The ROYAL MARSDEN
NHS Foundation Trust

Biomedical Research Centre for Cancer
The Royal Marsden NHS Foundation Trust
and The Institute of Cancer Research

Magnetic Resonance Tumour Regression Grade (mrTRG) as a Novel Biomarker to Stratify Management of Good And Poor Responders to Chemoradiotherapy: A Rectal Cancer Multicentre Randomised Control Trial

TRIGGER FEASIBILITY TRIAL

International Sites

Trial Overview and Trial Set-up Steps

NCRN

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TRIGGER Key Contacts
Royal Marsden

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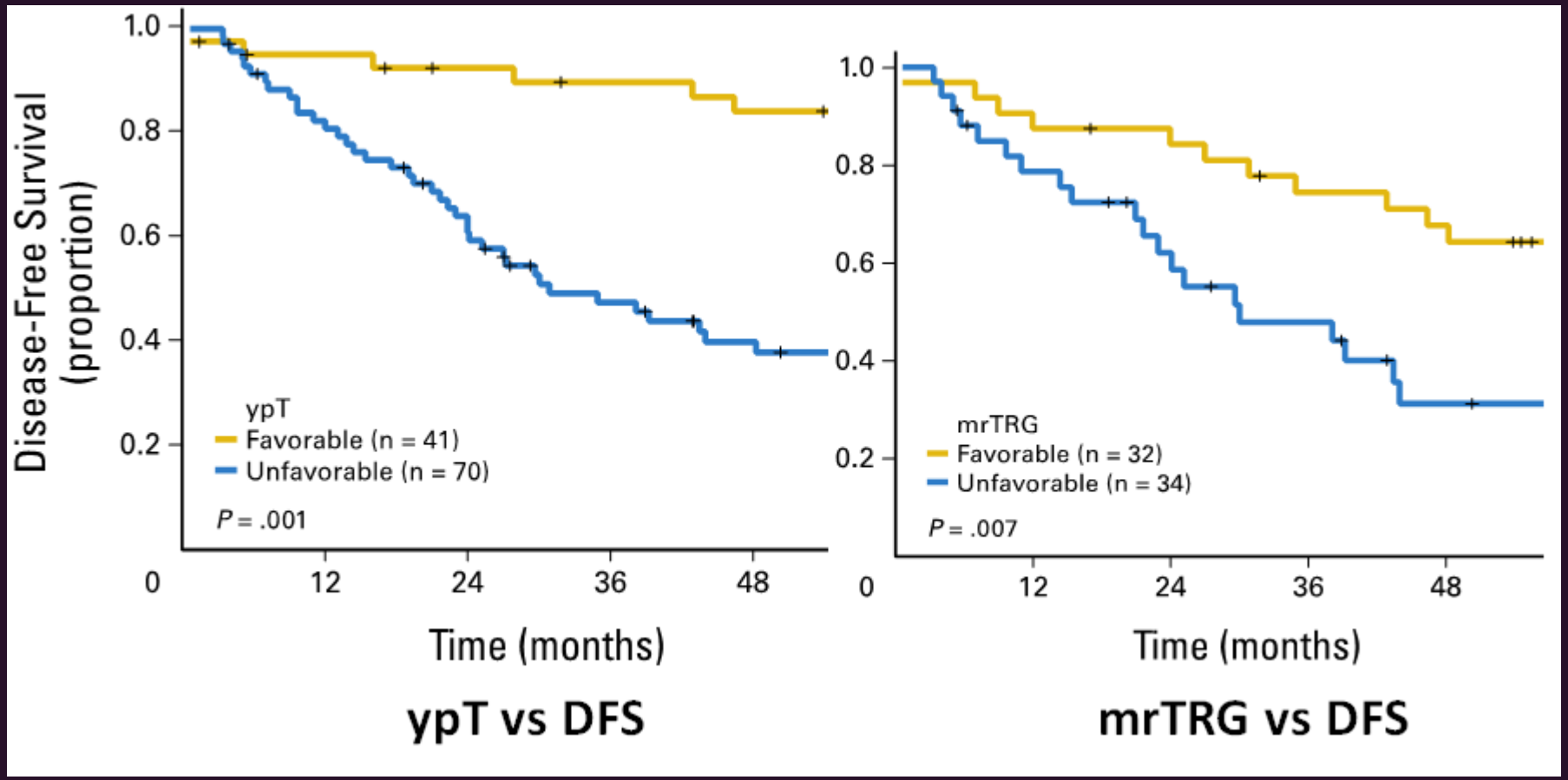
mrTRG as a predictor for DFS

Magnetic Resonance Imaging–Detected Tumor Response for Locally Advanced Rectal Cancer Predicts Survival Outcomes: MERCURY Experience *J Clin Oncol 29:3753-3760*



Study Rationale

- To evaluate mrTRG as an imaging biomarker for the stratified management of patients with locally advanced rectal carcinoma

RATIONALE FOR FEASIBILITY STUDY

- To assess patient recruitment rate
  - Target: 6/month during last 4 months of recruitment

- To assess safety of offering consolidation chemotherapy to ‘poor responders’ and deferral of surgery to ‘good responders’

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Feasibility Trial Endpoints

- Primary: number of patients randomised during last 4 months of recruitment
- Secondary:
  - pCRM rate
  - Toxicity
  - Surgical morbidity (30 days & up to 12 months)
  - Surgical quality
  - mrTRG agreement site vs central review

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Primary endpoint for Phase III: 3-yr disease free survival

Target Recruitment

- Feasibility:
  - ~ 90 patients
  - ≥ 6 randomised patients/month
- Phase III:
  - 633 patients
  - 3 year recruitment period

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Inclusion Criteria

- Biopsy-confirmed adenocarcinoma 0-15cm from the anal verge (on MRI or rigid sigmoidoscopy)
- Locally Advanced Rectal Carcinoma diagnosed by MRI (mrCRM unsafe or ≥mrT3c [>5mm beyond muscularis propria] or mrEMVI positive disease)
- Be deemed to require chemoradiotherapy
- Scheduled to receive 45Gy - 55Gy long course radiotherapy
- Be aged 18 years or over

Exclusion Criteria

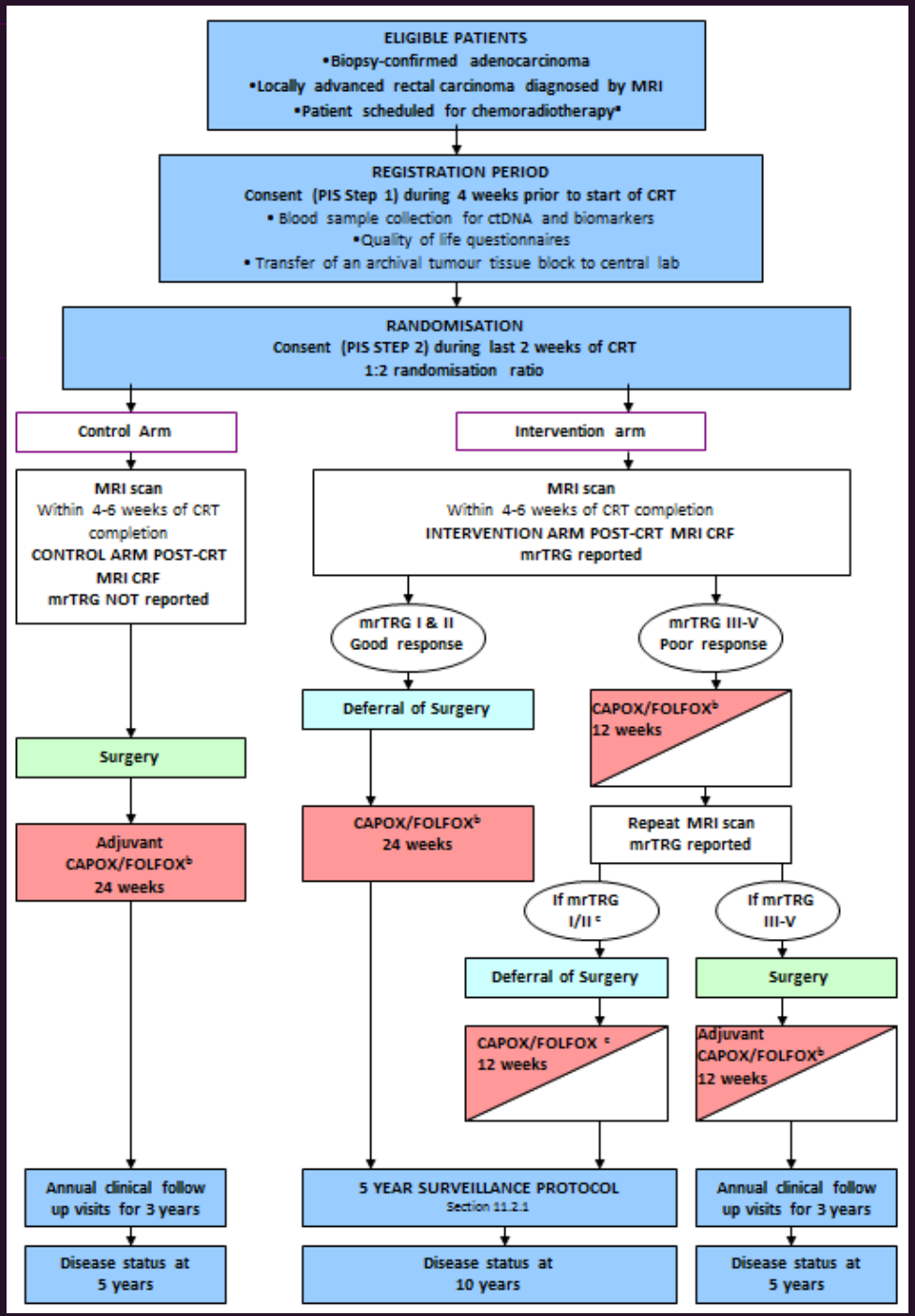
- Metastatic disease, including resectable liver metastases
- MRI contraindicated
- Scheduled to receive < 45Gy or > 55Gy long course radiotherapy
- CRT contraindicated
- Hypersensitivity or contraindication to the drug(s) associated with the planned choice of systemic chemotherapy as stated in the SmPC for each of the drugs.

