NCCHTA

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Health Technology Assessment Programme

Full Proposal Application - Project No 05/41/02 & 03

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A multistranded study to determine the minimum cellularity required for the reliable assessment of Liquid Based Cytology (LBC) for cervical screening.

Detailed Project Description

Changes since outline submission:

This full proposal is a merger of two outline proposals previously submitted from the North West Region (05/41/02 and 05/41/03) and is **led jointly by Dr Lesley Turnbull and Dr Minaxi Desai**. For purposes of communication, Dr Turnbull has been nominated as the Principal Investigator. The revised study design is a synthesis of both previous protocols and incorporates comments from Commissioning Board Members. The Study Centre will be based at the North West Quality Assurance Reference Centre, The Liverpool Women's Hospital Foundation Trust, Liverpool. The study will be managed by a full-time Research Manager (grade 6 pt 3) assisted by a full-time Clerical Assistant (grade C). The Study Management Group will comprise all members of the study team, together with the Research Manager and Clerical Assistant. The budget will be held by Professor Henry Kitchener, Professor of Gynaecological Oncology, University of Manchester. Data handling and statistical evaluation will be undertaken by Dr Chris Roberts, Biostatistics Group, University of Manchester and Professor Peter Sasieni, Wolfson Institute of Preventative Medicine. A Research Assistant will be employed for a 6-month period to assist with the data handling and statistical evaluation. An epidemiological, public health and screening overview is provided by Dr Gary Cook for the Public Health Department, Government Office North West. The costing includes £5,000 for the production and maintenance of a number of databases which will be used both to document the many different slide sets and for direct data entry at the study sites. There is a further 6 months of BMS 3 and BMS 1 time for the production of and assistance in the detailed cataloguing of slide sets in part 2 of the study.

Expertise of the Team:

Dr Lesley Turnbull: Director, North West Region Cervical Screening Quality Assurance; Director, Liverpool Cytology Training Centre; Consultant Cytopathologist, Royal Liverpool University Hospital. Extensive experience with LBC technology. Trained NICE LBC pilot sites; developed protocols for national roll-out of LBC and technical evaluation of novel LBC systems. Joint project lead, trial design and coordination. Cytological evaluation of prepared slides in part 2.

Dr Mina Desai: Clinical Head of Manchester Cytology; Director, Manchester Cytology Training Centre; Council Member and Honorary Meetings Secretary of British Society for Clinical Cytology BSCC; Chairperson of the BSCC working group on defining the adequacy of liquid based cytology samples; co investigator for the HTA funded ARTISTIC Trial and MAVARIC Trial in Manchester; joint project lead, trial design and coordination. Cytological evaluation of prepared slides in part 2.

Professor Henry Kitchener: HCK has considerable experience in cervical screening, randomised trials and project management. His contribution will be to provide ongoing intellectual input to the conduct of the study and analysis of results, with particular interest in the clinical implications.

Dr Chris Roberts: Senior Lecturer in medical statistics. Expert in statistical methods for reliability studies of categorical scales and design and analysis of clinical trials.

Professor Peter Sasieni: Professor of Biostatistics and Cancer Epidemiology. Expertise in statistics in medical research, cervical screening research and quantitative research methods.

Dr Gary Cook: Consultant in Public Health. Specialist expertise in systems evaluation.

Dr John Smith: Chairman of the British Society for Clinical Cytology. Consultant Histo/Cytopathologist with many years of experience in the field of cytology.

Relevance to Commissioning Brief:

This proposal addresses all aspects of the commissioning brief as follows:

- Current working practice in a large number of laboratories throughout England, Scotland and Wales will be surveyed to determine what minimum cellularity levels are currently being used to assess whether an LBC sample is adequate.
- The reasons for the choice of minimum cellularity by these laboratories will be examined.
- A comparison of declared and actual practice will provide evidence of how closely laboratories adhere to these local guidelines.
- In the second part of the study, multiple slides will be prepared from individual samples to assess the impact of overall cellularity; relative proportion of abnormal cells; and the type and presentation of abnormal cells on the ability of primary screeners to routinely detect those abnormalities.
- This will provide an estimate of the level of cellularity at which a satisfactory pick-up rate of high and low grade disease can be detected
- It will also allow the estimation of a level of cellularity which minimises samples being wrongly labelled ‘negative’ when they are inadequate.
- The study will compare both of the current LBC platforms and will assess any operational differences relating to cell counting.
- The study will establish a reliable method of determining the total cellularity for both current LBC systems.
- The use of transformation zone indicators as a quality indicator of smear taker practice will also be examined.

