PROTOCOL

Multi-centre validation of digital whole slide imaging for routine diagnosis

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ABBREVIATIONS

Abbreviation	Explanation
CI	Chief Investigator
CONSORT	*Cons*olidated *S*tandards *o*f *R*eporting *T*rials
DP	Digital Pathology
eCRF	Electronic Case Report Form
GCP	Good Clinical Practice
GI	Gastrointestinal
GT	Ground Truth
HRA	Health Research Authority
HTA	Health Technology Assessment
ICC	Intra Class Correlation
IMS	Philips Image Management System
IRAS	Integrated Research Application System
ISRCTN	International Standard Randomised Controlled Study Number
LM	Light Microscopy
MDT	Multi-disciplinary team
NIHR	National Institute for Health Research
PI	Principal Investigator
PPI	Patient & Public Involvement
REC	Research Ethics Committee
SOP	Standard Operating Procedure
SMG	Study Management Group
SSC	Study Steering Committee
WCTU	Warwick Clinical Trials Unit
WSI	Whole slide imaging

Contents

1. STUDY SUMMARY SCHEMA

Literature review

Objective: To establish and review the known data

Training of pathologists in Digital Pathology

All pathologists participating in the study who do not use DP as part of regular practice will be trained on DP. Training sets will be created for each site (covering all the specialties) where training is required. Up to 30 samples (minimum 20 plus practise slides) reviews will be required for each untrained pathologist in DP. Sample mix will include a range of samples including biopsies and resection, simple, complex and variety of stains (H&E, special and immunocytochemistry). Training will be ratified per RCPath guidelines.

Pilot study and survey of pathology staff

Pilot study: Sample size: 20 (renal) and 40 (breast, GI and skin) including difficult samples. **Duration:** 10 weeks. **Objective:** To test the working practices of the study for any unforeseen problems. **Design:** Based on the methodology of the main study.

Focus groups/key informant interviews

Objective: To identify potential barriers and facilitators to the adoption of DP. **Design:** Focus groups and key informant interviews. **Sample:** Convenience sample of pathology and laboratory staff in each study site. **Analysis:** Thematic analysis of qualitative data.

Main study

Sample size: 2000 slide sets from 5 sites (Coventry, Belfast, Lincoln, Oxford, Nottingham). **Primary Objective:** To compare pathologists' diagnoses made by assessment of glass slide microscopy (LM) of breast, GI, skin and renal samples, with the same pathologists' diagnoses of the same samples (intra-rater reliability) using digital whole slide imaging (DP). **Study design**: A multi-centre, randomised cohort study comparing interpretation of slides by pathologists using LM and DP. **Enrolment:** Samples will be enrolled between July 2019 and April 2021 from five participating NHS histopathology departments. **Data analysis:** Concordance will be quantified in this study as complete agreement, clinically unimportant difference or clinically important difference.

Secondary objectives

Eye tracking

Objective: To measure how pathologists examine DP images to establish if the technique of examining these images contributes to error in interpretation

Design: Visual search parameters including overall search time, visual search patterns, the initial Areas of Interest (AOI) in the sample and visual fixation times will be observed.

Analysis: Visual search behaviour will be statistically linked to initial DP expertise and also to the development of DP expertise by the less DP experienced participants through the study.

Qualitative study

Objective: To explore views and experiences of pathologists and laboratory staff migrating from LM to DP.

Occurrence: At initiation of main study and 12 months into the study

Design: Qualitative study utilising face-to-face/telephone semi-structured interviews

Data analysis: Thematic analysis

Health Economics

Objective: To assess the incremental costs involved in DP vs LM-based pathology

Design: Data from existing deployments of DP in the study group will inform the estimates of cost to implement DP. A micro-costing exercise will then be carried out to assess the impact of DP on process efficiency.

2. INTRODUCTION

Digital pathology (DP) refers to the use of high throughput slide scanners to digitise diagnostic histopathology slides that are then reported on computer workstations as opposed to a conventional microscope. Such a development allows pathologists to report samples remote from the laboratory producing slides. In addition to providing some mitigation to the mismatch of pathologist capacity to workload present in many NHS hospitals, there are important implications for sharing difficult samples more easily, which may help reduce error, and for low volume high complexity specialties such as renal pathology, that also require pathologist expertise out of hours. Prior to widespread adoption, it is important to demonstrate that current DP solutions are fit for the purpose of providing the pathologist with tissue imaging of sufficient quality to ensure diagnostic accuracy equivalent to the brightfield and immunofluorescent light microscopy (LM) which is the current standard of care. A number of comparison studies have already been published but the majority have not been adequately powered to provide data of non-inferiority. Concerns have been expressed by researchers as to whether there is sufficient evidence of equivalence to enable full-scale deployment of DP in the NHS, particularly in respect of the breast and colorectal cancer screening programmes.

Moreover, since the image produced in most DP systems is inferior to resolution provided by LM, it is questionable as to whether sufficient numbers of challenging samples have been examined in the data published, to prove equivalence, particularly in specialties requiring fine resolution such as renal biopsy interpretation. In addition, none of the published studies have examined the use of DP in immunofluorescence, which is essential if the DP is going to be used for renal biopsies.

This study is designed around teams of four pathologists, blind to the original diagnoses, all examining the same series of samples, using both LM and DP. The modality each pathologist views/reports on first will be randomised for each batch of samples, and there will be a minimum of a six-week washout period between LM and DP viewings. Reports will then be scrutinised by a trained Research Fellow independent of the reporting pathologists. Differences detected will be classified by an independent pathologist into clinically important (would alter the clinical management) or clinically unimportant (would not alter the clinical management). The original diagnosis will serve as the reference diagnosis. The ground truth (GT) for each sample is decided on conclusion of the readings, by consensus of the study pathologists, taking into account the reference diagnosis. This allows comparison of each pathologist's performance on LM and DP against the GT. The study will examine 2000 histopathology samples including 600 samples each of breast, gastrointestinal (including 200 cancer screening samples) and skin, and 200 renal samples taken for native or transplant related renal disease. The renal biopsies will include immunofluorescence for detection of immunoglobulin deposits. The population of samples enrolled will be a combination of sequentially selected samples and those from study centres' archives. With the exception of renal, samples will also be enriched with at least 10% moderately difficult and at least 10% difficult samples.

A Health Economic evaluation will involve estimating the core costs and benefits associated with DP, compared with LM. This will involve estimating the impact of switching to DP on throughput, and translating this into the impact on the time to establishing a treatment plan. It will further involve assessing samples of discrepancy to investigate the impact on treatment decisions, and the incremental costs and benefits resulting from this impact. This will be for all discrepancies if feasible, or a purposive sample (selected based on material impact on health and cost outcomes).

A qualitative study will examine, by means of focus group and semi-structured interview, the barriers and facilitators to DP and perceptions and experiences of pathologists and laboratory staff prior to, and during, the progress of the study. Eye tracking hardware will examine pathologists' examination

techniques and this will be analysed alongside reporting discrepancies to identify if poor technique contributes to errors in reporting.

3. BACKGROUND & RATIONALE

The use of digital whole slide imaging to view histopathology slides offers a number of potential benefits to pathology departments. It allows the pathologist to view the slides remote from their site of production, thereby allowing work to be moved easily between pathologists, either to assist flow, provide multi-disciplinary, expert or out of hours review, or review where patients move between sites for treatment. Digitising the slides also allows the use of computer algorithms to help improve pathologists' performance. The potential benefits offered by digital pathology (DP) will only be fully delivered once it becomes the preferred method of examining microscope slides. Reluctance amongst pathologists to use DP is partly based on a lack of comprehensive multi-centric evidence proving that DP is safe to use for primary diagnosis. Reluctance to change may also be due to the fear of adopting unfamiliar technology. For disruptive innovations to spread beyond early adopters to the majority of users, clear evidence of relevance is required (1). The impact of DP on productivity and efficiency has not been studied so the return on investment is unknown preventing business sample development. We plan a large multi-centric light microscopy (LM)/DP comparison study with multiple pathologist viewings to address this need.

Histopathological diagnosis using LM is the key step in many major disease pathways. Advances, particularly around early detection of cancer and improved life expectancy, are placing additional burdens on overstretched Cellular Pathology resources (2). This is partly because early stage disease is more difficult to detect leading to more challenging and often increased numbers of samples, and partly because greater data are required from these samples to provide the best standard of care. There is an emerging crisis of Cellular Pathology NHS consultants: 32% of consultants are over 55 and expected to retire within 5 years; the number of new consultants is less than half the number expected to retire; and 55% of the histopathology departments surveyed hold vacancies (2). DP offers better productivity, efficient workload distribution and centralised slide production. This delivers economies of scale and improved access of tissue blocks for molecular analysis which is important for personalised medicine (3, 4). Improved diagnostic accuracy by peer and expert review of samples (5) is greatly increased by DP.