Exclusion Criteria cont.

- Are receiving or planned to receive treatment outside of that stipulated by the protocol e.g. alternative cytotoxic or investigational drug
- Are pregnant, breastfeeding or unable / unwilling to comply with pregnancy prevention guidelines*
- Any other malignant disease within the preceding 5 years with the exception of non- melanomatous skin cancer, carcinoma in situ and early stage disease with <5% recurrence risk

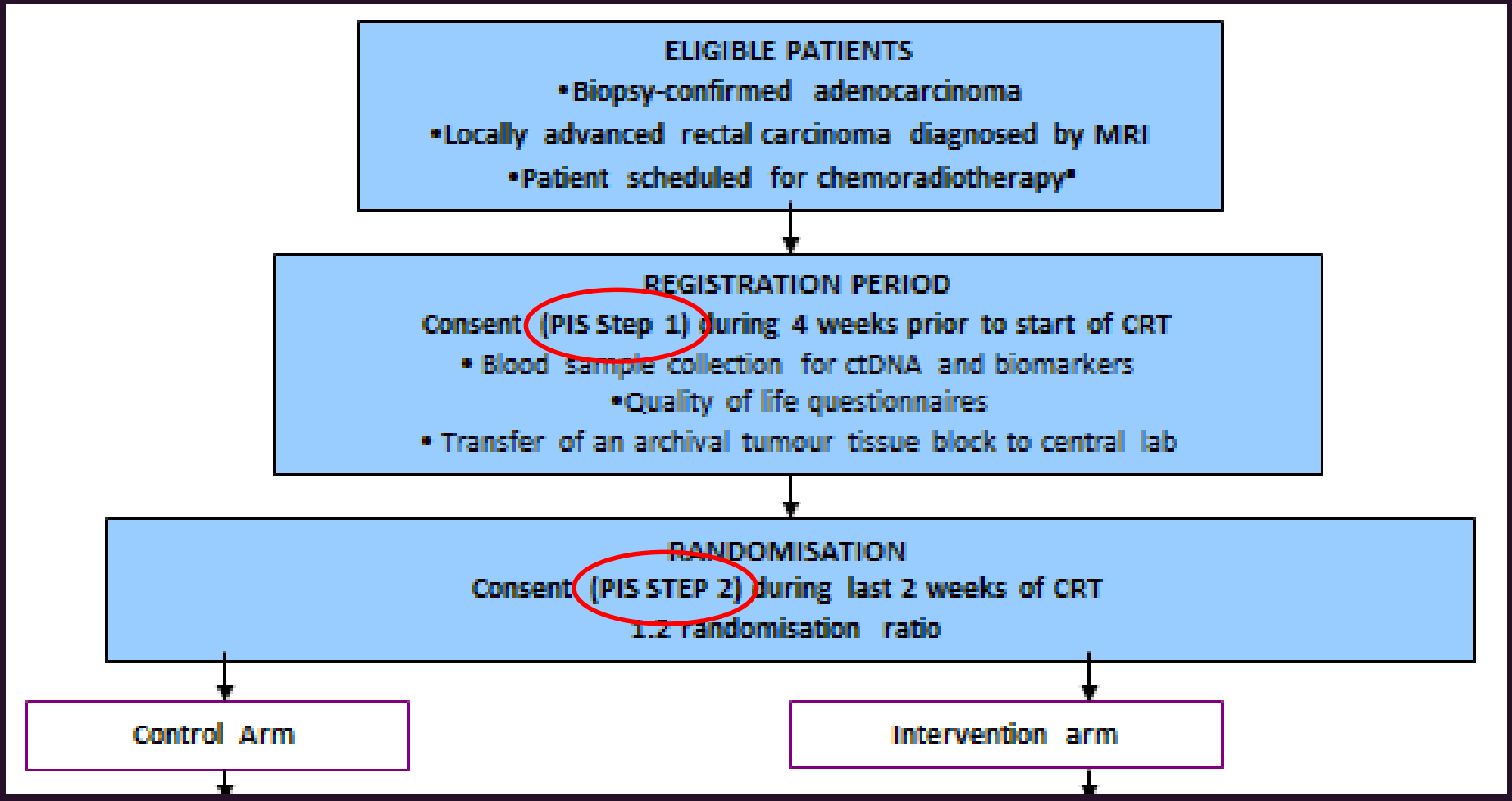
* Females of childbearing potential and males must be willing to use a highly effective (failure rate < 1% year) method of contraception.

  - PIS 2 – contraception use during and 12 month after last dose of chemotherapy

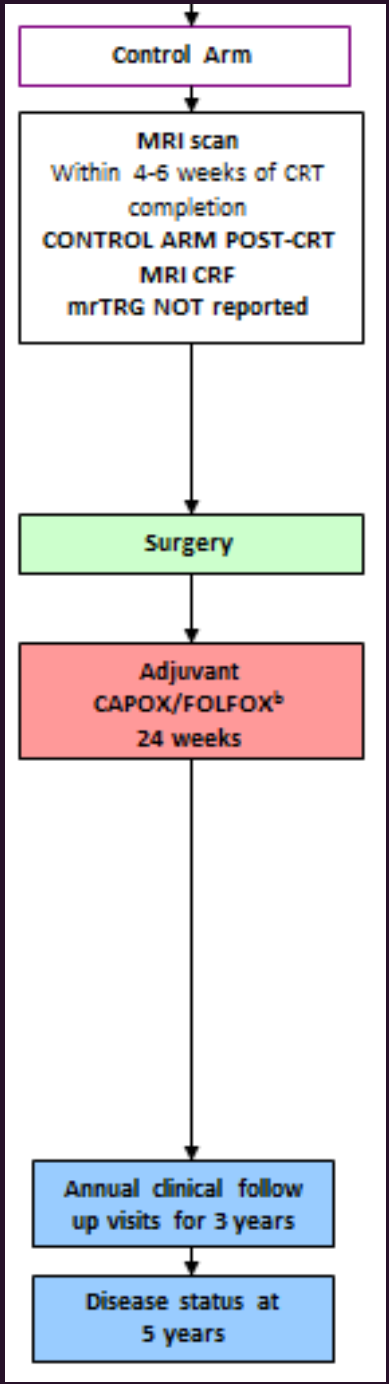


Trial Flowchart

Registration & Randomisation

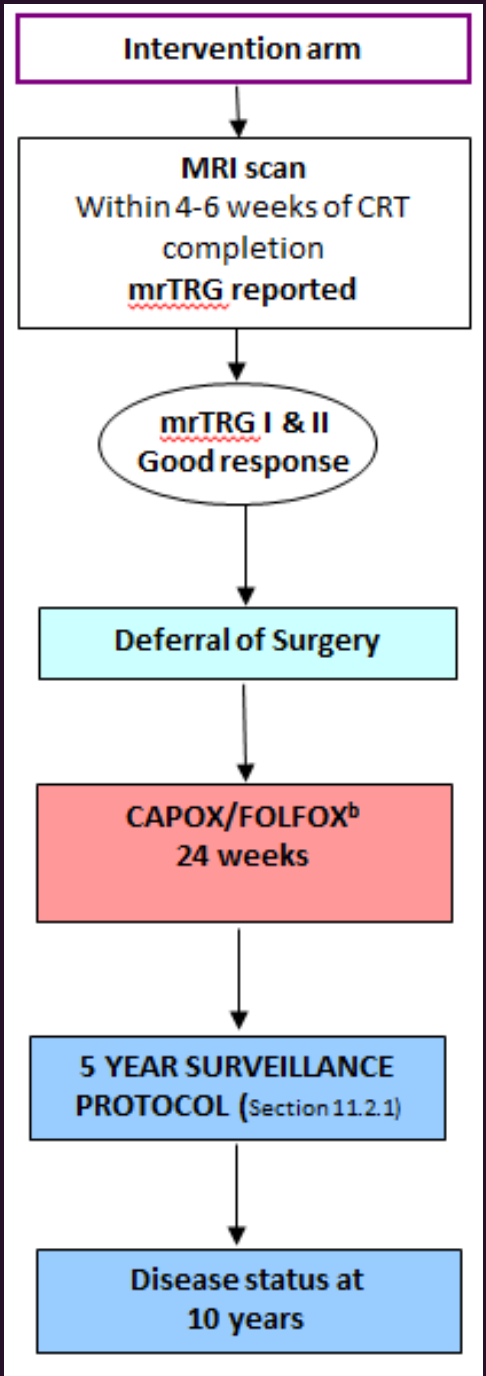


Stratification variables: recruiting site, mrEMVI grade, tumour height, planned choice of systemic chemotherapy



