The NCRI Cellular and Molecular Pathology (CMPath) Initiative

Annual Report 2020-2021

Background

The CMPath initiative in cellular and molecular pathology was launched in June 2016 and is funded by ten of the NCRI Partner organisations. A three-year review, conducted as part of the initial CMPath five- year funding agreement to secure the funding for the final two years of the programme, was presented tothe NCRI Strategy Advisory Group (SAG) in March 2019. The NCRI SAG recommended that funding be continued for CMPath in years four and five of the five-year funding agreement but advised that objectives for the next two years needed to be more clearly defined, with a stronger focus on achieving impact.

In August 2019, David Harrison was appointed as Chair for the remaining two years of the programme. Subsequently, CMPath has undergone very significant restructuring and reprioritisation. In the current report we discuss progress during the final two years of the original programme as David Harrison's period as Chair comes to an end.

Action required

The NCRI Annual Report Committee members are asked to review the following report and to:

- Note changes made to the structure, objectives and timeline of the CMPath Programme
- Note progress to date against new objectives and next steps
- Discuss any additional areas where it is felt that CMPath can benefit the cancer research community in years four and five
- Note proposed transition plan for CMPath after year 5
- Discuss ideas for CMPath after the five-year funding has complete

CMPath Aims and Objectives

The refocused aim of CMPath under the chairmanship of David Harrison from 2019-2021 is "to change the way pathologists engage with, conduct, and are recognised for their work in clinical studies in the UK."

This addresses a gap which is not currently met by any other organisation purporting to enhance the usefulness of pathology and the standing of pathologists. The objectives derived from this aim are as follows:

- Increase the number and availability of trials-active pathologists
- Raise the profile of pathologists in clinical trials
- Lead to more comprehensively planned clinical trial protocols
- Enhance clinical trial design and drug development through earlier pathology input
- Make participation in research more accessible through better use and access to pathology data and tissue

This will be achieved by:

- Facilitating international consensus in how pathology needs for clinical studies should be assessed
- Creating a group of pathologists with recognised skills and training in supporting clinical trials, by developing an online GCP training module for pathologists, to complement that already available for laboratory scientists
- Make participation in research more accessible through better use and access to pathology data and tissue, by engaging with patients and consumers
- Prepare for pathology to be brought into the NRCI fold, rather than being a special case

Progress against these objectives is described below.

Other changes in CMPath

COVID-19 had a significant impact on some of the planned development activities but led to a focus on the core objectives of preparedness for clinical studies, training in clinical studies to create a new group of recognised pathology specialists, and to engage with consumers in order to broaden access to research.

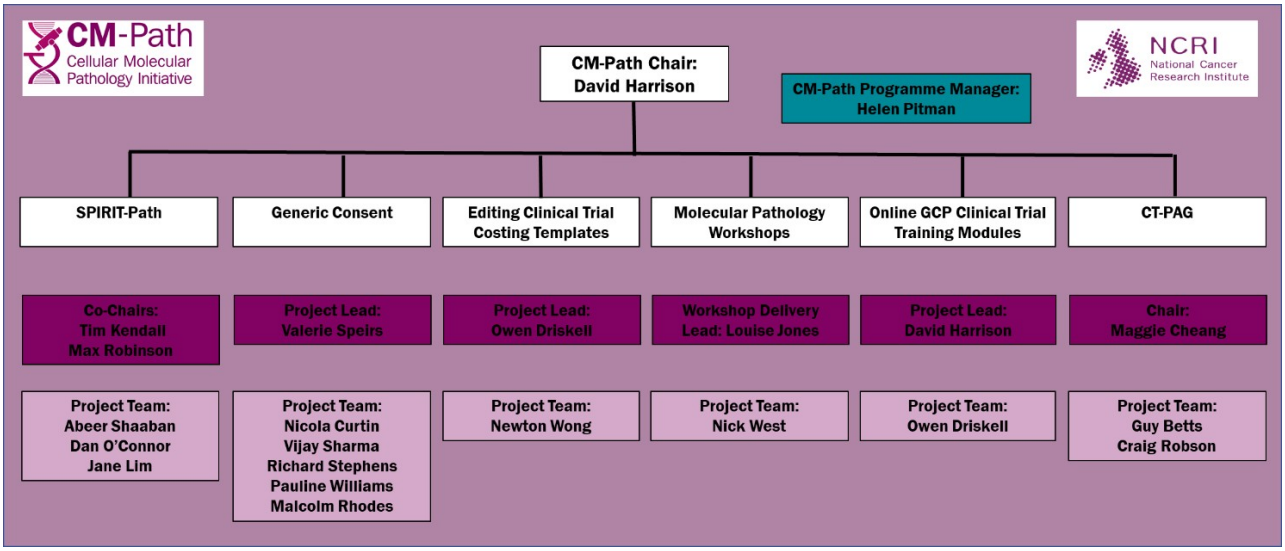
CMPath Objectives and Progress

1. CMPath engaged in an iterative consultation and Delphi process to develop pathology guidelines according to SPIRIT (https://www.spirit-statement.org/). This has been achieved in full, under the able leadership of Tim Kendall (Edinburgh) and Max Robinson (Newcastle) with a core steering group and international advisory group. A systematic review of pathology contribution into trials was published in Journal of Pathology: Clinical Research, written by Jane Lim, a trainee in Newcastle, on behalf of the steering group (https://onlinelibrary.wiley.com/doi/epdf/10.1002/cjp2.199), and the full SPIRIT-Path protocol has been accepted for publication in The Lancet Oncology. A more detailed summary of the project is provided in Appendix 1.

2. There has been discussion with RCPath and NIHR who are supportive of developing pathologist-focussed, clinical study-relevant modules for inclusion into GCP. This will build upon SPIRIT-Path and provide a recognised certification for pathologists which will be useful for CPD, job planning discussions and career development. This workstream has been delayed, but now that SPIRIT-Path has completed its first milestone, plans are in place to progress.
3. With SPIRIT-Path as the anchor for pathology activities the next step will be to address usefulness of the tool, and relate it to costing models and whether it makes a difference to pathologists' job planning and availability for research. CMPath, or its successor in whatever form, will amend the costing templates utilised in the UK including the NIHR industry costing template and the SoECAT, as well as the HRA Schedule of Events and Statement of Activities.
4. CTPAG has continued to evolve as a core part of NCRI and during the pandemic successfully moved its proposal guidance and application review processes to virtual, online activities (see Appendix 2). Along with other CMPath functions we regard it desirable that CTPAG activities will become mainstream NCRI rather than standing alone as a special case.
5. With significant patient engagement, we will seek to increase access for patients to clinical studies where access to human tissue is a perceived problem. CMPath explored the feasibility of generating a generic consent form as a nationally available template, but increasingly this seems a futile way to progress because many centres have their own systems in place that we will never replace. However, a template may still be of value to pathologists who have adopted the role of "clinical study pathologist", to facilitate a move towards competence of support for trials, rather than false and divisive self-designation as "centres of excellence". In addition to advice from three Consumers within NCRI we are in discussion with a network of patient support groups in kidney cancer, and an EU funded project using publicly available data, to explore how pathology research studies can be made more accessible for patients, and thus exemplify the value of patients' donation of tissue, digital images and associated metadata. It is recognised that this will not solve all the problems around tissue provision for trials, and that thereis still a serious cultural issue at times about concepts of ownership, retention and use.
6. It was agreed that CMPath would support for a limited time molecular pathology training until the Royal College assumed that role. This has happened.
7. Work on costing templates will follow from SPIRIT-Path.

CMPath Structure

The notional structure of CMPath as envisaged in 2020 is provided below: CMPath Programme Manager Helen Pitman left the project to take up another role at the NCRI just prior to the COVID-19 pandemic and support was provided by Head of Strategy and Initiatives Ian Lewis and latterly by Research Group Coordinator Francesca Parody; The generic consent workstream did not function, but there was a meeting with Ian Lewis, David Harrison and the three Consumer representatives, Richard Stephens, Pauline Williams and Malcolm Rhodes and this work will now restart; molecular pathology workshops ended as planned.



CMPath transition post year five – a personal view from the Chair

I have come to an end of my two-year helming duties. CMPath has made good progress in several key areas that distinguish this NRCI-supported initiative from other organisations, largely because of the excellence of the pathologists involved and their commitment, and the support of NCRI. It has delivered on fairly significant steps to consolidating pathologists with clinical trials training into a distinct and valued professional group. Those who have been involved, often more up-and-coming than established in their careers, have had a refreshing "can do" attitude to change and inclusion, rather than fretting over requests for more funding or pre-occupation with status and centres of excellence. They should pick up the task from here. There is still work to be done, but that should probably be incorporated into mainstream NCRI activity wherever possible, rather than being a special case. Outcomes that do need monitoring, updating and continuous promotion of uptake include:

- Promote the uptake of the SPIRIT-Path extension, review the guidance produced as part of SPIRIT-Path and update as appropriate, analyse how SPIRIT-Path has affected trials by undertaking the search protocols that allowed us to develop the guidelines to see if more trials have pathology appropriate protocols.

- Develop the Pathology GCP module and work with NIHR, RCPath and NCRI to encourage dissemination and credibility.

- Use SPIRIT-Path to inform costing templates as new tests and practices are introduced into the NHS to ensure that activities that pathologists undertake in trials are continuously updates and represented on these forms. This will be updated according to the schedule by HRA and NIHR.

- Continue CT-PAG proposal guidance meetings and reviews for NCRI Partners and other charities as appropriate

- Promote accessible research by continuing the consumer led focus on making tissue and related metadata more generally available and be providing guidance to empower pathologists with clinical trials interest to make a difference in their local setting.

Appendix 1

SPIRIT-Path Overview, NCRI Festival Abstract Submission

Guidelines for cellular and molecular pathology content in clinical trial protocols: the SPIRIT-Path extension

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Background

Despite the importance of trial protocols, their quality and content are known to be variable. The SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) 2013 Statement provides evidence-based recommendations for the minimum content of clinical trial protocols to address this variability and is widely endorsed by medicines developers, academia, regulators and medical journals.

SPIRIT-Path is an international project coordinated by the National Cancer Research Institute's (NCRI) Cellular and Molecular Pathology Initiative (CMPath) that has now extended the SPIRIT 2013 Statement for trials that include cellular and molecular pathology protocol content.
The extension offers guidance to authors of clinical trial protocols to ensure all possible steps, including aspects of specimen handling and reporting, are identified at trial inception.

Method

The SPIRIT-Path Extension was developed using an international Delphi process assessing candidate items generated from a prior systematic review, followed by an expert consensus meeting. 74 selected individuals from five continents responded, including clinicians, statisticians, laboratory scientists, patient advocates, funders, industry representatives, journal editors, and regulators.

Results

The SPIRIT-Path guidelines recommend 14 additional items, 7 extensions to the SPIRIT checklist and 7 elaborations, that should be addressed in trial protocols with pathology content alongside the SPIRIT 2013 Statement items. SPIRIT-Path recommends that protocols should document the individuals, processes, and standards for all cellular and molecular pathology components of the trial protocol, including all stages of the specimen pathway, any digital pathology methods, and with specific consideration of the value of trial data and tissue for additional translational studies.

Conclusion

The SPIRIT-Path extension will allow trial protocols to comprehensively address cellular and molecular pathology aspects, ensuring adequate skills and resources are available at trial commencement to facilitate the smooth running of laboratory-based components of the trial and fully leverage the value of biospecimens for translational research.

Impact statement

The SPIRIT-Path extension was conceived as a means of both maximising the value of pathology content of clinical trial protocols and facilitating its execution. We believe that this guidance is the necessary first step towards enabling an international next-generation approach to pathology that fully meets the needs of precision medicine.

Appendix 2

The Clinical Trials Pathology Advisory Group (CTPAG)

The Clinical Trials Pathology Advisory Group (CTPAG) sit within NCRI's cellular molecular pathology initiative, CMPath, and provides advice on pathology requirements in clinical trial design to researchers, NCRI Group members, funders and others. Specifically, the advisory group provides guidance and critique on pathology and biomarker components of trials.

In 2020/21 we did receive fewer applications to review due to the reduced number of open funding calls. However, CTPAG did successfully adapt the planned face to face proposal guidance meeting to a virtual event at the start of the year, and through the year provided support to CRUK by reviewing a number of applications and expressions of interest, details of which are below:

Date	Review Type	Proposal	Applicant (s)
May-20	Proposal Guidance Meeting (Presentations by Applicants to virtual CTPAG panel)	DETERMINE (aDvancing gEnomically maTchEd tReatMents IN rare cancErs)	Dr Emma Darlington/Dr Aida Sarmiento Castro
		Engrailed-2 (EN2) as a marker of bladder cancer relapse	Prof Richard Morgan
		CArPEt: Circulating tumour DNA and Patient initiated follow up in Endometrial cancer	Dr Esther Moss/ Dr David Guttery
Oct-20	Proposal Review Meeting- CRUK CRC Committee (Virtual panel discussions of proposals by CTPAG members)	ELECTRA – intraoperativE eLECtron radioTherapy in Rectal cAncer	Professor Alexander Mirnezami/Professor Maria Hawkins/Dr Simon Crabb
		PRIMUS 006	Dr David Chang/Prof Jeffry Evans
		CCLG Biobank Renewal	Prof Deborah Ann Tweddle/ Dr John Moppett/Dr Alexandra Smith
		DETERMINE (aDvancing gEnomically maTchEd tReatMents IN rare cancErs)	Dr Emma Darlington/Dr Aida Sarmiento Castro
Mar-21	EXPRESSION OF INTEREST: BIOMARKER PROJECT AWARD-CRUK Review	Role of ccfDNA-related biomarkers for prognosis and disease surveillance in adrenocortical carcinoma (ACC)	Cristina L Ronchi, MD, PhD
	EXPRESSION OF INTEREST: BIOMARKER PROJECT AWARD-CRUK Review	Validation of biomarker assays for prognostication in operable oesophagogastric cancer	Professor David Cunningham

May-21	Written CRUK Review - CRC Committee	POLAR: Predicting Treatment RespOnse in BLAdder Cancer with MRI (Application supported by CTPAG prior to submission)	Dr Shaista Hafeez

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