL+	High Grade Squamous Intraepithelial Lesion or worse
HPV	Human papillomavirus
HrHPV	High Risk Human Papillomavirus
HTA	Health Technology Assessment
IARC	International Agency for Research on Cancer
IBM™	International Business Machines
IQC	Internal Quality Control
KPI	Key Performance Indicator
LBC	Liquid Based Cytology
LLDNO	Llandudno General Hospital
LSIL	Low Grade Squamous Intraepithelial Lesion
LSIL+	LSIL or worse
LIMS	Laboratory Information Management System
LPCA	Laboratory Process Calibration Assessment
LREC	Local Research Ethics Committee
MAVARIC	Manual Assessment versus Automated Reading in Cytology
MDM	Multi-disciplinary meeting
MLA	medical laboratory assistant
mRNA	Messenger Ribonucleic Acid
MSC	Managed Service Contract
MSD	Most Significant Dot
NFR	No Further Review
NHS	National Health Service
NHSCSP	NHS Cervical Screening Programme
NICE	National Institute for Health and Clinical Excellence
NPP	Negative Predictive Potential
NPV	Negative Predictive Value
NSI	Neuromedical Systems Inc., Suffern, NY, USA

Pap	Papanicolaou
PC	Personal Computer
PCR	Polymerase Chain Reaction
PCT	Primary Care Trust
PHE	Public Health England
PHW	Public Health Wales
PII	Patient Identifiable Information
PPV	Positive Predictive Value
QC	Quality Control
RGH	Royal Gwent Hospital
RNA	Ribonucleic Acid
ROU	Resolution of Uncertainty
RQA	Rapid Quality Assurance
SBS	Source BioScience
SCJ	Squamo-columnar Junction
SD	Standard Deviation
SIL	Squamous Intraepithelial Lesion
SOP	Standard Operating Procedure
TIS	ThinPrep™ Imaging System
TOC	Test of cure
TPR	True Positive Rate
TZ	Transformation Zone
UK	United Kingdom
UKAS	United Kingdom Assessment Service
VDU	Visual Display Unit
VPN	Virtual Private Network
WG	Welsh Government
WHO	World Health Organisation
WTE	Whole Time Equivalent
WXM	Wrexham
Y2K	Year 2000 bug (Year coded in computer software as “YY” and not “YYYY”)
YGC	Glan Clwyd Hospital

List of Presentations and Publications

Published papers, and professional guidance documents

Cuscheri K, Denton K, **Nuttall D,** Sargent A. **Laboratory quality control and assurance for human papillomavirus testing. January 2017**. Public Health England. NHS Cervical Screening Programme. www.gov.uk – accessed June 1, 2017.

Hibbitts S, Tristram A, Beer H, McRea J, Rose B, Hauke A, **Nuttall D**, Dallimore N, Newcombe RG, Fiander A. **UK population based study to predict impact of HPV vaccination. 2014.** Journal of Clinical Virology. Feb;59(2):109-114.

Denton K, **Nuttall D,** Cropper A, Desai M. **Implementation of 'No Further Review' (NFR) using the BD FocalPoint™ Slide Profiler**. 2013. NHS Cervical Screening Programme: Good Practice Guide No. 4.

Submitted for publication – awaiting decision:

Nuttall DS, Fox R, Hillier S, Dallimore N, Clayton H, Martin C, O'Leary JJ, Sloan S, Savage A. **A Retrospective Validation of the Becton Dickinson Focal Point GS Slide Profiler NFR Technology by Analysis of Interval Disease Outcomes Compared to Manual Cytology Screening.**

In preparation:

Nuttall DS, O'Leary JJ, Martin C. **The Effect of Variation in Screening Population on the FocalPoint™ Point GS No Further Review Technology: 'The Algorithm Super-saturation and Quintile Cascade Effect'.**

Presentations

2016:

European Congress of Cytology, 40th Conference. Liverpool.

Oral Presentation: **Improved Detection of CIN 2+ Lesions by the Becton Dickinson Focal Point™ GS Slide Profiler No Further Review Technology Compared to Routine Manual Slide Reading: An analysis of interval outcomes."**

United States and Canadian Association of Pathology (USCAP) Annual Scientific Meeting. Seattle, USA.

Oral Presentation: Improved Detection of CIN 2+ Lesions by the Becton Dickinson Focal Point™ GS Slide Profiler No Further Review Technology Compared to Routine Manual Slide Reading: An analysis of interval outcomes.

2014:

Cervical Screening Wales 15th Anniversary Conference – Cardiff.

Oral Presentation: **Cervical Screening Laboratory Services – the next 15 years!**

2013:

Update course for Consultant Biomedical Scientists

East Pennine Cytology Training School.

Oral Presentation: **Cervical Screening Wales – A Different Perspective".**

Cervical Screening Wales Colposcopy Conference – Llandrindod Wells.

Oral Presentation: **Introduction and Clinical Management of HPV Testing.**

2012:

British Association for Cytopathology. Annual Scientific Conference.

Oral Presentation: **An Evaluation of the BD Focal Point™ Imaging System No Further Review Slide Scan Result Category for Routine Use within the Cervical Screening Programme in Wales – the story so far.**

2011:

Conference of the Cytology Society of Belgium - Antwerp.

Oral Presentation: **The Role of Biomarker Assisted Morphology in the Cervical Cytology Laboratory – The Welsh SuPerLy Project.**

European Congress of Cytology – Istanbul.

Poster Presentation: "An Evaluation of the BD Focal Point™ Imaging System – **The Significance of the No Further Review Slide Scan Result Category for Routine Use within the Cervical Screening Programme in Wales.**
Nuttall DS, Rose B.

Meeting of the Cytology Society for the South of England and South Wales.

Oral Presentation: **The Role of Biomarker Assisted Morphology in the Cervical Cytology Laboratory – The Welsh SuPerLy Project.**

2010:

National Association of Cytology. Keele University.

Oral Presentation: **The potential for Computer Assisted Screening within the cervical screening programme in Wales.**

Acknowledgements

During the course of carrying out this research study, I have been very fortunate to receive a great deal of help, and I wish to gratefully acknowledge those that have provided that support.

Firstly, I am indebted to Professor John O'Leary and I wish to acknowledge his great support and unstinting advice and guidance. I have had the good fortune to collaborate with Prof. O'Leary on several occasions and his enthusiasm for his field of endeavour, his teaching and his mentorship of the students fortunate enough to study under his supervision, is truly inspirational. I clearly remember that day in 2009 when I was introduced to Prof. O'Leary and his subsequent invitation to study under his mentorship at TCD. It has been a roller coaster of personal highs and lows, mostly highs and I shall be eternally grateful for the opportunity.

I wish to express my sincerest thanks to Prof. Cara Martin, who has provided immeasurable support, help and advice in writing up this thesis as well as helping me fulfil the requirements of TCD of its students. Without Prof. Martin, I do not think that I would be in the fortunate position of writing up this acknowledgement!

Sincerest thanks are also due to Dr James O'Mahony for his help and advice with the cost evaluation assessment and with proof reading the thesis.

I would also like to acknowledge the Screening Division, Public Health Wales for partly financing my candidature. I would like to thank the following individuals for their help and support:
Mr. Bryan Rose, former Head of Programme – Cervical Screening Wales for his enthusiasm, his willingness to help and advice and for being a friend.
Mrs Gwyneth Carey, for all the help with the formatting of this thesis, which she carried out with consummate ease. Gwyn, thanks for all you've done over the years!
Drs. Hilary Fielder and Rosemary Fox, former Directors of Screening Division for their support and I am also grateful to Dr Sharon Hillier, currently Acting Director of Screening Division.

My thanks are also due to Mrs Helen Clayton, Acting Head of Informatics, Screening Division for her help with some of the statistical analyses and to Mr Rhys Blake, for advising me on PHW business, financial and statutory matters and his continual encouragement.

To the staff of the Welsh laboratories that have contributed to this study, in particular to Amanda Savage, Sonia Sloan, Virginia Seager and Steve Court. Your contributions have been invaluable.

Finally, to my wife, Enid, and my family. Words are not enough to express my thanks for all the family time lost to this study and the sacrifices you made. Caru chi oll!

Chapter 1

Introduction and Background

1.1 Cervical cancer – definition, development rates and time trends

Cervical cancer is a malignant neoplasm of the cervix uteri. In 2012, 528,000 new cases of cervical cancer were diagnosed worldwide, and 266,000 women died of the disease - almost 90% of these women were from low to middle income countries. Cervical cancer is the leading cause of cancer deaths in Eastern and Central Africa. Without urgent attention, deaths due to cervical cancer are projected to rise by up to 25% over the next 10 years (WHO; 2014)

The incidence of cervical cancer and mortality rates in most countries has decreased significantly in the last 30 years (WHO, 2014). In the UK, mortality from cervical cancer has been declining and in 2012, was at a low of <5 deaths per 100,000 women. However, there were 3,224 new cases of cervical cancer reported in the UK in 2014 and the peak rate of these cases were in the 25-29 year age group. Cervical cancer European Age Standardised (EASR) incidence rates have decreased in the UK since the early 1990s, however, in the last decade EASR incidence rates have increased by 5%. This increase reflects the death by cervical cancer of a young celebrity (Lancucki *et al*., 2012).

1.1.1. Epidemiology of cervical cancer

The incidence rates of cervical cancer show strong birth cohort effects (Sasieni, Adams, 2000). This means that women born at one time might be at relatively high risk of cervical cancer in their 20s and 30s and remain at relatively high risk through their 40s, 50s, 60s and 70s. My understanding of this effect is that there is an underlying characteristic of increasing rate of disease with age, but the level is determined by environmental exposure (to a sexually transmitted agent) in the late teens and twenties. Environmental exposure level will be determined by social norms and will vary between ethnic groups as well as over time. Modelling of the incidence and mortality rates by age and cohort effects works well until the 1980s. More recent data require the addition of age specific time-trends corresponding to a beneficial effect of screening, particularly in younger women, to provide a satisfactory model.

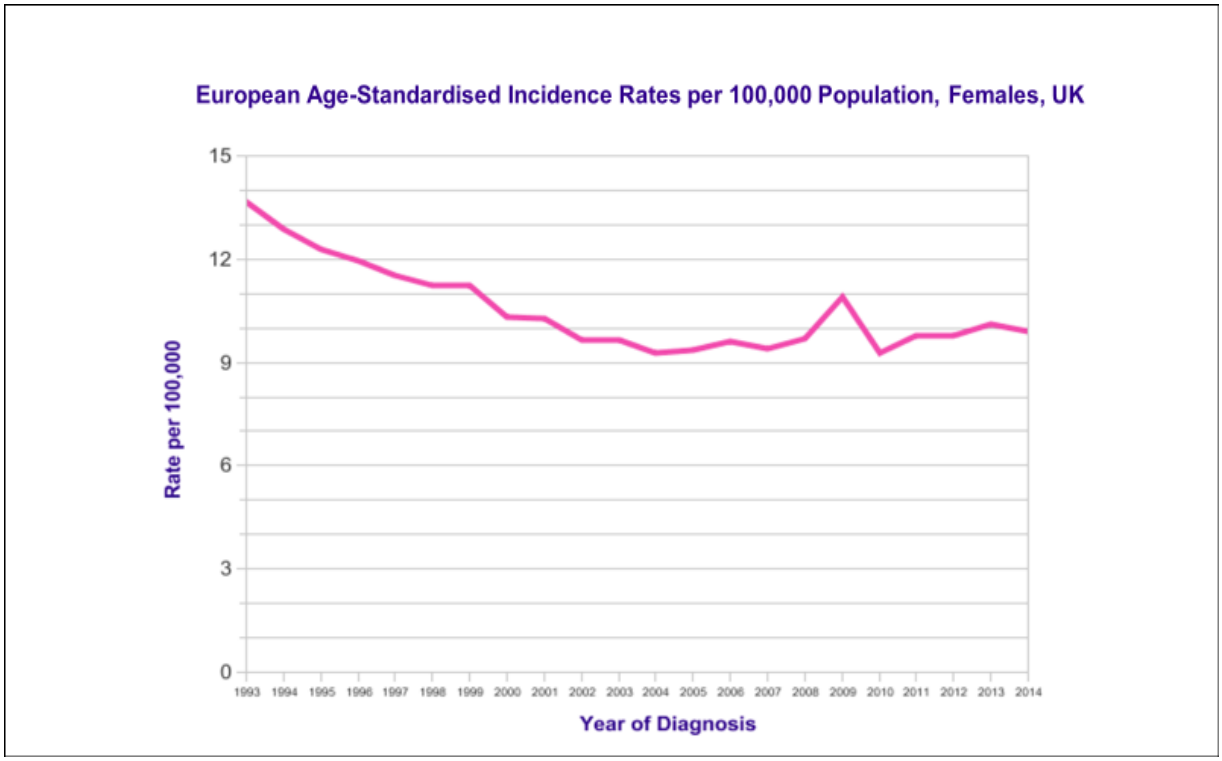


Figure 1.1: European Age-Standardised Incidence Rates of Cervical Cancer per 100,000 population. Source: CRUK data – accessed September 8th, 2017

1.1.2. Incidence of cervical cancer

From a public health perspective, it is important to note that:

- women born in the 1960s are three to four times greater risk of cervical cancer than women born in the 1930s.
- after adjusting for cohort effects, the incidence of cervical cancer increases between ages 20 and 55 years, most rapidly between ages 30 and 40, and decreases steadily after age 55.

Therefore, the cumulative risk of cervical cancer in women born during the 1960s is likely to be around 4-5%, thus emphasising the importance of cervical screening.

1.1.3. Risk factors

The evidence for an association between cervical cancer and sexual activity dates back to 1842. In that year, Rigorni-Stern then published data showing that married women were more likely to die of cancer of the uterus (predominantly cervix) than breast cancer, whereas nuns only very rarely died of cancer of the uterus. Since then the epidemiological evidence suggestive of a sexually transmitted causative agent for cervical cancer has grown. The risk

factors usually quoted include number of sexual partners and age at first sexual intercourse (Brinton et al. 1992). The behaviour of men is also a factor, as shown by increasing risk in women with just one partner, depending on the number of partners that their husband has had (Buckley *et al*., 1981). More recently, the sexually transmitted agent has been identified as certain types of the human papillomavirus (HPV), now known as high-risk human papillomaviruses (Hr-HPV).

Human papillomavirus (HPV) is a common, sexually transmitted infection. In rare cases, infection with high-risk forms of this virus can cause a woman to develop cervical cancer. There is consistent evidence from across the world that high-risk HPV infection is a necessary cause of cervical cancer, and optimal testing systems have identified the virus in all invasive specimens (NHS Cancer Screening Programmes, 2008). HPV is implicated in both squamous cell carcinoma (SCC) and adenocarcinoma (Adeno Ca), as well as in over 95% cases of the cancerous precursor, cervical intraepithelial neoplasia, grade 3 (CIN3).

Co-factors that appear to increase the risk of developing cervical cancer in HPV-infected women include the use of oral contraceptives, smoking, high parity, unidentified genetic factors possibly related to immunity, and previous exposure to other sexually transmitted diseases, such as chlamydia trachomatis and herpes virus type 2. Women exposed to human immunodeficiency virus (HIV) are at high risk of HPV infection, HPV persistence, and cervical cancer. Immunosuppression certainly increases the risk of cervical cancer, as evidenced by studies on renal transplant patients receiving immunosuppressive drugs (NHS Cervical Screening Programme Publication No. 20; 3rd edition; 2016), and smokers are thought to be at increased risk due to the immunosuppressive effects of tobacco smoke inhalation. Diet may play a role in the immune response to HPV, but studies on diet and cervical cancer are inconclusive to date (Garcia-Closas *et al*. 2005).

More recently, genetic factors that modify the risk of cervical cancer have been identified, but the understanding of the factors that determine why some women develop cervical cancer after infection with oncogenic HPVs, whilst the majority do not, is incomplete.

Cervical screening and treatment of high-grade CIN have the potential to prevent the development of cervical cancer in HPV-infected women, and screening programmes have

had a substantial impact on cervical cancer incidence in many countries (NHS Cancer Screening Programmes, 2008).

1.1.4. Squamous cell carcinoma and adenocarcinoma

There are two main types of cervical cancer. The most common is squamous cell carcinoma. It used to be said that this accounted for around 90% of all cervical cancer. However, more recent data shows that adenocarcinoma (including adeno-squamous) is accounting for a growing proportion of diagnoses particularly in younger women (Stockton *et al*., 1997). Squamous cell carcinoma now only accounts for around 75% of all cervical cancer. The reason for the increasing proportion of adenocarcinoma seems to be three-fold:

- Adenocarcinoma really is becoming more common having been a very rare disease because of the greater awareness of adenocarcinoma.

- It is being reported more often on pathology reports - previously the cell type may not have been reported and so was assumed to be squamous.

- Cytological screening is better able to detect pre-cancerous squamous lesions than pre-cancerous glandular (adeno) lesions and thus the relative incidence of the two types of cancer has changed.

There is some suggestion that adenocarcinoma is associated with HPV type 18, whereas squamous cell carcinoma is associated with the more common type 16 (International Agency for Research on Cancer). HPV types 31 and 33, although less common in the UK, are also associated with cervical cancer (IARC, 1995).

1.1.5. Natural history

For the vast majority (estimated as over 95%) of cervical cancers, the first step is exposure to one of the oncogenic HPVs. The time from infection to the development of invasive cancer is thought to be between five and thirty-five years. Longitudinal studies on young women show that most HPV infections are transient (Wheeler *et al*., 1996; Hildesheim *et al*., 1994) and that the virus is indeed sexually transmitted (Burk *et al*., 1996). Persistence of infection has been shown to be associated with the development of cervical lesions (Remmink *et al*.,

1995) and viral load can be used as a surrogate for persistence (Cuzick, 1997). It is now generally accepted that one of the key steps in the development of cancer is integration of the viral DNA in the host genome (Cullen *et al.*, 1991).

Cervical neoplasia appears to constitute a disease continuum (Kiviat *et al*., 1992) ranging from cervical intraepithelial neoplasia (CIN) grades 1 to 3, to micro-invasive and finally fully invasive cancer. Follow-up studies of women with CIN have found that about 60% of CIN 1 regresses compared to about 33% of CIN 3; whilst 11% and 22% of CIN 1 and 2, respectively, progressed to CIN3 (Ostor *et al*., 1993). Although the details of progression and regression are largely speculative, at most about a third of high grade CIN will progress to cancer over about 15 years and that the majority of CIN 1 will regress.

CIN 3 is very rare in women under the age of 20 (Evans *et al*. 1997). The rates rise rapidly peaking at about age 30 and fall again rather more slowly to about half their peak by age 40 and just 10-20% by age 50.

1.1.6. Treatment and survival

Five-year survival after diagnosis of cervical cancer is strongly related to the stage of the tumour at diagnosis. Studies show over 90% survival for discreet tumours in women under 50 at diagnosis, 50% for cancers with local involvement and just 11% in women over 50 years with distant metastases. Survival (5-year) after diagnosis of micro-invasive cancer (stage 1a1/1a2) is around 94-98% (Quinn *et al*., 2006).

Micro-invasive cancers may be treated by cone biopsy alone, but hysterectomy may be the preferred treatment, particularly if the patient has completed her family. Surgery (Wertheim's hysterectomy) is the usual treatment for invasive cancer that has not spread beyond the pelvic area. It may be followed by radiotherapy if the cancer recurs. Radiotherapy alone is the standard treatment for more advanced cancer, chemotherapy is also used.

Although the five-year relative survival of women after treatment of CIN 2 or 3 is virtually 100%, there are numerous case reports of women developing invasive cancer following treatment for CIN and it seems likely that perhaps 1 in 200 women treated for high grade

CIN (CIN 2 and 3) will develop invasive cancer within 10 years. Ablative treatments used to be popular but are now becoming less so. Excision can be done by various means. LLETZ (large loop excision of the transformation zone) is widely used, but laser, cold-knife cone biopsy, cold coagulation and cryotherapy are still used on occasion.

1.2 The National Health Service cervical screening programme

1.2.1. Evidence of the effectiveness of cervical screening

The NHS Cervical Screening Programme (NHSCSP) implemented a managed, structured programme of call and recall of screening participants in 1988 and this programme is estimated to save as many as 5000 lives per year in the UK Peto *et al*. 2004). It is now recognised as one of the leading cervical cancer prevention programmes worldwide.

The use of new technology to improve service quality and efficiency is a key strategy of the NHSCSP. Within screening cytology, improving sensitivity and specificity and reducing human workload are key desirables and the number of screening tests has dropped in recent years because of service improvement. For example, the implementation of liquid-based cytology (LBC) in 2004-2008, saw the number of inadequate samples and subsequent repeat testing drop from 9% in 2004–5 to 2.9% in 2007–8 (Kitchener *et al*., 2011). The introduction of human papillomavirus (HPV) triage and test of cure (TOC) in the UK has reduced the number of repeat tests taken by triaging the treatment and management of women based on their HPV results. Women attending for routine tests who are found to have a low-grade abnormality and a positive HPV result are referred directly to colposcopy without repeat cytology testing, and those who are HPV negative are returned to routine recall without cytological follow-up. (HPV Sentinel Sites implementation project, 2008).

1.2.2. Current manual screening practices in the UK

At present, current standards (British Society for Clinical Cytology Code of Practice, 2009) mandate that all cytology is primary screened. Slides reported as negative or inadequate receive a rapid quality assurance (QA) screen (rapid preview or review) and suspected abnormal slides are reviewed and reported by senior laboratory staff. Cytology screeners (cytoscreeners, cytotechnologists) should only screen slides at the microscope for a maximum of 5 hours in a 24-hour period, with a complete break from the microscope at

least every 2 hours.

Rapid QA screening is carried out by screening staff performing a rapid internal quality control (IQC) review of the whole slide in around 90 seconds. Current screening techniques are labour intensive requiring a large and committed laboratory workforce. The initial training and ongoing competency assessment of staff is managed on a national scale and the external quality assessment schemes (EQA) for participating staff and technical slide preparation are a seriously resource intensive undertaking.

1.2.3. Screening intervals and coverage

In England, currently, women aged 25–49 years are invited every 3 years, and women aged 50–64 years are invited every 5 years (NHS Cancer Screening Programme Annual Review, 2008). Of the 3.6 million women aged 25–64 years who were screened in 2008–9, around 6.7% received an abnormal result. In the same period, there were 134,000 referrals to colposcopy prompted by an abnormal screening result, 28.9% of which were for results of moderate dyskaryosis or worse, the remainder resulting from low-grade cytological abnormalities (The Health and Social Care Information Centre. Cervical Screening Programme, England 2008–09).

1.2.4. Future NHS cervical screening programme considerations

Following the publication of the MAVARIC report (Kitchener *et al*., 2011), computer assisted screening (CAS) was approved for use in the UK within the NHS cervical screening programme (NHS CSP). This approval concerned the BD (Becton Dickinson - BD, Franklin lakes, NJ, USA) FocalPoint™ GS Imaging System "No Further Review" (NFR) reporting technology and the guidance for implementation is set out in NHS CSP Guidance Document No. 4 (Denton *et al*.; 2013 "Implementation of 'No Further Review' (NFR) using the BD FocalPoint^{TM} Slide Profiler").

As well as the implementation of CAS, several other organisational challenges faced the NHSCSP at that time. In 2007 the Department of Health (DoH) published the Cancer Reform Strategy, (Department of Health; 2007). This document recommended that to achieve the Government's target of a 14-day turnaround time (from cervical sample being taken to the result being received by the woman), laboratories and screening offices should be

reconfigured to make them larger and more efficient. Some laboratories currently operate as “hub and spoke” with larger central laboratories processing the LBC samples and returning them to the smaller laboratories for screening. Amalgamation of smaller laboratories will see further changes to this service configuration. In the NHS in Wales, pathology cervical screening services were reviewed and restructured in 2009-10 in anticipation of the implementation of CAS and HPV testing. This resulted in two “hub and spoke” networks implemented in Wales – one in North Wales linking the laboratories in Llandudno, Bodelwyddan and Wrexham via the A55 trunk road and the other in South Wales, linking laboratories in West Wales (Carmarthen and Haverfordwest), Swansea, Cardiff and Newport via the M4 motorway corridor. In 2010-11, this structure was replaced by a single hub laboratory (Magden Park, Llantrisant, Cardiff) servicing a single North Wales screening laboratory at Glan Clwyd Hospital along with two other laboratories in South Wales, at Newport and Swansea. Following the recommendations and subsequent validation of CAS (Appendix 13), arising from the CAESAR studies, and presented to the all-Wales Management Group of Cervical Screening Wales (CSW) the FocalPoint™ NFR technology was approved for use in Wales in 2012.

The HPV vaccination programme will also impact on the cervical screening programme. Implemented in September 2008, young girls were vaccinated at ages 12–13 years followed by a 3-year catch-up campaign to vaccinate older girls aged 14–17 years. Once the evidence regarding screening in a vaccinated population becomes clearer, screening intervals and follow-up protocols will need to be reviewed to reflect these findings. The importance of following up the screening outcomes of recently vaccinated girls was stressed by the Advisory Committee on Cervical Screening (ACCS) in 2009 when reviewing current screening policy in women aged 20–24 years. Following recommendations from the ACCS, the DoH decided against making any changes to current policy regarding screening in women aged 20–24 years. Instead, further education of general practice staff will ensure that symptomatic women aged < 25 years are assessed appropriately.

1.3 The National Service Framework for the Cervical Screening Programme in Wales

In January 1998, the Government’s White Paper on the NHS in Wales *Putting Patients First* announced that a National Service Framework (NSF) was to be developed for the cervical screening programme in Wales. The aim of the NSF was and is to ensure that national

published standards were in place and that all eligible women receive the same standard of service and quality of care for the same level of need. The decision to develop an NSF followed concern about failures of the UK programme, particularly in the Kent & Canterbury NHS Trust, and about the fact that previous reports and recommendations in Wales had not been fully implemented. The Health Minister at that time, Win Griffiths, invited Velindre NHS Trust, to work alongside the Welsh Office to develop and implement the National Service Framework.

1.3.1 Cervical Screening Wales

Cervical screening began in Britain in the mid-1960s. By the mid-1980s, although many women were having regular cytology tests, there was concern that those at greatest risk were not being tested, and that those who had positive results were not being followed up and treated effectively. The NHS Cervical Screening programme was set-up in 1988 when the Department of Health instructed all health authorities to introduce computerised call-recall systems and to meet certain quality standards. Cervical Screening Wales (CSW) is responsible for the Cervical Screening Programme (CSP) in Wales. CSW was launched in 1999 to provide women with equal access to a uniform and high quality cervical screening service across Wales. The programme aims to reduce the incidence of and mortality from invasive cervical cancer. This is accomplished by regularly screening all women at risk so that conditions which might otherwise develop into invasive cancer can be identified and treated. At the time of this study, Cervical Screening Wales invited women aged 20-64 for a cytology test every three years. Cervical screening is free for all eligible women. Screening is not offered to women who have had a total hysterectomy.

1.3.2 Cervical Screening Intervals

At the time of this study the cervical screening invitation and screening intervals were as presented in Table 1.1. The NHS call-and-recall system invites women who are registered with a GP. It also keeps track of any follow-up investigation, and, if all is well, recalls the woman for screening after three years.

Women should receive their first invitation for routine screening at or just before their 20th birthday. Migrants should receive their first invitation (between the ages of 20 and 64) soon after registering with an NHS GP.

Table 1.1: Cervical age of first invitation and subsequent screening intervals

Age group (years)	Frequency of screening
20	First invitation
20-64	3 yearly
65+	Screen those who have recent abnormal tests until these have been resolved

The programme screens on average around 223,500 women in Wales each year. For clinical reasons, some women have more than one test during a year thus around 236,800 samples are examined by pathology laboratories annually. Whilst no cervical screening intervention can be 100 percent effective, cervical screening programmes have been shown to dramatically reduce the incidence of cancer in a population of women.

Since the introduction of the NHSCSP in the UK in 1988, the number of diagnoses has halved, from 16.5 per 100,000 women in 1988 to 8.5 per 100,000 women in 2008 – despite increased rates of underlying disease.

1.3.3 Burden of cervical cancer in Wales

Between 1999 and 2009, 1863 cases of cervical cancer were registered in Wales with an average European age-standardised incidence rate (EASR) of 10.3 per 100,000 women. Mortality is substantially lower than incidence of cervical cancer with 735 cases reported between 1999 and 2009 (average EASR mortality rate 4.1 per 100,000).

1.4 The technologies used in cervical screening

1.4.1 The Papanicolaou smear test

The Papanicolaou or “Pap” smear was first described in 1943, (Papanicolaou GN, Traut H, 1943) but was not implemented in the UK until 1964 (Appendix 1). The screening of a cervical cytology sample is performed manually under a cytologist’s microscope. Apart from great improvements in quality assurance and structured training and assessment of the cytologists working in the laboratories that provided a cervical cytology service, little changed in the production of the “Pap” smear in the UK until the advent of Liquid Based Cytology in 2004.

This important milestone changed cervical cytology radically (see Section 1.4) and provided a springboard for the amalgamation of laboratories into large high-throughput units that have the required critical mass of work needed to implement expensive technologies such as Computer Assisted Screening technologies most effectively.

1.4.2 Liquid Based Cytology

The conventional method of producing cervical cells on a glass slide involved a sample being obtained from the cervix using a spatula which was smeared onto a glass slide and then fixed. Fifty years on, this method is still widely used worldwide. The quality of the slide material is variable, with the cells often unevenly spread along with excess blood cells and mucus capable of obscuring the cervical cells. This leads to a large number of slides being designated as 'inadequate' for reporting, resulting in the woman requiring a repeat sample to complete the test.

With LBC, the cervical sample is dissipated in a fluid medium which contains a cell fixative. The liquid sample is then subjected to either a process which filters the cells onto a slide (ThinPrep™ LBC, Hologic, Bedford, MA, USA) or cell enrichment [Becton Dickinson (BD) SurePath™ LBC, BD, Franklin lakes, NJ, USA] producing a cleaner, more homogeneous preparation which facilitates improved examination of the cervical cells. From 2001–3 an NHSCSP pilot study was performed in England in order to evaluate LBC in comparison with conventional cytology in a historical population. The findings were that inadequate samples were reduced from around 7%–8% to around 1%, and that LBC was certainly not less sensitive than conventional cytology and possibly more so, that laboratory throughput was more efficient, and that laboratory staff preferred LBC. LBC was determined to be cost-effective and meant that far fewer women were recalled because of an 'inadequate' smear. The National Institute for Health and Clinical Excellence (NICE) recommended its adoption (National Institute of Clinical Excellence, 2003) and between 2003 and 2008 LBC was rolled out across the entire UK. The new technology (SurePath™ version) was introduced across Wales between 2004-2005.

As well as manual and automated reading of LBC slides, the residual LBC sample can be used for real-time reflex testing such as HPV testing to triage low-grade cytological abnormalities. The adoption of LBC provided the means for a more efficient cytology service, enabling both

HPV testing and the potential to move to automated technology if the requirement arose.

1.4.3 HPV DNA testing

There are over 100 types of Human Papillomavirus (HPV) and most do not cause significant disease in humans. However, around 15 HPV types have been implicated in cervical cancer, notably types 16 and 18 which give rise to about 70% of all cervical cancers. Research has shown that women with no evidence of high risk HPV infection are extremely unlikely to have concurrent cervical pre-cancerous disease or to develop such disease or cervical cancer over the next 6 years.

HPV testing has been evaluated in various settings:

- To triage women with low grade dyskaryosis including borderline changes on cytology
- As a "test of cure" to reduce the duration of surveillance following treatment for CIN
- To replace cytology as the primary screening test

1.4.4 Cervical screening and HPV vaccination

Two prophylactic HPV vaccines have been shown to be highly effective at preventing persistent HPV infection and the high-grade disease (CIN3) caused by infection. In September 2008, a national programme was introduced to vaccinate girls against HPV 16 and 18. This programme was aimed at girls aged 12-13, however a catch-up programme for those born during 1990-1995 was also initiated.

The NHS cervical screening programme continues to screen women who have not been vaccinated and the role of cervical screening for vaccinated women remains to be clarified. This role will depend on the age at which the woman was vaccinated, the cross-protection given by the vaccine for other HPV types and the duration of protection provided. The impact of HPV vaccination will require monitoring alongside the cervical screening programme. In the interim, continued work is needed to determine the most effective means of monitoring the impact of both vaccination and cervical screening.

1.5 Development of CAS technologies

The main challenge with cervical screening has been to find a needle in a haystack (even though >90% of the haystacks contain no needle!) and doing this with the utmost accuracy

and consistency (Desai, 2009). Detecting these rare occurrences with the high level of accuracy required has been a continual challenge to the early pioneers developing automated screening technologies.

Initial experimentation with CAS took place in Europe following attempts to automate scanning of samples stained with the Feulgen stain for DNA/RNA (Desai, 2009). Developments then shifted to the USA with the development of the Cytoanalyser by the Airborne Instruments Laboratories, Inc. of Mineola, New York, as described by Tolles (1955). This company was exploring ways to utilise its war-time technologies for other uses, including medical applications. The instrument was designed to compare cell size as well as nuclear size and density.

Early researchers soon discovered that the complexities of cellular morphological analysis and recognition were very challenging. The problems encountered included:

- Similarities between benign and abnormal cells were greater than the differences
- The computing resources at that time were inadequate and unable to process the amount of morphological data generated by several hundred thousand cells on a Pap slide.
- Thick, 3D clusters of cells compounded these problems
- Detecting nuclear: cytoplasmic boundaries proved difficult.

Since these early beginnings, computers have become faster, the introduction of LBC has revolutionised cytology with the production of thinner slide preparations and the advancement of technology in general means that CAS technology can now compete with manual cytology screening in terms of throughput and accuracy.

The US Food and Drug Administration (FDA) has since approved two automated machines that were developed in the 1990s, the AutoPap™ 300 QC (NeoPath™, Redmond, WA, USA) and the PapNet™ (Neuromedical Systems Inc., Suffern, NY, USA - NSI). Both these systems were designed to work with conventional cytology slides.

AutoCyte™ also developed a machine known as the AutoCyte-Screen which was able to read

AutoCyte-Prep slides (now BD SurePath LBC). AutoPap was a computerised image processor that used high-speed video microscopy, image analysis software and FOV computers to classify cell images of conventional Pap smears by means of special algorithms designed to classify cells and slides. A proportion of the ranked slides were then selected for manual screening or review by a cytologist.

The PapNet™ system used computer imaging technology and neural network software to provide location-guided primary screening of conventional Pap smears. The system selected and presented up to 128 images of potentially abnormal cells to the cytologist.

These machines are no longer available. The AutoCyte™ was not year 2000 (Y2K) compliant and the PapNet™ company went into receivership in 1999. The story of NSI's PAPNET® System in the USA is an interesting one. In 1995, both NeoPath and NSI were approved by the FDA for the over-screening (secondary screen for quality assurance purposes) of negative conventional smears and they both then proceeded to market their products commercially. While NeoPath marketed its instrument to large laboratories by leasing the scanner for use on site, NSI aggressively marketed PAPNET® to clinicians and even directly to patients in the lay press, arguing that the added cost of PAPNET® QC screening ($40 a screen which was not covered by most health insurance companies) was worth it to ensure "peace of mind". The implication was that human screening was so unreliable and this undermined conventional human screening to the point where it was perceived that its use alone was almost dangerous. Some laboratories used PAPNET® as a means of establishing cytological "truth", even reprimanding cytologists whose negative cases turned positive on PAPNET® QC screening. The impact on the morale of the laboratory community, already under siege by the lay press, was considerable. Adding to the company's image problem were articles by a representative of the company intimating that failure to offer the superior PAPNET® QC screening might result in medicolegal liability.

NSI had difficulty in getting consistent reimbursement by health insurers and several published studies suggested only a minimal improvement in detection rate over manual screening with poor cost effectiveness added to pressures on the company. In October 1999, and depleted of funds, NSI was declared bankrupt. NeoPath™ bought NSI's intellectual property. Roche™ sold its thin layer technology to Autocyte™, which merged with NeoPath™

in 1999 to form TriPath™ Imaging Inc. (Burlington, NC, USA). TriPath™ discontinued both the AutoCyte™ and the AutoPap 300 QC, replacing the systems with the AutoPap™ Primary Screening System, which is now known as the BD FocalPoint™ GS Imaging System (BD Diagnostics, Franklin Lakes, NJ, USA).

1.5.1 Current systems in production

Currently, two commercially available FDA-approved automated screening systems – the BD FocalPoint™ GS Imaging System and the ThinPrep™ Imaging System (Hologic™, Bedford, MA, USA). The BD FocalPoint™ Slide Profiler scans the slides and assigns each one a score which ranks them according to the likelihood of abnormal cells being present. The slides are assigned to quintiles, with quintile 1 containing the highest-ranking slides. The machine also categorises slides into one of four of categories: review (comprising quintiles 1–5), no further review (NFR; up to 25% of slides), process review (indicating a technical problem) and quality control review (requiring a full screen). The NFR category contains the slides least likely to contain an abnormality which could be reported as negative and archived without a full manual primary screen. The NFR technology is approved for use in the UK with each slide so designated being subjected to a rapid QA screen (rapid review or preview). Slides that are designated for review by the FocalPoint™ are examined by cytology screening staff using the BD FocalPoint Guided Screener Workstation (GSW, previously known as the TriPath™ Slide Wizard™). This technology comprises of a standard screening microscope fitted with an electronic stage linked to a desktop computer. The GSW directs screening staff towards 10 electronically marked fields of view on the slide. If abnormal cells are seen in any of the FOVs the entire slide is screened, and appropriate action taken in line with laboratory protocols. The BD FocalPoint Guided Screener (GS) Imaging System has received FDA approval to scan both conventional and BD SurePath LBC slides.

In contrast, the ThinPrep™ Imaging System is designed to work with ThinPrep™ LBC slides (stained with the Hologic™ Imager stain) alone. The ThinPrep™ (TIS) Imaging System scans all of the slides and presents 22 FOVs to screening staff on the review scope. The review scope is a Hologic™ automated screening microscope with a motorised stage to guide screeners to each of the 22 FOVs. If an abnormality is suspected in any of the 22 FOVs then a full screen of the slide is undertaken. Unlike the FocalPoint™, the TIS does not score and rank slides and is therefore unable to select slides for archiving without further intervention.

1.5.2 Computer Assisted Screening in cytology – where are we?

The use of Computer Assisted Screening (CAS) in cervical screening is well established in the USA (Wilbur *et al*., 2009) and Europe (Passamonti *et al*., 2007; Troni *et al*., 2007) and has undergone a major trial in the UK (MAVARIC – Kitchener *et al*., 2011) which was funded by the United Kingdom Health Technology Assessment (HTA) programme. Several other studies have been conducted in the UK and the Republic of Ireland, including the Cervical Screening Wales CAESAR Studies (described in this thesis and cited by Kitchener *et al*. 2011) and the study conducted by Cropper *et al*. 2010, using the BD FocalPoint™ GS Imaging System. Bolger *et al*. (2006) and the Scottish Cervical Cytology Review Group (Feasibility Sub Group - 2009) have reported on the Hologic ThinPrep™ Imager.

Four published systematic reviews were conducted on the potential of CAS (Broadstock, 2000; Willis *et al*., 2005; Kitchener *et al*., 2011; Della Palma *et al*., 2012). Willis *et al,* in a review commissioned by the Health Technology Assessment (HTA) programme and published in 2005 concluded that there was a need for rigorous, unbiased public-sector research into the effectiveness of automated screening technologies. In the earlier review by Broadstock in 2000 for the New Zealand HTA programme reached a similar conclusion and recommended large-scale trials to be conducted under normal laboratory conditions against reliable gold standards for diagnostic verification. Both these reviews focused on early technologies that are no longer commercially available. The study by Kitchener *et al.*, "Manual Assessment Versus Automated Reading In Cytology" (MAVARIC) appraised both the FocalPoint™ and TIS CAS systems but did not recommend either for implementation. However, the study concluded that the NFR reporting technology of the FocalPoint™ system presented promising results and recommended further research into its potential.

The report by Della Palma *et al*. (2012) differed in approach from the others in that it involved a review of live installations of the current CAS technologies which were surveyed by questionnaire. The areas surveyed included laboratory management; social/ethical issues and workload. Prices of the technologies were obtained direct from the providers and costs were calculated from the literature and observed data. Several questions regarding the technology were required to be addressed by the study:

Efficacy:

1. Is there sufficient evidence that automatic screening is as least as accurate as the manual process?
2. If two methods are essentially equivalent in terms of accuracy, can it be stated that this also means that they are essentially equivalent in terms of efficacy in the prevention of cervical cancer?

Cost Effectiveness:

1. Is there evidence that automatic reading increases productivity per reader?
2. If so, by how much?
3. How is productivity affected by the screening of liquid-based cytology (LBC) slides?

Results: For conventional Pap-smear samples the break-even point was at about 49,000 cases per annum. For liquid based cytology samples, it was at the maximum capacity of the CAS technology – about 70,000 cases per annum. Therefore, efficiency increased with the volume of slides scanned – with screening time decreasing by two-thirds for conventional slides and by less than one half for LBC slides. It was also reported that acceptance of the technology by users was good.

The report concluded that CAS technology might increase productivity but at increased cost in most situations. Furthermore, HPV primary screening will drastically reduce the need for cytology.

Table 1.2: Previous CAS (FocalPoint™ related) publications

Study and design	Comparison groups	CIN detection rates	Sensitivity/ Specificity	PPV/NPV
Schiffman M, Yu K, Zuna R, Terence Dunn S, Zhang H, Walker J, Gold M, Hyun N, Rydzak G, Katki HA, Wentzensen N. Proof-of-principle study of a novel cervical screening and triage strategy: Computer-analysed cytology to decide which HPV-positive women are likely to have ≥CIN2. Int J Cancer. 2017 Feb;140(3):718-725.	3026 cases from a high disease prevalence population of women were scanned. This required a new FP algorithm targeting precancer/cancer. This was used to triage HPV tested cases for CIN	94% for ≥CIN2 for conventional results of ASC-US compared to 91% for the FocalPoint triage of HPV positive samples depending on sub-type.	94% for conventional results of ASC-US compared to 91% for the FocalPoint triage group. Note: scanned slides were ThinPrep™ LBC samples, SurePath ™ samples (optimal for FocalPoint™) should provide even more robust results.	Not given
Sugiyama Y, Sasaki H, Komatsu K, Yabushita R, Oda M, Yanoh K, Ueda M, Itamochi H, Okugawa K, Fujita H, Tase T, Nakatani E, Moriya T. A Multi-Institutional Feasibility Study on the Use of Automated Screening Systems for Quality Control Rescreening of Cervical Cytology. Acta Cytol. 2016;60(5):451-457.	Study of 12,000; 9,000 conventional and 3,000 LBC slides. Slides in the highest 15% (1,496) probability of abnormality rescreened.	117 were confirmed as abnormal of which 40 were confirmed as HGSIL. Authors suggest that FocalPoint™ is effective for QC rescreening of cervical cytology	Not given	Not given
Rebolj M, Rask J, van Ballegooijen M, Kirschner B, Rozemeijer K, Bonde J, Rygaard C, Lynge E. Cervical histology after routine ThinPrep or SurePath liquid-based cytology and computer-assisted reading in Denmark. Br J Cancer. 2015 Nov 3;113(9):1259-74.	Total of 674,248 samples in four regions in Denmark compared TP and SP LBC technologies and Imaging to conventional cytology.	Detection rates (≥CIN2) were improved for FocalPoint™ compared to Conventional Screening but TIS was not significantly improved.	Not given (Note: authors concluded that CAS performance was likely to be patient age/scanner brand dependent.	Calculated as frequency of ≥CIN2 per 100 cases of ASC-US. Not comparable with other trials using the more accepted definition of PPV.

Table 1.2: Previous CAS (FocalPoint™ related) publications – continued

Study and design	Comparison groups	CIN detection rates	Sensitivity/ Specificity	PPV/NPV
Bowditch RC, Clarke JM, Baird PJ, Greenberg ML. Morphologic analysis of false negative SurePath® slides using Focalpoint™ GS computer-assisted cervical screening technology: An Australian experience. Diagn Cytopathol. 2015 Nov;43(11):870-8.	From a total of 2,198 SP slides, 47 were confirmed as HG. In all 47, FP selected FOV containing HG cells. Some were initially reported as Neg.	Not given. Neg cases were reviewed along with others and morphology presented to help users identify the features associated with HG disease.	Not given	Not given
Saieg MA, Motta TH, Fodra ME, Scapulatempo C, Longatto-Filho A, Stiepcich MM. Automated screening of conventional gynecological cytology smears: feasible and reliable. Acta Cytol. 2014;58(4):378-82.	Retrospective study of 120 cases, aged between 18 – 85. Cases were classified into quintiles – 1 & 2 for high risk cases and 3,4,5 for low risk cases.	83/120 (69.2%) of cases could be classified into quintiles. 31/120 as high risk and 52 as low risk.	Sensitivity and specificity of FocalPoint was 100% and 70.3% respectively.	Not given

Table 1.2: Previous CAS (FocalPoint™ related) publications – continued

Study and design	Comparison groups	CIN detection rates	Sensitivity/ Specificity	PPV/NPV
Stein MD, Fregnani JH, Scapulatempo C, Mafra A, Campacci N, Longatto-Filho A; RODEO Study Team From Barretos Cancer Hospital. Performance and reproducibility of gynecologic cytology interpretation using the FocalPoint system: results of the RODEO Study Team. Am J Clin Pathol. 2013 Oct;140(4):567-71.	10,165 slides scanned using FocalPoint™ GS Imaging system and then manually screened blinded to the FP results. After 12 months slides were reviewed on the GSW and the differences were reviewed by a panel of 6 cytologists	83% of ASCUS+ cases were classified as quintiles 1 and 2.	Calculated from 337 histology biopsies. **FocalPoint™:** **S**ensitivity = 45.3% Specificity = 85.8% **Manual screening:** Sensitivity = 52.8% Specificity = 81.8% AFTER CYTOLOGIST REVIEW **FocalPoint™:** **S**ensitivity = 60.4% Specificity = 76.0% **Manual screening:** Sensitivity = 59.6% Specificity = 83.0%	Calculated from 337 histology biopsies. **FocalPoint™:** PPV = 75.4% NPV = 63.2% **Manual screening:** PPV = 72.7% NPV = 65.5% AFTER CYTOLOGIST REVIEW **FocalPoint™:** PPV = 69.6% NPV = 67.9% **Manual screening:** PPV = 76.2% NPV = 69.2%
Renshaw A, Elsheikh TM. A validation study of the Focalpoint™ GS imaging system for gynecologic cytology screening. Cancer Cytopathol. 2013 Dec;121(12):737-8.	Not given Letter to Editor commenting on findings of Colgan *et al*. and noting the impact of workload on screener performance with CAS. The authors also point out that this is consistent with the findings of other researchers, e.g. the ARTISTIC trial.	Not given	Not Given	Not given

Table 1.2: Previous CAS (FocalPoint™ related) publications – continued

Study and design	Comparison groups	CIN detection rates	Sensitivity/Specificity	PPV/NPV
Colgan T. Reply to a validation study of the Focalpoint GS imaging system for gynecologic cytology screening. Cancer Cytopathol. 2013 Dec;121(12):738.	Not given	Not given	Not given	Not given
Colgan T *et al*. (2013) Prospective two-armed blinded validation study. on 10,233 slides. Truth adjudication used as the gold standard.	10,233 slides scanned using FocalPoint™ GS Imaging system and then manually screened blinded to the FP results. Discordant cases were resolved by cytological review or "truth".	False negative rates of FP comparable for Ca and HSIL, but FP FN rates statistically inferior to manual screening for LSIL.	Sensitivity and specificity of FP comparable to manual screening for Ca; HSIL+ and LSIL. Significantly reduced for ASCUS.	Not given
Renshaw AA, Elsheikh TM. Assessment of manual workload limits in gynecologic cytology: reconciling data from 3 major prospective trials of automated screening devices. Am J Clin Pathol. 2013 Apr;139(4):428-33.	Data from 3 major Trials of CAS were compared /evaluated. This study concluded that workload was a significant factor in the efficacy of CAS systems for the detection of cervical lesions.	Those rates from other trials were compared and evaluated.	Those rates published in other trials were compared and evaluated.	Those rates published in other trials were compared and evaluated.
Halford *et al*. (2010) Prospective two-armed masked study. Histology taken within 6 months of the Pap smear was used as the reference standard	87,284 split sample conventional slides read manually and ThinPrep™ LBC slides read with the ThinPrep™ imaging System. Biopsy data were available for 1083 HSIL lesions	Automated-LBC reading showed a 3.2% increase in possible high-grade and HSIL reports compared with manually reading convention slides	For ASCUS+ the sensitivity of automated was 96.0% and manual 91.6% (p = 0.001)	For 1083 biopsy confirmed HSIL cases automated was correct in 61% of cases and 59.4% on manual (p = 0.05)

Table 1.2: Previous CAS (FocalPoint™ related) publications – continued

Study and design	Comparison groups	CIN detection rates	Sensitivity/Specificity	PPV/NPV
Wilbur *et al*. (2009) Prospective two-armed masked study. Truth adjudication used as the gold standard	12,313 slides screened using both the BD FocalPoint GS Imaging System's FOV and QC and manually with manual QC	Not given	HSIL+ sensitivity 85.3% in automated arm and 65.7% in manual ($p < 0.0001$) with a 2.6% decline ($p < 0.0001$) in specificity. LSIL+ sensitivity 86.1% automated and 76.4% in manual ($p < 0.0001$) with a 1.9% ($p = 0.0032$) in specificity ASCUS+ sensitivity and specificity were not significantly different between the two arms	NPV of a not HSIL+ slide in the automated arm was 99.7% and 99.4% in the manual arm
Passamonti *et al*. (2007) Routine consecutive conventional Pap slides prospectively processed on the BD FocalPoint GS Imaging System. Histology was obtained for 67% of slides showing abnormalities	37,306 conventional Pap slides processed and screened using the BD FocalPoint GS Imaging System. All slides then received a manual rapid screen before the results were compared	91% of CIN2+ cases were ranked in high risk quintiles along with 93% of CIN1. 97% of HSIL+ and 98% of LSIL slides were triaged for a full manual review by screening the FOVs	Not given	Not given
Troni *et al*. (2007) Concurrent cohorts retrospectively identified with a negative screen at baseline. Screening modality at repeat smear was independent of the baseline screen. All subjects with CIN2+ at repeat screening were identified	AutoPap Primary Screening System 300 using conventional slides compared with manually read conventional slides. 33,646 women at baseline, 30,658 of whom returned for repeat screening. 30% randomised to manual reading	No significant difference in CIN2+ detection at repeat screening when comparing baseline automated and manual cohorts	Not given	Not given

Table 1.2: Previous CAS (FocalPoint™ related) – continued

Study and design	Comparison groups	CIN detection rates	Sensitivity/Specificity	PPV/NPV
Bulgaresi *et al*. (2006) An evaluation of rapid review of slides designated NFR as a QC procedure. ASCUS– SIL+ samples were reviewed before referral. Negative colposcopy or biopsy used as the gold standard	24,503 slides classified as NFR by the AutoPap™ Primary Screening System 300	98.6% of slides reviewed as negative, 0.4% as inadequate, 0.4% as ASCUS-R and 0.12% (31 cases) as ASCUS–SIL+	Not given	Estimate of 99.99% NPV for NFR based 51.6% compliance rate with repeat cytology and 83.3% with colposcopy referral
Parker *et al*. (2004) sponsored by TriPath Imaging Two-armed retrospective masked study. Discrepant results screened by a single cytopathologist	1275 SurePath slides seeded with abnormals. Screened manually with 10% QC and with BD FocalPoint GS Imaging System with NFR slides classed as WNL and review slides screened and triaged to WNL or requiring full screen	58% of HSIL+ slides ranked in Q1 and 83% in Q1 and Q2. All HSIL slides were ranked as review	Not given	Not given
Stevens *et al*. (2004) Two-armed retrospective study. Truth was taken as a concordant diagnosis. Discrepant pairs reviewed by a discrepancy panel	6000 conventional slides screened manually and with the AutoPap Primary Screening System using PapMaps	AutoPap identified 35 additional abnormal slides but missed 92 (94.5% of which were low grade). The difference between low-grade detection in the two arms was significant. AutoPap was equivalent to manual for the detection of high grade abnormalities. NFR correctly identified 975/986 slides as normal	Not given	Not given

Table 1.2: Previous CAS (FocalPoint™ related) – continued

Study and design	Comparison groups	CIN detection rates	Sensitivity/Specificity	PPV/NPV
Ronco *et al*. (2003) Retrospective comparison, with the result of the manual read taken as the gold standard	481 conventional slides read manually then reviewed several months later by the same cytotechnologist using PapMaps	Not given	Sensitivity of PapMaps for selecting abnormal slides = 100% for SIL and 80% for ASCUS	Not given
Confortini *et al*. (2003) Retrospective comparison with histology obtained from punch and loop biopsies. The worst result was taken used as the gold standard	14,145 conventional slides read manually then rescreened (unless classified as NFR) 3–4 days later by the same cytotechnologist using PapMaps with the AutoPap Primary Screening System	Not given	AutoPap and manual reading are equivalent in terms of sensitivity. The AutoPap had a slightly higher specificity than manual reading	Not given
Wilbur *et al*. (2002) supported by TriPath Imaging Two-armed retrospective, masked study. Cytological truth adjudication taken as the gold standard	1275 AutoCyte PREP slides (seeded with known abnormals) read manually and with the AutoPap system using the Slide Wizard 2	False-positive rate was 3.8% for AutoPap and 4.4% for manual	Sensitivity of AutoPap for truth determined HSIL+ = 98.4% and manual 91.1%. Specificity of AutoPap = 96.1% and manual 95%	Not given
Vassilakos *et al*. (2002) Two-armed comparison study using the manual reading as the gold standard	8688 AutoCyte PREP slides read manually and compared with the AutoPap Primary Screening System's review rankings	47.4% of LSIL slides were in Q1, 20.8% in Q2, 10.6% in Q3, 10.1% in Q4, 5.3% in Q5 and 5.8% in NFR 85.2% of HSIL slides were in Q1, 12.7% in Q2, 2.1% in Q3. 0% were in Q4, Q5 and NFR. 84% of all abnormalities were in the highest scoring group along with 100% of HSIL	Not given	Not given

Table 1.2 (updated from Kitchener *et al.*; 2011) summarises the results of previous studies, in which some studies cited present increased rates of abnormality detection in the automated arm. Kitchener *et al*. claimed some of these studies are characterised by methodological weaknesses - including the use of outdated systems, using split samples, the use of manually read conventional (as opposed to liquid-based) cytology, using the same slide set for retrospective comparative readings and not reporting histological outcomes.

MAVARIC concluded that the CAS technology was less sensitive than manual screening, suggesting that there was no justification for introduction – however the reliability of the "No Further Review" (NFR) reporting category was investigated further and this investigation has underpinned the introduction of the technology in the UK (Denton *et al*., NHSCSP Good Practice Guide No. 4, Second Edition, April 2013).

Those studies that followed MAVARIC have not really challenged the findings of Kitchener *et al*. and this is for a number of reasons. The quality of the UK laboratory screening programme in the UK is one of the highest in the world and therefore, in MAVARIC, CAS competed against a very high manual benchmark.

Other authors report better performance by CAS but note that performance varies between CAS systems (Rebolj *et al*., 2015); that throughput of work for the directed screening systems with manual intervention is a factor affecting quality (Renshaw and Elsheikh, 2013) and the efficiency of the detection of high and low grade cervical lesions is variable (Colgan *et al*., 2013).

For the cervical screening programmes and laboratory screening services in the UK, MAVARIC was the definitive study in terms of the implementation of computer assisted screening. Since its publication, however, and in the intervening period the cervical screening world has certainly changed. HPV testing, with its promise of a high negative predictive potential, has now come into its own. However, the cytology services that are necessary for the reflex testing of those cases that test HPV positive case are becoming increasingly beleaguered as medical and scientific staff leave or retire, or re-train in laboratory disciplines that are developing rather than diminishing, as in the case of cervical cytology. In summary, HPV testing promises to deliver as a "Test of risk" for cervical

screening programmes, however, at the time of writing the provision of a "Test of Disease" to support/replace cytology remains somewhat of an enigma.