Patient Pathway Control Arm

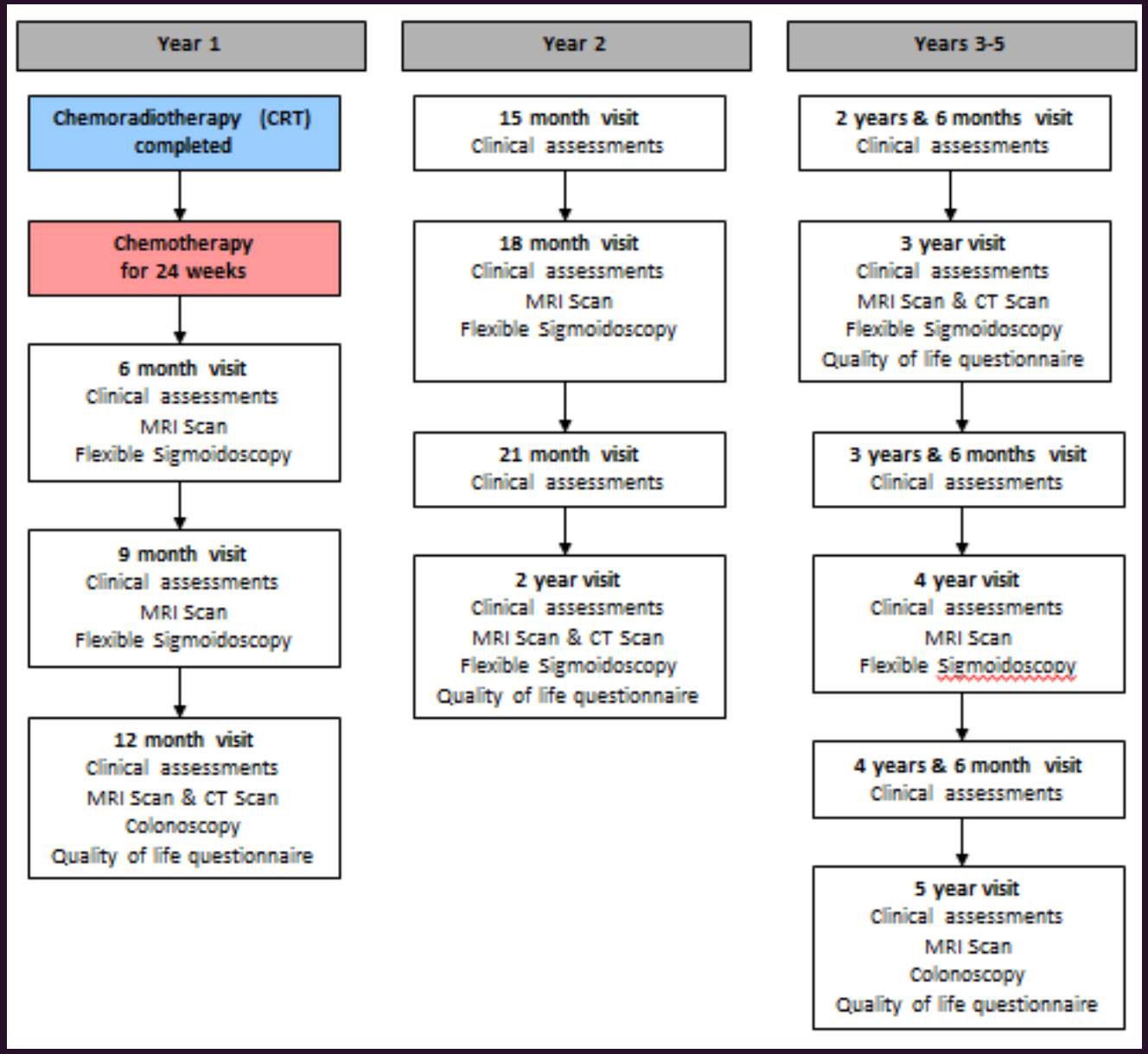
- Post-CRT MRI within 4-6 weeks (no later than 10) from CRT completion
  - mrTRG not reported
- Surgery within 6-12 weeks from CRT completion:
  - Surgical Morbidity: 6 weeks post surgery and 12 months
- Chemotherapy 24 weeks:
  - Toxicity: end of each cycle and residual toxicity at 12 months
- Annual follow up for 3 years
- QoL: Registration, 12 months, 36-months



Intervention Arm – mrTRG I/II Good Responders

- Post-CRT MRI within 4-6 weeks (no later than 10) from CRT completion.
- mrTRG I/II
- 24 weeks of chemotherapy to commence within 12 weeks of CRT:
  - Toxicity: end of each cycle and residual toxicity at 12 months
- 5 year Surveillance Schedule
- Suspected Regrowth Pathway
- QoL: Registration, 12, 36 and 60 months