Objectives:

- To assess current standards and practice for the reporting of LBC preparations across England, Scotland and Wales
- To determine the cellularity of samples deemed inadequate, negative or abnormal by a range of laboratories across the country.
- To determine the cellularity of samples deemed negative, HPV+ in the ARTISTIC/MCM trial.
- To assess the impact of varying the overall cellularity; relative proportion of abnormal cells and the type and presentation of dyskaryotic cells on their likelihood of detection.
- To determine the threshold of cellularity of LBC preparations which allow the majority of samples containing abnormal cells to be detected by routine screening.
- To establish a reproducible method for rapidly estimating the cellularity of an LBC sample.

Background and Introduction:

Criteria for the assessment of adequacy of a cervical sample have been widely discussed over the years and remain the subject of debate. While there is general agreement, that for routine screening the squamous cell content is the primary indicator of adequacy, there is no clear agreement as to the definition of an adequate cervical sample in respect of Liquid Based Cytology (LBC). At a pragmatic level, it may best be defined as the minimum acceptable squamous cellularity which will allow the detection rate for squamous abnormalities to be at least as good as that for conventional cervical smears.

The current version of the Bethesda Terminology system [(1)] requires a minimum of 5,000 squamous cells for a liquid based preparation to be deemed 'satisfactory'. However, this figure appears to be based on anecdotal experience [(2,3)] rather objective evidence. Cervical Screening Wales and some regions in England, including the North West, have adopted an interim figure of 15,000 cells pending definitive guidance. The Scottish Cervical Screening Programme, which only uses Cytyc ThinPrep® as its sole LBC technology, uses a figure of 5,000 cells. Even within these declared values there is considerable variation and subjectivity as to the assessment of cellularity. This uncertainty inevitably leads to variable repeat smear rates and has capacity and funding implications for the local providers of these screening programmes.

The NICE Technology Appraisal (2003) concerning the use of LBC for cervical screening recommended its use as the primary means of processing samples in the screening programmes in England and Wales and gave a completion date of October 2008. Wales has already achieved full implementation. Many regions in England are either in the process of conversion or are near to full conversion. Scotland converted in 2004. There is thus an ever growing requirement for definitive guidance on cervical sample adequacy.

Setting:

The study will encompass a large number of NHS Acute Trust laboratories which participate either in the NHS Cervical Screening Programme, the Scottish Cervical Screening Programme or Cervical Screening Wales and which have implemented Liquid Based Cytology (LBC) for population based cervical screening.

Target Population:

LBC samples and slides will be obtained from women between the ages of 25-64 who have presented for routine cervical screening. All such women will have received a copy of 'The Facts' leaflet or national equivalent which gives implied consent for cervical screening.

Ethical considerations:

This study uses both archived slides and 'residual' tissue from cases which have already been reported and patient management previously defined. Neither part of the study will review nor aim to challenge existing diagnoses and hence neither will have clinical or management implications for individual women. However, one of the aims of the study is to improve the reliability of those samples assessed as negative. This is likely to be of long-term benefit to all women participating in the national cervical screening programmes.

An application will be submitted to the Liverpool Research and Ethics Committee in respect of the second part of the study as this uses 'residual' tissue which would normally be discarded once the final report was issued. Individual patient consent will not be required. The Human Tissue Act 2004 states that 'consent is not needed for the use of 'residual' tissue in **research**, provided that the research project has ethical approval, and that the researcher cannot identify the tissue donor and is not likely to be able to do so in the future'. All material (slides and residual tissue) will be anonymised on accessioning to the study. There will be no use of named patient data in any part of the study.

Health Technologies being assessed:

The study will assess material and slides from the only two LBC systems currently in use in the UK; the Cytyc ThinPrep® LBC system and the SurePath™ LBC system.

HTA brief, part 1: to survey which thresholds are used in current practice at laboratories using LBC and the reasons for their choice of threshold

The first part of the study surveys current working practice to establish both the declared formal laboratory thresholds for LBC specimen adequacy and the active thresholds which are operating in practice, with a view to determining the respective levels of each and whether they are different.