More recently, several studies report on novel implementations of CAS. Saieg *et al*. report on a retrospective study of 120 cases which were scanned using FocalPoint™. Of these cases, 70% could be classified into FocalPoint quintiles and the authors report that for those cases so classified, the detection of high and low-grade cases was feasible and reliable. Schiffman *et al*. report on a novel cervical screening and triage strategy where CAS is used to triage HPV positive women to predict which are more likely to develop ≥ CIN2.

These developments may herald the further investigation of CAS as a triage mechanism for HPV testing in an organised cervical screening programme and some avenues of possible investigation will be considered within this thesis.

1.5.3 The FocalPoint™ technology

The BD FocalPoint™ GS slide profiler is a semi-automated imaging system designed to assist in the primary screening of SurePath™ and conventionally prepared cervical cytology slides. It consists of a FocalPoint™ slide profiler and a FocalPoint™ Guided Screening Workstation or "Slide Wizard" (Figure 1.2).

In 1995 the FocalPoint™ received FDA approval for the quality control of conventionally spread Pap smears. This was followed up by FDA approval for primary screening of conventional slides in 1998 and SurePath™ LBC preparations in 2001.

1.5.3.1 Laboratory Preparation Calibration Assessment

The Laboratory Calibration Preparation Assessment (LPCA) is a validation and qualification of a subset of slides that represent the lab's routine slides to calculate detection thresholds based on different variables such as staining, slide preparation and unusual events within the regional population.

Figure 1.2: BD FocalPoint™ GS Imaging System, along with GSW microscope workstation and PC interface and printer

1.5.3.2 The scanning process

The system involves 3 cameras that capture slide images via x4 and x20 objectives. Each slide is scanned three times using the x4 objective to generate a 3D map of the slide preparation (Figure 1.3). Each x4 FOV is divided into 25 x20 subsections that score between 1 and 10. The FOVs are further scanned at x20 for segmentation (separation of significant objects from the background) which are classified as single cells, groups and thick groups (Figure 1.4). The instrument is designed to detect slides with evidence of squamous carcinoma and adenocarcinoma and their usual precursor conditions. To do this, up to 300 individual features are captured by the scanning cameras and evaluated by the BD FocalPoint™ using both morphometric and densitometric algorithms, these features include:

- Size of nuclei
- Perimeter / shape of nuclei
- Texture of nuclei
- Cytoplasm features
- Nuclear density

- Nuclear/Cytoplasmic ratio
- Contrast

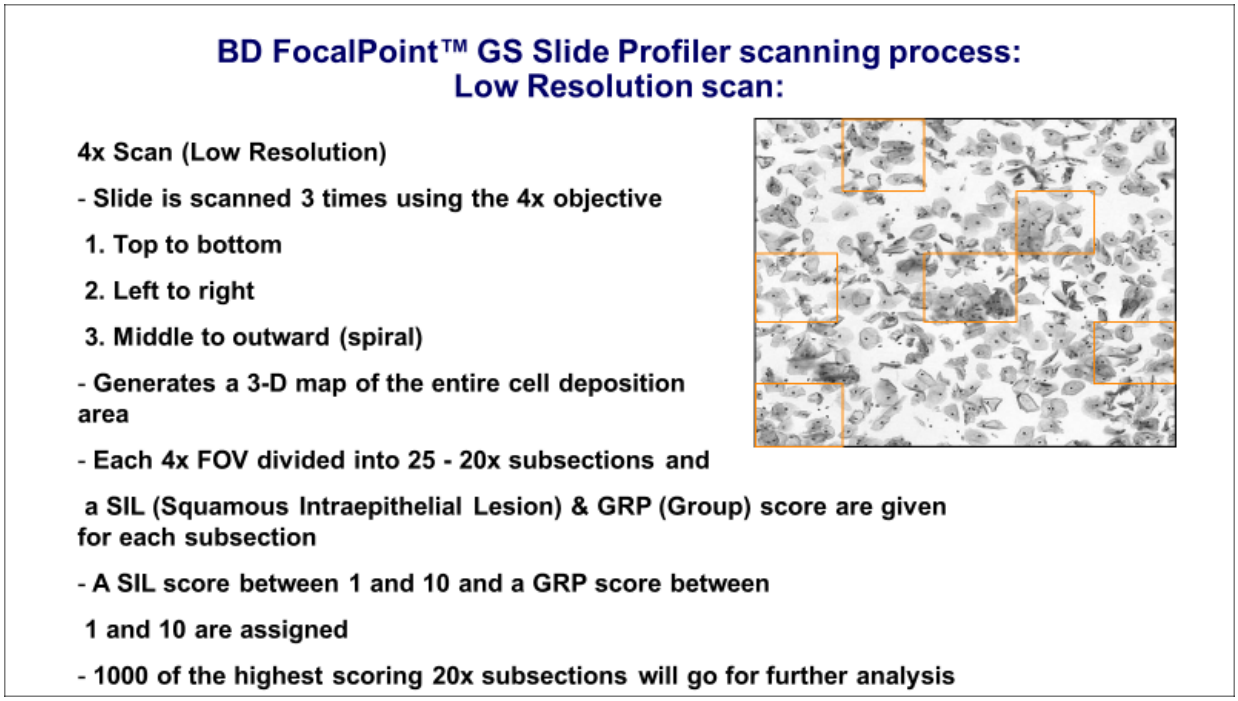


Figure 1.3: BD FocalPoint™ Low Resolution Scanning process

Using these algorithms, the FocalPoint™ assigns each FOV a score. These scores are combined, and the slide is finally scored between the values of 0 and 1, based on the likelihood of an abnormality being present. 0 is negative and 1 is abnormal and the slide ranking is presented to the operator as a quintile, ranging from 1 (most abnormal potential) to 5 (least abnormal potential) – see Figure 1.5.

When used in conjunction with a BD FocalPoint™ Guided Screener Review Station (Slide Wizard™), the 10 highest scoring Fields of View (FOV) from each qualified slide are presented to the screener for review, using an automated stage fitted to a standard laboratory microscope (note: the guided screener option is not currently approved by the NHS Cervical Screening Programme (Denton *et al*., 2013 – NHS CSP Good Practice Guide No. 4). In addition to the 5 ranking quintiles, the FocalPoint™ identifies up to 25% of successfully processed, (i.e. with a viable scanning result) slides requiring "No Further Review" (NFR), depending on the characteristics of the population screened. Slides ranked and categorised as NFR are considered as having a very low abnormality potential and therefore do not have FOV available for review.

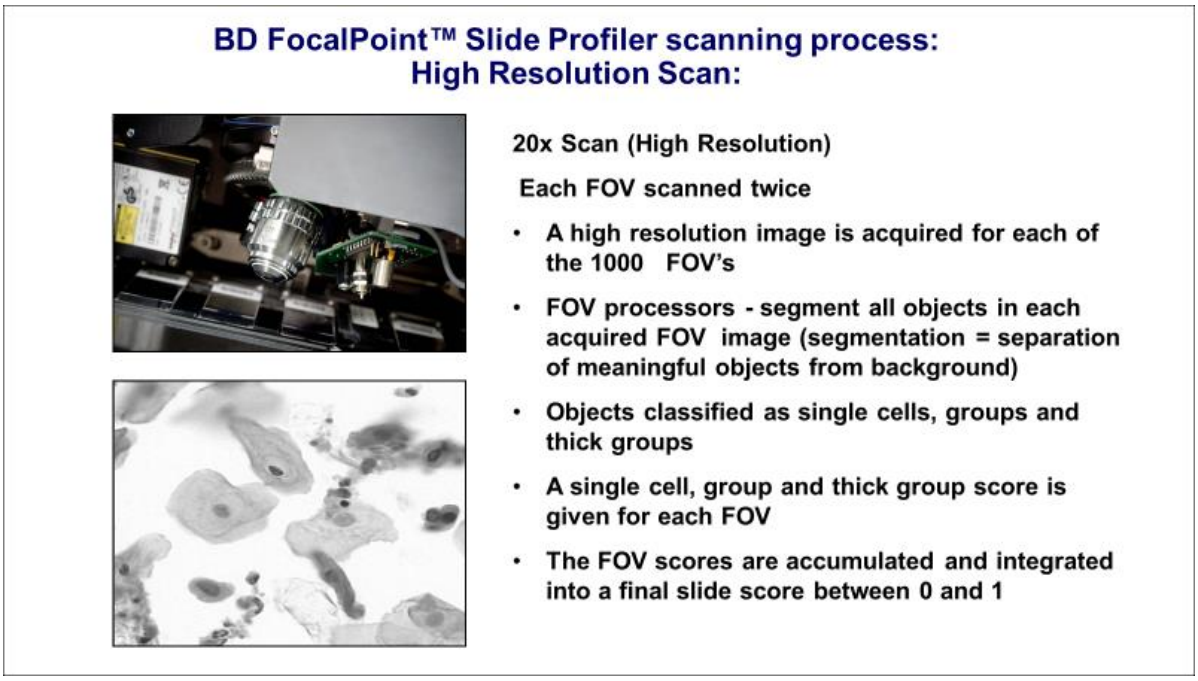


Figure 1.4: BD FocalPoint™ High Resolution Scanning process

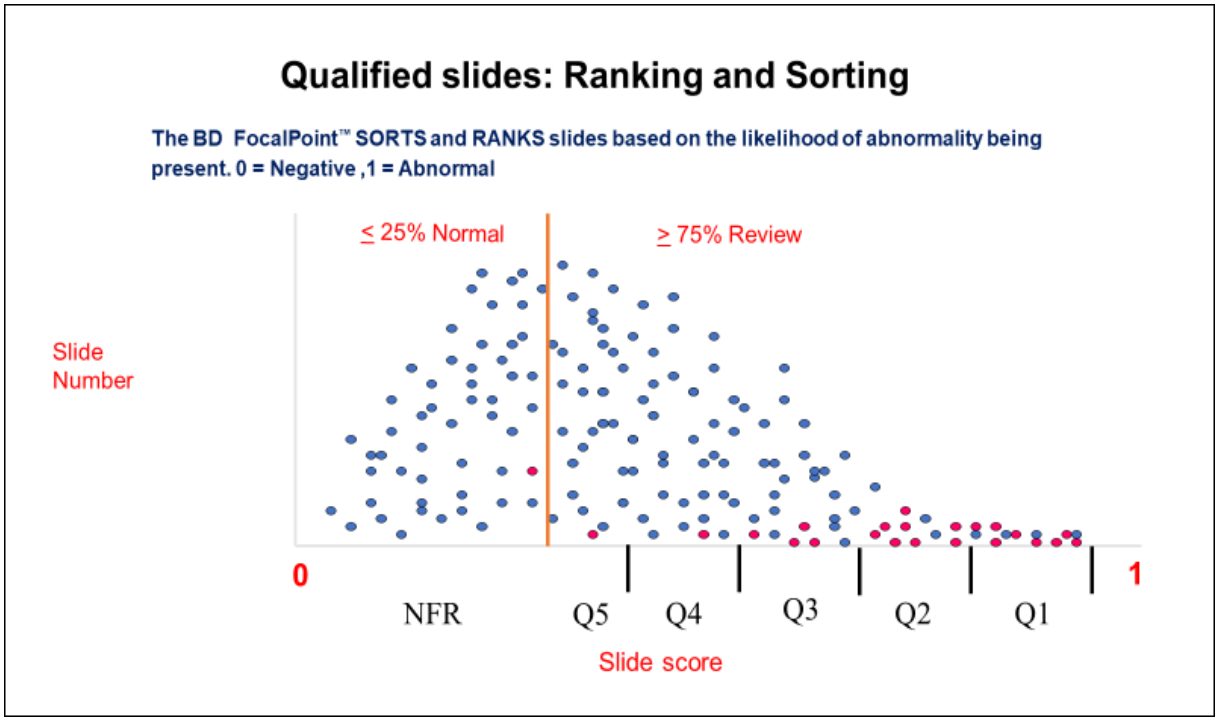


Figure 1.5: Schematic diagram of the FocalPoint™ process for ranking slides and sorting them into quintiles according to probability of morphological abnormality

In operation, slides are labelled with a bar-code that is compatible with the FocalPoint™ barcode reader. Slides (minimum = 120, maximum = 288) are then loaded into the slide racks provided (Figure 1.6) and the instrument is set to run. Further slides can be added continuously as the instrument completes scanning of those loaded earlier.

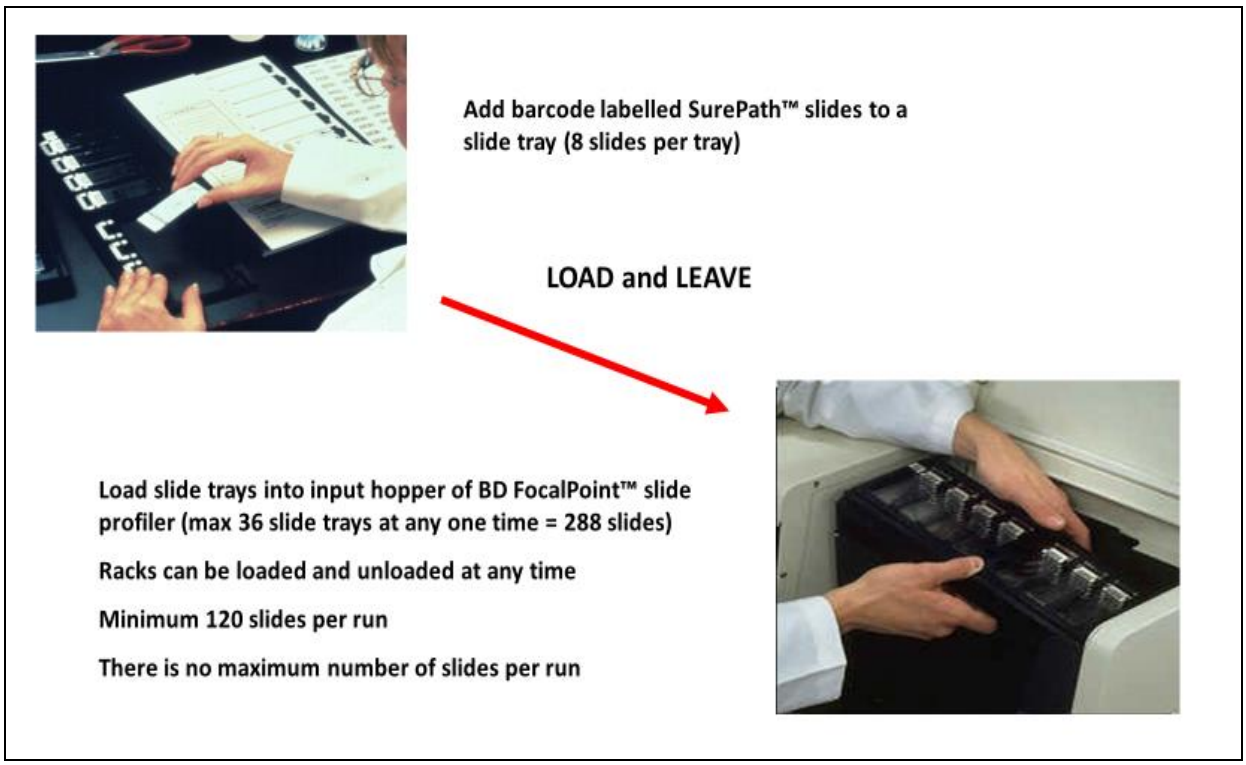


Figure 1.6: Labelling and Loading the FocalPoint™ GS Imaging System

Once the run is initiated the FocalPoint™ runs through a system integrity test. This test involves the scanning of a bespoke calibration plate (Figure 1.7) at the beginning and end of each slide tray which checks the performance of the optical, mechanical and electronic sub-systems. This ensures optimal functioning of the system by validating FocalPoint™ performance at the beginning and end of each slide tray.

Successful completion of this test ensures that validated results are released by the system. If the check fails, then the 8 slides affected will need a repeat scan or “re-run”. When the scanning process is completed, the resultant slide data is captured and transferred to the interfacing PC, where it can be viewed via VDU or printed as hard copy. Captured images can be transferred to the GSW instruments via Virtual Private Network or removable hard drive (Figure 1.8). The images and associated FOV data are then presented to the cytologist in ranked order of abnormality via the automated microscope stage, synchronising the VDU image with the image seen down the microscope.

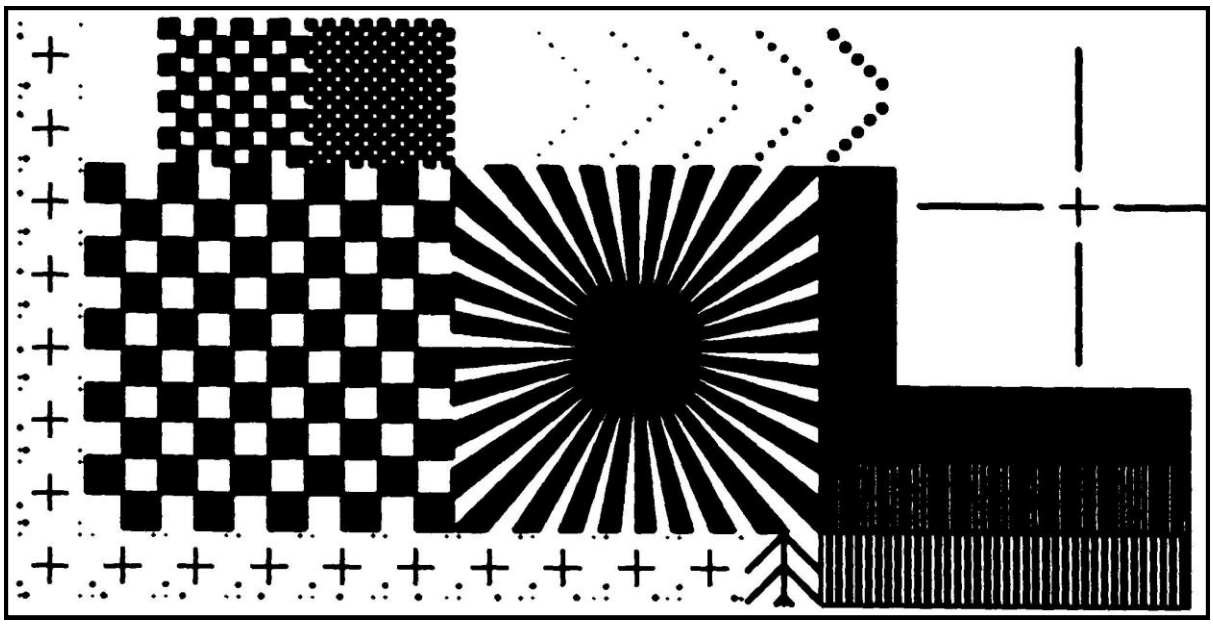


Figure 1.7: FocalPoint™ Calibration Plate required to perform the System Integrity Test

The BD FocalPoint™ GS Imaging system can be configured to suit different laboratory service models, ranging from single laboratory sites to laboratory networks. With the introduction of HPV testing as a primary screening test for cervical pre-cancer, the high throughput of HPV analysers is driving the move to larger laboratory services to provide that greater critical mass.

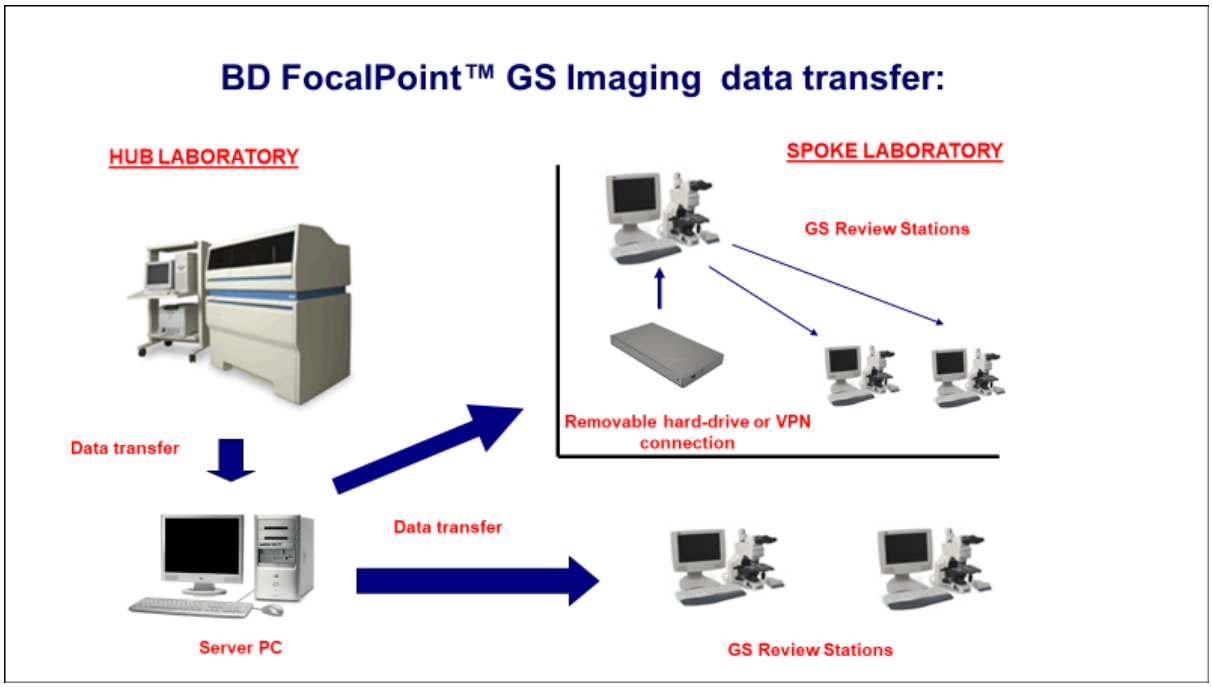


Figure 1.8: FocalPoint image and data transfer pathways for various laboratory service configurations

We are now seeing those larger laboratory services, however given the declining cytology community, novel managed services such as hub and spoke networks are being developed, especially where there are difficulties in recruiting cytology staff. Therefore, service structures that make the most of existing staff on several sites are being developed.

These larger services also suit CAS, which is also a high throughput technology. This study is primarily concerned with the FocalPoint™ technology and is designed to evaluate the effects of the introduction of this technology into cervical cytology both by gathering evidence from the published literature and by qualitative and quantitative research.

The results of this thesis have already informed Cervical Screening Wales in implementing FocalPoint™ and, in terms of the validation of the NFR aspect of the technology has important implications for cervical screening programmes around the world. As an example, the experiences gained from the work documented in this thesis have already been incorporated into the "NHSCSP Good Practice Guide No 4: Use of NFR Technology in Cervical Screening".

1.5.4. Aims and hypotheses

This study aims to evaluate a computer assisted screening (CAS) technology, in a bid to identify areas for its application and thereby evaluate the potential benefits that may be realised by its introduction into an organised cervical screening programme.

As described earlier in the Introduction, the assessment concerns the BD FocalPoint™ GS Imaging technology which either presents the operator with 10 fields of view (FOV) of potential abnormalities within a sample, or, in up to 25% of cases, the sample is classified as" No Further Review" or NFR. The technology also has the facility to report on the presence or absence of endocervical and squamous cell components. This is a useful feature as in the review cases where only 10 FOV are presented to the operator, there is a real possibility that endocervical cells are not presented to the cytologists or are missed because the individual concerned is occupied in examining the sample for dyskaryosis. In samples categorised as NFR, the sample can be consigned to file without manual screening intervention, and so this feature is a useful indicator of sample quality.

1.5.4.1. FocalPoint™ as a means of primary screening LBC samples

There are been several studies, both in the UK and abroad that have investigated the potential of the BD

FocalPoint™ to replace manual primary cytology screening, with mixed outcomes. Some workers, (Wilbur *et al*.) report favourably, advocating better sensitivity than manual screening for dyskaryosis/squamous intra-epithelial lesions, others (Kitchener *et al*., 2011; Colgan *et al*., 2013) report to the contrary – claiming inferior performance of CAS compared to manual primary screening. In this study, I intend to examine the performance of the FocalPoint™ technology by comparison of its sensitivity for high grade dyskaryosis (high grade squamous intraepithelial lesion - HSIL) and all grades of dyskaryosis with that of its conventional counterpart. However, I also intend to compare interval outcomes of cervical screening cases that were reported as negative by both methods and compare the rates of subsequent disease development, for cervical cancer, cervical pre-cancer and all disease (CIN2+/HSIL+). This will provide an indication of the longitudinal effectiveness of the CAS technology compared to current methods, which has not been reported in previous publications to date. Historically, when compared to the UK based laboratory cervical screening programmes by previous researchers, CAS has not performed to the standard of manual cytology screening and that is the basis for my hypothesis in this comparison:

"Manual cytology outperforms the BD FocalPoint™ GS imaging system for the manual screening of cervical Liquid Based Cytology slides".

1.5.4.2 FocalPoint™ as a means of IQC for Manual Primary Cytology Screening

The quality assurance (QA) of manual cytology screening is accomplished by a rapid internal quality control (IQC) screen and this IQC procedure has been shown to appreciably improve the sensitivity of manual primary screening in the detection of CIN/SIL (Faraker and Boxer, 1996; Brooke *et al.*, 2002). As well as for primary cytology screening, I wanted to evaluate the FocalPoint™ technology for the IQC of manual primary cytology, to find out if the technology could be applied in this modality. The hypothesis for comparison in this instance was:

The BD FocalPoint™ GS imaging system as an IQC tool improves the quality of manual primary cytology screening.

1.5.4.3 FocalPoint™ for monitoring smear taker performance

Failure to adequately sample the cervix can result in a false-negative or an underestimate of the severity of any cervical disease that may be present, leading to inappropriate or too conservative a management regime and failing that individual (Young, 2000). Poor sampling technique can result in upwards of 20%

of dyskaryosis being missed. If high grade disease is missed and or the participant fails to attend for subsequent screening, then the outcome is potentially very serious. Guidance exists within screening programmes to manage quality and clinical proficiency. The guidance and associated performance indicators provide a quality framework for sample taking however inconsistency in application can happen and this negates the potential for positive benefits.

One of the key performance indicators for the quality of sample taking is the presence/absence of transformation zone (TZ) sampling. Detection of the TZ constituents in an LBC slide helps determine that an adequate cervical sample has been taken and this indicator is commonly used to assess sample taker performance, especially of those sample takers that are undergoing training. When using the FocalPoint™ NFR reporting facility in the laboratory setting, one function that is lost is the manual assessment of LBC slides for the presence/absence of transformation zone (TZ) sampling. However, the FocalPoint™ does have the capacity to detect and report on the presence/absence of both endocervical and squamous components on the LBC slide. Therefore, I wanted to find out if this function could be used as a substitute for manual TZ detection, or more accurately, the detection of endocervical cells for those slides reported as NFR.

So, if the detection of endocervical components by the FocalPoint™ technology is comparable to that of manual screening, then the technology can still be used to assess smear taker performance. Automated reporting of the presence or absence of the squamous cell components is also useful in those NFR cases that are not subject to manual screening as the laboratory can be assured that squamous cells were present in these samples. If they are not, then the FocalPoint™ technology reports that sample as having *"Insufficient Reference Cells"*.

I therefore posed two questions to be addressed in this application of the FocalPoint™ technology, thus:

1. Does the FocalPoint™ technology detect endocervical cells in a manner that is comparable to that detected by manual screening?
2. How consistent is that detection rate between individual laboratories compared to manual screening?

The former comparison is important to ascertain if the FocalPoint™ technology can be used equitably in combination with manual screening. The latter query is to ascertain if the FocalPoint™ technology offers any advantage over manual screening in application.

Cervical Screening Wales monitoring data reports that the inter-laboratory endocervical detection rates by manual screening can vary by as much as 15-20% (Table 4.8) and so any improvement in consistency would translate into a more equitable performance indicator. Therefore, the hypothesis in this instance was:

That the FocalPoint™ technology is comparable in the detection of endocervical cells as manual cytology screening.

1.5.4.4 Economic analysis

In today's health economy, there are many demands on service budgets and even though a new development may promise improvements in clinical quality, nowadays great emphasis is placed on achieving cost efficiencies in service delivery as well.

For this reason, an economic analysis of the technology was conducted.
This analysis took the form of a cost-minimisation analysis which was carried out by comparison of cost of the new technology with the existing one. Processes and procedures common to both technologies were exempt from the cost evaluation, which concentrated on the areas that differed and costed those. In this manner, any difference in costs resulting from introducing the new technology were identified and a comparative evaluation of the relative cost burdens to the service was made. The results are presented in the results section of this thesis (Chapter 5).

1.5.4.5 Screener acceptance of the FocalPoint GS technology

Even the most innovative and efficient new technology available in any field of endeavour will be severely limited in application if it proves to be difficult to deploy, operate and maintain by the individuals that are designated to use it. To canvass opinion regarding user acceptability, a questionnaire was circulated to staff that were involved in using the technology as part of the CAESAR studies. The results are presented in the results section (Chapter 5).

1.5.4.6 FocalPoint™ NFR result reporting related to HrHPV testing

Following the successful validation of the FocalPoint™ NFR reporting technology from the results of this study, it was implemented for primary cervical screening in the Welsh CSP in 2012. Late in 2014, HrHPV testing was introduced into the Welsh CSP as a test of cure/clearance of HPV following the treatment of the patient for high-grade CIN (HSIL). For a

few months before the FocalPoint™ technology was abandoned in the move to ThinPrep™ LBC (which was incompatible with FocalPoint™, however findings by Schiffman *et al.,* 2017 may indicate otherwise) a small number of samples scanned via the FocalPoint™ also received a HrHPV test. The results of a small number of samples (n=124) were correlated and the results presented in results, chapter 5.

The research question I wished to address by this correlation was:

Is there a relationship between the presence of HPV in a cervical LBC sample and the FocalPoint™ quintile ranking of that sample?

Chapter 2

Materials and Methods

2.1 Study Design

This study is a prospective, multi-centre randomised controlled trial that presents the results of a health technology assessment (HTA) of Computer Assisted Screening (CAS) commissioned by Cervical Screening Wales to evaluate the Becton Dickinson FocalPoint™ GS slide profiler CAS technology. The study is designed in accordance with the principles of the CONSORT (Consolidated Standards of Reporting Trials – see Appendix 2.) guidance for the reporting of randomised controlled trials. The author was the lead researcher for the assessment, designated as **CAESAR** (**C**omputer **A**ssisted **E**valuation – **S**creening **a**nd **R**eporting).

In the study, women aged 20-64 years undergoing primary cervical screening in areas of Wales in the United Kingdom (UK) were randomly assigned to receive manual reading only (n=93,473) or paired reading (manual and automated, n=45,317) of cervical screening LBC samples. The number of samples for paired reading was limited by the availability of the FocalPoint™ technology to perform the automated reading. This was because the CAS instrumentation was based at Source Biosciences Laboratories in Nottingham and stained slides were required to be transferred off-site by dedicated courier transport.

The assessment was carried out in three phases, designated as CAESAR 1, 2 and 3. This was primarily to balance the requirement for the study to be sufficiently powered to detect differences in the reporting rates of high grade squamous cell dyskaryosis with the requirements of maintaining an effective laboratory cervical screening service (see the section on statistical considerations – Section 2.10). In addition, there were other reasons why this approach was considered, as follows:

1. Using the CAS technology in parallel to primary manual screening is very resource intensive on the laboratory and the multiple phased approach was chosen to allow the labs the opportunity to bring the routine work back up to date.

2. A larger study size was recommended by the Local Research Ethical Committee (LREC) - Velindre NHS Trust Research Risk Review Committee, RRRC - see recommendations - Appendix 3.

3. The study depended on FocalPoint™ instrument availability as well as the transport of samples to and from the site of scanning and the referral laboratories. A multiple phase approach was found to be optimal regarding the requirement to manage the scanning logistics associated with an off-site scanning solution.

4. Only one FocalPoint™ GS instrument was available for use in the study and not exclusively so as the instrument was committed to other laboratories workload - separate to this study. A phased approach was therefore considered to be the most effective way forward.

5. This phased approach also allowed the participation of up to four laboratories within Wales -which was perceived as a positive benefit, for the following reasons:

- The laboratories were invited to participate in the assessment so that an adequate enough number of samples were processed, and that inter-observer variability was minimized.
- It was considered essential that the evaluation was conducted in different areas of Wales so that as many individuals as possible were exposed to the technology. This was to ensure that user opinion of the technology would be based on as many opinions as possible to evaluate user acceptance prior to a live implementation.
- Any differences in dyskaryosis prevalence and detection rates within regional populations as determined by the technologies could also be studied by this approach.

2.1.1 Study phases

CAESAR 1 was the initial study initiated in December 2006 and completed in December 2007. It facilitated an initial period of familiarisation with CAS technology for laboratories in the form of an informal internal service evaluation. The main aim of CAESAR1 was to investigate the FocalPoint™ technology as a rapid quality assurance tool (rapid quality control; rapid screen).

In this phase of the study, the 10 FOV from each scanned slide that were presented to the operator by means of the FocalPoint™ guided screening facility were evaluated and compared to the manual equivalent. It was not possible to fully investigate the technology as a primary screening tool because the NHS CSP issued an executive directive to the UK cytology community, expressively prohibiting the use of the technology as a primary screening tool until the then newly-initiated Health Technology Assessment, MAVARIC, (Kitchener *et al*., 2011) had reported its findings.

However, following CAESAR 1, it was discovered that an assessment on the technology in a primary screening mode was possible, using only the 10 FOV available. This, by necessity, was a minimalistic approach, in that the cytotechnologist was restricted to just the 10 FOVs in assessing the case and not being able to examine the remainder of the slide. However, if this approach provided acceptable performance compared to manual primary screening, then there were potential gains in cytotechnologist time saved.

Three laboratories were initially included from within the North Wales area:

- Glan Clwyd Hospital (GCH), situated near Rhyl.
- Llandudno General Hospital (LLGH), Llandudno.
- Maelor General Hospital (WMH), Wrexham.

Following the completion of CAESAR 1, it became apparent that the FocalPoint™ NFR function showed considerable promise in terms of its negative predictive potential, as an adjunct to primary screening within the laboratory service. To further investigate this potential, along with the requirement to increase the number of participants' samples included, CAESAR 2, the second phase of the study, was conducted from July 2009 to May 2010. For this phase, a fourth additional laboratory from South Wales was recruited:

- Royal Gwent Hospital (RGH), Newport.

Following the decision to implement CAESAR 2, as lead investigator, I felt that there should be project management oversight of the study, and so the FocalPoint™ Executive Group (FPEG - Appendix 6), was convened. This group provided clinical and quality assurance of the

project, effectively overseeing and having overall responsibility for the activities of the FocalPoint™ Project Operational Group (FPOG). This group was responsible for the operational management of the project (see Section 2.6 for further details and function of the group).

CAESAR 3, the final phase of the study, was conducted from Dec 2010 to July 2011 and was initiated specifically to examine the reporting characteristics of the FocalPoint™ NFR reporting category further following a change in the manufacturer's calibration protocol. This meant a departure from carrying out an initial Laboratory Process Calibration Assessment (LPCA) on 250 slides from each laboratory to a continual LPCA carried out by BD on any given instrument and the workload scanned.

This change was driven by an adverse incident that occurred in one of the laboratories participating in CAESAR 2. This resulted when an unexpected increase in high grade samples were received by Llandudno General Hospital, resulting in an increase in the number of samples that were categorised as NFR (a complete account of the issue is documented in Chapter 4, Section 4.1). Due to staffing and other constraints on the laboratories during this time, only one laboratory (RGH) took part in this study.

All four laboratories used the SurePath™ LBC technology to examine cervical screening samples, the assessment was conducted on routine samples which were received and processed over different time periods (Table 2.1) in the laboratories.

Table 2.1: CAESAR studies – dates of sampling

Study	Start Date	Finish Date
CAESAR 1	*December 14th, 2006*	*December 6th, 2007*
CAESAR 2	*July 1st, 2009*	*May 31st, 2010*
CAESAR 3	*December 1st, 2010*	*July 31st, 2011*

2.1.2 Protocols for the studies

(please refer to Appendices 7 and 8)

Routine cervical samples from screening participants were received at the participating laboratories by means of the usual routine transport arrangements. The samples were accepted and patient identifiable information (PII) and sample associated data were recorded on the TelePath™ Laboratory Information Management System (LIMS) system, which is used by all four laboratories enrolled in the study. Note that, as samples were received in a random manner at the laboratory, therefore, they were randomised in date receipt order from the routine screening workload of the laboratories. Samples were further randomised by the random availability of the FocalPoint™ Imaging System at the Source BioScience (SBS) laboratories, dictating when samples could be scanned.

Once a laboratory accession number had been assigned, the samples were processed using the SurePath™ LBC technology (refer to Section 2.3) and the resultant slides were labelled, and bar coded in accordance with a standard protocol for FocalPoint™ scanning and subsequently dispatched to Source Bioscience Ltd. (SBS), in batches of a minimum of 120 slides as per the manufacturer's recommendations (Operator's Manual—BD FocalPoint™ System - Doc. No. 780-06424-00 Rev C.).

The slides were transported for FocalPoint™ scanning by commercial courier arranged by SBS to their laboratories in Nottingham, tracked using an MS Excel based tracker system that allowed the slides to be scanned onto the tracker and then the file was e-mailed to SBS where the slides were receipted by SBS laboratory staff and an acknowledgement e-mailed back to the referral laboratory, (Appendix 10). It should be noted that the protocol used only the laboratory accession number and no PII was stored. Once scanned, slides were returned to their laboratory of origin for assessment, together with the associated FocalPoint™ scanning data transferred to and stored on an external computer hard disk drive.

As part of the evaluation, a Guided Screening Workstation was installed at each laboratory for the GSW assessment process. The GSW consists of a standard laboratory microscope to which a motorised slide stage is attached (see Figure 2.1). The stage is interfaced to a personal computer (PC) that holds the scanning information for a given slide (designated by

FocalPoint™ as a review case). This information is accessed by scanning the barcode on the slide identification label using a barcode reader. At the start of each GSW session the technology is calibrated by aligning the image down the microscope with that presented on the PC visual display unit (VDU), by means of the GSW's calibration software. Ten FOV, specific to the slide in question, are presented to the operator who decides on the result of the slide based on the morphological content of those FOV.

Figure 2.1: FocalPoint™ Guided Screener™ Workstation (GSW) system or "SlideWizard™"

Slides that are designated by the FocalPoint™ as having a high negative predictive potential are allocated to the NFR category and as such, do not have any FOV that can be viewed via the GSW.

Because of the high negative predictive potential of the NFR category, the results from the FocalPoint™ scanning process were blinded to screening staff so that their manual screening opinions were not biased in any way.

The comparison of the GSW evaluation and the routine reporting results of the assessment were correlated and recorded on the TelePath™ LIMS before a final cytology report was issued.

Figure 2.2 is a schematic representation of the sample process flow adopted for the CAESAR projects.

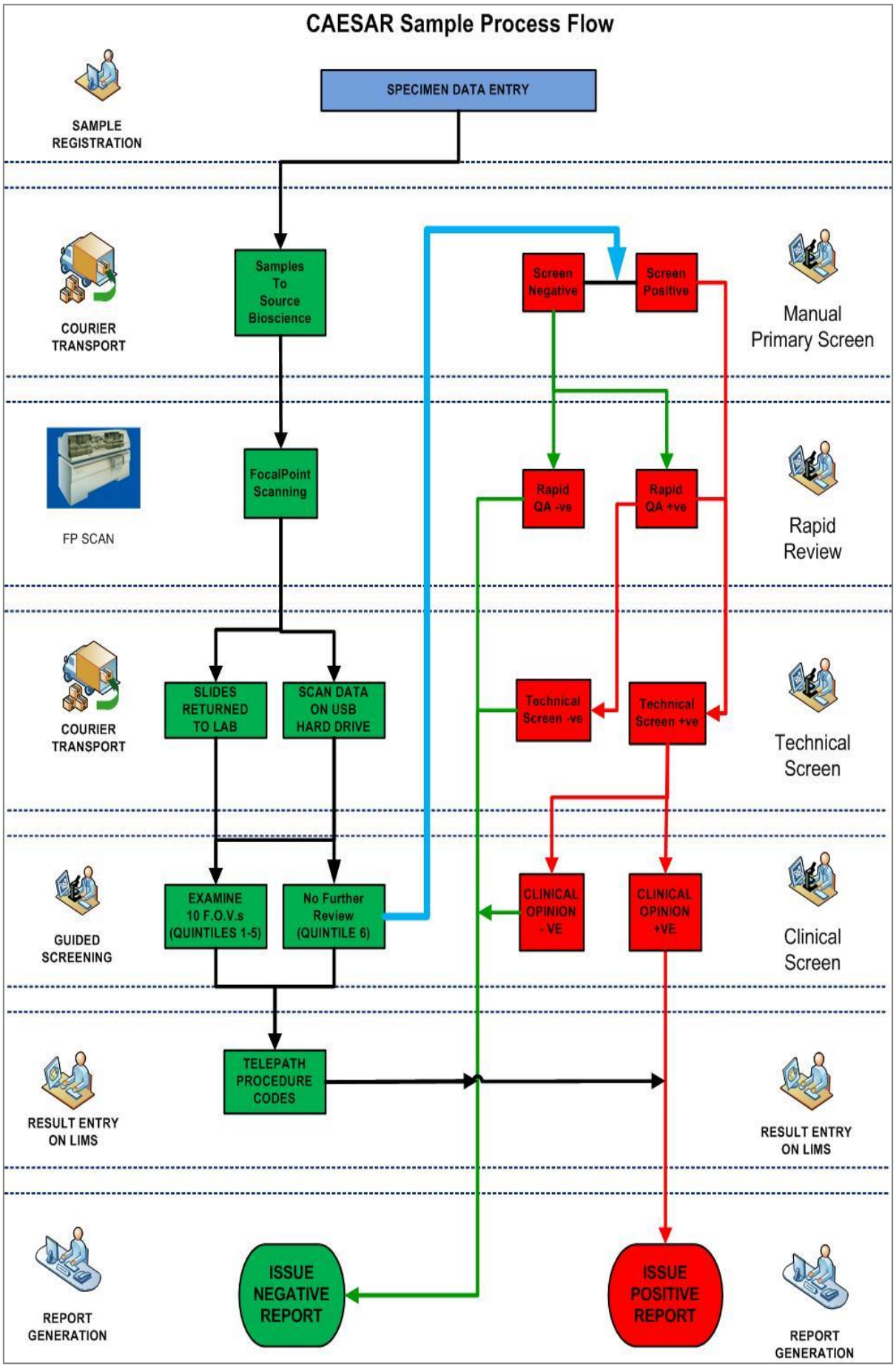


Figure 2.2: CAESAR Sample Process Pathway

2.2 Sample LBC Processing

As stated previously, cervical screening in Wales is carried out using the SurePath™ LBC technology. Samples are taken by the sample taker from the cervix using five 360^0 rotations of the CERVEX™ broom, and the detachable head of the broom is dropped into the SurePath™ vial which contains $10cm^3$ of SurePath™ preservative (Figure 2.3). The vial is then labelled with the patient's individual identifying data and sent to the laboratory.

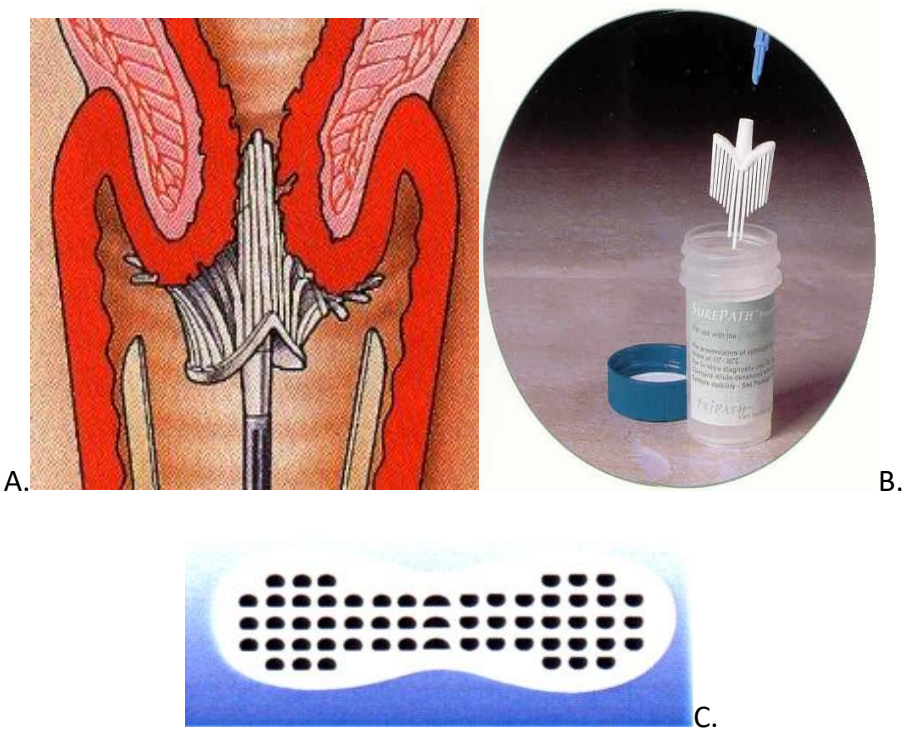


Figure 2.3: SurePath™ Liquid Based Cytology Sample Taking Process:

A. Schematic diagram of the use of the Cervex™ Broom in taking a cervical sample.

B. Transferring the broom head to the vial.

C. A cross section of the broom head, representing the "D" shaped profile of the bristles, claimed by the manufacturer to improve sample quality.

At the laboratory, the sample is checked against the cervical screening request form and if correct, the laboratory specimen reception/data entry staff accept the sample and register the patients' details on the LIMS.

The samples are labelled and then are processed using the SurePath™ methodology. First, the sample vials are agitated to re-suspend the cellular content, and then the vials are

installed on the SurePath™ PrepMate™ pipetting instrument, which draws up an aliquot of 8 cm^3 of the suspended cells and dispenses them into a tube containing proprietary density gradient (see Figure 2.4).

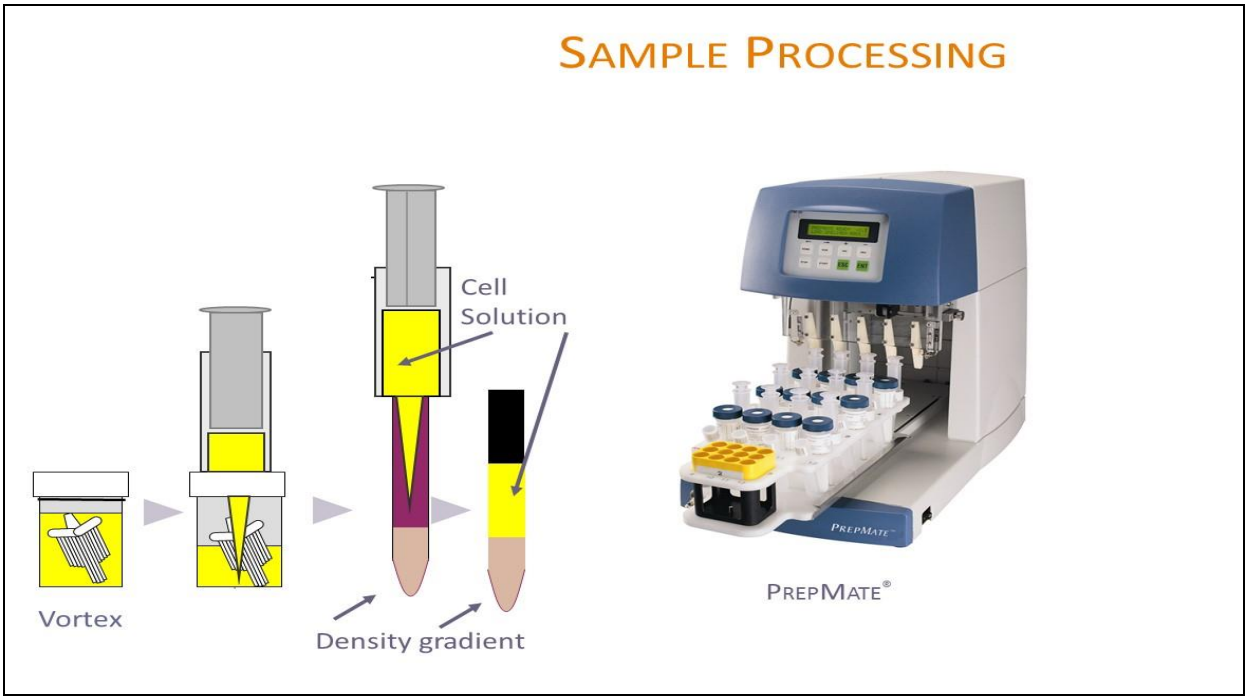


Figure 2.4: Sample pre-treatment to remove excess inflammatory and blood elements using the PrepMate™ pipetting station

The samples are then centrifuged for the manufacturer's recommended speed and time so that the yield of cervical cells is optimised, with as much inflammatory exudate and blood removed by the density gradient.

Following re-suspension of the samples, they are transferred to the Autocyte Prep™ slide preparation instrument, where an aliquot of the cellular suspension is transferred to a settling chamber attached firmly to the slide, and the cells are allowed to settle onto the slide, which are electrically charged, and the cells are therefore retained by the charged surface. Excess density gradient is then aspirated from the chamber and replaced with a series of nuclear (haematoxylin) and cytoplasmic (Papanicolaou variant) stains, which are applied for the appropriate periods as specified by the laboratory (Figure 2.5).

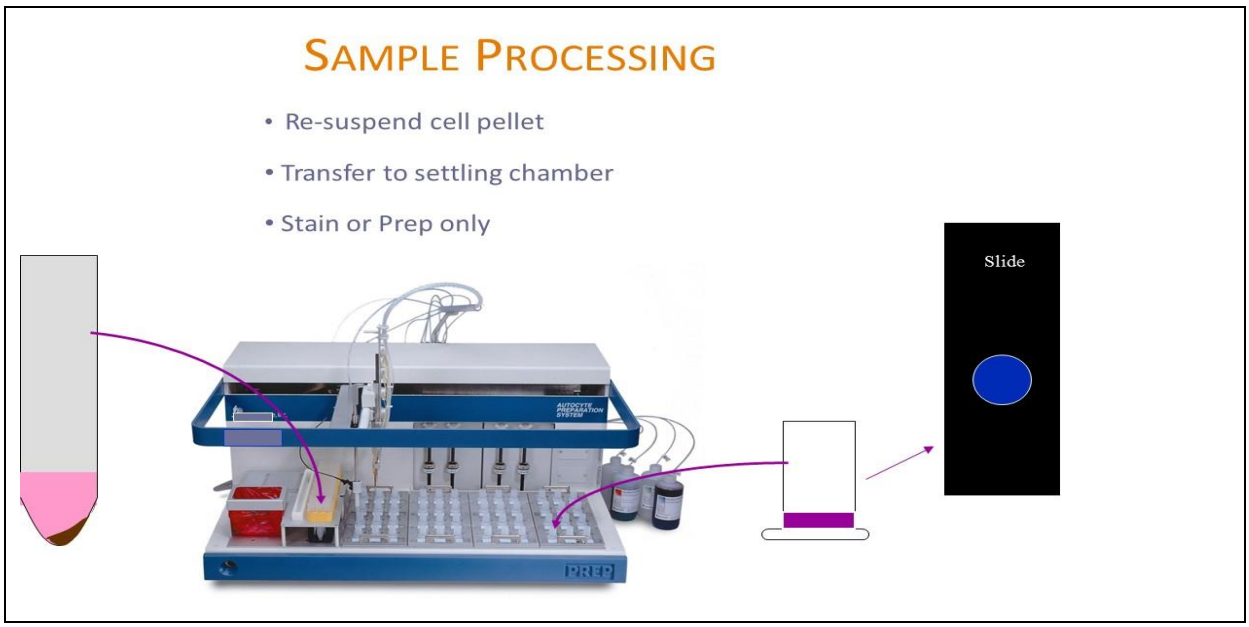


Figure 2.5: Slide preparation using the SurePath™ Autocyte Prep™ instrument

Once the processing cycle is complete, the prepared slides are dehydrated in industrial methylated spirit, cleared in xylene and coverslips applied. For the CAESAR 1 study, two of the participating laboratories used glass coverslips that were applied manually. One laboratory used a Sakura™ resin tape coverslipper, which offered several advantages, thus:

- Minimised laboratory staff exposure to Xylene vapour
- Freed up staff time
- Provided more consistent coverslips, which significantly improved FocalPoint™ sample rejection or "Process Review" rates – this finding is reported on in the results – Chapter 3, Section 3.2.1.

Prepared slides were then labelled with the appropriate bar-coded label that could be read by the FocalPoint™ scanner, allowing the slide to be identified for scanning. The slides were then packaged in batches of a minimum of 120 slides (Appendix 9), tracked using the SBS/CSW FocalPoint™ sample tracker software and transported by commercial courier to the SBS laboratories in Nottingham. Collection and delivery times were agreed by SBS and the participating laboratories – see Appendix 10).

2.3 Use of the Guided Screener Workstation

A t each GSW session, the operator is required to set the microscope stage calibration from the top edge of the slide and similarly, from the right-hand edge of the slide (Figure 2.6).

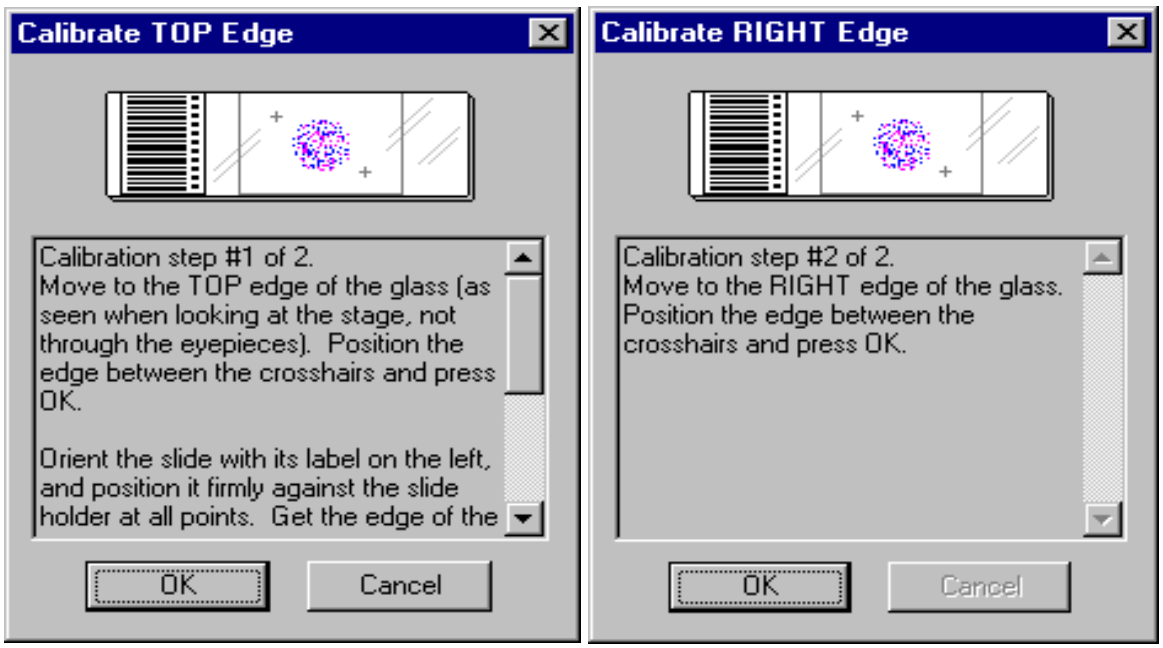


Figure 2.6: Stage Calibration of the FocalPoint™ Guided Screener™ Workstation

Once calibrated, the GSW could be operated and the cytotechnologist is presented with the first field on screen. The operator is then required to fine tune the on-screen image with that presented by the microscope using a feature called “offset” (Figure 2.7). This is to ensure that all the images presented to the operator are exactly coordinated with their microscopic counterparts. Once this is accomplished the operator can then view the 10 FOV presented on screen and examine the fine detail of the field presented synchronously down the microscope (Figure 2.8).