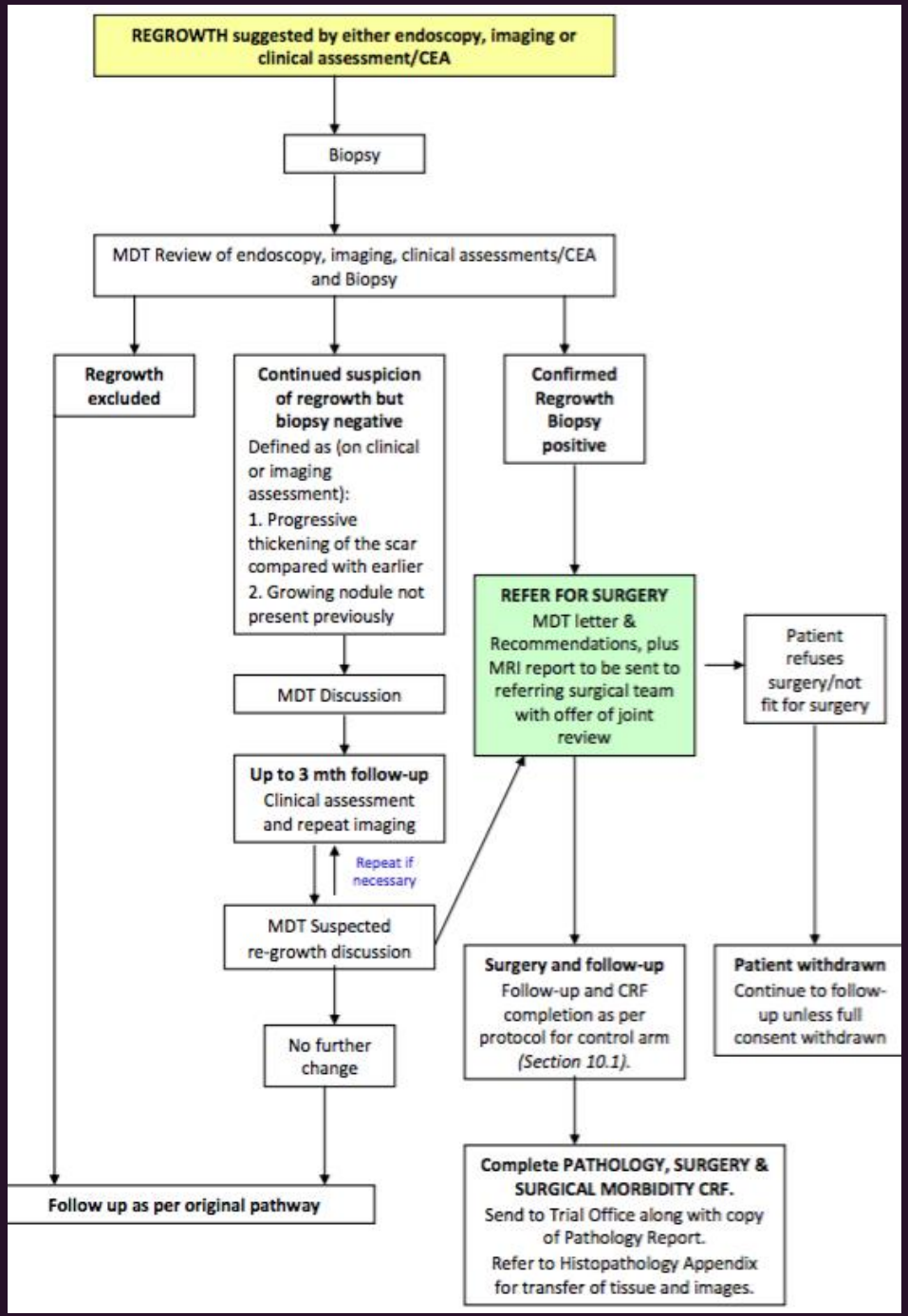
5 year Surveillance Schedule



MRI
Year 1:
6, 9, 12 mths
Years 2 & 3:
6 monthly
Years 4 & 5:
annually

CT
12, 24 & 36 months

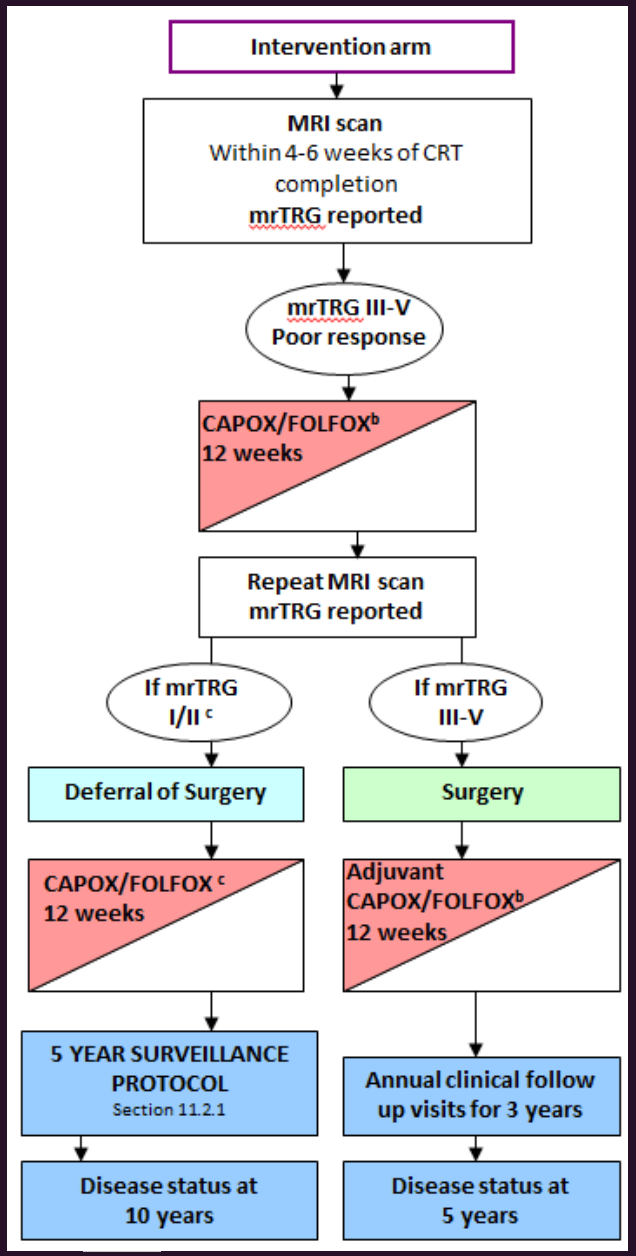
Endoscopy
Year 1:
6, 9, 12 mths
Year 2:
6 monthly
Years 3-5
annually



Suspected Regrowth Pathway

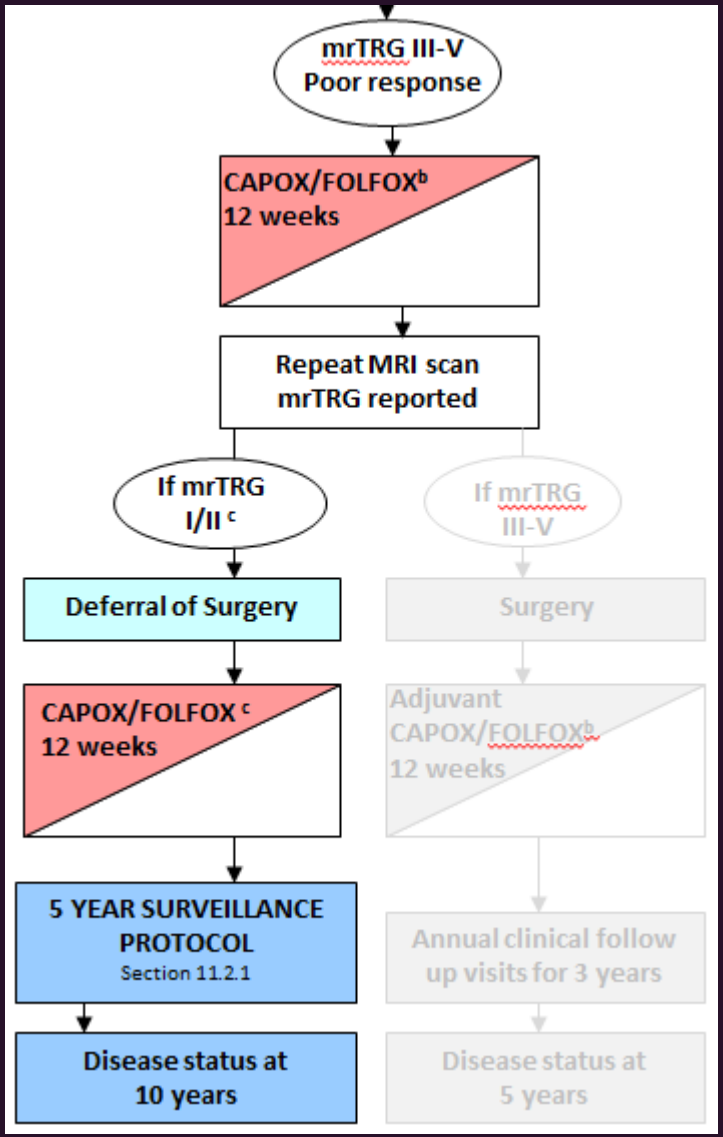
Protocol Section 8.2.3

Intervention Arm – mrTRG III-V Poor Responders



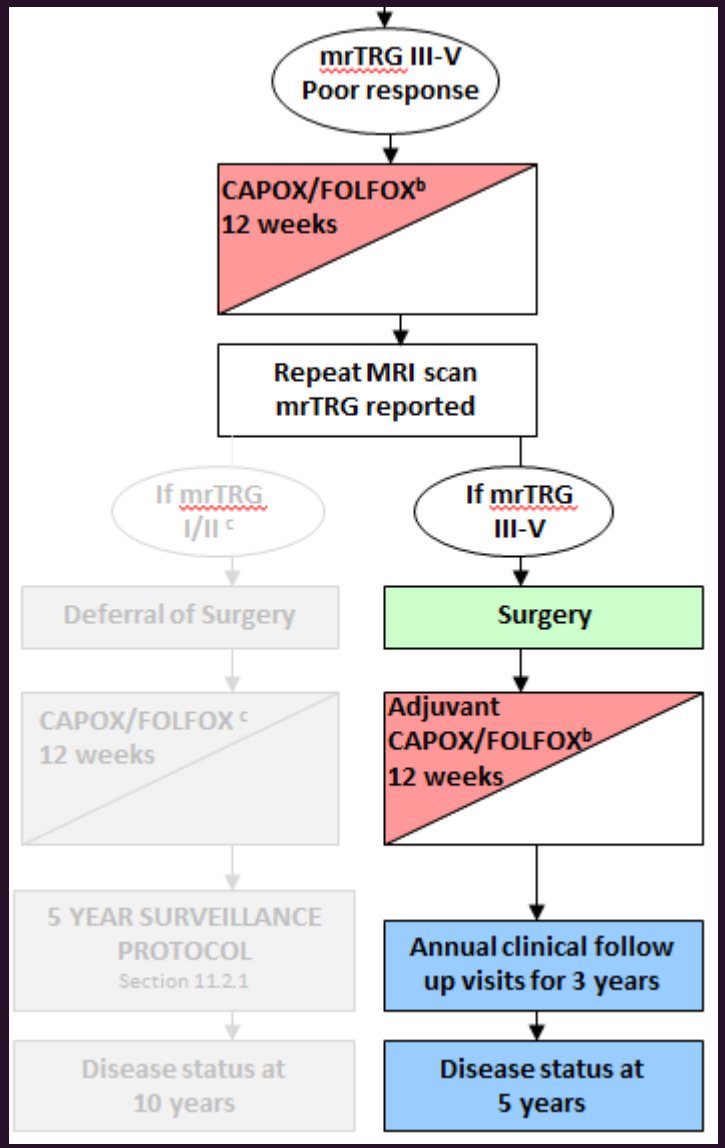
- Post-CRT MRI within 4-6 weeks (no later than 10) from CRT completion
  - mrTRG reported
- **12** weeks of chemotherapy to commence within 12 weeks of CRT:
  - Toxicity: end of each treatment cycle
- REPEAT MRI

Intervention Arm
mrTRG III-V to mrTRG I/II



- Remaining 12 weeks of chemotherapy:
  - Toxicity: end of each treatment cycle and residual toxicity at 12 months
- 5 year Surveillance Schedule
- Suspected Regrowth Pathway
- QoL: Registration, 12, 36 and 60 months

