Study Protocol V2.4 01/02/2016

Title: MRI IN STaging REctal polyp planes

Short Title: MINSTREL

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<thead>
<tr>
<th>Role</th>
<th>Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chief Investigator</td>
<td>Gina Brown, Professor &amp; Consultant Radiologist</td>
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<td>Gina Brown, Consultant Radiologist</td>
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<td>Karen Thomas</td>
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</tbody>
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Protocol Reference:

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<tr>
<td>Effective Date:</td>
<td>01.02.2016</td>
</tr>
<tr>
<td>Superseded Version Number &amp; Date (If applicable)</td>
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1. Background

Early rectal cancer (ERC) can be defined as invasive disease being confined to the submucosa +/- the muscle of the rectal wall without lymph node metastasis. The prospects for surgical cure in these patients are excellent.

Transanal endoscopic microsurgery (TEMS) excision has been practiced for over 30 years now allowing patients to be treated with reduced physical insult. Unfortunately most of the patients with early rectal cancer that are eligible for organ preserving surgery such as TEMS instead proceed with a radical resection. Radical resection carries with it double the mortality, longer hospital stays, greater expense and the attendant life long extra morbidity of sexual dysfunction, colostomies and decreased continence.

Data published by the NBOCAP shows 45% of the 9,433 rectal cancers treated by radical resection in the UK annually were either T1 or T2 and 66% were node negative. Despite this 77% those operated on underwent major resection whilst only 11% were locally excised[1].

This NBOCAP data does not identify the number of patients with benign rectal tumours, a proportion of whom may also undergo radical resection.

The assessment of rectal lesions in the UK is currently un-standardised with the use of pit pattern, paris morphology, ultrasound and MRI varying from patient to patient, clinician to clinician and institution to institution. National guidelines currently advise that imaging is broadly unhelpful in assessment the malignant polyp[2].

The reasons for underutilization of organ preserving surgery are complex but some of the reasons are listed below:

- There currently is no imaging protocol recognized that can reliably exclude metastatic lymph node spread in early rectal cancer. Many surgeons will therefore recommend radical surgery to excise the mesorectal nodes and analyse with histopathology.
- Superficial early rectal cancers and adenoma can be over-staged in the MDT as more invasive and advanced disease.
- Rectal lesions incorrectly assessed as amenable to endoscopic excision have already undergone an incomplete resection attempt before MDT discussion and imaging. MDT’s reviewing piecemeal histology may well recommend completion radical resection.
- TEMS excision is not available in every institution and it may be MDTs do not always refer eligible patients.
- Local resection may be unfeasible for technical rather than oncological reasons.

Trials are underway to evaluate the role of neoadjuvant radiotherapy followed by local excision in patients identified with early rectal cancer. There remains some concern with this proposed treatment pathway.

- Of 10 patients with early rectal cancer irradiated only 2 will have lymph node spread and the other 8 will have been subjected to the morbidity of pelvic radiotherapy without benefit to the mesorectum.
Dash et al found that in a cohort of 167 rectal lesions evaluated as benign by endoscopic and ultrasonographic criteria 21 (8%) will turn out to have an unexpected malignancy on histopathology[3].

Large studies by expert groups have shown Patterns III IV and IIIIs to rarely contain cancer but V and Vn pit pattern types to contain cancer in 28.3% and 90% respectively[4]. Morphology has also been shown to correlate with submucosal invasion with 88% of >20mm depressed colorectal neoplasms versus 29% of protruded lesions showing malignancy[4].

<table>
<thead>
<tr>
<th>I</th>
<th>Round pit (normal pit)</th>
</tr>
</thead>
<tbody>
<tr>
<td>II</td>
<td>Asteroid pit</td>
</tr>
<tr>
<td>III s</td>
<td>Tubular or round pit that is smaller than the normal pit (Type 1)</td>
</tr>
<tr>
<td>III l</td>
<td>Tubular or round pit that is larger than the normal pit (Type 1)</td>
</tr>
<tr>
<td>IV</td>
<td>Dendritic or gyrus-like pit</td>
</tr>
<tr>
<td>V t</td>
<td>Irregular arrangement and sizes of III l, III s, IV type pit pattern</td>
</tr>
<tr>
<td>V n</td>
<td>Loss or decrease of pits with an amorphous structure</td>
</tr>
</tbody>
</table>


When local excision is contemplated some tumours are initially being taken in too superficial a plane. Local excision of early rectal cancer with curative intent often requires full thickness excision to minimise the chances of deep margin involvement.

Bach et al reported that of the early rectal cancers submitted to the UK TEM database, 44% of pT1 and 31% of pT2 cancers were incorrectly presumed to be benign preoperatively[5]. This may lead surgeons to undertake less than full thickness excision by flexible endoscopic excision or transanal endoscopic surgery. On sub-analysis Bach et al. found that considering a lesion benign when in fact it is malignant is associated with a hazard 1.98 of leaving residual disease after excision with TEMS[5]. Patients with
residual disease will need re-TEMS or even completion radical surgery, depriving these patients the potential benefit of organ preserving treatment.

High-Spatial-Resolution magnetic resonance imaging (MRI) is a standard of care in assessing the circumferential resection margin of rectal tumours and triaging patients with more advanced tumours to neoadjuvant therapy to reduce local recurrence. MRI is the established modality for identifying rectal cancer position, the relationship of tumour to the peritoneal reflection, is less user dependent than ultrasound, provides reliable information about extramural disease and is available in all centres that operate on rectal cancer.

There is a paucity of evidence base clarifying the current accuracy of MRI in assessing T stage and lymph node involvement in early rectal cancer. There are also no prospective trials we are aware of evaluating any imaging modality on a population of rectal lesions unselected by endoscopic criteria or biopsy.

(i) Description of the population to be studied.

Adult patients found to have rectal tumours (assessed benign or malignant) endoscopically estimated as being 20 to 50mm in size and located within 150mm of the rectal verge.