It also establishes cohorts of inadequate, negative and abnormal cases which have been reported in a routine screening setting for which total cell counts are known. This information will supplement that from part 2 and will provide an estimate of screening sensitivity at different levels of cellularity.

Design:

Laboratory Practice Survey

This part of the study will be conducted in England through the national network of Regional Cervical Screening Quality Assurance Directors, and in Wales and Scotland through Cervical Screening Wales and the Scottish Cervical Screening Programme respectively. A total of 39 laboratories from the 9 English QA regions, 7 from Scotland and 10 from Wales to be recruited to ensure an approximately even representation of the two current LBC systems, giving a total of 56 laboratories (28 laboratories for each system). They will include a cross-section of low, intermediate and high workload laboratories and all will have implemented LBC for population based cervical screening for a minimum of 6 months post LBC training and accreditation. This will avoid recognised learning curve issues. The suggestion that the NHS LBC pilot sites and training centres should supply the bulk of the cases is impractical given the substantial imbalance in representation of the two LBC companies across those sites and would be likely to greatly extend study timescales.

All participating laboratories will be asked to nominate a Study Liaison Officer and a deputy. These persons will normally be senior BMS staff and will act as the contact point for all communication with the LBC Adequacy Study Centre. Each laboratory will initially be asked to complete a questionnaire which will cover the following points:

- Type of LBC system used
- Approximate date of completion of LBC training
- Date of full conversion to LBC
- Criteria used in laboratory for assessing adequacy including declared threshold, with copy of relevant laboratory Standard Operating Procedure (SOP)
- Copy of any other relevant SOPs e.g. cell counting methodology
- Current KC61 figures (DH return giving laboratory performance data) or equivalent data but to include only LBC cases (some labs may not have full 12 months LBC data)

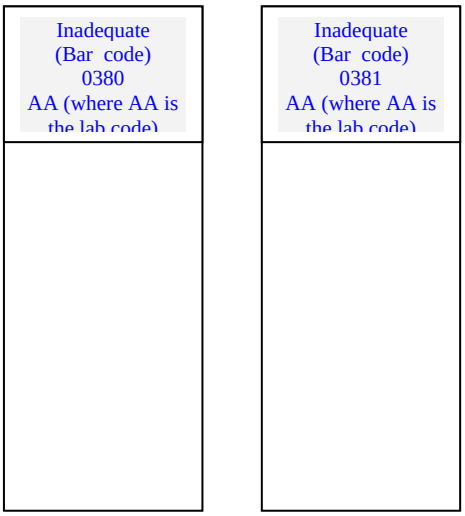

Figure 1- Examples of normal and additional slide labels

Additional laboratories may be recruited to increase the total number undertaking slide assessments and to spread this workload more widely. The same requirements for study entry will apply as stated above, but these laboratories will not be asked to complete a questionnaire or to submit slides. It will be important to ensure an approximately even representation of the two LBC

systems in all aspects of the study and on occasion this may require minor modifications to laboratory selection.

Slide Survey

The 56 participating laboratories will be asked to submit 20 consecutive cervical screening LBC cases from each of the following report categories: inadequate, mildly dyskaryotic and high grade (moderate dyskaryosis and above). All high grade cases must be histologically confirmed. While histological confirmation of the mildly dyskaryotic cases is preferable it is acknowledged that this may not always be possible. It is important that as many cases as possible and certainly all high grade abnormalities are histologically proven to validate outcome. If outcome were determined by expert panel this could easily lead to a change in the original proffered diagnosis. This has serious and potentially negative implications for submitting laboratories and could lead to some declining participation.

Slides reported as borderline nuclear change will not be included in the study as this is a much less robust diagnostic category than higher grade abnormalities and its use is not consistently applied across laboratories.

50 consecutive negative cervical cytology LBC cases from the same time period will also be requested from each of these laboratories. They will be asked specifically not to pre-select good examples of individual diagnostic categories but to adhere strictly to number sequences. A total of 110 slides will thus be provided by each of the 56 laboratories resulting in a total of 6,160 slides in this arm of the study. Laboratories will have 3 months to gather and submit these slides.