Intervention Arm
Remain mrTRG III-V



- Surgery within 6-12 weeks of completion of pre-op chemotherapy:
  - Surgical Morbidity: 6 weeks post surgery and 12 months
- Remaining 12 weeks of chemotherapy:
  - Toxicity: end of each treatment cycle and residual toxicity at 12 months
- QoL: Registration, 12, 36 months

Please refer to assessment schedules in protocol

INTERVENTION ARM POOR RESONDERS		REGISTRATION PERIOD	INTERVENTION PHASE								ANNUAL FOLLOW-UP			DISEASE STATUS
VISIT TYPE	Prior to patient entry	Registration	Randomisation (BASELINE)	Post CRT	MDT	Chemo-therapy for 12 weeks	MDT	Surgery	Surgical follow up	Adjuvant Chemotherapy for 12 weeks	12	24	36	60
TIMELINES		≤ 4 weeks prior to CRT	During last 2 weeks of CRT	4-6 weeks post CRT		≤ 12 weeks post CRT. Toxicity assessed at end of each cycle	A further MRI scan should be performed 4-6 weeks from end of chemotherapy. If mrTRG now I or II the option of deferral of surgery should be discussed. If patients defers surgery patients should receive the remaining 12 weeks of chemotherapy and follow surveillance schedule in section 11.2.1 and assess disease status at 10 years (as for good response sub-group). If surgery performed follow-up according to this table.	6-12 weeks after pre-op chemo	6 weeks post surgery	Toxicity assessed at end of each cycle during chemotherapy	Months from end of CRT			
Informed consent [a]		X	X											
Check eligibility criteria		X	X											
Diagnosis & Clinical Assessment		X												
Randomisation			X											
Quality of life		X									X		X	
Chemoradiotherapy			X											
Blood sample [b]		X		X		X			X	X	X	X	X	
Baseline MRI	X													
Restaging MRI [c]				X		X[h]								
Surgery								X						
Surgical Morbidity [d]									X		X			
Pathology [e]									X					
Chemotherapy [f]						X end of each cycle				X end of each cycle				
Toxicity Assessment						X end of each cycle				X end of each cycle	X			
Annual follow-up											X	X	X	X
Adverse events [g]				X		X end of each cycle				X end of each cycle				
Concurrent medications		X	X	X		X end of each cycle		X	X	X end of each cycle	X			

Withdrawal criteria and Discontinuation of trial treatment

- Patient withdrawal
  - Post CRT MRI > 10 weeks from completion CRT
  - Failure to comply with deferral of surgery surveillance schedule

- Patient may discontinue trial treatment but remain in follow-up

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Translational Sub-study

Patients	All patients		For patients who undergo surgery						For patients who defer surgery only [5]									All patients
Visit/Event	Registration	Post CRT	Surgery	Surgical follow-up		Follow up months end of CRT			Follow up months from end of CRT									Relapse
Timelines	≤ 4 weeks prior to CRT	4-6 weeks post CRT	Time of surgery	4-8 weeks post surgery	3-months post surgery[4]	12	24	36	6	9	12	18	24	30	36	48	60	≤ 2 weeks of relapse
Archival diagnostic tumour tissue[1]	X																	
Surgical specimen[2]			X															
Circulating tumour DNA[3]	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Blood collection for ctDNA – optional for international sites.

Summarised in Section 10.4 & Appendix 7 of Protocol
TRIGGER Lab Manual
Tissue and blood stored centrally at Royal Marsden

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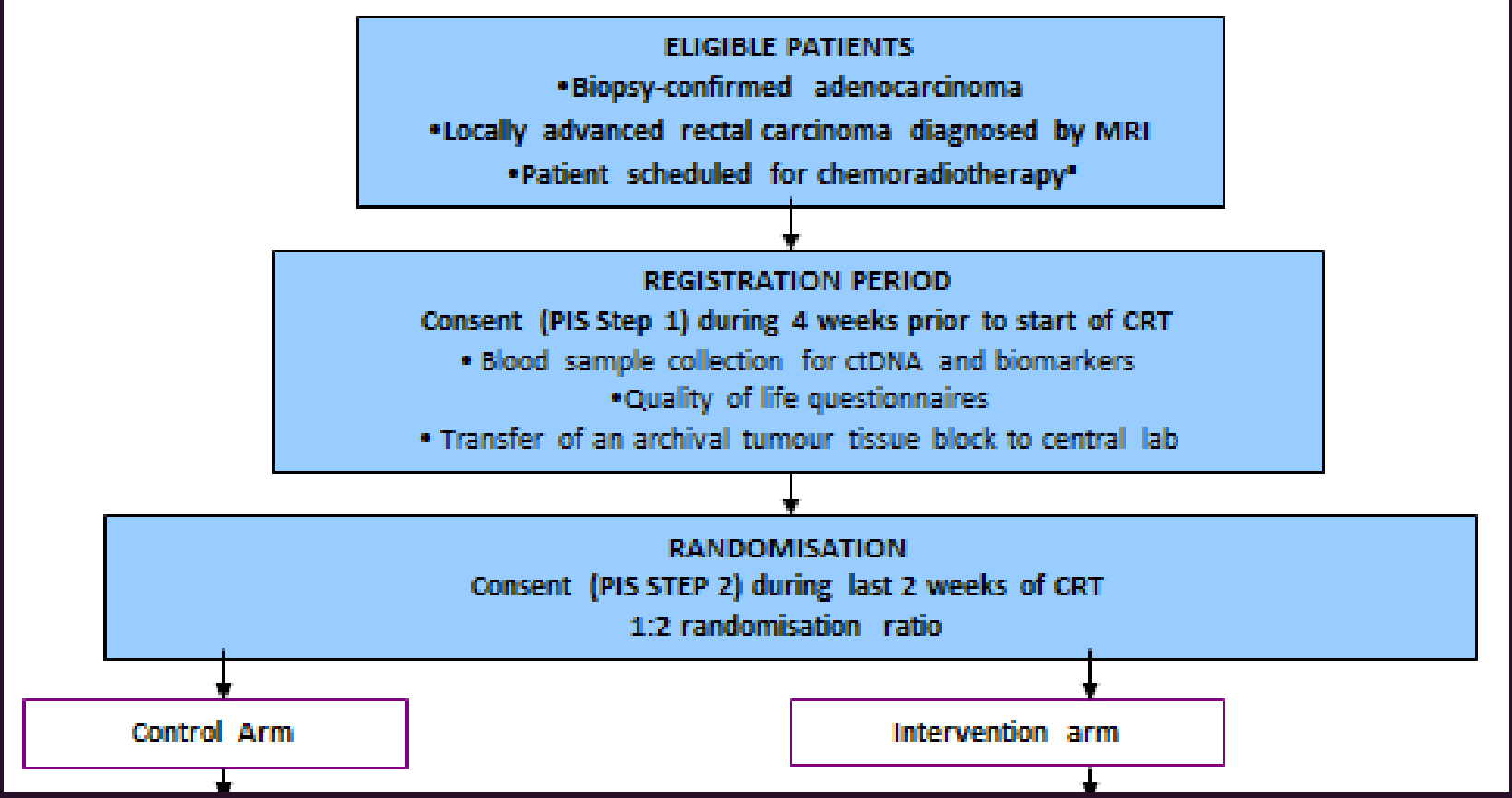
Registration & Randomisation



- Informed consent by medically-qualified investigator at both registration and randomisation
- Registration logistics: radiotherapy & chemotherapy new patient clinics, radiotherapy planning

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MRI Imaging & Reporting

- TRIGGER Imaging Manual:
  - Section 3.2.2 – scan acquisition parameters
- 0.6 x 0.6 x 3mm high resolution images:
  - $1mm^3$ voxel size
- MRI Proforma based reporting
  - Baseline & Post-treatment
  - Copy of report required at baseline to confirm patient eligibility

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Central Review of MRI Scans

Retrospective as batches to examine agreement for mrTRG

Local MRI report inc. mrTRG used by site for patient management and entered on trial database

Histopathology

- Protocol Appendix 5 & Laboratory Manual
- Attach histopathology evaluation summary & CRF to pathology request form
- Photography prior to dissection
- Macroscopic specimen dissection
- Cross-sectional slicing and photography
- Specimen sampling
- Microscopic reporting
- Pathology CRF
    - Correlating tissue with MRI: block and slice number

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IMPs
Systemic chemotherapy

- Treatment choice made upfront prior to trial registration
  - CAPOX (8 cycles)
  - FOLFOX (12 cycles)
  - Or single agent capecitabine or 5-FU (if oxaliplatin contraindicated)

Potential issue: treatment choice may not be made at time of MDT at some sites. Should be recorded in source notes.

