ISRCTN14513591 https://doi.org/10.1186/ISRCTN14513591

Is the use of digital pathology in routine diagnosis reliable and safe in comparison to standard microscopy?

Submission date
30/10/2018

Recruitment status
No longer recruiting

Registration date
05/12/2018

Overall study status
Completed

Last Edited
14/07/2025

Condition category
Other

[X] Prospectively registered
[X] Protocol
[_] Statistical analysis plan
[X] Results
[_] Individual participant data

Plain English summary of protocol

Background and study aims
Pathologists (doctors who diagnose disease by studying tissue samples) use a microscope to examine tissue samples collected from patients. This is called light microscopy. It enables them to make a diagnosis and to give information on treatment and prognosis to clinicians (doctors). Digital pathology is a process to scan microscope slides into computer image files (digitised slides) which the pathologist can then examine on a computer screen. Digitised slides can be transferred electronically to allow pathologists to view cases at any location. This makes cases easy to share with colleagues, confirm diagnoses for patients, reduce errors and create better practices for sharing workload between departments. This will save time and resources for the NHS. Computer assisted tools can also be used to help make the diagnosis. None of these benefits can be realised until it is known how pathologists can use digital pathology safely and accurately for routine reporting.

Who can participate?
This study will not directly involve patients; instead, it will use samples from the breast, gastrointestinal tract, skin and kidney that have already been used in diagnosis

What does the study involve?
The present study attempts to explore if the use of whole slide imaging (Digital Pathology) is a safe, reliable and cost effective health technology for diagnosis, in routine clinical practice in comparison to standard microscopy.

What are the possible benefits and risks of participating?
There are no known benefits or risks.

Where is the study run from?
University Hospital Coventry and Warwickshire NHS Trust and 4 other hospitals in the UK

When is the study starting and how long is it expected to run for?
November 2018 to April 2023

Who is funding the study?
National Institute for Health Research (NIHR) Health Technology Assessment programme (HTA) (UK)

Who is the main contact?
Prof. D Snead
Consultant Pathologist
UHCW NHS Trust
Coventry CV2 2DX
+44 (0)2476968649

Contact information

Type(s)
Scientific

Contact name
Prof David Snead

ORCID ID
https://orcid.org/0000-0002-0766-9650

Contact details
Cellular Pathology Department, 4th Floor, West Wing, Clifford Bridge Road, Walsgrave
Coventry
United Kingdom
CV22DX
+44 (0)2476968649
david.snead@uhcw.nhs.uk

Additional identifiers

Integrated Research Application System (IRAS)
258799

Protocol serial number
DS411118, IRAS 258799

Study information

Scientific Title
Multi-centred validation of digital whole slide imaging for routine diagnosis

Study objectives
Light microscopy diagnosis is safe and reliable in comparison to the use of whole slide imaging (Digital Pathology) in routine practice

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 29/08/2019, West Midlands - South Birmingham Research Ethics Committee (The Old Chapel, Royal Standard Place, Nottingham NG1 6FS; +44 (0)207 104 8345; southbirmingham.rec@hra.nhs.uk), ref: 19/WM/0215

Study design
Multi-centre randomised comparison study

Primary study design
Other

Study type(s)
Diagnostic

Health condition(s) or problem(s) studied
Histopathological diagnosis

Interventions
The study involves exploring concordance between the results of histopathological sample analysis performed by pathologists examining the same series of samples using both light microscopy (LM) and digital microscopy (DP). The tissue samples selected for the study will have completed their appropriate clinical assessment at the respective site thus we do not plan any follow up or observation.

Each site will select appropriate samples and these link anonymised samples (glass slides) will be forwarded to University Hospital Coventry and Warwickshire (UHCW). Once received, the samples will be scanned at UHCW and digital slides of the samples will be created additionally, these slides, both glass and digital, will be given study numbers for anonymisation. These samples will then be randomised in batches, for viewing either LM first or DP. On completion of analysis of a particular sample, by all four pathologists, the samples will be returned to their original site.

Intervention Type
Other

Primary outcome(s)
Intra-pathologist agreement between digital pathology and light microscopy diagnoses, measured by comparing the concordance between the results of 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 (pathologists) reliability) using DP.
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:
1. Whether for each pathologist's DP and LM diagnoses agree
2. Whether each of the four DP diagnoses agree with the ground truth (GT)
3. Whether each of the four LM diagnoses agree with the GT.
This will be completed after all results have been completed and analysed (20-30 months)

Key secondary outcome(s))
Current secondary outcome measures as of 17/03/2022:
1. Inter-pathologist level of agreement across the four DP diagnoses and the ground truth (GT).