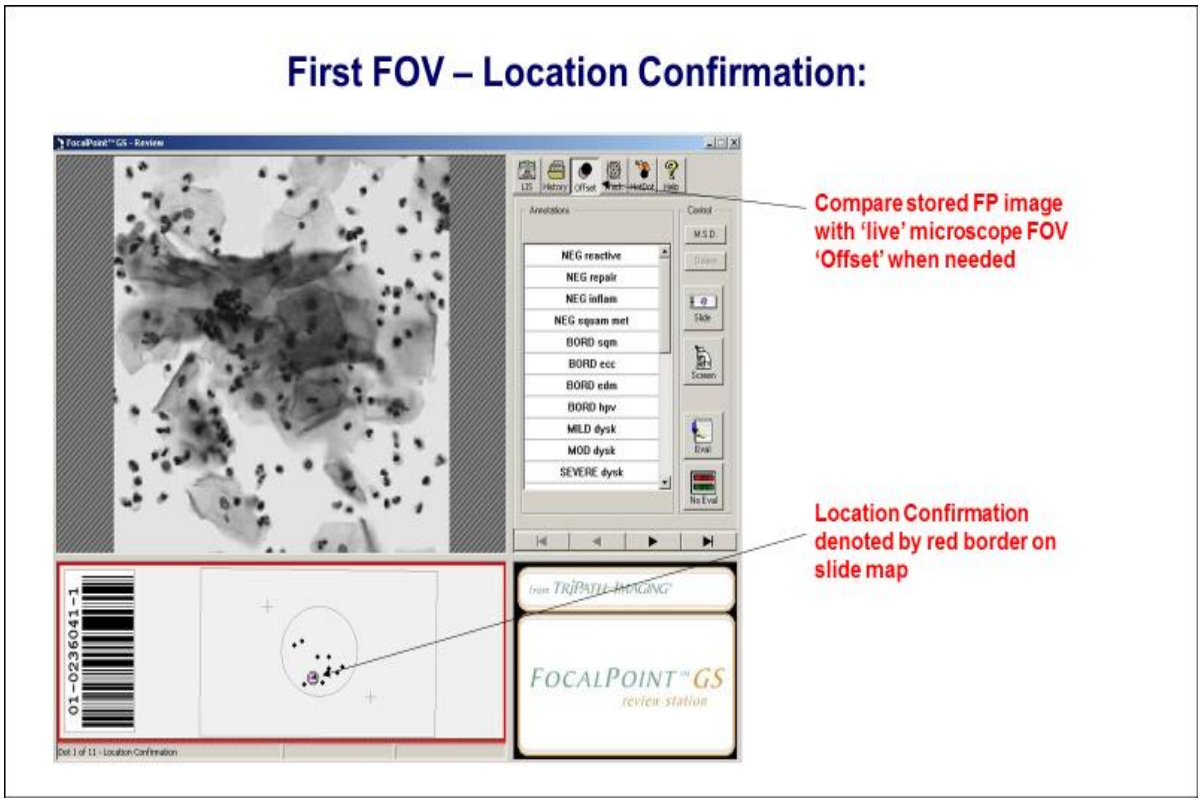


Figure 2.7: Image presentation by the FocalPoint™ Guided Screener™ Workstation

FOV images are presented in ranked order of abnormality and include what the technology has considered to be the image of most risk – known as "most significant dot" – "MSD". These FOVs are simultaneously reviewed by the operator on the screen and the microscope. The cytologist must review the entire 10 FOVs, taking manual stage control when required. Microscope magnification can be changed at will and clicking a foot switch or mouse or using keyboard arrows will take the operator to the next FOV for scrutiny.

The GSW also provides:

- Automated X-Y relocation of points of interest
- Electronic dotting including Most Significant Dot (MSD – see below)
- On-screen location labelling

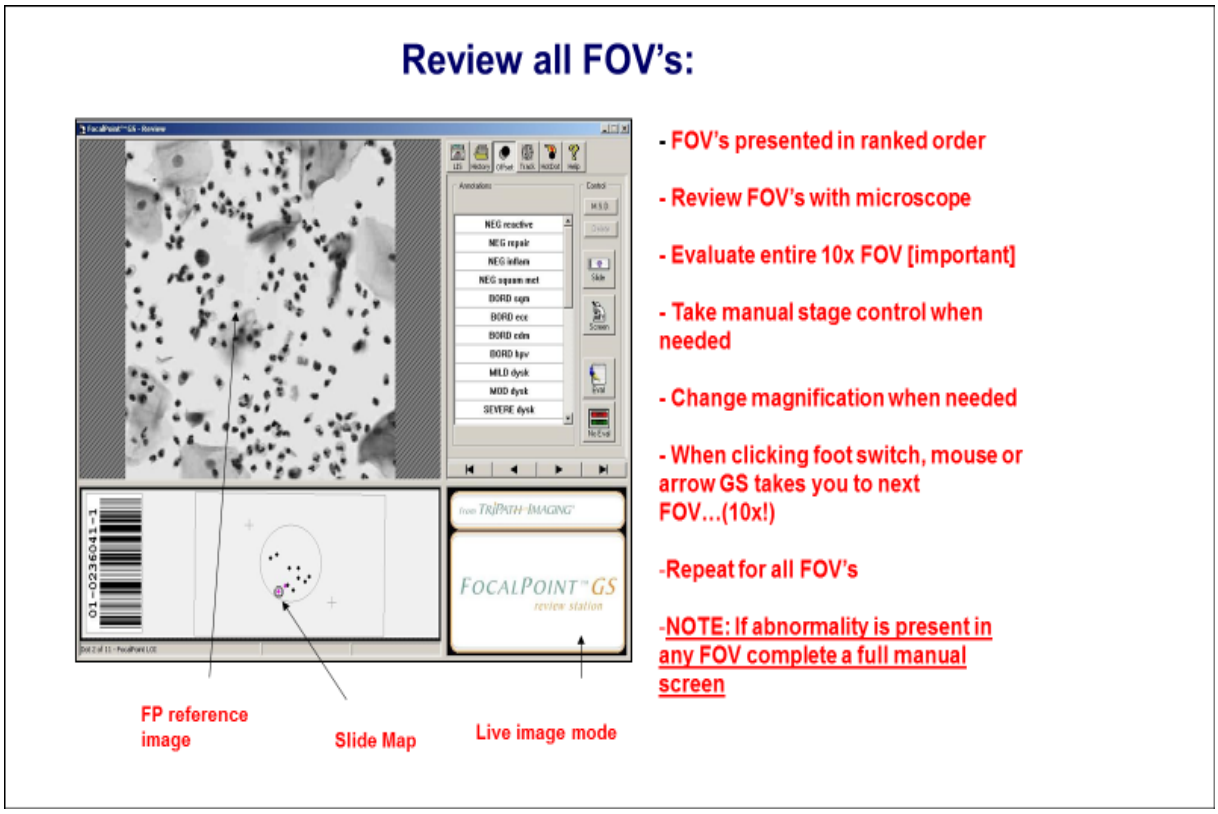


Figure 2.8: GSW screen presented to the Cytologist when reviewing FOVs

2.4 Staff Training

Laboratory staff participating in the study were trained and assessed competent by staff trainers from Source Biosciences Ltd. The training was delivered in a series of modules:

- Module 1: Presentation to introduce trainees to the FocalPoint™ GSW technology.
- Module 2: Hands-on experience at the GS Workstation designed to familiarise the trainees with all functions using 10 training slides. The training in module 2 also provided for the calibration of the GS workstation
- Module 3: Discussion and questions/answers session.
- Module 4: Introduce the trainees to location verification; FOV screening techniques, this time using 10 learning slides.
- Module 5: Discussion and questions/answers session.
- Module 6: Further training in the interpretation of sample morphology presented via 10 FOVs. This was followed by a diagnostic performance assessment of 100 test slides.

The assessment of each individual required them to achieve a number of correct responses to provide a minimum sensitivity of 95% for high grade (HSIL+; High Grade (Moderate) Dyskaryosis+). Training was also provided for processing and slide scanning, including the

interpretation of the operation and error messages generated by the FocalPoint™ and the Guided Screener™ Workstation system.

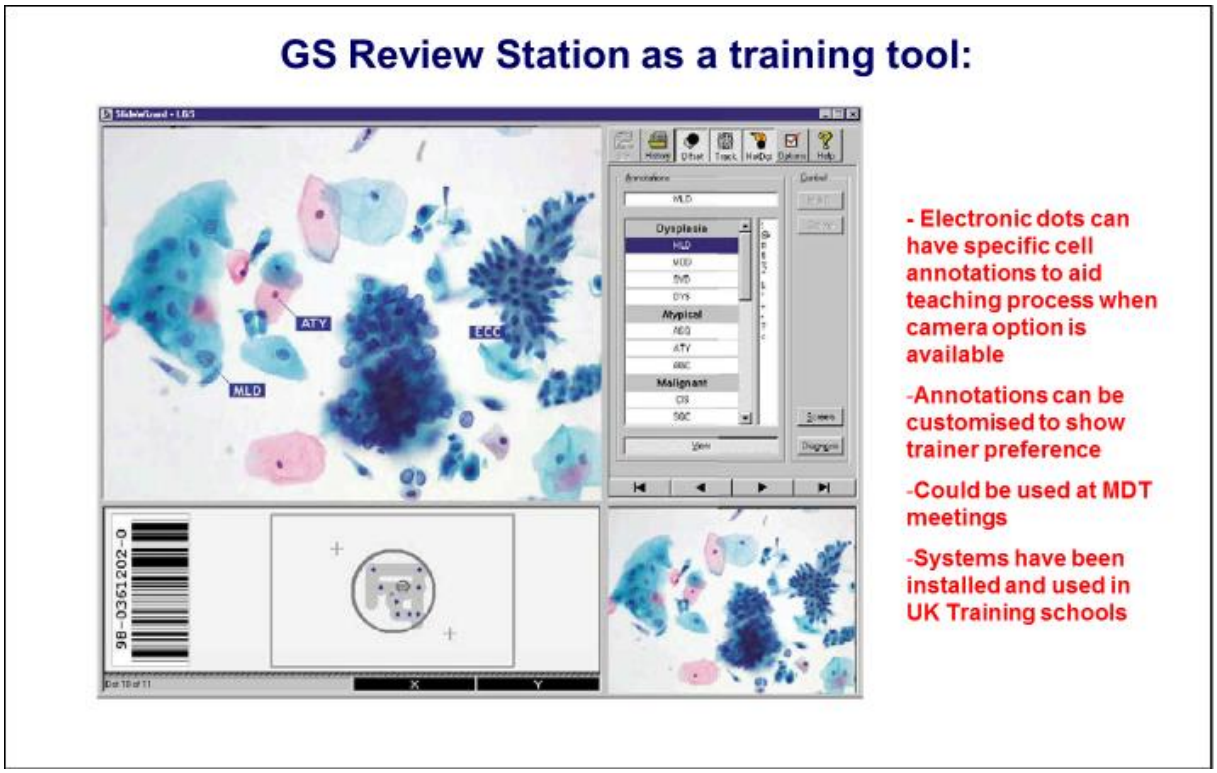


Figure 2.9: FocalPoint™ GSW screen data available for morphology training of cytologists

The FocalPoint™ GSW can also be used as a training tool in its own right. Slides can be marked and annotated, labelling features of interest. The system is equally useful for multi-disciplinary patient management meetings, where annotated images from scanned slides can be displayed electronically at the meetings – Figure 2.9.

2.5 CAESAR project management

Following an initial appraisal of the CAESAR 1 results, including a recommendation from the LREC (Appendix 3) - it was necessary to increase the number of samples investigated (Section 2.10.1). This was so that sufficient sample numbers were available to detect significant key performance indicator (KPI) differences between FocalPoint™ and manual screening. Once the decision had been made to enlarge the study participant base, an additional laboratory was recruited (RGH) to enable that, and the CAESAR 2 phase was initiated. To manage the project and coordinate the project activities between the participating sites, the FocalPoint™ Project Executive (FPEG) and Operational Groups (FPOG) were convened. FPEG had executive responsibility for the project and provided clinical

governance and quality assurance oversight of the project. The membership of the group included:

- Dave Nuttall – Head of Laboratory Services and Principle Investigator (author and PhD candidate)
- Bryan Rose – Head of Programme, Cervical Screening Wales
- Helen Beer – Senior Informatics Analyst
- Nick Dallimore – Quality Assurance Pathologist
- Sally Williams – Quality Assurance Pathologist
- Thomas Hockey – Director, Welsh Cytology Training School
- Wilma Anderson – Cytology Manager, Source BioScience Ltd.
- Mrs Christine Payne – Clinical Cytologist, Royal Gwent Hospital
- Louise Pickford – CSW Regional Coordinator – North Wales

The FPOG was concerned with the routine operational issues that required a single standardised approach across the participant sites. The membership of the group included:

- The Principal Investigator (author and PhD candidate)
- Laboratory Managers from each of the participating sites
- The Programme Manager for Cervical Screening Wales
- Information Analyst/Manager for Screening Services
- The Cytology Manager for Medical Solutions Ltd.

The group met at regular intervals to discuss and agree the implementation plan and associated processes, such as Standard Operating Procedures (SOPs – Appendix 9), LIMS code dictionaries (Appendix 11) and transport arrangements (Appendix 10). Notes of the meetings were recorded and shared with the four participating laboratories.

2.6 Further arrangements required prior to initiation of the CAESAR projects

Electronic slide label printers were installed in all labs to fulfil slide ID requirements for FocalPoint™. An alpha-numeric slide accession number format was agreed for the project and each participating laboratory was issued with its own uniquely formatted bar code

printer, pre-programmed to print the slide label, based on the sample accession number and the unique lab identifier.

A standardised FocalPoint™ report code dictionary (Appendix 11) was developed for TelePath™ LIMS coding and data transfer to CSW data servers. Operators of the GSW were then able to code results from the GSW screen to the LIMS, and the results could then be extracted by the CSW Informatics Team.

In addition, each laboratory was required to submit 250 slides for the LPCA. This is a validation and qualification of a subset of slides representing the lab's routine samples to calculate thresholds based on different variables such as staining, slide preparation and unusual events within the regional population, calibrating the instrument accordingly. Therefore, the workload for each laboratory was scanned independently of the other laboratories work, under the FocalPoint™ calibration settings for that laboratory. The instruments were recalibrated prior to scanning a different laboratory's slides.

The transport arrangements for LBC slides to SBS Laboratories in Nottingham were agreed by the FocalPoint™ Operational Group (FOG) and the collection schedules (Appendix 10) were provided for the individual participant laboratories. Once slides had been scanned on the FocalPoint™ GS slide profiler, they were returned to the laboratory of origin. SBS also provided the solid state removable hard disk drives for data transfer to support the project. These drives were connected to the PCs managing the guided screener software and directing the microscopes equipped with automated slide stages.

2.7 Study Participants

Participants were enrolled into the study from routine screening invitations and were included in a randomised manner based on the sample being received in the laboratory. The number of samples that were submitted for FocalPoint™ scanning (n=45,317) is lower than the total number of participants manually screened (n=137,805) because of the scanning capacity constraints of using one FocalPoint™ GS imager at that time. It must be noted that samples were presented to the imager in a totally randomised manner as this was dictated by availability of the equipment and consisted of samples from the general screening

population as well as from colposcopy, Genito-urinary Medicine (GUM) and local community clinics.

2.8 Ethical Approval

When Cervical Screening Wales came into existence as the screening programme responsible for cervical screening in Wales, the governance for the participants became the responsibility of the Screening Services division of the Velindre NHS. The programme subsequently transferred to Public Health Wales which now holds that responsibility via its Screening Division. This is documented as part of the Public Health Wales National Health Service Trust (Establishment) Order 2009.

An application was made to the Screening Division Research and Development group for approval to proceed with the study and it was agreed that this project was classified as a Health Technology Assessment and given the operational criteria around anonymised patient identifiable information in force at that time, ethical approval via the LREC would not be required.

For the avoidance of any doubt, the Executive Officer, South East Wales Research Ethics Committee was contacted to seek further advice and after some weeks a reply was received via e-mail on October 31st, 2008 (Appendix 4). However, in the interim period and since no reply had been received, an application was made to the LREC hosted by the Velindre NHS Trust, 14 Cathedral Road, Cardiff, CF11 9LH. The study was approved by the committee (Appendix 3), on September 30th, 2008, subject to the issues identified by the reviewers being satisfactorily addressed. These included:

- *"Since rapid screening is not being carried out it cannot be directly compared with CAS unless there is a historical review. I understand that this will be the case, but this is not clear in the protocol."*

Rapid Quality Assurance screening was subsequently introduced into the protocol for the study as a potential application area for CAS.

- *"The sample size of 15,000 is appropriate, but the study would clearly benefit from a larger study number."*

The study was enlarged by carrying out further studies in the manner detailed in section 2.1 Study Design. Total samples scanned by CAS that were included in the study was 45,317.

- *"Although CAS could undoubtedly introduce cost savings this project does not appear to be trying to directly address this. I do not believe this is a major issue. "*

An Economic Analysis (EA) has subsequently been performed on the CAS technology and is reported in this thesis.

The response from the LREC also stated that if patients were recruited from other Welsh Health Trusts, then local R&D approval should be gained before commencing the studies. It was considered that, when women are invited for screening as part of the programme in Wales, they are invited by Cervical Screening Wales, which statutorily holds the clinical governance for cervical screening patients in Wales, up to the point of diagnosis and treatment of any cervical disease detected by the screening programme. Screening participants are consented for their cervical samples to be screened at each episode, including their use in an anonymised way for technology assessments, internal quality assurance etc. Specific patient consent was therefore not required in this instance.

As detailed earlier, after LREC approval was granted, a reply was received from the Executive Officer, South East Wales Research Ethics Committee, who provided guidance regarding the difference between research and service evaluations and clinical audits and suggested that the LREC could be contacted for advice – confirming the action already taken.

2.9 Statistical Considerations

2.9.1. Power calculation

The primary function of a cervical screening programme is to detect cervical pre-cancer. The natural regression rates (Kitchener *et al*. 2011) for low grade dyskaryosis are relatively high (approximately 70% will regress to normal), and therefore whilst it is important to detect low grade dyskaryosis, these regression rates mean that there is a good chance that the patient will be cured of low grade disease. However, the

regression rates for high grade dyskaryosis are considerably reduced (30-40% regress and 10-20% will progress to invasive cancer) and it therefore follows that for a screening programme to be a success, it is important for the high grade dyskaryosis detection rates to be as high as possible.

The ARTISTIC study (Kitchener et al. 2009) reported that the sensitivity of cytology alone for CIN2+ (HSIL+) was within the range 91.5% - 95.4%, depending on age cohort of women screened. In achieving this standard, the cytotechnologists participating in the ARTISTIC study were required to demonstrate a minimum sensitivity of 95% for high grade (moderate +) dyskaryosis as per the NHSCSP standard at the time, which is still current (see below). As stated above, this study was mainly concerned with the optimal detection of high grade dyskaryosis, and the NHS CSP standards for cytotechnologists were therefore maintained.

The current NHSCSP minimum standard for primary screener sensitivity for the detection of high grade dyskaryosis is >95% (NHS CSP Publication No. 1, Third Edition, January 2013). It has been shown that the sensitivity of the FocalPoint™ NFR reporting category exceeds 99% (Kitchener *et al*. 2011). On this basis, the study is powered to detect a difference of 4% (99% - 95%) in the detection rate of high grade (HG) dyskaryosis. To demonstrate that automated screening was at least the equivalent to manual screening the study is powered to 90% at a 5% level of significance.

To detect a difference of 4% in HG dyskaryosis with 90% power at a 5% level of statistical significance – a minimum of 382 samples reported as HG dyskaryosis are required.

In Wales, the prevalence of HG dyskaryosis in the screening population is approximately 1.0 - 1.9%. It therefore followed that the study should include at least 38,200 samples to be adequately powered. As stated earlier, 45,317 samples were processed via the automated arm.

This number has exceeded the minimum numbers required, however, given the different performance measures that were applicable to the various applications under investigation in this project, it seemed prudent to ensure that the worst possible case was considered to adequately power the study.

2.9.2. Statistical analyses performed as part of this project

The Chi-Squared test (χ^2) was used as a test of association, particularly in combination with a *p* value to denote significance. This combination has been used to evaluate the significance of the differences between 2 and subsequently 3 year interval outcomes of CIN 2+ between manual primary screening and the FocalPoint™ NFR reporting category [publication in process of submission].

Confidence Interval (CI) - these intervals have been calculated and presented to indicate a range within which the true value lies.

Cohen's kappa correlation (κ) is used to compare the results of manual versus automated detection of endocervical cells in LBC samples.

The statistical functions for the study were calculated or confirmed using the SPSS™ analytical software by IBM™.

2.10 Data collection

As reported previously, specific code tables (Appendix 11) were developed for the project which enabled the FocalPoint™ scanning results to be allocated to the patient computer record. All qualifying FocalPoint™ results along with the corresponding manual screening result for each sample were collected via regular electronic downloads by the CSW Information Department and recorded.

The Information Department then identified the number of all scanned samples along with their results and histology outcomes over 2 and 3-year post-screening periods. In this way, the performance of the FocalPoint™ technology could be compared to that of routine manual screening, which forms the basis of this study.

NOTE: The Information Department was unable to gather some of the CAESAR 1 histology outcome data that was related to the NFR samples. This was due to a result coding anomaly which was subsequently corrected in the later phases of the study. Details of the samples affected are provided later in this chapter, Section 2.12.4.

2.11 Methodology used to evaluate the research objectives of the study

2.11.1. Performance against Key Performance Indicators (KPIs)

KPIs that were monitored in this study (where appropriate):

- **False Negative and False Positive rates, defined as:**

False negative – percentage of diseased individuals who incorrectly receive a negative result.

False positive – calculated as 1 minus test specificity.

NOTE: True False Negative and False Positive rates cannot be calculated accurately for the NFR reporting category which does not present fields of view to the operator. This means that there is no morphological result for up to 25% of the FocalPoint™ results, and an NFR False Positive and True Positive comparison is not possible.

- **Test Sensitivity and Specificity**

Sensitivity:

Defined as:

Sensitivity = [Total Positives / (Total Positives + False Negatives)]

In this study the sensitivity was calculated in this manner for the rapid QA screening application as well as the comparison of automated versus manual primary screening. As a further comparison, in order to provide additional assurance and confidence in the results, interval outcome analysis at 2 and 3 years was also carried out, specifically to compare high grade disease incidence rates between manual vs automated interventions.

Sensitivity was not estimated for the NFR cohort of samples for the reasons already stated, but again, interval outcome analysis was carried out at 2 and 3 years, comparing high grade disease incidence rates as described below.

In the UK this KPI is reported on a rolling basis and monitored by the laboratory. The minimum limits are >95% for high grade dyskaryosis and >90% for all grades of dyskaryosis.

- **Considerations regarding the comparison of sensitivity of automated screening (including NFR) versus full manual rescreen**

In the MAVARIC study (Kitchener et al, 2011), the sensitivity of automated versus manual

reading (screening) was determined by the respective ability of these methods to detect CIN2+ (HSIL+), with these outcomes representing the thresholds for patient treatment. This sensitivity calculation was termed the *relative sensitivit*y, calculated thus:

1. Sensitivity of Automated Screening

Sensitivity (%) = (A+C) / (A+B+C+[D]) x 100

2. Sensitivity of Manual Screening

Sensitivity (%) = (A+B) / (A+B+C+[D]) x 100

Where

A = (AS+ve + MS+ve) B = (AS-ve + MS+ve)

C = (AS+ve + MS-ve) D = (AS-ve + MS-ve) – assumed to be 0

and

AS = Automated Screening MS = Manual Screening

As D cannot be calculated, the relative sensitivity is calculated thus:

Relative Sensitivity = (A+B) / (A+C)

The sensitivities calculated in this way do not provide the absolute sensitivity for each method because the number of automated and manually screened slides that are both negative (total false negatives) cannot be accurately assessed. However, the numerical value is relatively small and therefore has little overall effect. A valid comparison is therefore achievable between the sensitivity values calculated in this study and those presented in the MAVARIC trial.

- **Specificity**

Defined as:

Specificity = [Total Negatives/(False Positives + Total Negatives)]

- **Positive Predictive Value(PPV) – defined as:**

$$\frac{\textit{Number without disease \& screened +ve}}{\textit{Number without disease}} \times \frac{\textit{Number without disease}}{\textit{Total number screened}} =$$

% of LBC samples reported as having high grade cytology that are histologically confirmed

with high grade CIN.

Comparison of histological outcomes (CIN2+/HSIL+) for CAS and manual primary screening at 2 and 3-year intervals

Given the difference in the calculation of absolute sensitivity already referred to, a further comparison of the 2 and 3 year interval outcomes (CIN2+/HSIL+) of those cases that were reported as "Negative, no dyskaryosis seen" by manual primary screening were compared with the same interval outcomes for those cases classified negative by CAS following the examination of 10 FOV by FocalPoint™ LGS as well as NFR.

Note that, where the methodology employed to assess the research objectives of this study indicated positive quality benefits in comparison to manual alternatives, then a cost evaluation analysis was performed to further assess the overall applicability in the cervical screening programme.

2.11.2. Rapid quality assurance screening

Rapid Quality Assurance screening (RQA) or Partial Rescreening is a technique recommended in the UK (British Association of Cytopathology – Code of Practice, 2015) for the internal quality control of primary screening in cervical cytology.

The technique is employed either before or after (rapid preview or rapid review) primary cytology screening and involves the cytoscreener screening the slide in diagonal/horizontal directions in a stepwise fashion. The process has been described in several publications Brooke *et al*. 2002; Currens *et al*. 2012 and should take between 60 and 90 seconds per slide.

RQA (or Rapid Quality Control – RQC) by the FocalPoint™ technology was compared to the conventional manual rapid quality assurance screen, by evaluating the 10 FOV that are presented to the observer by the GS component of the FocalPoint™ slide imager. Patients' samples were received and processed in the routine manner and the resultant LBC slides were scanned by the FocalPoint™. Those slides designated as NFR were subjected to a manual RQA screen, whilst manual primary screened slides designated as "negative – no

dyskaryosis seen" were examined by a cytology screener using the FocalPoint™ GS slide wizard, scrutinizing the 10 FOV provided by the technology. The process pathway for this application is presented in Figure 2.10.

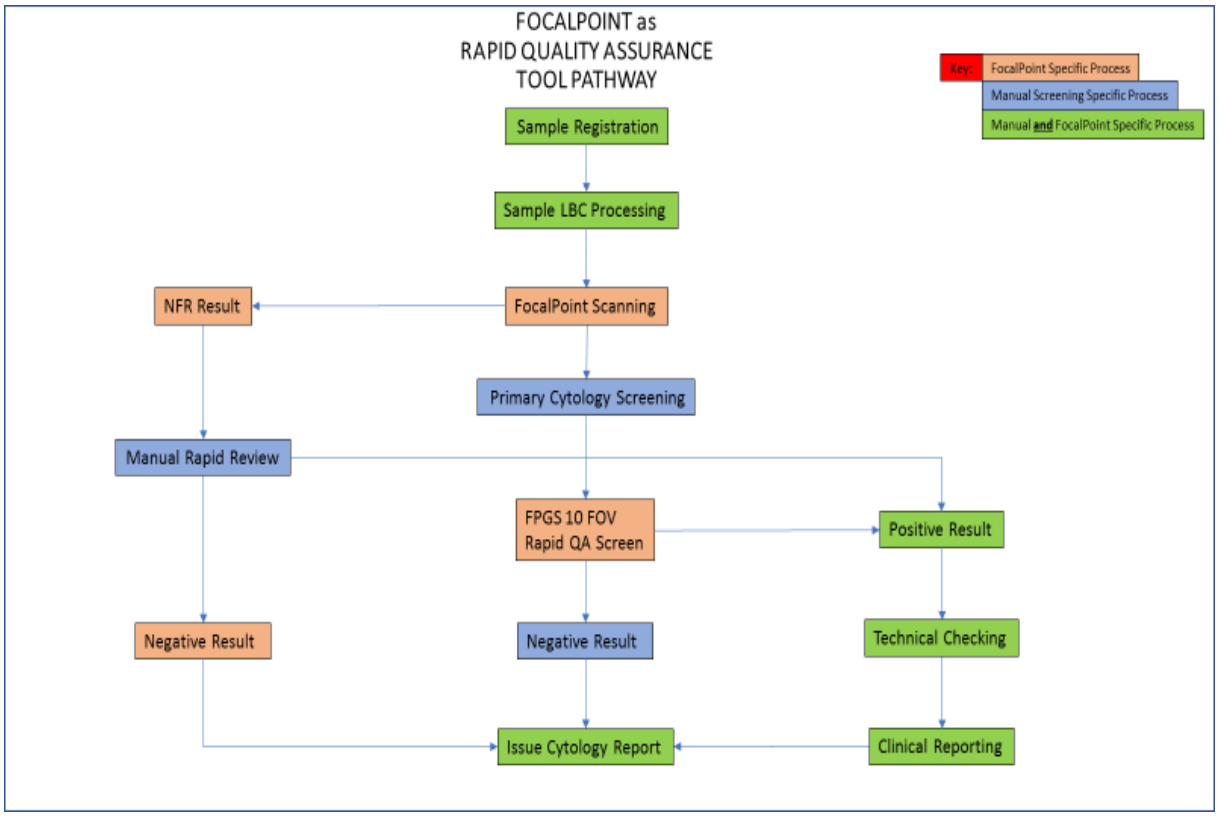


Figure 2.10: FocalPoint™ Guided Screener™ Workstation used in rapid QA of manually primary screened LBC samples

The parameters for comparison included:

1. Time taken to review 10 FOV compared to performing a manual rapid QA screen:

When taking a batch of slides for manual rapid QA screening, screeners were asked to start a stop watch at the beginning of each session. The time taken to complete the batch of slides in question was divided by the number of slides in that batch and so an average time per slide was calculated.

This approach meant that the time taken per slide QA screened also included the administrative part of the task, that is, result recording and associated actions, were included in the timing, on a case by case basis.

The results of the exercise were recorded in minutes and seconds and presented in table 3.6, chapter 3, section 3.3.

2. Since the purpose of a rapid QA screen is to provide quality assurance of a negative primary screening result, the effectiveness of the 10 FOVs presented to the screener and the NFR category was compared to that of a manual QA screen.

This was accomplished by comparison of the false negative rates and sensitivities/specificities of the automated technology and manual rapid QA screens. The results are presented in chapter 3, section 3.3.2.

2.11.3. Evaluation of automated screening compared to manual primary screening

The comparison of automated primary screening by FocalPoint™ compared to manual primary screening has been the subject of investigation by workers since the technology has been available, with variable results cited. Several workers, notably Passamonti *et al*., 2007 and Parker *et al*., 2004 have reported favourably regarding the technology whilst others (Kitchener *et al*., 2011 and Colgan *et al*., 2013), less so.

As stated in the introduction, the NHS Cervical Screening Programme issued an operational restriction on UK cervical cytology laboratories, forbidding the use of CAS for the primary screening of cervical LBC samples taken as part of the NHS CSP.

Cervical Screening Wales' interpretation of this restriction resulted in the evaluation of the CAS technology only as a rapid QA tool, however, it is possible to evaluate the technology in a primary screening modality, albeit restricted to the examination of 10 FOV only.

In normal primary screening mode, the cytotechnologist operating the system would not be restricted by protocol and would therefore have access to the remainder of the LBC preparation outside of the 10 FOV presented by the FocalPoint™ technology. The workflow for samples processed in this manner is presented in Figure 2.11.

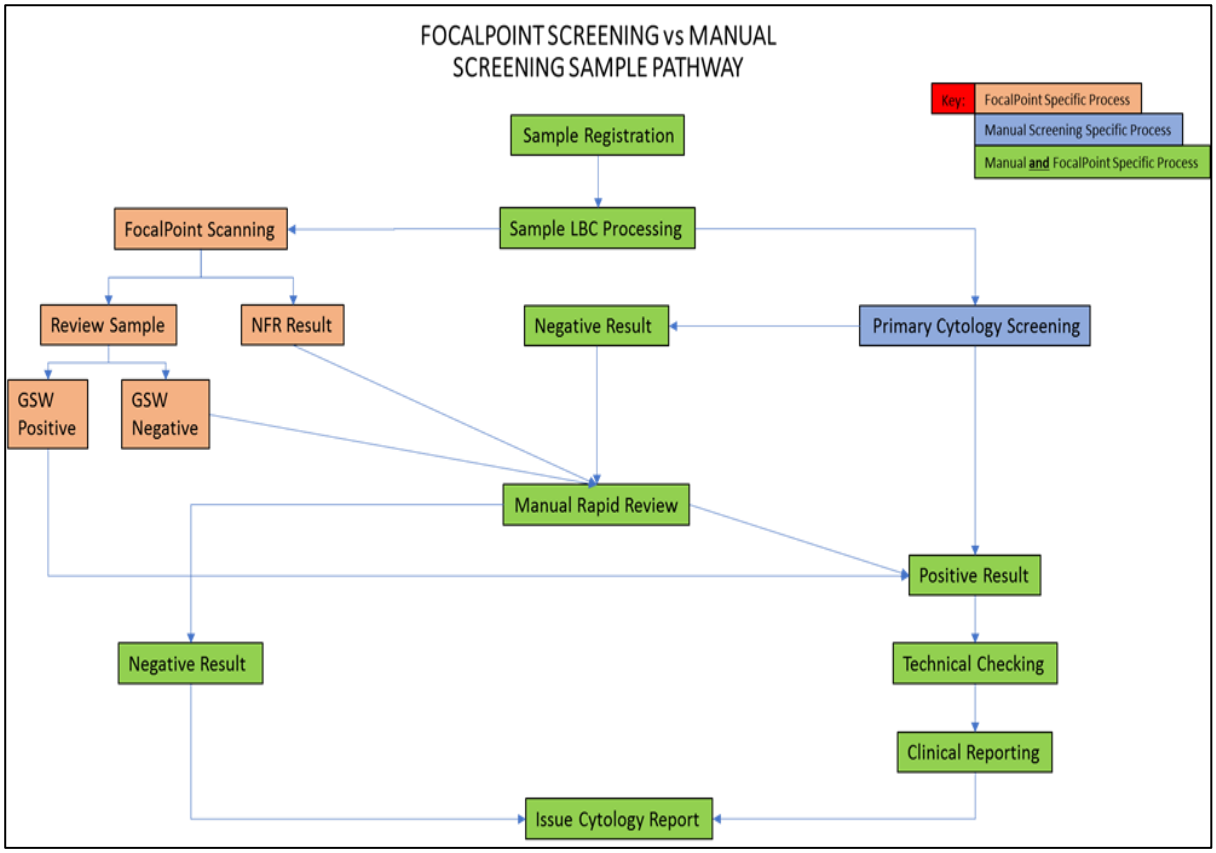


Figure 2.11: FocalPoint™ GS Imager primary cytology screening mode pathway

The parameters evaluated in this comparison between screening technologies are:

- False Positive and False Negative rates

The results of these observations are presented in Table 3.8, Chapter 3, Section 3.3.2. and are discussed in comparison with other similar reports from other studies.

2.11.4. No Further Review (NFR) reporting category

As stated previously the FocalPoint™ NFR technology is a reporting category which is part of the sample scoring stratification function of the FocalPoint™ GS Imager for cases that have a very high NPP. No images are provided to the cytotechnologist and so, a cytological grade such as Atypical Squamous Cells of Uncertain Significance (ASCUS) or Low Grade Dyskaryosis (LGD) cannot be applied. All cases are designated negative and this means that sensitivity and specificity as KPI cannot be used for this technology.

The samples were received and processed in the manner already outlined and the sample pathway is illustrated in Figure 2.12. The numbers of NFR cases, compared to the total

scanned by FocalPoint™ and manually screened is presented in Table 2.2 below.

Table 2.2: Total numbers of cases scanned by FocalPoint, categorised as NFR and manually screened during the CAESAR studies

	CAESAR 1	CAESAR 2	CAESAR 3	Total
Cases scanned by FocalPoint	**12,976**	**21,538**	**10,803**	**45,317**
Cases designated as NFR by FocalPoint	**2,842**	**5,328**	**2,199**	**10,369**
NFR Cases with Histological outcome of CIN2+	**603**	**5,328**	**2,199**	**8,130**
Cases manually screened	**12,617**	**60,389**	**20,467**	**93,473**

Since over three years had elapsed since the project started issuing NFR negative reports, the author decided that a comparison of the interval outcomes of those cases compared to negative manually screened equivalents would be the most appropriate means to do so. Therefore, a search of all the NFR cases and manually screened cases that had presented with a CIN2+ (HSIL+) outcome within 2 and subsequently 3 years was initiated. These interval high grade outcome rates were compared and evaluated in this study.

As referred to in Section 2.11 (Data Collection), the CSW Information department were unable to gather data on the 3-year follow up of some of the cases assigned to NFR in CAESAR 1. Therefore, it was not possible to determine if any histological outcome was available, and so some of the CIN2+ histological outcome data was lost to the project. This was due to a coding anomaly on the laboratory (LLDNO) LIMS as the correct code was not applied in the early stages of the trial. As shown in Table 2.2 only 603/2,842 NFR cases were included in the NFR evaluation. The true total (2842) was calculated from a LIMS query searching for the incorrect code and confirmed by manual count of the NFR totals from the FocalPoint™ paper print output from each scan run.

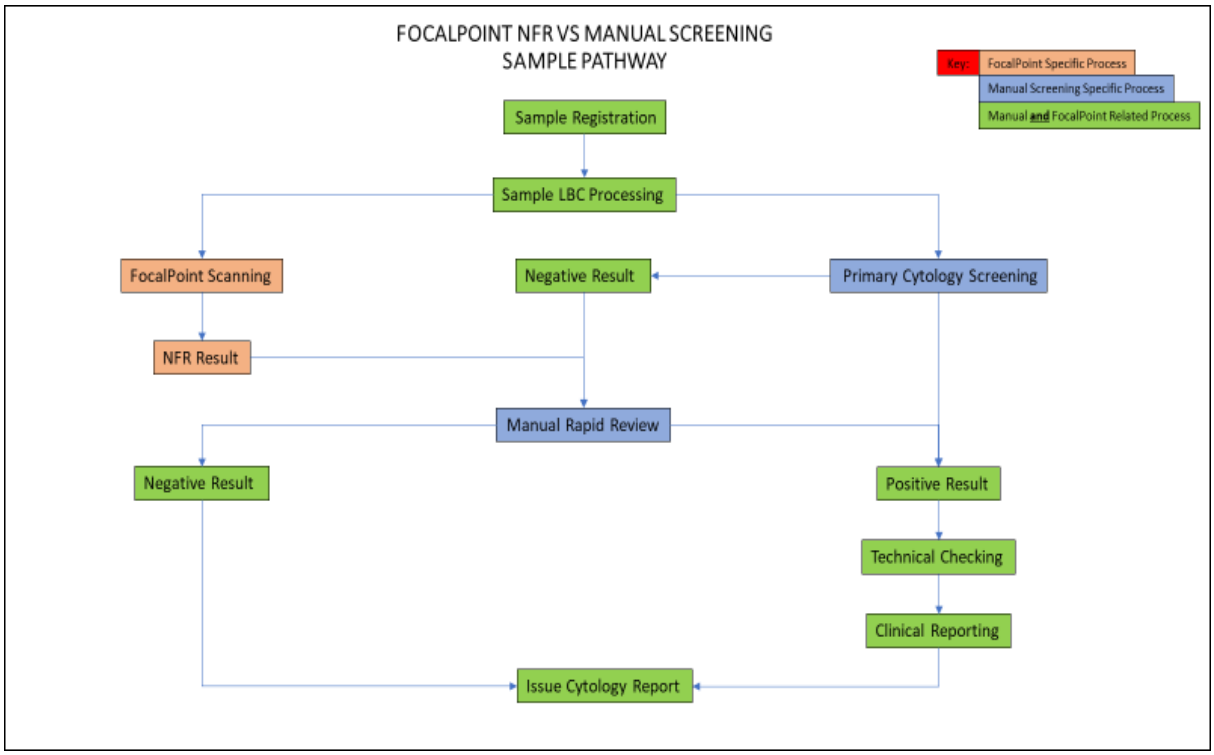


Figure 2.12: FocalPoint™ NFR and Manual Primary Screening Pathway

2.11.5. Automated detection of endocervical cells

In the UK, TZ sampling is monitored for sample takers in training and therefore it is important that an automated screening technology can detect and differentiate these cells as a quality indicator. In addition, it is important that endocervical cells are seen in follow-up samples for treated endocervical abnormalities, to provide additional assurance that the affected area has been successfully treated.

For those reasons, it is important that the FocalPoint™ is a) able to present these cells to the cytotechnologist and b) to be able to detect these cells reliably in NFR mode. Therefore, two questions were addressed in this application of the FocalPoint™ technology, thus:

1. Does the FocalPoint™ technology detect endocervical cells in a manner that is comparable to that detected by manual screening?

2. How consistent is the FocalPoint™ endocervical component detection rate between individual laboratories compared to manual screening?

To ascertain if the FocalPoint™ technology performed comparably to manual screening in

the detection of endocervical cells, a sample of 284 of the slides scanned were re-screened solely looking for endocervical cells and the results of the re-screen were recorded, along with the FocalPoint™ Endocervical Component detection status.

To ascertain the consistency of laboratory transformation zone detection rates on an inter-laboratory basis, the transformation zone detection rates from three of the participant laboratories (Llandudno, Glan Clwyd and Wrexham Maelor Hospitals) were compared to the FocalPoint™ Endocervical Component detection status. The results are presented in Chapter 4, Section 4.5.1, (Table 4.8).

2.11.6. Economic Analysis

The FocalPoint™ technology has the potential to deliver productivity gains and therefore cost and throughput benefits for laboratory cervical screening and this was commented upon by the LREC in their feedback (Appendix 3). An Economic Analysis (EA) was therefore carried out to estimate the potential costs and benefits to the laboratory cervical screening service. The approach taken proposed that unit costs were calculated for each cost generating event and compared. Costs thus calculated refer to the NHS cervical screening programme in Wales during 2014-15 and are derived using the NHS Agenda for Change (Agenda for Change – Pay Rates) pay index to arrive at total costs per slide and per woman screened.

The Health Technology Assessment (MAVARIC, Kitchener *et al*. 2011) study looked at the following cost generating events:

- Staff time to load and unload automated equipment
- Average time for primary screening
- Average number of slides screened per day
- Average workload per year per cytoscreener
- Average total time per slide for reading (including checking/consultant pathologist or consultant biomedical scientist review)
- Other organizational factors potentially influencing productivity

In this study, it became evident that several cost generating events are common to both CAS

and manual screening processes - such as sample reception, data entry and clinical reporting. As these processes are required whatever pathway the sample follows then it was assumed that their cost is a constant across all pathways. Therefore, the approach taken in this study was to identify the cost generating events that are specifically associated with CAS and manual screening and calculate their costs. In this manner, it will be possible to calculate differences in cost effectiveness between the two processes.

If a potential application of the FocalPoint™ was found to be inferior in performance to the manual equivalent, then it was not considered in the economic analysis unless there were compelling reasons to do so, for example unsustainable workforce to maintain manual services.

Plan for the Economic Analysis:

1. Established which areas of service operation that an EA is applicable to and then established if FocalPoint™ is comparable/superior to manual screening in those areas:

a. NFR – results indicate that this feature of the FocalPoint™ technology is at least equivalent and arguably superior to manual primary screening.
b. The 10 FOV feature of the FocalPoint™. This feature was evaluated and found not to be as sensitive and specific in comparison to manual primary screening.
c. FocalPoint™ as a rapid quality assurance tool for manual primary screening. This application was evaluated and found to compare favourably with manual rapid QC processes.
d. The application of CAS is most likely to be a combined and holistic combination of all suitable applications.

2. Parameters/variables for consideration as part of the EA:

a. Individual screener slide screening output. We know from departmental individual performance data that 5000 slides per whole time equivalent (WTE) is achievable per individual. A WTE screener is available for work:

365 (days a year) - (52 weekends or 104 days) -30 (days holiday per annum)- 8 Bank Holidays per annum) = 231 days a year. Average screening output is therefore 5000/231 = ***22 slides per day****.*

b. In the UK cytology screeners are only permitted to screen up to 5 hours a day under NHS Cervical Screening Programme guidelines (NHS CSP Publication No. 14, 2003).
c. All-Wales laboratory staffing costs including on-costs.
d. All-Wales actual workload data (2013-14).
e. FocalPoint Managed Service Contract (MSC) lease costs.

From these costs, we can derive the following process costs:

f. Manual screening of a sample, including the rapid QA screen.
g. FocalPoint™ scanning per sample, including the rapid QA screen.
h. Manual screening of a sample, including the rapid QA screen and FocalPoint™ scanning.

From the laboratory quality perspective, it is important that the functionality of CAS remains comparable to manual screening. For example, in the detection of endocervical cells so that the monitoring of smear taker performance is maintained. If any functionality is lost, then the service needs to evaluate the loss in terms of the overall acceptability of CAS. This issue is discussed fully in Chapter 6 – Discussion.

2.11.7. Screener acceptance of the FocalPoint™ GS technology

Cytology screener perceptions of the CAS technology were recorded and evaluated to see if acceptance (or not!) of the technology had any positive or adverse effects on implementation in the workplace. To gain a consistent approach for evaluating user opinion and comment, a questionnaire was circulated to laboratory staff via the FPOG members as a means of collecting these opinions so that user acceptance could be estimated.

The questionnaire (reproduced in Appendix 12), was designed to collect the following data for comparison/evaluation:

- Staff grade
- How long the individual used the FocalPoint™ technology

- Years of experience working in Cytology
- How the individual found the training provided for using the FocalPoint™ technology
- How could the training be improved?
- Did you prefer using automated to manual screening?
- Did you find it was easier to concentrate using the automated system compared manual screening?
- Did you find that it was more challenging to use the automated system than manual screening?
- Was it more monotonous to use the automated system than manual screening?
- Is there any physical discomfort in using the manual system compared to the automated system – yes or no? If "y", please specify - (noise, strain, motion sickness)

2.11.8. FocalPoint™ GS Imaging and HPV testing

As discussed in the Introduction, following the implementation of the FocalPoint™ NFR technology by Cervical Screening Wales, there followed the introduction of Human Papillomavirus (HPV) testing for Test of Cure (ToC) following the treatment of high grade CIN and for the Resolution of Uncertainty (ROU), for example, with persistent low-grade abnormalities, as aids to the management of screening participants in a colposcopy setting.

During this period, HPV testing using the Qiagen Hybrid Capture 2 (HC2) technology and FocalPoint™ scanning of samples were carried out simultaneously and an internal audit of FocalPoint™ and HPV test results was carried out in an anonymised fashion.
By carrying out this audit, the author hoped to establish if any relationship existed between the FocalPoint™ scan results and HPV positivity, or not. A sample of 128 cases were included in the audit and the results are presented in Chapter 5, Section 5.3, Table 5.10.

Chapter 3

FocalPoint™ performance for Rapid Quality Assurance and Primary Screening

3.1. Project Overview

The total number of samples manually processed during all three CAESAR studies was 137,806 - of which 45,317 were successfully scanned by the FocalPoint™ technology. The number of samples scanned and screened over the three CAESAR study periods were as follows:

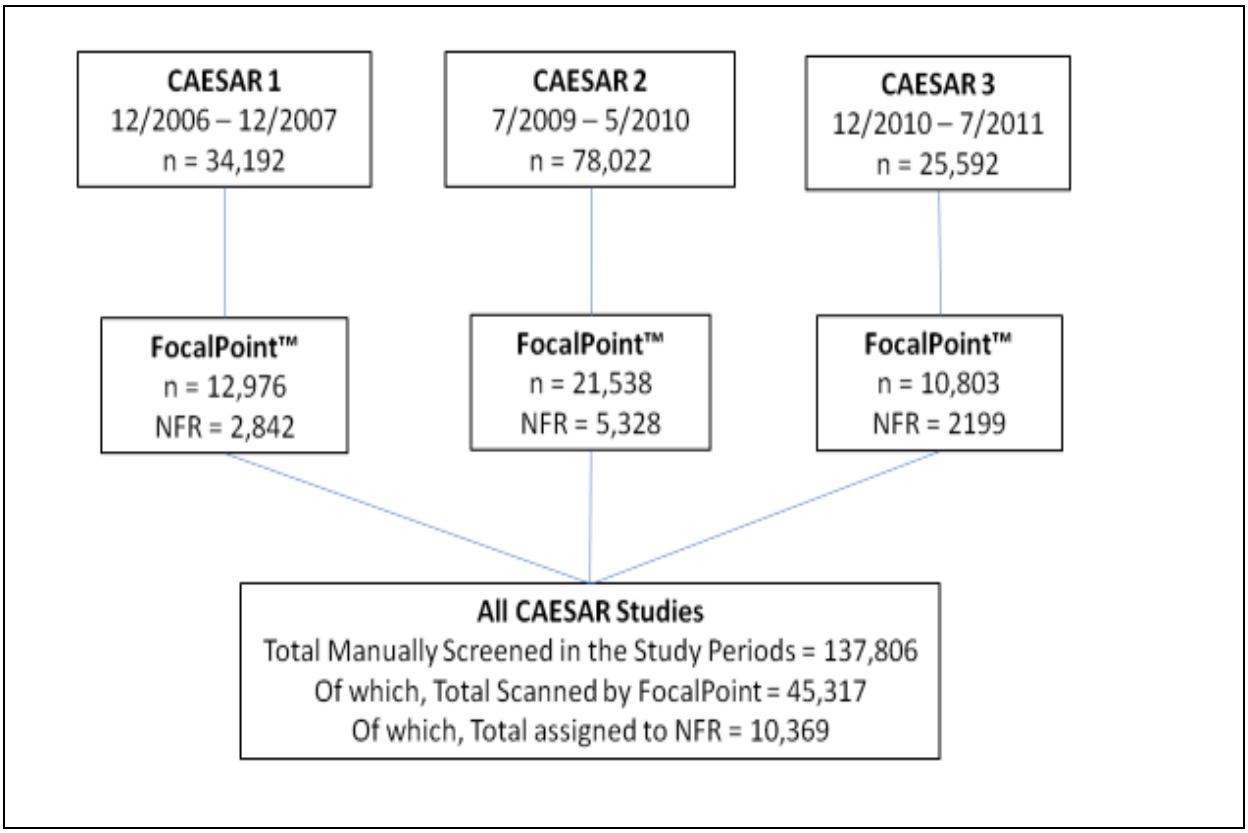


Figure 3.1: CAESAR study periods, total manually screened and scanned by FocalPoint™

Of the 10, 369 FocalPoint™ scanned cases that were assigned to the NFR reporting category, only 8130 could be followed up for three years to determine if any histological outcome was available. This was due to a data coding error at the laboratory concerned and is discussed in greater detail in Chapter 2, Material and Methods, Section 2.12.4 and Table 2.2.

The samples were collected and processed by several Laboratories participating within Cervical Screening Wales, Table 3.1, thus:

Table 3.1: Total samples processed, by participating laboratory

Laboratory	CAESAR 1	CAESAR 2	CAESAR 3	Total
Llandudno	13,230	14,689	0	27,919
Glan Clwyd	12,343	12,636	0	24,979
Wrexham	8,619	13,422	0	22,041
Royal Gwent	0	37,275	25,592	62,867
Total	34,192	78,022	25,592	137,806

Cytological outcomes of all the samples screened routinely and included in the study were recorded and are summarised in Table 3.2.

Table 3.2: Total samples processed by cytological outcome

Cytology	CAESAR 1	CAESAR 2	CAESAR 3	Total
Inadequate	546	1,168	230	1,944
Negative	31,035	69,507	23,254	123,796
Low Grade Dyskaryosis	2,191	6,075	1,743	10,009
High Grade Dyskaryosis	420	1,272	365	2,057
Total	34,192	78,022	25,592	137,806

Of the 137,806 samples routinely screened, 45,317 samples were sent for scanning by the FocalPoint™ technology. 92,489 samples were not scanned for the logistical reasons already discussed in this thesis. The cases that were scanned by FocalPoint™ in the project originated from the participating laboratories as detailed in Table 3.3.

Table 3.3: Total samples scanned by FocalPoint™, by participating laboratory

Laboratory	CAESAR 1	CAESAR 2	CAESAR 3	Total
Llandudno	5,741	9,163	0	14,910
Glan Clwyd	3,336	2,294	0	5,630
Wrexham	3,893	4,974	0	8,867
Royal Gwent	0	5,107	10,803	15,910
Total	12,976	21,538	10,803	45,317

The cytological outcome (by routine manual screening) of those samples scanned by the FocalPoint™ technology was recorded and is presented in Table 3.4.

Table 3.4: Total samples scanned by FocalPoint™, by cytological outcome of manual screening

Cytology	CAESAR 1	CAESAR 2	CAESAR 3	Total
Inadequate	207	346	99	652
Negative	11,850	19,307	9,828	40,985
Low Grade Dyskaryosis	777	1,598	732	3,107
High Grade Dyskaryosis	142	287	144	573
Total	12,976	21,538	10,803	45,317

3.2. Sample Processing Considerations

3.2.1. FocalPoint™ Process Review

Some slide preparations are rejected by the FocalPoint™ because of technical inconsistencies such as coverslipping problems, barcode read failures and so on. These invalid results are reported by the FocalPoint™ as the Process Review rate (PRV Rate). The PRV rates were investigated during the CAESAR 1 project phase and the results are presented in Table 3.5.

Table 3.5: Process Review rates reported during the CAESAR 1 study

Laboratory	Samples Scanned	Samples to PRV	PRV Rate (%)
Llandudno	5749	253	4.40
Wrexham	3337	198	5.93
Glan Clwyd	3897	69	1.80
Total	12983	520	4.04

The low result experienced by the Glan Clwyd laboratory is associated with the use of an automated slide coverslipper using coverslip tape. This makes for more consistent slide preparations which the FocalPoint™ scanning mechanism is less likely to reject. For workload throughput calculations, the Process Review rate was set at 4.0%.

3.2.2. Re-Run Samples

If a slide fails the system integrity test the FocalPoint™ reports that the slides cannot be read and the term "re-run" is reported against the case in question on the FocalPoint™ run report (Chapter 1, Section 1.5.3.2), This error code may also be reported for other system integrity failures which potentially compromise the scanning process on a slide.

3.3. Rapid Quality Assurance Screening -

Comparison between FocalPoint™ and manual operator of time taken to rapid screen a slide

In this section, the use of the FocalPoint™ system was assessed for rapid quality assurance screening. The FocalPoint™ provides several automated reports including an average time to examine 10 FOV by each operator. These results are summarised in table 3.6 for slides scanned by FocalPoint™ during the CAESAR 1 phase of the study. These results were then compared to the average manual QA screening time averaged over a total of 2159 slides and the results are presented in Table 3.7.

From the results presented in Tables 3.6 and 3.7, it is seen that the overall time taken to perform a rapid QA screen a slide is reduced by 13 seconds a slide when FocalPoint™ was used.

Table 3.6: Average time to examine 10 FOV (CAESAR 1)

Laboratory	No. of Slides	Time Range *from*	(min:sec) *to*	Mean time (min:sec)
LLandudno	5,747	00:02	18:03	01:26
Wrexham	3,336	00:03	22:58	01:26
Glan Clwyd	3,893	00:02	17:18	01:23
Average				**01:25**

Table 3.7: Average time to manually Rapid QC a slide (CAESAR 1)

No. of Slides	Time Taken (mins)	Time/Slide (min:sec)
2159	3596	**01:38**

3.3.1. Comparison of manual to automated rapid quality assurance screening performance

The FocalPoint™ LGS rapid QA screen outcome was compared to the final cytology report and the findings are presented in Table 3.8. From this data, the sensitivity of the LGS rapid screen was calculated for high grade dyskaryosis (HGSIL), low grade dyskaryosis (LGSIL) and all dyskaryosis (all SIL) findings.

A parallel exercise was carried out for manual rapid preview screening and the results are presented in Table 3.9. The respective sensitivities of both methods were subsequently compared.