- Toxicity assessed end of each cycle and residual toxicity assessed at 12 months (CTCAE v4.0)

- IMPs provided, prepared and administered at sites according to local guidelines (Pharmacy Pack)

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Reference Safety Information
IMP Expectedness Assessment

Drug	Brand	SmPC Date
Capecitabine 150mg film coated tablet	Accord	16 June 2015
Capecitabine 500mg Film coated tablet	Accord	19 June 2015
Fluorouracil 25mg/ml Injection	Hospira UK	24 Sep 2014
Fluorouracil 50mg/ml Injection	Hospira UK	24 Sep 2014
Oxaliplatin 5mg/ml Concentrate for Solution for Infusion	Hospira UK	17 Aug 2015
Calcium folinate 10mg/ml Injection	Hospira UK	31 Oct 2011

- Section 4.8 of SmPCs

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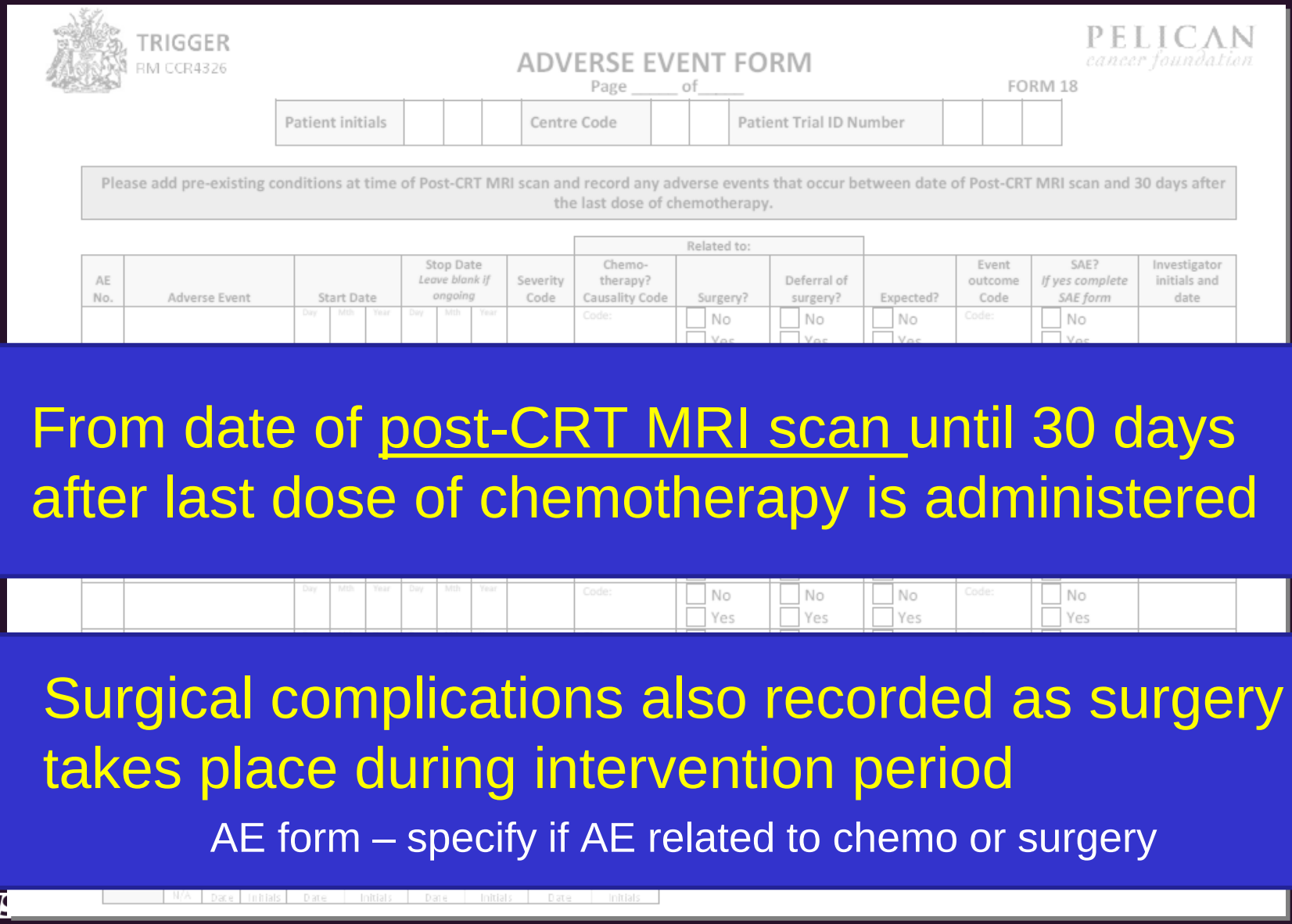
AE Reporting



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ADVERSE EVENT FORM

Page _____ of _____

FORM 18

Patient initials				Centre Code			Patient Trial ID Number			

Please add pre-existing conditions at time of Post-CRT MRI scan and record any adverse events that occur between date of Post-CRT MRI scan and 30 days after the last dose of chemotherapy.

						Related to:						
AE No.	Adverse Event	Start Date	Stop Date *Leave blank if ongoing*	Severity Code	Chemo-therapy? Causality Code	Surgery?	Deferral of surgery?	Expected?	Event outcome Code	SAE? *If yes complete SAE form*	Investigator initials and date
		Day Mth Year	Day Mth Year		Code:	No Yes	No Yes	No Yes	Code:	No Yes	
		Day Mth Year	Day Mth Year		Code:	No Yes	No Yes	No Yes	Code:	No Yes	

From date of post-CRT MRI scan until 30 days after last dose of chemotherapy is administered

Surgical complications also recorded as surgery takes place during intervention period

AE form – specify if AE related to chemo or surgery

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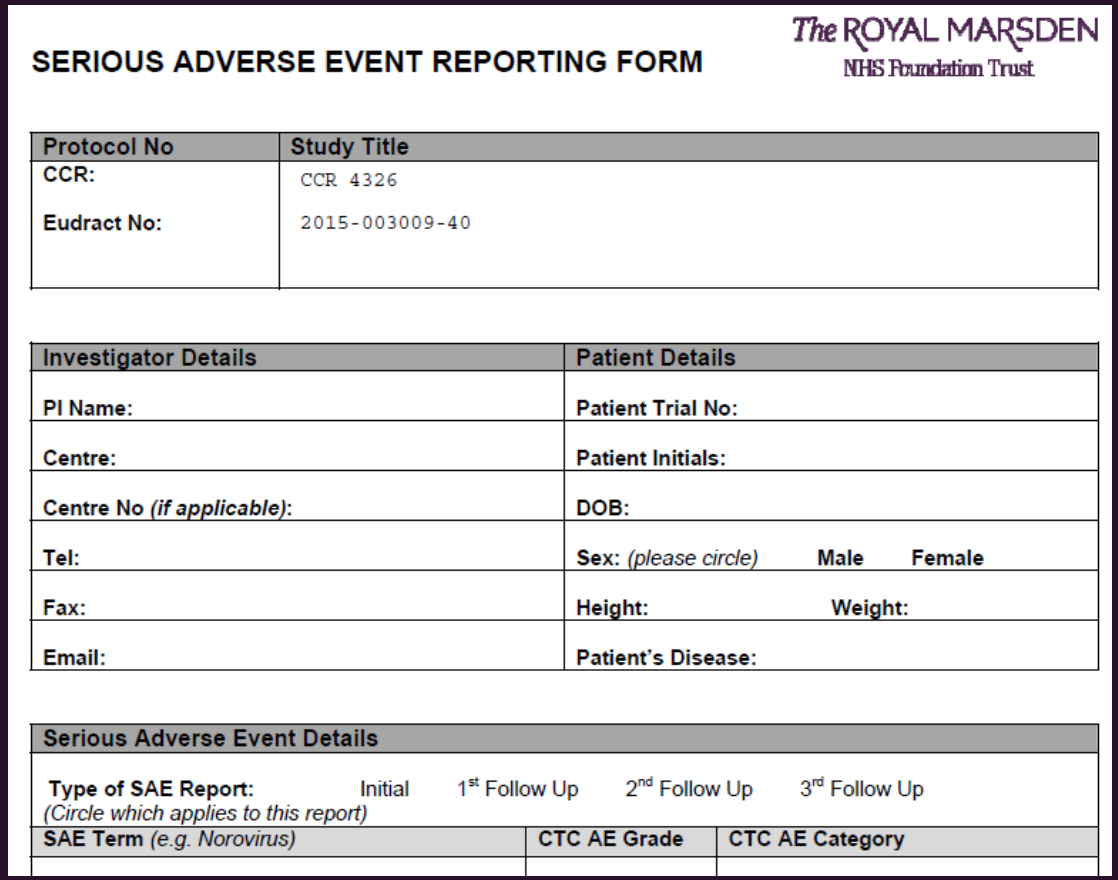
SAE Reporting



SERIOUS ADVERSE EVENT REPORTING FORM

The ROYAL MARSDEN NHS Foundation Trust

Protocol No	Study Title
CCR:	CCR 4326
Eudract No:	2015-003009-40

Investigator Details	Patient Details
PI Name:	Patient Trial No:
Centre:	Patient Initials:
Centre No *(if applicable)*:	DOB:
Tel:	Sex: *(please circle)* Male Female
Fax:	Height: Weight:
Email:	Patient's Disease:

Serious Adverse Event Details

Type of SAE Report: Initial 1st Follow Up 2nd Follow Up 3rd Follow Up
(Circle which applies to this report)

SAE Term *(e.g. Norovirus)*	CTC AE Grade	CTC AE Category

SAE / SAR?