2. Inter-pathologist level of agreement across the four LM diagnoses and the GT.
3. Individual pathologist non-concordance rates will be measured throughout the study.
4. Costs and benefits associated with DP when compared with LM will be measured for all samples, if feasible, once all samples have been analysed. If not, analysis will be carried out for a purposive sample selected on the basis of clinical materiality and the availability of decision-analytic models in the literature to support cost-benefit calculations.
4.1. The throughput efficiencies of DP vs LM will be measured using simulation models of the pathway to diagnosis and establishment of a fully specified treatment plan.
4.1.1. Pathologists will be asked to provide time and motion data and anonymised summary data from the pathology service will be collected.
4.2. The effect of increased accuracy on choice of treatment will be made using estimates of the cost and health impact of the treatment strategies suggested as a result of DM or LM use.
5. Experiences of pathologists and laboratory staff
5.1. Focus groups / key informant interviews will be undertaken during the pilot study.
5.2. Semi-structured interviews at baseline will explore staff experiences and perspectives on DP.
5.3. Semi-structured interviews at mid-point of study will explore staff experiences over time, training needs and the perceived impact on day-to-day working in multidisciplinary teams.

Previous secondary outcome measures:
1. Pathologist agreement to GT and LM vs GT and DP will be measured using using text reports.
1.1. For each pathologist it will be recorded if DP and LM have complete agreement, have clinically unimportant differences or clinically important differences.
1.2. Discordant samples will be circulated to each of the subspecialty pathologists, along with the reference diagnosis. Each subspecialty group will then meet and agree a consensus GT for each discrepant sample using multi-headed microscope discussion and majority view where necessary. The agreement between GT and LM vs GT and DP will then be determined.
2. Inter-pathologist agreement for LM and DP separately will be measured using text reports. Reports without any differences will be deemed concordant, with the concordant diagnosis being accepted as the GT.
3. Individual pathologist non-concordance rates will be measured throughout the study.
4. Costs and benefits associated with DP when compared with LM will be measured for all samples, if feasible, once all samples have been analysed. If not, analysis will be carried out for a purposive sample selected on the basis of clinical materiality and the availability of decision-analytic models in the literature to support cost-benefit calculations.
4.1. The throughput efficiencies of DP vs LM will be measured using simulation models of the pathway to diagnosis and establishment of a fully specified treatment plan.
4.1.1. Pathologists will be asked to provide time and motion data and anonymised summary data from the pathology service will be collected.
4.2. The effect of increased accuracy on choice of treatment will be made using estimates of the cost and health impact of the treatment strategies suggested as a result of DM or LM use.
5. Experiences of pathologists and laboratory staff
5.1. A web-based survey will be conducted along with the pilot study.
5.2. Semi-structured interviews at baseline will explore staff experiences and perspectives on DP.
5.3. Semi-structured interviews 18 months into the implementation of DP will explore staff experiences over time, training needs and the perceived impact on day-to-day working in multidisciplinary teams.

Completion date
30/04/2023

Eligibility

Key inclusion criteria

Current participant inclusion criteria as of 17/03/2022:
Histopathology samples:
Case identification and selection will take place between September 2019 - October 2021 at five participating NHS histopathology departments. All samples are collected for the purpose of routine histopathology reporting and only entered into the validation study on completion of their clinical review at the respective NHS participating site, with the following specification:
1. Breast (Belfast, Lincoln & Nottingham) – A total of 600 sequential samples including 200 cancer screening biopsies enriched with at least 10% resected tumours (moderately difficult) and 10% difficult cases: 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.
2. GI (Coventry, Belfast & Nottingham): – A total of 600 sequential samples including 200 cancer screening biopsies enriched with at least 10% resected tumours (moderately difficult) and 10% difficult: oesophageal dysplasia, polyp cancers, inflammatory bowel disease, minimal change colitis, graft versus host disease, giardiasis, cytomegalovirus, H. pylori and herpes virus infection.
3. Skin (Coventry, Belfast & Lincoln) : A total of 600 sequential samples enriched with at least 10% non-basal cell carcinoma cancer resections (moderately difficult) and 10% difficult: sentinel nodes, dysplastic naevi, spitz naevi, lentigo maligna, early and desmoplastic melanoma, herpes virus infection, leischmaniasis, leprosy, amyloid, angioscaroma, and Kaposis sarcoma.
4. Renal (Coventry, Nottingham & Oxford): 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.

