MitPro: Multi-Site Validation Study of Automatic Mitosis Profiling

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Contact Details

Commercial Partner	Histofy Ltd Unit 33, The Venture Centre University of Warwick Science Park Sir William Lyons Road Coventry CV4 7EZ Email: info@histofy.ai	CTO	Dr Simon Graham Unit 33, The Venture Centre University of Warwick Science Park Sir William Lyons Road Coventry CV4 7EZ Email: s.graham@histofy.ai
CMO	Prof David Snead Unit 33, The Venture Centre University of Warwick Science Park Sir William Lyons Road Coventry CV4 7EZ Email: d.snead@histofy.ai	CEO & CSO	Prof Nasir Rajpoot Unit 33, The Venture Centre University of Warwick Science Park Sir William Lyons Road Coventry CV4 7EZ Email: n.rajpoot@histofy.ai

Main study

Design: A multi-centre study evaluating whether MitPro improves mitosis counting consistency, speed, and accuracy compared to conventional pathologist counting.

Enrolment: Fifty slides per committed cancer type will be collected from multiple international sites.

Primary Objective: Compare the time required for and inter-observer consistency of mitosis counting with and without AI assistance.

Secondary Objectives:

1. Compare AI-assisted mitosis counts with conventional counts.
2. Assess the accuracy of detected mitotic figures against consensus pathologist ground-truth (at least 3 reviewers).

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1. Background

Mitosis, a key cell-life cycle process, involves chromosome replication and separation into two nuclei, resulting in two identical cells. Detection and counting of mitotic figures, particularly relevant for tumour analysis in various cancers, have demonstrated a strong correlation with cell proliferation, serving as a key parameter in tumour grading systems, and patient outcome. Therefore, as part of routine practice, it is common for pathologists to count the number of mitotic figures in selected tissue regions. This can be tedious, time-consuming and naturally prone to human error. Artificial intelligence algorithms offer significant promise in reducing this burden, while producing results quicker and with higher consistency.

2. Mitosis Profiling with MitPro

MitPro is a tool developed by Histofy for automatic mitosis detection, counting and profiling in multiple cancer types and species. The tool detects mitotic figures over the entire tissue sample, returns the hotspots with the greatest proliferation rate and returns mitotic counts within these regions.

It remains the pathologist's responsibility to report the final count. The purpose of MitPro is to **streamline**, not completely automate, the task of mitosis counting.

In **Figure 1**, we outline how MitPro is integrated within the digital pathology workflow when considering mitosis counting.

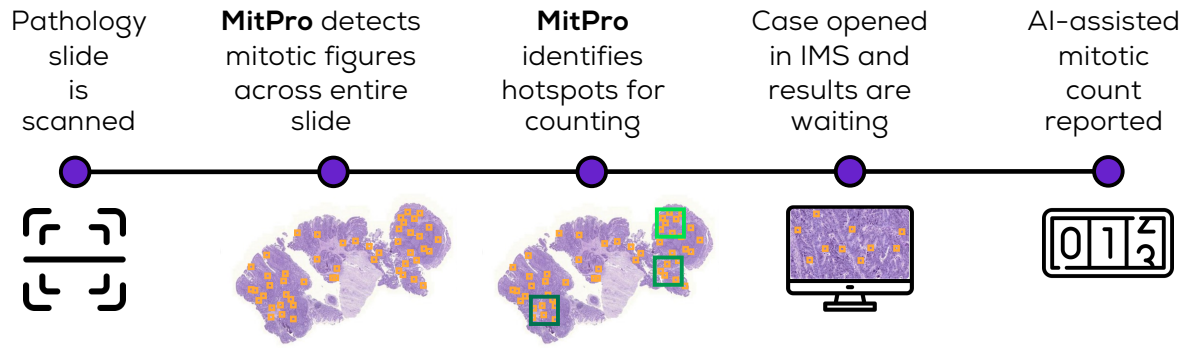

Figure 1: *Mitosis counting workflow with AI assistance using MitPro. MitPro detects mitotic figures over the entire tissue, identifies hotspot regions and presents them to pathologists to improve the task of mitosis counting.*

3. Intended Purpose

MitPro is a device intended for use by qualified medical practitioners, designed to be non-invasive, non-sterile, non-active, and non-implantable. From an image of a Haematoxylin & Eosin (H&E) stained tissue slide, its purpose is to identify cells undergoing mitotic division (mitotic figures) to enable mitosis counting, i.e. providing an objective count of mitotic figures detected that can be used to inform cancer grade and in some instances diagnosis, as well as allowing for the spatial mitotic profile to be potentially explored further for prognostic purposes. The device detects mitotic figures in the selected region(s) of interest or across the whole-slide image, which aid pathologists in making accurate and consistent counts. Mitotic figure counting is one aspect of tumour grading, and tumour grade is an important factor in decisions regarding treatment options. It is the responsibility of the practitioner to make the final decision. The device leads to enhanced efficiency and consistency in mitotic counting. The tissue sample is taken from the patient and analysed away from the patient. Therefore, whilst the analysis is performed, the patient can maintain normal function. The

cancers that the device considers in humans are breast cancer, lung cancer, Melanoma (including uveal melanoma) , sarcoma, leiomyoma, neuroendocrine tumours, glioblastoma, meningioma, thyroid cancer and retinoblastoma. The cancers that the device considers in animal tissue are canine mast cell tumour, canine mammary tumour, canine lymphoma and feline lymphoma. 2mm^2

