Core Outcome measures in Squamous Intra-epithelial precursor lesions of the Anus (COrSIcA)

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Manchester:Preston Collaboration

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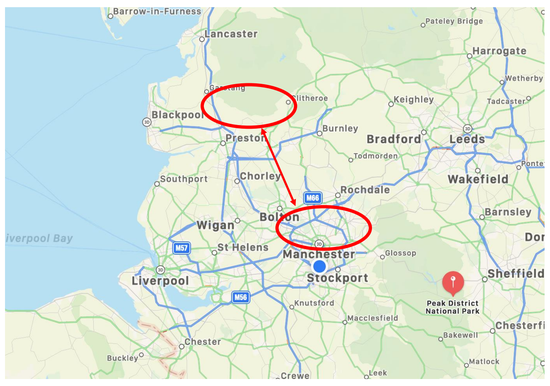
COrSIcA brings together clinical researchers (Parkin; Mitchell) at Preston, clinical academic at the MCRC and Manchester BRC (Renehan); methodological expertise in core outcome sets (Fish) and qualitative research (Morris), with research leadership (Martin-Hirsch).

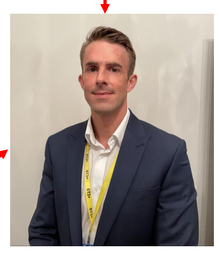
Undertaking this project is David Finch, ST7 colorectal trainee surgeon within the North West deanery. David is the first student in this component of the BRC programme and will be central to coordinating this collaboration.

Located between both the Royal Preston Hospital and the Manchester Cancer Research Centre, David will be integrated into the Manchester NIHR BRC Cancer Prevention and Early Detection theme.



Preston:

Clinical researchers, Mr Ed Parkin and Mr Pete Mitchell.
Director of Research and innovation, Professor Pierre Martin-Hirsch



David Finch
Preston-Manchester (MCRC) PhD Studentship

Manchester:

Clinical researcher, Miss Rebecca Fish. Qualitative researcher, Dr Rebecca Morris. Clinical academic at the MCRC and Manchester BRC, Professor Andrew Renehan.

Project Background and Aims

Background:

Anal squamous cell carcinoma (ASCC) is a HPV- related cancer with approximately 1400 new cases in the UK per year. Incidence rates has increased threefold in the last 30 years. Initial treatment is chemoradiotherapy, associated with substantial short-term and long-term side effects.

There are a number of sub-populations at increased risk of developing ASCC. These include men who and sex with men (MSM) whether they are HIV positive or not, other HIV positive groups, immunosuppressed groups such as transplant patients, and women who have previous valval, vaginal and cervical cancers.

In addition, there is a recognised precursor lesions, known as anal intra-epithelial neoplasia (AIN), which has some similarities to the precursor lesion of cervical cancer, known as CIN. While the natural history of CIN is will well-quantified, and there is a well-worked out management strategy of screening and treatment of CIN, with reduction in incidence of cervical cancer, this paradigm is not proven for AIN.

AIN is stratified into low grade and high grade squamous intra-epithelial lesion (HSIL). Positive p16 immunohistochemical staining is a useful marker for HSIL.

There are multiple treatments for HSIL broadly categorised as medical (for example, topical imiquimod, 5-FU, and anti-viral agents such as cidofovir) and surgical (laser, infra-red coagulation, electrocautery, and local excision) therapies. Vaccination is a possible third management strategy.

To-date, there are few phase III randomised controlled trials for the treatment of HSIL. Our scoping search identified two – namely the AIDS malignancy consortium ANCHOR trial (https://clinicaltrials.gov/: NCT02135419) and TreatAIN (NCT04055142). Both are in HIV positive patients.

Both trials have utilised different primary and secondary outcomes. This hinders evidence synthesis and presents challenges to the selection of optimal outcomes in future trials. The ANCHOR trial developed a trial-specific QoL questionnaire but its generalisability is not known.