> Cases reported as inadequate because of the absence of transformation indicators following previous treatment of CIN, or the absence of endocervical cells in the case of previously treated CGIN will be specifically excluded from the study as the reason for inadequacy does not relate to specimen cellularity.
>
> It is recognised that mucus and blood may block the filter pores in the Cytyc ThinPrep® LBC system. This problem should be addressed in routine work by the pre-treatment of the sample prior to a repeat preparation being made. The study will collect both the original preparation and any repeat preparations which have been made.
>
> If additional preparations have been made, then all available slides should be submitted and included within the category of the issued cytological report, irrespective of the appearance of individual slides.

Given the numbers of slides which will be gathered during the various parts of the study, it is critical that they are handled in such a way as to preserve patient anonymity; to be fully compliant with the Data Protection Act 1998; with the Human Tissue Act 2004; and to ensure that all slides can be traced and rapidly returned to the originating laboratory if required for clinical review. To facilitate these requirements, all laboratories will be provided with a Preparatory Package that will include:

- A full written protocol for this part of the study with contact details for the Study Centre to obtain advice if required.
- A laboratory anonymisation code e.g. lab code AA
- A floppy disc or CD pre-loaded with a database listing cases 1-20 in 3 of the diagnostic sub-groupings and 1-50 for negative cases. Laboratories will be required to enter the slide laboratory accession numbers against the appropriate entries in the database and to ensure that this process is subject to quality control. The details should be saved as a password-protected file and the floppy disc/CD stored in a locked cabinet. **Hence only the originating laboratory will have access to named patient details.**
- 110 pre-printed slide labels giving study name, the laboratory anonymisation code, diagnostic category and case number. See Figure 1. (Spare labels will be provided for any additional slides. The laboratory will need to add the slide diagnostic category, numerical sequence, lab code and be asked to suffix the slide number with “a” e.g. slide 15a.) These must be applied to the slides to cover the existing laboratory labels. The database will be used to ensure that the correct label is applied to each slide. This step should be double checked to ensure accuracy.

- 5 Slide transport boxes (each with capacity for 25 slides) pre-labelled with study name, laboratory anonymisation code.
- A paper check list will be produced by the database to accompany slide boxes to confirm that the full complement of 110 slides (plus details of any additional slides) has been sent
- Pre-labelled padded packaging

On receipt at the Study Centre, all slide sets will be checked to ensure they are complete; that there has been no damage in transit; and that the slides have been labelled in accord with instructions. Thereafter slides will be relabelled with an anonymised code and placed in a further set of 275 transport boxes in a pre-determined randomised order, established by the study statistician. Boxes will therefore contain a mixture of different diagnostic groupings from different originating laboratories. The anonymisation code will be abased on the lab to which the slides are being sent, the bax they are eneterd in and the position within the box. Details of the content of each box will be held in a secure database.

A further database will be established which will again be provided to each participating laboratory as an individualised CD. Each disc will contain details of the anonymised slide set allocated to that laboratory and will allow direct entry of the individual cell counts for each slide (number to be determined – see below); whether transformation zone (TZ) material (metaplastic squames or endocervical cells) is detected; and details of the eyepiece magnification, FN value of the microscope used for that individual slide assessment, and the start point for the cell count based on clock face e.g 12 o'clock, 3 o'clock. The laboratories will not be required to calculate the total cellularity for each slide. This will be calculated at the Study Centre using the following formula:

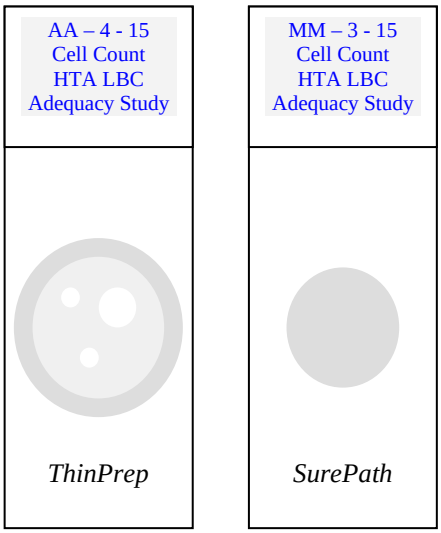

Figure 2 - Diagrammatic representations of Cytyc and SurePath preparations

Total cell count = mean cell count x area of cell deposit x area of ocular

The boxes will be sent in sets of 5 with the corresponding CDs to each of the participating laboratories via courier. All details including the date and time of despatch will be recorded electronically.