4. Study Design

4.1. Aims and Objectives

The aim of this study is to demonstrate the potential of MitPro to improve the current standard of care in pathology practice. Specifically, the three hypotheses that the study aims to explore are:

1. MitPro reduces the time of mitosis counting.
2. MitPro delivers more consistent mitosis counting between pathologists.
3. How does the accuracy of MitPro in detecting mitoses compare with pathologists.

The study will explore the above across different tumours and species.

4.2. Study Organisation

The overall study will be split into analytical and clinical validation components, as required by In Vitro Diagnostic Device Regulation (IVDR). Prior to the study, it must be decided whether sites will actively participate in the clinical validation study. If so, partners will be required to record mitotic counts across different settings as described in **Section 4.4**.

Data will be transferred to Histofy and uploaded to supported Image Management System (IMS) **test environments** to reflect clinical practice. Currently, supported IMS vendors are Sectra and Indica Labs (HALO AP).

4.2.1. Analytical Validation

In accordance with IVDR Article 2 (40), the analytical performance focusses on the gathering of evidence that the Medical Device in question reliably, accurately and consistently measures and/or detects an analyte(s).

The analytical validation measures the accuracy of outputs generated by MitPro against pathologists' results, the current standard of care.

We provide a more detailed overview of the experimental setup for analytical validation in **Sections 4.4.2 – 4.4.4.**

4.2.2. Clinical Validation

In accordance with Article 2 (41) of the IVDR, the clinical validation study provides evidence that MitPro, operated by pathologists, provides mitotic counting comparable to the current standard of care and measures if consistency between pathologists is improved. For this, we will compare the mitotic count reported by pathologists using conventional practice to counts reported with AI-assistance using MitPro. The main purpose of the clinical validation study is to demonstrate that MitPro enables mitosis counting with increased **consistency** and **efficiency**.

Figure 6 presents a summary of the clinical validation study, comprising two stages, evaluating the impact of AI support on counting speed and accuracy. We provide further details on the stages in **Sections 4.4.5 – 4.4.7.**

4.3. Study Population

The study aims to explore the hypotheses in the following cancer types and species:

Human
Breast cancer
Neuroendocrine tumour
Melanoma (including uveal melanoma)
Soft tissue sarcoma
Leiomyoma
Lung cancer
Glioblastoma
Meningioma
Thyroid cancer

Retinoblastoma

Animal
Canine cutaneous mast cell tumour
Canine mammary tumour
Canine and feline lymphoma

For each species and cancer type, we require **30-50** slides per centre from at least two centres. Prior to the commencement of the study, centres commit to providing data from selected cancer types. It is **not** imperative to provide data from all cancer types investigated during the study.

A secondary aim is that data comes from multiple countries, with representation across multiple continents and that we include representation from minority ethnic backgrounds within the study population. This approach not only enhances the robustness of our findings but also ensures inclusivity and equality.

Figure 2 provides an overview of the data organisation, transfer and utilisation during the study. All data sourced from partners must undergo de-identification and transfer to Histofy for both clinical and analytical validation purposes. Once transferred, data will be managed by Histofy during the study.

4.4. Experimental Setup

4.4.1. Data Identification and Transfer

An expected total of 500 human tissue slides and 200 animal tissue slides will be recruited. Each site will contribute 30-50 slides from 30-50 unique subjects per committed cancer type to be involved in the study, as far as possible representing the range of mitotic counts encountered in clinical practice. Overall, we will aim to recruit approximately 20% of the human tissue slides from non-Caucasian patients. All tissue image data must be exported to Histofy servers for running the MitPro algorithm on the images.

All transferred data will be used to assess the impact that MitPro has on the consistency and speed of mitotic counting. A representative sample of the data (~25%) will be used to assess the counting accuracy and mitotic figure detection performance.

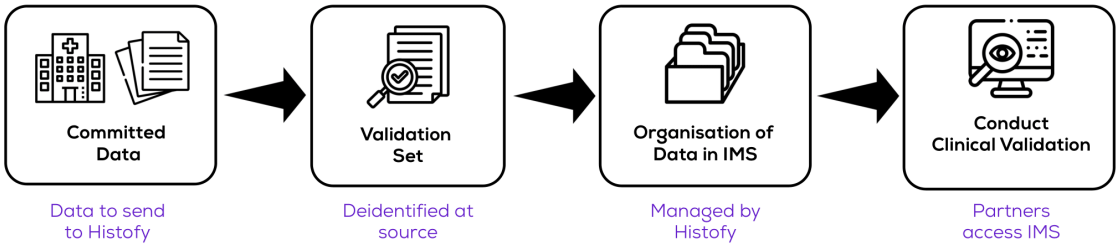

Figure 2: *Data commitment, transfer and utilisation for validation.*

4.4.2. Analytical Validation: Ground Truth Collection of Mitotic Figures

As mentioned in **Section 4.4.1**, a sample of the transferred data will be used for assessing the mitotic figure detection performance. For this, we will collect ground truth data from multiple pathologists. Annotations will be collected using HistomicsUI[1] instance installed on Histofy servers.