Aims:

To determine the priority outcomes for all stakeholders and reach agreement on a standardised COS to be measured and reported in all future trials in all patients with HSIL.

Rationale and Experimental Plan

Rationale:

To-date the limitations of the AIN trials include: limited to select high-risk sub-populations; the outcome measures of invasive cancer does not appear to be included; treatment-related factors e.g. frequency of hospital attendance, are not included; and other morbidities e.g. pain, incontinence, and not listed.

Our research group have previously developed a core outcome set (COS) for trials including chemoradiotherapy for non-metastatic ASCC. This was called CORMAC (1) and used COMET methodological principles (https://www.comet-initiative.org/). The present COrSIcA proposal will extend this work and develop a COS for patients with HSIL recruited to later phase intervention trials. A COS will facilitate evidence synthesis in HSIL and ensure future trials utilise outcomes that are relevant to all stakeholders.

Experimental Plan:

There will be four workstreams (WSs). These will be consecutive:

WS1: Systematic review

- A systematic review of the literature will be performed to identify a comprehensive list of all outcomes in use in late phase trials and observational studies in patients with AIN undergoing medical or surgical interventions.

WS2: Patient consultation

- Participants will be purposively drawn from the prospectively maintained databases of patients with AIN at the Christie NHS Foundation Trust and Royal Preston Hospital. A purposive approach to sampling will be selected with the aim of maximising diversity within the study participants. Criteria will be selected to ensure that subsets within the study population that may express contrasting views and experiences are represented.
- Interviews will explore patients' perceptions, priorities and experiences of living with and having treatment for AIN, using a semi-structured format. Between 20 and 30 patients will be interviewed.

WS3: Delphi process

- A process of iterative international surveys (Delphi process) will be undertaken involving the two key stakeholder groups (patients and HCPs, including clinician trialists) adhering to the standards recommended by the COMET Minimum Standards In COS Development project. Questionnaires will be administered in two sequential rounds, with anonymised feedback of the results of the previous round provided to participants before completion of the subsequent round.
- This process is intended to achieve consensus among participants by minimising the potential for bias towards the opinions of those who are more outspoken or whose views might be perceived as superior. The aim of the Delphi process is to move towards consensus among stakeholders.
- Two rounds of the Delphi questionnaire will be undertaken. The spread of scores (for example, using the Likert scale) for each question item should be seen to reduce from round 1 to round 2 as consensus is reached. For all rounds after the first round, participants will be able to review the results from earlier rounds as they rate each outcome.

WS4: Consensus meeting

- The results of the Delphi process will be discussed at a consensus meeting involving an invited sample of Delphi participants from all stakeholder groups. The consensus meeting can be virtual – for example, using the www.menti.com voting system. Representatives from secondary stakeholder groups (intended users of the COS including non-clinician trialists; users of the information generated from use of the COS including policy makers guideline developers) will be invited at this stage. If a final COS is not agreed at the end of the first consensus meeting, subsequent meetings will be considered.

PPI A patient and public involvement (PPI) group will be established with patients with experience of squamous intra-epithelial precursor lesions of the anus or family members. The group will help inform the study from design, commenting on patient-focused information (e.g. adverts, and PIS), wording of interview questions, through to dissemination and wider public engagement.

SAG An international study advisory group (SAG) will be assembled to oversee the project, and will include patient representation. We will explore registering this proposal with international professional organisations, such as IANS (International Anal Neoplasia Society).

Additional work within the PhD project will focus on the development of a clinical scoring system to facilitate the objective evaluation of AIN in future trials.

Conclusion

This poster celebrates the new collaborative research partnership between Manchester and Preston. COrSIcA will serve as an exemplar for developing academic links between the MCRC, Christies and Preston, raising profile of research in Preston, with potential spin-offs for future student projects at Preston.

References

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2. Fish R, et al. Core outcome research measures in anal cancer (CORMAC): protocol for systematic review, qualitative interviews and Delphi survey to develop a core outcome set in anal cancer. BMJ Open. 2017;7(11):e018726.