Nusko et al established 46% of 16mm to 42mm rectal polypoid tumours will contain cancer[6]. In the TEMS registry of 448 analysed rectal cancers 20mm to 50mm in size removed by local excision, it was found 58 (30%) were T1sm1 whilst 192 had deeper invasion[5]. So in unselected rectal tumours 20mm to 50mm in size we estimate the prevalence of cancer sm2 or greater, to be approximately 32%.

(ii) Name and description of the procedures.

Colonoscopy – endoscopic examination of the colon following full bowel preparation as directed by the local policy of the participating centre.

Endoscopic ultrasound – a high frequency mini-probe will be passed through the working channel of a standard colonoscope to measure the tumour depth and any associated local lymphadenopathy.

EMR, ESR - Endoscopic mucosal/submucosal resection – the lesion will be excised by passing instruments through the working channel of the colonoscope. The specimen will be retrieved and sent for histopathological analysis.

TEMS - Transanal endoscopic microsurgery. Specially designed instruments and a microscope are used to remove rectal lesions through the anus.
MRI – Magnetic resonance imaging using a standard protocol for assessment of rectum. The parameters for each MRI will agree with the following agreed sequences.

<table>
<thead>
<tr>
<th>Sequence</th>
<th>Sagittal TSE T2</th>
<th>Axial TSE T2</th>
<th>Axial TSE T2 High Res</th>
<th>Coronal TSE T2 High Res</th>
</tr>
</thead>
<tbody>
<tr>
<td>TR</td>
<td>3961</td>
<td>4018</td>
<td>5362</td>
<td>5362</td>
</tr>
<tr>
<td>TE</td>
<td>125</td>
<td>80</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>TSE factor</td>
<td>23</td>
<td>20</td>
<td>16</td>
<td>16</td>
</tr>
<tr>
<td>FOV /RFOV</td>
<td>250/100%</td>
<td>300/100%</td>
<td>160/90%</td>
<td>160/90%</td>
</tr>
<tr>
<td>Slice</td>
<td>3/0.4</td>
<td>5/1</td>
<td>3/0.3</td>
<td>3/0.3</td>
</tr>
<tr>
<td>Number of slices</td>
<td>24</td>
<td>32</td>
<td>24</td>
<td>24</td>
</tr>
<tr>
<td>NSA</td>
<td>4</td>
<td>2</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>Matrix</td>
<td>320/512r</td>
<td>256/512r</td>
<td>256/256</td>
<td>256/256</td>
</tr>
<tr>
<td>Sat bands</td>
<td>Ant/Sup</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Acquisition time</td>
<td>6.00</td>
<td>3.28</td>
<td>7.35</td>
<td>7.35</td>
</tr>
</tbody>
</table>

(iii) A summary of the findings from non clinical studies that potentially have clinical significance and from clinical trials which are relevant to the trial

**MRI T stage in ERC**

The ACPGBI found little evidence to support the use of MRI in T staging in T1 cancer when evaluating published data[2]. They summarise the evidence in their table below:

Table 13 Accuracy of magnetic resonance in depth of invasion (T stage) assessment of early rectal cancers.

<table>
<thead>
<tr>
<th>n</th>
<th>Overall accuracy* (%)</th>
<th>T1 accuracy* (%)</th>
<th>T2 accuracy* (%)</th>
<th>Author</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>.38</td>
<td>21 (65)</td>
<td>2/7 (29)</td>
<td>2/4 (50)</td>
<td>Hadfield et al. [197]</td>
<td>1997</td>
</tr>
<tr>
<td>217</td>
<td>176 (81)</td>
<td>3/4 (75)</td>
<td>20/37 (54)</td>
<td>Kim et al. [198]</td>
<td>2000</td>
</tr>
<tr>
<td>92</td>
<td>70 (76)</td>
<td>–</td>
<td>6/13 (46)</td>
<td>Beets Tan et al. [201]</td>
<td>2001</td>
</tr>
<tr>
<td>56</td>
<td>48 (86)</td>
<td>8/10 (80)</td>
<td>8/10 (80)</td>
<td>Gagliardi et al. [195]</td>
<td>2002</td>
</tr>
<tr>
<td>98</td>
<td>75 (76)</td>
<td>2/6 (33)</td>
<td>13/22 (59)</td>
<td>Brown et al. [193]</td>
<td>2003</td>
</tr>
<tr>
<td>39</td>
<td>25 (64)</td>
<td>1/4 (25)</td>
<td>5/11 (45)</td>
<td>Fuchsberger et al. [194]</td>
<td>2003</td>
</tr>
<tr>
<td>42</td>
<td>31 (74)</td>
<td>–</td>
<td>8/13 (62)</td>
<td>Poon et al. [202]</td>
<td>2005</td>
</tr>
<tr>
<td>91</td>
<td>60 (66)</td>
<td>1/4 (25)</td>
<td>10/16 (63)</td>
<td>Videlhult et al. [200]</td>
<td>2007</td>
</tr>
<tr>
<td>48</td>
<td>46 (96)</td>
<td>6/6 (100)</td>
<td>10/12 (83)</td>
<td>Giunti et al. [196]</td>
<td>2012</td>
</tr>
</tbody>
</table>

*Accuracy is the number of patients where the T stage, as assessed by magnetic resonance, is similar to the pathological T stage in the resected specimen and broken down for T1 and T2 tumours.

The number of T1 and T2 tumours included in each study are low and the radiologists reviewing scans were often examining the utility if MRI in evaluating advanced disease rather than focusing on early rectal cancer. The only publication included from the last 7 years was a retrospective series from Italy and published an accuracy of 100% correlation of mriT1 with pT1 and 83% correlation of mriT2 with pT2 using MRI[7].

**MRI lymph node status in ERC**
If the presence or absence of pathological nodal involvement can be confidently established in early rectal cancer it is likely MDTs could further maximise organ preserving surgery without the consequences of increased local recurrence.