Below we outline the key steps for collecting this ground truth data, depicted in **Figure 3**:

1. A consultant pathologist selects a single representative 2mm^2 region in the tissue.
2. At least three pathologists exhaustively annotate mitotic figures in the region.
3. Individual annotations are combined to yield consensus annotations.
4. Results of individual pathologist vs consensus and MitPro vs consensus will be calculated to compare performance of MitPro recognition of mitotic figures with that of individual pathologists.

This will be performed across up to 5 representative slides from each tumour type, resulting in up to 50 annotated regions in human cancers and up to 20 annotated regions in non-human cancers. These slides will be selected from the main clinical validation study, while ensuring sufficient variation in morphology and appearance.

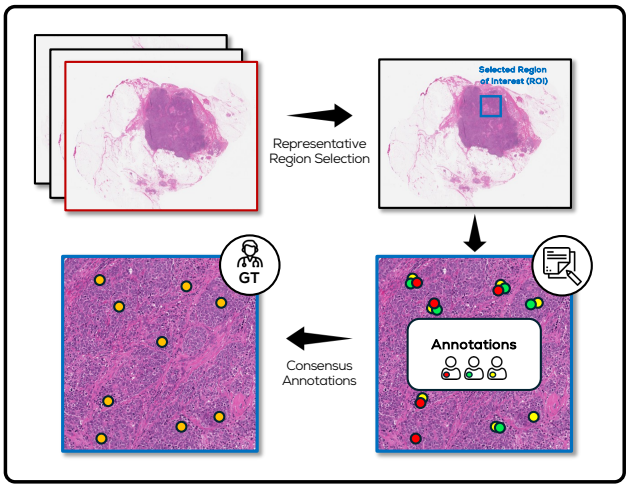

Figure 3: *Summary of key steps for collecting annotations of mitotic figures.*

[1] https://github.com/DigitalSlideArchive/HistomicsUI

4.4.3. Analytical Validation: Evaluating Detection Performance

After assembling a dataset of labelled regions with consensus pathologist annotations, we will evaluate MitPro's and individual pathologists' detection outputs by comparing the algorithm's identified mitotic figures against ground-truth annotations. This comparison will quantify how accurately MitPro captures mitoses through standard metrics such as precision, recall, and F_1-score (**Section 4.5**).

This analytical validation phase demonstrates the tool's capacity to identify mitotic figures accurately and consistently across different tissue specimens and cancer types, providing assurance that MitPro's outputs meet the expectations for precision and reproducibility in a clinical setting.

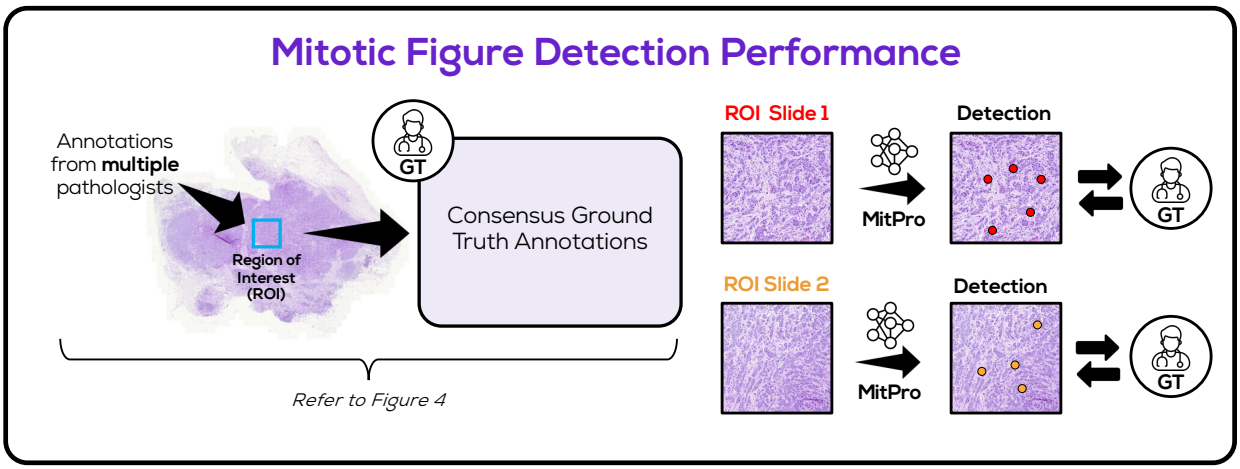

Figure 4: *Comparing MitPro mitotic figure detection results with pathologist consensus annotations.*

4.4.4. Analytical Validation: Evaluating Hotspot Selection

Hotspots are defined as areas within the tumour exhibiting increased mitotic activity. While accurate detection of mitotic figures should naturally lead to effective hotspot selection, an additional verification step is undertaken to ensure this.