While most previous studies show good LM/DP agreement, (6) (7, 8) (9) some (10) raise concerns over the suitability of DP for diagnosis. Particular concern has been raised about the use of DP for examining samples taken as part of the NHS cancer screening programmes for breast, bowel and cervical cancers.

Our team includes UK leaders in pathology at six NHS teaching hospitals and a large pathology network. We have world leading experience in DP having pioneered its use in routine practice, as well as vast experience of pathology practice and research. The pathologists taking part are a diverse group including highly experienced, relatively junior, early adopters of DP and - a majority - new to DP. The study plan is based on eight viewings of each sample by four pathologists with LM and also with DP, culminating in a consensus ground truth (GT), enabling measurement of agreement within and between readers. Samples enrolled will reflect routine practice. The samples will include cancer screening biopsies and will be enriched for areas of difficulty such as dysplasia (7, 10, 11). State-of-the-art DP equipment designed for diagnosis and holding either CE or FDA approval will be used in this study.

4. STUDY DESIGN

This is a multi-centre validation comparison study comparing pathologists' diagnoses using digital whole slide imaging (DP) with their diagnoses using glass slide light microscopy (LM), the current standard practice within the NHS. The order in which the pathologists view the images (DP and LM) will be randomised.

To achieve objectivity, we have introduced a washout period of a minimum of six weeks between the two viewings (LM and DP) of the same sample by the same pathologist.

An integrated pilot study will test the working practices and processes of the study for any unforeseen problems. It also aims to assess whether it is feasible to include at least 10% difficult cases and 10% moderate cases for the skin, GI and breast specialties. The results of this study will be reviewed by the Study Steering Committee.

5. AIMS AND OBJECTIVES

Pilot study objectives

- Assess the ability of different sites to identify appropriate samples in time and on target
- Examine the intricacies involved in selecting samples and forwarding the appropriate glass slides to Coventry coordinating centre for scanning, as well as observe the rotation of sample case sets between sites following each pathologist's review (site/pathologist)
- Assess access to the digital slides on the central server by pathology investigators, and ability to view and report them appropriately
- Assess access and functionality of Warwick CTU database system (web application)
- Eye tracking of the pathologists will be carried out to ensure that there are no local unforeseen technical difficulties with the approach prior to the main study, and to familiarise study pathologists with the technique
- Identify potential barriers to the adoption of DP and explore the experiences and views of pathology staff migrating from LM to DP by means of focus groups and semi-structured telephone interviews

Main study primary objective

The primary objective of this study is to compare pathologists' diagnoses made by assessment of LM of breast, GI, skin and renal samples, with the same pathologists' diagnoses of the same samples (intra-rater reliability) using DP.

Main study secondary objectives

- Compare DP to LM in reporting histopathology slides to measure variation between pathologists on both modalities (inter-rater reliability)
- Explore the likely costs and benefits associated with DP compared with LM using a Health Economic evaluation

- Explore the existing views of the pathology staff (pathologists and technicians) and the impact of introducing DP (migration from LM to DP) on pathologists and laboratory workforce with a view to understanding the barriers and facilitators to DP

- Determine how the study pathologists examine DP images of different pathology modalities to establish how the techniques used to examine these images contribute to error in their interpretation

6. OUTCOME MEASURES

Primary outcome measure

Level of agreement between each pathologist's DP and LM diagnoses (intra-pathologist)

Secondary outcome measures

- Inter-pathologist level of agreement across the four DP diagnoses and the ground truth (GT)

- Inter-pathologist level of agreement across the four LM diagnoses and the GT

- Individual pathologists' non-concordance rates over the course of the study, and clinical relevance of these non-concordances, including treatment decision-making and cost analysis of error

- Measurement of the productivity of pathologists using DP in comparison to LM, the contribution of DP to reducing error and the cost and benefits associated with avoiding significant errors

- Qualitative assessment of barriers and facilitators to DP, and experiences and views of pathologists and laboratory staff using DP

- Pathologist observer error (visual perceptual and cognitive) using eye tracking software

7. SAMPLE PATHWAY

7.1 Sample selection criteria

Histopathology samples from five participating NHS trusts will be selected. All samples are collected for the purpose of routine histopathology reporting and only entered into the study on completion of their clinical review at the respective NHS participating site.

There are four sub-specialty areas that are included in the study: breast, gastrointestinal (GI), skin and renal. The sample selection process will be devised to include cancer screening biopsies and will be enriched (20%) for areas of difficulty, with the exception of renal samples where all are considered difficult cases:

- Breast (Belfast, Coventry, Lincoln & Nottingham): A total of 600 samples including at least 200 cancer screening biopsies enriched with:
    - At least 10% resected tumours (moderately difficult)
    - 10% difficult samples: low grade ductal carcinoma in situ, atypical hyperplasia, screening category B3 and B4, lesions with calcium oxalate (Weddellite calcification), sclerosing and papillary lesions, and micrometastases
- GI (Coventry, Belfast & Nottingham): A total of 600 samples including at least 200 cancer screening biopsies enriched with:
    - At least 10% resected tumours (moderately difficult)
    - 10% difficult: oesophageal dysplasia, polyp cancers, inflammatory bowel disease, minimal change colitis, graft versus host disease, giardiasis, cytomegalovirus, H. pylori and herpes virus infection
- Skin (Coventry, Belfast & Lincoln): A total of 600 samples enriched with:
    - At least 10% non-basal cell carcinoma cancer resections (moderately difficult)
    - 10% difficult: sentinel nodes, dysplastic naevi, spitz naevi, lentigo maligna, early and desmoplastic melanoma, herpes virus infection, leischmaniasis, leprosy, amyloid, angioscaroma, and Kaposis sarcoma
- Renal (Oxford only): A total of 200 sequential native biopsies for glomerular, tubulointerstitial and vascular disease and transplant biopsies for graft rejection. No enrichment is planned in the renal biopsy group as all of these biopsies are difficult to report.

Please note: Difficult cases might have more diagnostic entities than listed above. All cases will be accompanied with a pseudonymised histopathology report. Samples with either broken or missing slides, or with missing clinical data, will not be considered; neither will megablocks or oversized slide sets. Cases where a prior sample is important to the interpretation of the study sample should also be excluded.

7.2 Inclusion into the study

Warwick Clinical Trials Unit will provide a bespoke online sample tracking database. Site staff will be able to access this from their workplace to enrol samples. Individual log in details (usernames and passwords) will be provided.

7.2.1 Samples from Belfast, Nottingham and Lincoln (breast, GI and skin)

The pathologist at site will identify each sample for the study following its routine diagnosis and pass it to their technicians for processing and shipping to Coventry coordinating centre. Upon receipt of the sample from the pathologist, the technician will need to:

- Enrol each sample on the Warwick Clinical Trials Unit (WCTU) database system. Sample details including non-identifiable patient details, sample difficulty level, number of parts/blocks/slides, reference diagnosis etc will need to be provided as part of the enrolment process.
- Pseudonymise the slides and associated histopathology report(s) by redacting all patient identifiable information leaving only the histology number visible. This will enable the samples to be returned to their original site once the study has been completed. The pseudonymised histopathology report(s) will need to be provided during the enrolment process, either as a file upload or as free text.
- Log the sample(s) as being sent to Coventry coordinating centre, as per local SOP and on the WCTU database system. The database will alert the coordinating centre about this forthcoming shipment.
- Send the sample(s) to Coventry coordinating centre

When the samples are received by Coventry coordinating centre, each sample will be checked for quality control (for example that slides are in good condition) prior to being scanned onto the IMS. If all criteria are met, the sample will be allocated a unique 'study number' generated by the database system. The study number certifies the sample as fully anonymised. This study number, along with other details, will be barcoded by trained coordinating staff using the current UHCW process, and the barcode will be placed on the slides. Following this, the slides will be immediately digitised.

If the sample selection criteria are not met, the case is declined. The sample is marked as ineligible on the WCTU database then returned to the originating site. Return of the sample is tracked on the WCTU database.

7.2.2 Samples from Coventry (breast, GI and skin)

A similar process as above will be followed for samples identified from Coventry site, including the allocation of study numbers and barcode labelling, so that these samples are not identifiable to the research team at Coventry.

