

IMPLEMENTATION OF 'NO
FURTHER REVIEW' (NFR) USING
THE BD FOCALPOINT™ SLIDE
PROFILER

NHSCSP Good Practice Guide No 4
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INTRODUCTION

1. The BD FocalPoint™ Slide Profiler is an image analysis system that is intended to detect squamous carcinoma and adenocarcinoma, and their precursor lesions, in cervical cytology preparations.
2. The system is distributed in the UK by Source BioScience.
3. The system uses proprietary algorithms to score slides according to the probability that they contain cells that are abnormal. The lowest-scoring portion, which will not exceed 25%, is classified as 'No Further Review' (NFR). A number of studies, including the MAVARIC trial,¹ have shown that this method is effective and safe, and have demonstrated that its sensitivity is at least equivalent to that of primary screening. As a result, implementation within the NHS Cervical Screening Programme (NHSCSP) has been approved by the Advisory Committee on Cervical Screening.
4. It is important to note that this system requires calibration with screening slides from the local population. This calibration is critical, and can be influenced by wider changes in the human population being screened, source distribution, and other factors.
5. Calibration is performed by the manufacturers, who are able to 'dial in' to the equipment remotely.
6. Guidance in this document differs in some respects from the manufacturer's recommendations, due to differences between the English cervical screening programme and practice in North America. All divergent recommendations have been fully evaluated as part of the MAVARIC trial, which has validated these changes for English practice.
7. This document sets out practical requirements for implementing NFR in the NHSCSP in England.

ACCOUNTABILITY

8. In accordance with existing NHSCSP guidance, cervical cytology cases reported as negative, but not seen by a consultant, are the responsibility of the designated lead consultant for cervical cytology. This includes cases assigned to NFR.

PREPARATION

9. Although the BD FocalPoint™ Slide Profiler can be used with a variety of preparation techniques, it is validated in the NHSCSP for use only with liquid-based cytology prepared using the SurePath technique.

1. Kitchener HC, Blanks R, Dunn G, et al. Automation-assisted versus manual reading of cervical cytology (MAVARIC): a randomised controlled trial. *Lancet Oncol*, 2011, 12: 56–64.

TRAINING

10. Individuals operating the system will be trained and certificated by Source BioScience. Hands-on operation is minimal and straightforward. Training will include troubleshooting and quality management.

LABORATORY PREPARATION CALIBRATION ASSESSMENT

11. This procedure is completed following the installation of the BD FocalPoint™, before the system is used on diagnostic material. During the laboratory preparation calibration assessment (LPCA), thresholds are set on the system using sequential slides from the host laboratory. These thresholds are then used as a basis for each subsequent run of slides. During the LPCA, the system sets the thresholds based on criteria including staining, cover slipping, and barcodes.
12. The minimum number of slides required for the LPCA in the NHSCSP is 1,000.
13. The LPCA is repeated monthly to ensure that no drift has occurred in the population being screened. The manufacturer performs these automatic repeats, and then sends a report to the laboratory. This should be reviewed and retained for internal quality monitoring purposes, and for inspection by the Quality Assurance (QA) team.
14. The following changes in preparation technique will require a new LPCA:
 - change in staining parameters.
 - change of coverslip procedure.
 - change of coverslip mountant.
15. Samples prepared in the revised way will not be assigned to the NFR category until a new LPCA has been completed. The laboratory must contact Source BioScience to arrange this recalibration.
16. Where two populations are screened, it is necessary to undertake a separate LPCA calibration for each. A single instrument can accommodate multiple LPCAs for different populations, provided that a 'switch slide' is used to separate these populations. Laboratories must follow the manufacturer's guidance on use of the switch slide.
17. If laboratories merge onto a single site, it will be necessary to undertake a combined LPCA, as described in the 'Geographical Screening Areas' section of this guidance.
18. If two laboratories are using the same FocalPoint™ machine, the laboratory that does not host the technology must have a robust mechanism in place for reporting changes in the screened population to the hosting laboratory. This will allow a new LPCA calibration to be performed. The host laboratory should ensure the non-hosting laboratory is informed of the NFR rates and percentage variation. The responsibility for reporting variations of more than 5% in the NFR rate to the manufacturer lies with the laboratory holding the contract. However, the non-hosting laboratory must be informed of the outcomes of any investigations.

SOURCE OF SAMPLES

19. Samples from all sources, including primary care and colposcopy, can be included in the imaging process. However, it is vital that work from all sources is randomly distributed and not concentrated into one screening run.
20. If, for any reason, a batch cannot be included, laboratories must investigate the population from which the excluded batch of samples was taken. The day's scanning may safely proceed if the excluded batch is determined to be from a practice that is average for the laboratory's area, but should not proceed if this is not the case (for example, if the excluded batch consists of work from sources known to cater to a population at higher than average risk). Legitimate reasons for the exclusion of a batch must go beyond laboratory preference (they might include, for example, transport or instrument failure). If more than one Focalpoint™ imager is being used, work from all sources must be evenly distributed between all instruments.
21. In accordance with results from the MAVARIC study, samples with a non-negative screening history can also be included in the NFR category.

GEOGRAPHICAL SCREENING AREAS

22. The BD FocalPoint™ Slide Profiler may be used where laboratories are providing services to more than one former screening programme, as a result of a merger.
23. Where laboratories merge, a new LPCA (1,000 slides) must be completed on combined material from both original sites before slides can be assigned to the NFR category. The new LPCA will prevent differences in underlying rates in such populations from having a detrimental effect on performance.
24. As they cannot be included in an LPCA, short-term 'backlog' contracts must not be scanned and assigned to the NFR category.

EFFECT OF AGE

25. 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) should be processed for NFR.
26. Where a laboratory merger has brought together two or more screening areas, significant differences in the age distribution between them can have a major effect on results. This will be addressed by repeating the LPCA as described above.
27. In the past, publicity has resulted in a sudden increase in attendance among women of a certain age range, who are at particularly high risk. As soon as this type of activity is detected in a laboratory, the laboratory must inform Source BioScience that urgent recalibration is necessary.

EFFECT OF HUMAN PAPILLOMAVIRUS TRIAGE AND TEST OF CURE

28. For 2–3 years after the implementation of human papillomavirus (HPV) triage and test of cure, changes in the detection rate of both high-grade and low-grade abnormalities may be observed. This will be addressed by monthly recalibration.
29. Samples involved in any pilot of HPV primary screening with cytology triage should not be scanned and assigned to the NFR category, as the technology has not been evaluated in this setting. This may be revised when further information becomes available.

WOMEN RESIDENT/REGISTERED IN SCOTLAND AND WALES

30. Many laboratories in areas of England bordering Scotland and Wales receive samples from women from these countries. These samples should be processed according to the protocols of the receiving laboratory, including NFR if applicable.

RAPID REVIEW

31. The FocalPoint™ imager's classification of a slide as 'NFR' replaces the manual primary screen. Samples classified as NFR must still be subjected to rapid review or rapid preview, in accordance with NHSCSP guidelines.
32. This process will also identify slides that are inadequate (usually owing to insufficient cellularity), which have been classed as NFR.
33. Note that, if rapid preview is used, the slides must not be marked in any way. All slides must still be entered for scanning, even if they have been identified as abnormal at rapid preview. These requirements are already standard in the NHSCSP, but are reiterated here because failure to comply will cause scanning to fail and/or will invalidate the LPCA.

QUALITY ASSURANCE

34. 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 $\pm 5\%$ should be reported immediately to Source BioScience. 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 (see Appendix 1).
35. Process review rate and rerun rate are technical QA 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 Source BioScience immediately, as it may be possible for them to identify the cause of the variation remotely (see Appendix 2).
36. In relation to points 34 and 35 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.
37. 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. These data should be reviewed both internally and by the QA team. Source BioScience will automatically recalibrate if certain parameters are breached (Appendix 2). The laboratory should record all such recalibrations.

38. All laboratories utilising the FocalPoint™ Slide Profiler must make arrangements to ensure that the temperature of the room in which the machine is housed does not exceed the manufacturer's limits.

SUMMARY OF REQUIREMENTS

39. Only samples prepared with the SurePath technique can be processed with the BD FocalPoint™ Slide Profiler.
40. Individuals operating the system will be trained and certificated by Source BioScience.
41. An initial sample of 1,000 consecutive slides will be used to calibrate the system before use.
42. Recalibration with a sample of 1,000 consecutive slides will automatically be repeated at least monthly.
43. Recalibration must be requested by the laboratory in the event of technical changes to slide preparation.
44. Recalibration must be requested by the laboratory when significant changes in the population being screened are suspected.
45. Recalibration will be initiated by the manufacturer in response to abnormal profiles, as described.
46. Samples from all sources, including colposcopy, may be scanned and classified as NFR.
47. Slides from women who fall outside the screening age range must not be scanned.
48. Slides classified as NFR must be subject to rapid review or rapid preview.
49. Internal and external QA measures must be in place, as described.

REVISION

50. This guidance should be revised as implementation of the technology expands experience. No revision should occur before April 2014 (to allow for full implementation of HPV triage and test of cure).

APPENDIX 1

NFR MONITORING FOR BD SUREPATH SLIDES, PROCESSED ON BD FOCALPOINT™ SLIDE PROFILER, UK

- A1.1. Upon installation, or at a defined point in the existing routine, a threshold percentage of NFRs will be set (e.g. 23% NFR). This will serve as a reference point moving forward.
- A1.2. Once a reference has been set, a NFR percentage rate drop of at least 5% (e.g. from 23% to 18%) for three or more consecutive print sets of at least 120 slides should trigger a request from the laboratory for an investigation by Source BioScience.
- A1.3. In such a case, answers to the following questions need to be provided by the laboratory:
- What are the print set numbers, the corresponding NFR rates, and start and end dates of each run?
 - Have there been any changes to sample preparation or sample taking in one or more of the participating laboratories?
 - Are there any changes in contributions from participating laboratories, or are new laboratories submitting slides?
 - Is there any change in the screened population?
- A1.4. Based on the input, BD FocalPoint™ Slide Profiler will propose changes to optimise results, and analyse the process review and staining results.

APPENDIX 2

MONITORING FOR BD SUREPATH REVIEW SLIDES, PROCESSED ON BD FOCALPOINT™ SLIDE PROFILER, UK

- A2.1. Slides that score below the threshold level are classified as 'No Further Review' (NFR). They will not exceed 25% of any given batch of slides (or print set).
- A2.2. When a print set is created, the BD FocalPoint™ Slide Profiler first checks the percentage of slides that fall below the threshold determined by calibration. If it is lower than, or equal to, 25%, all of these slides are classified as NFR (the exact percentage will be reported by the BD FocalPoint™ Slide Profiler). If the percentage is higher than 25%, the BD FocalPoint™ Slide Profiler will select the 25% with the lowest slide scores for classification as NFR, and remaining slides will be classified for review (these are known as 'supplemental review' slides, and the normal supplemental review rate should be close to 0%). Increases in the supplemental review rate suggest that the calibrated threshold is no longer representative for the slides that are being processed (this may be due to changes in the screened population). In this case, the thresholds need updating via a recalibration. If the supplemental review rate exceeds 5% over the last processed 1,000 slides, BD FocalPoint™ Slide Profiler will automatically recalibrate, but will not import the new threshold level.