It has been established that prediction of nodal involvement in rectal cancer with MR imaging is improved by using the border contour and signal intensity characteristics of lymph nodes instead of size criteria[8]. Whilst up to 30% of T1 and T2 rectal cancers have lymph node disease spread the median metastasis size is only 0.3mm in T1 tumours and 4.1mm in T2 tumours reducing the accuracy of endorectal ultrasound for predicting lymph node involvement to an accuracy of 48%[9]. Previous studies examining the accuracy of both MRI and endorectal ultrasound in predicting lymph node metastasis have mostly examined populations with more locally advanced cancers which tend to have larger pathological nodal deposits.

The ACPGBI reviewed the evidence base in 2013 for the accuracy of MRI for predicting nodal positivity and concluded that “A proportion of involved lymph nodes associated with a malignant polyp can be identified by MRI or endoluminal ultrasound. However, on available evidence (or lack of it) CT, MRI or ultrasound are not accurate enough to enable a judgment to be made as to whether a visible lymph node does not contain cancer (Level IIb)”[2].

ACPGBI position statement evidence summary:

<table>
<thead>
<tr>
<th>Author</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kim et al. [198]</td>
<td>2000</td>
</tr>
<tr>
<td>Blomqvist et al. [192]</td>
<td>2000</td>
</tr>
<tr>
<td>Gagliardi et al. [195]</td>
<td>2002</td>
</tr>
<tr>
<td>Matsuda et al. [220]</td>
<td>2003</td>
</tr>
<tr>
<td>Fuchsberger et al. [194]</td>
<td>2003</td>
</tr>
<tr>
<td>Ferri et al. [219]</td>
<td>2005</td>
</tr>
<tr>
<td>Giusti et al. [196]</td>
<td>2012</td>
</tr>
</tbody>
</table>

(iv) **Summary of the known and potential risks and benefits, if any, to human subjects.**

This pilot study will require patients to undergo an MRI before excision or resection of their rectal tumour. In most institutions such lesions are not removed at first endoscopy and there is a natural window for our MRI to take place whilst arrangements are made for a full colonoscopy, space on a dedicated polypectomy list, a clinician with EMR/ESR expertise or MDT discussion.

Patients with a contraindication to MRI such as a certain pacemakers will be excluded from the trial.
As a prospective diagnostic accuracy study this trial phase will not recommend a treatment arm but instead rely on the MDT to suggest resection modality by a suitably experienced surgeon or endoscopist.

**(v) Description of and justification for the treatment.**

This is a pilot study to examine the utility of MRI in polypoid rectal tumours. We would like to prospectively investigate the accuracy of a pre intervention MRI reported with a rigorous and reproducible new staging system in an unselected cohort of both adenoma and carcinoma. This will assess safety at all levels of the rectal wall and appropriateness for excision modality.

Our pilot data has established an accuracy of 93% for identifying the correct sm3 or deeper invasion for excision in a retrospective selected group[10].

Our new MRI scoring will to divide these tumours into the following four planes:

<table>
<thead>
<tr>
<th>A) Mucosal – EMR (mucosal) resection could clear deep margin</th>
<th>No definite SM (submucosal) invasion</th>
<th>1mm SM invasion seen but &gt;1mm SM preserved to MP</th>
</tr>
</thead>
<tbody>
<tr>
<td>B) Submucosal - Endoscopic Sub-mucosal Resection / partial thickness TEMS</td>
<td>Definite SM invasion of &lt;1mm in depth</td>
<td>SM invasion seen, &lt;1mm of SM preserved but no definite muscle invasion</td>
</tr>
<tr>
<td>C) Deep submucosal / muscle invasion – Full thickness TEMS</td>
<td>Definite muscle invasion seen but greater than 1mm muscle preserved to mesorectum</td>
<td></td>
</tr>
<tr>
<td>D) Deep Muscle or extramural disease - Full oncological resection required</td>
<td>Less than 1mm of muscle preserved but no mesorectal invasion</td>
<td>Definite invasion of mesorectum</td>
</tr>
</tbody>
</table>
It is important to state that whilst only some institutions perform TEMS that all colorectal departments manage rectal adenomas and carcinomas in endoscopy and theatre and all these patients would benefit from improved staging.

Local excision may either not be technically possible or even appropriate for some tumours allocated to superficial planes because of other tumour or patient characteristics. These patients are still likely to still benefit from MRI, MDT discussion and exploration of options at an early rectal cancer MDT.

(vi) A statement that the trial will be conducted in compliance with the protocol, GCP and the applicable regulatory requirements
The trial will be conducted in compliance with the protocol, standard operating procedures, policies, local R&D management guidance, Good Clinical Practice including the Research Governance Framework 2005 (2nd edition) and other applicable regulatory requirement(s) including but not limited to the Human Tissue Act 2004, Human Tissue (Quality and Safety for Human Application) Regulations 2007, the Medical Devices Regulations 2002, Ionising Radiation (Medical Exposures) Regulations 2000.

(vii) List references to literature and data that are relevant to the trial, and that provide background for the trial.
Please see: Chapter 17. References

2. Rationale
A detailed description of the objectives and the purpose of the trial.
Organ preserving therapy is being underused creating excess mortality and morbidity. Currently the assessment of rectal lesions and their pathway to intervention is un-standardised. MDT discussion is not mandated of lesions presumed benign. There is a paucity of evidence to support the use of either MRI or ultrasound in assessing large adenoma and early rectal cancer. Despite this MRI is currently being used to select patients with early rectal cancer to trials for neoadjuvant therapy without a validated MRI assessment tool.

The purpose of this trial is to prospectively validate MRI in a prospective trial in a population of rectal adenoma and carcinoma 20mm to 50mm in size to standardise the assessment of such lesions.

2. Objectives:
The primary research question we wish to answer is:
“Is MRI or clinical assessment superior in gauging the correct surgical plane for 20 to 50mm rectal polyps?"