Cell Counting

The 56 laboratories will be asked to nominate primary screening staff to participate in the study. All slides in the study sets will be assessed for the presence of transformation zone indicators and each will have a formal cell count. The latter will be performed according to protocols agreed with the Cytyc and TriPath Corporations to ensure corporate ownership of subsequent results. There is a tendency for Thin Prep® slides of low cellularity to show an uneven cell distribution with either a peripheral rim of enhanced cellularity and/or poorly cellular 'holes' which typically occur towards the centre of the deposit [5]. SurePath™ preparations tend to be more homogeneous with an even cellular distribution throughout the deposit (Figure 2). Note also that the size of the cell deposits is different. These differences in cellular presentation between the two systems may need to be taken into account in determining the counting methodology and to ensure neither system is disadvantaged. As indicated in the original protocol a sub-study will be undertaken to establish robust methodologies for cell counting for both of the existing LBC systems. The Team acknowledges that there are flaws in the existing methodology recommended in the Bethesda Terminology System and is already working with the companies to ensure these are rectified. Once agreed, detailed standard operating procedures will be supplied to all participating laboratories.

It is not feasible for the material from the slide survey to be assessed for cellularity at a single centre. This would be a monumental task for any one laboratory even if distributed between a number of staff and could seriously impact on the routine service. The Study Team is of the view that this work should be distributed across all participating laboratories. In order to reduce bias due to inter-laboratory variability, a balanced design will be used with similar proportions of slides from each laboratory and of each cytological type being sent to each laboratory.

Cell count data will be entered on the pre-formatted disc and returned with the slide sets to the Study Centre.

ARTISTIC / MCM Cases

A further 1,200 cases previously documented as smear negative, HPV+ in the ARTISTIC/MCM trial will also be subject to cell counting according to protocols previously described. These cases represent true cytological false negatives and as such are a unique resource. Cell counts will determine whether there is a relationship between cellularity and false negative status. These will be compared with cell counts from both the negative and mildly dyskaryotic cases in part 1.

Sample Size

Declared inadequate slides will be used to determine the distribution of cellularity in such slides. With a sample of 1,120 a proportion of say 5% falling above the specified threshold can be estimated with a 95% distance from the percentage to the 95% c.i. of 1.3%. Declared negative slides will be used to estimate the proportion falling below the specified threshold. With 2,800 slides a proportion of 1% falling below the required threshold can be estimated with distance from the percentage to the 95% c.i. of 0.4%. We hypothesise that the greatest proportion of slides with low cellularity will be seen in mildly dyskaryotic slides and lowest proportion in negative slides, with high-grade dyskaryotic slides between the two. With 2,800 negative slides, 1,120 high grade and 1,100 mildly dyskaryotic slides, a chi-squared test of trend will have a power of 87% to detect a difference between 1% of negative slides falling below a threshold increasing to 2.5% in the mildly dyskaryotic cases and a power of 74% to detect an trend increasing from 1% to 2%.

Statistical Analysis

Statistical analysis would be used estimate the proportion of slides falling above or below the specified threshold. Covariates for smear result, "LBC system" and relevant data from the survey of practice would be included as covariates in logistic random effects model of the proportion falling either side of the specified threshold. This analysis would be carried out using each laboratory's current threshold and that derived in part 2 of the study.

Outcome Measures

Outcome would indicate how closely laboratories achieve declared criteria and levels derived by part 2. Statistical modelling may give some indications of practices (SOPs) that are more successful.

HTA brief, part 2 : to establish a threshold of adequacy by carrying out multiple analyses from individual samples to ascertain the number of cells necessary to ensure that samples cannot be wrongly labelled 'negative' when they are inadequate.

The total number and relative proportion of dyskaryotic cells compared with normal squamous cells in a cervical sample will influence the probability of their reliable detection. In a case control study of women with CIN3 who wrongly received negative reports, the number of abnormal cells was the strongest differentiating factor. Mitchell and Medley reported that where there were less than 50 abnormal cells on the slide, the odds of a false negative report being issued was 23.7 times greater than when there were 200 or more abnormal cells [(6)]. However, cell size [(7)], staining characteristics and pattern of presentation will also influence detection rates [(8)].