↓

Complete SAE Reporting Form

↓

PI or delegate: Causality and expectedness assessment

↓

Send form within 24 hrs of knowledge of SAE/SAR

↓

RM CTU
SAE Fax Number
+44 208 915 6762

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Exemptions from SAE reporting

- Any event that occurs after 30 days post last dose of chemo (except pCRM involvement)
- Elective hospitalisation and surgery for treatment of locally advanced rectal carcinoma or its complication
- Elective hospitalisation to simplify treatment or procedures
- Disease progression leading to hospitalisation, prolongation of hospitalisation, or death as a result of disease progression

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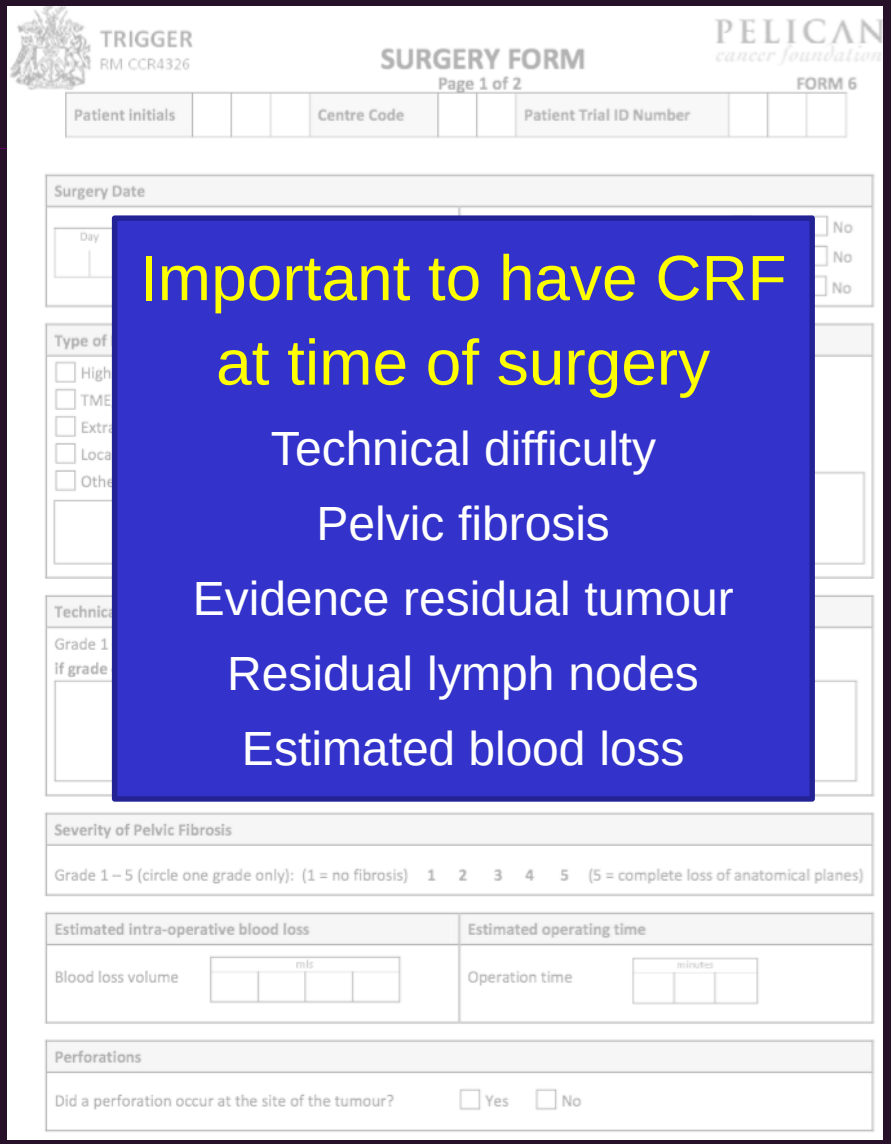
The Royal Marsden

Case Report Form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RM CCR4326

SURGERY FORM
Page 1 of 2

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FORM 6

Patient initials | Centre Code | Patient Trial ID Number

Surgery Date

Day

Type of

Technic

Grade 1

if grade

Severity of Pelvic Fibrosis

Grade 1 – 5 (circle one grade only): (1 = no fibrosis) 1 2 3 4 5 (5 = complete loss of anatomical planes)

Estimated intra-operative blood loss

Blood loss volume

mls

Estimated operating time

Operation time

minutes

Perforations

Did a perforation occur at the site of the tumour? Yes No

Important to have CRF at time of surgery

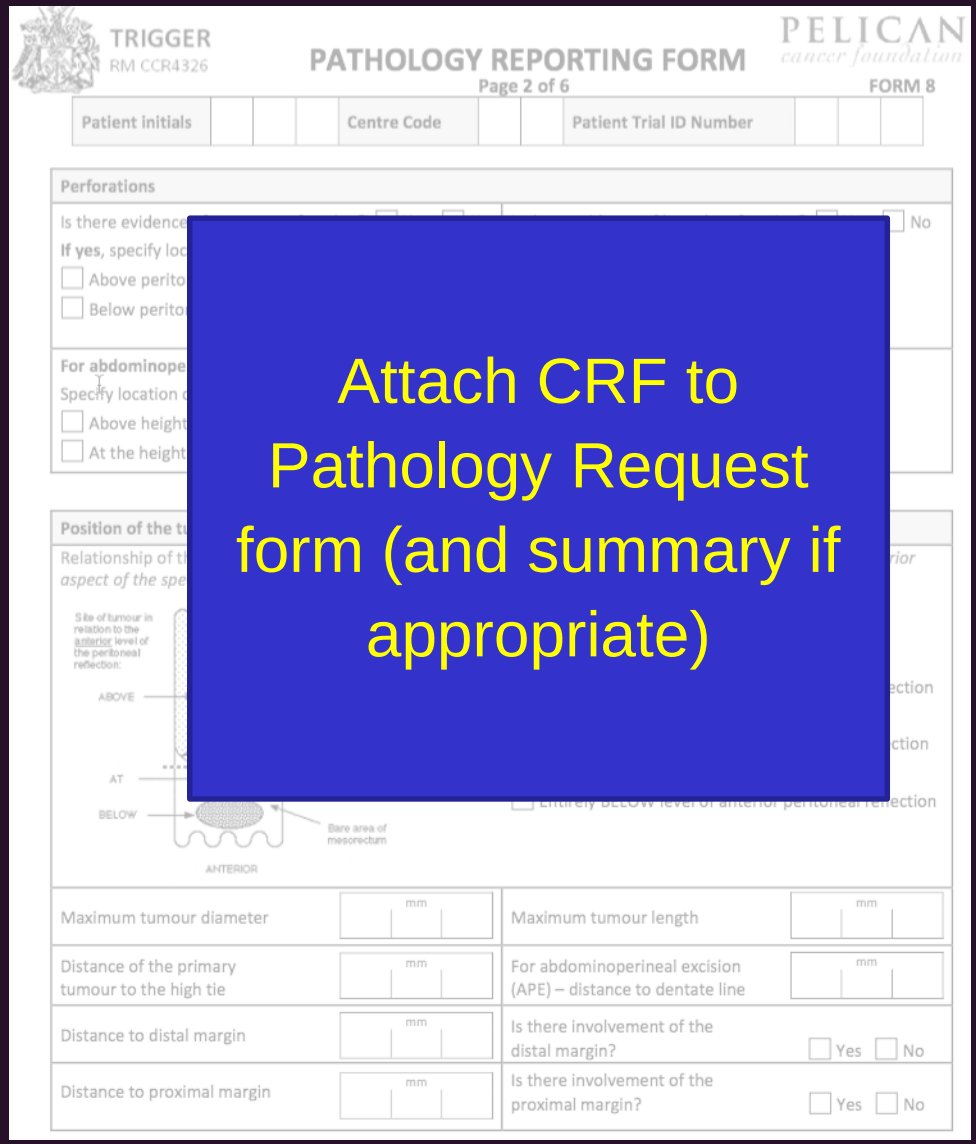
Technical difficulty

Pelvic fibrosis

Evidence residual tumour

Residual lymph nodes

Estimated blood loss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PATHOLOGY REPORTING FORM
Page 2 of 6

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FORM 8

Patient initials | Centre Code | Patient Trial ID Number

Perforations

Is there evidence

If yes, specify loc

Above perito

Below perito

For abdominope

Specify location

Above height

At the height

Position of the tu

Relationship of t

aspect of the spe

Site of tumour in relation to the anterior level of the peritoneal reflection:

ABOVE

AT

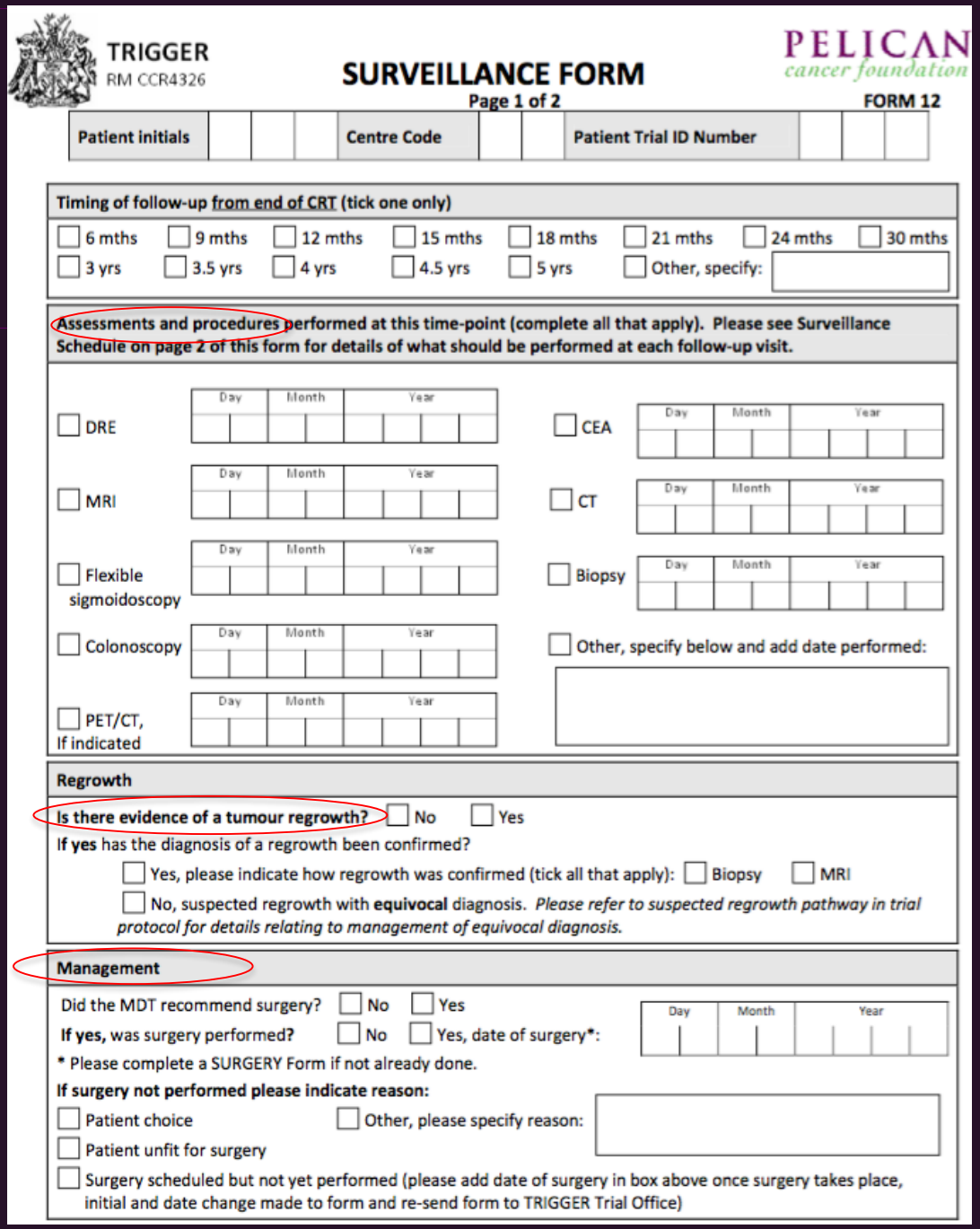
BELOW

Bare area of mesorectum

ANTERIOR

Maximum tumour diameter	mm	Maximum tumour length	mm
Distance of the primary tumour to the high tie	mm	For abdominoperineal excision (APE) – distance to dentate line	mm
Distance to distal margin	mm	Is there involvement of the distal margin?	Yes No
Distance to proximal margin	mm	Is there involvement of the proximal margin?	Yes No

Attach CRF to Pathology Request form (and summary if appropriate)



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SURVEILLANCE FORM
Page 1 of 2

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FORM 12

Patient initials		Centre Code		Patient Trial ID Number	

Timing of follow-up from end of CRT (tick one only)

☐ 6 mths ☐ 9 mths ☐ 12 mths ☐ 15 mths ☐ 18 mths ☐ 21 mths ☐ 24 mths ☐ 30 mths
☐ 3 yrs ☐ 3.5 yrs ☐ 4 yrs ☐ 4.5 yrs ☐ 5 yrs ☐ Other, specify:

Assessments and procedures performed at this time-point (complete all that apply). Please see Surveillance Schedule on page 2 of this form for details of what should be performed at each follow-up visit.

☐ DRE — Day / Month / Year
☐ MRI — Day / Month / Year
☐ Flexible sigmoidoscopy — Day / Month / Year
☐ Colonoscopy — Day / Month / Year
☐ PET/CT, If indicated — Day / Month / Year
☐ CEA — Day / Month / Year
☐ CT — Day / Month / Year
☐ Biopsy — Day / Month / Year
☐ Other, specify below and add date performed:

Regrowth

Is there evidence of a tumour regrowth? ☐ No ☐ Yes

If yes has the diagnosis of a regrowth been confirmed?

☐ Yes, please indicate how regrowth was confirmed (tick all that apply): ☐ Biopsy ☐ MRI

☐ No, suspected regrowth with **equivocal** diagnosis. *Please refer to suspected regrowth pathway in trial protocol for details relating to management of equivocal diagnosis.*

Management

Did the MDT recommend surgery? ☐ No ☐ Yes

If yes, was surgery performed? ☐ No ☐ Yes, date of surgery*: Day / Month / Year

* Please complete a SURGERY Form if not already done.

If surgery not performed please indicate reason:

☐ Patient choice ☐ Other, please specify reason:
☐ Patient unfit for surgery
☐ Surgery scheduled but not yet performed (please add date of surgery in box above once surgery takes place, initial and date change made to form and re-send form to TRIGGER Trial Office)

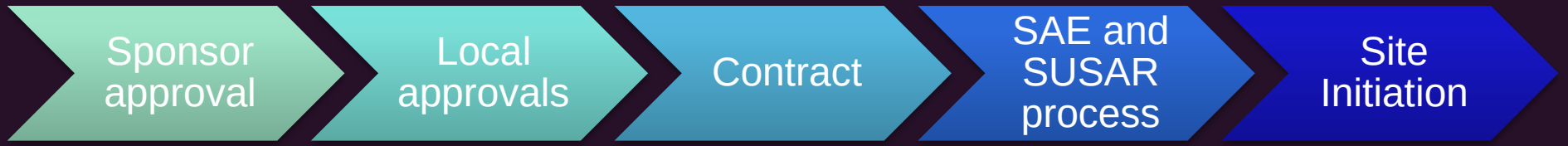
Surveillance CRF

- Assessments and procedures at each follow-up visit
- Regrowth
  - Suspected regrowth
- Patient management

Monitoring

- Central monitoring
  - Delegation log
  - Patient eligibility
  - Patient consent forms
  - Screening, Registration & Randomisation Logs
  - CRF review and data clarification queries
- Self-assessment monitoring
  - Form completed every 3-6 months
  - Limited to check of version of trial docs in use and filed in ISF, and SAEs
- Non-compliance (for cause) on-site monitoring

Set-up steps for TRIGGER International sites



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First step

- Review protocol and return site feasibility questionnaire
- No further action required by site at this stage
- Approval takes 2-3 weeks

Sponsor approval | **Local approvals** | Contract | SAE and SUSAR process | Site Initiation

Clinical Trial Liability Insurance

- Appropriate insurance required at site to cover clinical negligence
- Copy of relevant insurance certificate and letter of indemnity to CI/Royal Marsden

Ethics Committee approval

- Translation of patient information sheet, consent forms, trial flyer (optional), LARs questionnaire
- Copy of ethics approval to CI/Royal Marsden

Regulatory approval

- TRIGGER is classified as a drug trial (CTIMP)
- Requires approval from drug regulatory authority (MHRA in UK)
- Copy of approval to CI/Royal Marsden

International Site Agreement

- Includes delegated responsibilities
  - e.g. obtain ethics approval, report SAEs to sponsor
- Material transfer agreement included as annex
- Signed by PI, International site representative, Royal Marsden

SAE and SUSAR Reporting Process

- Assessment of causality and expectedness for SAE/SARs
- Report SAEs to sponsor
- Follow-up of SAEs until their conclusion
- Report SUSARs to Ethics Committee and national regulatory authority
- Submit annual reports to Ethics Committee and regulatory authority

Sponsor approval → Local approvals → Contract → SAE and SUSAR process → Site Initiation

Final steps prior to patient recruitment

- Confirmation of successful completion of mrTRG assessment by nominated Radiologist
- Site Initiation Visit
  - Webinar or TC
- ‘Green light’ letter from CI at Royal Marsden

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NHS Foundation Trust

Thank you

Biomedical Research Centre for Cancer
The Royal Marsden NHS Foundation Trust
and The Institute of Cancer Research

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