The null hypothesis being:

“There is no difference in percentage correct allocation of plane of between clinical and MRI assessment of 20 to 50mm rectal polyps.”

Our secondary objectives include:

1. The appropriateness of MR directed surgery calculated from the primary radiology assessment
2. The appropriateness of MR directed surgery calculated from the central radiology assessment
3. The appropriateness of ultrasound directed surgery for adenoma / early rectal cancer
4. The calculation of the sensitivity and specificity of MRI in detecting positive nodal metastasis of the primary radiologist in this population
5. To calculate the inter-observer agreement of MR safe excision plane allocation
6. 3 year loco-regional recurrence, metastasis and overall survival
7. Assessment of baseline tumour characteristics will be compared across all imaging and clinical assessment including size, position, morphology, relation to peritoneal reflection.
8. Measure the effect of polyp sub-mucosal lifting on the accuracy of MRI reporting sub-stages and inter-observer agreement of MRI reports.

4. Study Design

(i) **A description of the type/design of trial to be conducted (e.g. observational, tissue collection, survey, non-interventional design) and a schematic diagram of trial design, procedures and stages.**

This is a multi centred pilot study to examine the utility of MRI in polypoid rectal tumours. This will be a non interventional prospective trial to validate the use of a novel MRI staging tool in assessing rectal adenoma and early rectal cancer across several sites.

Participating trusts will be asked to ensure that, in accordance with best practice, endoscopy reports have the minimum dataset required for >20mm rectal polyps which includes the following parameters:

1. Size
2. Position from anal verge
3. Pit pattern & paris morphology
4. A recommendation of appropriate excision technique

The completeness of source reporting may be facilitated by a dedicated template/proforma reporting tool that augments the report. For example:

<table>
<thead>
<tr>
<th>MORPHOLOGY</th>
<th>sessile/flat</th>
<th>pedunculated</th>
<th>mucinous</th>
</tr>
</thead>
<tbody>
<tr>
<td>stalk / no stalk</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>SIZE</th>
<th>maximum</th>
<th>diameter (mm)</th>
<th>thickness (mm)</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Lesion in the</th>
<th>12 to 3 o'clock</th>
<th>3 to 6 o'clock</th>
<th>6 to 9 o'clock</th>
<th>9 to 12 o'clock</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Central depressed portion in the</th>
<th>12 to 3 o'clock</th>
<th>3 to 6 o'clock</th>
<th>6 to 9 o'clock</th>
<th>9 to 12 o'clock</th>
</tr>
</thead>
</table>

Lift attempted? : □ no □ yes (non lifting) □ yes (lifting)

Polypectomy attempted at this colonoscopy? □ no □ yes (completed) □ yes (abandoned)

Pit Pattern: □ Not assessed □ I □ II □ IIIa □ IIIb □ IIIc □ IV □ V

Paris Morphology: □ Not assessed □ Is □ Isp □ Ip □ IIa □ IIb □ IIc □ III

Biopsy □ Biopsy taken today □ Biopsy not taken today □ Previous biopsy result known

Imaging to date □ lesion not yet imaged (preferred) □ MRI □ Ultrasound (please complete US CRF)

TUMOUR HEIGHT: MM to anal verge and MM to the top of the puborectalis sling

Surgical plane necessary to achieve 1mm deep clearance:

A [ ] Mucosa – EMR (mucosal) resection could clear deep margin

B [ ] Sub-mucosa – Endoscopic Sub-mucosal Resection / partial thickness TEMS

C [ ] Deep submucosal / muscle invasion – Full thickness TEMS

D [ ] Deep Muscle or extramural disease – Full oncological resection required

E) [ ] Unknown

It is recommended that CRF are filled contemporaneously by appropriate staff. It should be ensured that all fields are present in the patient record e.g. endoscopy report as source data as well as on the CRF.
Eligible patients will be identified on colonoscopy, if they are found to have a 20mm to 50mm rectal tumour within 150mm of the anal verge. Endoscopic assessment +/- ultrasound +/- biopsies may be taken as per local policy for review at the local multidisciplinary team meeting.

Patients will be invited to enter the trial after the index colonoscopy. Patients will have fully recovered from the endoscopy and any sedation given before being approached to join the trial. Patients will be given a minimum of 24hrs to consider their patient information sheet before taking consent for the study.

All patients who enter the study will be sent for an MRI. The MRI will be reported on site using our novel staging proforma. The results of all the staging investigations, the MRI and any biopsy will be made available to the local clinician and any MDT discussion.

The patients will proceed to excision or resection of the tumour as per clinician / MDT discussion. Patients will be followed up as per routine NHS care as determined by local polyp surveillance protocol or MDT discussion.

After data collection images will be made available to a central radiologist to secondarily report the MRI scans. Slides and tissue will also be made available for secondary central histopathology review. The secondary radiologist will again be blinded to the endoscopic assessment but now also to the report of the primary reports. This data will be used for calculating inter observer agreement as a secondary outcome measure. The central reports of MRI will not be used to calculate the primary or other secondary outcome measures which will be calculated from primary assessment.

*It is recognised that some trusts use submucosal injection to lift polyps when assessing rectal polyps. Submucosal lifting will be recorded on the CRFs and affect on MRI accuracy observed.*
Trial design schematic:
(ii) A description of the measures taken to minimize/avoid bias, including randomisation

As a stipulation of site inclusion all endoscopy units must be staffed with JAG accredited endoscopists. Endoscopists assessing polyps should either be certified as competent for level 2 polypectomy (>1cm) by JAG or be currently approved locally to endoscopically excise >1cm polyps (the common reason being they qualified before the JAG training programme was introduced to units in the UK).

The MRI will be examined by an on-site specialist GI radiologist blinded to the endoscopic assessment +/- any ultrasound assessment.

The histopathological analysis will be performed by an experienced on-site GI pathologist and all data will be recorded on standardised reporting pro formas. As detailed the histopathology will be quality assured by secondary central review.