Table 3.8: FocalPoint™ LGS Rapid QA data against manual cytology final report

Test Result	LGS neg	LGS Pos	F/N HG cases	Total HG cases	F/N LG cases	Total LG cases
1 Inadequate	138					
2 Negative	7,897					
8 Borderline	187	421			199	421
3 Mild dysk	41	284			47	284
7 Mod dysk	5	35	5	35		
4 Severe dysk	8	83	8	83		
5 ?Invasive Ca	0	5	0	5		
6 ?Glandular	1	5	1	5		
TOTAL	**8,277**	**833**	**14**	**128**	**246**	**705**

Summary of results:

Total of abnormal cases – all grades: **833**

Total of false negative cases – all grades: **260**

Sensitivity for high grade dyskaryosis =
Total HG positives/(Total HG positives + HG false negatives): **90.14%**

Sensitivity for low grade dyskaryosis =
Total LG positives/(Total LG positives + LG false negatives): **74.13%**

Sensitivity for all grades of dyskaryosis =
Total positives/(Total positives + Total false negatives): **76.21%**

Table 3.9: Manual rapid preview screen data against manual cytology final report

Test Result	MPS Neg	MPS Pos	F/N HG cases	Total HG cases	F/N LG cases	Total LG cases
1 Inadequate	925					
2 Negative	45,671					
8 Borderline	1,191	2,471			1,191	2,471
3 Mild dysk	326	1,329			326	1,329
7 Mod dysk	71	378	71	378		
4 Severe dysk	70	478	70	478		
5 ?Invasive Ca	3	28	3	28		
6 ?Glandular	11	36	11	36		
TOTAL	**48,268**	**4,720**	**155**	**920**	**1,517**	**3,800**

Summary of results:
Total of abnormal cases – all grades: **4720**
Total of false negative cases – all grades: **1672**
Sensitivity for high grade dyskaryosis =
Total HG positives/(Total HG positives + HG false negatives): **85.58%**
Sensitivity for low grade dyskaryosis =
Total LG positives/(Total LG positives + LG false negatives): **71.47%**
Sensitivity for all grades of dyskaryosis =
Total positives/(Total positives + Total false negatives): **73.84%**

From these results, the FocalPoint™ LGS results are marginally improved compared to the

manual rapid re-screen results. A summary of the sensitivities for rapid QA screening reported by other published peer reviewed reports is presented in Table 3.10.

The results from this study (CAESAR 2) are also included in the table for comparison and compare very well – exceeding the sensitivities of rapid QA screening results presented by other researchers.

Table 3.10: Summary of published results for sensitivity of rapid QA screening (for HG dyskaryosis+ (HSIL+) unless otherwise stated) compared to CAESAR manual and automated results

			Sensitivity		
Study	**Year**	**Total**	**Low**	**High**	**Average**
Faraker *et al*.	1996	9,517	82	91	**86.5%**
Brooke *et al*. HIGH GRADE	2002	86,881	54	92	**73%**
Brooke *et al*. ALL GRADES	2002	86,881	33	74	**53.5%**
Renshaw *et al*.	1999		38	89	**63.5%**
Tavares *et al*.	2008	6,135	71.3	92.2	**81.75%**
Djemli *et al*.	2006	8,364	15.4	72.7	**44.05%**
Patten *et al*.	1997	14,914	52		**52%**
CAESAR 2 automated HIGH GRADE	2010	8,277			**90.14%**
CAESAR 2 automated LOW GRADE	2010	8,277			**74.13%**
CAESAR 2 manual HIGH GRADE	2010	48,268			**85.58%**
CAESAR 2 manual LOW GRADE	2010	48,268			**71.47%**

3.4. Comparison of manual to automated primary screening performance

In the UK, the NHS cervical screening programme introduced the minimum performance standards for primary cytology screening sensitivity (NHS Cervical Screening Programme Publication No. 1, 2nd edition, 2000). The sensitivity for high grade dyskaryosis (HSIL+) was set at a minimum of 95% and at 90% for all grades of dyskaryosis.

These KPIs for primary screening sensitivity have recently been reaffirmed in the NHS England Service Specification No. 5 – NHS Cervical Screening Programme 2016-17. The sensitivity of manual primary screening by FocalPoint™ is therefore compared to these

minimum cervical screening programme requirements. As stated earlier, the restrictions placed by the NHS CSP on the use of CAS for primary screening meant that a full unrestricted evaluation of the 10 FOVs presented to the cytotechnologist by the FocalPoint™ was not possible and so the sensitivity of the technology in full primary screening modality is not available. For the purposes of this study, therefore, the sensitivities for high grade dyskaryosis and all grades of dyskaryosis achieved by the operator by examination of 10 FOVs only is compared to the minimum national standard in Table 3.11, below.

Table 3.11: Comparison of the sensitivity of 10 FOV presented to cytotechnologists by FocalPoint™ compared to NHS CSP national minimum standards

Sensitivity for primary cytology screening	Value
NHS CSP minimum sensitivity – high grade dyskaryosis	**>95%**
NHS CSP minimum sensitivity – All grades dyskaryosis	**>90%**
FocalPoint™ sensitivity by 10 FOV – high grade dyskaryosis	**90.14%**
FocalPoint™ sensitivity by 10 FOV – All grades dyskaryosis	**76.21%**

From the results presented in Table 3.11, it is evident that the sensitivity of the FocalPoint™ 10 FOV presented to the cytotechnologist by the LGS does not meet the minimum requirements of the NHS CSP for primary cytology screening. Furthermore, when these values for the individual laboratories sensitivity for manual primary cytology are examined along with the FocalPoint™ results, they are appreciably reduced in comparison (Table 3.12).

Table 3.12: Comparison of the sensitivity of 10 FOV presented to cytotechnologists by FocalPoint™ to that of manual screening in the participant laboratories during the CAESAR studies

	Sensitivity High Grade Dyskaryosis	Sensitivity All Grades of Dyskaryosis
Manual screening – All Laboratories	**98.49%**	**87.12%**
FocalPoint™ LGS – All Laboratories	**90.14%**	**76.21%**

As a further analysis, the 2 and 3-year interval outcome data of those FocalPoint™ 10 FOV that were reported as negative for dyskaryosis were identified and compared to similar outcomes for manual primary screening. The results are presented in Table 3.13 below.

Table 3.13: CIN 2+(HSIL+) cases at 2 and 3 years for FocalPoint™ LGS 10 FOV vs. manually screened negative samples

Outcomes	LGS 10 FOV Total samples = 19,655	Samples manually screened as per existing CSW SOPPs Total Samples = 93,473
CIN 2+(HSIL+) cases @ 2 years	**74**	**208**
Percentage (of total) @ 2 years	**0.376%** (95% CI 0.27% to 0.48%)	**0.22%** (95% CI 0.18% to 0.24%)
CIN 2+(HSIL+) cases @ 3 years	**105**	**366**
Percentage (of total) @ 3 years	**0.534%** (95% CI 0.35% to 0.72%)	**0.39%** (95% CI 0.35% to 0.43%)

There were 74 cases of CIN2+ (HSIL+) detected after 2 years following a negative screening result by the FocalPoint™ LGS compared to 208 following the issue of a negative result by the manual arm. This constitutes 0.376% of the total number screened by LGS and 0.22% of the total screened via the manual arm. It follows that the LGS screen is therefore not equivalent to the manual arm ($p = 0.101$).

When the data was refreshed and the histological outcomes at 3 years were examined, 105 cases of CIN2+ (HSIL+) were detected following a negative screening result by the FocalPoint™ LGS compared to 366 cases following the issue of a negative result by the manual arm. This is 0.534% of the total number screened by LGS and 0.39% of the total screened via the manual arm, further indication that the LGS screen is therefore not equivalent to the manual arm ($p = 0.240$).

The results presented in table 3.14 show that the number of histological interval outcomes of cervical pre-cancer cases for a negative FocalPoint™ LGS examination of 10 FOV exceed those of a manual primary screen over a 2-year period. After 3 years, the differential increases, a further indicator that the LGS screen is inferior to manual primary cytology screening ($p=0.093$ and $p=0.310$ at 2 and 3 years respectively).

With the cancer outcome cases, the differential is negligible at 2 years ($p = 0.978$) but by 3 years, there is a more pronounced difference, with LGS screening performance proving inferior to manual primary cytology screening at this state ($p=0.447$).

Table 3.14: Cancers and Pre-cancers at 2 and 3 years for FocalPoint™ LGS 10 FOV vs. manually screened negative samples

	LGS 10 FOV Total samples = 19,655		**Samples manually screened as per existing CSW SOPPs** Total Samples = 93,473	
	Pre-cancers	**Cancers**	**Pre-cancers**	**Cancers**
After 2 years	**72**	**2**	**198**	**10**
Percentage of total – 2 years	**0.366%** (95% CI 0.36% to 0.37%)	**0.01%** (95% CI 0.002% to 0.017%)	**0.199%*** (95% CI 0.17% to 0.23%)	**0.011%** (95% CI 0.006% to 0.02%)
After 3 years	**96**	**9**	**345**	**21**
Percentage of total – 3 years	**0.488%** (95% CI 0.46% to 0.51%)	**0.0457%** (95% CI 0.004% to 0.005%)	**0.37%** (95% CI 0.33% to 0.41%)	**0.022%** (95% CI 0.015% to 0.034%)

3.5. Observations on the relationship between FocalPoint™ Quintile Ranking and cytology outcome

From the CAESAR 1 data (n = 12982), the majority of abnormal cases were assigned to FocalPoint quintile 1, with correspondingly lower numbers assigned to the other quintiles. The lowest numbers were found in quintile 5 (Table 3.15).

Samples assigned to the 'No Quintile' category included:

- 510 (3.93%) samples reported as FPPRV (Process Review – sample could not be processed).
- 2842 (21.89%) samples reported as NFR.
- 60 (0.46%) samples that were unclassified or were not scanned due to bar-code read failure or omission.

Table 3.15:The distribution of final cytology test results within the FocalPoint™ Quintiles

Test Result	FP1	FP2	FP3	FP4	FP5	No Quintile	Total
1 Inadequate	10	35	18	38	80	26	**207**
2 Negative	1,454	1,676	1,772	1,773	1,943	3,236	**11,854**
8 Borderline	161	96	76	47	40	60	**480**
3 Mild Dysk	160	53	29	25	17	24	**308**
7 Mod Dysk	28	3	3	0	0	2	**36**
4 Severe Dysk	54	14	8	7	0	4	**87**
5 ?Invasive Ca	5	0	0	0	0	0	**5**
6 ?Glandular	1	2	1	1	0	0	**5**
Total	**1,873**	**1,879**	**1,907**	**1,891**	**2,080**	**3,352**	**12,982**
Percentage	**14.4%**	**14.5%**	**14.7%**	**14.6%**	**16.0%**	**25.8%**	**100%**

The final cytology results associated with the NFR category are presented in Table 3.16, below, by participating laboratory.

Table 3.16: NFR cases by laboratory and final cytology result

Test Result	Llandudno	Wrexham	Glan Clwyd	Total
1 Inadequate	6	0	5	**11**
2 Negative	1,242	695	757	**2,694**
8 Borderline	19	24	12	**55**
3 Mild Dysk	13	4	4	**21**
7 Mod Dysk	0	0	0	**0**
4 Severe Dysk	1	0	0	**1**
5 ?Invasive Ca	0	0	0	**0**
6 ?Glandular	0	0	0	**0**
Total	**1,281**	**723**	**778**	**2782**

When the final cytology outcome of the samples scanned in the CAESAR 1 phase of the study by FocalPoint™ quintile ranking is presented graphically, then it is apparent that the majority of the abnormalities fall into quintiles 1 and 2. Fewer cases are allocated to quintiles 3 and 4, with virtually no high-grade samples allocated into quintile 5 and NFR. Interestingly, the number of low grade (LSIL) cases allocated to NFR bucks this overall trend and increases

slightly. This is thought to be related to cases exhibiting koilocytosis – see Chapter 6, Section 6.4.2.1.

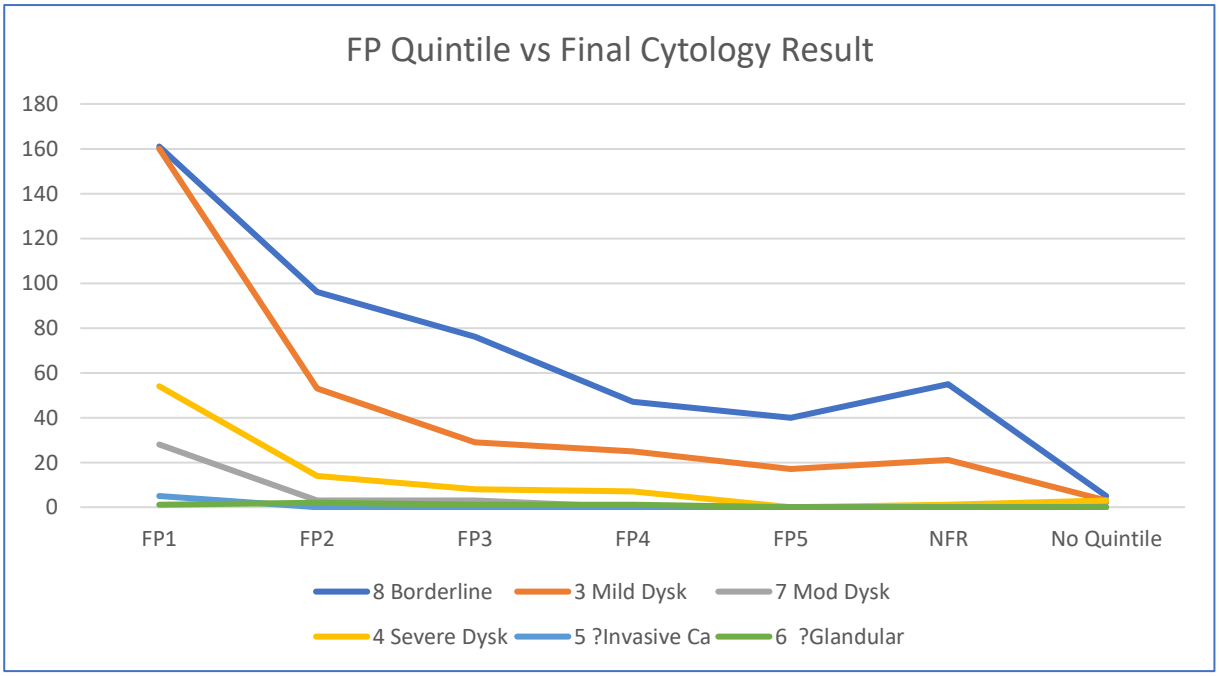


Figure 3.2: FocalPoint Quintile Ranking by abnormal cytology result

Chapter 4

Report on the NFR technology and the automated detection of endocervical cells

4.1. No Further Review (NFR) reporting category

This slide scanning result category is unique to the FocalPoint™ CAS technology. As detailed in the thesis introduction, no images from the scanned slides are presented to the user and this aspect of the CAS technology is worthy of assessment by virtue of the negative potential for cervical disease of the cases assigned to it.

Up to 25% of the cases scanned may be allocated to the NFR category and in the three phases of the CAESAR studies as a whole, from the 45,317 cases scanned using the FocalPoint™, 10,369 cases (22.9%) were classified as NFR. However, as detailed previously in the thesis, (Chapter 2, Section 2.12.4), due to a coding anomaly in one laboratory, only 8,130 cases were available for follow up for histological outcome. Therefore, some of the CIN2+ histological outcome data was lost to the project. In order to test the negative predictive potential of the technology, the interval outcomes of CIN2+ (HSIL+) of the 8,130 scanned samples assigned to NFR with follow up were compared to those of manually screened samples at 2 years and then subsequently at 3 years.

4.2. CIN 2+(HSIL+) disease outcome data for all CAESAR studies

Outcomes of CIN 2+(HSIL+) at 2 and 3 years of the samples designated by FocalPoint™ as NFR were compared to samples designated as negative by manual screening over the duration of the studies, results presented in Table 4.1.

The proportion of samples designated NFR by FocalPoint™ but subsequently presented as CIN2+(HSIL+) cases was approximately half that seen in those cases that were manually screened and reported during the study periods.

Table 4.1: CIN 2+(HSIL+) cases at 2 and 3 years for NFR vs. manually screened negative samples

Outcomes	NFR Total samples = 8,130	Samples manually screened as per existing CSW SOPPs Total Samples = 93,473
CIN 2+(HSIL+) cases @ 2 years	**9**	**208**
Percentage (of total) @ 2 years	**0.11%** (95% CI 0.05% to 0.21%)	**0.22%** (95% CI 0.18% to 0.24%)
CIN 2+(HSIL+) cases @ 3 years	**19**	**366**
Percentage (of total) @ 3 years	**0.23%** (95% CI 0.15% to 0.36%)	**0.39%** (95% CI 0.35% to 0.43%)

These levels are statistically significantly different (p=0.043 at 2 years and p=0.027 at 3 years). Note also that the overlap in the confidence intervals is less at 3 years when compared to that at 2 years.

4.3. Pre-cancer and Cancer outcome data for all CAESAR studies

Outcomes of pre-cancer and cancer cases detected amongst samples designated by FocalPoint™ as NFR compared to samples designated as negative by manual screening over the duration of the studies.

Table 4.2: Cancers and Pre-cancers at 2 and 3 years for NFR vs. manually screened negative samples

	NFR Total samples = 8,130		Samples manually screened as per existing CSW SOPPs Total Samples = 93,473	
	Pre-cancers	**Cancers**	**Pre-cancers**	**Cancers**
After 2 years	**8**	**1**	**198**	**10**
Percentage Of total – 2 years	**0.098% *** (95% CI 0.05% to 0.19%)	**0.012%** (95% CI 0.002% to 0.07%)	**0.199% *** (95% CI 0.17% to 0.23%)	**0.011%** (95% CI 0.006% to 0.02%)
After 3 years	**17**	**2**	**345**	**21**
Percentage Of total – 3 years	**0.21%** (95% CI 0.13% to 0.33%)	**0.025%** (95% CI 0.07% to 0.09%)	**0.37%** (95% CI 0.33% to 0.41%)	**0.022%** (95% CI 0.015% to 0.034%)

The pre-cancer outcome levels for NFR samples was half that of manual screening. This is statistically significant, (p=0.023 at 2 years and p=0.026 at 3 years). Cancer outcome rates were the same for NFR and manual screening at 2 and 3 years.

All cases designated as NFR were manually screened, and any false negative cases by NFR were reported by manual cytology. To model a working laboratory implementation of the CAS technology, this study compares positive incidental outcomes, so in effect, comparing the cases that were consigned to file for manual cytology reading and NFR, but subsequently presenting for further screening/investigation after 2 and then 3 years.

4.4. Unpredicted behaviour of the NFR technology

4.4.1. Finding of high grade cases categorised as NFR

During the CAESAR 1 phase of the study, the behaviour of the NFR reporting category had been entirely predictable, with only one high grade (finally reported as severe dyskaryosis/HSIL) case assigned by the technology to the NFR category (Table 4.3). This prevalence rate for high grade dyskaryosis (>moderate dyskaryosis) or HSIL was 1/2842 or 0.035%.

Table 4.3: Samples assigned to the FocalPoint™ NFR category by laboratory and final cytology outcome

	Llandudno	Wrexham	Glan Clwyd	TOTAL
Inadequate	6	0	5	**11**
Negative	1,242	695	816	**2,753**
Borderline	19	24	13	**56**
Mild	13	4	4	**21**
Moderate	0	0	0	**0**
Severe	1	0	0	**1**
? Invasive	0	0	0	**0**
? Glandular	0	0	0	**0**
TOTAL	**1.281**	**723**	**838**	**2,842**

However, during the CAESAR 2 phase, several occurrences of increased incidences of samples with a final report of high grade dyskaryosis were encountered within the FocalPoint™ NFR reporting category. The incidence levels experienced were significantly higher than those encountered previously and between January and March 2010, several FocalPoint scan runs were a cause of concern to the project (Table 4.4).

The incidence of high grade dyskaryosis cases allocated to NFR were several orders of magnitude greater than normally encountered, with 2 - 3 cases occurring in one run (Run 43,

Table 4.4), where normally only one would be detected over several runs. Source Bioscience Ltd. was contacted about this anomaly, and in turn contacted BD as the manufacturer of the FocalPoint™ GS Imaging System and notified them of the incident.

Table 4.4: Abnormal samples assigned to the FocalPoint™ NFR category by laboratory and final cytology and histology outcomes

Laboratory	Run No.	Cytology Result	Histology result
Llandudno	9	BNA/?HG	CIN3
	43	Severe Dyskaryosis	CIN3
	43	BNA/?HG	CIN3
	43	Severe Dyskaryosis	CIN3
	47	Severe Dyskaryosis	CIN3
	60	AGUS & Mod [6H,7]	CIN2
	60	Moderate Dyskaryosis	CIN3
	65	Severe Dyskaryosis	CIN3
	24	Severe Dyskaryosis	CIN 1
Royal Gwent	15	Moderate Dyskaryosis	Not available
	27	Moderate Dyskaryosis	CIN2

SBS and BD staff requested access to the slides concerned and arranged to meet at the laboratory. The slides concerned were examined by laboratory and representatives of the supplier on January 20th, 2010 and an action list was drawn up to facilitate further investigation of the issue. One of the actions involved photographing the slides and forwarding them to SBS and BD. Example images from the cases concerned are reproduced below (Figures 4.1 to 4.4).

BD carried out specialised diagnostic procedures via remote login to the system and on receipt of the images, commissioned a formal investigation into the incident, and an investigation plan was implemented. The resultant report concluded that there was an issue with the technology at that time - most likely to be related to its calibration in the setting of the LPCA.

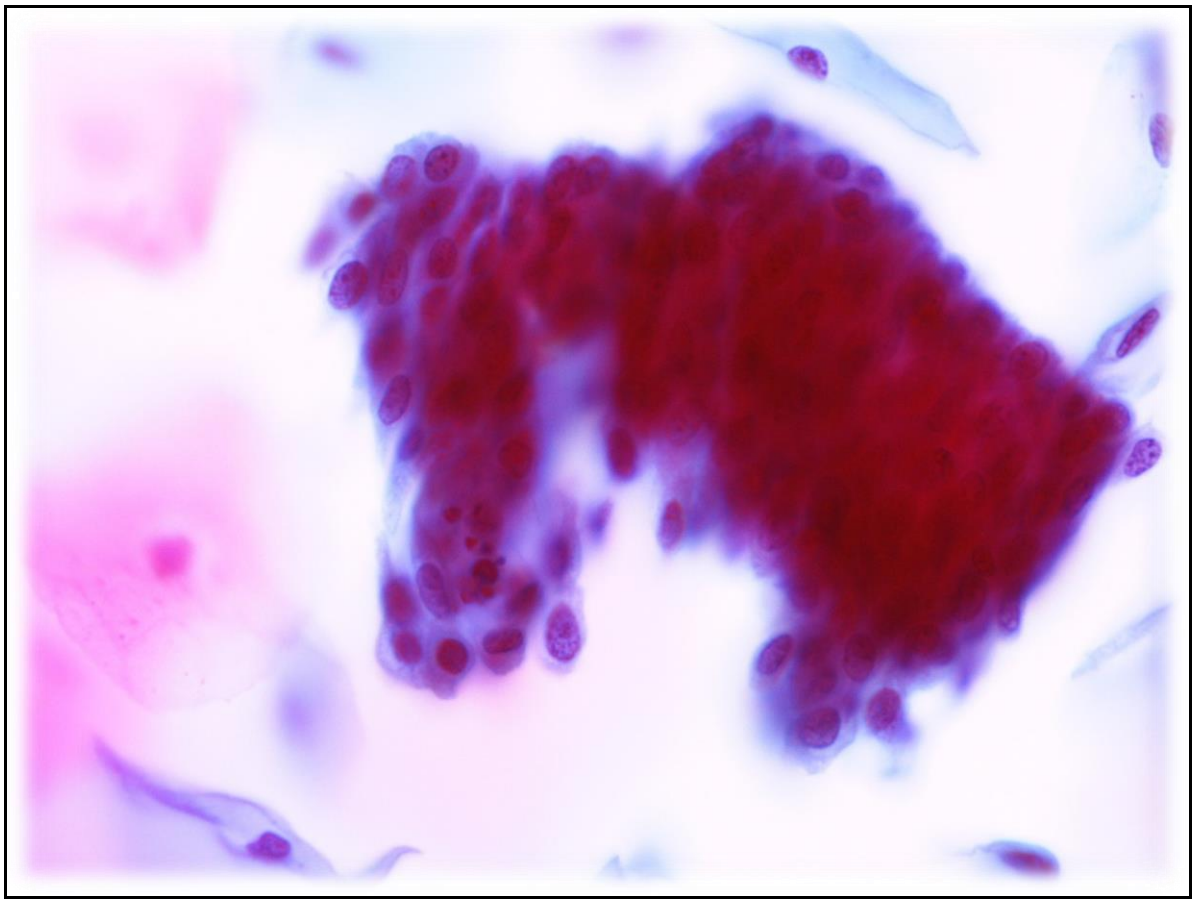


Figure 4.1: NFR case finally reported as high grade dyskaryosis. Microbiopsy. X40 objective

These images (Figs 4.1 – 4.4) illustrate typical features associated with the slides that were allocated into the NFR category. These features include:

- Dense microbiopsies with a steep edge relief and featuring anisonucleosis
- Dyskaryotic, small squamous cells typically seen in cases of severe dyskaryosis (HSIL)

The report by BD concluded that the FocalPoint™ instrument showed no malfunction following investigation of the instrument and examination of the images of the slides affected. The investigators had looked at the operation history of the instrument since the start of the project in February 2009, and system integrity was within the technical operating parameters required for the instrument.

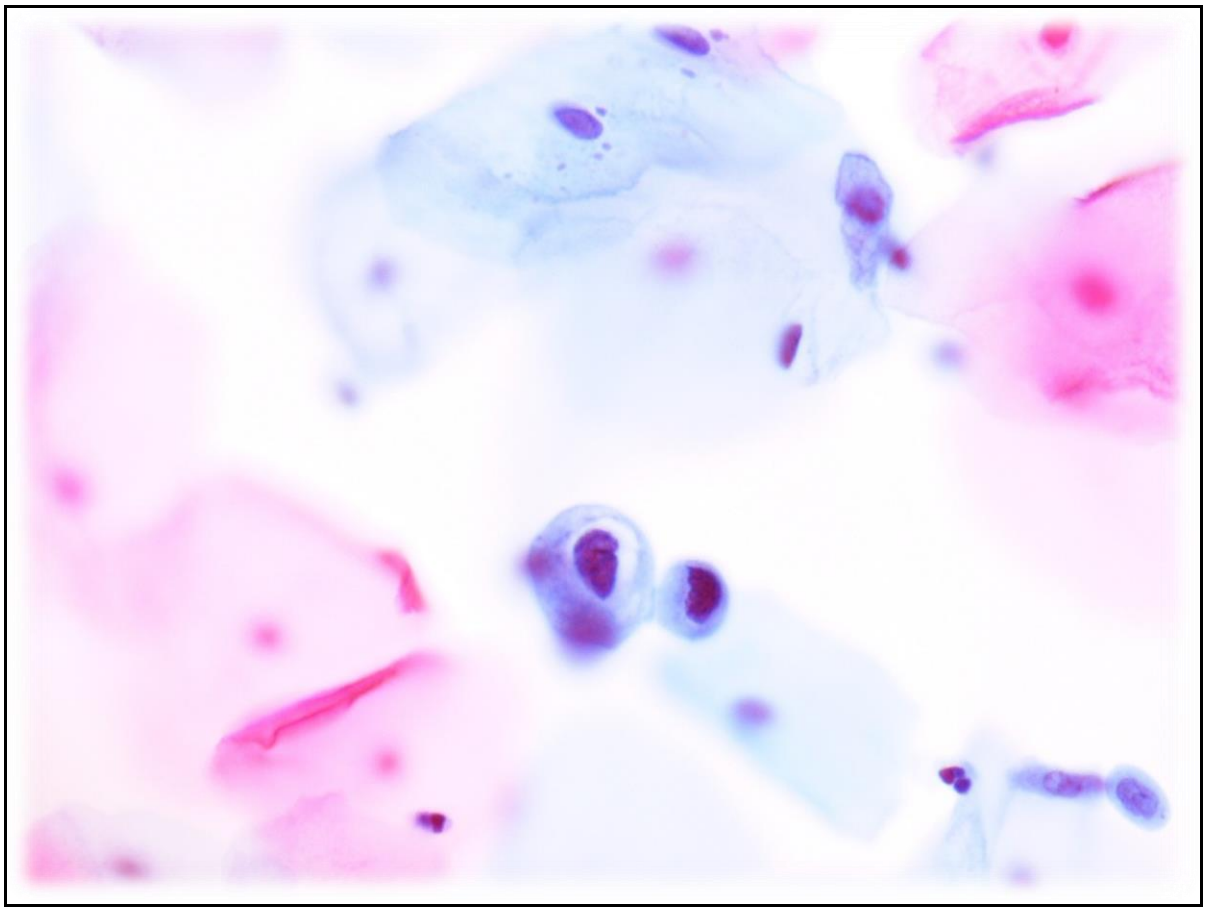


Figure 4.2: NFR case finally reported as high grade dyskaryosis. X40 objective. Individual dyskaryotic squamous cells are featured

It was noted that the calibration set by LPCA was carried out by initial scanning of 250 slides for each laboratory and changing the LPCA setting prior to scanning a new laboratory's work as per the current protocol. Following this initial calibration, a further LPCA calibration was carried out, using one single calibration by LPCA for all 4 laboratories. No further calibration had been carried out up to the reporting of the incident.

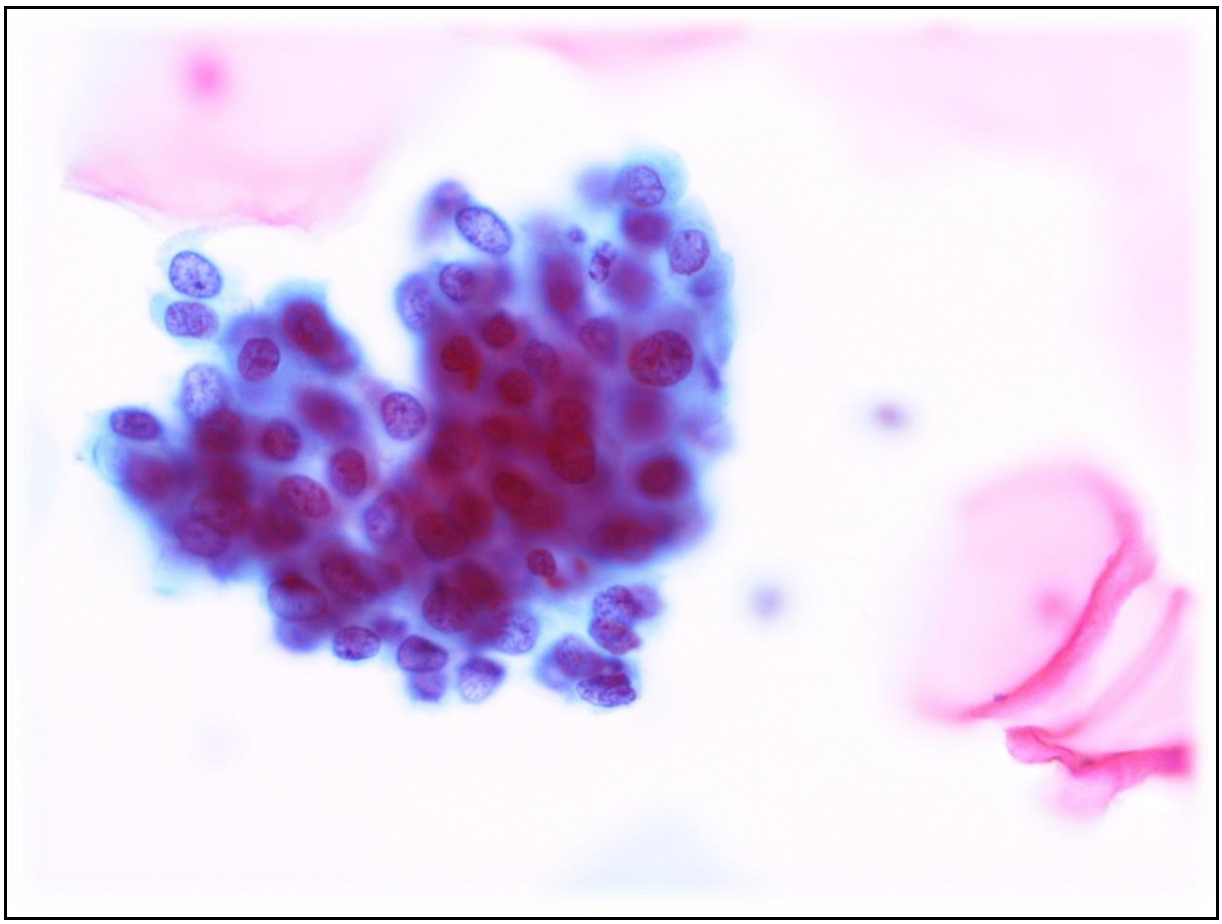


Figure 4.3: NFR case finally reported as high grade dyskaryosis. Microbiopsy. X40 objective

One reason cited for this change in calibration strategy was because one or more of the laboratories could not provide adequate numbers of slides for carrying out the calibration and so in carrying out a blanket LPCA, it was feasible that one or more laboratories might have experienced a shift in the prevalence of high grade cases, leading to a potential "misclassification" of high grade slides. As part of the investigation, BD reset the LPCA calibration and re-scanned a batch of 400 slides that contained 3 of the "misclassified" slides. The results were as follows:

- 1 slide classified as "re-run" so a repeat scan was required
- 1 slide was classified as quintile 5, with the associated 10 FOV
- 1 slide was classified again as NFR

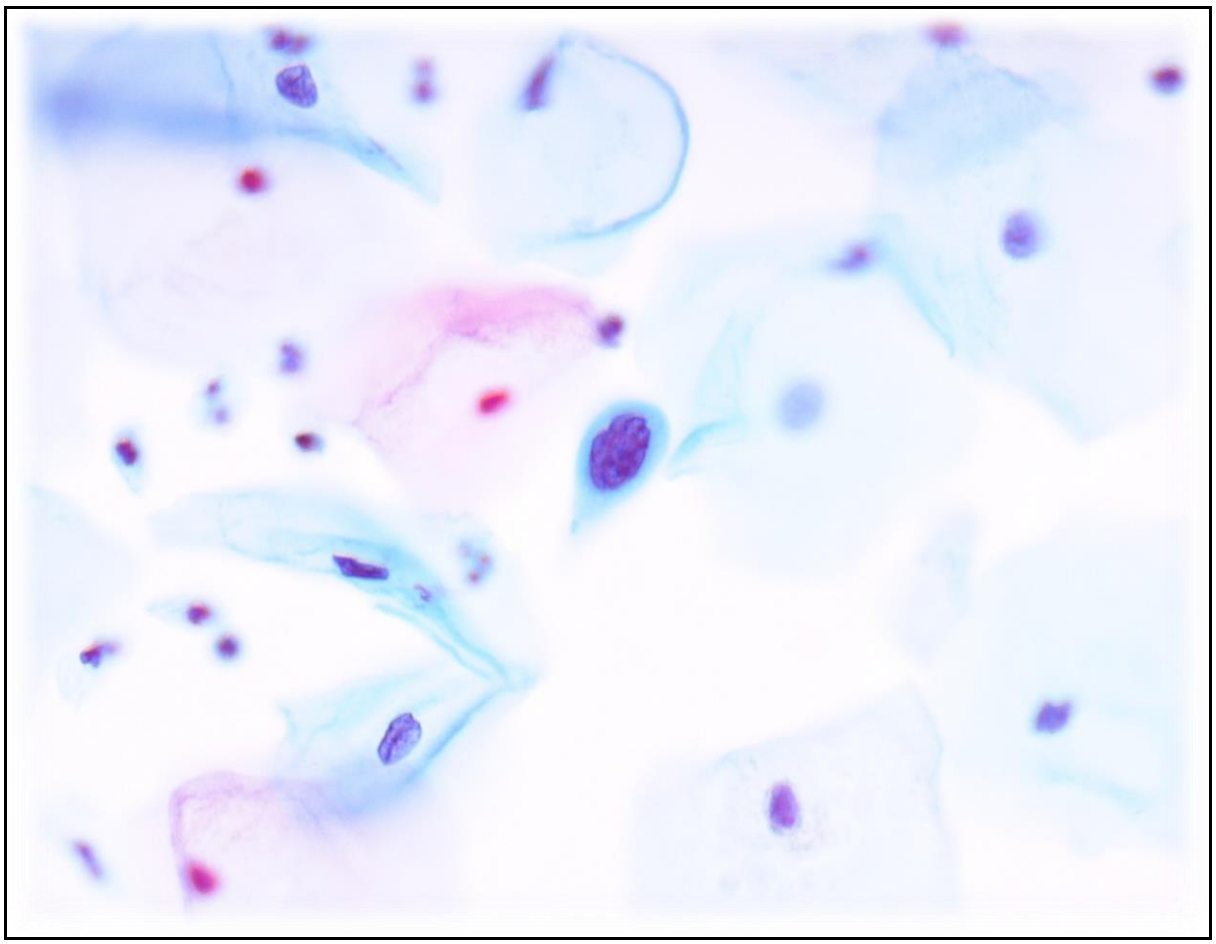


Figure 4.4: NFR case finally reported as high grade dyskaryosis. X40 objective. Single small dyskaryotic squamous cells are featured

When the instrument's NFR threshold was set to zero, all three slides produced **abnormal cells** in some of the FOV presented to the operator via the LGS (note that setting NFR technology to zero forces the instrument to produce 10 FOV for examination on **all** slides). By doing this, and because of abnormal cells being detected by the instrument in this mode, it is likely that the threshold for the detection of abnormality was set too high for the samples scanned.

4.4.2. Evaluation of the FocalPoint™ scanning workload and outcomes

To investigate this anomaly, those samples that were scanned and authorised between July 2009 and February 2010 were retrieved and the results were examined in greater detail to try and identify a cause for the increased number of samples classified as NFR.

Table 4.5: Total slides scanned by FocalPoint™ from July 2009 to February 2010

Laboratory	Scan Total
Llandudno	7,324
Royal Gwent	1,425
Wrexham	4,118
Glan Clwyd	4,065
TOTAL	**16,932**

During this time, 16,932 samples were scanned by the FocalPoint ™ GS Imager (Table 4.5). The prevalence of high grade cytology (>moderate dyskaryosis/HSIL+) between the participating laboratories is reported in Table 4.6.

Table 4.6: High grade cytology prevalence during the period of July 2009 to February 2010

Laboratory	Jul-09	Aug-09	Sep-09	Oct-09	Nov-09	Dec-09	Jan-10	Feb-10
Llandudno	1.52%	1.23%	1.44%	1.59%	1.71%	1.33%	1.39%	2.20%
Gwent		3.03%	0.43%	0.28%	0.00%	0.00%	0.20%	0.00%
Wrexham			0.92%	1.84%	1.48%	0.72%	1.26%	2.82%
Glan Clwyd	0.88%	2.06%	0.77%	1.37%	1.18%	0.96%	0.93%	1.84%

The total overall numbers scanned by the Royal Gwent Laboratory at this period in the study were relatively low - 1,425 cases, making the prevalence rates for high grade cytology rather unreliable (see highlighted row, Table 4.6). The prevalence rates for the detection of high grade dyskaryosis (HGSIL+) in the other laboratories was relatively consistent (Figure 4.5).

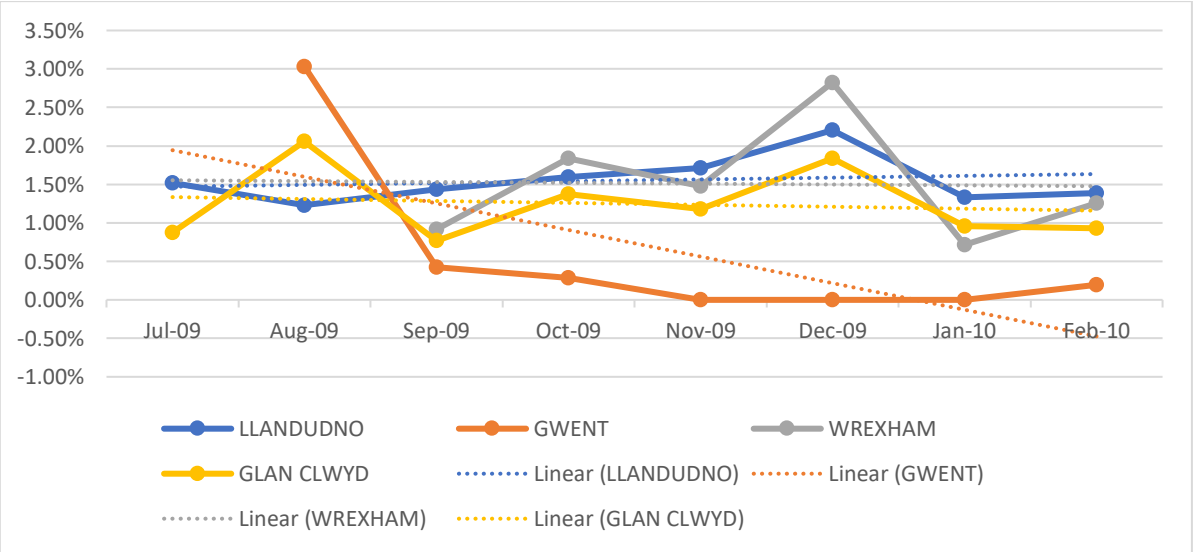


Figure 4.5: Comparative high-grade cytology prevalence July 2009 to February 2010

Note that, the low relative numbers of high grade samples for the Royal Gwent laboratory are not representative, as supported by the steep downward trend line in Figure 4.5.

When the number of NFR cases finally reported as high grade dyskaryosis or worse (HSIL+) are presented as a percentage of the NFR cases by month and laboratory, then the results presented in Table 4.7 and Figure 4.6 are seen.

To identify the laboratories having the greatest number of high grades as a proportion of the total NFR cases, those results with less than 5 NFR cases per laboratory per month were discounted from the findings due to the artificially raised result that a single high-grade case would have on the findings.

Note also that all the Royal Gwent laboratory results are set to zero because of the low scan numbers for this laboratory in this period. This resulted in the following findings:

Table 4.7: High grade cytology incidence in NFR cases/total number of NFR cases

Laboratory	Jul-09	Aug-09	Sep-09	Oct-09	Nov-09	Dec-09	Jan-10	Feb-10
Llandudno	0.00%	0.00%	0.00%	17.65%	5.56%	12.50%	0.00%	11.11%
Gwent	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%
Wrexham	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	11.11%
Glan Clwyd	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%

From the data presented in Table 4.8 and Figure 4.6, it can be seen that much higher numbers of high grade (>moderate dyskaryosis / HGSIL+) cases presented in the NFR category as a proportion of the total number of NFR cases for the Llandudno laboratory. Note also that both Llandudno and Wrexham laboratories' high grade slides/NFR category rates are increased between January and February 2010. This confirms the FocalPoint™ run data (Table 4.4) and indicates that the anomaly began to manifest itself as early as September 2009.

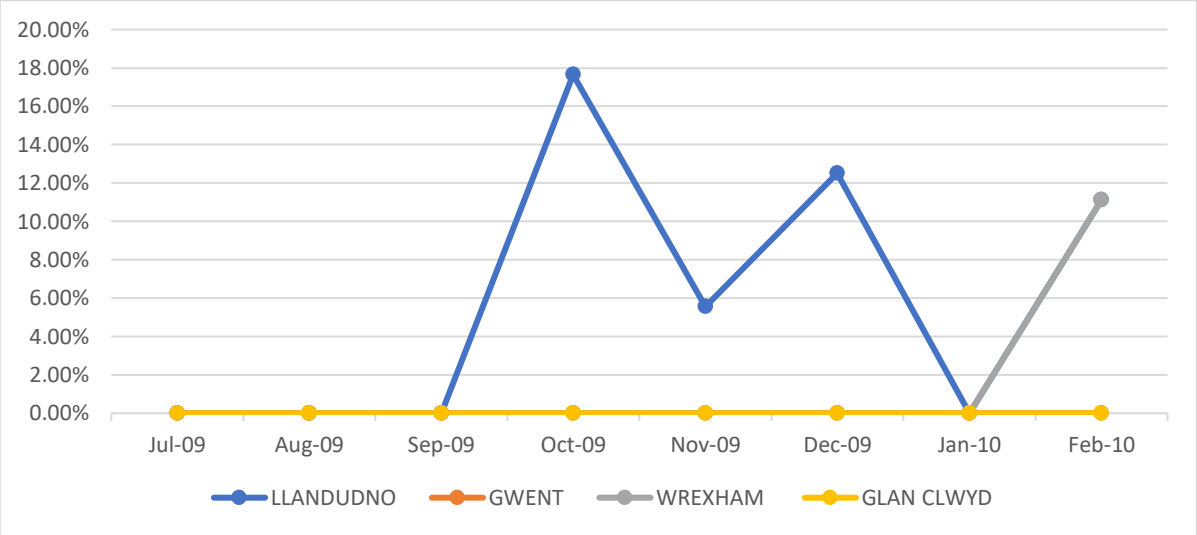


Figure 4.6: High grade cytology incidence in NFR cases/total number of NFR cases

Following on from this investigation and the issue of the report, BD responded to David Nuttall (PhD candidate) as the lead for the study detailing a revised protocol for carrying out the LPCA calibration. For future FocalPoint™ installations, the initial LPCA would be conducted on a scan of 1000 slides, not 250 as was previously the case. Additionally, ongoing instrument LPCA calibration checks against required parameters would be carried out continuously and feedback provided to laboratories if any anomalies were detected.

4.5. Evaluation of the automated detection of endocervical cells

The FocalPoint™ GS has the capability to identify slides that contain an endocervical cell component within the sample. As the presence or absence of this feature has traditionally provided a soft performance indicator for sample taker competence, it's presence or absence is often routinely recorded by laboratories for manually screened samples. A correlation was carried out between manual and automated screened samples to evaluate if the two arms were comparable in detecting endocervical cells in LBC samples.

4.5.1. Comparison of transformation zone reporting rates

During the CAESAR 1 study phase a comparison of transformation zone (TZ) reporting rates was performed – Table 4.8. From this table, FocalPoint™ endocervical component detection rates are much more consistent than manual TZ reporting, as confirmed by the respective standard deviation (SD) values.

Table 4.8: Consistency of manual TZ reporting versus FocalPoint endocervical reporting rates

Laboratory	Manual TZ Reporting Rates <50	Focal Point Endocervical Component Detection Rates
Glan Clwyd	81.0	84.7
Llandudno	96.5	81.5
Wrexham	85.4	78.4
Average	**87.6**	**81.5**
S.D.	**8.0**	**3.1**

Note that the manual TZ reporting rates are for women under 50 years of age because TZ detection is more reliable in this age group than in post-menopausal women. Compare these rates to those for all Welsh cytology laboratories (Table 4.9) and it is seen that there is a comparable range of detection rates with a slight reduction in standard deviation, but not as low as the SD for FocalPoint™ endocervical component detection rates.

This range of detection rates – from 96.5% to 76.8%, almost 20% difference between laboratories is a cause for concern as it means that the minimum 80% TZ detection rate for smear taker competency is inconsistently applied in different areas of Wales.

Table 4.9: All-Wales laboratory TZ detection rates

Laboratory	TZ <50	Total	% TZ <50
Bridgend	5658	7322	77.3
Royal Glamorgan	14000	15201	92.1
Llandudno	10617	10999	96.5
Llandough	22264	26485	84.1
Prince Charles	4914	6166	79.7
Royal Gwent	20674	26935	76.8
Shrewsbury Telford	2027	2469	82.1
Singleton	16902	19684	85.9
Withybush	4888	5122	95.4
Glangwili	11561	12988	89.0
Wrexham	8495	9953	85.4
Glan Clwyd	6907	8524	81.0
Average			**85.4**
S. D.			**6.7**

The smaller deviation between laboratories using the FocalPoint™ technology would be an advantage in this application, however, there remains the question of whether the FocalPoint™ endocervical cell component detection rate is comparable to the manual TZ screen or not. The results of a comparison of the results of rescreening a total of 284 slides, reporting on endocervical cells detected and the FocalPoint™ endocervical component are presented in Table 4.10.

Table 4.10: Level of agreement between FocalPoint™ endocervical component and manual detection of endocervical cells

FocalPoint™ +ve	Manual +ve	Total	Comments
Yes	Yes	184	Concordant
No	No	36	Concordant
No	Yes	33	Discordant
Yes	No	29	Discordant
Insufficient cells	No	2	Disqualified
	TOTAL	**284**	

4.5.2. Endocervical cell detection comparison - summary of results

- FocalPoint™ endocervical cell component reporting range = 78.4 – 84.7%, SD = 3.1
- Manual TZ component reporting range = 81.0 – 96.5%, SD = 8.0
- FocalPoint™ / Manual endocervical cell detection concordance: Cohen's kappa statistic (K = 0.78) – good agreement.

The intra-laboratory detection of endocervical component by FocalPoint™ is more consistent than the detection of TZ components by manual screening.

There is good correlation between endocervical component detection rate by the FocalPoint™ technology and manual detection of endocervical cells.

Chapter 5

Economic Analysis, Screener Acceptance of FocalPoint™ and comparison of FocalPoint™ results with HPV test results

5.1 Economic Analysis

This section presents the results of the cost-minimisation analysis carried out on a modelled implementation of the FocalPoint™ technology within the laboratory cervical screening service in Wales. As stated in Chapter 2, the modelling was carried out using data from 2013-14, which was representative of the laboratory service in its final configuration and most suited to a service implementation of the computer assisted technology.

The cervical sample pathway within the laboratory was mapped, and the areas of application of the FocalPoint™ identified. These applications were compared to their manual counterparts and compared for quality of results against standard KPIs and the results of these comparisons are presented in this chapter of the thesis.

5.1.1 Processes exempt from the EA

From the proposed process pathway (Figure 5.1), certain contributory processes are common to both the manual and the automated arms. These processes are identified by the text boxes that are filled in green, for example, sample data entry, technical checking and clinical reporting.

The volume of samples proceeding through each of these processes is the same irrespective of which strategy (automated or manual) is upstream or downstream of these common processes. Accordingly, it is assumed that they impact equally on both and therefore can be excluded from the overall economic analysis. This assumption that omits costs common to two interventions when comparing them is accepted practice in health economic analysis as described by Drummond *et al*, 2015.

In summary therefore, this analysis is not intended to provide an overall costing exercise, but rather to compare the differences between the alternative strategies and the resultant costs and operational benefits to the laboratory screening service.

5.1.2 Processes Included in the EA

At the outset of the project, it was proposed that an economic analysis be conducted on those applications of the technology that were applicable within the LBC sample screening pathway. For inclusion, these processes must be comparable, in terms of the quality of the respective results produced, to the existing manual equivalents in this process pathway.

The processes initially considered were:

- Rapid Internal QC
- Primary cytology screening by means of the FocalPoint™ NFR technology and LGS (Slide Wizard™) functions
- Primary cytology screening using the FocalPoint™ NFR technology only

From the results presented in Chapters 3 and 4, the FocalPoint™ technology **demonstrated non-inferiority** in the following functions:

- Rapid Internal QC
- Primary cytology screening using the FocalPoint™ NFR technology

The primary screening of LBC slides using the FocalPoint™ LGS (Slide Wizard™) feature **did not demonstrate non-inferiority** and was therefore excluded from the proposed laboratory cytology screening pathway model of choice (Figure 5.1). To create this model, the laboratory screening pathways illustrated in the algorithms presented in Chapter 2 (Figures 2.10; 2.11; 2.12) were incorporated into this single all-encompassing algorithm.

Only the automated processes that were of comparable quality (demonstrated non-inferiority) to manual equivalents were incorporated and thus formed the constituent procedures making up the model process pathway. The analysis calculated costs on the assumption that the volumes of tests processed down the various algorithms were equivalent to those observed over one year in Wales based on 2013-14 data.

5.1.3 Samples rejected by the FocalPoint™ GS Slide Imager

As discussed in previously in Chapter 3 (Section 3.2.1), some slide preparations are rejected by the FocalPoint™ because of technical inconsistencies such as coverslipping problems, barcode read failures and so on. These invalid results are reported by the FocalPoint™ as the Process Review rate (PRV Rate), and which were investigated during the CAESAR 1 project phase. For

the purposes of the economic analysis here, the PRV rate has been included as 4% in the calculations.

5.1.4 Workload data (for the year 2013-14, identified on an all-Wales basis

a. Workload:

- In Wales, approximately 220,000 cervical LBC samples were processed and primary screened by cytology.
- Of the 220,000 samples scanned by FocalPoint™, on average 4% were invalid due to aforementioned technical issues (PRV rate – see Section 5.1.3), resulting in approximately 96% (211,200) with a valid scan result.
- On average, 22.9% of all valid samples were categorised as NFR by the FocalPoint™, and so, 48,365 samples proceeded down that pathway. Following a manual rapid QC screen of these samples, 99.98% were finally authorised as "Negative, no abnormality detected".
- The remainder, some 162,835 samples were processed down the manual pathway, 92% of these samples were subjected to an automated Rapid QC screen before final authorisation as "Negative, no abnormality detected".

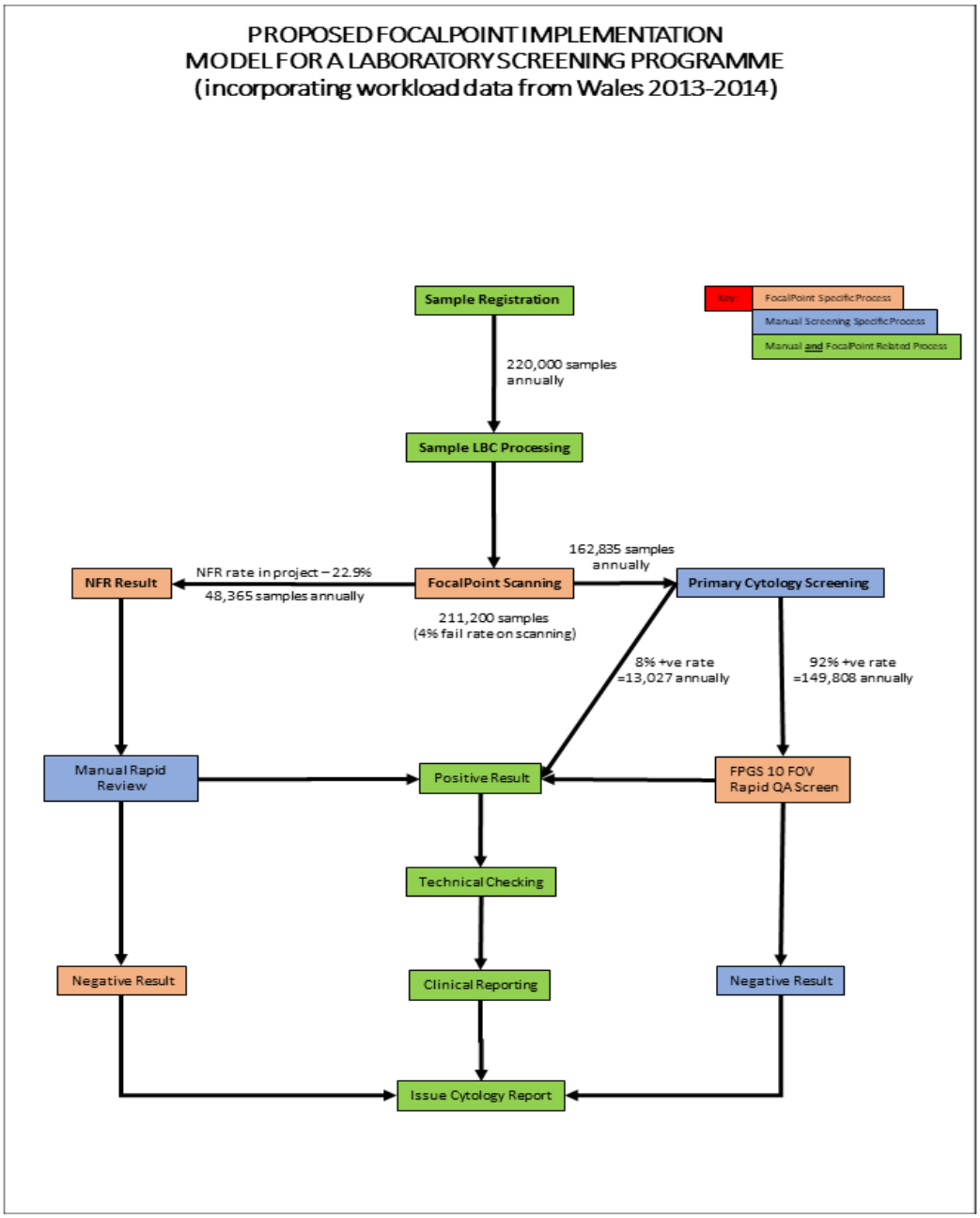


Figure 5.1: Proposed Laboratory Screening Pathway

b. Staffing:

The following staff were working within the laboratory cervical screening service in Wales in 2013-14. Staff are presented as whole-time equivalents (WTE) by NHS Agenda for Change (A4C – Agenda for Change Pay Rates) grade or band and salaries are calculated at mid-point of the salary scale with organisational on-costs added.