Staff (for the qualitative part of the study):
Staff employed at the participating sites, including any of the following:
1. Pathologists
2. Trainee doctors
3. Biomedical scientists
4. Biomedical assistants
5. Advanced practitioners
6. Medical laboratory assistants

Previous participant inclusion criteria:
Histopathology samples:
Case identification and selection will take place between January 2019 – January 2022 at five participating NHS histopathology departments. All samples are collected for the purpose of routine histopathology reporting and only entered into the validation study on completion of their clinical review at the respective NHS participating site, with the following specification:
1. Breast (Belfast, Lincoln & Nottingham) – A total of 600 sequential samples including 200 cancer screening biopsies enriched with at least 10% resected tumours (moderately difficult) and 10% difficult cases: 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.
2. GI (Coventry, Belfast & Nottingham): – A total of 600 sequential samples including 200 cancer screening biopsies enriched with at least 10% resected tumours (moderately difficult) and 10% difficult: oesophageal dysplasia, polyp cancers, inflammatory bowel disease, minimal change colitis, graft versus host disease, giardiasis, cytomegalovirus, H. pylori and herpes virus infection.
3. Skin (Coventry, Belfast & Lincoln) : A total of 600 sequential samples enriched with at least 10% non-basal cell carcinoma cancer resections (moderately difficult) and 10% difficult: sentinel nodes, dysplastic naevi, spitz naevi, lentigo maligna, early and desmoplastic melanoma, herpes

virus infection, leischmaniasis, leprosy, amyloid, angioscaroma, and Kaposis sarcoma.
4. Renal (Coventry, Nottingham & Oxford): 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.

Staff (for the qualitative part of the study):
Staff employed at the participating sites, including any of the following:
1. Pathologists
2. Trainee doctors
3. Biomedical scientists
4. Biomedical assistants
5. Advanced practitioners
6. Medical laboratory assistants

Participant type(s)
Other

Healthy volunteers allowed
No

Age group
Other

Sex
All

Total final enrolment
2024

Key exclusion criteria
Current participant exclusion criteria as of 17/03/2022:
1. Cases with either broken or missing slides
2. Cases with missing clinical data
3. Megablocks or oversized slide sets
4. Cases where a prior sample is important to the interpretation of the study sample

Previous participant exclusion criteria:
Cases with either broken or missing slides

Date of first enrolment
06/09/2019

Date of final enrolment
14/10/2021

Locations

Countries of recruitment
United Kingdom

England

Northern Ireland

Study participating centre
University Hospital Coventry and Warwickshire NHS trust
Clifford Bridge Road
Coventry
United Kingdom
CV22DX

Study participating centre
Nottingham University Hospitals NHS Trust
Hucknall Road, Nottingham
Nottingham
United Kingdom
NG5 1PB

Study participating centre
United Lincolnshire Hospitals NHS Trust
Greetwell Rd
Lincoln
United Kingdom
LN2 5QY

Study participating centre
John Radcliffe Hospital Oxford NHS Trust
Headley Way, Headington,
Oxford
United Kingdom
OX3 9DU

Study participating centre
Belfast Health and Social Care Trust
Faculty of Medicine, Health & Life Sciences, Elmwood Exchange, 90 Lisburn Road,
Belfast
United Kingdom
BT9 6AG

Study participating centre
University Hospitals Birmingham NHS Foundation Trust
Queen Elizabeth Hospital
Mindelsohn Way
Edgbaston
Birmingham
United Kingdom
B15 2GW

Sponsor information

Organisation
University Hospital Coventry and Warwickshire (UHCW) NHS Trust

ROR
https://ror.org/025n38288

Funder(s)

Funder type
Government

Funder Name
Health Technology Assessment Programme

Alternative Name(s)
NIHR Health Technology Assessment Programme, Health Technology Assessment (HTA), HTA

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location
United Kingdom

Results and Publications

Individual participant data (IPD) sharing plan
The data sharing plans for the current study are unknown and will be made available at a later date

IPD sharing plan summary

Data sharing statement to be made available at a later date

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Results article		17/01/2024	15/05/2024	Yes	No
Results article		17/08/2024	02/07/2025	Yes	No
Results article		01/07/2025	14/07/2025	Yes	No
HRA research summary			28/06/2023	No	No
Protocol file	version 2.0	08/10/2020	15/02/2023	No	No