The secondary (central) reporting radiologist will be blinded to the endoscopic assessment +/- ultrasound assessment and the report of the primary radiologist and the histopathology.

5. End Points

Specific statement of the primary endpoint and the secondary endpoints, if any, to be measured during the trial

The primary endpoint is the binary assessment of the primary radiologist’s MRI assessment to assign each case to its correct tissue plane A to D in this novel MRI staging tool.

(MRI allocated plane = histopathology allocated plane) = “correct MRI plane allocation”.

(MRI allocated plane ≠ histopathology allocated plane) = “incorrect MRI plane allocation”.

and the binary assessment of the clinician’s ability to assign each case to its correct tissue plane A to D.

(Clinician allocated plane = histopathology allocated plane) = “correct clinical plane allocation”.

(Clinician allocated plane ≠ histopathology allocated plane) = “incorrect clinical plane allocation”.

(Clinician allocated plane = E Unknown) = “incorrect clinical plane allocation”.
The following table will be used to calculate planes A to D from the histopathology

<table>
<thead>
<tr>
<th>Plane</th>
<th>Description</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>A)</td>
<td>Mucosal – EMR (mucosal) resection could clear deep margin</td>
<td>T0 / Adenoma (includes both LGD or HGD)</td>
</tr>
<tr>
<td>B) Submucosal - Endoscopic Sub-mucosal Resection / partial thickness TEMS</td>
<td>T1 cancer with invasion of SM but &gt;1mm of deep submucosa preserved (If amount of preserved SM cannot be confirmed then include if &lt;2mm of SM invasion)</td>
<td></td>
</tr>
<tr>
<td>C) Deep submucosal / muscle invasion – Full thickness TEMS</td>
<td>T1 cancer with SM invasion seen and &lt;1mm of SM preserved (No definite muscle invasion). (If amount of preserved SM cannot be confirmed then include if &gt;2mm of SM invasion)</td>
<td></td>
</tr>
<tr>
<td>D) Deep Muscle or extramural disease - Full oncological resection required</td>
<td>T2 Less than 1mm of muscle of deep muscle preserved but not T3</td>
<td></td>
</tr>
</tbody>
</table>

- T3 Definite invasion of mesorectum
- T4
The secondary endpoints

1. The appropriateness of MR directed surgery for adenoma / early rectal cancer calculated from the primary radiology assessment as appropriate or not appropriate for each patient and also quoted as an overall percentage. The table below will allow correlation with histopathology as the gold standard.

<table>
<thead>
<tr>
<th>MRI Primary review</th>
<th>T0</th>
<th>T1</th>
<th>T2</th>
<th>T3</th>
<th>T4</th>
</tr>
</thead>
<tbody>
<tr>
<td>A No definite SM (submucosal) invasion</td>
<td>☐</td>
<td>☒</td>
<td>☒</td>
<td>☒</td>
<td>☒</td>
</tr>
<tr>
<td>B Definite SM invasion of &lt;1mm</td>
<td>☐</td>
<td>☐</td>
<td>☒</td>
<td>☒</td>
<td>☒</td>
</tr>
<tr>
<td>B &gt;1mm SM invasion seen but &gt;1mm SM preserved to MP</td>
<td>☒</td>
<td>☐</td>
<td>☒</td>
<td>☒</td>
<td>☒</td>
</tr>
<tr>
<td>C SM invasion seen, &lt;1mm of SM preserved but no definite muscle invasion</td>
<td>☒</td>
<td>☐</td>
<td>☐</td>
<td>☒</td>
<td>☒</td>
</tr>
<tr>
<td>C Definite muscle invasion seen but greater than 1mm muscle preserved to mesorectum</td>
<td>☒</td>
<td>☒</td>
<td>☐</td>
<td>☒</td>
<td>☒</td>
</tr>
<tr>
<td>D Less than 1mm of muscle preserved but no mesorectal invasion</td>
<td>☒</td>
<td>☒</td>
<td>☐</td>
<td>☐</td>
<td>☒</td>
</tr>
<tr>
<td>D Definite invasion of mesorectum</td>
<td>☒</td>
<td>☒</td>
<td>☒</td>
<td>☐</td>
<td>☐</td>
</tr>
</tbody>
</table>
2. The appropriateness of MR directed surgery for adenoma / early rectal cancer calculated from the secondary (central) radiology assessment as appropriate or not appropriate for each patient and also quoted as an overall percentage. The table below will allow correlation with histopathology as the gold standard.

<table>
<thead>
<tr>
<th>MR Central review</th>
<th>Primary histopathology</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>T0</td>
</tr>
<tr>
<td>A</td>
<td>No definite SM (submucosal) invasion</td>
</tr>
<tr>
<td>B</td>
<td>Definite SM invasion of &lt;1mm</td>
</tr>
<tr>
<td>B</td>
<td>&gt;1mm SM invasion seen but &gt;1mm SM preserved to MP</td>
</tr>
<tr>
<td>C</td>
<td>SM invasion seen, &lt;1mm of SM preserved but no definite muscle invasion</td>
</tr>
<tr>
<td>C</td>
<td>Definite muscle invasion seen but greater than 1mm muscle preserved to mesorectum</td>
</tr>
<tr>
<td>D</td>
<td>Less than 1mm of muscle preserved but no mesorectal invasion</td>
</tr>
<tr>
<td>D</td>
<td>Definite invasion of mesorectum</td>
</tr>
</tbody>
</table>
3. The appropriateness of ultrasound directed surgery for adenoma / early rectal cancer will be calculated as appropriate or not appropriate for each patient and also quoted as an overall percentage. The table below will allow correlation with histopathology as the gold standard.