7.2.3 Samples from Oxford (renal)

Renal samples will be enrolled from Oxford only. Pathologists identify the sample(s) for the study and pass to their technicians. Technicians then need to:

- Enrol each sample on the WCTU database system. Sample details including non-identifiable patient details, number of parts/blocks/slides, reference diagnosis etc will need to be provided as part of the enrolment process.
- Pseudonymise the histopathology report(s) by redacting all patient identifiable information leaving only the histology number visible. The pseudonymised histopathology report(s) will need to be provided during the enrolment process, either as a file upload or as free text.
- The WCTU database system will produce a unique anonymised study number for each enrolled sample.

- Label the sample slides with the study number. If applicable, immunofluorescence (IF) stained slides of the original image will be anonymised with the same study number and used for the study.
- Digitise the slides
- Log the sample(s) as being sent to Coventry coordinating centre, as per the existing local laboratory SOP and on the WCTU database system, using the unique study number in the record. The database will alert the coordinating centre about this forthcoming shipment.
- Send the sample(s) to Coventry coordinating centre

Quality control and eligibility checks of renal samples at Coventry coordinating centre will follow the same process as for breast, GI and skin.

7.3 Batch process and randomisation

When enough samples per specialty have been received by the coordinating centre, the coordinating centre will batch the samples using the WCTU database system.

The system will allocate a unique batch number and then randomise the batch by selecting which group of pathologists will view using light microscopy (LM) first and which will view using digital pathology (DP) first.

7.4 Reporting pathologists

Six NHS histopathology laboratories (Coventry, Belfast, Lincoln, Oxford, Nottingham, Birmingham) will each have specialist pathologists to report on relevant disease areas. In each area, four pathologists will report the same series of samples twice, once each with LM and DP, thereby allowing comparison within and between observers over both platforms.

Specialist reporting pathologists at each centre by specialty are shown below:

Centre/disease specialty	GI	Skin	Breast	Renal
Coventry	S Sah	D Snead YW Tsang		K Gopalakrishnan
Belfast	P Kelly M Loughrey	D Boyle	C Boyd	
Lincoln		D Clark	A Bickers	
Nottingham	M Ilyas		I Ellis E Rakha	
Oxford				I Roberts M Soares
Birmingham				D Neil

The estimated time to make these readings based on current work-diary exercise data is one 4 hour session per week over 24 months.

7.5 Blinding

To maintain objectivity,

- Pathologists will be blind to the reference diagnosis
- There will be a minimum six-week washout between reviews of the same sample using LM and DP
- The sequence of which modality (LM or DP) is used first will be randomised

7.6 Distribution and tracking of samples following enrolment, batching and randomisation

Following batching and randomisation, the two pathologists in the 'DP first' group will be assigned the digital images. These pathologists will view the samples on the Philips Image Management System (IMS) and report their findings using WCTU database system's electronic Case Report Form (eCRF). Once one of these pathologists has completed the reporting of the entire batch, the system will prompt the technicians at Coventry coordinating centre to package up the glass slides and dispatch to the first pathologist in the 'LM first' group.

As and when a site receives a batch of glass slides, the technician (or other trained staff member) should record the received date on the WCTU database system and check the condition of the slides, then pass them on to the pathologist for viewing and reporting.

Once the first pathologist in the 'LM first' group has completed reporting, the system will prompt the pathologist to pass the slides back to the technician(s). The technician(s) will then send the glass slides to the site at which the second pathologist in the 'LM first' group is based.

For each of the pathologists, a 6 week washout period begins from the date on which their first read is completed.

For the second reads, the glass slides will be made available to the pathologists in the 'DP first' group (one followed by the other, in a fixed order, and only when each pathologist's 6 week washout period has ended). The glass slides will then be returned to Coventry coordinating centre.

When 6 weeks have passed since the completion of the 'LM first' pathologists' first reads, the WCTU database system will prompt the technicians at Coventry coordinating centre to assign the digital images to the 'LM first' pathologists.

7.7 Sample pathway flow diagrams

Figure 1: Study flow diagram - Breast, GI & skin samples

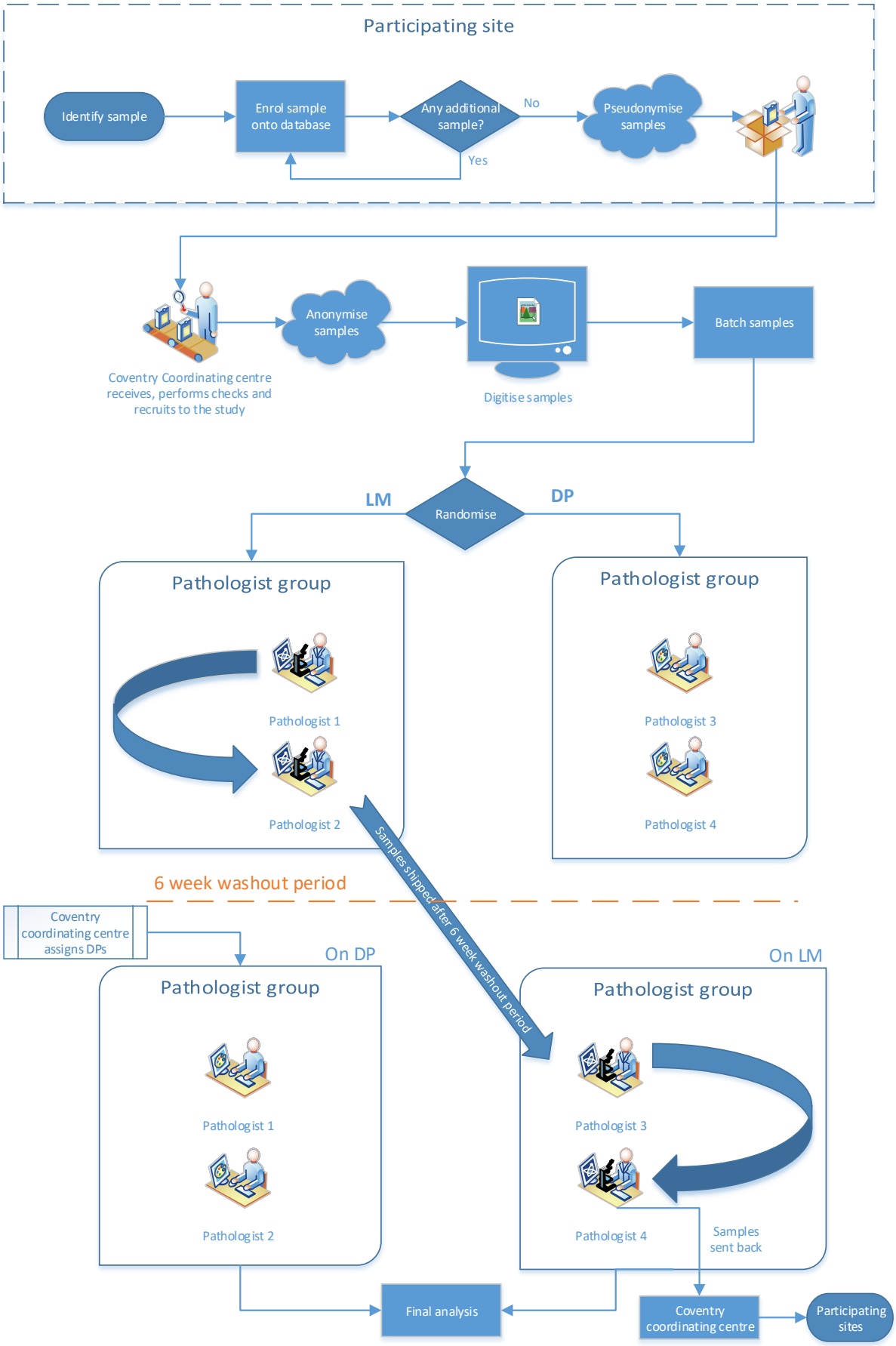


Figure 2: Study flow diagram – Renal samples

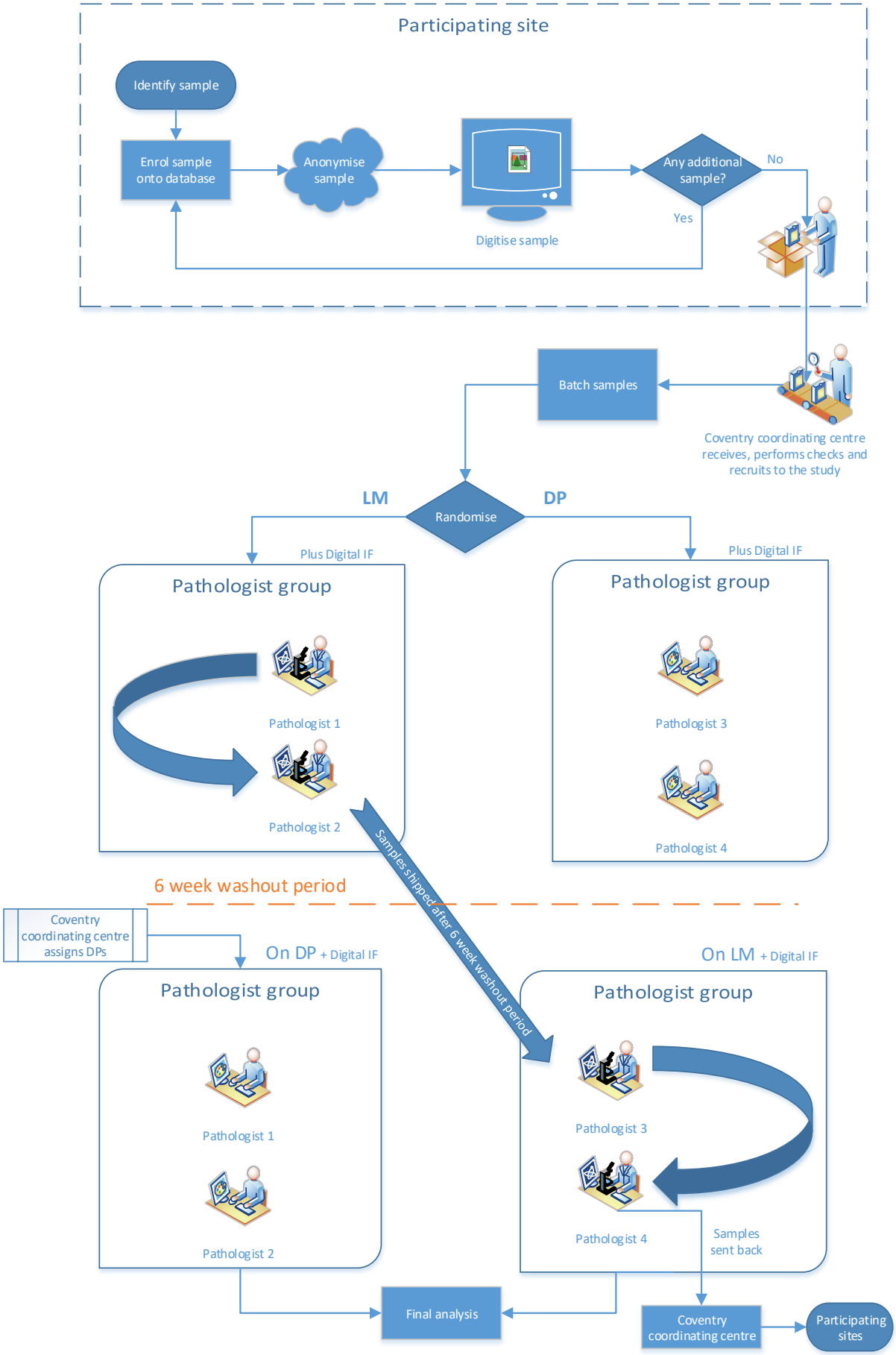
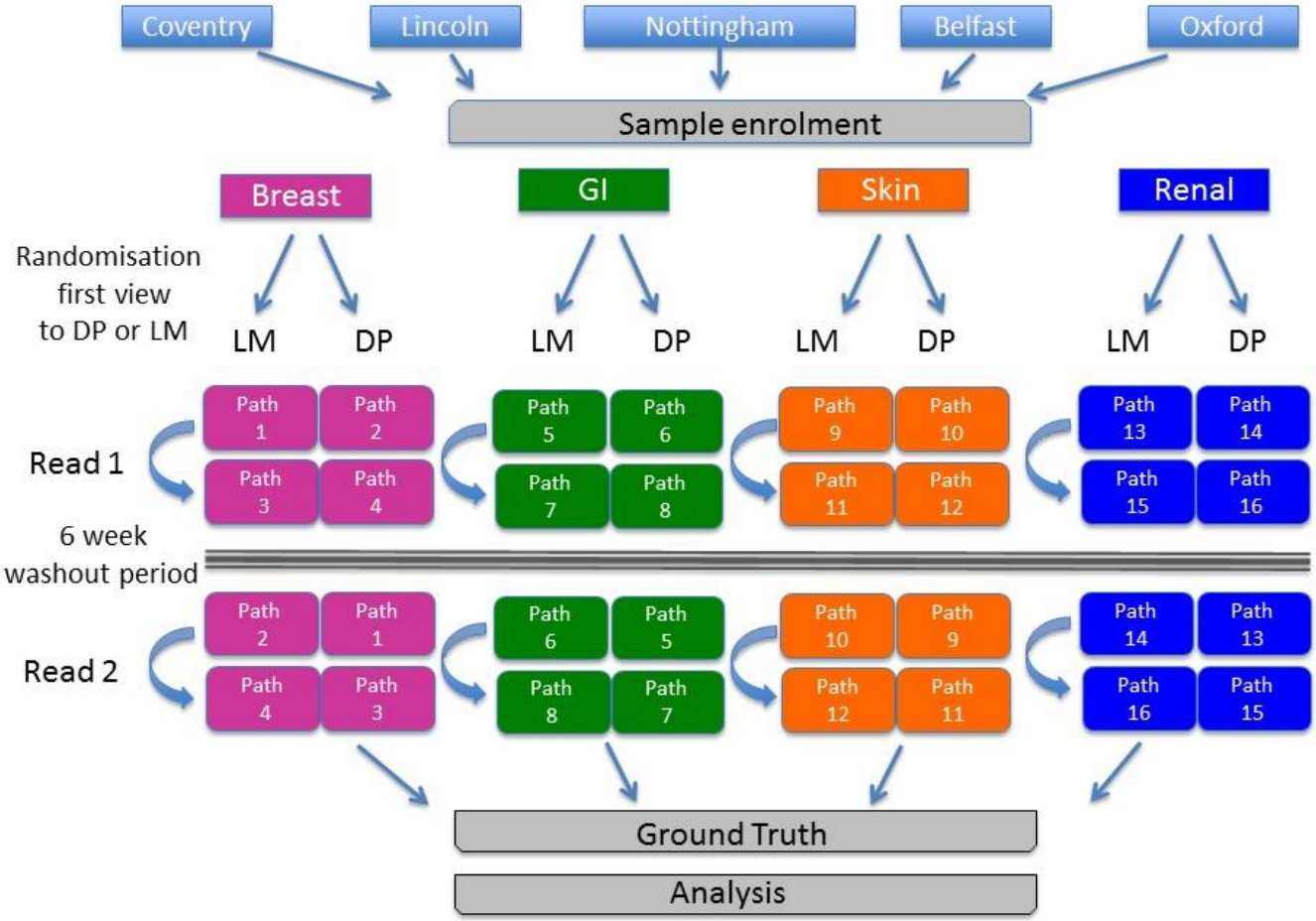


Figure 3: Sample reporting



Key:

DP – Digital Pathology

GI – Gastrointestinal

LM – Light Microscopy

Path – Pathologist

Legend: Belfast, Coventry, Lincoln and Nottingham enrol reported samples of breast, gastrointestinal and skin. Renal biopsy samples are enrolled by Oxford only. These samples are divided into batches and randomised to which pathologists review on DP first and which on LM first (Read 1). Curved arrows indicate circulation of batched samples between the LM reviewing pathologists. After 6 weeks, pathologists swap to the alternative platform in Read 2. For each sample where there is considered to be a clinically important difference between reports, participating pathologists meet after read 2 to agree the ground truth diagnosis.

8. TRAINING

Training in the use of Digital Pathology

The aim of initial training is to train the pathologist in the use of the digital pathology (DP) system. Training will be provided to pathologists who do not use DP as part of regular practice by the study Pathology Research Fellow and Philips training manager using the Royal College of Pathologists 'Best practice recommendations for implementing digital pathology' January 2018 (26).

Training slide sets will be compiled for each site. Glass slides will be scanned at Coventry and sent back to the home site. Digital slides will be available to view on the Philips Image Management System. Training will include an initial basic skills training to demonstrate how to use the system. This will be followed by providing 5-10 practice samples to each pathologist which they can review and practise in their own time. Finally, a test set of 20 cases will be provided to the pathologist from the Royal College of Pathologists 'Best practice recommendations for implementing digital pathology' guidance and findings will be recorded on the proforma to see how confident they are in analysing digital slides. RCPath approval has been gained for 6 CPD credits for training. The outcomes of the training will be recorded and if needed further training can be provided. Once the training process is complete and sign off has been granted by the Pathology Research Fellow, pathologists will be ready to review study cases.

Site initiation

Each site underwent a site initiation where the lead pathologist and their teams participated in an induction session. This was carried out by site initiation visit.

A checklist was completed for all sites to confirm that pre-activation activities were completed. Support is offered by relevant study team members to staff at participating sites to ensure they remain fully aware of study procedures and requirements. Additional support and training is offered to sites where necessary.

9. INFORMED CONSENT

The study involves use of previously collected tissue for routine pathology assessment. All samples will be anonymised and returned to the site once all diagnoses have been completed. Therefore, no patient consent is required.

10. WITHDRAWALS AND REPLACEMENT

Case samples may be excluded from the study if they are damaged during their transportation. In this situation, a further slide set will need to be identified as a replacement.

11. END OF STUDY

The completion of the ground truth and analysis of all reports by consensus diagnosis will be considered as end of study.

The study will be stopped prematurely if funding for the study ceases.

The Health Research Authority will be notified in writing within 90 days when the study has been concluded or within 15 days if terminated early.

12. STATISTICAL ANALYSIS

12.1 Power and sample size

Three measures will be used to quantify concordance in this study: percentage concordance, Kappa Statistic (KS) and intra class correlation (ICC). In consideration of the appropriate sample size for this study, we assessed the precision of percentage concordance estimates.

Percentage concordance for the routine samples is assumed to be 98.8% (7). The percentage concordance for the difficult samples ranges from 40%-70% (16-25), and so we assume it to be 55%. We assume the percentage concordance for moderate samples to be 75% (a percentage between those for difficult and routine samples). The weighted percentage concordance within our study, with the specified 10% difficult, 10% moderate and 80% routine proportions, is expected to be 90%.

For each of breast, GI and skin, 600 specimens will be included, leading to 4,800 diagnoses (i.e. 600*4 pathologists*2 readings). For renal, 200 specimens will be included, leading to 1,600 diagnoses.

Taking into account the expected percentage concordance, we take ICC for routine, moderate and difficult samples to be 0.9, 0.7 and 0.4 respectively. This corresponds to an overall ICC of about 0.8. Hence, the design effect is (1+ICC(observations per specimen-1))=3.4.

Consequently, 2400 paired diagnoses (a pair consists of DP and LM diagnoses of each sample by a pathologist) is equivalent to 705 (2400/3.4) independent observations. With 705 independent observations the margin of error (1.96 x Standard error) is 2.2% so that the precision while analysing breast cancer, skin and GI specimens separately is high. Due to a smaller sample size for renal specimens, the margin of error is 3.1%.

12.2 Statistical analysis plan

Primary analysis

There will be three categories for the level of agreement: complete agreement, clinically unimportant difference and clinically important difference. For each sample, three sets of agreements will be reported:

- whether each pathologist's DP and LM diagnoses concur
- whether each of the four DP diagnoses concur with the GT
- whether each of the four LM diagnoses concur with the GT

Two measures will be used to quantify concordance: percentage concordance and ICC. Logistic regression models will be used to estimate the probability that diagnoses are concordant and will include a random effects term to account for multiple results per sample.

For cancer resections, as well as diagnosis, comparisons will also be made across all RCPath dataset items.

Interim analysis

Interim reports will be created after approximately 6 and 12 months from the start of sample enrolment into the main study informing on the selection of samples and the flow and timing of pathology reviews. The steering group, who will advise if any adjustments are required, will review these data. If it is concluded that the enrolment of suitable samples is falling well below target or substantial delays in pathology review are making the required sample flow rates unattainable, and that suitable protocol amendments cannot be determined to rectify the situation, then this may require alterations of milestones which will be agreed by the steering group to ensure successful delivery of this study.

Subgroup analyses

The above analyses will be performed using specimens from all specialties. Subgroup analyses will investigate results from each of the four specialties separately. The subgroups containing routine, moderate and difficult samples will also be explored.

Procedure(s) to account for missing or spurious data

We will utilise a bespoke tracking database designed for this study, which will record and update the progress of the study. It will auto-populate updates to show the sample enrolment rates, track the inventory (glass slides) and notify pathologists to submit the reports. Additionally, a Research Fellow will be employed in the study to rigorously oversee the flow of study samples. They will ensure safe and timely transition of samples between pathologists. Thus, we anticipate little to no missing data.

13. HEALTH ECONOMICS EVALUATION

Aim

The aim of the health economic study will be to assess the incremental costs involved in DP vs LM-based pathology and estimate the health benefits and resource use impact of a sample of diagnostic inaccuracies identified in the study, in order to support an informed assessment of the sample for investing in DP-based pathology processes.

Methods and analysis

This aim will be achieved by answering the following questions, which have been identified in consultation with our PPI colleagues:

1. What are the costs involved in investing in DP?
2. What is the knock-on effect on resource use within pathology of switching to DP, resulting from the process efficiencies it enables?
3. Where does the switch from LM to DP generate value for patients and the health service, as a consequence of improved speed and accuracy of the provision of diagnostic information?
4. What health benefits and cost impacts accrue as a result?

Data from existing deployments of DP in the study group will inform the estimates of cost to implement DP. A micro-costing exercise will then be carried out to assess the impact of DP on process efficiency. This will involve direct observation of existing LM reporting and multi-disciplinary team (MDT) processes including time for supervising histopathology trainees.

During the study, DP reporting and MDT processes will be observed to inform a comparative costing exercise. Costings derived from the timing and staff grade required for each task in the process will be performed, allowing direct comparison of the two different workflows. Pathologists will be required to assess the time taken to report samples on DP compared to LM by stopwatch. Making corrections for interruptions, pathologists will record the time taken to examine slides and compile the reports on all samples in the study both on DP and LM.

How these measurements change over the time of the study will be assessed so allowances can be made for increasing experience with DP. The cost of peer review of samples between pathologists using DP compared to LM will also be estimated. This will include peer review of samples within departments, and referral for expert review outside of the department. The cost of collation of samples for MDT review will also be compared between DP and LM. This will include stopwatch recording of the time taken to find sample slides for the MDT review, as well as the time taken to review slides for MDT with DP and LM workflows.

This detailed information will be used to estimate throughput and capacity under each system. The simulation model for UHCW breast cancer pathway developed by Madan et al. will be used to estimate how increased throughput might lead to reductions in delays along the diagnostic pathway (up to the point at which the treatment plan has been finalised). A similar model will be developed for the other cancers in the study (GI, skin and renal).

Drawing on expert guidance, illustrative examples of the potential gains from increased throughput and the resulting reduction in time to treatment initiation will be presented. Any differences in diagnostic accuracy will lead to potential changes in health outcomes and the cost of health care provided. Potentially, there may be a range of choices around treatment which might be influenced by diagnostic accuracy, and it is unlikely to be feasible to assess such changes for every example found

in the study. Therefore, we will focus on examples where the impact is likely to be significant. This follows previous work done at Warwick Medical School which identified HER2 status as information where changes in diagnostic accuracy could lead to substantial impact on health outcomes and treatment costs. We will identify similar examples from incremental improvements in diagnostic efficiency identified in the study, and determine the likely number of similar samples that might be processed in the service per annum. We will identify suitable cost-effective cancer treatment models from the existing literature to source estimates of the health and cost impact of correct versus incorrect diagnosis. This work will allow us to provide only a partial estimate of the downstream costs and benefits of investing in DP, as it will not cover all the samples where it might impact treatment. However, we will be able to assess whether the samples identified are sufficient to justify investment in DP. If not, we will provide estimates of the further benefits required beyond those identified within the study, together with an expert-based assessment of the plausibility of observing these additional benefits in practice.

14. QUALITATIVE STUDY

Aim

The aim of the qualitative study is to identify potential barriers and facilitators to the adoption of DP and explore the experiences and views of pathology staff migrating from LM to DP. There are two components to the qualitative study:

- Focus groups/key informant interviews
- Semi-structured telephonic interviews

Sample

The focus groups/key informant interviews will be undertaken during the pilot study, while semi-structured interviews will take place on two occasions: at initiation of the main study and at mid-point of study.

Focus groups/key informant interviews: In each study site, we will adopt a convenience sampling strategy with knowledge of the group used to select representative subjects, and select 4-6 staff to participate in the focus group discussion. In some sites, key informant interviews will be undertaken instead of focus groups. The key informants will be identified through discussions with the lead clinician or manager in these sites.

Semi-structured interviews: We will adopt a purposive sampling strategy and select the participants using a maximum variability logic. This strategy will allow us to interview staff with different levels of experience and familiarity with DP.

Recruitment of pathologists and lab staff

The key informants will be identified through discussions with the lead clinician or manager in these sites.

The lead clinician or manager for each study site will contact the staff and invite them to participate in the study. A timetable will be prepared with the lead clinician/manager of:

- Date for briefing staff members about the qualitative study, for example, during a staff meeting at least four weeks before the focus groups/key informant interviews
- Start and end date of the interviews

Participants will be given information outlining the purpose of the study and an informed consent form. They will be notified that their involvement is voluntary and can be withdrawn at any time, and that confidentiality is protected through the anonymisation of all collected data. For telephone interviews, the information and consent form will be emailed to the participant in advance of the interview and consent confirmed before the interview commences.

Data collection

<u>Pilot study: focus groups/key informant interviews</u>

Focus groups will explore individual and contextual barriers and facilitators to DP uptake. The focus group guide will address the following topics: participants' beliefs and experiences with DP, specifically; willingness to adopt DP in their routine practice; and perceptions regarding the potential of DP.

We will ask participants to discuss both their own experiences and those of their colleagues in their workplace. By adopting this approach, we aim to capture the complex and multi-dimensional processes and relationships involved in the use and adoption of DP across different stages of implementation.

For key informant interviews, the topic guide will be adopted to explore the barriers and facilitators to DP uptake from an organisational perspective. As with focus groups, the key informants will be encouraged to discuss both their own experiences as a manger/clinical lead but also those of their colleagues in their workplace.

Focus groups and key informant interviews will be audio-recorded.

Main study: semi-structured interviews

The interviews will explore the diverse range of views of pathology staff, with different levels of expertise in DP, towards migrating from LM to DP. The initial interviews at the start of the main study will explore staff's experiences and perspectives on DP. The interviews will focus on the use of DP, any difficulties encountered in using it, acceptability, and modifications to make it more acceptable. Participants will also be asked about the use of glass slide microscopy and its acceptability compared to what they have experienced using. 12 months into the implementation of DP, another set of interviews will explore staff's experiences over time, training needs, and perceived impact on day-to-day working in multidisciplinary teams.

We estimate to interview around 15-20 participants (3-4 per site) on both occasions; the final number will be guided by analysis and data saturation. The interviews will be audio-recorded.

Data management

All qualitative data will be given an identifier, typed up/transcribed and during this process anonymised. NVivo software will be used to manage this data.

Data analysis

Analysis of data will be ongoing over the course of the study. To safeguard internal validity, all data will be transcribed fully and qualitative coding software will be used to facilitate data storage and retrieval in analysis. Analysis will draw on elements of grounded theory, in particular the constant comparative approach. Codes will be created both horizontally (by coding each interview or focus group as a standalone hermeneutic unit) and vertically (by scanning across the data for specific terms), and then developed into categories and themes.

Given the need for generalisable evidence about the processes and relationships involved in the use and adoption of DP, we will present qualitative data in two parts: (1) a systematic summary of specific processes and practices that are present in each study site, and (2) a cross-comparison between study sites, identifying the similarities and differences between sites to develop a set of themes which represent the whole corpus of data and the processes of DP uptake.

15. EYE TRACKING STUDY

Aim

The eye tracking study will determine how the pathologists examine DP images of different pathology modalities to establish how the techniques used contribute to error in their interpretation. The study will take place at the various pathology laboratories over the course of the project.

Methods and analysis

The eye tracking study will examine the visual search behaviour of pathologists using DP to develop both practical and theoretical understanding of the nature of diagnostic errors. This will build on the research in breast screening radiology, which has identified three sources of observer error (visual, perceptual and cognitive) that can then be targeted to improve performance. For a selected number of cases, the pathologists' visual search behaviour will be recorded in situ in each laboratory as they examine DP slides. This procedure is fully transparent and will not affect their ability to examine the images normally. Subsequently, the eye tracking data will be related to the DP images and the combined data examined in terms of known abnormal locations and correct/incorrect abnormal image site identifications. In doing so, the data will also incorporate the image examination recorded timing information.

As part of the pilot study, eye tracking of some pathologists will be carried out to ensure that there are no local unforeseen technical difficulties with the approach prior to the main study, and to familiarise study pathologists with the technique.

The eye tracking data will yield information concerning how individual pathologists' expertise with DP relates to how they examine the samples and the types of errors they may make. Data will be recorded over the course of the study at each site as pathologists examine the same selected cases.

Visual search parameters including overall search time, visual search patterns, the initial Areas Of Interest the sample and visual fixation times will be related to the pathologists' performance data using a multiple reader multiple samples experimental design coupled with Receiver Operator Characteristic and Jackknife Alternative Free-response Receiver Operating Characteristic analyses. Visual search behaviour will be statistically linked to initial DP expertise and also to the development of DP expertise by the less DP experienced pathologists through the study.

16. PATIENT AND PUBLIC INVOLVEMENT (PPI)

In the design of the study, we discussed with PPI members which areas of pathology should be included in the study, the plan of how the validation of digital microscopy should be conducted, the size of the study and the approach to enrichment with difficult samples, the practicalities around using prospective and retrospective samples, and the ethical considerations around the lack of patients' consent. They reviewed the feedback given on the stage 1 application and contributed to the changes made in the submission for stage 2. We have encouraged engagement of our PPI colleagues in this study by inviting them to sit on the SSC and we will be providing the training necessary to enable them to carry out this task. We have consulted widely with interested patients and lay members of the public on the lay summary relevant to this study.

PPI members have also been involved in examining the justification of the study costs, and reviewing where efficiencies have been made and the value for money offered by this study.

One PPI member has been working with our group to review the study design and provide advice regarding areas to be studied. Another has professional expertise in a number of aspects of digital imaging, having spent most his career working for Canon. He is excited to be able to bring this expertise to bear on digital pathology. Both of these PPI members sit on the SSC.

A further two PPI representatives have attended research meetings and given valued feedback into the study design and the Plain English Summary. One of these PPI representatives also sits on the SSC.

We will continue to work with our existing PPI representatives to enlarge the group and link with other interested lay groups with whom the results of the study will be shared, and who will help advise us on the impact of the study and the development of future research.

The project has been presented to members of the UHCW Patient and Public Research Advisory Group. This group comprises patients, carers and members of the public who are interested in influencing research by participating in PPI. The group members have provided valuable input to the study design, consent and ethical issues as well as the prioritisation of the proposed disease sites under review, and contributed valuable feedback on the Plain English Summary.

17. DATA MANAGEMENT

17.1 Database and data storage

The database will be a web application developed by the Programming Team at WCTU and all specifications (i.e. database variables, validation checks, screens) will be agreed between the programmer and research team. Reports will be completed on the study database by the study pathologists. Report comparisons will be carried out by the independent arbitrator and Pathology Research Fellow.

17.2 Confidentiality

All essential documentation and study records will be stored by WCTU in conformance with the applicable regulatory requirements. Access to stored information will be restricted to authorised personnel. An audit may be arranged at a site if the Study Management Group feels it is appropriate. Audits will be conducted by an independent team, determined by the Study Management Group.

17.3 Data shared with third parties

Will individual participant data be available (including data dictionaries)?	Yes
What data in particular will be shared?	The variables required to undertake the analysis proposed by the researchers and agreed by the Digital Pathology Study Management Group. The digital images and relevant descriptive variables required for reference and teaching purposes as proposed by the applicants and agreed by the Digital Pathology Study Management Group.
What other documents will be available?	Latest approved protocol
When will data be available (start and end dates)?	Start date: - For images and descriptive variables for reference/teaching purposes: Date of favourable opinion for v2.0 of protocol - For any other data: 2 years after publication End date: 5 years after publication
With whom?	Data will be made available to researchers whose full proposal for their use of the data has been approved by the Digital Pathology Study Management Group and whose research group includes a qualified statistician. Digital images and related data will be made available to applicants whose full proposal for their use of the images/data has been approved by the Digital Pathology Study Management Group. Data/images will be provided after completion of a data sharing agreement. Data sharing agreements would be set up by the

	Sponsor, funder, study coordination centre, Study Steering Committee and Study Management Group.
For what types of analyses?	Data will be made available for approved specified purposes only.
By what mechanism will data be made available?	Requests for data or digital images should be made to digitalpath@warwick.ac.uk. Data/images will be provided after approval by the Digital Pathology Study Management Group and completion of a data sharing agreement.

17.4 Essential documentation

A Study Master File will be set up according to Warwick SOP and held securely at Warwick Clinical Trials Unit (WCTU).

WCTU will provide Investigator Site Files to all participating centres involved in the study.

17.5 Archiving

Following the resolution of queries and confirmation of study close-out by the Chief Investigator, all essential documentation will be transferred to a third party archiving service, which provides suitable fire and water-resistant facilities. Anonymised data will be held for a period of 25 years after completion of the study. Access to the study documentation will be restricted to named individuals within the study team with express permission from the Chief Investigator.

18. STUDY RESPONSIBILITIES, OVERSIGHT AND MANAGEMENT

18.1 Sponsor and governance arrangements

University Hospitals Coventry and Warwickshire will act as sole Sponsor for this study.

Sponsor's responsibilities include, but are not limited to:

- Central sample collection and verification
- Reporting to the independent Study Steering Committee (SSC) according to the Study Monitoring Plan

18.2 Ethical approval

The study will be conducted in accordance with all relevant regulations.

Health Research Authority (HRA) and Research Ethics Committee (REC) approval for the study was issued on 29 August 2019. Before any site started to enrol samples into the study, confirmation of capacity was sought from the site's research and development (R&D) department.

Substantial amendments that require HRA and REC review will not be implemented until the HRA and REC grants a favourable opinion. For any amendment that will potentially affect the site's permission, the R&D department at each site must confirm that permission is ongoing.

It is the responsibility of the CI to ensure that an annual progress report is submitted to the REC within 30 days of the anniversary date on which the favourable opinion was given, annually until the study is declared ended. The CI is also responsible for notifying the REC of the end of study within 90 days. Within one year of the end of study, the CI will submit a final report with the results, including any publications/abstracts, to the REC.

18.3 Responsibilities

Chief Investigator (CI):

The Chief Investigator's responsibilities include, but are not limited to:

- Ensuring that the study is conducted as set out in the protocol and supporting documents
- Delegating study related responsibilities only to suitably trained and qualified personnel and ensuring that those with delegated responsibilities fully understand and agree to the duties being delegated to them
- Allowing access to source data for monitoring, audit and inspection
- Ensuring the study is conducted in accordance with GCP principles

Study Management Group (SMG):

The Study Management Group, consisting of the project staff and co-investigators involved in the day-to-day running of the study, will meet regularly throughout the project. Significant issues arising from management meetings will be referred to the Study Steering Committee or Investigators, as appropriate.

The SMG's responsibilities include, but are not limited to:

- Coordinating development of protocol and study management documents
- Correspondence with study funder (NIHR-HTA)
- Setting up and maintaining the Study Master File
- Ensuring necessary approvals are in place before the start of the study
- Providing training to study personnel
- Providing data management support including data input, maintenance of the study database and raising of queries
- Producing study progress reports and coordinating SSC meetings and minutes
- Ensuring data security and quality and ensuring data protection laws are adhered to
- Ensuring complete records are in place for audit and monitoring purposes

- Ensuring the study is conducted in accordance with GCP guidelines
- Archiving all original study documents in line with UHCW NHS Trust policy

The full remit and responsibilities of the SMG will be documented in a Charter which will be signed by all members.

Study Steering Committee (SSC):

The study will be guided by a group of respected and experienced personnel and researchers as well as at least one 'lay' representative. The SSC will have an independent Chairperson. Face to face meetings will be held at regular intervals determined by need but not less than once a year. Routine business is conducted by email, post or teleconferencing.

The SSC, in the development of this protocol and throughout the study, will take responsibility for:

- Major decisions such as a need to change the protocol for any reason
- Monitoring and supervising the progress of the study
- Reviewing relevant information from other sources
- Informing and advising on all aspects of the study

The full remit and responsibilities of the SSC will be documented in the Committee Charter which will be signed by all members.

Funder:

The study is funded by the National Institute for Health Research, Health Technology Assessment (HTA) Programme. The design and management of the study are independent of the funder, however regular updates will be forwarded in study 'Progress report task' within the NETSCC Management Information System (MIS) portal.

18.4 Study management arrangements

Warwick Clinical Trials Unit, University of Warwick will manage the study.

University Hospitals Coventry and Warwickshire NHS Trust (UHCW) will act as study sponsor. Warwick Clinical Trials Unit (WCTU) will undertake the central study coordination, data collection, monitoring and statistical analyses. The co-applicants for the project and other experts they may choose to co-opt will form the Study Management Group (SMG) and will contribute their specialist knowledge to the study set-up and running of the study. The SMG has responsibility for ratification of all major decisions concerning study conduct including protocol amendment and publication. Day to day management of the study will be the responsibility of the core management team which is expected to meet every 2 weeks. The core management team will comprise a subset of the SMG and WCTU project staff. A senior project manager will oversee the day to day running of the study, with CTU and UHCW study managers being responsible for the delivery of the CTU activities and sample processing, respectively. The Study Steering Committee (SSC) will provide oversight of the study and will have an independent chair and include the Chief Investigator (Snead), the study manager(s), patient representative(s) and other members of the SMG as appropriate to the ratio of external members. The SSC will monitor the study at appropriate intervals (expected to meet before the start of enrolment then at least annually through the project) to ensure that planned targets are met.

18.5 Monitoring, audit and inspection

The study is constructed around five collaborating centres each of which will select the study samples, with an additional further site reporting. The study will be managed by the Study Steering Committee (SSC), which has an independent chair. The data collection and storage are managed by Warwick Clinical Trials Unit.

Statistical analysis is being performed by Dr P Kimani and this is monitored by WCTU. To avoid bias, the decision on which reports are discordant is made by a pathologist not involved in reporting the samples and blind to the reports' author and the diagnostic platform used. Interim analyses will be conducted after approximately 6 and 12 months from the start of sample enrolment into the main study, informing on the selection of samples and the flow and timing of pathology reviews. These data will be reviewed by the SSC, who will advise on suitable protocol amendments or alterations of milestones to ensure successful delivery of this study.

It is not expected that any differences detected between ground truth and reference diagnosis will have a clinical impact, however the levels of clinically important differences (which would alter the clinical management) and clinically unimportant differences (which would not) will be monitored by the SSC who will decide the appropriate action, if any, on a case by case basis. Any clinically important differences between ground truth and reference diagnosis that need to be flagged to the SSC will be dealt with as soon as possible.

A Study Monitoring Plan will be developed and agreed by the Study Management Group (SMG) and SSC based on the study risk assessment which may include on site monitoring.

18.6 Indemnity

NHS indemnity covers NHS staff, medical academic staff with honorary contracts, and those conducting the study. NHS bodies carry this risk themselves or spread it through the Clinical Negligence Scheme for Trusts, which provides unlimited cover for this risk. The University of Warwick provides indemnity for the design of the research protocol and conduct of the study.

18.7 Study timetable and milestones

Month 0-11	Finalisation of main study protocol. Gain relevant approvals. Contracts for research sites. Workstation set up. Fitting of scanners. Training of pathologists on Digital Pathology. Qualitative survey. Eye tracking set up.
Month 11	Enrolment of samples in pilot study
Month 12	SSC meeting to review protocol and timelines
Month 13-14	Continue with enrolment of samples into main study
Month 15-24	Report comparisons for pilot study
Month 24	SSC meeting to review pilot study results
Month 24-30	Continue with sample enrolment
Month 30	SSC review

Month 30-34	Complete sample enrolment, viewing and reporting
Month 35-36	Final analysis

19. DISSEMINATION AND PUBLICATION

19.1 Dissemination

All data arising from the conduct of this study will remain the property of University Hospitals Coventry and Warwickshire NHS Trust. All efforts will be made to ensure that the results arising from the study are published in a timely fashion, in established peer-reviewed journals. Results will be disseminated via internal and external conferences and seminars, newsletters, and via interested groups, including local healthcare commissioning groups.

The results of the study will be reported first to study collaborators. The main report will be drafted by the study co-ordinating team, and the final version will be agreed by the Study Steering Committee before submission for publication, on behalf of the collaboration.

The success of the study depends on the collaboration of pathologist, technicians and researchers from across the UK. Equal credit will be given to those who have wholeheartedly collaborated in the study.

The study will be reported in accordance with the Consolidated Standards of Reporting Trials (CONSORT) statement (www.consort-statement.org).

19.2 Publication

It is planned to publish the following papers for peer review, open access publication, following presentation at national and international conferences:

- Multi-centre study measuring the precision and accuracy of digital whole slide imaging in the reporting of histopathology samples. To record the overall level of agreement within and between pathologists using DP and LM in cancer screening and non-screening histopathology samples.

- Is digital pathology an alternative to conventional light microscopy for reporting of renal biopsies? – Implications for the future of renal pathology in the NHS. To examine if DP is a realistic alternative to LM for renal biopsies and whether it is a viable proposition to underpin developing a national NHS virtual renal pathology department, capable of delivering 24/7 diagnostic support.

- Experiences of using digital whole slide imaging for routine histopathology reporting in the NHS – a multi-centre study. To record the results of the qualitative study and examine the contribution of DP to delivering improved peer review of slides and training of trainee pathologists.

- The cost of implementing digital pathology solutions in the NHS and the expected return on investment. Examining the cost of implementation against the efficiencies delivered.

- The cost of diagnostic inaccuracies in histopathology and can these be mitigated by adopting digital pathology? Examining the detail around inaccuracies identified in the study, the costs in terms of additional treatment and expected outcomes as well as the human cost of these mistakes and a realistic assessment of whether widespread adoption of DP would reduce these errors

- How pathologists examine digital whole slide images – can improved examination technique reduce error? Reporting the findings of the INFORMANS eye tracking data from the DP arm in relation to diagnostic accuracy across the study. The eye tracking data will identify the types of error made when using DP. Strategies to minimise future DP errors will be proposed. Engage and inform patients, NHS and the wider population.

In addition to these publications, UHCW, the lead trust and sponsor, plans a series of press releases and media interviews on the progress and findings of the studies. We plan reports to the NHS Patient Safety Group regarding the costs of pathology errors, the role of DP in reducing error through improved expert and peer review of samples, and findings of the eye tracking study.

Generalisability of findings across pathologists with different levels of expertise:

The study pathologists are all NHS consultants and range in experience from 3 to 35 years consultant experience, working in a mix of teaching hospital and district general hospital pathology departments across the UK. The study will recruit a trainee pathologist as its Research Fellow. Three pathologists are already using digital pathology for routine practice.

We will develop a strategy in consultation with our PPI group and UHCW/Warwick University Communications team (e.g. a lay summary of the findings available on the study websites, and dissemination through social media) to help patients, patient representatives and wider public learn about the project's findings.

20. REFERENCES

1. Berwick DM. Disseminating innovations in health care. JAMA. 2003;289(15):1969-75.

2. Bainbridge S, Cake R, Meredith M, Furness P, Gordon B. Testing times to come an evaluation of pathology capcity across the UK. Report. Cancer Research UK, 2016.

3. Carter L. Report of the Second Phase of the Review of NHS Pathology Services in England. In: Health Do, editor.: http://webarchive.nationalarchives.gov.uk/+/http://www.dh.gov.uk/en/Healthcare/Pathology/DH_075531; 2010.

4. NHS, England. National Pathology Programme. Digital First: Clinical Transformation Through Pathology Innovation. In: England N, editor. https://wwwenglandnhsuk/2014/02/npp-digital-first/2014.

5. Kuijpers CC, Burger G, Al-Janabi S, Willems SM, van Diest PJ, Jiwa M. Improved quality of patient care through routine second review of histopathology specimens prior to multidisciplinary meetings. Journal of clinical pathology. 2016;69(10):866-71.

6. Goacher E, Randell R, Williams B, Treanor D. The Diagnostic Concordance of Whole Slide Imaging and Light Microscopy: A Systematic Review. Archives of pathology & laboratory medicine. 2017;141(1):151-61.

7. Snead DR, Tsang YW, Meskiri A, Kimani PK, Crossman R, Rajpoot NM, et al. Validation of digital pathology imaging for primary histopathological diagnosis. Histopathology. 2016;68(7):1063-72.

8. Mukhopadhyay S, Feldman MD, Abels E, Ashfaq R, Beltaifa S, Cacciabeve NG, et al. Whole Slide Imaging Versus Microscopy for Primary Diagnosis in Surgical Pathology: A Multicenter Blinded Randomized Noninferiority Study of 1992 Samples (Pivotal Study). The American journal of surgical pathology. 2017.

9. Williams B, Hanby A, Millican-Slater R, Nijhawan A, Verghese E, Treanor D. Digital Pathology for the Primary Diagnosis of Breast Histopathological Specimens: An Innovative Validation and Concordance Study. Histopathology. 2017;10.1111/his.13403.

10. Elmore JG, Longton GM, Pepe MS, Carney PA, Nelson HD, Allison KH, et al. A

Randomized Study Comparing Digital Imaging to Traditional Glass Slide Microscopy for Breast Biopsy and Cancer Diagnosis. Journal of pathology informatics. 2017;8:12.

11. Williams BJ, DaCosta P, Goacher E, Treanor D. A Systematic Analysis of Discordant Diagnoses in Digital Pathology Compared With Light Microscopy. Archives of pathology & laboratory medicine. 2017.

12. Marsch A, High WA. Medicolegal issues with regard to melanoma and pigmented lesions in dermatopathology. Dermatol Clin. 2012;30(4):593-615, v-vi.

13. Gaudi S, Zarandona JM, Raab SS, English JC, 3rd, Jukic DM. Discrepancies in dermatopathology diagnoses: the role of second review policies and dermatopathology fellowship training. Journal of the American Academy of Dermatology. 2013;68(1):119-28.

14. Barisoni L, Nast CC, Jennette JC, Hodgin JB, Herzenberg AM, Lemley KV, et al. Digital pathology evaluation in the multicenter Nephrotic Syndrome Study Network (NEPTUNE). Clinical journal of the American Society of Nephrology : CJASN. 2013;8(8):1449-59.

15. Gale AG, Scott H. Measuring radiology performance in breast cancer screening. In: Mitchell M, editor. Contemporary issues in cancer imaging - Breast Cancer: Cambridge University Press; 2010.

16. Rakha EA, Bennett RL, Coleman D, Pinder SE, Ellis IO, Pathology UKNCCfB. Review of the national external quality assessment (EQA) scheme for breast pathology in the UK. Journal of clinical pathology. 2017;70(1):51-7.

17. Schuh F, Biazus JV, Resetkova E, Benfica CZ, Ventura Ade F, Uchoa D, et al. Histopathological grading of breast ductal carcinoma in situ: validation of a web-based survey through intra-observer reproducibility analysis. Diagnostic pathology. 2015;10:93.

18. Ellis IO, Coleman D, Wells C, Kodikara S, Paish EM, Moss S, et al. Impact of a national external quality assessment scheme for breast pathology in the UK. Journal of clinical pathology. 2006;59(2):138-45.

19. Sikka M, Agarwal S, Bhatia A. Interobserver agreement of the Nottingham histologic grading scheme for infiltrating duct carcinoma breast. Indian journal of cancer. 1999;36(2-4):149-53.

20. Knuttel FM, Menezes GL, van Diest PJ, Witkamp AJ, van den Bosch MA, Verkooijen HM. Meta-analysis of the concordance of histological grade of breast cancer between core needle biopsy and surgical excision specimen. The British journal of surgery. 2016;103(6):644-55.

21. Longacre TA, Ennis M, Quenneville LA, Bane AL, Bleiweiss IJ, Carter BA, et al. Interobserver agreement and reproducibility in classification of invasive breast carcinoma: an NCI breast cancer family registry study. Modern pathology : an official journal of the United States and Canadian Academy of Pathology, Inc. 2006;19(2):195-207.

22. Ormsby AH, Petras RE, Henricks WH, Rice TW, Rybicki LA, Richter JE, et al. Observer variation in the diagnosis of superficial oesophageal adenocarcinoma. Gut. 2002;51(5):671-6.

23. Vennalaganti P, Kanakadandi V, Goldblum JR, Mathur SC, Patil DT, Offerhaus GJ, et al. Discordance Among Pathologists in the United States and Europe in Diagnosis of Low-Grade Dysplasia for Patients With Barrett's Esophagus. Gastroenterology. 2017;152(3):564-70 e4.

24. Rakha EA, Ahmed MA, Aleskandarany MA, Hodi Z, Lee AH, Pinder SE, et al. Diagnostic concordance of breast pathologists: lessons from the National Health Service Breast Screening Programme Pathology External Quality Assurance Scheme. Histopathology. 2017;70(4):632-42.

25. Thomas JSJ, Provenzano E, Hiller L, Dunn J, Blenkinsop C, Grybowicz L, et al. Central pathology review with two-stage quality assurance for pathological response after neoadjuvant chemotherapy in the ARTemis Trial. Modern pathology : an official journal of the United States and Canadian Academy of Pathology, Inc. 2017;30(8):1069-77.

26. Cross S, Furness P, Igali L, Snead D, Treanor D. Best practice recommendations for implementing digital pathology, by Royal College of Pathologists, January 2018

27. Glaser, B. and A. Strauss, The discovery of grounded theory. 1967, Hawthorne, NY: Aldine Publishing Company