Table 5.1: Non-medical staff working within Cytology in Wales, 2013 -2014

A4C Grade	Mid-point	Including On-costs	WTE	Total Cost
Band 4	£20,638.00	£24,765.60	18.0	£445,780.80
Band 5	£24,799.00	£29,758.80	9.0	£267,829.20
Band 6	£29,759.00	£35,710.80	7.0	£249,975.60
Band 7	£35,536.00	£42,643.20	12.8	£545,832.96
Band 8a	£43,822.00	£52,586.40	1.6	£84,138.24
Band 8b	£52,235.00	£62,682.00	1.1	£68,950.20
			49.5	**£1,662,507.00**

a. FocalPoint™ Costs:

These were derived from the annual CSW equipment costs, projected where required, for the modelled workload/throughput - see notes, below.

Table 5.2: Annual FocalPoint™ costs

FocalPoint GS™ System Components	Cost
Annual Managed Service Contract for 3 x FocalPoint™ GS Imaging Systems	**£180,000**
8 x FocalPoint GS (Slide Wizard™) instruments and ancillaries/annum	**£240,000**
TOTAL	**£420,000**

Notes:

b. Each FocalPoint™ GS Imaging System has a nominal throughput capacity of approximately 120,000 to 140,000 samples per annum (manufacturer's data). Two instruments were installed initially; however, it was soon found that in the event of instrument failure, one single FocalPoint™ instrument lacked sufficient capacity to manage the total workload for the Welsh laboratory services, leading to a screening backlog situation. Following discussions with the supplier, three instruments were specified; at an annual cost of £60,000 each (2013 contract price).

c. Primary slide screening. Cytotechnologists can manually screen (primary screening) for up to 5 hours a working day (NHS CSP Publication No. 1). From the Welsh primary screening workload in 2013-14, 151,946 slides required a rapid QC screen (table 5.8). Because only 2 hours a day remain for rapid QC Screening (7.5 hours a day – 5 hours primary screening – allowing for breaks etc.) this equates to approximately 637 slides a day (based on annual Welsh workload). To enable the staff to manage this throughput at 1.42 minutes per slide (table 5.8) means that a minimum of 8 LGS stations would be required.

d. All instrumentation was leased as part of a Managed Service Contract (MSC) with the provider. All equipment prices are exclusive of Value Added Tax (VAT) as this is reclaimable in the UK from Her Majesty's Revenue and Customs (HMRC) when an MSC is implemented (terms and conditions apply).

e. The instruments will require daily attention such as "start of the day" checks, loading and unloading and filing of the slides. In practice, these tasks are minimal and as such are readily absorbed by the current processing staff in the laboratory.

5.1.5 Modelling and calculation of the cost of manual primary screening

Table 5.3 (below) presents the staffing establishment requirements to screen the 2013-14 Welsh cervical cytology workload to the professional standards required by the NHS CSP (NHS CSP Publication No. 1, 2013). For the purpose of this modelling exercise, these standards include:

- A maximum of 5 hours a day primary screening slides;
- A minimum of 3000 primary screened samples per annum to maintain screening competence.

In Wales, the minimum achievable output for a whole-time equivalent primary cytology screener was 5000 slides per annum. This output was consistently achieved by full-time staff and therefore adopted by the screening programme for workload/workforce planning purposes. The benchmark has proved to be robust for these purposes and is used as an achievable output in this cost-minimisation analysis.

Table 5.3: Annual staffing establishment required to screen Welsh workload in 2013-14 and costs

A4C Grade	TOTAL SALARY	Individual WTE	Total WTE	Total Cost
Band 4	£24,765.60	1.1	19.8	£490,358.88
Band 5	£29,758.80	1.1	9.9	£294,612.12
Band 6	£35,710.80	0.9	6.3	£224,978.04
Band 7	£42,643.20	0.6	7.7	£327,499.78
Band 8a	£52,586.40	0.1	0.2	£8,413.82
Band 8b	£62,682.00	0.1	0.1	£6,895.02
			43.95	**£1,352,757.66**

Notes:
Number of smears screened/individual/annum was set at 5,000
The staff cost of screening a smear under the assumption of no overtime (sum cost of the WTE/the **total number of samples) is £6.15 (£1,352,758/220,000).**

It is evident that values for individual whole-time equivalents presented in this table exceed 1.0 WTE for band 4 and 5 screeners. This is because there was (and still is) a national shortage of cytology screeners and screening slide backlogs often exist within laboratories. This situation was managed in Wales by staff working overtime and the excess establishment reported in the table reflects this situation. If the laboratory screening staff did not work overtime, then the total throughput for the staffing available would only reach 147,250 slides per annum – Table 5.4.

Table 5.4: Annual staffing establishment capacity in 2013-14 and costs

A4C Grade	Mid-Point	Individual WTE	Total WTE	Total Cost
Band 4	£24,765.60	0.67	12.06	£298,673.14
Band 5	£29,758.80	0.67	6.03	£179,445.56
Band 6	£35,710.80	0.67	4.69	£167,483.65
Band 7	£42,643.20	0.5	6.4	£272,916.48
Band 8a	£52,586.40	0.1	0.16	£8,413.82
Band 8b	£62,682.00	0.1	0.11	£6,895.02
			29.45	**£933,827.68**

Notes:
For modelling purposes, the number of smears screened/WTE/annum was set at 5,000. This reflects the number consistently achievable for a full-time individual working within the Welsh Cervical Screening Programme. The total annual output using this model was 147,250 samples screened.

The staff cost of screening a smear under the assumption of working within existing capacity without overtime is £6.34 (£933,827.68/147,250).

During 2013-14 in Wales, overtime working was required to maintain the timeliness standards of the Welsh cervical screening programme – Cervical Screening Wales. Overtime salary rates for A4C paid staff in the UK is generally set (unless local agreements have been negotiated) at "time and a half" - 1.5 times the normal hourly rate. Under the A4C regulations, overtime payments at this enhanced rate only routinely apply to band 4-7 staff only. The following table (5.5) illustrates the cost of overtime to screen the backlog slides.

Table 5.5: Staffing model and costs for samples screened via overtime working

A4C Grade	TOTAL SALARY	Individual WTE	Total WTE	Total Cost	TOTAL COST * 1.5
Band 4	£24,765.60	0.43	7.74	£191,685.74	£287,528.62
Band 5	£29,758.80	0.43	3.87	£115,166.56	£172,749.83
Band 6	£35,710.80	0.23	1.61	£57,494.39	£86,241.58
Band 7	£42,643.20	0.1	1.28	£54,583.30	£81,874.94
Band 8a	£52,586.40	0	0	£0.00	£0.00
Band 8b	£62,682.00	0	0	£0.00	£0.00
			14.5	**£418,929.98**	**£628,394.97**

Notes:
Number of smears screened during overtime = 72,500
Staff cost/sample screened with overtime = £8.67

From the data presented in the models already described, the following data can be derived:

- The total cost for manually primary screening LBC cases in Wales during 2013-14, including overtime, was (£933,827.68 + £628,394.98) = **£1,562,222.60**
- The staff cost per smear, therefore, is (1,562,222.60/220,000) = **£7.10**

5.1.6 FocalPoint™ GS Imaging system potential for improvement in laboratory throughput

From the modified process pathway proposed for laboratory cytology primary screening, the impact of the pathway can be compared to manual-only processes in two distinct areas, using the FocalPoint™ NFR technology for primary screening and using the FocalPoint™ LGS (Slide Wizard™) for the rapid QC of manually screened slides.

a. FocalPoint™ NFR Technology

The FocalPoint™ NFR technology can be implemented in a fully staffed department and can be used to primary screen slides that are screened in the normal working day, Monday to Friday. In this scenario, the NFR screen would replace screening at £6.34 per case, resulting in a potential labour cost saving of £306,634.10 per annum (Table 5.6), before any offsetting costs of the NFR technology has been considered.

Table 5.6: Productivity gain and associated cost saving realised using the NFR feature in the proposed cytology screening process pathway at normal time rates

Samples processed via NFR Pathway	48,365	Slides
Staff cost per slide – normal working time	£6.34	
Cost savings realised by using NFR (48, 365 * £6.34):	**£306,634.10**	**/annum**

Implementing the NFR technology in a department using overtime to manage a screening staff deficiency and slide backlog results in a greater cost benefit, as presented in Table 5.7. This is because the NFR technology can be used to offset a more expensive unit screening cost of £8.67.

Table 5.7: Productivity gain and associated cost saving realised using the NFR feature in the proposed cytology screening process pathway at overtime rates

Samples processed via NFR Pathway	48,365	slides
Cost of manual primary screening of slides via overtime working	£8.67	
Cost savings realised by using NFR (48,365 * £8.67):	**£419,324.55**	**/annum**

b. FocalPoint™ LGS feature

This application of the FocalPoint™ technology involves the use of the Location Guided Screening feature via the (Slide Wizard™) attachment to the screener's microscope. As described in the Chapter 2 of this thesis, in this FocalPoint™ modality, 10 FOV is presented to the operator, indicating the most potentially abnormal areas for scrutiny. The average time to view these FOV (Chapter 3, Table 3.6) and decide on a result is compared to the manual rapid screen is presented in Table 5.8.

From the results presented, the screening time to view 10 FOV is 0.21 minutes less than for a manual rapid screen. Referring to the proposed screening pathway in Figure 5.1, the cost of rapid quality assurance screening was calculated (Table 5.8) and compared to manual rapid quality assurance screening in the 2013-14 laboratory cervical screening service (Table 5.9).

Table 5.8: Labour costs associated with using combined manual and LGS Rapid QC screening in the proposed cytology screening process pathway

Average time to manually rapid screen one LBC slide	1.63	minutes
Average time to examine 10 FoV via FocalPoint LGS	1.42	minutes
Number of slides that require RQC via LGS	149,808	slides
Total time required for FP LGS/annum (1.42 x 149,808)/60	3,545.46	hours
Total time required for manual RQC of NFR samples/annum (1.63 x 48365)/60	1,313.92	hours
WTE carrying out manual and LGS RQC screening within proposed model (3545.46 +1313.92)/7.5	647.917	Working days
(647.917 days) / (231 available working days)	2.80	WTE
COST 2.80 * (£1,352,757.66/43.95 WTE)	**£86,182.51**	

Table 5.9: Labour costs associated with manual Rapid QC screening in the 2013-14 laboratory screening service

Average time to manually rapid screen one LBC slide	1.63	minutes
Assuming an 8% positivity rate (positive samples are not submitted to rapid QC screen, then (220,000 x 0.92) =	202,400	samples
Total time required for manual RQC of NFR samples/annum (1.63 x 202,400)/60	5,498.533	Hours
WTE carrying out manual screening within current lab service (5,498.533/7.5)	733.1378	Working days
(733.1378 days)/(231 available working days)	3.17	WTE
COST 3.17 * (£1,352,757.66/43.95 WTE)	**£97686.54**	

5.1.7 Operational potential of using the FocalPoint™ technology in the cytology laboratory:

a. Savings in human resources.

From the results in the previous tables the implementation of the FocalPoint™ NFR technology could potentially save 23% (48,365/220,000) in primary screening workforce establishment, so 9.18 WTE when applied to the Welsh scenario in 2013/14.

From Tables 5.8 and 5.9, the FocalPoint™ LGS would save a further 0.37 (3.17 – 2.80) WTE, making a cost saving of **£11,388.40,** and a total saving of 9.55 WTE**.**

b. Cost of implementing the FocalPoint™ technology:

In summary, the potential cost benefits of implementing the FocalPoint™ GS Imaging system are as follows realised exclusively by savings to workforce time. In the Welsh screening programme model, the potential savings were:

At normal pay rates, the amount realised = **£318,022.50** (£306,634.10 + £11388.40)

With overtime rates, the amount realised = **£430,712.95** (£419,324.55 + £11388.40)

As noted earlier in this chapter, the costs of implementation (2013-14) amount to £180,000 + £240,000 (see Section 5.1.4.c)

This indicates an overall cost to the service of **£420,000**

From the results of this economic analysis, there is therefore no expectation of any net savings under usual working conditions of a 5-day week. However, if overtime working was a possibility in a laboratory service, then there would be a point when use of the technology would save money.

5.2 Screener acceptance of the FocalPoint™ GS technology

Cytology Screener perceptions of the CAS technology were evaluated by questionnaire (Appendix 12), recorded and evaluated to see if acceptance (or not!) of the technology had any positive or adverse effects on implementation in the workplace.

The questionnaire was circulated to staff in the laboratories that participated in CAESAR studies 1 and 2 (Glan Clwyd, Llandudno and Wrexham). This was because these studies evaluated the FocalPoint™ GS system in its entirety and included the FocalPoint™ LGS aspect of the technology.

14 questionnaires were circulated to the laboratories and 7 of the 14 were returned – a response rate of 50%. The responses to the questions posed were as follows:

Question 1. What is your staff grade?

Responses were received from: 2 Cytoscreeners
1 Biomedical Scientist
2 Senior Biomedical Scientists
2 Lead Biomedical Scientists

Question 2. Roughly how many months were you using the FocalPoint™

Responses received were as follows:

Cytoscreeners	6-12	months
Biomedical Scientists	6-12	months
Senior Biomedical Scientists	6-12	months
Lead Biomedical Scientists	6-12	months

Question 3. How many years' experience do you have working as a cytologist?

The responders' cytology experience ranged from 2 years to 43 years.

Question 4. Were you satisfied with the training for using FocalPoint™?

Excellent	Very good	Good	Fair	Poor
3	**3**	**1**		

Question 5. Do you have any specific comments about how the training could be improved?

1. No
2. No
3. Good overall training with assessment – cannot improve

Question 6. Overall, I prefer using the FocalPoint™ system compared with only using manual screening:

Strongly agree	Agree	Neutral	Disagree	Strongly disagree
	1	4	2	

Opinions were distributed amongst the staffing groups as follows:

STAFF GROUP	CS	BMS	SBS	LBS
NEUTRAL	**X**	**X**	**X**	**X**
DISAGREE	**X**		**X**	**X**
AGREE				

Question 7. I find it easier to concentrate using the FocalPoint™ system compared with manual screening.

Strongly agree	Agree	Neutral	Disagree	Strongly disagree
		5	2	

Opinions were distributed amongst the staffing groups as follows:

STAFF GROUP	CS	BMS	SBS	LBS
NEUTRAL	X	X	X	XX
DISAGREE	X		X	
AGREE				

Question 8. My work is more challenging using the FocalPoint™ system compared with manual screening:

Strongly agree	Agree	Neutral	Disagree	Strongly disagree
		4	3	

Opinions were distributed amongst the staffing groups as follows:

STAFF GROUP	CS	BMS	SBS	LBS
NEUTRAL	XX		XX	
DISAGREE		X		XX
AGREE				

Question 9. My work is more monotonous using the FocalPoint™ system compared with manual screening:

Strongly agree	Agree	Neutral	Disagree	Strongly disagree
	1	3	3	

Opinions were distributed amongst the staffing groups as follows:

STAFF GROUP	CS	BMS	SBS	LBS
NEUTRAL	X		XX	
DISAGREE		X		XX
AGREE	X			

Question 10. Did you experience any discomfort using either the manual or automated system?

Yes	No
0	7

Question 11. Please describe any physical discomfort (noise, physical strain, motion sickness) you experienced and the circumstances around that experience:

No comments were received.

The number of responses to the questionnaire was small, limiting the conclusions that can be drawn from the findings; however, the responses were representative of all staff grades involved in primary screening.

In summary, laboratory staff were happy with the manufacturers' training and assessment. Most staff were accepting of the technology and enjoyed using it in addition to the routine microscopy, although two respondents stated that they preferred manual screening. The same two staff reported that they found it harder to concentrate when using the FocalPoint™ LGS units. Three respondents thought it more challenging to use the automated technology, but most respondents thought that using the automated technology was not as monotonous as manual primary screening. No respondents reported any discomfort when using the technology.

Anecdotally, however, some staff did not appear to trust the technology and prolonged the rapid QC process per slide – almost to the point where it was another primary screen. This may have had a negative impact on the overall throughput of the technology and correspondingly – the potential benefits of the technology. It would be interesting to monitor workload throughput in greater detail over time to ascertain if acceptance improved.

5.3 Observations on the relationship between FocalPoint™ Quintile Ranking and HrHPV test results

When the Magden Park TelePath™ LIMS database was searched for cases with routine cervical cytology screening along with HrHPV ToC results as well as FocalPoint™ quintile ranking results - 128 samples were found matching these search criteria. The results are presented in Table 5.10.

Table 5.10: HrHPV test result presented by FocalPoint™ Quintile

HrHPV Test Result	FP1	FP2	FP3	FP4	FP5	NFR
HrHPV Positive	1	6	4	2	10	10
HrHPV Negative	14	15	13	16	17	16
% HPV Positive/Total HPV	0.81	4.84	3.23	1.61	8.06	8.06

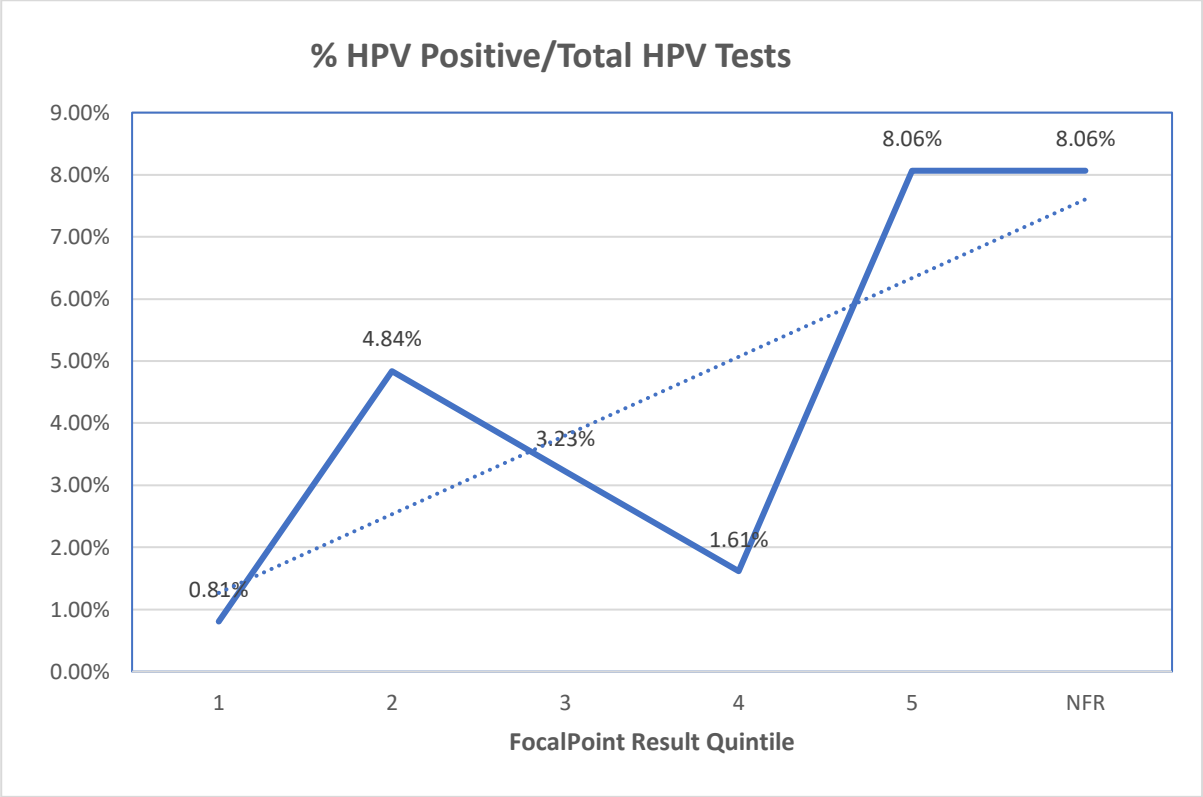


Figure 5.2: Overall HrHPV positivity rate by FocalPoint result quintile

From the chart in Figure 5.2, the overall HPV positivity rate increases with FocalPoint™ result quintiles 1 through to 5 and NFR. The anomaly is quintile 4, where a pronounced drop occurs, however this may be the result of small total numbers in the overall sample.

Chapter 6

Discussion

6.1 Introduction

Cervical cytology has been likened to the "tedious task of finding a needle in a haystack, where the majority of haystacks have no needle", (Desai, 2009). It is also true that this endeavour is becoming increasingly difficult because of the balancing act required in managing public and therefore government expectations on the one hand and the achievement of an accurate quality-based service on the other.

The last two decades has seen service improvement and modernisation initiative after initiative unfold in the world of pathology and laboratory medicine. Screening cytology is no exception and ever since the introduction of the "Pap" smear (Papanicolaou and Traut, 1943), screening for cervical precancer has developed continually. Cervical screening was first introduced in an ad hoc manner in the UK in 1964, however there was no structured programme with robust call and recall arrangements in place and those women most at risk were not protected (Farmery and Gray, 1994). To address these deficiencies the Department of Health and Social Security issued a circular to all District Health Authorities in 1988, requiring them to introduce a computerised call and recall system, recommending that all-women aged 20-64 be called for screening every 3-5 years (DHSS, 1988).

During the 1990s, much research was conducted and published on various aspects of the screening programme – including call-recall, smear taking and reading, counselling, colposcopy clinics, treatment, pathology services and costs to women (including anxiety caused by screening, especially receiving a positive test result. On a positive note, morbidity and mortality from cervical disease was declining (Macgregor *et al*., 1994). However, against this backdrop of progress several darker periods were to blight the developing programme, such as the laboratory screening incident in 1996 at the Kent and Medway NHS Trust. This incident involving the laboratory service at the Kent and Canterbury hospital resulted in the deaths of 8 women and involved the re-screening of over 90,000 cervical samples. Other incidents include the incident at Prince Charles Hospital at Merthyr Tydfil, South Wales in 1995, where over 18,000 samples were re-screened following allegations that a consultant pathologist was under reporting positive smears. In 1997, 20,000 samples were misread at

the Inverclyde Royal Hospital in Greenock, Scotland.

Towards the end of the nineties, a number of quality initiatives were implemented by the NHS CSP and at the same time the Welsh Office unveiled a National Screening Framework (NSF) for cervical screening, modelled on the successful NSF for breast cancer screening – Breast Test Wales. The Welsh screening programme, Cervical Screening Wales, was implemented in 1999. Since then, all the national screening programmes have striven to improve quality of screening for women, and the investigation and appraisal of new technology will naturally form an important part of the culture for continual improvement.

6.2 Technology Advances in Laboratory Cervical Screening

6.2.1 Liquid Based Cytology

In the UK, laboratories had operated with the conventional Pap smear since the early sixties. Thin or mono layer cytology had been around for several years, mainly in diagnostic cytology and the technology wasn't implemented for screening purposes, mainly because of the sheer numbers involved in cervical screening to which the direct Pap smear was better suited. It wasn't until 2003 that the National Institute for Clinical Excellence released a report recommending the introduction of Liquid Based Cytology as offering improved performance over conventional cytology in terms of improved detection of dyskaryosis and reduced rates of inadequate samples, which meant that not as many women required repeat tests. Two systems were evaluated and approved, the ThinPrep™ filtration system by Hologic™ Inc. and SurePath™ density gradient and cellular enrichment system by Becton Dickinson (BD). LBC was then implemented in the UK between 2004 and 2008. The adoption of Liquid Based Cytology by the UK is important in that it provided the springboard for the acceptance and implementation of CAS by the NHS and UK screening programmes.

6.2.2 Automation in cervical cytology

The early development of CAS has been described in Chapter 2, the introduction of this thesis. From early beginnings as a spin-off of wartime military technology in the 1950s in the form of Cytoanalyzer (Tolles, 1955), a lot of time effort and expense has been devoted to the automation of cervical cytology. Despite all this effort, cervical cytology still remains as one of the few largely manual, high volume laboratory disciplines. It is only in the last 10 years or so that substantial progress has been made in the development and implementation of CAS

that finally promises to make an impact on cervical cancer screening. In the UK, progress in the implementation of CAS is even more recent, with the introduction of the BD FocalPoint™ NFR technology into the NHS CSP (Denton *et al*., 2013) and the adoption of the Hologic™ Imager by the Scottish CSP, also in 2013.

6.3 CAESAR's contribution in developing CAS in Wales and the UK

Following on from the introduction of LBC in the UK between 2003 and 2008, the service looked to the automation of cytology screening as a natural progression given that LBC preparations are the medium of choice for the implementation of CAS. Coincidentally, the two NICE approved LBC providers to the UK, TriPath, (now BD) and Hologic also manufactured the only two FDA approved CAS platforms. Therefore, it was inevitable that these two systems were promoted by the respective manufacturers.

The CAESAR studies were initiated by Cervical Screening Wales in December 2006 primarily to evaluate cytology automation available for SurePath™ LBC – the BD FocalPoint™ GS Imaging System. The principal investigator was David Nuttall (author of this PhD thesis), and the studies were completed in 2011 and culminated in the validation of the FocalPoint™ NFR technology for cervical screening within the Welsh screening programme in Wales in 2012. This PhD thesis resulted from a collaboration between Cervical Screening Wales and the CERVIVA research consortium of Ireland, with the author as the nominated collaborator.

During 2011-12, the author also collaborated with an NHS CSP task group that was convened to produce the guidelines for the adoption of the BD FocalPoint™ NFR technology as following on from one of the recommendations of the MAVARIC study (Kitchener *et al*., 2011). During the MAVARIC study the NFR reporting category of the FocalPoint™ had shown a low false negative rate for CIN2+/HSIL+ and the recommendation was that this should be investigated further. CAESAR 1 also reported a low false negative rate for NFR and the author presented these findings from CAESAR 1 in 2007 (BSCC ASM, Cardiff) - pre-empting MAVARIC, which did not report until 2011.

Following on from the CAESAR 1 results, one of objectives for the CAESAR 2 and 3 studies was to confirm the NFR findings. These findings, in the form of the Cervical Screening Wales NFR validation data (Appendix 13) were presented at the annual scientific meeting of the British Association of Cytopathology in 2012 and again at the United States and Canadian

Association of Pathology (USCAP) in 2016.

The NHS CSP task group proceeded to write the NHS CSP Good Practice Guide No. 4, which advised on the implementation of the NFR technology and incorporated several CAESAR findings in the recommendations. These included the requirement for the NFR results to have a subsequent manual rapid QC screen and, the need for LPCA calibration to the manufacturer's revised specification as recommended from the CAESAR 2 study results – see Chapter 4 of this thesis.

It is important to note that the manufacturers recommend that patients who are at higher risk of cervical disease (such as those patients who are symptomatic or have had treatment for CIN) should be manually screened in the conventional manner. In the CAESAR studies, all patient samples were randomised by date received and none were excluded in the manner described. It follows, therefore, that the findings presented in this thesis are applicable to a whole screening population, and no special exclusion rules need apply.

6.4 Discussion of the results of this study

6.4.1 FocalPoint™ performance for Rapid Quality Assurance and Primary Screening

6.4.1.1 Rapid Quality Assurance Screening

The evaluation of the performance of FocalPoint™ in the provision of a rapid quality assurance screen of manual primary screened LBC samples was carried out in three exercises:

a. A comparison of the time taken to perform an automated rapid screen compared to a manual rapid screen.
b. A comparison of the sensitivity of automated rapid QA screen to that of a manual rapid QA screening by the participating laboratories.
c. A comparison of the sensitivity of the automated rapid QA screening performed in this study with that recorded by other manual rapid QA screen studies reported in peer reviewed journals.

We found that rapid QA screening using the FocalPoint Guided Screening Workstation took less time than manual rapid QA screening, by 13 seconds (0.22 minutes) per slide screened. Given the number of QA screens carried out by a cervical screening programme in a year,

this will have beneficial effect in terms of staffing capacity. Furthermore, we also found that automated rapid QA screening by FocalPoint™ was marginally improved in terms of sensitivity for high grade, low grade and all grades of dyskaryosis. This was also true when compared with the other published results. From this data, it is reasonable to assume that automated rapid QA screening can be safely substituted for the manual equivalent in the screening laboratory.

6.4.1.2 Comparison of manual to automated primary screening performance

The evaluation of the performance of FocalPoint™ using the 10 FOV provided by the LGS as a means of primary screening of LBC samples was carried out as follows:

a. By comparison of sensitivity of the 10 FOV images with that of manual primary screening.
b. Comparing the 2 and 3-year outcome data between the two screening interventions.

The results indicate that the sensitivity of the FocalPoint™ LGS derived images is less than for manual primary screening. Furthermore, the number of histological outcomes of CIN2+/HSIL+ at two and three years is greater for FocalPoint™ processed samples. When this data was further sub-categorised into pre-cancers and cancers, the totals were greater for FocalPoint™ screened cohort than the manually screened one.

Interestingly, the differential between the two modalities increased between the 2 and 3-year samples, indicating that the differences between the two increased over time. It would be reasonable to assume that this trend would eventually plateau as the routine screening recall interval arrived and passed.

We can therefore conclude that conventional manual primary screening offers better performance than screening via the 10 FOVs provided by the FocalPoint™. This might change if the screeners could screen outside the FOVs and look at the slide further, however, the time taken to this would increase. Consequently, this would impact on the biggest benefit of CAS, that of providing a labour saving.

This conclusion was also arrived at by the MAVARIC study (Kitchener *et al*., 2011) as well as by Colgan *et al*. (2013). There is a good deal of data in peer reviewed journals, indicating that CAS is superior to manual primary screening, as evidenced by authors such as Wilbur *et al*., 2009; Confortini *et al*., 2002; Parker *et al*., 2004. A systematic review of 3 major prospective

trials reporting on the efficiency of manual screening versus FocalPoint™ was conducted by Renshaw and Elsheikh in 2013. They concluded that CAS did not compare well with manual screening in programmes where the daily screening time was restricted to less than 6 hours daily, at least 6 minutes per slide and fewer than 50 slides per day.
Furthermore, they suggest that location efficiency for HSIL+ is related to the length of time spent screening per day, whilst improved interpretation is related to the amount of time spent on a particular case.

This finding would seem to fit with the situation in England and Wales, given that both MAVARIC and the CAESAR results discussed here indicate inferiority of CAS compared to manual primary screening, and both studies were carried out in laboratories screening within UK screening programmes and operating to NHS CSP standards (5 hours screening a day, approximately 5,000 slides per annum).

6.4.2 Report on the NFR technology and the automated detection of endocervical cells

6.4.2.1 The performance of the FocalPoint™ NFR reporting category compared to manual primary screening

In this comparison, a quantitative analysis of interval outcome data of CIN2+/HSIL+ on patients presenting at colposcopy following negative manual primary screened cytology, compared to the same outcome data following a FocalPoint™ NFR result over the same intervals, was performed. The comparison of data was carried out initially for CIN2+/HSIL+ cases presenting at 2 years and followed up by refreshing the data at 3 years and carrying out the same comparison.

As far as the author is aware, this is the first instance that an analysis of this nature, involving interval outcome data of patients presenting at colposcopy following a negative manual screen compared with NFR, has been carried out. This exercise formed the basis of the validation of the NFR technology for implementation in the cervical screening programme in Wales, and formed the basis of a submission for publication, which is awaiting a decision from the editors, at the time of writing.

The results show that NFR demonstrates non-inferiority to manual primary screening, with fewer CIN2+/HSIL+ and cervical precancer (CIN2/CIN3) (HSIL) cases presenting at 2 years for

the NFR screened cohort and moreover, the improvement is sustained and is even greater at 3 years. Cancer incidence rates were similar between the cohorts compared, however, if precancer rates are lower for the NFR cohort, we might assume that, over further time, the cancer rates should drop accordingly as fewer precancer cases progress to become cancers.

Coincidentally, aside from a manual rapid QA screen, the FocalPoint™ NFR technology requires no manual intervention and can therefore be substituted entirely for a conventional manual primary screen on up to 25% (NFR results accounted for up to 22.9% of the population scanned by FocalPoint in this study) of the screening throughput of the laboratory. This workload saving will result in throughput benefits for the laboratory, which are discussed later in this chapter. The NFR technology showed slightly increased false negative rates for low grade dyskaryosis compared to quintiles 4 and 5, (Table 3.15). This is thought to be related to cases with koilocytosis and with minimal nuclear aberration which are classified as low grade (LSIL) in the NHS CSP.

6.4.2.2 Unpredicted behaviour of the NFR technology in respect of an unprecedented increase in high grade cases categorised as NFR

This anomaly in the FocalPoint™ technology became evident in January 2010. The staff of laboratory in question (Llandudno General Hospital) became aware of an increased number of high grade cases assigned to NFR by FocalPoint™ and informed David Nuttall as lead investigator. Subsequent investigation involving the laboratory concerned, the suppliers (SBS), the manufacturer (BD) and the lead biomedical scientist, Amanda Savage, generated the results presented in Chapter 4, Section 4.4.

In summary, the findings were as follows:

1. Three of the four participating laboratories experienced relatively stable detection rates of HG dyskaryosis from July 2009 to November 2009 (Figure 4.5). Glan Clwyd and Royal Gwent Hospitals experienced high rates in August 2009, however, this is attributable to low numbers scanned at the start of CAESAR 2, where an increase of one or two cases of HG dyskaryosis created a disproportionate result in the data. The graph clearly shows a peak in HG incidence for Llandudno and Wrexham in December 2009, which would account for the issue being reported early in January 2010.

2. We then looked at the HG cases that been categorised as NFR microscopically. We concluded that these were cases that were unequivocally high grade, although several showed scanty small cell HG dyskaryosis.

3. The report from BD stated that the instrument concerned was performing within expected limits and the instrument calibration or LPCA was suspected. Re-scanning the affected slide runs following recalibration confirmed this theory when a high proportion of the HG cases originally categorised as NFR were re-categorised within the review population as quintiles 1-5.

   The original LPCA was set by the initial scanning of 250 cases with representative slides of varying abnormality included. This calibration was then adopted for all four laboratories and when the instrument was challenged with a greater than hitherto expected number of HG cases expected by the LPCA settings, the instrument algorithm scored these accordingly. It is thought that once the quota for HG cases to be allocated to Q1 was exceeded, then the excess was placed in quintile 2 and so on for quintile 3, quintile 4 etc. The resultant phenomenon is essentially an algorithm supersaturation and cascade effect, which resulted in higher than usual number of cases being categorised as NFR.

   Subsequent to this discovery, the re-calibration procedure or LPCA adopted by BD was the initial scanning of 1,000 as opposed to 250 slides, taken from the population that would be scanned on an ongoing rather than on an initial sample basis. In addition, the LPCA would be refreshed monthly where possible, in order to re-calibrate the instrumentation for subtle population shifts. Any planned changes in screening population, for example, screening another laboratories backlog, required the laboratory to contact BD, requesting the resetting of the LPCA for the new population. The following text is an extract from the laboratory standard operating procedure adopted for calibration and ongoing monitoring of the BD FocalPoint™ NFR technology, based on NHS CSP guidance.

   Laboratory Standard Operating Procedure

   Setting the Laboratory Process Calibration Assessment (LPCA) for the FocalPoint™ NFR Technology

   FOR THE INITIAL 1000 SAMPLES – SETTING THE LPCA

1. *Prior to initiating routine slide scanning, contact Source Biosciences (SBS) to inform Source BioSciences(SBS)/Becton Dickinson(BD) that the calibration process for a given FocalPoint™ instrument is about to be initiated*

2. *Begin slide scanning on Focalpoint™ – see relevant SOP.* ***Do Not proceed to the implementation of the NFR process until BD/SBS have confirmed that the instrument has passed the calibration check and is approved to proceed.***

IMPORTANT: The FocalPoint must be recalibrated in any event involving a change in the screening population being scanned and <u>specifically after the following events, including:</u>

1. Changes in preparatory and processing procedures:

- *Change in staining parameters.*
- *Change of coverslip procedure.*
- *Change of coverslip mountant.*

2. Changes in geographical screening areas.

- *If laboratory mergers occur, the BD FocalPoint™ Slide profiler may be used in laboratories providing services to more than one laboratory, region or screening programme.*

- *A new LPCA (1000 slides) on the combined merged workload must be completed before slides can be assigned to NFR. The new LPCA will prevent differences in underlying rates in such populations from having a detrimental effect on performance.*

- *Because they cannot be included in an LPCA, short term "backlog" contracts must not be scanned and assigned to the NFR category.*

Once the laboratory process calibration assessment is set as confirmed by Becton-Dickinson (following scanning of a minimum of 1000 samples as per NHSCSP guidelines).

3. The Effect of Age

- *Because younger women have a higher incidence of abnormality, calibration can be affected by changes in the age of the population being screened. For this reason, no samples from women outside the screening age range (25-64 years) can be processed for NFR.*

- *Where a laboratory merger has occurred, bringing together two or more screening areas with significantly different age distributions can have a major effect. This will be addressed by repeating the LPCA as described above.*

- *Publicity has in the past resulted in a sudden increase in attendance of women in a particular age range (and at particularly high risk). As soon as this type of activity is detected in a laboratory, the laboratory must inform SBS/BD in order that recalibration can be carried out urgently.*

Ongoing monitoring of the FocalPoint™ instrument performance

Becton Dickinson will continually monitor FocalPoint™ technical performance. Parameters monitored include:

- *Proportion of scanned slides assigned to NFR reporting category*
- *Process review rates.*
- *LPCA recalibration will be completed on at least 1000 consecutive slides at least monthly.*

Requirements of the Laboratory

- *The laboratory must monitor the proportion of slides assigned to the NFR reporting category.*

- *A paper report of each run is produced and must be reviewed by a suitably trained member of staff. The rate of NFR will vary slightly but variation of more than ± 5% should be reported immediately to SBS/BD. It should be noted that the system defaults to safety settings when NFR rises above 25%. A fall in the NFR rate means that the system defaults to manual screening.*

- *Process review rate and rerun rate are technical quality assurance measures. Rates should be reviewed by trained staff after each run. Sudden changes may have a laboratory technical explanation. In such circumstances the laboratory should contact SBS/BD immediately, as it may be possible for them to identify the cause of the variation remotely.*

- *In points (1) and (2) above, samples must not be reported as negative based on a classification of NFR until a satisfactory resolution is reached. Laboratories must keep documentation of all such episodes.*

- *Slides classified as NFR, which are subsequently reported as abnormal or inadequate on rapid review or rapid preview, should be recorded. Sensitivity for all grades, and for high grade abnormalities, should be calculated and recorded on a rolling annual basis, using the same methods and criteria as apply to the individuals performing primary screening. False negative cases assigned to NFR should also be recorded and total monitored on a monthly basis. These data should be reviewed both internally and by the QAT.*

- *SBS/BD will automatically recalibrate the system if certain parameters are breached. The laboratory should record all such recalibrations.*

(with acknowledgement to the Public Health Wales Screening Division Laboratory Service, Magden Park, Llantrisant, Rhondda Cynon Taf, Wales. U.K.)

This unprecedented behaviour of the NFR reporting technology was first reported because of the findings of this study and brought about a significant revision of the manufacturer's operating and monitoring procedures. This was communicated to the NHS CSP task and finish group producing the NFR guidance document and the revised LPCA calibration

procedure incorporated into the guidance (Denton *et al*., 2013), which was a major change in practice impacting on a very large population of women (mainly outside the UK and Ireland) who have received an improved screening outcome as a result of this study.

6.4.3 Evaluation of the automated detection of endocervical cells

To maintain a successful cervical screening programme, it is important that the quality of the Pap test is assessed and monitored (Mintzer *et al*., 1999). The Pap test is a screening test and by its subjective nature cannot be expected to be as accurate as a diagnostic test as it is subject to human error at from the time the sample is taken to cytological examination under the microscope. The laboratory aspect of the test has well documented KPIs to monitor performance such as, Sensitivity, Specificity, Positive Predictive Value, Referral Value, False Negative and Positive rates etc. However, none of these performance indicators provide information on the quality of the sample taken initially. Failure to take an adequate cervical sample may result in a false negative report or an under-estimate of the degree of abnormality present (Young, 2000).

The presence or absence of Transformation Zone (TZ) material in a cervical sample has been regarded as a good quality indicator of the adequacy of sample for a number of years (Narine and Young, 2007). Material that originates from the TZ, and therefore appropriate as an indicator as to its sampling (BSCC, 1990), include:

- Endocervical cells and/or
- Metaplastic cells and/or
- Endocervical mucus

Whilst the practice is no longer mandatory within the current cervical screening guidelines (NHS CSP Publication No. 1, 2013; British Association of Cytology Recommended Code of Practice, 2016), many laboratories use the TZ quality indicator to monitor sample takers in training.

Whilst this is possible for manually screened samples, there arises the question of what can be done with these samples when they are scanned and reported via the NFR pathway. The FocalPoint™ System can detect and report on the presence or absence of both the

endocervical and squamous components in a cervical sample and we considered that the instrument's results might be comparable with the manual results and if so, there would be no requirement to separate the trainees' samples from the routine workload. This deviation from routine laboratory practice would create an additional sample pathway and the associated risk of lost or misplaced samples is contrary to good laboratory practice and to be avoided if possible.

Transformation zone components are not as reliably detected in an LBC sample as was previously the case with conventionally taken and directly spread samples. This is because the LBC process removes endocervical mucus, which historically was one of the TZ components that cytologists noted as an indicator. In addition, the presence or absence of metaplastic cells, another indicator, is unreliable with LBC as the cells tend to lose their cytoplasmic protuberances in the transport medium and look more like parabasal cells. This leaves endocervical cells as the only remaining reliable indicator of transformation sampling that remains unaffected and laboratory monitoring of TZ sampling post the introduction of LBC relies on their detection almost exclusively. The Bethesda System (2015) advocates the presence of 2 groups of at least 5 endocervical cells as confirmation of the presence of endocervical cells in a cervical cytology sample. Therefore, I wished to determine if the detection rate of endocervical cells was comparable between FocalPoint™ and manual screening.

The results indicated that the comparison of the FocalPoint™ technology for the detection of endocervical cells showed good agreement with manual primary screening ($\mathcal{K} = 0.78$). When the historical TZ detection rates of all the Welsh laboratories where compared, there was a significant variance between them (SD = 6.7). Similarly, when the TZ reporting rates of the four laboratories participating in the CAESAR studies were compared, significant variance was also seen, with an SD of 8.0. In comparison, the FocalPoint™ endocervical cell detection rates for the four labs rates showed a marked improvement in consistency, with an SD of 3.1.

There are quality benefits from adopting the FocalPoint™ endocervical detection function as a measure of sample taker performance. The results are comparable and moreover, more consistent, which must contribute to a more equitable means of monitoring this key performance indicator and with it, sample taker performance.

6.4.4 Cost-minimisation analysis carried out on a modelled implementation of the FocalPoint™ technology

Automation in cytology has productivity improvement implications on staff time taken up with the microscopic examination of LBC samples in the laboratory. However, this benefit is offset by the additional costs of the CAS system of choice. It follows therefore, that it is important to carry out an evaluation of the cost versus the benefits of introducing the new technology, in order to have an evidence-based rationale for its introduction.

The systematic review by Willis *et al*, HTA report, (2005) reported that
Several studies have concluded that there are productivity gains available from the use of CAS, however, up until that time there was little detailed costing data published and most of that was concerned with the ThinPrep™ Imager or instruments that were no longer current such as PAPNET™ and the AutoPap 300.

This situation did not progress significantly until the completion of the MAVARIC study (Kitchener *et al*. 2011). This study included a cost evaluation analysis on the BD FocalPoint™ which was better suited for comparative purposes with the findings of this study. MAVARIC reported that, overall it costed more to read LBC slides with CAS than with manual screening. The findings assumed a workload capacity of 120,000 cases per annum per instrument.

As part of the economic analysis carried out in this study we identified from the data from the Cervical Screening Wales implementation of 2013-14, that two FocalPoint™ instruments were insufficient to manage a workload of 220,000. Whilst the instruments were capable of operating at >100,000 samples over 7 days, this was at the limit of their capacity and the cost of maintaining a rota of staff to maintain the instruments workload over the weekend offset any benefits obtained with 7 day working. Also, any instrument down-time meant that the remaining instrument could not maintain this level of throughput. After several meetings, laboratory management managed to convince the suppliers (SBS) that the level of downtime experienced seriously compromised the output of the laboratory, defaulting on contractual commitments with associated reputational damage to the service. As a result, a third instrument was provided.

The Cervical Screening Wales data was based on actual operational experience as opposed to the conclusions presented in the MAVARIC study, which were derived from modelling exercises. Despite

the differences in approach the conclusions were similar. We also found that the costs to read LBC slides using CAS were greater than for manually read slides, however, the difference was greatly reduced if automation was used to offset staffing deficiencies that required the use of overtime working at enhanced rates of pay or, indeed, locum staff at expensive agency rates. In this kind of application, the maximum cost minimisation benefits were realised if the amount of work screened at enhanced staffing remuneration rates was equal to or exceeded the amount of work that was progressing through the FocalPoint™ NFR pathway as this reduced primary manual screening requirement by up to 25%.

One further operational consideration identified by this study that does not appear to be reported in the scientific press to date is the operation of CAS in a network of laboratories. In the CSW implementation of 2013-14, the LBC processing of sample vials has been centralised to one "hub" laboratory which processes the samples and sends the prepared slides for screening to 3 "spoke" laboratories. The hub lab also screens slides. Rather than pay for 4 FocalPoint™ instruments, one for each laboratory, it was deemed to be more efficient to install the instrumentation in the hub lab so that the slides were stained and scanned and then sent to the spoke labs with the FocalPoint™ scanning data. This provided a saving of one instrument, using 3 instead of 4, however, the requirement to change batches of work for each instrument (along with requesting BD to change the calibration for the slides of the laboratory in question) adds to the total scanning time. It was discovered that, over time, once the network is stable and the work arriving at the hub is more or less constant in nature, then a single calibration exercise of LPCA could be applied – smoothing out the work flow.

6.4.5 Screener acceptance of the FocalPoint GS technology

It is interesting to note that this study received more responses to the questionnaire than was reported in MAVARIC (5 responses to 7 in CAESAR).

The findings of this study that agreed with the findings of by Kitchener *et al*., 2011; (MAVARIC, Appendix 11, pages 135-140), are as follows:

- Laboratory staff were happy with the manufacturers' training and assessment.
- Staff reported that they found it harder to concentrate when using CAS.
- The respondents thought it more challenging to use the automated technology

- Most respondents thought that using the automated technology was not as monotonous as manual primary screening.
- No respondents reported in discomfort when using the technology.

In this study we also found that some staff did not appear to trust the technology and prolonged the rapid QC process per slide – almost to the point where it was another primary screen. This may have had a negative impact on the overall throughput of the technology and correspondingly – the potential benefits realised. It would be interesting to monitor workload throughput in greater detail over time to ascertain if acceptance improved.

6.4.6 Observations on the relationship between FocalPoint™ Quintile Ranking and HrHPV test results

The results presented in Table 5.2, Chapter 5 indicated that the overall HPV positivity rate increases with FocalPoint™ result quintiles 1 through to 5 and NFR. The anomaly is quintile 4, where a pronounced drop occurs, however this may be the result of small total numbers in the overall sample.

This result was a somewhat unexpected as we thought that the opposite would have occurred – decreasing HPV positive rate with increased quintile number 1-5 and NFR.

The reason for this is not clear but might be because of low overall numbers (n = 128), and also, the samples were taken for HPV Test of Cure (TOC) or Resolution of Uncertainty (ROU), which according to the NHS CSP HPV algorithms are only performed on patients treated for CIN. It is probable (but not certain) that treated patients are more likely to be HPV negative as well as treated for disease. Further investigation of the interaction of CAS with HPV testing is plainly needed and is a recommendation of this thesis.

6.4.7 Summary

The findings of this study are summarised as follows:

- FocalPoint™ provided no appreciable quality benefits when compared to manual primary screening, apart from the NFR technology which demonstrated increased sensitivity for CIN2+ (HSIL+).

- FocalPoint™ LGS provided acceptable performance when operated as a rapid quality assurance tool for the IQC of manual primary screening.

- FocalPoint™ provided comparable results to the manual detection of endocervical cells and showed improved inter-laboratory consistency than manual primary screening.

- For optimum performance, it is vital that the FocalPoint™ GS Imaging system is calibrated according to BD recommendations and operated in line with the guidance provided in NHS CSP Good Practice Guide No. 4. (Denton *et al*., 2013).

- Overall it costs more to read slides with FocalPoint™, however the system is at its most optimal when used to offset overtime working and locum staff. In situations where staff are difficult to recruit, the technology could maintain a viable laboratory service.

- Laboratory staff generally adapt very well to using the FocalPoint™ technology.

- Further investigation is needed into the potential application of FocalPoint™ CAS in conjunction with HPV testing.

Chapter 7

Future Directions

7.1 Introduction

Firstly, let me say a little bit about myself. Who am I? I'm a Welshman from the Isle of Anglesey, in scenic North Wales. I'm married to Enid and I have a grown son and daughter and two grand-daughters. I am a registered Biomedical Scientist since 1979 and started my training at the University Hospital of Wales, Cardiff. I have worked in the field of Cytopathology since 1979.

In the 38 years I have worked in laboratory cervical screening, I have seen the screening programme and laboratory screening services develop from the conventional smear test provided by the laboratory, with general practice managed recall systems to the highly developed and organised screening programmes we now have in Ireland and the UK.

In terms of the evolution of screening for cervical precancer, one of the greatest, quantum leaps forward must be the establishment of structured, computerised call and recall arrangements. Research has shown that regular screening is the most effective means of preventing cervical cancer (Peirson *et al*., 2013).

The implementation of organised laboratory screening services, with improved quality standards for screening and reporting have enhanced service quality immensely. Also, the adoption of LBC has facilitated the use of other technologies, including computer assisted screening, which as this study shows, are now a reality within our laboratories.

One of the most important more recent developments must be the discovery of the proven association between high-risk human papilloma virus (HPV) and the development of cervical precancer. This has led to vaccines against the virus being developed, and vaccination programmes aimed mainly at young girls of school age are now well established, which will provide protection from cervical disease in the years to come. Another revelation is the high negative predictive potential (NPP) of a negative HPV test has for a woman. So, if a woman tests negative for the high-risk strains of HPV, then the chances of that woman developing cervical disease are very, very small: NPV = 99.7% (Kitchener *et al*., 2009). However,

although it is unquestionable that a HPV test is a useful investigation if the result is negative – meaning that the woman is highly unlikely to have cervical disease. However, one of the negative aspects of this important development is that if the result is positive, things are not so clear cut. This is because the association between the presence of the virus and the presence of the disease is a complex one, dependent on several factors:

- Persistence of infection
- Immunocompetency of the woman
- Integration of the virus with the woman's genome
- HPV sub-type

So, in summary, the presence of the virus does not mean that the disease is present and, in any case, most women will clear the virus over time. Younger women will have a higher rate of HPV positivity than older women, because, in general, they will be exposed more to the virus and therefore subject to more transient infections.

So, with an HPV test we have a test of risk – not of disease.

The question then arises as to what is done with those women at risk – with a HPV positive result, (about 12-14% - from data released from the HPV Primary Testing Pilot in England). The current strategy is for those HPV positive women to be offered cytology and follow an algorithm and pathway depending on the result. This strategy is not without its problems as we shall see from the following SWOT (Strengths, Weaknesses, Opportunities and Threats) analysis of the current situation.

7.2 SWOT analysis of the current situation in the laboratory cervical screening programme

7.2.1 Strengths

At the time of writing, the UK cervical screening programmes have enough staff to manage a core cytology reflex testing service to maintain cervical screening by primary screening with HPV molecular assays. However, staff are leaving the service and training and recruitment of replacements to manage future service requirements is proving to be a challenge.

To avoid a crisis in the continued provision of cytology services, screening programmes urgently need to plan for future services in partnership with pathology services providers, which are also in a state of reconfiguration (NHS Improvement Pathology Network Proposals, September 2017). Until April 2017, the author was fortunate enough to participate in the planning and provision of laboratory screening services in Wales and planning for the provision of next generation cervical and bowel screening laboratory services began in 2010. Wales, in terms of population and screening footprint, is equivalent to a regional health authority in England, for example. The model adopted by Wales would therefore be applicable on a regional basis for the NHS CSP, but to date, the planning is somewhat "behind the curve". The long-term solution is achievable, but demand and service analysis to arrive at a plan for sustainable cervical screening delivery is urgently required.

Research into new technologies for the detection of cervical disease is advancing apace, and several developments initially show promise as an alternative "test of disease". These include:

7.2.1.1 Biochemical analysis

RAMAN microspectroscopy – (Rashid N *et al*., 2014), Vibrational spectroscopy (Ostrowska KM *et al*., 2010) and Fourier-Transform Infrared (FTIR) spectroscopy (Ostrowska KM *et al*., 2011) provide the ability to biochemically "fingerprint" cells by their spectroscopic signatures (Kelly *et al*. 2010). In a HPV test of risk screening programme, the ability to reliably identify dyskaryotic cervical cells biochemically would provide an alternative test of disease to cytology.

7.2.1.2 Immunochemical biomarkers

The tumour suppressor protein, p16(INK4A), used immunohistochemically as an indicator of squamous cell carcinoma and strongly associated with high risk HPV infection, along with Ki67 - a cell proliferation marker, are both used widely in cellular pathology. Recently however, these markers have been combined to form the CINtec PLUS® (Roche Holding AG, Basel, Switzerland) cytology test for abnormal cells, which is currently being evaluated as an alternative test for disease as a reflex to primary HPV screening.

7.2.1.3 Computer Assisted Screening

As reported in this thesis, CAS technology has several potential applications worthy of further investigation as an adjunct to primary HPV testing. These include:

- BD FocalPoint GS Imaging System. During this study, the NFR technology aspect of the system demonstrated a very high negative predictive potential for CIN2+/HSIL+ (chapter 4, section 4.1). This property of NFR warrants further study and potentially, modification of the imaging algorithms (Schiffman *et al*., 2017) in order optimise the system for the higher disease prevalence of a HPV positive scanning population. We also saw that the NPP of quintile 5 (chapter 3, section 3.5) was similarly high. This indicates that the current FocalPoint™ algorithms have a certain degree of flexibility, depending on the LPCA that is set, to manage a range of disease prevalence. Given that NFR and Q5 account for over 36% of the scanned total that would indicate a considerable productivity gain for cytology in a reflex capacity as a test of disease, against a backdrop of a declining workforce.

- CAS technology was initially developed to analyse and quantify cells stained for a specific component (Feulgen stain and DNA/RNA, chapter 1, section 1.5). If the technology could be adapted to detect and quantify the immunohistochemical reaction products of biomarkers that predict cervical carcinoma and its precursors in assays such as CINtec PLUS®, then the CAS technology would overcome the single biggest criticism of the current application of these biomarkers – that of intra-observer variation, leading to inconsistency in their reading and interpretation. In addition, given the improved consistency provided by CAS, the technology could be calibrated to vary the sensitivity so that a clinically appropriate threshold or “cut-off” can be determined and set.

7.2.2 Weaknesses

Unfortunately, cervical cytology as a screening method for cervical pre-cancer is in decline. One of the biggest challenges facing laboratories within cervical screening programmes is the loss of qualified skilled individuals through retirement and new career opportunities. This is compounded with difficulties in recruiting replacement staff because of the increased uptake of HPV testing and staff de-motivation related to this development. This worrying situation is only just registering with policy makers and planners, despite concerns raised by

the service in the last few years. The UK screening programmes are now in the situation where backlogs are increasing because of this lack of planning and investment.

Training replacement staff is a lengthy process, currently with a 2 to 3 year lead time. At present, there are very few trainees in the system and nowhere near the number required to replace those leaving. In addition, it must be recognised that the requirements for a primary HPV screening based programme will be different:

- The prevalence of disease in the HPV positive cohort of women that will receive reflex cytology will be different to that experienced in a primary cytology screening population.

- Overall numbers requiring a cytology test will be small - estimated at 15 to 20% of current levels.

- The current recommended minimum throughput of cytology laboratories is 35,000 samples per annum (ScHARR, 2006). Given that a cytology screener can screen 3,000 – 5,000 samples per annum, and a consultant cytopathologist or consultant biomedical scientist must see >750 samples to maintain competence (BAC, 2016) then a 35,000-cytology sample throughput is about the minimum cytology workload that would result in a sustainable laboratory (cytology) service.

- Because of the high throughput potential of HPV molecular testing platforms, and to ensure that the cytology testing is sustainable in terms critical mass (>35,000), there will be fewer laboratories. This will have an impact on the interaction with histology laboratories and cytology: histology correlation and in the support of colposcopy units and the respective multi-disciplinary meetings (MDM).

To manage increasing backlogs, several laboratories in the primary HPV pilot programme, as well as in Wales, have implemented a partial implementation of HPV primary screening. This has the added advantage of being potentially scaled up to manage staff leaving the service. The biggest concern, however, is that trained staff will leave the service in sufficient numbers to undermine the provision of a sustainable reflex cytology service in a primary HPV screening era.

7.2.3 Opportunities

The cervical screening programmes urgently need to plan for this uncertain future. The emerging technologies and thinking (Test of Risk versus the Test of Disease) must be embraced and the evaluation and routine use of the following applications must be initiated without delay:

- Using biomarkers and development of automated ICC protocols for multi-protein biomarker reporting
- Introduce IR and RAMAN spectroscopy biochemical fingerprinting
- Develop screening protocols for HPV vaccinated kindreds
- Develop new screening approaches in the context of changed disease landscape

7.2.4 Threats

The high negative predictive potential of Human Papillomavirus DNA or RNA assays for cervical disease indicates that these molecular testing modalities are set to underpin laboratory cervical screening for the foreseeable future. Kitchener *et al*. conclude in the ARTISTIC trial that, whilst HPV testing does not add significantly to liquid based cytology, it has two advantages over LBC namely, high NPV and high throughput capability through a much more automated platform.

The case for cytology is not likely to improve – with a HPV vaccinated screening population, the prevalence of CIN2+ cervical disease will decrease. It is proposed that with the advent of HPV vaccination and a move to a HPV primary screening modality, screening intervals could be safely lengthened (Kitchener *et al*., 2009). This will inevitably mean that the presentation of high grade lesions to the cytologist and histopathologist will become an increasingly uncommon event. Individual professional expertise and competence will be more difficult to maintain, and it is increasingly certain that a sustainable test of disease will be required to maintain a triage function to a primary HPV based screening intervention.

Paradoxically, therefore, the ascendency of the new primary test is a primary cause of the decline of the existing one – however, it is also fair to say that no consideration was given by the innovators to the overall impact that the innovation would have. The future of cytology as a triage test for HPV primary screening is therefore rather uncertain at the present time.

Chapter 8

Conclusion

At the outset of this study we undertook a review of the literature in order to determine the current state of the art of computer assisted cervical screening. We then sought to test these findings to validate the technology for use by the Welsh cervical screening programme (Cervical Screening Wales) and this thesis presents those findings. This investigation into the applications of Computer Assisted Screening for cervical screening indicate that the technology can improve productivity as well as maintaining and even improving quality of laboratory cervical cytology, but at a cost.

We modelled those CAS applications that offered quality improvement benefits in the current programme based on a cervical cytology primary screening test. The technology provided equivalent or improved performance for primary screening via the NFR reporting technology feature and for the internal quality assurance of manual cytology screening. When the model was costed via a cost-minimisation approach, we found that the implementation of the technology became more economically viable when adopted in circumstances of backlog management due to staffing shortages. We have reported on the current situation in terms of the decline of cervical cytology in Chapters 6 and 7 and these benefits of CAS must be seen as a means of maintaining this vital but vulnerable service.

We then looked at the potential for CAS in a HPV primary screening test scenario, with the technology operating as a “test for disease” following a positive HPV test as a “test of risk”. There is potential for the technology in this role, also, and we believe that there is further benefit to be gained from the technology by more innovation in the application of NFR and Q5 (chapter 7).

As discussed, the case for cytology is declining and with a HPV vaccinated screening population, the prevalence of CIN2+ cervical disease will decrease. The presentation of high grade lesions to the cytologist and histopathologist will become an increasingly uncommon event and individual competence in cervical cytology will be difficult to maintain.

On a positive note, this study has shown that there is further development potential for the BD FocalPoint™ GS Imaging system and it has been demonstrated in the literature that the technology's operating algorithms can be modified and adapted for a lower disease prevalence screening population. It can also be used to scan different LBC platforms, including ThinPrep™.

It may be that, in conjunction with other emerging diagnostic technologies, CAS can provide the support that the morphologist will need maintain a triage function for a primary HPV based cervical screening intervention. Hopefully, this means that the quest for a sustainable "test of disease" is nearing its end.

Appendix 1

MILESTONES FOR CERVICAL SCREENING IN WALES

Cervical Screening Wales

Screening Division
Public Health Wales

August 2013

Event	References
Management/reporting arrangements reviewed, development of Quality and Clinical Management Board which replaced the All Wales Management Group	
new Smear Taker Guide published	
Commencement of LIMS 'development'	
HPV testing policy advice	
Change of HPV vaccine From September 2012 the human papillomavirus (HPV) vaccine supplied for the routine NHS vaccination programme will switch from bivalent Cervarix® to quadrivalent Gardasil®. Girls who have started their course of Cervarix® vaccinations this year (2011/12) should complete with Cevarix® Girls who missed out on any of their three vaccinations this year should complete their course with Cervarix® next academic year (2012/13) Any eligible girl aged up to 18 years who started with Cervarix® but has not had 3 doses should complete with Cervarix® Girls starting Year 8 in September 2012 will receive three doses of Gardasil® Gardasil®, like Cervarix®, protects against two types of HPV virus (16 and 18) that cause over 70% of cervical cancer in the UK, and in addition protects against two types of HPV virus (6 and 11) that cause around 90% of genital warts.	The Chief Medical Officer for Wales on 29 November that from September 2012 girls entering year 8 at school (so 12–13 years of age) will receive Gardasil® vaccine instead of Cervarix®.
New cancer screening resources launched Women in Wales with a learning disability look set to benefit from new screening resources, designed to help them if they need further tests following NHS breast or cervical screening. Two new resource packs have been developed for health professionals working with people with a learning disability, with both packs containing very little text and plenty of photographs. The packs are the latest in a series of teaching resources developed by the Screening Promotion Department of Public Health Wales. Other packs include 'Having a Breast Test' and 'Having a Smear Test' which were launched in 2008 and 'Having a Bowel Test' which was produced in 2010.	(September)
Technology changes: Focal point/HPV	

Event	References
assessment	
ABC changes	
Public views sought on screening programmes in Wales. MEN and women across Wales are being invited to share their views on NHS breast, bowel and cervical cancer screening tests. A brand new 'Public and Patient Involvement' leaflet has been developed in a bid to encourage more members of the public to air their opinions, and actively promote the benefits of attending for regular screening tests. Developed by the Screening Division of Public Health Wales, the bi-lingual leaflet will be distributed in communities throughout the country, in the hope of encouraging more people to step forward with their views, and help spread positive screening messages.	(November)
From Thursday 1 October, responsibility for the functions and services of Cervical Screening Wales has been taken on by the new NHS Trust, Public Health Wales. Services provided by the Congenital Anomaly Register and Information Service (CARIS), the NPHS, Screening Services, the Wales Centre for Health and the Welsh Cancer Intelligence and Surveillance Unit (WCISU) will remain unchanged. So will the names and contact details for each of these services.	
QM update	
'The report of the project to assess the screening promotion and public information needs of Cervical Screening Wales' published.	(May)
On 1st April 2009 CSW held a 10th anniversary conference at the All Nations Conference Centre in Cardiff in which Dr Cerilan Rogers, Director NPHS Wales, the original Director of CSW on its implementation, delivered the opening address to the conference. Guest speakers included Professor John O'Leary and Miss Theresa Freeman-Wang. The subjects covered included the Cerviva project, Recent Advances in Colposcopy, and HPV – a Wales update. The Director of CSW, Dr Hilary Fielder, gave a brief overview of the future direction and challenges faced by the programme, in the light of recent scientific developments.	
The plans for a cervical screening audit scheme noted in 2007 were implemented and the CSW	

Event	References
audit of cervical cancers (CSWACC) was introduced from April 2009. Information from the CSWACC is submitted for inclusion in the Cancer Research UK (CRUK national cervical cancer audit, lead by Professor Sasieni, Wolfson Institute of Preventive Medicine, London	
Fully established North Wales Screening Network incorporating laboratories previously located in all three Trusts across North Wales.	
Welsh Assembly Government introduce a programme on HPV vaccination	
The previous CSW structure of five regions was reduced to three; North Wales, West Wales and South East Wales, in line with other programmes managed by Screening Services.	
Introduction of first laboratory screening network system commenced in North Wales, initially involving two Trusts.	
Digital imaging rolled out to all colposcopy clinics in Wales.	
A Cervical Cancer Audit project commences in Wales to develop a database and standard operating policies and procedures to ensure that all cervical cancers are audited in a standard way using routinely collected and recorded information (which can also be shared with other stakeholders to inform any national audit exercises).	
As part of a campaign designed to address a fall in the number of women having a smear test, the first television, cinema and poster advertising campaign to encourage screening uptake is launched in Wales.	
Decision on whether HPV vaccine should be introduced in the UK is awaited from the Joint Committee on Vaccination and Immunisation	
Screening Link Person project rolled out to the remainder of areas in Wales.	
All cervical smears taken in Wales are processed using LBC technology.	
Statistics from Cervical Screening Wales records show that 75.4% of women offered a smear test during 2005/06, took it up; compared with 85% in 1992.	
Digital imaging piloted in colposcopy clinics in Wrexham.	
A cervical cancer vaccine targeting HPV types 16, 18, 6 and 11 is licensed for use within the	

Event	References
European Union.	
The English NHS Cervical Screening Programme publishes an Audit of Invasive Cervical Cancers to monitor the effectiveness of the screening programme and to identify areas of good practice and where improvements can be made.	NHSCSP (2006). *Audit of Invasive Cervical Cancers*. NHSCSP publication no. 28.
The National Public Health Service for Wales and Screening Services Wales issues a joint position statement in respect of HPV vaccination in Wales.	Roberts R, Fielder H (2006). Position Statement on Human Papillomavirus (HPV) Vaccines. NPHS/Screening Services: Cardiff.
One of the trials of vaccines against human papillomavirus (HPV) infection, the primary risk factor for cervical cancer, announces that Merck's investigational vaccine GARDASIL™ is both safe and effective, preventing 100% of cervical pre-cancers and non-invasive cervical cancers associated with HPV types 16 and 18 in a new clinical study.	Press release 6 Oct 2005. Villa LL *et al.* (2005). Prophylactic Quadrivalent Human Papillomavirus (Types 6, 11, 16, and 18) L1 Virus-Like Particle Vaccine in Young Women: A Randomised Double-Blind Placebo-Controlled Multicentre Phase II Efficacy Trial.*Lancet Oncology*, 6, 271-8. Skjeldestad FE *et al.* (2005). *Prophylactic Quadrivalent Human Papillomavirus (HPV) (Types 6, 11, 16, 18) L1 Virus-Like Particle Vaccine (Gardasil™) Reduced Cervical Intraepithelial Neoplasia 2/3 Risk.* Presented at: Infectious Disease Society of America 43rd Annual Meeting; October 7, 2005; San Francisco, California. Abstract LB-8a. [Online]. Mao C *et al.* (2006). Efficacy of Human Papillomavirus-16 Vaccine to Prevent Cervical Intraepithelial Neoplasia: A Randomized Controlled Trial. *Obstetrics & Gynaecology*, 107(1), 18-27.
Colposcopy Highlight Rules is rolled out across Wales (after being piloted in Gwent) – further failsafe system linked to SafetyNet to ensure women have correct management in, and discharge from, colposcopy.	
Screening Link Person project piloted in some areas of Wales – to identify links to primary care to improve two-way communication between CSW and primary care and to help with dissemination of information.	
Research is published demonstrating that Cervarix™ (a bivalent vaccine aimed at preventing HPV types 16 and 18) is both safe and effective, preventing 100% of HPV type 16 and 18 infections.	Harper DM *et al.* (2004). Efficacy of a Bivalent L1 Virus-Like Particle Vaccine in Prevention of Infection with Human Papillomavirus Types 16 and 18 in Young Women: A Randomised Controlled Trial. *Lancet*: 364, 1757-65. Harper DM *et al.* (2006). Sustained

Event	References
	Efficacy Up to 4.5 Years of a Bivalent L1 Virus-Like Particle Vaccine Against Human Papillomavirus Types 16 and 18: Follow-Up From a Randomised Control Trial. *Lancet*; DOI: 10.1016/S0140-6736(06)68439-0. Kahn JA (2005). Vaccination As A Prevention Strategy for Human Papillomavirus-Related Diseases. *Journal of Adolescent Health*; 37, S10-6. GlaxoSmithKline (2006). *Press Release: New Data Show Cervarix™, GSK's HPV 16/18 Cervical Cancer Candidate Vaccine, Is Highly Immunogenic and Well-Tolerated in Women Over 25 Years of Age*. [Online]. Schwarz TF *et al.* (2006). An AS04-containing human papillomavirus (HPV) 16/18 vaccine for prevention of cervical cancer is immunogenic and well-tolerated in women 15-55 years old. *Journal of Clinical Oncology*, 24(18S), abstract 1008.
Cancer Research UK publishes a paper stating that Britain's cervical cancer screening programmes have averted an epidemic that would have killed about one in 65 women born after 1950. The article suggests that screening programmes in the UK have saved 100,000 women born between 1951 and 1970 from premature death due to cervical cancer.	Peto J, Gilham C, Fletcher O, Matthews FE (2004). The cervical cancer epidemic that screening has prevented in the UK. Lancet; 364, pp. 249–256.
A revised version of the UK cervical screening reference manual is published.	NHS (1994). *Cervical Screening Reference Manual Version 2.8*. NHS Information Authority.
Health Commission Wales authorises the roll-out of LBC technology across the remainder of laboratories in Wales. [In addition, a training programme is set up for all laboratory staff in Wales from July 2004 and, with the exception of a small number of staff, completed by June 2005. LBC conversion training for all smear takers runs concurrently with laboratory training]	
New SafetyNet system which directly links to Welsh Exeter system is launched by Cervical Screening Wales to ensure that all women who require a referral to colposcopy are not lost to follow up.	
ColpSafe system introduced to all CSADs to identify women who DNA colposcopy appointments.	

Event	References
Evidence is published demonstrating that a new technology – liquid-based cytology (LBC) - reduces the number of 'inadequate' smears taken and hence the number of women who are recalled for repeat testing, reduce pressure on the laboratory workforce and also reduce levels of anxiety in screened women due to the quicker reporting time and a reduction in the number of women whose tests have to be taken again.	Karnon J, Peters J, Platt J, Chilcott J, and McGoogan E (2003). Liquid-based cytology in cervical screening: an updated rapid and systematic review. Technology Assessment Report prepared for the National Institute for Clinical Excellence: i-67.
The National Institute of Health and Clinical Excellence (NICE) recommends that liquid-based cytology (LBC) is used as the primary means of processing smear samples in the cervical screening programme in England and Wales.	NICE (2003). *Guidance on the use of liquid-based cytology for cervical screening: Technology Appraisal 69.* NICE: London
The NHS Cervical Screening Programme in England announces the introduction of liquid based cytology (LBC) in some laboratories at the 'Britain Against Cancer' conference.	
The NHS Cervical Screening Programme in England changes the age and frequency of screening following research by Cancer Research UK scientists. English screening policy is changed to offer first screening invitation to women at age 25 years, screen women aged 25 to 49 three-yearly and those aged 50 to 64 five-yearly.	Sasieni P, Adams J, Cuzick J (2003). Benefits of cervical screening at different ages: evidence from the UK audit of screening histories. *British Journal of Cancer*; 89: 88-93.
In Wales, a decision is made to continue to offer first screen to women at age 20 years and invite all women three-yearly.	
The evaluation of the LBC pilot project in Wales demonstrates a significant reduction in the number of inadequate smears and a fall in the number of women referred for colposcopy.	Cervical Screening Wales (2003). *Liquid Based Cytology – Pilot Project: Project Report*; Cardiff: Cervical Screening Wales.
Information System for Clinical Organisations – Colposcopy Information System (ISCO-CIS) is rolled out to every colposcopy clinic in Wales to capture clinical details for every patient requiring a colposcopic referral.	
SafetyNet system (already implemented in Dyfed Powys) is rolled out across Wales to ensure that all women requiring a referral to colposcopy are not lost to follow up.	
Cervical Screening Wales issues a revised quality assurance manual.	CSW (2001). *CSW Quality Manual (Administration).* CSW: Cardiff.
CSW achieves the Investors in People award.	
Cervical Screening Wales introduces liquid based cytology (LBC) - a new technology to process smear samples - in four laboratories in Wales, as a pilot project to assess whether or not	

Event	References
LBC should be implemented fully across Wales.	
The National Institute for Clinical Excellence publishes guidance for the use of liquid-based cytology for cervical screening.	NICE (2000). *Guidance for the use of liquid-based cytology for cervical screening*. Technology Appraisal Guidance No. 5; NICE: London.
The National Assembly for Wales publishes the 'Performance Management Framework' to accompany the 'Putting Patients First' document and details a target for cervical cancer screening rates in Wales that can be used to assess overall impact of, and access of different socio-economic and geographical groups to, screening.	National Assembly for Wales (2000). *Performance Management Framework: Putting Patients First (framework document and rationale report and baseline data).* National Assembly for Wales: Cardiff.
Cervical Screening Wales releases figures showing that in 2000/2001, 81% of all eligible women (aged 20 to 64 years) had been screened at least once in the previous 5 years.	Cervical Screening Wales (2002). *Cervical Screening Programme, Wales 2000/2001*. KC53/61 Statistical Report; CSW: Cardiff..
Cervical Screening Wales issues its quality assurance manual.	CSW (1999). *CSW Quality Manual (Administration)*. CSW: Cardiff.
Cervical screening is reported to be directly responsible for a 42% drop in incidence of cervical cancer between 1988 and 1997 in England and Wales, saving around 1,300 lives per year.	Sasieni P, Adams J (1999). Effect of screening on cervical cancer mortality in England and Wales: analysis of trends with an age period cohort model. *BMJ*; 318: 1244-1245 Office for National Statistics (2000). Health statistics quarterly 07. ONS: London.
The Cervical Screening Information Project (CSIP) is undertaken, identifying the type of information that should be collected and analysed in order to aid evaluation of screening in Wales.	
Experts are aware that most cervical cancers are associated with human papillomavirus (HPV) infection, opening up the possibility of better screening and detection via HPV as well as standard techniques and also the potential prevention and treatment of the disease through vaccination.	Borysiewicz L, Fiander A, Nimako M, Man S, Wilkinson G, Westmorland D *et al*. (1996). A recombinant vaccinia virus encoding human papillomavirus type 16 and type 18, e6 and 37 proteins as immunotherapy for cervical cancer. *Lancet*; 347: 1523-1527. Schiller JT (1999). Papillomavirus-like particle vaccines for cervical cancer. *Molecular Medicine Today*; 5. Murakami M, Gurski K, Steller M (1999). Human papillomavirus vaccines for cervical cancer. *Journal of Immunotherapy*; 22: 212-218.
A UK cervical screening reference manual is published.	NHS (1994). *Cervical Screening Reference Manual Version 2.0*. NHS Information

Event	References
	Authority.
Research is published in respect of the accuracy of the smear test (including sensitivity, specificity, PPV and false positive rate).	Raffle AE, Alden B, Mackenzie EF (1995). Detection rates for abnormal cervical smears: what are we screening for? *Lancet*; 345 (8963): 1469-73 Herrero R *et al* (1997). *Evaluation of multiple screening techniques in a high-risk area: the Guanacaste Project.* In: Franco ELF, Monsonego J eds. New developments in cervical cancer screening and prevention. Oxford: Blackwell Science; pp: 389-399. Kinney WK, Manos MM, Hurley LB, Ransley JE (1998). *Where's the high grade cervical neoplasia? The importance of minimally abnormal papanicolau diagnoses. Obstetrics & Gynaecology*; 91(6): 973-976.
Research is published in respect of the different aspects of a cervical screening programme (e.g. call-recall, smear taking and reading, counselling, colposcopy clinics, treatment, pathology services and costs to women (including anxiety caused by screening, especially receiving a positive test result).	Wilkinson C, Jones JM, McBride J (1990). Anxiety caused by abnormal result of cervical smear test: a controlled trial. *BMJ*; 300(6722): 440. Havelock C (1994). *The cost of the cervical screening programme – an activity-based approach. NCN report on costings.* Oxford: National Coordinating Network, NHS Cervical Screening Programme. Cuzick J, Sasieni PD (1997). *Estimates of the cost impact of introducing human papillomavirus testing into a cervical screening programme.* In: Franco ELF, Monsonego J eds. New developments in cervical cancer screening and prevention. Oxford: Blackwell Science: 364-372.
Cervical screening is shown to be effective in a number of countries, although not by means of randomised controlled trials.	Sigurdsson K (1999). The Icelandic and Nordic cervical screening programs: trends in incidence and mortality rates through 1995. *Acta Obstet Gynecol Scand*; 78: 478-85.
'Cervical Screening Wales' is launched by Welsh Health Minister, Jon Owen Jones, to provide women with equal access to a uniform and high quality cervical screening service across Wales. The Welsh cervical screening programme follows the model detailed in the aforementioned National Service Framework document, published in 1998.	Dobson R (1999). Wales sets up cervical screening body. *BMJ*; 318: 1510.

Event	References
The English NHS Cervical Screening Programme produces a report on histopathology reporting in cervical cancer.	NHSCSP (1999). *Histopathology reporting in cervical screening - working party of the Royal College of Pathologists and the NHS Cervical Screening Programme*. NHSCSP publication no. 10.
'Quality Care and Clinical Excellence: National Service Framework for the Cervical Screening Programme in Wales' is published.	NHS Wales (1998). *Quality Care and Clinical Excellence: National Service Framework for the Cervical Screening Programme in Wales*. Cardiff: NHS Wales & Welsh Office.
NHS Wales announces 'Putting Patients First', a document outlining a national commitment to enhance the role of health care professionals, local authorities and local people to take the lead in organising health services for their communities.	NHS Wales (1998). *Putting Patient First:* . Presented to Parliament by the Secretary of State for Wales by command of Her Majesty. NHS Wales: Cardiff.
The English NHS Cervical Screening Programme publishes a resource pack for training smear takers	NHSCSP (1998). *Resource Pack for Training Smear Takers.* NHSCSP; ISBN 1 871997 28 3.
Further observational research evidence is published demonstrating that cervical screening had been effective at reducing cancer incidence and mortality in Nordic countries.	Hakama M (1997). Screening for cervical cancer: experience of the Nordic countries. In: Franco ELF, Monsonego J eds. New developments in cervical cancer screening and prevention. Oxford: Blackwood Science:190-199
The English NHS Cervical Screening Programme publishes guidelines for clinical practice and programme management.	NHSCSP (1997). *Guidelines for clinical practice and programme management (2nd edition).* NHSCSP publication no. 8.
The English NHS Cervical Screening Programme publishes a practical guide for health authorities.	NHSCSP (1997). *A practical guide for health authorities*. NHSCSP publication no. 7.
The English NHS Cervical Screening Programme publishes guidelines to improve the quality of written information sent to women about cervical screening.	NHSCSP (1997). *Improving the quality of the written information sent to women about cervical screening: guidelines on the presentation and content of letters and leaflets*. NHSCSP publication no. 5.
The English NHS Cervical Screening Programme publishes guidelines to improve the quality of written information sent to women about cervical screening.	NHSCSP (1997). *Improving the quality of the written information sent to women about cervical screening: Part 1 – evidence based criteria for the content of letters and leaflets; Part 2 – evaluation of the content of current letters and leaflets.* NHSCSP publication no. 6.
The English NHS Cervical Screening Programme produces guidance on the safe use of diathermy loop excision for the treatment of cervical intraepithelial neoplasia.	NHSCSP (1997). *Guidance on the safe use of diathermy loop excision for the treatment of cervical intraepithelial neoplasia*. NHSCSP publication no. 4.
60% of health authorities are reported to be operating a three-year screening interval for	National Audit Office (1992). *Cervical and breast screening in England: a report by the*

Event	References
cervical cancer, compared with 39% in 1991.	*Comptroller and Auditor General.* London: HMSO. National Audit Office (1998). *The performance of the NHS cervical screening programme in England: a report by the Comptroller and Auditor General.* London: The Stationary Office.
Research is published estimating the protective effect of participating in screening.	Sasieni PD, Cuzick J. Lynch-Farmery E (1996). Estimating the efficacy of screening by auditing smear histories of women with and without cervical cancer – the National Coordinating Network for Cervical Cancer Screening Working Group. *Br J Cancer*; 73 (8): 1001-5.
The English NHS Cervical Screening Programme publishes standards and quality in colposcopy.	NHSCSP (1996). *Standards and Quality in Colposcopy*. NHSCSP publication no. 2.
The Welsh Expert Advisory Group (convened to respond to the All Wales Advisory Group report on cervical screening) issues a significant report on cervical screening in Wales, recommending that all components of a screening programme be reviewed and actions taken to provide a high quality, unified service across Wales.	Expert Advisory Group (1995). *Cervical Screening in Wales: Report of the Expert Advisory Group.*
The English NHS Cervical Screening Programme publishes achievable standards, benchmarks for reporting and criteria for evaluating cervical cytopathology.	NHSCSP (1995). *Achievable standards, benchmarks for reporting and criteria for evaluating cervical cytopathology – report of a working party set up by RCPath, BSCC and NHSCSP*. NHSCSP publication no. 1.
Evidence is published showing that screening is effective in reducing the incidence of, and mortality from, cervical cancer in north east Scotland.	MacGregor JE, Campbello MK, Mann EMF, Swanson KY (1994). Screening for cervical intraepithelial neoplasia in north east Scotland shows fall in incidence and mortality from invasive cancer with concomitant rise in preinvasive disease. *BMJ*; 308:1407-1411.
The English NHS Cervical Screening Programme issues guidelines on fail-safe actions.	NHSCSP (1992). *Guidelines on Fail-Safe Actions*. NHSCSP; ISBN 1 872263 35 6.
A 'Report of the All-Wales Advisory Group on Cervical Screening' is presented to the Secretary of State for Wales, detailing the current state of cervical screening in Wales, outlining technical guidance and proposing a way forward to improve the existing programme.	All-Wales Advisory Group on Cervical Screening (1991/1992). *Report of the All-Wales Advisory Group on Cervical Screening to the Secretary of State for Wales.* Welsh Office: Cardiff.
Declining mortality from cervical cancer is reported to have occurred in the UK since the 1950s, except in young women (aged 20 to 39 years) in whom rates doubled between 1970 and the mid 1980s.	Sasieni P (1991). Trends in cervical cancer mortality. *Lancet*; 338(8770):818-9

Event	References
(At this time, cervical cancer affected 1 in 60 women and, without screening, was predicted to become more common over the next 4 or so decades. At this time, about 50% of women diagnosed with cervical cancer died from it.)	(Office of Population Censuses and Surveys (1998). *Cancer survival in England and Wales: 1981 and 1989 registrations*. HMSO: London, 98/1.)
The English cervical screening programme (NHSCSP) publishes 'Cervical Screening in Primary Care', detailing measures to be taken to encourage primary care involvement in cervical screening.	NHSCSP (1990). *Cervical screening in Primary Care*. ISBN 1 872263 00 3
Financial incentives for GPs are introduced.	Anderson CM, Nottingham J (1999). Bridging the knowledge gap and communicating uncertainties for informed consent in cervical cytology screening; we need unbiased information and a culture change. *Cytopathology*; 10: 221-228.
The National Coordinating Network of the National Health Service Cervical Screening Programme is formed to unite the aims of UK cervical screening programmes	
The Department of Health issues a circular requiring all district health authorities to introduce a computerised call-recall system and recommended that women aged 20 to 64 be screened every three to five years.	Department of Health and Social Security (1988). *Health Services Management: Cervical Cancer Screening*. Heywood: DHSS (Health Circular HC (88)1.
Further evidence is published indicating a gradual fall in mortality from cervical cancer due to national screening programmes.	Anderson GM *et al*. (1988). Organisation and results of cervical screening programmes in British Columbia, 1955-1985. *BMJ*; 296: 975.
The Welsh Office issues a circular setting out the essential elements for the current Cervical Screening Programme.	Welsh Office (1988). *Cervical Cytology Screening Services WHC (88)44*. Welsh Office NHS Directorate: Cardiff.
The Cancer Health Education Working Group of the Health Education Advisory Committee (Wales) consults on 'Health Education Relating to Cervical Screening in Wales'.	
More evidence is published demonstrating the effectiveness of cervical screening (using the smear test), based on observational studies undertaken in the Nordic countries.	Laara E, Day NE, Hakama M (1987). Trends in mortality from cervical cancer in the Nordic countries: association with organised screening programmes. *Lancet*; 1 (8544): 1247-9.
The All Wales Health management Efficiency Group on Cervical Screening issues a report, recommending the appointment of programme directors and the computerisation of call-recall schemes.	
A Welsh Office Circular is published stating that cervical screening is to be included in the annual review of Health Authority Performance.	Welsh Office (1986). *Welsh Office Circular (86)31.* Welsh Office: Cardiff.
Findings from a collaborative study carried out	IARC Working Group on the evaluation

Event	References
in eight countries demonstrates that cervical screening could be effective in identifying women at increased risk of developing cervical cancer.	of cervical screening programmes (1986). Screening for squamous cervical cancer: duration of low risk after negative results of cervical cytology and its implication for screening policies. *BMJ*; 293: 659-664.
Further evidence is published demonstrating that screening reduces incidence of, and mortality from, cervical cancer.	MacGregor JE *et al*. (1985). A case control study of cervical cancer screening in North East Scotland. *BMJ*; 290.
The NHS/Welsh Office Working Party is formed to look at the screening programme in Wales and produce guidelines for cervical screening in District Health Authorities that make 13 recommendations that all call-recall schemes should include.	
Cervical screening in Wales is reported to be based on local arrangements, targeting women aged 35 years and over (and those under 35 years who had had three or more pregnancies), on a five-year recall interval.	All-Wales Advisory Group on Cervical Screening (1991). *Report of the All-Wales Advisory Group on Cervical Screening to the Secretary of State for Wales.* Welsh Office: Cardiff.
Findings from the 'Cardiff Cervical Cytology Study' emphasise the need for repeat cytological or histological examinations in women with evidence of dyskaryosis in a cervical smear.	Evans DMD, Hibbard BM, Jones JM, Sweetnam P (1981). The Cardiff Cervical Cytology Study: prevalence of cytological grades and initial histological findings. *BMJ*; 282: 689.
Early evidence of effectiveness of cervical screening (using the 'pap' smear test) is published.	MacGregor JE (1975). *Evaluation of mass screening programmes for cervical cancer in NE Scotland.* Presented at the Fifth European Congress of Cytology, Milan, Italy.
Ad hoc cervical screening is introduced in England. However, the programme fails to cover those women who are at greatest risk and some individuals with positive results are not followed up successfully.	Farmery E, Gray JAM (1994). *Report of the first five years of the NHS cervical screening programme*. Oxford: National Coordinating Network.
The 'pap' smear test is developed to facilitate the early detection and treatment of premalignant changes of the cervix. It was described as an effective, simple and safe screening test to reduce incidence of, and mortality from, cervical cancer.	Papanicolaou GN, Traut H (1943). *Diagnosis of Uterine Cancer by the Vaginal Smear.* New York.

Appendix 2

CONSORT 2010# checklist of information to include when reporting a randomised trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	
	2b	Specific objectives or hypotheses	
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	
Participants	4a	Eligibility criteria for participants	
	4b	Settings and locations where the data were collected	
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	
	6b	Any changes to trial outcomes after the trial commenced, with reasons	
Sample size	7a	How sample size was determined	
	7b	When applicable, explanation of any interim analyses and stopping guidelines	
Randomisation: equence generation	8a	Method used to generate the random allocation sequence	
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	
location concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	

Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how	
	11b	If relevant, description of the similarity of interventions	
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	
	13b	For each group, losses and exclusions after randomisation, together with reasons	
Recruitment	14a	Dates defining the periods of recruitment and follow-up	
	14b	Why the trial ended or was stopped	
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	
Other information			
Registration	23	Registration number and name of trial registry	
Protocol	24	Where the full trial protocol can be accessed, if available	
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.

Appendix 3

YMDDIRIEDOLAETH GIG FELINDRE
VELINDRE NHS TRUST

Correspondence to: Mrs Sarah Townsend, Research and Development Manager, Velindre NHS Trust, 3rd Floor, 14 Cathedral Road, Cardiff, CF11 9LH
Email: Sarah.Townsend@velindre-tr.wales.nhs.uk
Tel: 02920 316165

Mr David Nuttall
Cervical Screening Wales
Preswylfa
Hendy Road
Mold
CH7 1PZ

30th September 2008

Dear Mr Nuttall

Computer Assisted Evaluation, Screening and Reporting in Cervical Cytology – assessing its application in routine practice.
The Cervical Screening Wales Focal Point project

The above proposed project was assessed by the Research Risk Review Committee held on 24th September 2008, at which the following Committee members were present:

Dr Richard Jones (Vice Chair), Medical Director & R&D Lead, Director of Welsh Blood
Mrs Sarah Townsend, Research and Development Manager
Mrs Jill Masters, Research and Development Officer
Dr Geraint Lewis, Head of Physics, Velindre Cancer Centre
Mr Bryan Rose, Programme Manager, Screening Services
Dr Eve Gallop-Evans, CTU Director
Mrs Jane Darmanin, CTU Manager
Mr Darren Lloyd, Information Governance Manager, Health Solutions Wales
Dr Anne Donald, Consumer Representative
Mrs Denise Hughes, Risk Manager, Corporate Services
Mr Steve Jenkins, Business Manager, Screening Services

I am pleased to confirm that the study has been approved by the Committee for commencement in this Trust subject to the issues detailed within this letter being satisfactorily addressed and ethical approval being awarded if required. Amended versions of all documentation should be forwarded to the R&D Office for consideration on completion.

If the project requires an ARSAC certificate recruitment **must not** commence until the certificate has been received by the Trust. If your project includes patients recruited from other Trusts it is your responsibility to contact the relevant R&D Office(s) in order to gain R&D approval to commence.

Without individual R&D approval from all Trusts where patients will be recruited Welsh Risk Pool indemnity will not be afforded to the researcher.

Approval lapses if the project does not commence within 12 months of approval. The Committee reserve the right to information on the progress of the project at any time and should receive a progress report six monthly and a written report on completion. Random audits may be carried out to ensure that projects comply with the clinical guidelines for research.

Any serious adverse incidents relating to the project should be reported to the R&D office and a Clinical Incident Form completed.
Reviewer's comments are listed below for your action:

Reviewer 1
I understand the purpose of the research, but it is not particularly well outlined in the proposal submissions. As I understand it the chief purpose is to assess the impact on the service, both in terms of delivery and acceptability, but also in terms of likely outcomes. Since rapid screening is not being carried out it cannot be directly compared with CAS unless there is an historical review. I understand that this will be the case, but this is not clear in the protocol.

The sample size of 15,000 is appropriate, but the study would clearly benefit from a longer study number.

Transport of slides to medical solutions in Nottingham is a small but obvious risk. Should slides be lost or damaged is transit there would be repercussions for the women involved (as re-testing) and for the image of the Trusts involved.

Although CAS could undoubtedly introduce cost savings this project does not appear to be trying to directly address this. I do not believe this is a major issue

Reviewer 2
This appears to be a well written proposal that follows on from previous work done in this field.

On completion of the project please inform the R&D office.
correspondence should be forwarded to Sarah Townsend, R&D Manager, R&D Office, 3rd Floor, 14 Cathedral Road Cardiff Cf11 9LJ, ext 6165.

Yours sincerely

Dr Richard Jones
Medical Director, Welsh Blood Service & Vice Chair RRRC

Appendix 4

Gwyneth Carey

From: Carl Phillips [Carl.Phillips@bsc.wales.nhs.uk]
Sent: 31 October 2008 11:58
To: Dave Nuttall
Subject: Research/Service Evaluation
Attachments: ACTIVE_Defining research_revised0608[1].pdf

Dear Mr Nutall,

Thank you for e-mail which I received today the 31 October 2008. It would appear that your original e-mail was either not received or not addressed to me.

I have tried to contact you by telephone without success. That being the case I thought that I would e-mail a brief response.

It would appear that you have considered the remit of an NHS REC, details of which are available from the website of the National Research Ethics Service. I do not know if you have considered the leaflet entitled *"Defining Research"*, but if not, you may wish to do so. To assist you I have attached a copy of the leaflet, which I trust that you will find helpful.

If you, and the study sponsor are both satisfied that the project in question is a service evaluation or an audit, then you are indeed correct in thinking that an application to an REC is not required.

If however you are unsure, you can contact the your local REC by email with a description of your proposal (one side of A4) and seek their opinion.

I am unclear from your e-mail which REC is appropriate in this case. The location of the sponsor would not be the determining factor but rather where the project is to take place/and or the location of the individual taking lead responsibility for the project. The Chair of the SE Wales REC would give a view on projects taking place in SE Wales and where the Chief Investigator was based in SE Wales, but if the lead individual was based in North Wales he would not unreasonably expect the appropriate North Wales REC to be approached for advice.

Alternatively you can send your A4 summary to NRES for an opinion (please email: queries@nres.npsa.nhs.uk).

I would not advise seeking the advice of both a REC and NRES. It may well prove simpler to send a summary to NRES, particularly if the project is multi-centred across the UK.

I do hope the above is of some help to you. I am expecting to be available for most of next week if you would like to discuss the matter further. I would recommend doing so by telephone if at all possible.

Kind regards

Carl Phillips

Executive Officer

South East Wales Research Ethics Committees

Tel : 02920 376822 & 376823
Fax: 02920 376835

Business Services Centre, Churchill House, 17 Churchill Way, Cardiff CF10 2TW

13/11/2008

Appendix 5

Cervical Screening Wales
Sgrinio Serfigol Cymru

CAESAR 2

FOCALPOINT PROJECT

STANDARD OPERATING PROCEDURE

VALIDATION HISTORY

DATE OF ISSUE	AUTHOR	AUTHORISED BY	DATE OF REVIEW
08.12.2009	Dave Nuttall	FP Operational Group	08.12.2010

RISK ASSESSMENT			
Personnel: BMS Cytoscreener	Training: Senior BMS Ref:	Hazards: None Ref:	Quality Controls: None Ref:

Procedure:

1. Identify slides for Focal point scanning and set aside in a batch (note: a batch must contain a minimum of 120 slides and must not exceed 412 slides)

2. Packaging of slides to send. Using slide transport boxes for 20 position slide trays provided by Source Biosciences, which are more secure and result in fewer breakages during transport. The transport boxes also have an outer cardboard sleeve and drawstring to hold all trays in place. **All slide trays in a transport box should be bound with elastic bands to secure them for transport. It is also advisable to use bubblewrap or other form of soft packaging material to fill any empty space in the slide transport box before securing the lid. Please refer to the slide packaging guidance provided by Source Biosciences – [CAESAR 2 slide packaging guidance.pdf].**

3. Scan the slides for referral into the Source Biosciences Sample Tracker software to ensure an audit trail of transfer is maintained. (See procedure reference LP-CSWFP-Scanning-P003.doc).

4. Arrange collection of slides as per the schedule below. This is accomplished by e-mailing **courier@sourcebioscience.com.**

5. **Do not forget** to include the number of boxes to be collected **and** the day of collection.

Note that each participating laboratory must designate a contact person responsible for arranging collections, along with an alternate to cover annual leave or other absence of the designated contact. These contact details should be sent to Source Biosciences FAO Luke Nottage and Wilma Anderson. Source Biosciences will provide name of Courier and contact details for person responsible at Source Biosciences for arranging the transport to the labs – All staff should contact Jason Simpson-Young for queries regarding transport of slides to and from Source Biosciences

Email: courier@sourcebioscience.com
Direct Number: 0115 9739049

Notes:
Source Biosciences require that any cancellations of courier collections be made by 4pm the day before the collection is due. A charge for the collection may be incurred if cancellations are made after this deadline.

If the courier has not arrived for a scheduled collection Source Biosciences request that this is reported to Jason or Diana no later than 3.30 pm on the day of a missed collection, that will allow time to try and resolve the matter. Even if the courier arrives after this time, a check can be carried out to see if the collection is scheduled for that day.

Obviously, if there is no resolution forthcoming, the collection of the batch is abandoned and the slides concerned are manually screened. Source Biosciences would request that this notification be submitted by e-mail only to the following e-mail addresses provided:

courier@sourcebioscience.com
diana.williams@sourcebioscience.com

CAESAR 2 Slide Collection Schedules:

NORTH WALES LABORATORIES

Friday	collection from Llandudno
Monday	slides received at Source Biosciences and scanned on FP
Tuesday	slides removed from FP and despatched to lab
Wednesday	slides received back at Llandudno

Monday	collection from Wrexham
Tuesday	slides received at Source Biosciences and scanned on FP
Wednesday	slides removed from FP and despatched to lab
Thursday	slides received back at Wrexham

Scan data will be transferred on removable USB pen drives, which will be duplicated at Source Biosciences and sent to the originating lab for distribution with the slides to Glan Clwyd duplicated at the laboratory receiving the samples and sent to Glan Clwyd with slides for screening.

ROYAL GWENT (two collections per week)

First collection:

Thursday	slides collected from Newport
Friday	slides delivered to Source Biosciences and placed on FP for scanning. FP can be topped up by Source Biosciences if necessary
Monday	slides removed from Focalpoint data transferred to USB pen and Source Biosciences server. Slides packaged and despatched
Tuesday	slides delivered to Newport

Second collection:

Tuesday	slides collected from Newport
Wednesday	slides delivered to Source Biosciences and scanned on FP after removal of North Wales slides
Thursday	slides removed from FP data transferred to USB pen and print run copied. Slides packaged and despatched
Friday	slides delivered back to Newport

Appendix 6

Cervical Screening Wales
Sgrinio Serfigol Cymru

Cervical Screening Wales CAESAR Project Executive

Terms of Reference

Name of Committee	FocalPoint™ Executive Group
Summary of Role:	The FocalPoint™ Executive Group is responsible for the executive management of the Cervical Screening Wales (CSW) CAESAR projects. The Executive Group will have executive responsibility for the project and ensure that it is managed to deliver the strategic objectives of Cervical Screening Wales. The role of the Executive Group is to ensure that the project conforms to current national and local guidance and delivers a high quality outcome to inform the cervical screening service to the women of Wales.
Remit:	The FocalPoint™ Executive Group is required by the CSW All-Wales Management Group to deliver a high quality project outcome that will inform the laboratory screening service for women in Wales. The group will also ensure that the project is delivered to the highest standards of Research and Development. The FocalPoint™ Executive Group will Support the Lead Investigator in delivering all aspects of the project, in the investigation of the application of Computer Assisted Screening (CAS) for CSW. Implement all All-Wales Management Group and North Wales Local Management Group directives and proposals in order to deliver a high quality research project. Determine how best the service can be configured across the three North Wales sites to deliver the service according to 1.1 above. Ensure that the workforce committed to the project is adequate and sustainable and that the needs of the routine service are not compromised. Ensure that robust channels of communication exist to maintain an informed, successful outcome. Ensure that the financial implications for the Velindre NHS Trust have been adequately assessed and are

	acceptable. Ensure that the service implications of the service for the Velindre NHS Trust have been assessed and are acceptable. Consider risk management implications of each development proposal against Welsh Risk Management Standards Ensure that there is a lead individual who will be responsible for the project and who will report any adverse incidents associated with it. The Committee Chair will be drawn from the FocalPoint™ Executive Group membership. The Committee Chair will normally serve no longer than a three year period. Secretary to the Committee will be the North Wales Network Manager The Committee meetings should be attended by the Cervical Screening Wales Programme Manager, North Wales Network Manager, North Wales Programme Coordinator, the Lead Pathologist for the service and at least one other lead pathologist from representing each of the network sites.
Reporting to: **Communicates with:** **Monitoring of:**	Cervical Screening Wales – All Wales Local Management Group FocalPoint™ Operational Group N/A
Sub Committees:	Task to finish groups may be elected as and when required
Chaired by:	Lead Investigator
Secretary:	CSW All Wales Secretary
Membership	Dave Nuttall – Head of Laboratory Services and Lead Investigator Bryan Rose – Head of Programme, Cervical Screening Wales Helen Beer – Senior Informatics Analyst Nick Dallimore – Quality Assurance Pathologist Sally Williams – Quality Assurance Pathologist Thomas Hockey – Director, Welsh Cytology Training School Wilma Anderson – Cytology Manager, Source BioScience Ltd. Mrs Christine Payne – Clinical Cytologist, Royal Gwent Hospital Louise Pickford – CSW Regional Coordinator – North Wales

Meeting Frequency:	Monthly or as necessary depending on the ongoing business of the committee	
Documentation Required/Submitted From:	**Documentation**	**Submitted From**
	All Wales Management Group Meeting Minutes Focal Point Operational Group Minutes North Wales Cytology Service Operational Management Group Minutes	Cervical Screening Wales Lead Investigator North Wales Network Manager
Outputs (i.e. minutes of meeting submitted to other committee meetings)	Minutes submitted to R&D Committee and CG and RM Committee Quarterly report to National Research Register Trust research activity for R&D Annual Report	
Contact: **Secretary to meeting** Dave Nuttall	**Date ToR Last Revised**	**Next Review Date**
Lead Investigator 01352 803633	December 2008	November 2009

Appendix 7

CERVICAL SCREENING WALES

PROJECT INITIATION DOCUMENT

Computer Assisted Evaluation, Screening and Reporting (CAESAR)

The Cervical Screening Wales Focal Point™ GS Project

Version: V1.0
Release: 1.00
Date: 25/10/06

Author: Dave Nuttall

Document Number: FPPID.V1.0

Project Initiation Document History

Document Location

This document is kept in the Programme Managers Office, Cervical Screening Wales.
Filenames: Focal Point Project
This document is not controlled if copied.

Revision History

Version	Date	Summary of Changes	Changes marked
1.00	25/10/06		
2.00			
3.00			
4.00			
5.00			

Approvals

This document requires the following approvals.
Signed approval forms are filed in the Management section of the project files.

Name	Signature	Title	Date of Issue	Version
Hilary Fielder		Director of Screening Services, Velindre NHS Trust	25/10/06	V1.0

Distribution

This document has been distributed to

Name	Status	Date of Issue	Version
Project Team members	For information and reference	25/10/06	V1.0
Cervical Screening Wales – North Wales Local Management Group	For information and distribution		V1.0
Cervical Screening Wales – All-Wales Management Group	For information		V1.0

Contents:

1. Purpose of Document

The purpose of this document is to define the project and to form the basis for its management and the assessment of overall success. This document will provide a framework to give those providing the project mandate the ability to view the whole project and to give approval to proceed.

2. Background

Introduction and Strategic Context

1) Philosophy

2) Principles

- Targeting performance improvement

Key Issues
In order to monitor outcomes and deliverables a number of key issues have been identified by service providers. These include:

Informatics
During this study Medical Solutions plc will be in possession of Cervical Screening Wales (CSW) data and Liquid Based Cytology (LBC) microscopical preparations. This issue will be the subject of a data sharing agreement between the two institutions.

Data downloads are currently a feature of the laboratory based cervical cytology in Wales. These downloads are achieved by weekly extraction of standard coded data items from the laboratory information management and transfer to the CSW Information Department. It is proposed that code dictionaries are replicated on the LIMS (TelePath) databases of the three laboratories involved and the information for the project downloaded via the weekly data extractions for collection and analysis by the Information Department.

Workforce
Training for staff will be required for laboratory staff involved. This will be provided by Medical Solutions plc as part of the joint nature of the project.

Standards
All Cervical Screening Wales screening standards will continue to apply. Use of the Focal Point GS™ Slide Profiler will follow the standard operating procedures of *TriPath Imaging® Europe.*

Technological issues and equipment
Medical Solutions plc will undertake to supply, install and calibrate (as required) the following equipment for the duration of the study:
3 Location Guided Screening workstations – one at each of the participating laboratory sites
Mechanical microscope stages suitable for use with a designated microscope at each site
Sufficient removable Hard Disk Drives (HDD) to facilitate timely data transfer of the scanned slide results.
Transport containers suitable for the safe carriage of stained microscope slides for scanning by the FP GS.

Transport arrangements
Medical Solutions plc will undertake to arrange courier transport of the slides and HDDs from the participating laboratories to Medical Solutions HQ at Nottingham

3. Project Definition

3.1 Aim and Objectives of the Project:

a. Project Aim:

b. Project Objectives:

3.2 Scope:

3.3 Exclusions:

3.4 Deliverables:

3.5 Known Constraints/Considerations

3.6 Interfaces with Other Projects

4. Method of Approach

The Project Lead will
a) Provide an executive function for the Project approving all major project plans, authorising any major deviations from agreed plans,
b) Ensure that required resources are committed, arbitrating between conflicts within the Project and negotiating solutions to problems between the Project and external bodies.
c) Provide firm central direction via the National Framework and an executive decision making mechanism for developments and investments within Cervical Screening services.

The Project Manager will:
a) Run the Project on behalf of the Lead within any agreed constraints
b) Ensure that the Project produces the required products to meet the aim and objectives
c) Develop the Project Team
d) Advise the Lead on the requirements necessary to ensure that project requirements are met and to ensure that all opportunities are considered.

5. Assumptions

a) That all patient management will be based on the worse cytological result derived form either the manual or the automated arms of the project
b)
c)
d)
e)

6. Project Organisation Structure

See Appendix 1 for detailed structure.

Project Board

Name	Details	Position
Mr Bryan Rose	Programme Manager, Cervical Screening Wales.	Project Lead
Mr Dave Nuttall	Cervical Cytology Manager, Glan Clwyd Hospital, Scientific Advisor – CSW	Project Manager
Mrs Virginia Seager	Cervical Cytology Manager, Maelor General Hospital	Project Team Member
Ms Amanda Savage	Cervical Cytology Manager Llandudno General Hospital	Project Team Member
Ms Helen Beer	Screening Services Information Analyst/Manager	Project Team Member
Mrs Wilma Anderson	Cytology Manager, Medical Solutions plc	Project Team Member
Mrs Karen Winder	CSW IT Advisor - Advice on coding and data extraction	Project Advisor
Mr David Addington Hall	CSW IT Advisor – providing advice LIMS form and function	Project Advisor
Dr Louise Pickford	Programme Coordinator	Project Advisor

7. Communications Plan

See Appendix 2
The plan presented as a table defines all parties with an interest in the project and means and frequency of communication between them and the project.

8. Project Quality Plan

See Appendix 3
The Quality Plan is to ensure that the project products (deliverables) are fit for purpose, conform to their requirements, are designed and produced to do the job properly, and meet customer requirements. The project will include quality assurance of relevant products by the Project Team and Cervical Screening Wales.

9. Initial Project Plan

See Appendix 4.
The initial plan covers approximately a six month time frame and involving XXXX cervical sam ples.. The Project Organisation and Structure Diagram (4b) shows how the various elements of the Project fit together. The Gantt Chart (4c) details activities, timescales and costs for each component of the Project.

10. Project Controls

The Project Manager will report directly to the Project Team with progress reports, end stage reports and the next stage plans for each stage. Project meetings are planned on a regular basis, starting in September 2006. Highlight reports will be produced regularly monthly for the members.

Budgetary Controls

Budgetary control will be exercised by the appropriate Officers of CSW and the NHS Trusts involved. Cervical Screening Wales will hold responsibility for direct financial support of Project Team activities – in consultation with the Project Champion/Lead. The Project Manager will provide a financial update if required at any team meeting.

11. Exception Process

If implementation of the project plan is under threat an exception report will be submitted by the Project Manager to the Project Champion/Lead. The report will forecast deviation, the impact on plans, risks and the options available for development into an exception plan. Minor deviations from the project plan will be identified in Highlight Reports to the Project Team and through Endstage Reports.

13. Initial Risk Log

See Appendix 5.
The purpose of the Risk Log is to:

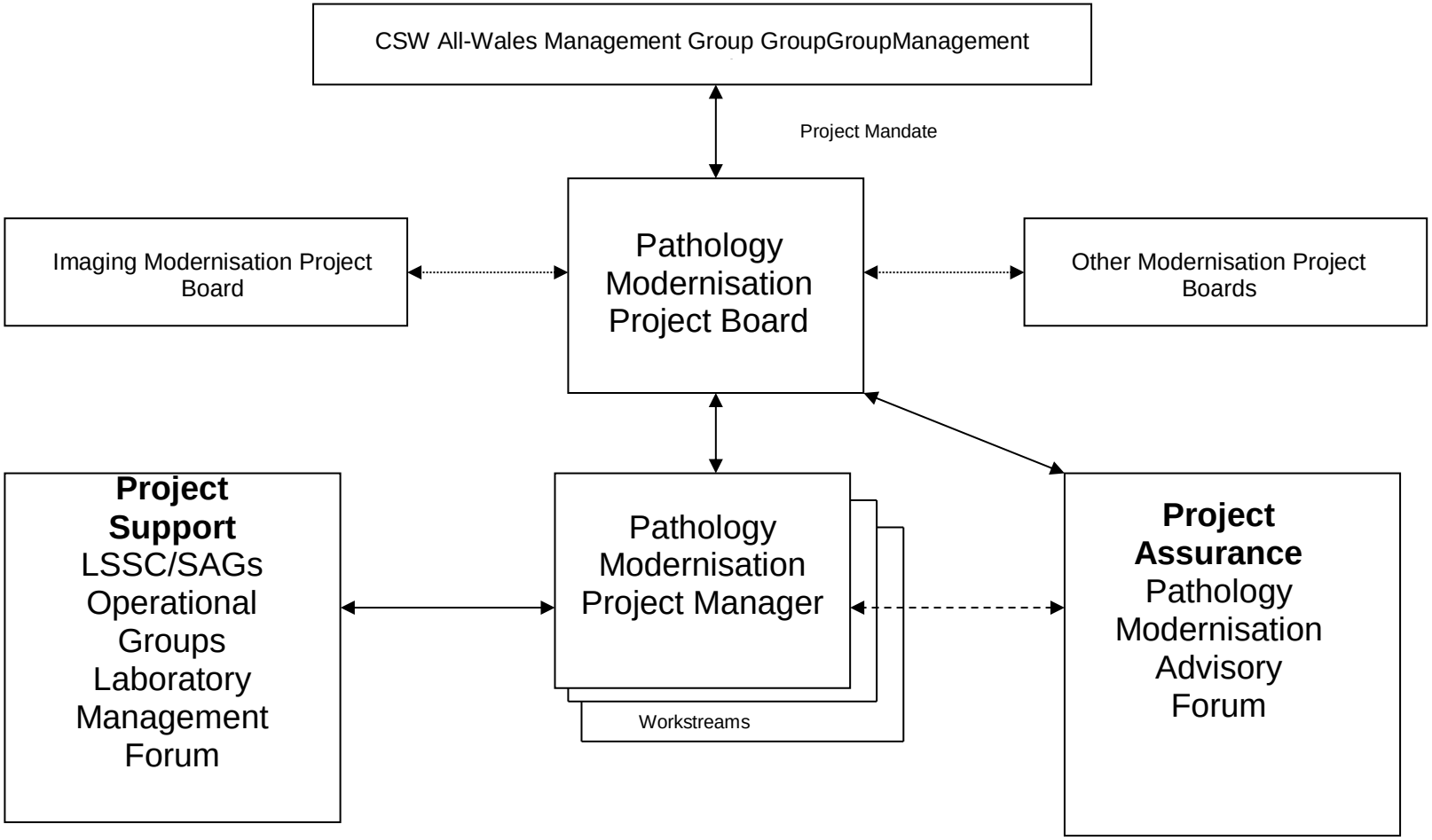
a) Allocate a unique number to each risk
b) Record the type of risk
c) Provide a summary of the risks, their analysis and status.