<table>
<thead>
<tr>
<th>ULTRASOUND REPORT</th>
<th>Primary histopathology</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>T0</td>
</tr>
<tr>
<td>A</td>
<td>☐</td>
</tr>
<tr>
<td>B</td>
<td>☐</td>
</tr>
<tr>
<td>B</td>
<td>☒</td>
</tr>
<tr>
<td>C</td>
<td>☒</td>
</tr>
<tr>
<td>C</td>
<td>☒</td>
</tr>
<tr>
<td>D</td>
<td>☒</td>
</tr>
<tr>
<td>D</td>
<td>☒</td>
</tr>
</tbody>
</table>

4. The calculation of the sensitivity and specificity of MRI in detecting positive nodal metastasis of the primary radiologist in this population

5. The inter-observer agreement of MR safe excision plane allocation will be analysed by kappa correlation after secondary central radiology assessment

6. 3 year loco-regional recurrence, metastasis and overall survival

7. Assessment of baseline tumour characteristics will be compared across all imaging and clinical assessment including size, position, morphology, relation to peritoneal reflection.

8. Measure the effect of polyp sub-mucosal lifting on the accuracy of MRI reporting sub-stages and inter-observer agreement of MRI reports

6. Inclusion/ Exclusion Criteria
Inclusion Criteria

Patients aged over 18 years of age presenting with 20 to 50mm tumours found at flexible sigmoidoscopy/colonoscopy presumed either adenoma or adenocarcinoma.

Patients must be able to undergo colonoscopy, adequate bowel preparation, MRI, and surgery if necessary.

Exclusion Criteria

Patients who are unable to consent, who withhold consent or who withdraw consent will be excluded.

Patients will be excluded if they have a contraindication to MRI (e.g. intraocular metal fragments, certain pacemakers, severe claustrophobia).

Patients will be excluded if they have no histopathology available after the MRI e.g. if they are sent for neoadjuvant radiotherapy.

Subject Withdrawal Criteria

Subjects will be withdrawn from the project if they withdraw consent, or if they are unable to undergo resection of their polyp. They will also be withdrawn if they are unable to tolerate the MRI. Patients will be withdrawn if the blinding is compromised e.g. the polyp histopathology is known to the reporting radiologist.

7. Methodology

- Treatment Administration
- Treatment Withdrawal
- Treatment Modification in the Event of Adverse Reaction
  i) A description of the trial treatment(s) to be administered, including the name(s) of all the product(s), the dose(s), the dosing schedule(s), the route/mode(s) of administration, and the treatment period(s), including the follow-up period(s) for subjects for each trial treatment group/arm of the trial.
    N/A
  ii) Other medication(s)/treatment(s) permitted (including rescue medication) and not permitted before and/or during the trial.
    N/A
  iii) Procedures for monitoring subject compliance.
    N/A
  iv) A description of the “stopping rules” or “discontinuation criteria” for individual subjects, parts of trial and entire trial.
    N/A
8. Data Acquisition

Patient details including demographics will be recorded onto paper CRFs at host institutions.

Endoscopy: Participating trusts will be asked to ensure that, in accordance with best practice, endoscopy reports have, at the minimum, a dataset required for >20mm rectal polyps that includes an assessment of the following parameters:

1. Size
2. Position from anal verge
3. Pit pattern & paris morphology
4. Plane of invasion and therefore appropriate excision technique

This will enable an endoscopy CRF to be filled.

This may be facilitated by a dedicated template/proforma reporting tool that augments the proforma example and an example is available earlier in this protocol.

NB a study endoscopy CRF (available in the appendix) completed by the endoscopist at the time of assessment & be acceptable as source data, this can be photocopied and placed in the notes.

CRF proformas will be used to record data from source data produced by reporting endoscopists, radiologists and histopathologists. These CRFs are included in the appendix. For each subject, a separate proforma will be completed. Data will be anonymised using a unique patient identification number. According to Caldecott principles only relevant information will be collected. Patients will only be identifiable by patient number and date of birth. Data recorded on CRFs and will be faxed to a secure
fax number at the host institution & being transported for analysis at the host institution. A secure database for the trial will be housed on a password protected server at the host institution. The database will be built using CRSWeb and maintained by the Research Data management and Statistics Unit (RDSU). Pathology results and treatment data will be recorded on this database which will remain on the RMH NHS network.

9. Data Analysis

   i) Please see Case Report Forms (appendix 1)

The primary outcome measure will be the percentage correct allocation to histopathological group.

The percentage correct MRI allocation to tissue plane will be calculated from the data:

\[
\text{N correct MRI plane allocation} \times 100 = \% \text{ correct MRI plane allocation}
\]

Total N of cases

And also the percentage correct clinical allocation to tissue plane will be calculated from the data:

\[
\text{N of cases clinically allocated correct Plane} \times 100 = \% \text{ correct clinical plane allocation}
\]

Total N of cases

The confidence intervals for the percentage correct allocation to tissue plane will be calculated by the exact method for both clinical and MRI assessment outcome measures.

Secondary outcome measures:

1. The appropriateness of MR directed surgery calculated from the primary radiology assessments
2. The appropriateness of MR directed surgery calculated from the central radiology assessments
3. The appropriateness of ultrasound directed surgery for adenoma / early rectal cancer
4. The calculation of the sensitivity and specificity of MRI in detecting positive nodal metastasis of the primary radiologist in this population The confidence intervals for the sensitivity and specificity will be calculated by the exact method for both clinical and MRI assessment outcome measures.
5. The inter-observer agreement of MR safe excision plane allocation will be analysed by kappa correlation after secondary central radiology assessment
6. 3 year loco-regional recurrence, metastasis and overall survival
7. **Assessment of baseline tumour characteristics will be compared across all imaging and clinical assessment including size, position, morphology, relation to peritoneal reflection.**

8. **Measure the effect of polyp sub-mucosal lifting on the accuracy of MRI reporting sub-stages and inter-observer agreement of MRI reports.**

10. **Study Organisation/ Trial Monitoring and Management Strategy**

    • Responsibilities

    i) Prof Gina Brown will have overall responsibility for the study as the Chief Investigator under the Research Governance Framework Guidelines, Good Clinical Practice.