For all slides, a consultant pathologist will annotate the tumour region, allowing us to quantify the mitotic count per mm² across the entire tumour. We will then evaluate the mitotic count per mm² within the identified hotspot region. As expected, the density of mitotic figures within hotspots should be higher than the overall tumour density, confirming accurate hotspot selection. These steps are summarised in **Figure 4**.

4.4.5. Clinical Validation Overview

Power calculation

One slides from each tumour type will be subjected to standard of care mitotic counts by five separate consultant pathologists to establish the range of counts recorded and inform the range existing in the existing standard of care. A power calculation shall inform the number of slides required to deliver a study of at least 80% statistical power.

The clinical validation study will take place using Sectra and HALO AP image management systems. These systems will be managed by Histofy without full LIS integration, allowing smooth running of the study while reflecting clinical practice.

During clinical validation, we aim to demonstrate that MitPro-powered mitosis counting is superior to the standard of care. During the study, pathologists must record the following mitosis counts:

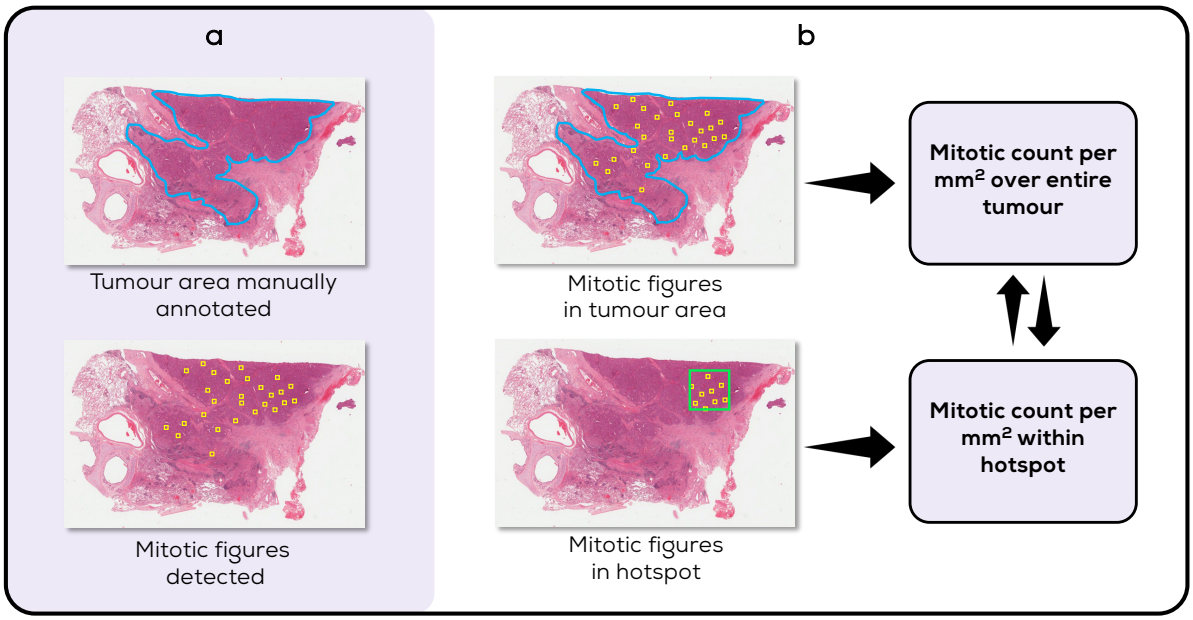

Figure 4: *Comparison of mitotic counts in hotspot and tumour regions. (a) Mitotic figures are detected with MitPro, and tumour areas are manually annotated. (b) Mitotic figures are isolated to either the hotspot or tumour region and the counts are inferred. If the hotspot counts are higher than or at least comparable to the overall tumour counts, then the hotspots have been suitably identified.*

1. **Conventional mitosis counts** in chosen high-power fields according to standard practice.
2. **AI-assisted mitosis counts** in chosen high-power fields, but with AI-assistance.

Note, AI-assistance will provide the overlays of all mitotic figures across the slide, the *recommended* hotspot(s), and the associated hotspot counts. The hotspots are produced according to recommended guidelines. A summary of this is provided in **Table 1**. It is not mandatory for pathologists to perform the count in the recommended hotspot. The hotspots serve as a guide for choosing the desired areas for counting.

For all steps, we will record the **count** and the **time**, allowing assessment of **interobserver consistency** and **efficiency** for mitotic counting. When recording the count, pathologists must do so in a blinded manner to prevent any bias during the process.

For each committed slide, we aim to source mitotic counts from at least 3 pathologists with a range of experience. It is also important that the same pathologists perform each step for a given slide to increase the reliability of results.

4.4.6. Clinical Validation: Conventional Mitosis Counting (Stage 1)

When reporting the conventional mitosis count according to the standard of care, pathologists have the flexibility to select high-power fields (HPFs) based on their clinical practice preferences. Typically, this is done in areas exhibiting high mitotic activity. Pathologists may choose a single region or multiple regions for the count, as befits their normal practice..

To facilitate assessment during the study, the selected HPFs must be marked in the IMS viewer. For instance, in HALO AP, regions must be pre-drawn prior to counting. In Sectra,

regions must either be pre-drawn or defined using the Sectra counting tool. The same method for defining the HPFs must be applied consistently across stages 1 and 2. The mitosis count is carried as it would be in clinical practice and recorded per unit area as shown in table 1.

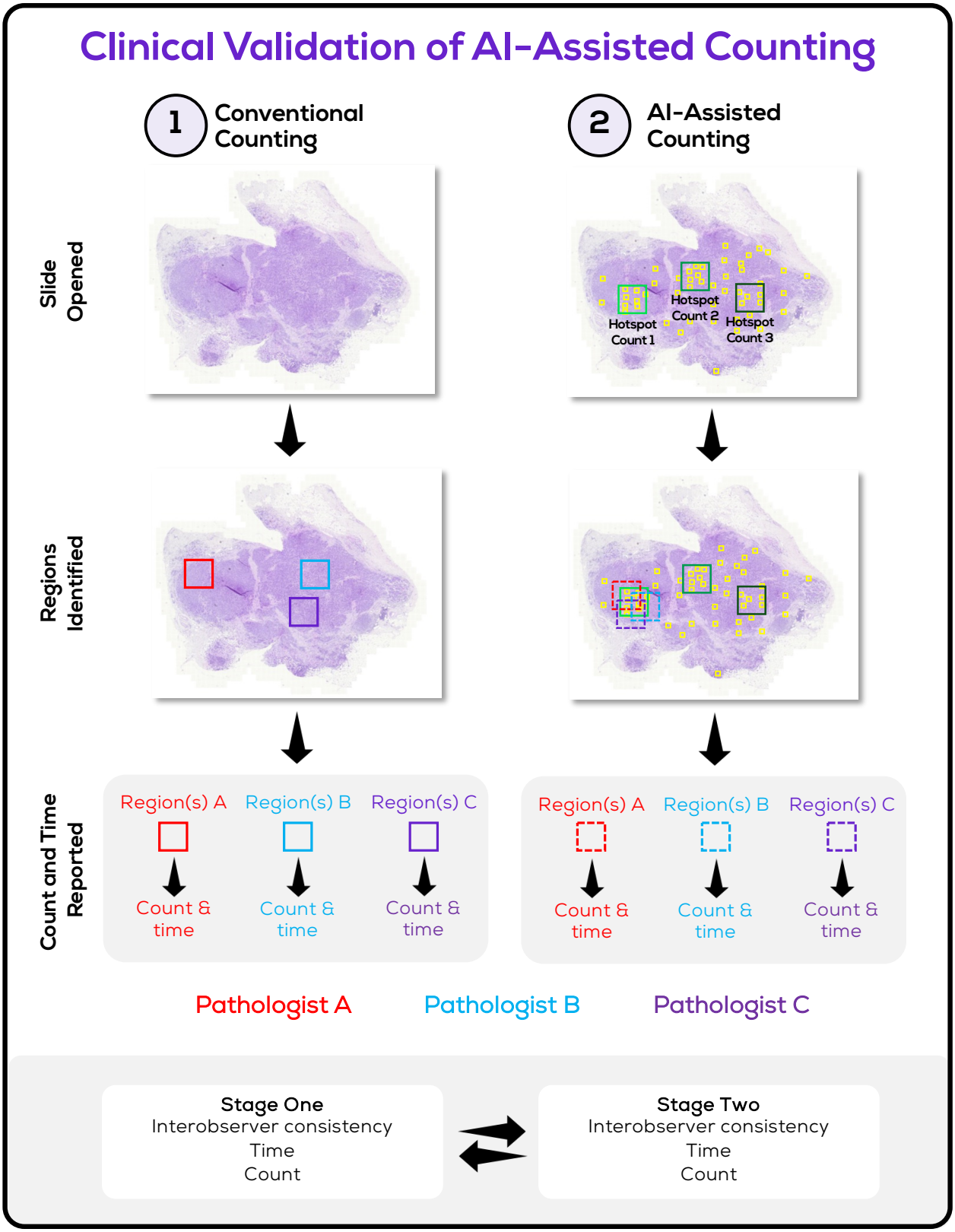

Figure 6: *Overall clinical validation study design. In Stage 1, pathologists record the mitosis count and time following the Standard of Care. In Stage 2, AI-generated overlays highlighting mitotic figures, hotspots, and hotspot counts are provided before the count is performed. In both stages, three pathologists independently*

record counts for each slide. Time, consistency, and counts are analysed between the stages to assess the impact of AI-assisted mitosis counting.

. Additionally, pathologists must record the time taken to perform the count, measured from the moment the slide is opened in the viewer to the final decision on the mitotic count.

For each image, the following details must be documented in a spreadsheet: the count, time taken.

4.4.7. Clinical Validation: AI-Assisted Mitosis Counting (Stage 2)

In Stage 2, mitosis counting is conducted again, this time with AI assistance. When the slide is opened in the IMS viewer, MitPro highlights all mitotic figures and identifies hotspot region (areas with the highest concentration of mitotic figures). **Table 1** summarises the generated outputs based on cancer type.

Each hotspot is accompanied by an AI-generated mitotic count. However, these counts should not be used without manual verification and are only applicable when directly counting within the suggested hotspots. It is important to emphasise that pathologists should independently select the most appropriate regions for counting based on their judgement practice. The hotspots serve as a guide, and the annotated mitoses can assist in the search for mitotic figures. The counts recorded shall be the decision of the pathologist using this additional infomation.

Counts and time measurements should be recorded using the same methodology as in Stage 1. Specifically, pathologists must document the mitotic count, time taken, method used for hotspot selection, and approach used for counting mitotic figures.

To minimise bias, pathologists should not complete Stages 1 and 2 consecutively for the same slide. A minimum washout period of one week is imposed before re-evaluating a slide.

4.5. Evaluation Metrics

4.5.1. Analytical Validation Metrics

In addition to the clinical validation metrics, analytical validation focuses on verifying MitPro's detection performance against detailed, pathologist-annotated ground truth:

1. **Mitotic Figure Detection**
    - **Metrics**: F_1 score, precision, recall.
    - **Goal**: Demonstrate that MitPro's F_1 score against the consensus annotation is at least as high as that of individual pathologists measured against the same consensus.
    - **Comparison with Literature**: Summarise MitPro's performance metrics (e.g., F_1, precision, recall) alongside reported metrics in peer-reviewed literature.

2. **Hotspot Selection**
    - **Rationale**: Ensure that areas of highest mitotic density (hotspots) identified by MitPro truly match pathologist-verified regions of interest.
    - **Metric**: Compare the mitotic density (mitoses per mm²) of MitPro-identified hotspots with the overall tumour density in the annotated tumour region. A higher or comparable count within the proposed hotspots would confirm successful hotspot localisation. Statistical significance may be assessed using,

for instance, a paired t-test or Wilcoxon test if each slide is treated as its own control.

4.5.2. Clinical Validation Metrics

At the conclusion of the study, the primary outcomes will be evaluated against the original hypotheses. A summary of the proposed metrics and analyses is as follows:

1. **MitPro reduces the time required for mitosis counting**
    - **Rationale**: Manual mitosis counting is often time-consuming.
    - **Metric**: Compare the median (or mean) time taken to complete the count under conventional practice (Stage 1) versus AI-assisted practice (Stage 2).
    - **Statistical Analysis**: A paired statistical test (e.g., Wilcoxon signed-rank test if non-parametric; paired t-test if assumptions of normality are met) will be used to determine whether any observed difference is statistically significant.

2. **MitPro leads to more consistent mitosis counting**
    - **Rationale**: The tool should reduce interobserver variability.
    - **Metric**: The interobserver correlation coefficient (ICC) or an equivalent measure of inter-observer agreement will be calculated for each stage to quantify consistency among pathologists. An increase in the ICC (or similar metric) with AI support would indicate improved consistency.

3. **MitPro achieves accuracy comparable to pathologist ground-truth data**
    - **Rationale**: The AI-assisted counts should align closely with current standards of care and pathologist consensus.
    - **Metric**: Where counts are treated as continuous data, Bland-Altman plots (to assess limits of agreement) or Lin's concordance correlation coefficient may be used. Where counts are categorised into discrete classes (e.g., high vs. low), Cohen's kappa can be computed to quantify agreement between AI-assisted counts and standard-of-care counts.
    - **Goal**: Demonstrate that the AI-assisted approach does not degrade accuracy and ideally maintains or enhances agreement relative to conventional practice.

Table 1: *Summary of hotspot configuration across different cancer and specimen types, according to guidelines.*

Cancer type	Size of Counting Region
Human Breast Cancer	$2mm^2$
Human Neuroendocrine tumour	$2mm^2$
Human Melanoma	$1mm^2$
Human Soft Tissue Sarcoma	$2mm^2$
Human Leiomyoma	$2mm^2$
Human Lung Cancer	$2mm^2$
Human Retinoblastoma	$2mm^2$
Human Glioblastoma	$2mm^2$
Human Meningioma	$2mm^2$
Human Thyroid Cancer	$2mm^2$
Canine cutaneous mast cell tumour	$2mm^2$
Canine mammary tumour	$2mm^2$
Canine lymphoma	$2mm^2$
Feline lymphoma	$2mm^2$

5. Data Processing and Management

5.1. Data Collection and Storage

Clinical data and results obtained during the study will be collected using Excel spreadsheets and transferred from sites to Histofy using OneDrive folders. A OneDrive folder will be set up for each site and access will be restricted to designated site staff.

Pseudonymised WSI files will be transferred from the partner sites to Histofy using a Secure File Transfer Protocol (SFTP), such as FileZilla. Once received, the WSI files will be stored only on Histofy servers, along with a copy of the data as a backup.

5.2. Confidentiality

All essential documentation and study records will be stored by Histofy 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 any of the sites require that. Audits will be conducted by an independent team agreed between the site(s) and Histofy.

5.3. Archiving

Anonymised data will be held for a period of 10 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 an individual authorised by the commercial partner.

Whole slide images and study data will be archived for 10 years after completion of the study so that they can be accessed for future studies.

Histofy will be responsible for archiving additional data needed to support review by regulatory bodies. Archived data will be stored for 10 years.

6. Consent

Patient cases will be recruited without consent and anonymised at the point of enrolment. The NHS data opt-out will be checked at point of enrolment by enrolling site, and those patients that have opted-out will not have their data included in the study. Sites who do not use the NHS data opt-out scheme will follow local process for using patient data in research.

7. Study Organisation and Oversight

7.1. Sponsor and Governance Arrangements

Histofy has agreed to act as sponsor for this trial and will undertake the responsibilities of sponsor as defined by the UK Policy Framework for Health and Social Care Research and ICH Good Clinical Practice. An authorised representative of the Sponsor has approved the final version of this protocol with respect to the trial design, conduct, data analysis and interpretation and plans for publication and dissemination of results. As sponsor, Histofy provides indemnity for this trial and, as such, will be responsible for claims for any negligent harm suffered by anyone because of participating in this trial. The indemnity is renewed on an annual basis and will continue for the duration of this trial.

7.2. Ethics and Health Research Authority Approval

The study will be conducted in accordance with all relevant regulations.
Health Research Authority advice (and approval, if needed) will be sought prior to the study commencing.

A potential ethical issue associated with this study is the use of patient data in anonymised form without consent except for following the NHS data opt-out. However, this is in line with existing guidelines and follows current practice. It would be impractical to gain consent for the numbers of cases included in the study given most cases are archived. The use of anonymised data presents no risk to the patients involved.

7.3. Responsibilities

Sponsor

The Sponsor'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.

Principal Investigator (PI)

Each site needs to provide a pathologist to act as the site Principal Investigator. This person takes responsibility for the following tasks:

- Overseeing the recruitment of all cases needed.
- Coordinating the delivery of the metadata for the cases recruited.
- Overseeing the export of WSIs for the algorithm to process.
- If participating in clinical validation providing at least one pathologist to participate in the study.

7.4. Study Group

Each site appoints a pathologist to be the principal investigator. Nominated individuals from the commercial partner and PIs form the Study Group. Once the study has been started, the Study Group will meet regularly to review progress of the study.

The Sponsor and CI will finalise the study protocol. The PIs will review the study protocol and arrangements for how the study is to be conducted, record keeping and record and investigate any study violations. Histofy will arrange site initiation with each site prior the study starting.

7.5. Qualitative study

Following the completion of the mitotic figure data and the examination of all the cases in the study pathologists will be asked to give an account f their experiences of using MitPro this will be via a free text document. Pathologists will be aske to comment on the following points as well as provide any feedback they may otherwise have in their own words.

1. How do you assess your own performance during the tasks and your understanding of the information provided by the device, its labelling and the training? Do you think extra training is required?
2. Is the use of the device in your experience comparable with existing devices? Do existing devices present you with any specific problems or perspectives on the way the subject device should be designed? Is the device easily integrated into existing

workflows or do you foresee any difficulties in terms of compatibility with other devices or systems?
3. Did you experience any difficulties during the test, such as confusing interactions, unexpected device operation or response, misinterpretation? Do you believe any device errors occurred? Do you believe any use errors occurred?
4. Did the reprocessed images provide any cause for hesitation or 'close calls', where no hesitation or 'close calls' would otherwise occur based on the image alone?
5. Did you experience any repeated attempts to complete a task or experience any confusion or have other difficulties?
6. Do you believe any (patient) data or other information should be added or changed in the user interface? Would this improve the clinical workflow?
7. Would you expect more feedback from the software regarding data (e.g. availability, transfer, integrity), delivery (e.g. quantity, rate), diagnostic information (e.g. results, artefacts) or functionality (e.g. performance, measurement)?
8. Can you identify any risks which are not controlled by the current design? Do you believe patients could in any way be misidentified because of the design? Do you believe the instructions for use are confusing or that any information may be missing? Do the results accurately represent the image data? Is the user interface, being the device output images, sufficiently visible and is the readability adequate? Are any slips, lapses and mistakes possible?
9. Are there any issues related to the logic of overall user-system interaction, including how, when and in what form information and/or feedback is provided to the user?
10. Can (patient) data be extracted efficiently and effectively from the device in an intuitive manner?

7.6. Study Timeline and Milestones

Table 1: *Summary of major milestones*

• Finalisation of study protocol. • Gain HRA approval. • Site recruitment and contracts.	14th February 2025
• Set-up and opening sites. • Data collection commences.	17th February 2025
• Clinical validation stage 1 commences	3rd March 2025
• Clinical validation stage 2 commences	1st April 2025
• Clinical validation complete	30th April 2025
• Analytical validation study complete	30th April 2025
• Study end date	15th May 2025

8. End of Study

The completion of the resolution of discrepant cases will be considered as end of study. 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.

9. Dissemination and Publication

9.1. Dissemination

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 the Study Group. The main report will be drafted and approved by the Study Group before submission for publication, on behalf of the collaboration and subject to approval of the Sponsor.

Individual sites will be entitled to publish their own data as a separate publication, subject to approval of the Sponsor.

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

9.2. Media Coverage

In addition to these publications, Histofy plans a series of press releases and media interviews on the progress and findings of the study. We will develop a strategy in consultation with study sites' and Histofy Communications teams (e.g. a lay summary of the findings available on the study websites, and dissemination through social media) to help patients and wider public learn about the project's findings.

10. Intellectual Property

Background intellectual property brought into this project is currently held by the University of Warwick, with Histofy holding an exclusive license. Any foreground intellectual property generated in this study will reside with Histofy.

11. Future use of the Tool

Partner sites participating in the validation study will have the opportunity to integrate MitPro into existing workflows as a lab-developed test in accordance with internal procedures, enhancing efficiency and accuracy in mitosis assessment. Additionally, Histofy provides the option of discounted utilisation of the MitPro tool for a length of time, empowering sites to streamline mitosis counting and cancer grading.

12. Class of Device

The device is a software-based solution running on a server, with no physical accessories. Therefore, under rule 1.4, both are to be considered for classification under the same rule. The product is used to aid in the diagnosis of cancer. It is therefore either Class C or D. The device will not be used to detect presence of transmissible agents in blood, or in situations where high-risk propagation is possible or used to monitor the disease. Therefore Rule 1 doesn't apply. It is not used to group blood. Therefore, Rule 2 doesn't apply. The device is used to diagnose disease that could affect the patient's treatment and outcome, but the device does not cause serious injury to the patient. The device is used to identify cells undergoing division (mitotic figures) in tissue to enable accurate mitosis counting and profiling, a crucial

indicator for evaluating grade across various cancers. The product is a diagnosis tool, therefore is **Class C under Rule 3h**.

13. Ethical Considerations and Regulatory Compliance

13.1. Reporting of Deviations:

The Clinical Investigation Plan (CIP) specifies that all deviations from the study protocol will be reported to the MHRA (Medicines and Healthcare products Regulatory Agency). This ensures that any departures from the approved protocol, which could potentially affect the safety of subjects or the validity of the data, are promptly communicated to the regulatory authority. Such reporting is in line with the MHRA's requirements and supports the transparency and integrity of the clinical investigation.

13.2. Serious Adverse Event (SAE) Reporting:

The reporting of Serious Adverse Events (SAEs) in the Clinical Investigation Plan is planned in strict accordance with the MEDDEV 2.7/3 guidance. This guidance outlines the requirements for the timely and accurate reporting of SAEs to ensure patient safety and regulatory compliance. The procedures detailed in the CIP adhere to the MEDDEV guidelines, ensuring that all SAEs are reported to the appropriate regulatory authorities and ethics committees within the specified timelines, including expedited reporting for events that meet the criteria for serious, unanticipated, and device-related events.

14. Information Security

The clinical investigation has implemented robust information security measures to protect the confidentiality, integrity, and availability of all data collected during the study. These measures are designed to comply with applicable data protection regulations, such as the General Data Protection Regulation (GDPR) and other relevant standards, such as ISO 27001.

Key aspects of our information security strategy include:

1. **Data Encryption:** All sensitive data, including personal health information, is encrypted during transmission and storage to prevent unauthorised access.
2. **Access Control:** Access to study data is restricted to authorised personnel only, based on the principle of least privilege. Multi-factor authentication (MFA) is required for access to critical systems and data repositories.
3. **Data Anonymization:** Personal identifiers are removed or anonymized where possible to protect participant privacy. Anonymised data sets are used for analysis to minimise the risk of re-identification.
4. **Audit Trails:** Comprehensive audit trails are maintained to monitor and record all access to and modifications of study data, ensuring traceability and accountability.
5. **Data Storage and Backup:** All data is stored in secure data centres with regular backups to prevent data loss. Disaster recovery plans are in place to ensure data continuity in case of unforeseen events.
6. **Training and Awareness:** All personnel involved in the clinical investigation receive regular training on data protection and information security best practices, ensuring that everyone understands their responsibilities in safeguarding participant data.

References

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2. Pantanowitz, Liron, et al. "Accuracy and efficiency of an artificial intelligence tool when counting breast mitoses." Diagnostic pathology 15 (2020): 1-10.