14. Contingency Plans

15. Project Filing Structure

Hard and electronic copies of files and other materials will be maintained by the project manager.

Appendix 1: Pathology Modernisation Project Organisation Structure

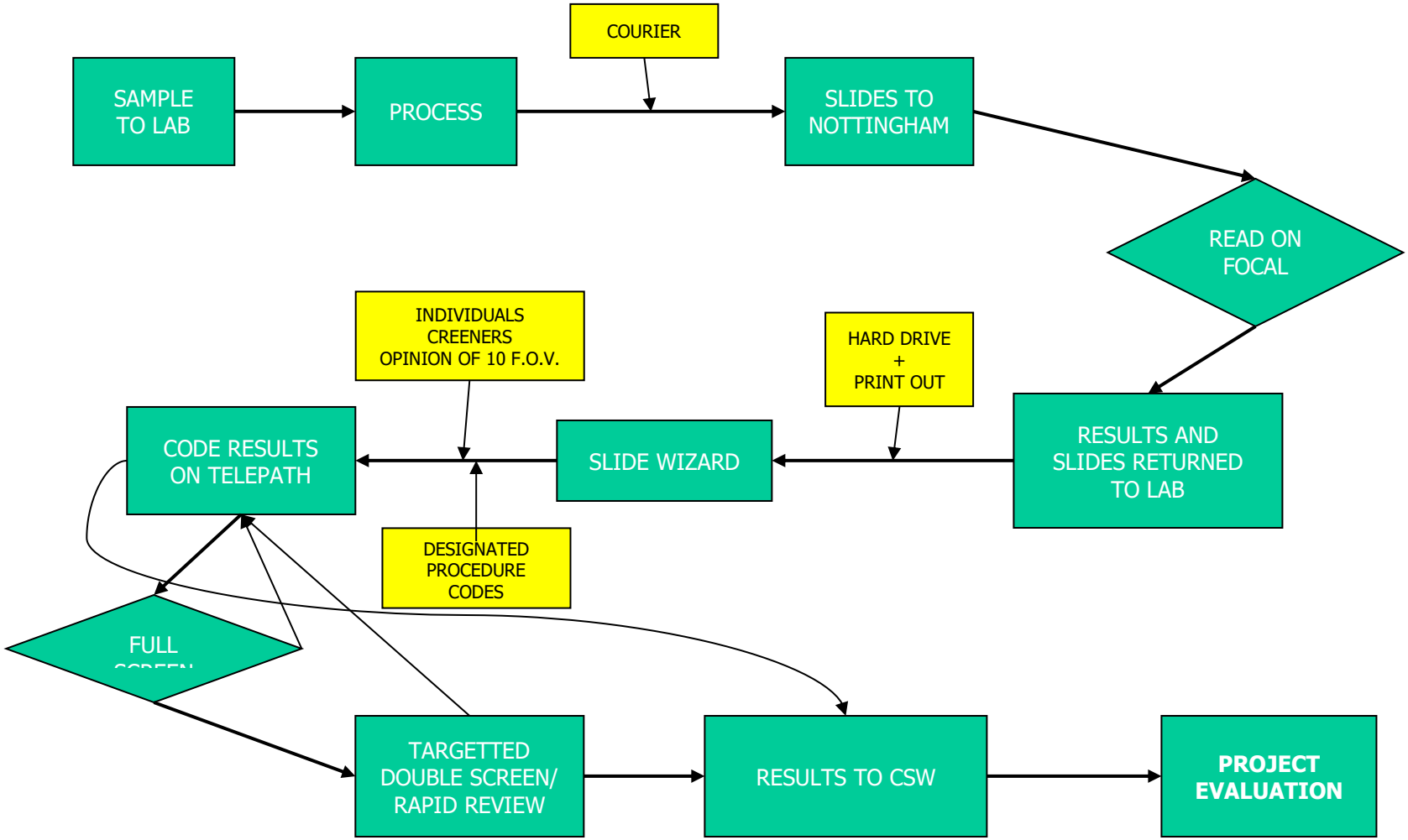


Appendix 2: Communication Plan				
Stakeholders	**Aim**	**Channel**	**Frequency**	**Responsibility**

Appendix 3: Quality Plan

Appendix 4: Project Plan
Appendix 4a: Summary
Appendix 4b: Project Overview Diagram
Appendix 4c: Gantt Chart
Appendix 4d: Workpackage Breakdown

APPENDIX 4D: CERVICAL SCREENING WALES FOCAL POINT PROJECT - PROCESS MAP



1.1 Equipment Evaluation

Overview:

1.2 Standards, Protocols and Method Evaluations

Overview:

1.3 Quality Management System

Overview:

1.4 Informatics

Overview

1.5 Transport

Overview:

Appendix 5: -Risk Log

Risk No:	Description	Probability	Impact	Countermeasure(s) (terminate; tolerate; transfer; treat)	Monitor	Status
1						
2						
3						
4						
5						
67						
7						
8						
9						
10						
11						
12						

Appendix 6: Roles and Responsibilities

Appendix 6a: Project Team
Appendix 6b: Project Lead
Appendix 6c: Project Manager
Appendix 6d: Project Assurance
Appendix 6e: Project Support

Appendix 6a: Project Team

Membership:

Role:

Appendix 6b: Project Lead

Role:

1. To Lead the Project:
2. To ensure that the Project delivers the desired aim and objectives
3. To work with key individuals and organisations to ensure that modernisation requirements are met
4. To ensure that all opportunities for modernisation are considered and implemented where appropriate

Appendix 6c: Project Manager

Role:
Reporting to the Project Lead

1. To lead the
2. 3. To manage the Project on behalf of the Project Lead, within any agreed constraints
2. To ensure that the Project produces the required products
3. To ensure that the Project delivers the desired aim and objectives
4. To work with key individuals and organisations to ensure that modernisation requirements are met
5. To ensure that all opportunities for modernisation are considered and implemented where appropriate

Appendix 6d: Project Assurance **Role**

The role of the Project Team is to provide quality assurance for the Project, giving advice on business, user and suppliers interests to the Project Lead and the Project Manager, thus ensuring that Project Aims are met.

Terms of Reference

• To review all project plans, structures and workpackages and to make recommendations regarding their acceptability in relation to delivery of the Project Aims
• To ensure that all business, user and supplier issues are addressed within the Project Plan, highlighting any deficiencies.
• To review all Reports produced by the Project Manager and to make recommendations on their acceptability.
• To act as a sounding board for the Project Lead and Manager in developing and managing the project via regular meetings and correspondence
• To ensure adequate links with other organisational, professional and advisory bodies and initiatives in relation to the Project
• Individual members to act as communications links for the Project

Appendix 8

Computer Assisted Evaluation, Screening and Reporting in Cervical Cytology; assessing its application in routine practice – the Cervical Screening Wales Focal Point Project.

Protocol Summary

Acronym: CAESAR 2 (Computer Assisted Evaluation, Screening and Reporting)

Principle Investigator: Mr. David Nuttall
Other Investigators: Mr. Bryan Rose, Dr Hilary Fielder, Dr Nick Dallimore, Ms Helen Beer, Mrs. Virginia Seager, Mrs. Sonia Sloan, Ms Amanda Savage.

Study Site(s): Cervical Screening Laboratories in Wales: Glan Clwyd Hospital, Llandudno General Hospital, Maelor General Hospital and Royal Gwent Hospital.
Source Bioscience Laboratories, Orchard Place, Nottingham Business Park, Nottingham.

Aim: The aim of the study is to evaluate the technology as a method of internal quality assurance (IQA) for manual primary screening of cervical samples across an established managed network of three laboratories in North Wales and one laboratory in South Wales – in comparison to the manual IQA procedures that are currently performed. This would inform future service planning and may provide a number of benefits, including improved methods of quality control, a release of resources associated with automated screening efficiency gains, active support for the current declining workforce adding stability to the programme, and potentially providing more consistent indicators of both screener and sample taker performance.

Objectives: Primary

- To evaluate the B-D Focal Point GS Imaging technology as a method of internal quality assurance (IQA) for manual primary screening of cervical samples across an established managed network of three laboratories in North Wales and one laboratory in South Wales – in comparison to the manual IQA procedures that are currently performed

Secondary

- Evaluate Focal Point GS Imaging (FPGS) across an integrated laboratory network
- Evaluate FPGS as a means of assessing sample quality - ?indicator of sample taker performance
- Assessment of the FPGS 'Quintile Ranking' facility against diagnostically confirmed sample abnormality profiles
- Assessment of the FPGS NFR (No Further Review) category as a reliable indicator of negative samples
- Monitoring screener performance using the Focal Point Slide Profiler

Methodology: This is a Health Technology Assessment (HTA) study

Number of Subjects: Minimum of 24,000 samples over a 6 month period

Inclusion Criteria: Cervico-vaginal Liquid Based Cytology (LBC) samples from women screened within selected laboratories contracted to Cervical Screening Wales (CSW) in 2008-2009.

Exclusion Criteria: As defined by the current CSW Standard Operational Procedures and Policies (SOPPs)

Computer **A**ssisted **E**valuation**, S**creening **a**nd **R**eporting **(CAESAR 2)** in Cervical Cytology; assessing its application in routine practice

Contents

1.0 Lay Summary

Computer assisted screening (CAS) technology has been established within the USA and Europe for many years and is currently undergoing Health Technology Assessment trials in the UK (The MAVARIC Project Manual Assessment versus Automated Reading in Cytology; a diagnostic accuracy study comparing two automated cervical screening technologies with manual screening

As Liquid Based Cytology (LBC) is now well established within the screening programme in Wales, Cervical Screening Wales (CSW) approved further assessment and development of the technology, which had been agreed with the suppliers of the technology, Medical Solutions plc, on its implementation.

The All-Wales Management Group of CSW recommended that an assessment of the application of CAS technology should be carried out to establish its potential application within the screening programme. This assessment Computer Assisted Evaluation, Screening and Reporting in Cervical Cytology (CAESAR) was supported by the supplier; Medical Solutions plc, with the cooperation of TriPath Europe, allowing CSW access to the automated slide scanning equipment – the Focal Point GS Slide Profiler. Following this initial assessment, which compared the instruments performance to standard screening it was noted that computer assisted technology performs sufficiently accurately to replace routine manual quality assurance processes known as rapid review.

In the current study, CAESAR-2, rather than use the technology in primary screening mode, it is proposed that the technology be evaluated as a method of internal quality assurance (IQA) for manual primary screening of cervical samples across a managed network of three laboratories in N. Wales – in comparison to manual IQA procedures that are currently performed. This would inform future service planning and may provide a number of benefits, including improved methods of quality control, a release of resources associated with automated screening efficiency gains, active support for the current declining workforce adding stability to the programme, and potentially providing more consistent indicators of both screener and sample taker performance.

1.0 Introduction

2.1 Cervical screening

Cervical screening identifies women at increased risk of developing cervical cancer and is estimated to save around 5,000 lives per year in the UK[1]. Screening is currently based on cervical cytology identifying dyskaryotic cells indicating the need for further assessment and possibly treatment of cervical intraepithelial neoplasia (CIN) to prevent potential progression to invasive disease. However, cytological screening is not infallible with up to half of the 1,000 women who die annually in the UK of cervical cancer having participated in Cervical Screening Programmes.

It is anticipated that Computer Assisted Screening will be introduced into cervical screening, however its use as a primary screening tool will depend on the findings of the National Health Service Cervical Screening Programme (NHS CSP) Health Technology Assessment (MAVARIC) study being conducted in Manchester, and which is due to report in 2009.

2.2 Objectives

The aim of the study is to evaluate the technology as a method of internal quality assurance (IQA) for manual primary screening of cervical samples across an established managed network of three laboratories in North Wales and one laboratory in South Wales – in comparison to the manual IQA procedures that are currently performed. This would inform future service planning and may provide a number of benefits, including improved methods of quality control, a release of resources associated with automated screening efficiency gains, active support for the current declining workforce adding stability to the programme, and potentially providing more consistent indicators of both screener and sample taker performance.

Primary

- To evaluate the Becton-Dickenson-TriPath FPGS technology as a method of internal quality assurance (IQA) for manual primary screening of cervical samples across an established managed network of three laboratories in North Wales and one laboratory in South Wales – in comparison to the manual IQA procedures that are currently performed

Secondary

- Evaluate FPGS across an integrated laboratory network
- Evaluate FPGS as a means of assessing sample quality - ?indicator of sample taker performance
- Assessment of the FPGS Quintile Ranking' facility against diagnostically confirmed sample abnormality profiles
- Assessment of the FPGS NFR (No Further Review) category as a reliable indicator of negative samples
- Monitoring screener performance using the FPGS

2.5 Rationale

Cervical cytology is currently subject to a number of service developments and pressures which are having a major impact on it's future delivery. These developments include new technologies such as HPV testing and CAS, a vaccination against HPV which will reduce the incidence of cervical

intraepithelial neoplasia (CIN) even further so as to substantially reduce the need for the morphological assessment of microscopical preparations from cervical samples.

The very nature of these developments will mean that fewer staff will be trained to screen cervical cytology samples. Fewer morphological samples will result in a lower incidence of dyskaryosis being presented to those still employed to diagnose such samples. It is possible, therefore, that CAS will have a vital role in presenting abnormalities of low incidence to the operator for diagnosis.

In addition, the Focal Point GS technology has additional functionality that may potentially further benefit the programme in Wales. There is the "No Further Review" (NFR) facility which employs computerized algorithms to exclude abnormalities in a sample and effectively categorize them in a low risk cohort. This facility has potential productivity and quality benefits for the screening programme.

The FPGS technology also has the facility to report on the cellular composition of a cervical LBC sample, evaluating its squamous and/or endocervical adequacy. This facility has the potential benefit of providing a high level indicator of sample taker proficiency. It is intended that this is evaluated as part of the project.

The organisation base in Wales is well positioned to carry out this evaluation of CAS technology as many of the operational variables commonly encountered within the laboratory screening service have been standardized across the service by virtue of the CSW SOPPs.

This work will inform the strategic direction of the laboratory based cervical screening service in Wales. In this context it is likely that CAS will form part of the specification of the re-procurement of the provision of LBC in Wales.

3.0 Investigational Plan

3.1 Overall Study Design

This is a Health Technology Assessment designed to evaluate Computer Assisted Screening technology as an Internal Quality Assurance tool within the screening Programme in Wales. The assessment will be carried out in parallel to the current CSW standard operating procedures and protocols (SOPP) for internal quality control (IQC) for primary screening of cervico-vaginal Liquid Based Cytology (LBC) samples within four cytology laboratories in Wales.

The primary outcome will establish if the technology is a viable IQC tool for the primary screening cervico-vaginal samples.

3.2 Study Population

It is estimated that >= 24,000 residual Liquid Based Cytology (LBC SurePath) samples are required to be examined as part of this investigation. This is so that the numbers of abnormal samples are sufficient to provide a valid comparison between the manual and automated arms of the study.

3.3 Inclusion and Exclusion Criteria

As far as possible, all samples collected from women attending for cervical screening at four of the Cervical Screening Laboratories in Wales will be included within the study. These laboratories are:

Glan Clwyd Hospital
Llandudno General Hospital
Royal Gwent Hospital
Wrexham Maelor Hospital

It is likely that, at certain times, some samples will be excluded because of local workload issues and practices. However, the main aim is to include as representative a proportion of the laboratories' screening as possible.

3.4 Sample Collection

Sample collection will be initiated in Jan 2009 for a period of 12 months. LBC samples will be processed and analysed by the local cervical screening laboratories in Wales according to the guidelines of the British Society of Clinical Cytology (BSCC), standard operating procedures and CSW guidelines. The resultant slides are then submitted for FPGS evaluation at SBS in Nottingham prior to routine screening within the laboratory.

3.5 Interventions

This study is designed to evaluate FPGS applicability and performance as QA tool for manual primary screening of cervical samples. Patient management will depend on the consideration of results from both the manual and automated QC arms of the study. All manual/automated arm mis-matches will be subject to further scrutiny and resolution according to project protocol.

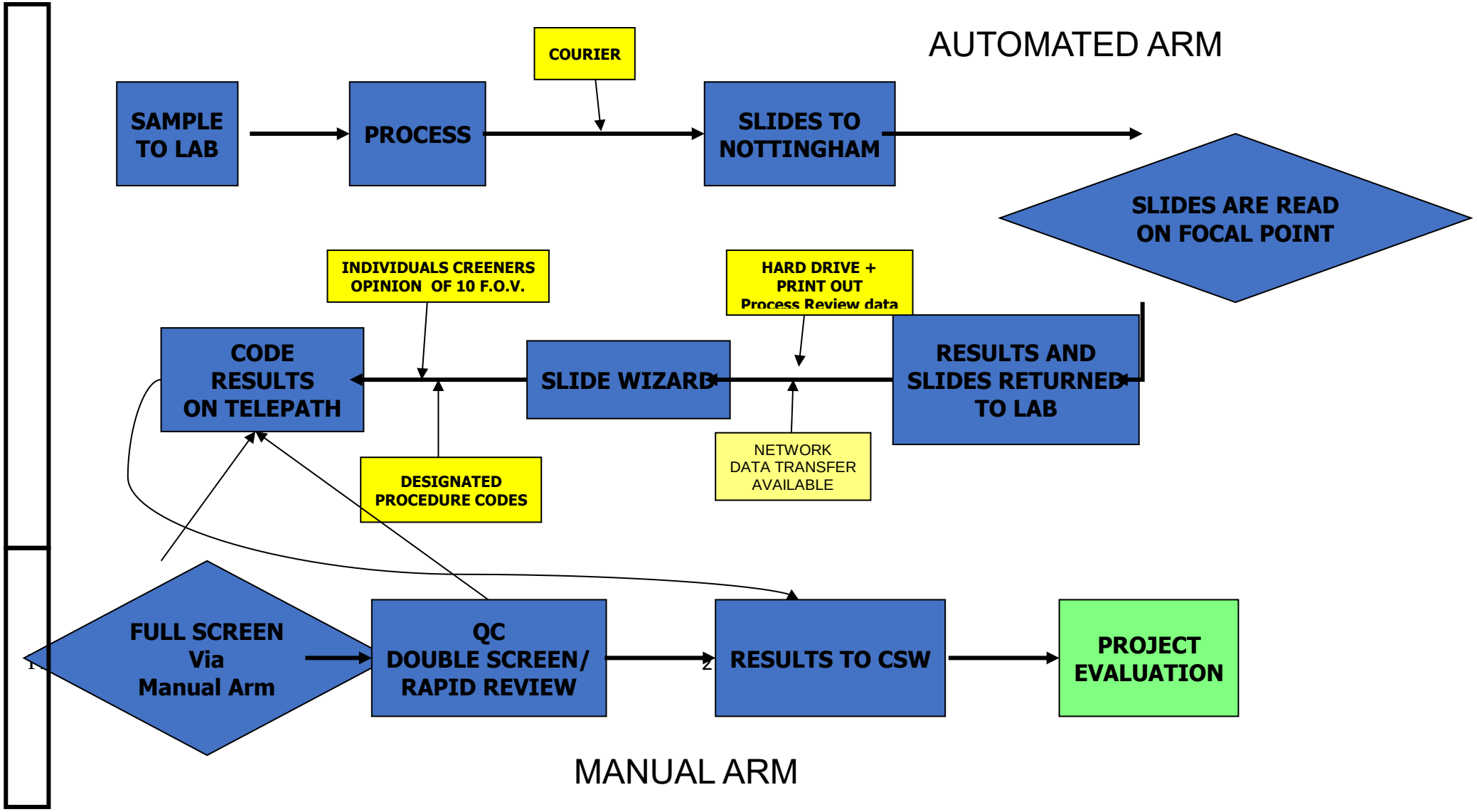
3.6 Blinding

Residual liquid based cytology samples are routinely assigned a unique laboratory accession code within the originating Cervical Screening Laboratory and will be forwarded to SBS' laboratories for FPGS scanning. The study SOPs are designed so that staff cannot perform laboratory functions on the manual as well as automated arms of the study as far as possible.

3.7 Study Plan

This is documented within the project GANTT charts which can be summarised as follows:
October 2008-December 2008 - Project initiation phase.
This involved arranging ethical review (if required), staff training by Source Biosciences and the installation of the Location Guided Screening (units) required within each lab. Project management was and is provided via an Executive Steering committee and Project Operational Group (FOG).

CERVICAL SCREENING WALES
FOCAL POINT PROJECT - PROCESS MAP



3.8 Endpoints

The sample collection and analysis llection and analysis part of the project will cease once the sample numbers required have been collected and processed or at 31st March, 2010, as appropriate.

4.0 Sample Management

Each LBC sample will be processed within the originating Cervical Screening laboratory according to the British Society of Clinical Cytology (BSCC) guidelines and CSW standard operating procedures.

4.1 Cytological analysis

Cervical samples are collected using a plastic broom device and placed into a vial of preservative fluid (SurePath Gyn Preservative). The head of the device is detached and left in the vial which is then capped and transported to the cytology laboratory. The vials are then vortexed to re-suspend the cell pellet and an aliquot is placed into a centrifuge vial using the SurePath PrepMate™ device. The aliquot is treated through a density gradient centrifugation process to remove unwanted material and a concentrated pellet of cervical cells is produced. The pellet is then re-suspended and the PrepStain® slide processor transfers an aliquot to a settling chamber mounted on a microscope slide. Cells sediment onto the slide to form a thin layer and the excess fluid and cells are discarded. The slides are routinely stained as part of the automated process. The cytology slides will be analysed in the normal manner, according to Cervical Screening Wales policy. They will undergo primary screening, checking and referral for consultant reporting as required. Residual samples are kept normally until a report has been issued with storage at room temperature.

4.2 FPGS Sample Scanning

Slides prepared from SurePath LBC samples will be collected, transported by courier to SBS' laboratories in Nottingham and scanned as per CSW CAESAR Standard Operating Procedures and Protocols (SOPPs). Slides are then returned to the originating laboratories along with the relevant scan data via USB pen drives. This data is then accessed and presented to the operator vial the Guided Screening Workstation,

4.3 Data Analysis

Results will be collected via specific procedure codes on the TelePath Laboratory Information Management System (LIMS) and collated and analysed via the weekly information downloads by the CSW Information department.

Discrepant results between the automated and manual QA screening arms will be identified at a high level by the FPQQ procedure code.

4.3 Quality Controls and Assurance

The manual QC arm will be carried out in accordance with CSW SOPP reference LP-CSW-P00"___"

5.0 References

1. Advice for Cytopathology Laboratories on the Implementation of Liquid Based Cytology for Cervical Screening LBC (2004) *Implementation Guide* **No2** Version 1.

2. S B do Nascrimento Tavares *et al*. "Rapid pre-screening of cervical smears as a method of internal quality control in a cervical screening programme" Cytopathology vol 19, no 4 - August 2008

3. Three articles on rapid review in Cytopathology Vol 17, No 3 June 2006

4. P.Cross. Editorial "Rapid Screening: Cervical cytology a simple method with a big impact" Cytopath vol 15 no 2 April 2004.

5. N.J.Wilson and A.J.Moyneux. "Rapid review in cervical cytology: a retrospective review of cases detected on rapid review within a DH cytology lab on outcome" Cytopath vol 15 no 2 April 2004

6. M.Saville and H.Mitchel. "A randomized controlled trial evaluating rapid pre-screen of cervical cytology specimens" Cytopath vol 15 no 1 Feb 2004

7. J.Smith *et al*. "Rapid pre-screening – a validated quality assurance measure in cervical cytology" Cytopath vol 14 no 5 Oct 2003

8. D.Brooke *et al* "Rapid (Partial) Pre-screening of cervical smears: the quality control method of choice" Cytopath vol 13 no 4 Aug 2002

Computer **A**ssisted **E**valuation**, S**creening **a**nd **R**eporting **(CAESAR 2)** in Cervical Cytology; assessing its application in routine practice

6.0 Project Management

- **Principal Investigator: Mr. David Nuttall**

- **Programme Manager: Mr Bryan Rose**

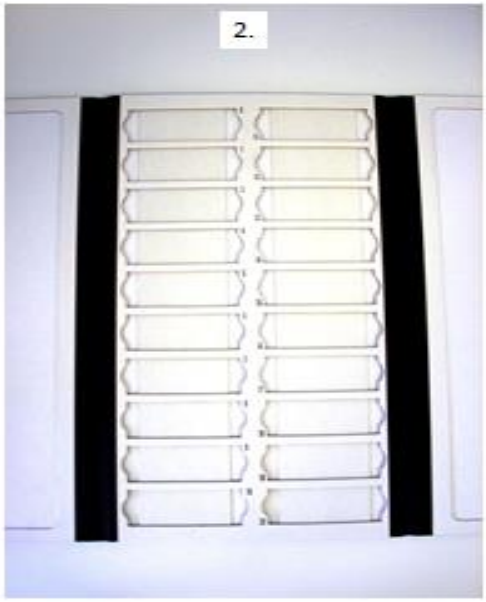
- **Management and Coordinator for record linkage: Helen Beer /Kate Gregory**

- Helen Beer is the Information Analyst/ Manager and Kate Gregory is the Senior Information Officer for Screening Services within Cervical Screening Wales.

Appendix 9

Laboratory Instruction – CAESAR 2

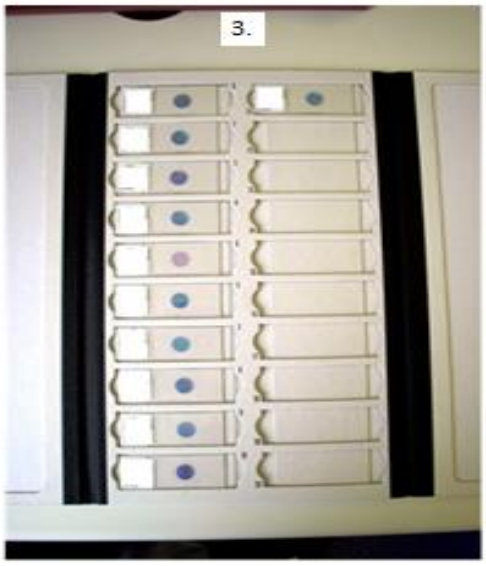
Slide Packaging Guidance



Use 20-position numbered slide trays only.

1. Place first slide for processing in position 1.
2. Fill tray following numbered sequence

3+4. Complete for all trays to be processed.



Place completed slide trays in batches with first tray at top of batch.

5. Secure tray batch with 2 horizontal elastic bands.
6. Secure tray batch with 2 vertical elastic bands.
7. Secure tray batch with 2 horizontal elastic bands.
8. Place trays in cardboard inner (flaps uppermost).

Place cardboard inner into slide transport box ensuring drawstrings loop around trays.
9+10. Tighten toggle on both draw strings to secure slide trays.
11. Fill any remaining space in transport box with bubble wrap
12. Close lid and secure both clips. Place address label in clear plastic holder

Appendix 10

Cervical Screening Wales
Sgrinio Serfigol Cymru

CAESAR 2

FOCALPOINT PROJECT

STANDARD OPERATING PROCEDURE

VALIDATION HISTORY

DATE OF ISSUE	AUTHOR	AUTHORISED BY	DATE OF REVIEW
01/01/2009	Medical Solutions	FP Operational Group	

RISK ASSESSMENT			
Personnel: BMS Cytoscreener	Training: Senior BMS	Hazards: None	Quality Controls: None

LABORATORY PROCEDURE

Introduction and purpose

Sample Tracking and Audit

Specimen requirements

Bar coded slides

Equipment and reagents

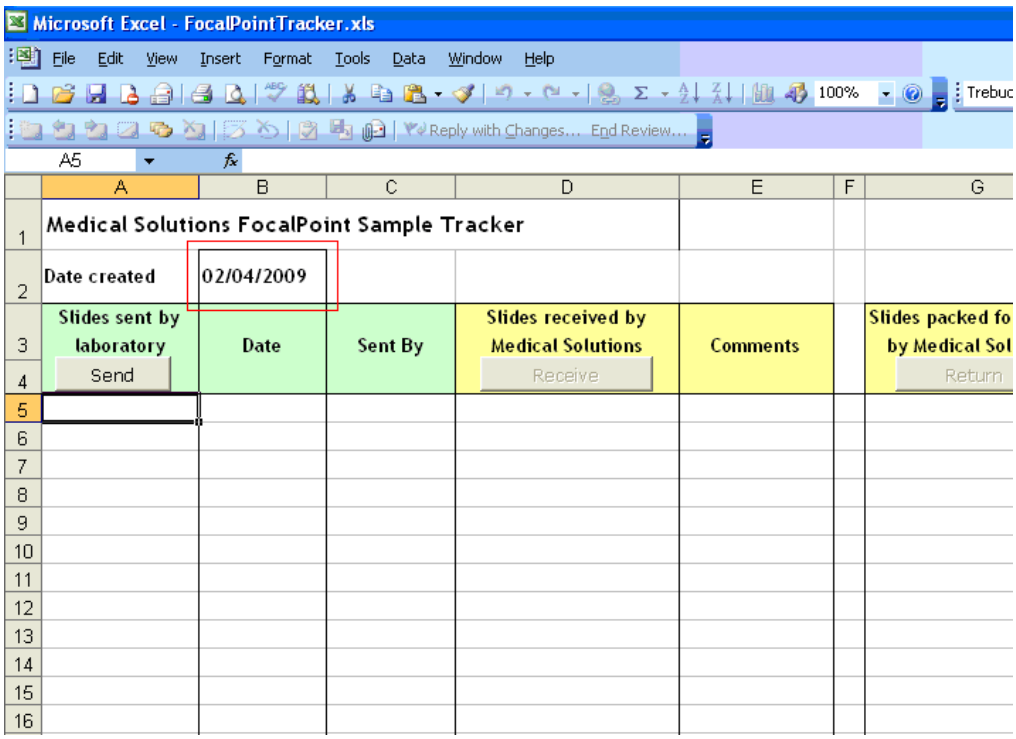
Personal computer and Medical Solutions Tracker software

Procedure

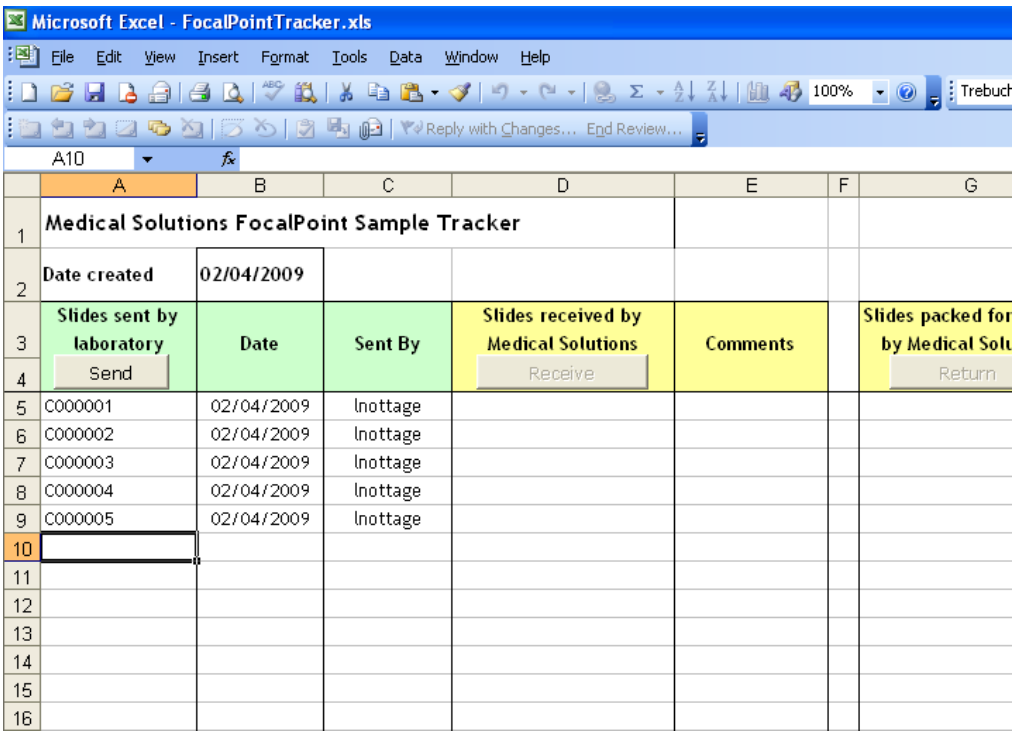
Using the FocalPoint Tracker Software

1. Open the FocalPoint Tracker template (Microsoft Excel spreadsheet).
N.B. It is important to note that the template form of this document should never be altered by a user saving any changes made to the original file.

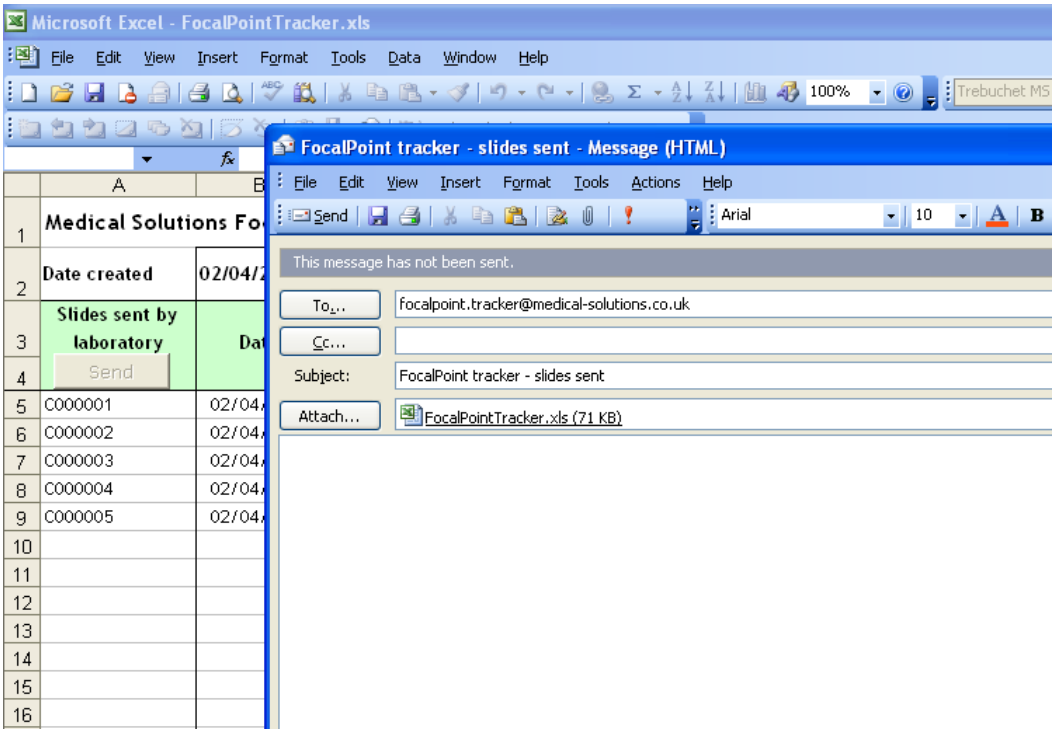
2. When the template form is opened the 'Date created' cell will autofill according to the date on the PC calendar.



3. Scan the barcodes of slides to be included in the batch to be sent to Medical Solutions. The form will start to fill a line of information for each slide: barcode number, date of scan and which user scanned in the slide (this is dependent on the username used when logging on to the PC).



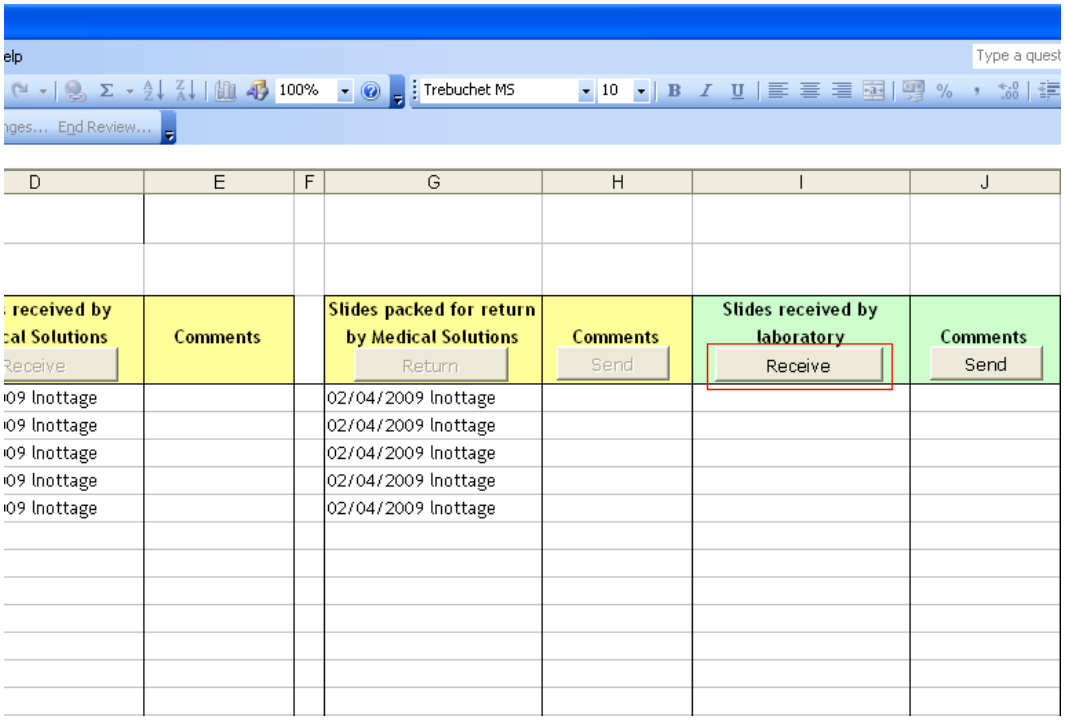
4. Once all slides to be sent in the batch have been entered click the 'Send' button. The form is then placed automatically as an e-mail attachment (Microsoft Outlook only) with the e-mail address autofilled.



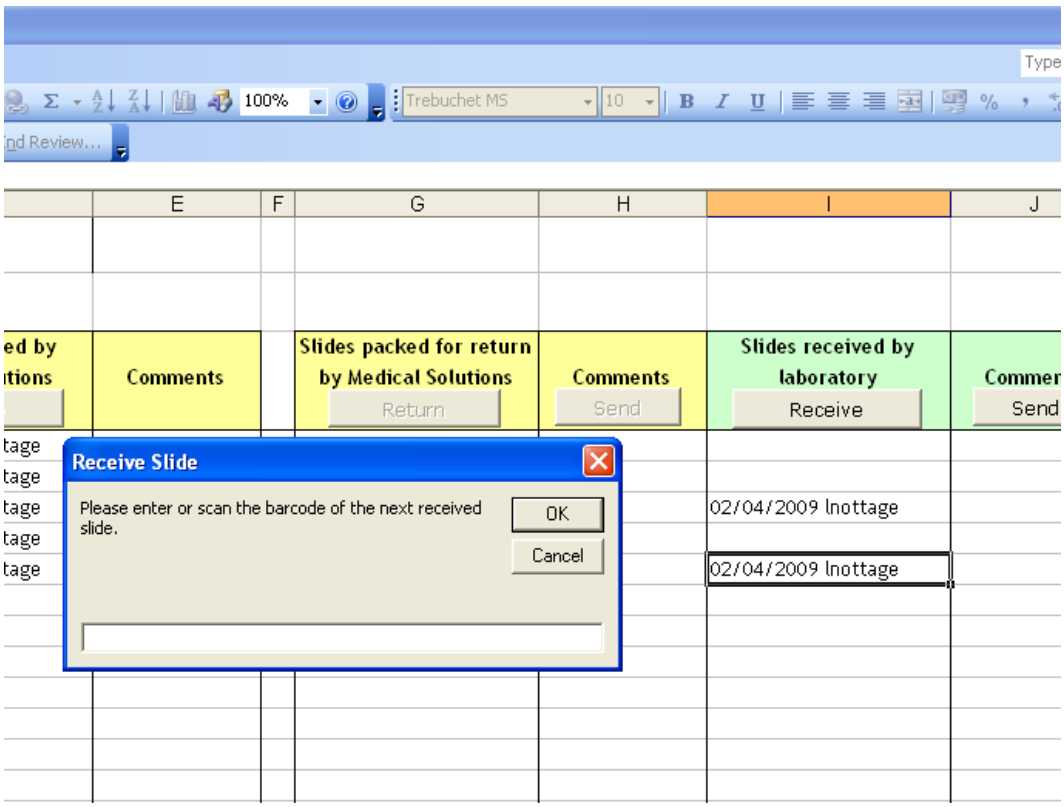
5. Add any comments needed to the body of the e-mail and then click 'Send'. The form is then sent to the relevant staff at Medical Solutions who will expect receipt of the slides via courier.

6. Close the FocalPoint Tracker form without saving changes made or alternatively save the form under a unique name e.g. FP_Tracker02.04.2009. It is important that any changes made are not saved under the original FocalPointTracker.xls filename.

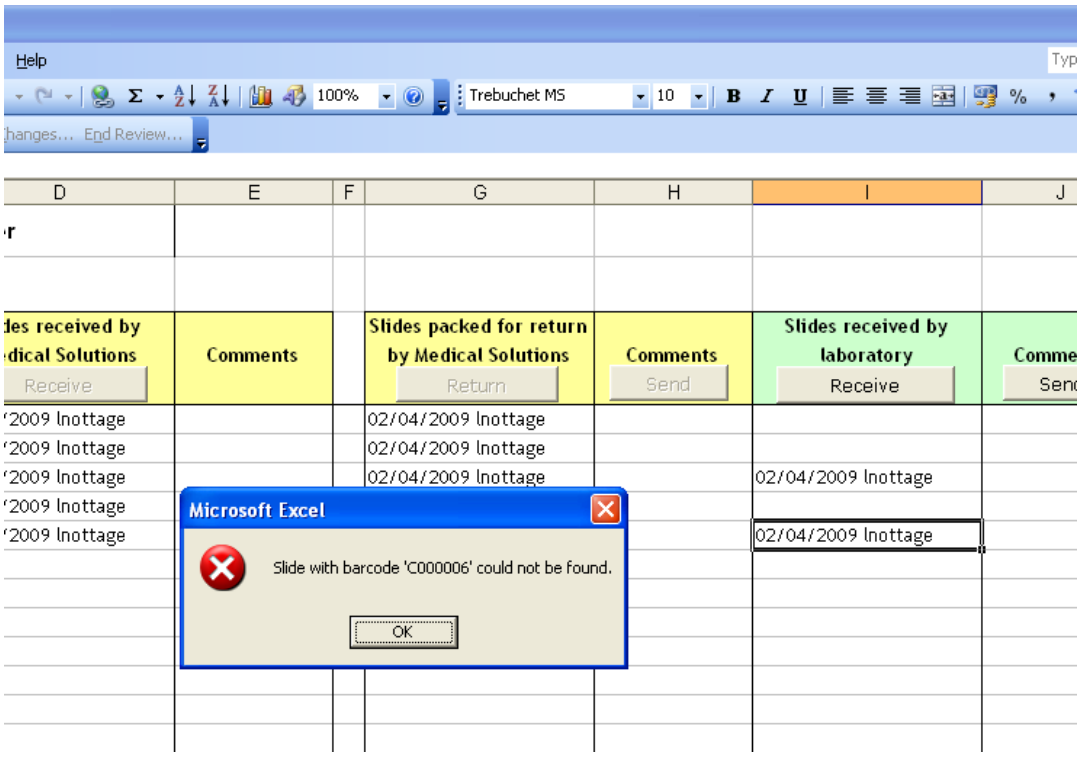
7. Upon receipt of slides back to the laboratory open the tracker form sent by Medical Solutions that corresponds to that particular batch and click 'Receive' in the 'Slides received by laboratory' column.



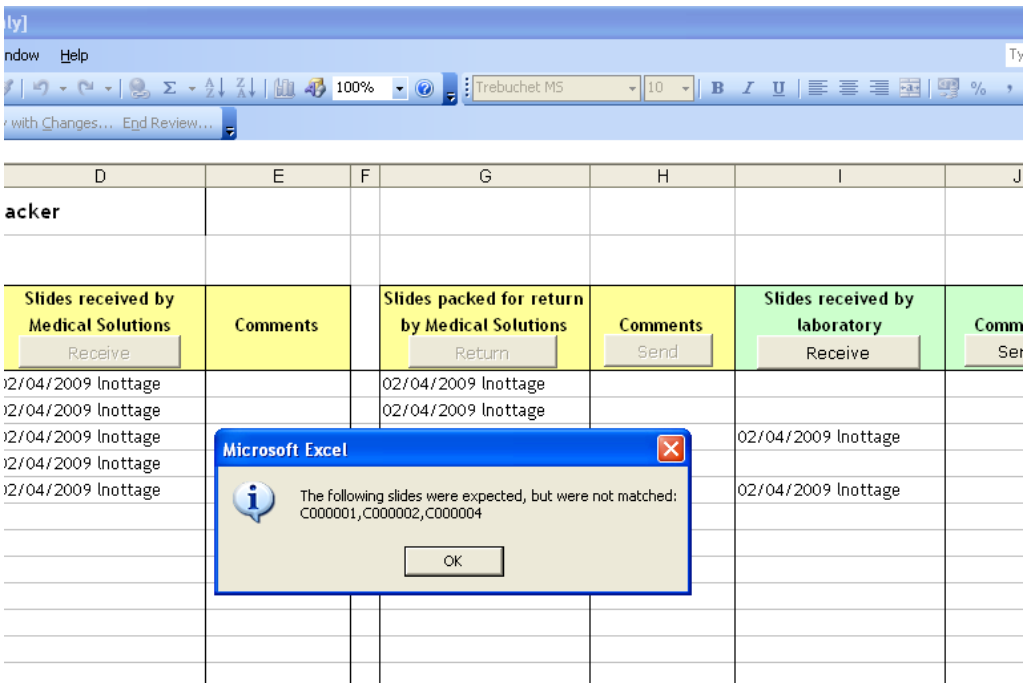
8. Scan all slides returned. When slides are scanned the 'Slides received by laboratory' column will autofill with the date and username of the logged in user. There is no need to scan slides received in a particular order as the program will recognise slides from the list in whatever order they are scanned back.



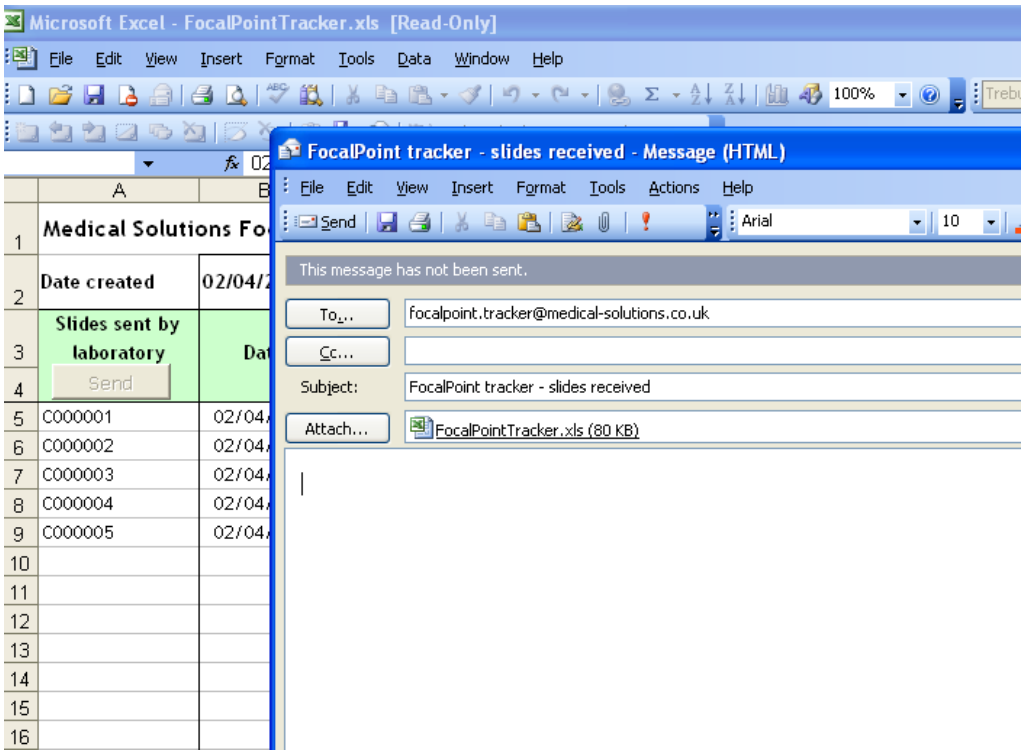
9. If a slide is scanned that was not part of the original batch the following message will be seen:



10. If the user clicks ok after scanning all slides from the batch and there are slides
that have either not been returned to the lab or not scanned correctly the following message will be seen:



11. Once all slides have been successfully scanned back in by the laboratory click the ‘Send’ button. The form is then placed automatically as an e-mail attachment (Microsoft Outlook only) with the e-mail address autofilled.



12. Add any comments needed to the body of the e-mail and then click ‘Send’. The form is then sent to the relevant staff at Medical Solutions who will file the completed audit trail for the batch.

13. Click ‘File’ then ‘Save As’ and give the file a unique name e.g. FP_Tracker02.04.2009. This will then be the laboratories completed audit trail of the slide batch.

Appendix 11

CAESAR
Focal Point Project - Result and workload codes

To be collected via procedure codes on TelePath and collated by CSW information unit.

– ***Highlighted text denotes additions or changes to the previous version***

PROPOSED CODES:

CODE	QUALIFIER	EXPANSION
SCRNEG	Where "SCR" = screener initials	**Screener FP opinion negative**
SCRABN	Where "SCR" = screener initials	**Screener FP opinion abnormal**
SCRFCR	Where "SCR" = screener initials	**Screener FP opinion further check required**
CHRNG	Where "CHR" = checker initials	**Checker FP opinion negative**
CHRAN	Where "CHR" = checker initials	**Checker FP opinion abnormal**
CHRFCR	Where "CHR" = checker initials	**Checker FP opinion further check required**
FPQ	FP = Focal Point Q code as for manual QC screen	**Positive correlation – Manual:Automated Arm**
FPQQ	FP = Focal Point QQ code as for manual QC screen	**Discrepancy – Manual:Automated Arm**
FOV+	FOV: Fields of View	**Abnormal: in FOV**
FOV-	FOV: Fields of View	**Abnormal:not in FOV**

GUIDANCE NOTES FOR IMPLEMENTATION AND USE

FP quintile results

FP followed by quintile number 1 – 5
FPSC – FP scant cellularity
(This code to be used if a slide is rejected by FP due to poor cellularity of the sample.

FP recommendations

NFR – No Further Review
FR – Further Review – *Full Manual Screen- manual screening arm*
FPPRV– Process Review – *Full Manual Screen – manual screening arm*
This code is employed when the Focal Point processor has been unable to read the slide – e.g. unable to read barcode or coverslipping problems. In this case, 10 F.O.V. will not be available.
Note Manual/Automated arm cannot be correlated, therefore FPQ/FPQQ cannot be used.
RR – Re-run – *Full Manual Screen – manual screening arm*
(This message is given if a tray fails the integrity Test performed at the beginning and the end of each tray by FP. On failing this test once the tray may be scanned again. On failing a second time the tray must be screened manually. This situation should only happen exceptionally). ***Note Manual/Automated arm cannot be correlated, therefore FPQ/FPQQ cannot be used.***

Action by Screener

Each of the following is preceded by the screener's initials

NEG - Negative
ABN - Abnormal
FCR - Not sure, Further Check Required
(This code is used to identify slides that the screener requires a full manual screen (FMS). These slides are not considered to be obviously abnormal, but may inflammatory or otherwise equivocal in nature).

Action by Checker – if indicated by screener, see ABN/FCR above

Each of the following is preceded by the checker's initials

NG - Negative
AN - Abnormal
FR - Not sure, Further Check Required
Note: middle character dropped to distinguish between screening/checking function by same person.

(It is important that the checker who performs the 10 FOV check on the LGS does not complete a manual screen on the same slide as well. In this way the two arms of the screening process can be compared totally independently of one another)

Pathologist/AP opinion – not required

(this can be picked up via the opinion log on TelePath)

Focal Point/Manual Screen correlation

Prior to release of the reports following completion of the manual arm, the CCM or senior member of staff will compare the results of the manual and automatic arms and will code as follows:

FPQ - positive correlation
FPQQ - discrepancy

Additional scenarios re: Focal Point

All cases reported by FP as NFR should be correlated FPQ/FPQQ depending on final result from the manual arm.

If a screener is not confident that the 10 FOVs are negative then FCR preceded with screener initials is recorded (NEG not ticked). If this case is not resolved as either negative or abnormal by checker - NO CORRELATION RECORDED (Hopefully these will be few and far between!). It is the checker in these FCR cases that will determine whether negative or positive as would happen in the normal lab QC, and subsequently whether or not the final result correlates between the manual and automated arms, therefore there is no need for the screener to tick the NEG box too.

Further Validation of FPQ/FPQQ codes
On microscopical validation of FPQQ samples, if it has been discovered that the abnormality is not in the 10 FOVs then the sample will be coded FOV- (Abnormal:not in FOV).
Conversely, if subsequent case validation indicates that the abnormality was in the FOVs then the sample will be coded FOV+ (Abnormal: in FOV)

This will help determine whether or not the abnormality was in the FOVs that were available to the screener, and will be an indicator of how effective is a QC screen that is limited to the FOVs only.

Appendix 12

CAESAR FocalPoint™ Trials
Staff User Experience Questionnaire

Dear Colleague,
I realise that it is a considerable time since you last used the FocalPoint Automated Screening technology, however, I would be very grateful if you could take some time to complete the questionnaire to the best of your ability!
Many, many thanks. Dave Nuttall.

1. **What is your staff grade?**

3. **Roughly how many months were you using the FocalPoint™?**

4. **How many years experience do you have working as a cytologist?**

TRAINING

4. Were you satisfied with the training for using FocalPoint™?

Excellent	Very good	Good	Fair	Poor

(Please tick the appropriate box)

5. Do you have any specific comments about how the training could be improved?

MANUAL AND AUTOMATED SYSTEM

6. Overall I prefer using the FocalPoint™ system compared with only using manual screening:

Strongly agree	Agree	Neu	Disag	Stro disa

(Please tick the appropriate box)

7. I find it easier to concentrate using the FocalPoint™ system compared with manual screening:

Stron agree	Agree	Neutral	Disagree	Strongly disagree

(Please tick the appropriate box)

8. My work is more challenging using the FocalPoint™ system compared with manual screening:

Strongly agree	Agree	Neutral	Disagree	Strongly disagree

(Please tick the appropriate box)

9. My work is more monotonous using the FocalPoint™ system compared with manual screening:

Strongly agree	Agree	Neutral	Disagree	Strongly disagree

(Please tick the appropriate box)

9. Did you experience any physical discomfort using either the manual or automated system?

Yes	No

11. Please describe any physical discomfort (noise, physical strain, motion sickness) you experienced and the circumstances around that experience.

Thank you for completing this questionnaire. Please return to Dave Nuttall, CSW, Preswylfa, Hendy Road, MOLD. CH7 1PZ.

Appendix 13

Report on the Evaluation of the BD FocalPoint™ "No Further Review" (NFR) Technology as part of Cervical Screening Wales.

1. **Author(s):** Dave Nuttall, Sharon Hillier	
2. **Date:** October 2012	3. **Version:** 1b
4. **Publication/ Distribution:** Focal Point NFR Task and Finish Group Cervical Screening Wales (CSW) All-Wales Management Group	
5. **Review Date:** Subject to recommendations from the CSW AWMG	
6. Purpose and Summary of Document: 7. This document outlines the evidence base and outcome of the CSW calibration exercise of the No Further Review technology. ***8.*** CSW All Wales Management Group is asked to consider the report and approve the recommendations that are made for the introduction and implementation of FR within CSW.	
9. **Work Plan reference:** This development forms part of the strategic work plan for the Public Health Wales Screening Division Laboratory Service.	