    ii) Mr James Read will be responsibilities for the following: patients, monitoring study progress, the day-to-day running of the study, data collection, Case Report Forms, consent forms, data analysis at the host institution.

    iii) Gina Brown will have responsibility for data storage and intellectual property.

    iv) There are no interventions requiring risk assessment. Standard MRI safety procedures will be conducted as per Trust guidelines and standard operating procedures.

    v) A clinical trial monitoring committee will perform an interim appraisal of results when half the number have been recruited.

    vi) A website will be created and made available at [www.mistrelstudy.co.uk](http://www.mistrelstudy.co.uk). The site will précis the protocol in a study video embedded in the site and hosted by youtube. The protocol and CRFs will be available for download from an investigator section and a twitter feed will keep the site up to date with study news, recruitment numbers and relevant information. Content will be updated by James Read and approved by Gina Brown. The site will provide public information in a similar fashion to the established CRUK site and clin.gov and will provide a user friendly and appealing interface. It will not act as a recruitment tool for patients.

**TMG:**
The trial management group will be composed of professionals representing the relevant disciplines from around England.

**Radiology**
Gina Brown, Radiology, RMH
Tony Higginson, Radiology, Portsmouth
Svetlana Balyasnikova, Radiology, RMH
Surgery
Paris Tekkis, Surgery, RMH
James Read, Surgery, RMH
Ian Swift, Surgery, Croydon
Greg Wynn, Surgery, Colchester
Chris Cunnigham, Surgery, Oxford

Gastroenterology
Pradeep Bhandari, Gastroenterology, Portsmouth
Parth Paskaran, Gastroenterology, Croydon

Pathology
Dr Neerja Agrawal, Pathology, Portsmouth

The start date of the study will be recruitment of the first patient.

i) Protocol must be submitted for scientific review by the Committee for Clinical Research and for local management R&D approval. The PI/CI will be notified in writing of the CCR/ R&D Approval. The study will then be activated on the Hospital Information System and the PI/CI, trial coordinator(s) will be notified that the study is open for recruitment. This date will be classified as start date for the R&D database.

i. Patient Screening
A screening log will be kept at recruiting sites detailing the numbers not recruited to the trial.

ii. Follow up plan
Local trust follow up protocols will not be altered and no study specific additional follow up is required. A 3 year follow up CRF will be filled to gather outcome data for study participants.

11. Adverse Events

- Adverse Event Definitions

No adverse events or adverse reactions are anticipated from participation in this study.

Any adverse events which occur will be reported in line with the Trust’s Generic SOP for Adverse Events Reporting for Non-CTIMP Trials sponsored and hosted by RMH/ICR (gSOP-08)

ACCIDENT/INCIDENT REPORTING AND INVESTIGATION POLICY INCLUDING SERIOUS UNTOWARD INCIDENTS (482)

12. Statistical Considerations & Sample size

This trial is a binary outcome superiority trial.

The primary research question:
“Is MRI or clinical assessment superior in gauging depth of invasion in 20 to 50mm rectal polyps?”

The null hypothesis:
“There is no difference between the percentage correct allocation of clinical and MRI assessment of rectal lesions.”

In the TEMS registry of 424 cancers of “early rectal cancers” not treated palliatively 161 were incorrectly considered benign and 28 were T3. We can therefore infer the accuracy of clinical allocation to stage will be 55%[5].

Our staging tool is novel and does not precisely follow traditional adenoma, T1, T2, T3 and T4 boundaries. Any power calculation based attempting to quantify traditional assessment is therefore a necessary compromise. This prospective pilot study will gather this valuable preoperative assessment data on an unselected UK population.

Our retrospective pilot data shows a 93% accuracy for MRI allocation to plane[10]. The difference in accuracy will be calculated as a percentage with exact 95% confidence interval. McNemar’s test with two-sided alpha of 0.05 will be performed to test the null hypothesis that there is no difference in accuracy.

The percentage of patients with appropriate MR directed surgery (as defined in section 5 previously) will be calculated with a 95% confidence interval. Likewise the percentage of patients with appropriate MR (central review) directed surgery, and with ultrasound directed surgery, will be calculated with 95% confidence intervals.

Secondary endpoints of sensitivity and specificity of MRI to predict pathological lymph node metastasis and sensitivity and specificity of clinical assessment to predict pathological lymph node metastasis will be calculated as percentage with exact 95% confidence intervals, Agreement between both radiologists for MRI allocation to plane will be calculated as a Kappa coefficient with 95% confidence interval.

Three year loco-regional recurrence and metastasis rates will be calculated (with 95% confidence intervals) from date of initial surgery using Kaplan-Meier methods. Patients without loco-regional recurrence (or metastasis) will be censored at date of last known follow-up or death. Only patients with successful complete resections will be included when calculating loco-regional recurrence rate. Overall survival will be calculated from date of surgery for all patients, with surviving patients censored at date of last known follow-up and death from any cause included as an event. Time to event outcomes will be described for all patients grouped together, no subgroup analysis will be performed.

Baseline tumour characteristics will be compared between all imaging modalities and clinical assessment using descriptive statistics only.

MRI accuracy and inter observer agreement will be reported in the subgroup undergoing submucosal lifting immediately before MRI.

Power calculation:
Each patient who has been assessed clinically, by MRI and by pathology will be classified as accurate or inaccurate on MRI, and accurate or inaccurate clinically (compared to the gold standard of pathology). Assuming that MRI will achieve at least 87% accuracy (a mildly conservative assumption based on 5% less than the previous observation of 93%) and clinical assessment will achieve 55% accuracy, the odds ratio for achieving accuracy on MRI compared to clinically is estimated at 4.6. The percentage of discordant pairs which are rated as correct on MRI is expected to be no less than 78%, corresponding to an overall figure of 58% of pairs discordant (figures illustrated below).