Many of the current defining publications on the effect of cellularity on the detection of cervical disease, including the Mitchell and Medley paper, are based on conventional spread cytology not on LBC samples. Further, most studies use the Bethesda Terminology System which has traditionally accepted as adequate, samples of lower cellularity than would be accepted under current UK guidance [(8)]. However, limited work on LBC samples would suggest that similar criteria for disease detection may apply. Bolick has shown that optimal detection rates for HSIL (high-grade squamous

intraepithelial lesion) and LSIL (low-grade squamous intraepithelial lesion) are achieved when sample cellularity is greater than 20,000 well visualised squamous cells [9,10].

In this part of the study, these variables will be assessed by producing serial dilutions of known cases of varying morphological type and by producing preparations with varying ratios of dyskaryotic to total squamous cells but with a similar background cellularity.

Design:

Given the operating characteristics of the two LBC systems the dilutions must be made using different techniques. In SurePath™, the slide preparation directly reflects the content of the sample. A poorly cellular sample will have a poorly cellular slide preparation. Serial dilutions can therefore be made according to standard methodologies. ThinPrep® is a filtration based system in which the fluid sample is repeatedly 'sipped' through the filter until a specific level of electrical impedance is reached. Hence in some samples most, if not all, of the specimen may be filtered to reach a system pre-determined adequacy level. In others, only a tiny fraction of the total specimen will be filtered. The cell yield on the slide does not therefore match the cellularity of the original sample. In order to produce serial dilutions of Thin Prep® samples, the machine must be offered highly dilute samples in which all of the available cellular material will be filtered. Increasingly cellular samples can be produced by adding increasing aliquots of a known sample to specimen vials containing only Preservcyt® fluid.

A total of 180 SurePath™ and 180 Thin Prep® cases will be selected from material routinely accessioned at the Royal Liverpool University Hospital and the Manchester Cytology Centre, which display a range of histologically confirmed low and high grade cytological abnormalities. Following selection, the cases will be entered on the study database and anonymised to ensure compliance with the Human Tissue Act 2004. The cases will range from those containing plentiful hyperchromatic (darkly staining) dyskaryotic cells, to those which have scanty abnormal cells; are pale staining; show minimal nuclear changes or form microbiopsy fragments. The latter sub-types are known to cause diagnostic problems.

Eight preparations will be made from each sample. Serial dilutions with approximate cellularities of 5-10k, 10-15k, 15-20k, 20-25k, 25-35k, 35-45k, 45-55k and 55+k will be made from half of the cases. The range of dilutions is skewed towards preparations of lower cellularity as these are expected to have higher false negative rates. The remaining cases will be mixed with known negative cases in varying proportion to establish sets of slides containing <25, 25-49, 50-99, 100-149, 150-199, 200-399, 400-799, 800-1600 and 1600+abnormal cells. In total 3,000 new slides will be prepared.

Each of the prepared slides will be assessed by two members of a four panel expert cytology group (to include LT and MD). Each slide will have a total cell count and a total abnormal cell count performed by the two panel members. Cases in which there is a variation of >10% between either of these counts will be assessed by at least three panel members on a multi-headed discussion microscope and a consensus decision reached.

The prepared slides will then be block randomised with 1,000 negative and 1,000 inadequate cases (total of 2,000) of similar cellularities in a ratio of 3:2 to minimise screener outcome bias.

Determination of "true" negative is always a problematic area in cervical cytology. In order to address this the Team proposes a modification to the existing protocol whereby 200 of the 1,000 negative slides will derive from confirmed HPV-ve cases. 100 of these HPV-ve slides will be acquired from archived material from the ARTISTIC/MCM trial. As the ARTISTIC/MCM trial used only Thin Prep® cases, these will be matched by newly acquired HPV-ve material from the SurePath™ system. It is estimated that 150 HPV tests will be required to obtain a cohort of HPV-ve, Cytology-ve cases.

A total of 5,000 slides will thus be gathered in this part of the study. Sets of 100 slides will then be established and recorded in a pre-determined database as for the first part of the study. A database will again be provided to each participating laboratory as an individualised floppy disc / CD. Each disc will contain details of the anonymised slide sets allocated to that laboratory and will allow direct entry of the morphological assessment for each slide. Laboratories will be asked to screen each slide once under routine primary screening conditions and to assess each slide as either inadequate, negative, low or high-grade dyskaryosis. Approximately 18-20 groups each of three laboratories will be established

to form ‘mini’ slide circulations. Each slide will therefore be subject to three independent reviews; however, the membership of each group will be withheld to avoid contamination of results. Approximately 15,000 slide-assessments will be performed in this arm of the study. The morphological assessments will be entered on the pre-formatted discs and returned with the slide sets to the Study Centre.

Sample Size

To have 80% power to compare a 95% pick-up rate in more cellular slides with an 80% pick-up rate in less cellular slides would require 90 slides in each bands of cellularity. Power will be increased by each slide being read by three reviewers. This can be estimated by applying a cluster sampling correction. If the agreement between reviews has a kappa coefficient of 0.75, power will increase to 87%. In total 1,440 slides would be required for each system (720 high grade / 720 mild moderate). A further 960 cases will be included of similar cellularity. These estimates ignore the matching of slides across bands. If this matching of slides can be incorporated in the statistical analysis, power will increase slightly.

Statistical Analysis

A logistic random effects model with variance terms for slide and source will be used to model pick-up rate for high and low grade abnormalities including covariates for cellularity and diagnostic sub-type. This will be used to estimate the levels of cellularity at which pick-up rate decreases. It is likely that inter-review agreement will change according to cellularity. This will be investigated by estimating the kappa coefficient according to bands of cellularity and by including random coefficient terms into the logistic random effects model.

Outcome Measures

Outcomes will include an estimate of the level of cellularity at which a satisfactory pick-up rate of high and low grade disease can be detected.

Trial Supervision

There will be a Study Management Group (SMC) consisting of applicants, which will meet monthly. An appropriately constituted Trial Steering Group (TSG) with an independent chair will be convened as soon as possible after the grant is awarded. The TSG will meet twice a year. There will be a Data Monitoring and Ethics Committee (DMEC) which will be independent of the applicants and of the TSC.

Project Milestones

Months into project	**0-3**	**3-6**	**6-9**	**9-12**	**12-15**	**15-18**
Set up phase						
Recruit staff						
Staff training						
Formulate database						
Ethics approval for part 2						
Part 1						
Development of questionnaire						
Questionnaire completed & returned						
Slides gathered & submitted to labs						
Slides counted & returned to SMC						
Part 2						
Preparation of new slides sets						
Evaluation of new slide sets						
Slide sets submitted to labs						

Slide circulation complete						
Analysis of data						
Report writing						

Summary of Project:

The first part of the study surveys current working practice to establish both the declared laboratory thresholds for LBC specimen adequacy and those thresholds which are operating in practice, with a view to determining the respective levels of each and whether they are different.

It also establishes cohorts of inadequate, negative and abnormal cases which have been reported in a routine screening setting for which total cell counts are known. This information will supplement that from part 2 and will provide an estimate of screening sensitivity at different levels of cellularity.

The second part of the study will assess the contribution of differing total cellularity; relative proportion of abnormal: normal cells; and dyskaryotic sub-type on the likelihood that the slide will be categorised as abnormal. Slide sets comprising serial dilutions of known abnormal cases and of preparations with varying ratios of dyskaryotic to total squamous cells will be assessed by independent review panels. The results will allow an estimate of a level of cellularity at which most abnormalities are likely to be detected and will provide an evidence base to inform national guidance relating to the minimum acceptable cellularity for a cervical LBC sample.

Summary in Plain English:

Liquid Based Cytology (LBC) was approved as the recommended method for preparing cervical samples in 2003. National pilot studies showed that this method was superior to conventional spread smears and reduced the inadequate rate from 10% to 1-2%. However, the number of cells required for these samples to be deemed adequate remains the subject of debate. There is a risk that samples may be described as negative when they are really inadequate and that abnormalities could therefore be missed.

An adequate LBC sample is one in which sufficient numbers of cells are present to allow the detection of an abnormality were it to be present. This study aims to establish the threshold of cellularity which will minimise the risk of false negative reports.

The first part of the study surveys current practice in laboratories throughout mainland UK using LBC for cervical screening and establishes the cellularity of a large cohort of inadequate, negative and abnormal slides. The second part of the study evaluates the ability of screeners to detect abnormalities of differing type and relative abundance. This will be done by preparing sets of slides which vary in their total cellularity and in the total number, type and relative proportion of abnormal cells. These will be presented to a large number of laboratories for independent evaluation. The results will allow an estimate of a level of cellularity at which most abnormalities are likely to be detected and will hence determine a safe minimum cellularity.

This study is led by a team of international and national experts with many years of experience in cervical screening, liquid based cytology and the conduct and evaluation of clinical trials.

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