CONTENTS

10. Executive Summary

The cervical screening programme is currently facing the greatest period of change in its history. This period of change has brought with it no small amount of uncertainty and has resulted in an unprecedented drop in recruitment and training of cytology screening staff of all grades.

There remains a real risk that the laboratory screening service will be seriously compromised unless an alternative technology is available soon. The Human Papilloma Virus (HPV) has been identified as a causative agent of cervical cancer since the mid - 1970s, but as yet, primary screening using an HPV assay is still some time away from implementation. Computer Assisted Screening is a potential means to relieve service pressures; however, before incorporating this technology the programme needs to be assured that the current high standards of the programme are maintained.

Cervical Screening Wales has worked to establish the evidence base and commenced the CAESAR series of studies in 2006. This report outlines the evidence from these studies whose outcome were also supported by the Health Technology Assessment "Manual Versus Automated Reading in Cytology" or MAVARIC study[1]. This stated that the 'NFR' technology was a viable alternative to manual slide screening. This was endorsed by an implementation group commissioned by the UKNSC which outlined implementation guidance for the introduction of NFR in the NHS Cervical Screening Programme[2].

This report outlines the evidence base and outcome of the CSW calibration exercise of the NFR technology for consideration for incorporation with the current cervical screening Wales programme.

11. Background

The automation of cervical cytology screening has been the "holy-grail" for researchers and practitioners alike almost since the introduction of the Papanicolaou or "Pap" test, well over half a century ago. However, despite considerable investment over the years, cervical cytology remains as one of the few, predominantly manual, high volume tests performed within the health service laboratory.

In recent years the NHS Cervical Screening Programmes in the UK have experienced considerable service change and demands in terms of modernisation and the response to increasing public expectations about turnaround times. Amongst these changes/demands are emerging new strategies and technologies including HPV testing, liquid based cytology allowing adjuvant laboratory investigations and Computer Assisted Screening (CAS). These developments have instigated a loss of stability within the screening workforce, as staff retire and training programmes fail to recruit to what is perceived as a pathology discipline of limited life expectancy. This perception has now progressed to the extent that it poses a real risk to laboratory service resilience, continuity and maintaining quality standards such as turnaround times.

The prime advantage of the NFR technology is the designation of up to 25% of scanned samples as negative for dyskaryotic cells. In line with NHS CSP guidance, this is achievable in conjunction with a rapid quality assurance screen, as recommended in association with the current conventional screening pathway. This has proven potential in terms of workload reduction on the screening workforce.

In addition, the technology has potential application in the performance monitoring of smear takers, as initial studies on the CAESAR data indicate that FocalPoint™ is a more consistent means of detecting endocervical cell components of liquid based cytology samples. It is intended that further work on the Endocervical Cell Component assessment of the FocalPoint™ for the purposes of monitoring smear take performance will be carried out.

11.1. Technology Overview

This report focuses on the BD Focal Point NFR technology and this is detailed below:

The BD FocalPoint™ slide profiler is an automated imaging system designed to assist in the primary screening of SurePath™ and conventionally prepared cervical cytology slides.

• The device is intended to detect slides with evidence of squamous carcinoma and adenocarcinoma and their usual precursor conditions.

• Up to 300 individual features are evaluated by the BD FocalPoint™ by using both morphometric and densitometric algorithms, including:

- Size of nuclei
- Perimeter / shape of nuclei
- Texture of nuclei
- Cytoplasm features
- Nuclear density
- Nuclear/Cytoplasmic ratio
- Contrast

- The BD FocalPoint™ identifies up to 25% of successfully processed, i.e. with a viable scanning result, slides as requiring No Further Review (NFR), depending on the characteristics of the population screened.

- The FocalPoint™ sorts and ranks scanned slides between the values of 0 and 1, based on the likelihood of an abnormality being present. 0 is negative and 1 is abnormal, and the slide ranking is presented to operator as a quintile, ranging from 1 to 5. When used in conjunction with a BD FocalPoint™ Guided Screener Review Station the 10 highest scoring Fields Of View (FOV) from each qualified slide are presented to the screener for review through the use of an automated stage fitted to a standard laboratory microscope (note that the guided screener option is not currently recommended for use in the UK). Slides ranked and categorised as NFR are considered as having a very low abnormality potential and therefore do not have FOV available for review. **See fig. 1**

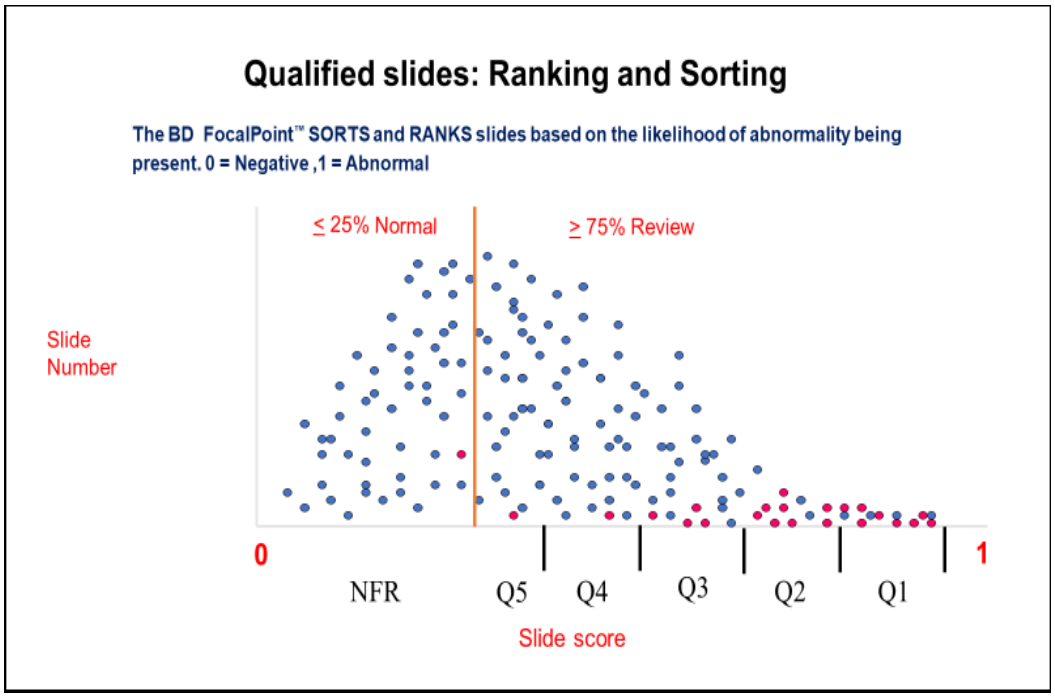


Fig. 1. FocalPoint sorting and ranking functions

11.2. Research

Computer Assisted Screening has recently been the object of the "MAVARIC" study which concluded that there was no advantage in using CAS (guided screening) compared to manual screening. However it did report that the No Further Review (NFR) category of the Becton, Dickinson and Company™ (BD) FocalPoint™ slide imager technology (FP) showed considerable promise in terms of increased diagnostic reliability and productivity and warranted further investigation.
Just preceding MAVARIC, in 2006, the CAESAR (Computer Assisted Evaluation, Screening And Reporting) series of studies on BD FocalPoint™ Guided Screener technology were initiated by CSW. This technology primarily evaluated CAS as an alternative to a rapid quality assurance screen, however, the functionality of the technology, in terms of the NFR function and the design of the studies subsequently allowed this functionality to be assessed. The NFR related results from the studies are presented in this report in section 3.

11.3. UK recommendations

MAVARIC concluded that the sensitivity of NFR was better than 99% for CIN2+ lesions. Furthermore, this conclusion was considered by the UK National Screening Committee (UKNSC) and an implementation group chaired by Dr Karin Denton, Chairman of the British Association of Cytopathology, was commissioned to recommend on the implementation of NFR for the NHS CSP. This group reported back in November 2011[2], with the implementation guidance for the introduction of NFR in the NHS Cervical Screening Programme.

12. Performance of NFR as demonstrated by the CAESAR studies

The CAESAR studies were carried out over the following time periods:
CAESAR 1: (15/02/2007 to 30/11/2007) The laboratories involved were: Llandudno General Hospital, Glan Clwyd Hospital and Maelor General Hospital.
CAESAR 2: (01/07/2009 to 31/05/2010) The laboratories involved were: Llandudno General Hospital, Glan Clwyd Hospital, Maelor General Hospital and the Royal Gwent Hospital.
CAESAR 3: (01/12/2010 to 31/07/2011) This study involved the Royal Gwent Hospital only.
The cases compared in this report were as follows:

1. Cases (n= 8130) that had been designated by the FocalPoint™ as NFR, had a negative rapid QA screen (rapid review or preview) and were reported negative, with a normal recall.

2. Cases (n= 93473) that were received and screened manually to current CSW procedures over the period that each study was conducted (see above), had a negative rapid QA screen (rapid review or preview) and were reported negative, with a normal recall.

The histological outcomes of these cases, in terms of any incidental interval findings were compared and correlated over a two year period after the cytology was reported. Two years was chosen as this review period gave the highest yield of suitable cases for comparison, given that the CAESAR 3 study was only completed as recently as July 2011.

12.1. Combined two year outcome data for all CAESAR studies

Cases designated by FocalPoint™ as NFR compared to cases designated as negative by manual screening over the duration of the studies.

Outcomes	**NFR**	**Cases manually screened as per existing CSW SOPPs**
CIN 2+ cases @ 2 years	9	196
Total Number of cases	8130	93473
Percentage	**0.11%**	**0.21%**

Considering all three CAESAR studies, those cases designated NFR by FocalPoint™ accounted for less than half the CIN2+

cases than those manually screened as per CSW SOPPs and reported during the study periods.

12.2. Interval cancer and precancer cases detected amongst cases designated by FocalPoint™ as NFR compared to cases designated as negative by manual screening over the duration of the studies.

NFR Total cases = 8130		**Cases manually screened as per existing CSW SOPPs Total Cases = 93473**	
Precancers	Cancers	Precancers	Cancers
8	**1**	**186**	**10**
8	**1**	**16***	**1***

Proportionally*, the interval precancer prevalence rate for FocalPoint™ NFR was half that of manual screening to current CSW SOPPs which was statistically significant (Confidence Interval Analysis – version 2.0.5). Interval cancer prevalence rates were the same for NFR and manual screening. It can be hypothesised that due to the lower prevalence of precancer with NFR; then, as time progresses this should result in decreased interval cancer rates.

13. Implementation considerations: Calibration

The appropriate calibration of the technology is a fundamental part to ensuring the technology is effective. A Laboratory Preparation Calibration Assessment (LPCA) is necessary which is the validation and qualification of a subset of slides that represent the lab's routine work. This is to calculate thresholds based on different variables such as staining, slide preparation and unusual events within the regional population. A minimum of 1000 slides are required from the laboratory:

- They must be representative of the workload that is proposed for scanning.

- This is set by Becton-Dickinson (BD) dialling in remotely to the FocalPoint™, monitoring internal parameters and calibrating the instrument accordingly.

- Any changes to the nature of the lab's workload, e.g. assimilation of another laboratories workload or change of age range or screening frequency must be notified to Source BioScience immediately for the LPCA to be reset.

13.1. Results of the LPCA calibration at Magden Park, Llantrisant

Two FocalPoint™ GS systems 202 and 328 were installed at Public Health Wales Screening Division laboratory at Magden Park, Llantrisant. Once installed just over 1000 slides were submitted for scanning by the two systems to undertake the LPCA calibration.
The calibration process involved putting the same batch of over a 1000 slides through each machine. On reviewing the results, the Head of Laboratory services discovered a discrepancy in process review rates and the NFR/review case correlation between the two instruments. This was regarded as an irregular finding considering that identical slides had been scanned and Source BioScience were informed. On investigation one instrument had developed a fault that was later diagnosed as a failed strobe unit.
The Head of Laboratory services requested that the LPCA was repeated as soon as the faulty instrument was repaired. This was carried out and compared to the original LPCA findings as described in section 4.1.1 and 4.1.2.

13.1.1. FocalPoints 202 and 328 – Results of the first LPCA

		FP328					
		NFR	**Q1**	**Q2**	**Q3**	**Q4**	**Total**
FP202	**NFR**	86	1	6	7	16	**163**
	Q1	1	0	0	0	0	**1**
	Q2	3	0	0	0	0	**3**
	Q3	17	0	0	0	0	**17**
	Q4	27	0	0	0	0	**27**
	Q5	36	1	0	0	0	**37**
	Total	**170**	**2**	**6**	**7**	**16**	**248**

		A FP 202		B. FP 328	
A. Cases FP202 NFR and FP238 Q1-5	**77**	**Final Result**	**Number**	**Final Result**	**Number**
		Inadequate	3	Neg	75
		Negative	71	Mild Dysk	1
B. Cases FP328 NFR and FP202 Q1-5	**84**	Mild Dysk	1	Mod Dysk	1
		Severe Dysk	1	Borderline	7
		Borderline	1		
			77		**84**

comparison on the 248 samples assigned by either instrument to NFR. There were 1092 samples in total

13.1.2. First LPCA – combined summary percentage for both instruments

	Number	**%**
Missed Low Grade Dyskaryosis	10	**6.2**
Missed High Grade Dyskaryosis	2	**1.2**
Total Dyskaryosis Missed – All Grades	12	**7.5**
Total	**161**	

13.1.3. FocalPoints 202 and 328 – Results of the second LPCA comparison of the 360 samples assigned by either instrument to NFR. There were 1151 samples in total

		FP328						
		NFR	**Q1**	**Q2**	**Q3**	**Q4**	**Q5**	**Total**
FP202	**NFR**	146	1	7	16	31	61	**262**
	Q1	2	0	0	0	0	0	**2**
	Q2	5	0	0	0	0	0	**5**
	Q3	15	0	0	0	0	0	**15**
	Q4	32	0	0	0	0	0	**32**
	Q5	44	0	0	0	0	0	**44**
	Total	**244**	**1**	**7**	**16**	**31**	**61**	**360**

		A FP 202		B. FP 328	
A. Cases FP202 NFR and FP238 Q1-5	**116**	**Final Result**	**Number**	**Final Result**	**Number**
		Inadequate	1	Inadequate	1
		Negative	109	Negative	92
B. Cases FP328 NFR and FP202 Q1-5	**96**	Severe Dysk	1	Mild Dysk	1
		Borderline	5	Borderline	1
				Bord ?HG	1
			116		**96**

13.1.4. Second LPCA – combined summary percentage for both instruments.

	Number	**%**
Missed Low Grade Dyskaryosis	7	**3.3**
Missed High Grade Dyskaryosis	2	**0.9**
Total Dyskaryosis Missed – All Grades	9	**4.2**
Total	**212**	

13.1.5. Discussion of the calibration results

The missed dyskaryosis rate is reduced for the analysis of the second LPCA although this is not significant. It's not known if this can be

directly attributed to the malfunction of FP 202 during the first LPCA setting exercise.

No comparative data in terms of multiple instrument concordance limits exists; indeed the manufacturers indicate that there will be variance between the outputs of multiple instruments even if the same samples are scanned. The results present data on those samples that were in the NFR section and these are 248 out of the 1092 samples for the first calibration and 360 out of the 1151 samples in the second calibration. It is important to note that the missed dyskaryosis percentage reflect that two instruments have been calibrated and the percentage are therefore averaged and the same slides have been scanned by them both. The important issue here is that these exercises are compared like with like so that that developing trends may be detected that may then allow calibration confidence limits/values to be developed.
The results of the two calibration exercises indicate that is is important that all instruments are fully functional before an LPCA is carried out, and that if any contraindication exists, for example, raised sample process review rates, then the manufacturer should be contacted immediately and the LPCA repeated soon as the instruments have been checked and declared fully functional by the manufacturer.
It is important to note that samples identified as NFR in routine practice would be subject to a further rapid review. Also, the remaining results were assigned to categories Q1-Q5 by both machines and would have been managed by the current conventional screening pathway. Finally, findings would seem to highlight that the LPCA process is vital to the satisfactory performance of the FocalPoint™ NFR technology, and local as well as manufacturers' recommended protocols and procedures must be adhered to ensure satisfactory results.

14. Conclusions and Recommendations.

14.1. Conclusions

This report outlines the evidence base and outcome of the CSW calibration exercise of the No Further Review technology for consideration for incorporation with the current Cervical Screening Wales programme. There is guidance from the UK for its implementation and evidence from research and also the calibration exercise undertaken in situ.

In conclusion, therefore, there is evidence that this technology is of sufficient quality to be implemented as part of the current Cervical Screening Wales programme. This technology works within acceptable levels of identifying samples that can be subject to a further rapid review and on that basis be issued with a result reported as negative that requires no further screening.

The implementation of this technology will offer potential benefits of increase throughput and relieve service pressure to ensure a sustainable laboratory service.

14.2. Recommendations

The Task Group responsible for the implementation of the FocalPoint™ technology within Cervical Screening Wales therefore recommend the adoption of the technology subject to the following provisos:

The manufacturers and CSW protocols and procedures will be adhered to at all times.

That each FocalPoint™ instrument is uniquely identified so that adverse performance can be fully traced, identified and subsequently rectified. It is recommended that each FocalPoint™ is designated on the Laboratory Information Management System (LIMS) in much the same manner as a cytoscreener/Biomedical Scientist. In this implementation, it should then be possible to produce performance data in terms of a comparison of the final outcomes of the samples that have been scanned.

That an LPCA is carried out periodically as a tandem scanning exercise on the same samples. It should be possible to arrive at tolerance values expressed as limits of concordance which indicate satisfactory performance. Once these become established, it may be prudent to carry out this exercise following a service visit and/or following a period of down time after repairs have been carried out on faulty equipment.

15. Acknowledgements

The authors wish to acknowledge the contribution of the following persons as members of the CSW Task Group involved in introducing the NFR technology in Cervical Screening Wales:

Dr Rose Fox
Mr Bryan Rose
Mr Rhys Blake
Ms Helen Beer
Dr Nick Dallimore

In an advisory capacity:

Professor John O'Leary, School of Medicine, Trinity College, Dublin.

16. References

1. Kitchener HC, Blanks R, Dunn G, Gunn L, Desai M, Albrow R, *et al*. Automation-assisted versus manual reading of cervical cytology (MAVARIC): a randomised controlled trial. Lancet Oncol. 2011 Jan;12:56-64.

2. Denton KJ, Nuttall D, Cropper A, Desai M *et al*. Implementation of "No Further Review" (NFR) using the BD FocalPoint™ Slide Profiler – Interim Guidance for the NHS Cervical Screening Programme. NHS CSP Good Practice Guide No. 4, March 2012.

References

Abulafia O, Sherer DM. Automated cervical cytology: meta-analyses of the performance of the AutoPap 300 QC System. Obstet. Gynecol. Surv. 1999 Jul;54(7):469-76.

Agenda for Change – Pay Rates. URL: https://www.healthcareers.nhs.uk/about/careers-nhs/nhs-pay-and-benefits/agenda-change-pay-rates – (Accessed on September 12th, 2017).

Alasio LM, Alphandery C, Grassi P, Ruggeri M, De Palo G, Pilotti S. Performance of the AutoPap Primary Screening System in the detection of high-risk cases in cervicovaginal smears. Acta Cytol. 2001 Sep-Oct;45(5):704-8.

Analysis and a simulation modelling exercise applied to the UK. Health Technol. Assess. 2005 Mar;9(13):1-207, iii. Review.

Arbyn M, Anttila A, Jordan J, Ronco G, Schenk U, Segnan N, Wiener H, Herbert A, von Karsa L. European Guidelines for Quality Assurance in Cervical Cancer Screening. Second Edition—Summary Document. Annals of Oncology 2010; 21: 448–458.

Baer A, Kiviat NB, Kulasingam S, Mao C, Kuypers J, Koutsky LA. Liquid-based Papanicolaou smears without a transformation zone component: should clinicians worry? Obstetrics and Gynaecology 2002; 99(6):1053-1059.

Bengtsson E, Malm P. Screening for Cervical Cancer Using Automated Analysis of PAP-Smears. Computational and Mathematical Methods in Medicine. Volume 2014, Article ID 842037, 12 pages. http://dx.doi.org/10.1155/2014/842037

Bentz JS. Liquid-based cytology for cervical cancer screening. Expert Rev. Mol. Diagn. 2005 Nov;5(6):857-71.

Bibbo M, Hawthorne C, Zimmerman B. Does use of the AutoPap assisted primary screener improve cytologic diagnosis? Acta Cytol. 1999 Jan-Feb;43(1):23-6.

Bibbo M, Hawthorne C. Performance of the AutoPap primary screening system at Jefferson University Hospital. Acta Cytol. 1999 Jan-Feb;43(1):27-9.

Birdsong G, Howell L, Atkison K, Marshall Austin R, Bibbo M, Bonfiglio TA, Davey DD, Keebler C, Mody D, Savaloja L, Papillo J, Prey M, Raab S, Schulz BL, Solomon D. Scientific issues related to the cytology proficiency regulations. Cytojournal 2006; 3(11).

Blatt AJ, Kennedy R, Luff RD, Marshal Austin R, Rabin DS. Comparison of Cervical Cancer Screening Results Among 256,648 Women in Multiple Clinical Practices. Cancer Cytopathology 2015; 282-288.

Bolger N, Heffron C, Regan I, Sweeney M, Kinsella S, McKeown M, Creighton G, Russell J, O'Leary J: Implementations and evaluation of a new automated interactive image analysis system for cervical cytology. Acta Cytol 2006; 50:483–491.

Bos A, Van Ballegooijen M, Akker-van Marle ME, Hanselaar AGJM, Van Oortmarssen GJ, Habbema JDF. Endocervical status is not predictive of the incidence of cervical cancer in the years after negative smears. American Journal of Clinical Pathology 2001; 115:851-855.

Bowditch RC, Clarke JM, Baird PJ, Greenberg ML. Morphologic analysis of false negative SurePath® slides using Focalpoint™ GS computer-assisted cervical screening technology: An Australian experience. Diagnostic Cytopathology. 2015 Nov;43(11):870-8. doi: 10.1002/dc.23314. Epub 2015 Jul 15. PubMed PMID: 26174002.

Brinton LA. Epidemiology of cervical cancer - overview. In Muñoz N, Bosch FX, Shah KV *et al*. Eds. The Epidemiology of cervical cancer and human papillomavirus. Lyon: International Agency for Research on Cancer; 1992.

British Association for Cytopathology. Recommended Code of Practice for Cytology Laboratories participating in the UK Cervical Screening Programmes. 2015.

British Society for Clinical Cytology. Cell content of cervical smears. Cytopathology. 1990,(1):129:130.

British Standards Institution Standards Publication. Medical Laboratories – Requirements for quality and competence (ISO 15189:2012)

British Society for Clinical Cytology. Recommended Code of Practice for Cytology Laboratories participating in the UK Cervical Screening Programmes. 2009.

Broadstock M. Effectiveness and cost effectiveness of automated and semi-automated cervical screening devices: a systematic review of the literature. N Z Health Technology Assessment Report 2000;3(1).

Brooke D, Dudding N, Sutton J. Rapid (partial) pre-screening of cervical smears: the quality control method of choice? Cytopathology. 2002 Aug;13(4):191-9.

Brown AD, Garber AM. Cost-effectiveness of 3 methods to enhance the sensitivity of Papanicolaou testing. JAMA. 1999 Jan 27;281(4):347-53.

Brown E. The ultimate goal? It depends. Physician Exec. 1996 Oct;22(10):50-2.

Buckley JD, Harris RW, Doll R, Vessey MP, Williams PT. Case-control study of the husbands of women with dysplasia or carcinoma of the cervix uteri. Lancet 1981;2(8254):1010-5.

Bulgaresi P, Cariaggi MP, Troni GM, Ciatto S. Quality control of the Autopap screening system employed as a primary screening device: rapid review of smears coded as no further review. Tumori. 2006 Jul-Aug;92(4):276-8.

Burk RD, Ho GY, Beardsley L, Lempa M, Peters M, Bierman R. Sexual behavior and partner characteristics are the predominant risk factors for genital human papillomavirus infection in young women. J. Infect. Dis. 1996;174(4):679-89.

Cancer Research UK. Cervical Cancer (C53): 1993-2014. European Age-Standardised Incidence Rates per 100,000 poulation, Females, UK. www.cancerrsearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/cervical-cancer/incidence#heading-Two -
(Accessed on September 8th, 2017).

Cenci M, Giovagnoli MR, Olla SV, Drusco A, Vecchione A. [Automation of cytological analysis of cervical smears]. Minerva Ginecol. 1999 Jul-Aug;51(7-8):291-8. Review.

Cengel KA, Day SJ, Davis-Devine S, Adams CL, Madison-Henness D, Hartman ME, Freund GG. Effectiveness of the SurePath liquid-based Pap test in automated screening and in detection of HSIL. Diagnostic Cytopathology. 2003 Nov;29(5):250-5.

Chang AR, Lin WF, Chang A, Chong KS. Can technology expedite the cervical cancer screening process? A Hong Kong experience using the AutoPap primary screening system with location-guided screening capability. Am. J. Clin. Pathol. 2002 Mar;117(3):437-43.

Chute DJ, Lim H, Kong CS. BD focalpoint slide profiler performance with atypical glandular cells on SurePath Papanicolaou smears. Cancer Cytopathol. 2010 Apr 25;118(2):68-74.

Colgan T. The adequacy of the Papanicolaou smear. Canadian Medical Association Journal 1994; 150(25).

Colgan T J, Bon N, Lee JS, Patten SF Jr. AutoPap 300 QC system scoring of cervical smears without "epithelial cell abnormalities". Acta Cytol. 1997 Jan-Feb;41(1):45-9.

Colgan T J, Patten SF Jr, Lee JS. A clinical trial of the AutoPap 300 QC system for quality control of cervicovaginal cytology in the clinical laboratory. Acta Cytol. 1995 Nov-Dec;39(6):1191-8.

Colgan T J, Smith J, Patten SF Jr, Lee JS. Enhancing the performance of the AutoPap 300 QC system with optimal staining and presentation of cervical smears. Acta Cytol. 1997 Jan-Feb;41(1):50-5.

Colgan T J, Bon N, Clipsham S, Gardiner G, Sumner J, Walley V, McLachin M. A Validation Study for the FocalPoint™ GS Imaging System for Gynecologic Cytology Screening. Cancer Cytopathology. 2013 Apr;121(4):189-196.

Colgan T. Reply to a validation study of the Focalpoint GS imaging system for gynecologic cytology screening. Cancer Cytopathol. 2013 Dec;121(12):738. doi: 10.1002/cncy.21335. Epub 2013 Jul 10. PubMed PMID: 23843272.

Confortini M, Bonardi L, Bulgaresi P, Cariaggi MP, Cecchini S, Ciatto S, Cipparrone I, Galanti L, Maddau C, Matucci M, Rubeca T, Troni GM, Turco P, Zappa M, Carozzi F. A feasibility study of the use of the AutoPap screening system as a primary screening and location-guided rescreening device. Cancer. 2003 Jun25;99(3):129-34. PubMed.

Cropper A, Roberts C, VanSchalkwyck G. Evaluation of the BD FocalPoint Guided Screening Imaging System – an audit of sensitivity when used as an additional QC tool in cervical screening. SCAN – Journal of the National Association of Cytologists. 2010 21:2:39.

Cullen AP, Reid R, Campion M, Lorincz AT. Analysis of the physical state of different human papillomavirus DNAs in intraepithelial and invasive cervical neoplasm. J. Virol. 1991;65(2):606-12

Curtis P, Mintzer M, Morrell D *et al*. Characteristics and quality of Papanicolaou smears obtained by primary care physicians using a single commercial laboratory. Arch. Fam. Med. 1999; 8:407-413.

Cuzick J. Viral Load as a Surrogate for Persistence in Cervical Human Papillomavirus Infection. In: Franco ELF, Monsonégo J - editors. New developments in cervical cancer screening and prevention. Oxford: Blackwell Science; 1997. p 373-378.

Davey DD, Cox JT, Marshall Austin R, Birdsong G, Colgan TJ, Howell LP, Husain M, Darragh TM. Cervical cytology specimen adequacy: patient management guidelines and optimising specimen collection. Journal of Lower Genital Tract Disease 2008; 12(2):71

Davey DD, Marshall Austin R, Birdsong G, Buck HW, Cox JT, Darragh TM, Elgert PA, Hanson V, Henry MR, Waldman J. ASCCP Patient Management Guidelines: Pap Test Specimen Adequacy and Quality Indicators. Journal of Lower Genital Tract Disease 2002; 6(3):195-199.

Della Palma P, Moresco L, Giorgi Rossi P. [Health technology assessment report: Computer-assisted Pap test for cervical cancer screening]. Epidemiol. Prev. 2012 Sep-Oct;36(5 Suppl 3): 1-43. Italian. PubMed PMID: 23139174.

Denton K, Nuttall D, Cropper A, Desai M. Implementation of 'No Further Review' (NFR) using the BD FocalPoint^{TM} Slide Profiler. NHS Cervical Screening Programme Good Practice Guide No. 4, Second Edition, April 2013.

Department of Health. Cancer Reform Strategy. London: Department of Health; 2007.

Depuydt CE, Arbyn M, Benoy IH, Vandepitte J, Vereecken AJ, Bogers JJ. Quality control for normal liquid-based cytology: rescreening, high-risk HPV targeted reviewing and/or high-risk HPV detection? J. Cell. Mol. Med. 2009 Sep;13(9B):4051-60.

Depuydt CE, Benoy IH, Bailleul EJ, Vandepitte J, Vereecken AJ, Bogers JJ. Improved endocervical sampling and HPV viral load detection by Cervex-Brush Combi. Cytopathology. 2006 Dec;17(6):374-81.

Desai, M. Role of automation in cervical cytology. Diagnostic Histopathology. 2009 15:7:323-329.

Djemli A, Khetani K, Case BW, Auger M. Correlation of cytotechnologists' parameters with their performance in rapid prescreening of papanicolaou smears. Cancer. 2006 Oct 25;108(5):306-10.

Drummond MF, Sculpher MJ, Claxton K, Stoddart GL, Torrance GW. Methods for the economic evaluation of health care programmes. Oxford university press; 2015 Sep 24. Chapter 7 - Cost Analysis: p237.

Duvall E. Should the laboratory assess the sampling adequacy of cervical smears? Cytopathology 1997; 8:409-416.

Eichhorn JH, Brauns TA, Gelfand JA, Crothers BA, Wilbur DC. A novel automated screening and interpretation process for cervical cytology using the internet transmission of low-resolution images: a feasibility study. Cancer. 2005 Aug 25;105(4):199-206.

Elsheikh TM, Kirkpatrick JL, Cooper MK, Johnson ML, Hawkins AP, Renshaw AA. Increasing cytotechnologist workload above 100 slides per day using the ThinPrep imaging system leads to significant reductions in screening accuracy. Cancer (Cancer Cytopathol). 2010; 118:75-82.

Erbarut Seven I, Mollamemisoglu H, Eren F. Reliability of reporting the presence of transformation zone material in Papanicolaou smears using an automated screening system. Cytopathology 2017; 28:280-283.

Evans J, Redburn J, Roche M. Cervical Cancer in Berkshire, Buckinghamshire, Northamptonshire and Oxfordshire. 1997. Oxford Cancer Intelligence Unit

Faraker CA, Boxer ME. Rapid review (partial rescreening) of cervical cytology. Four years' experience and quality assurance implications. J. Clin. Pathol. 1996 Jul;49(7):587-91.

Farmery E, Gray JAM (1994). Report of the first five years of the NHS cervical screening programme. Oxford: National Coordinating Network.

Ferenczy A, Franco E. Cervical-cancer screening beyond the year 2000. The Lancet Oncology 2001; Vol 2.

Fetterman B, Pawlick G, Koo H, Hartinger J, Gilbert C, Connell S. Determining the utility and effectiveness of the NeoPath AutoPap 300 QC System used routinely. Acta Cytol. 1999 Jan-Feb;43(1):13-22.

Garcia-Closas R, Castellsague X, Bosch X, Gonzalez C. The role of diet and nutrition in cervical carcinogenesis: A review of recent evidence. Int. J. Cancer: 117, 629-637.

Hartmann KE, Nanda K, Hall S, Myers E. Technologic advances for evaluation of cervical cytology: is newer better? Obstet. Gynecol. Surv. 2001 Dec;56(12):765-74.

Hildesheim A, Schiffman MH, Gravitt PE, Glass AG, Greer CE, Zhang T, *et al*. Persistence of type-specific human papillomavirus infection among cytologically normal women [see comments]. J Infect. Dis. 1994;169(2):235-40.

Hologic Inc. (Headquarters), 250 Campus Drive, Marlborough, MA 01752 USA.

Huang TW, Lin TS, Lee JS. Sensitivity studies of AutoPap System Location-Guided Screening of cervical-vaginal cytologic smears. Acta Cytol. 1999 May-Jun;43(3):363-8.

IARC. (1995) IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, Vol. 64, Human Papillomaviruses. Lyon. p99.

Kardos TF. The FocalPoint System: FocalPoint slide profiler and FocalPoint GS. Cancer. 2004 Dec 25;102(6):334-9. Review.

Kelly JG, Cheung KT, Martin C, O'Leary JJ, Prendiville W, Martin-Hirsch PL, Martin FL. A spectral phenotype of oncogenic human papillomavirus-infected exfoliative cervical cytology distinguishes women based on age. Clin. Chim. Acta. 2010 Aug 5;411(15-16):1027-33. doi: 10.1016/j.cca.2010.03.029. Epub 2010 Mar 30. PubMed PMID: 20359472.

Kitchener HC, Almonte M, Gilham C, Dowie R, Stoykova B, Sargent A, et al. ARTISTIC: a randomised trial of human papillomavirus (HPV) testing in primary cervical screening. Health Technol. Assess. 2009;13(51).

Kitchener HC, Blanks R, Cubie H, Desai M, Dunn G, Legood R, et al. MAVARIC – a comparison of automation-assisted and manual cervical screening: a randomised controlled trial. Health. Technol. Assess. 2011;15(3).

Kitchener HC, Castle PE, Cox JT. Achievements and limitations of cervical cytology screening. Vaccine. 2006; 05:113.

Kiviat NB, Critchlow CW, Kurman RJ. Reassessment of the morphological continuum of cervical intraepithelial lesions: does it reflect different stages in the progression to cervical carcinoma? In Munoz N, Bosch FX, Shah KV, Meheus A (Editors), The Epidemiology of Cervical Cancer and Human Papillomavirus (IARC Scientific Publications No. 119), Lyon, IARC 1992, pp. 59-66.

Lancucki L, Sasieni P, Vessey MP. The impact of Jade Goody's diagnosis and death on the NHS Cervical Screening Programme. J. Med. Screen. 2012 Jun; 19(2):89-93.

Lee JS, Kuan L, Oh S, Patten FW, Wilbur DC. A feasibility study of the AutoPap system location-guided screening. Acta Cytol. 1998 Jan-Feb;42(1):221-6.

Lee JS, Wilhelm P, Kuan L, Ellison DG, Lei X, Oh S, Patten SF Jr. AutoPap system performance in screening for low prevalence and small cell abnormalities. Acta Cytol. 1997 Jan-Feb;41(1):56-64.

Lee BC, Lam SY, Walker T. Comparison of false negative rates between 100% rapid review and 10% random full rescreening as internal quality control methods in cervical cytology screening. Acta Cytol. 2009 May-Jun;53(3):271-6.

Lee BC, Lam SY, Walker T, Leung KM, Lam M, Lee JWY, Yeoh GPS, Keeng WC. The significance of endocervical cells and metaplastic squamous cells in liquid-based cervical cytology. Diagnostic Cytopathology 2009; 37:4.

Levi AW, Galullo P, Gordy K, *et al*. Increasing cytotechnologist workload above 100 slides per day using the BD FocalPoint GS imaging system negatively affects screening performance. Am J Clin Pathol. 2012;138:811-815.

Lozano R. Comparison of computer assisted and manual screening of cervical cytology. Gynecologic Oncology 2007; 104:134-138.

MacGregor JE, Campbello MK, Mann EMF, Swanson KY (1994). Screening for cervical intraepithelial neoplasia in north east Scotland shows fall in incidence and mortality from invasive cancer with concomitant rise in pre- invasive disease. BMJ; 308:1407-1411.

Marshall CJ, Rowe L, Bentz JS. Improved quality-control detection of false-negative Pap smears using the Autopap 300 QC system. Diagnostic Cytopathology 1999 Mar; 20(3):170-4.

McQuarrie HG, Ogden J, Costa M. Understanding the financial impact of covering new screening technologies. The case of automated Pap smears. J Reprod Med. 2000 Nov;45(11):898-906.

Mintzer M, Curtis P, Resnick JC, Morrell D. The effect of the quality of Papanicolaou smears on the detection of cytologic abnormalities. Cancer Cytopathology 1999; 87(3)

Moss SM, Gray A, Marteau T, Legood R, Henstock E, Maissi E. Evaluation of HPV/LBC Cervical Screening Pilot Studies - Report to the Department of Health (revised October 2004). Sutton: Institute of Cancer Research; 2004.

Narine N, Young W. Transformation zone sampling rate is a useful performance indicator for practitioners collecting cervical samples using SurePath™ liquid-based cytology system. Cytopathology 2007; 18:220-224.

National Health Service Cancer Screening Programmes. HPV Sentinel Sites implementation project. 2008. URL: www.cancerscreening.nhs.uk/cervical/hpv-sentinel-sites.html.
(Accessed on September 12th, 2017).

National Health Service Cancer Screening Programmes. NHS Cervical Screening Programme Annual Review 2008. Sheffield: NHS Cancer Screening Programmes; 2008.

National Health Service Cancer Screening Programmes. HPV Sentinel Sites implementation project. 2008.
https://webarchive.nationalarchives.gov.uk/20150506215812/http://www.cancerscreening.nhs.uk//cervical/hpv-sentinel-sites.html.
(Accessed on September 12th, 2017).

NHS Cervical Screening Programme. Achievable standards, benchmarks for reporting, and criteria for evaluating cervical Cytopathology. NHS CSP Publication No. 1, Second Edition, 2000.

NHS Cervical Screening Programme. Achievable standards, benchmarks for reporting, and criteria for evaluating cervical Cytopathology. NHS CSP Publication No. 1, Third Edition, January 2013.

NHS Cervical Screening Programme: Laboratory Organisation: A Guide for Laboratories Participating in the NHS Cervical Screening Programme. NHS CSP Publication No. 14, January 2003.

NHS Cervical Screening Programme Colposcopy and Programme Management NHSCSP Publication number 20, 3rd edition, 2016. URL: https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/515817/NHSCSP_colposcopy_management.pdf.
(Accessed on September 10th, 2017).

NHS Cervical Screening Programme. NHS Public Health Functions Agreement 2016-17. Service Specification No. 25. Publications Gateway Reference: 04572
Third Edition - March 2016 NHS England.
NHS Improvement. Pathology Networks proposals. September 2017.
URL: https://improvement.nhs.uk/resources/pathology-networks/.
(Accessed on September 23rd, 2017).

National Institute for Clinical Excellence. Guidance on the use of liquid-based cytology for cervical screening (Technology Appraisal 69). London: National Institute for Clinical Excellence; 2003.

Operator's Manual—BD FocalPoint™ System—Doc. No. 780-06424-00 Rev A.

Orlassino R, Fabbrini T, Gallo C, Vineis C. The use of a computerised system in the reading of cytological cervicovaginal smears during programming of regional screening (one year of experience using the autopap system). Pathologica. 2005 Apr;97(2):78-83.

Ostor AG, Natural history of cervical intrepithelial neoplasia - a critical review. Int. J. Gynecol. Pathol. 1993; 12: 186-192.

Ostrowska KM, Garcia A, Meade AD, Malkin A, Okewumi I, O'Leary JJ, Martin C, Byrne HJ, Lyng FM. Correlation of p16(INK4A) expression and HPV copy number with cellular FTIR spectroscopic signatures of cervical cancer cells. Analyst. 2011 Apr 7;136(7):1365-73. doi: 10.1039/c0an00910e. Epub 2011 Feb 3. PubMed PMID: 21290054.

Ostrowska KM, Malkin A, Meade A, O'Leary J, Martin C, Spillane C, Byrne HJ, Lyng FM. Investigation of the influence of high-risk human papillomavirus on the biochemical composition of cervical cancer cells using vibrational spectroscopy. Analyst. 2010 Dec;135(12):3087-93. doi: 10.1039/c0an00571a. Epub 2010 Oct 21. PubMed PMID: 20967345.

Papanicolaou GN, Traut H (1943). Diagnosis of Uterine Cancer by the Vaginal Smear. New York.

Parker EM, Foti JA, Wilbur DC. FocalPoint slide classification algorithms show robust performance in classification of high-grade lesions on SurePath liquid-based cervical cytology slides. Diagnostic Cytopathology 2004 Feb;30(2):107-10.

Passamonti B, Bulletti S, Camilli M, D'Amico MR, Di Dato E, Gustinucci D, Martinelli N, Malaspina M, Spita N. Evaluation of the FocalPoint GS system performance in an Italian population-based screening of cervical abnormalities. Acta Cytol. 2007 Nov-Dec;51(6):865-71.

Patten SF Jr, Lee JS, Nelson AC. NeoPath, Inc. NeoPath AutoPap 300 Automatic Pap Screener System. Acta Cytol. 1996 Jan-Feb;40(1):45-52.

Patten SF Jr, Lee JS, Wilbur DC, Bonfiglio TA, Colgan TJ, Richart RM, Cramer H, Moinuddin S. The AutoPap 300 QC System multicenter clinical trials for use in quality control rescreening of cervical smears: I. A prospective intended use study. Cancer. 1997 Dec 25;81(6):337-42.

Patten SF Jr, Lee JS, Wilbur DC, Bonfiglio TA, Colgan TJ, Richart RM, Cramer H, Moinuddin S. The AutoPap 300 QC System multicenter clinical trials for use in quality control rescreening of cervical smears: II. Prospective and archival sensitivity studies. Cancer. 1997 Dec 25;81(6):343-7.

Peirson L, Fitzpatrick-Lewis D, Ciliska D, Warren R. Screening for cervical cancer: a systematic review and meta-analysis. Systematic Reviews. 2013 May 24; 2:35. doi: 10.1186/2046-4053-2-35.

Pisani P, Parkin DM, Ferlay J. Estimates of the worldwide mortality from eighteen major cancers in 1985. Implications for prevention and projections of future burden. Int. J. Cancer 1993;55(6):891-903.

Peto J, Gilham C, Fletcher O, Matthews F. The cervical cancer screening epidemic that screening has prevented in the UK. Lancet 2004;364:8.

Quinn MA, Benedet JL, Maisonneuve P, Beller U, Creasman, WT, Heintz AP, Ngan HY, Pecorelli S. Carcinoma of the cervix uteri. FIGO 26th Annual Report on the results of treatment in Gynecological Cancer. Int. J. Gynaecol. Obstet. 2006 Nov; 95 Suppl. 1:S43-103.

Rashid N, Nawaz H, Poon KW, Bonnier F, Bakhiet S, Martin C, O'Leary JJ, Byrne HJ, Lyng FM. Raman microspectroscopy for the early detection of pre-malignant changes in cervical tissue. Exp. Mol. Pathol. 2014 Dec;97(3):554-64. doi:10.1016/j.yexmp.2014.10.013. Epub 2014 Nov 3. PubMed PMID: 25445502.

Rebolj M, Rask J, van Ballegooijen M, Kirschner B, Rozemeijer K, Bonde J, Rygaard C, Lynge E. Cervical histology after routine ThinPrep or SurePath liquid-based cytology and computer-assisted reading in Denmark. Br. J. Cancer. 2015 Nov 3;113(9):1259-74. doi: 10.1038/bjc.2015.339. Epub 2015 Oct 8. PubMed PMID: 26448176; PubMed Central PMCID: PMC4815798.

Remmink AJ, Walboomers JM, Helmerhorst TJ, Voorhorst FJ, Rozendaal L, Risse EK, *et al*. The presence of persistent high-risk HPV genotypes in dysplastic cervical lesions is associated with progressive disease: natural history up to 36 months. International Journal of Cancer 1995;61(3):306-11.

Renshaw AA, Lezon KM, Wilbur DC. The human false-negative rate of rescreening Pap tests. Measured in a two-arm prospective clinical trial. Cancer. 2001 Apr25;93(2):106-10.

Renshaw AA, Cronin JA, Minter LJ, Nappi D, Whitman T, Jiroutek M, Cibas ES. Performance characteristics of rapid (30-second) prescreening. Implications for calculating the false-negative rate and comparison with other quality assurance techniques. Am. J. Clin. Pathol. 1999 Apr;111(4):517-22.

Renshaw AA. Estimating the percentage of Papanicolaou smears that can be reproducibly identified: modelling Papanicolaou smear interpretation based on multiple blinded rescreenings. Cancer. 2001 Aug 25;93(4):241-5.

Renshaw AA. Measuring sensitivity in gynecologic cytology: a review. Cancer. 2002 Aug 25;96(4):210-7. Review.

Renshaw A, Elsheikh TM. A validation study of the Focalpoint GS imaging system for gynecologic cytology screening. Cancer Cytopathol. 2013 Dec;121(12):737-8. doi: 10.1002/cncy.21336. Epub 2013 Jul 10. PubMed PMID: 23843282.

Renshaw AA, Elsheikh TM. Assessment of manual workload limits in gynecologic cytology: reconciling data from 3 major prospective trials of automated screening devices. Am. J. Clin. Pathol. 2013 Apr;139(4):428-33. doi: 10.1309/AJCP23YDFKKQNUAO. PubMed PMID: 23525612.

Repse-Fokter A, Caks-Golec T. Rapid prescreening as a quality assurance measure in cervical cytology. Acta Cytol. 2009 May-Jun;53(3):268-70.
Rigorni-Stern. Statistical facts about cancers on which Doctor Rigoni-Stern based his contribution to the surgeon's subgroup of the IV Congress of the Italian scientists on 23 September 1842. Giornale par service al Progressi della Terapeutica, Series 2, Volume 2, pp 507-517, 1842

Robb-Nicholson C. By the way, doctor. I read with interest your article regarding conventional Pap smears, PapNet, and AutoPap. Lately I've been reading about another test called ThinPrep. I'm not sure which one to request. Which of these techniques is better for detecting cervical cancer? Harv. Womens Health Watch. 1999 Aug;6(12):8.

Ronco G, Vineis C, Montanari G, Orlassino R, Parisio F, Arnaud S, Berardengo E, Fabbrini T, Segnan N. Impact of the AutoPap (currently Focalpoint) primary screening system location guide use on interpretation time and diagnosis. Cancer. 2003 Apr 25;99(2):83-8.

Ronco G, Vineis C, Montanari G, Orlassino R, Parisio F, Arnaud S, Berardengo E, Fabbrini T, Segnan N. Impact of the AutoPap (currently Focalpoint) primary screening system location guided use on interpretation time and diagnosis. Cancer. 2003 Apr 25;99(2):83-8.

Rosenthal DL, Acosta D, Peters RK. Computer-assisted rescreening of clinically important false negative cervical smears using the PAPNET testing system. Acta Cytologica. 1996; 40(1).

Rowe LR, Marshall CJ, Berry M, Larson MA, Bentz JS. Accuracy of a slide profiler for endocervical cell detection in no-further-review conventional Pap smears. Acta Cytol. 2003 Jul-Aug;47(4):602-4. PubMed PMID: 12920753.

Saieg MA, Motta TH, Fodra ME, Scapulatempo C, Longatto-Filho A, Stiepcich MM. Automated screening of conventional gynecological cytology smears: feasible and reliable. Acta Cytol. 2014;58(4):378-82. doi: 10.1159/000365944. Epub 2014 Sep 2. PubMed PMID: 25195537.

Sasieni P, Adams J. Analysis of cervical cancer mortality and incidence data from England and Wales: evidence of a beneficial effect of screening. Statistics in Society 2000; volume 163, issue 2:191-209.

ScHARR Report. Option Appraisal of a seven-day turnaround for the reporting of cervical smear results. School of Health and Related Research (ScHARR), University of Sheffield. Jan 2006.

Schiffman M, Yu K, Zuna R, Terence Dunn S, Zhang H, Walker J, Gold M, Hyun N, Rydzak G, Katki HA, Wentzensen N. Proof-of-principle study of a novel cervical screening and triage strategy: Computer-analyzed cytology to decide which HPV-positive women are likely to have ≥CIN2. Int. J. Cancer. 2017 Feb 1;140(3):718-725. doi: 10.1002/ijc.30456. Epub 2016 Oct 17. PubMed PMID: 27696414; PubMed Central PMCID: PMC5159264.

Scottish Cervical Cytology Review Group Feasibility Sub Group. Cervical Cytology ThinPrep Imager (TIS) Feasibility Study - Report from the Feasibility Sub Group to Cervical Cytology Review Group. Edinburgh: Scottish Pathology Network; 2009.

Smith BL, Lee M, Leader S, Wertlake P. Economic impact of automated primary screening for cervical cancer. J. Reprod. Med. 1999 Jun;44(6):518-28.

Smith JHF. Bethesda 2001. Cytopathology 2002; 13:4-10.

Solomon D, Davey D, Kurman R, Moriarty A, O'Connor D, Prey M, Raab S, Sherman M, Wilbur D, Wright T Jr, Young N; Forum Group Members; Bethesda 2001 Workshop. The 2001 Bethesda System: terminology for reporting results of cervical cytology. Journal of the American Medical Association 2002; 287(16):2114-9.

Spitzer M. Cervical screening adjuncts: recent advances. Am. J. Obstet. Gynecol. 1998 Aug;179(2):544-56.

Stein MD, Fregnani JH, Scapulatempo C, Mafra A, Campacci N, Longatto-Filho A; RODEO Study Team From Barretos Cancer Hospital. Performance and reproducibility of gynecologic cytology interpretation using the FocalPoint system: results of the RODEO Study Team. Am. J. Clin. Pathol. 2013 Oct;140(4):567-71. doi: 10.1309/AJCPWL36JXMRESFH. PubMed PMID: 24045555.

Stevens MW, Milne AJ, James KA, Brancheau D, Ellison D, Kuan L. Effectiveness of automated cervical cytology rescreening using the AutoPap 300 QC System. Diagnostic Cytopathology. 1997 Jun;16(6):505-12.

Stevens MW, Milne AJ, Parkinson IH, Nespolon WW, Fazzalari NL, Arora N, DoddTJ. Effectiveness of AutoPap system location-guided screening in the evaluationof cervical cytology smears. Diagnostic Cytopathology. 2004 Aug;31(2):94-9.

Stockton D. Cooper P. Lonsdale RN. Changing incidence of invasive adenocarcinoma of the uterine cervix in East Anglia. Journal of Medical Screening. 4(1):40-3, 1997.

Sugiyama Y, Sasaki H, Komatsu K, Yabushita R, Oda M, Yanoh K, Ueda M, Itamochi H, Okugawa K, Fujita H, Tase T, Nakatani E, Moriya T. A Multi-Institutional Feasibility Study on the Use of Automated Screening Systems for Quality Control Rescreening of Cervical Cytology. Acta Cytol. 2016;60(5):451-457. Epub 2016 Sep 28. PubMed PMID: 27673689.

Tavares SB(1), Alves de Sousa NL, Manrique EJ, Pinheiro de Albuquerque ZB, Zeferino LC, Amaral RG. Comparison of the performance of rapid prescreening, 10% random review, and clinical risk criteria as methods of internal quality control in cervical cytopathology. Cancer. 2008 Jun 25;114(3):165-70.

Tench WD. Validation of AutoPap primary screening system sensitivity and high-risk performance. Acta Cytol. 2002 Mar-Apr;46(2):296-302. Erratum in: Acta Cytol 2002 May-Jun;46(3):611.

The Bethesda System for Reporting Cervical Cytology. 2015. Nayar R and Wilbur D (Editors). ISBN 978-3-319-11074-5.

The Health and Social Care Information Centre. Cervical Screening Programme, England 2008–09. London: The Health and Social Care Information Centre; 2009.

Tolles WE. *S*ection of Biology*:* The Cytoanalyzer—an example of physics in medical research. The Transactions of the New York Academy of Sciences. January 1955.

Troni GM, Cariaggi MP, Bulgaresi P, Houssami N, Ciatto S. Reliability of sparing Papanicolaou test conventional reading in cases reported as No Further Review at AutoPap-assisted cytological screening: survey of 30,658 cases with follow-up cytological screening. Cancer. 2007 Apr 25;111(2):93-8.

Vassilakos P, Carrel S, Petignat P, Boulvain M, Campana A. Use of automated primary screening on liquid-based, thin-layer preparations. Acta Cytol. 2002 Mar-Apr;46(2):291-5.

Valente PT, Schantz D. Cytology Automation: An Overview. Laboratory Medicine. November 2001; 11(32):686-690.

Walts AE, Thomas P. Correlation of manual screening and automated (AutoPap300) analysis of conventional cervicovaginal smears with HPV typing using Digene HC II assay. Diagnostic Cytopathology. 2003 Nov;29(5):256-61.

Walts AE, Thomas P. Endometrial cells and the AutoPap System for primary screening of cervicovaginal Pap smears. Diagnostic Cytopathology. 2002 Oct;27(4):232-7.

Wertlake P. Results of AutoPap system-assisted and manual cytologic screening. A comparison. J. Reprod. Medicine. 1999 Jan;44(1):11-7.

Wheeler CM, Greer CE, Becker TM, Hunt WC, Anderson SM, Manos MM. Short-term fluctuations in the detection of cervical human papillomavirus DNA. Obstetrics & Gynecology 1996;88(2):261-8

Wilbur DC, Black-Schaffer WS, Luff RD, Abraham KP, Kemper C, Molina JT, Tench WD. The Becton Dickinson FocalPoint GS Imaging System: clinical trials demonstrate significantly improved sensitivity for the detection of important cervical lesions. Am. J. Clin. Pathol. 2009 Nov;132(5):767-75.

Wilbur DC, Bonfiglio TA, Rutkowski MA, Atkison KM, Richart RM, Lee JS, Patten SF Jr. Sensitivity of the AutoPap 300 QC System for cervical cytologic abnormalities. Biopsy data confirmation. Acta Cytol. 1996 Jan-Feb;40(1):127-32.

Wilbur DC, Norton MK. The primary screening clinical trials of the TriPath AutoPap System. Epidemiology. 2002 May;13 Suppl 3:S30-3.

Wilbur DC, Parker EM, Foti JA. Location-guided screening of liquid-based cervical cytology specimens: a potential improvement in accuracy and productivity is demonstrated in a preclinical feasibility trial. Am. J. Clin. Pathol. 2002 Sep;118(3):399-407.

Wilbur DC, Prey MU, Miller WM, Pawlick GF, Colgan TJ, Dax Taylor D. Detection of high grade squamous intraepithelial lesions and tumors using the AutoPap System: results of a primary screening clinical trial. Cancer. 1999 Dec 25;87(6):354-8.

Wilbur DC, Prey MU, Miller WM, Pawlick GF, Colgan TJ, Taylor DD. AutoPap system detection of infections and benign cellular changes: results from primary screener clinical trials. Diagnostic Cytopathology. 1999 Nov;21(5):355-8.

Wilbur DC, Prey MU, Miller WM, Pawlick GF, Colgan TJ. The AutoPap system for primary screening in cervical cytology. Comparing the results of a prospective, intended-use study with routine manual practice. Acta Cytol. 1998 Jan-Feb;42(1):214-20.

Wilgenbusch H, Mueller G, Neal M, Renshaw AA. Rapid prescreening is as effective at reducing screening error as postscreening with the FocalPoint automated screening device. Diagnostic Cytopathology. 2011 Nov;39(11):818-21. doi: 10.1002/dc.21469. Epub 2010 Oct 14.

Willey BB, Matz LR. Use of the Autopap as a primary automated cervical cancer screening system. Med. J. Aust. 2001 Feb 5;174(3):151-2.

Willis BH, Barton P, Pearmain P, Bryan S, Hyde C. Cervical screening programmes: can automation help? Evidence from systematic reviews, an economic analysis and a simulation modelling exercise applied to the UK. Health Technol. Assess. 2005;9(13).

World Health Organization. Comprehensive cervical cancer control: a guide to essential practice. Second edition, 2014.

Young W. Comparison of transformation zone sampling rates – a potentially useful indicator of smear taker performance. Cytopathology 2000; 11:116-123.

Er Cof am

Mam a Dad