<table>
<thead>
<tr>
<th>Percentage of total patients</th>
<th>Clinical assessment</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>accurate</td>
<td>not accurate</td>
</tr>
<tr>
<td>MRI accurate</td>
<td>0.42</td>
<td>0.45</td>
</tr>
<tr>
<td>not accurate</td>
<td>0.13</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>0.55</td>
<td>0.45</td>
</tr>
</tbody>
</table>

odds ratio 5.48
% discordant 0.58
difference in accuracy 0.32
pr of discordant pairs accurate on MRI 0.78

Using nQuery v7.0, a two-sided McNemars test with alpha=0.05, difference in proportions 0.32 and proportion of discordant pairs 0.58, a total sample size of 53 is needed for 90% power.

We estimate a low drop out rate of less than 5% so expect to recruit 55 patients to the trial. Recruitment will continue until a total of 53 evaluable patients have completed clinical assessment and MRI and have pathology results available.

13. Regulatory & Ethics Committee Approval

- Ethical Considerations

Local R&D approval will be obtained at each site. Ethical approval will be obtained from the Research Ethics Committee before commencing recruitment and the trial carried out in accordance with the Declaration of Helsinki (1996). The study will be conducted in accordance with the conditions of ethical approval.

- Informed Consent

Informed consent will be obtained in accordance with the Trust's Consent to Examination or Treatment Policy (325) available on the RMH intranet.

The study will be conducted in accordance with the Human Tissue Act 2004 and Codes of Practice for consent issued by the Human Tissue Authority.
• Patient Confidentiality

Confidential patient information will be treated in accordance with the Data Protection Act 1998 and also in accordance with the CONFIDENTIALITY CODE OF PRACTICE AND DATA PROTECTION POLICY AND PROCEDURE (277)

14. Data Handling and Record Keeping

The investigator(s)/ institution(s) will permit trial-related monitoring, audits, IRB/IEC review, and regulatory inspection(s), providing direct access to source data/ document.

Quality control and quality assurance.

QC/QA: imaging
Scans will be standardised and reporting criteria will be pre-defined. QA of the scans will be monitored by the investigators. Secondary central reporting of the scans is a secondary outcome measure. Images will be made available to the site either anonymised to study number only and transported via CD or alternatively through the NHS PACS system. Terms for safe transport will be agreed with each individual site in their site agreements.

QC/QA histopathology:
Histopathology assessment will be carried out according to the Royal College of Pathologists guidelines for reporting of colorectal cancers. QA measures including median lymph node count will be recorded. Secondary central review of histopathology will be performed. Tissue and slides will be made available to the central reporter and transported to their site. Terms for safe transport will be agreed with each individual site in their site agreements. Should there be a significant histopathology report amendment (one that affects a primary or secondary outcome) recommended on central review a 3rd independent opinion will be sought and the majority opinion used. The final (amended) histopathology report will be used as the gold standard to calculate endpoints.

QC/QA endoscopy
All sites will be expected to be staffed by JAG accredited endoscopists to ensure a quality standard of endoscopic assessment. Continuing overall site approval status by JAG is desirable but not an absolute necessity.

Patient records relating to the trial will be kept in a locked filing cabinet in a secure office at the Royal Marsden Hospital, including all completed CRFs. Data will be kept in accordance to the Data Protection Policy (102).

Data will be anonymised using unique Patient Identification numbers. No other patient identifiable information will be kept, other than contact details if a patient would like to be informed of the outcome of the study. When being digitised from CRFs all information will be encrypted and password protected, and held on the Royal Marsden Hospital or participating institution trust computers. Where it is necessary to move data between sites, this will only be done on an approved encrypted USB drive.

15. Financing, Indemnity & Insurance
i) Details of financing, indemnity and insurance if not addressed in a separate agreement.

Given there is no specified departure from routine care, specific financing for patient care, indemnity and insurance is not required. A Grant has been applied for to fund co-ordination of the trial.

ii) To state whether there is a collaboration agreement with another Hospital or University.

Other host institutions will be invited to participate and local ethical approval will be sought as required.

Where the Royal Marsden NHS Foundation Trust is either sponsoring or collaborating with externally sponsored research the NHS Litigation Authority will cover standard clinical negligence by employees, staff and health professionals employed by the Royal Marsden NHS Foundation Trust.

There is unlimited liability and no excess. Insurance is provided under the Clinical Negligence Scheme for Trusts and there is no cover for non-negligence claims.

For all notification of claims please contact the Board Secretariat.

Where the Institute of Cancer Research is sponsoring the study there are no special compensation arrangements for this study. The NHS Litigation Authority covers standard clinical negligence of NHS employees, staff and health professionals under its Clinical Negligence Scheme for Trusts.

For multicentre studies each participating site is responsible for ensuring insurance and indemnity arrangements are in place to cover the liability of the Principal Investigator.

16. Publication Policy

i) To state whether all presentations and publications require authorisation from the Principle Investigator or sponsor depending who is responsible for the intellectual property.

ii) To state the processes required in order to review submissions for publication.

Presentations and publications will require authorization from Dr Gina Brown, Chief Investigator. The principle investigator and co-investigators will review submissions for publication.

Refer to the Publications and Conference Presentations and Posters by Nurses and Allied Health Professionals Procedure for Support and Authorisation Trust Policy (30) available on the intranet.

17. Abbreviations
ACPGBI – Association Colo-Proctologists of Great Britain & Ireland
CRF – Case Report Form
CT – Computerised Tomography
ERC - invasive disease confined to the submucosa +/- the muscle of the rectal wall and has not spread to the lymph nodes. I.E. Rectal cancer that is T1 NO or T2 N0 disease in the WHO classification.

GFR – Glomerular Filtration Rate
MM - Millimetre
MRI – Magnetic resonance imaging
MR - Magnetic resonance imaging
MDT – Multi disciplinary team meeting
R&D – Research and development
RMH – Royal Marsden Hospital
SOP – standard operating procedure
US – Ultrasound
USB – Computer Data stick
QC & QA – Quality control and Quality assurance

18. References

List References to literature and data that are relevant to the trial, and that provide background for the trial in the following format:


