CHEMORADIOTHERAPY FOR RECTAL CANCER IN THE DISTAL RECTUM FOLLOWED BY ORGAN-SPARING TRANSANAL ENDOSCOPIC MICROSURGERY

CARTS study

CApecitabine, Radiotherapy and Tem Surgery

A PHASE II, FEASIBILITY TRIAL

http://www.cartsstudie.nl/

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STUDY SUMMARY

TITLE	Chemoradiotherapy for rectal cancer in the distal rectum followed by organ-sparing transanal endoscopic microsurgery **CARTS study**
INVESTIGATOR / TRIAL LOCATION	Multicenter study coordinated from Radboud University Nijmegen Medical Centre
STUDY DESIGN	Feasibility study
STUDY POPULATION • Main selection criteria: • Main exclusion criteria:	• T1-3 N0 M0 distal rectal tumour (below 10 cm), based on diagnostic imaging • Grade 1-2 T1N0M0 tumors • Faecal incontinence • Prior radiotherapy on the pelvis • Regional or distant metastases
STUDY OBJECTIVE(S) • Primary endpoint: • Secondary endpoints	• The number of patients with ypT0,1R0 after TEM surgery • Quality of life • Locoregional recurrence
DOSE AND TREATMENT REGIMEN	• <u>Radiotherapy</u> A dose of 50Gy, on the pelvic region, in 25 fractions of 2 Gy, 5 days a week. • <u>Capecitabine</u>: 825 mg/m² orally, b.i.d., 7 days a week (estimated creatinin clearance >50 ml/min). • <u>Surgery</u> Transanal Endoscopic Microsurgery or Total Mesorectal Excision will be performed 8 weeks after the end of the preoperative treatment.
EVALUATION CRITERIA	• Histopathological assessment of the rectal specimen • Toxicity and postoperative complications

STATISTICAL CONSIDERATIONS	This study is a feasibility trial to determine whether radiotherapy combined with capecitabine can be followed by TEM surgery. A three step analysis will be used after 20, 33 and 55 patients to ensure if this treatment is feasible.
PLANNED SAMPLE SIZE	55 patients
DURATION OF STUDY PERIOD (per subject)	Start of study: October 2010 Last patient enrolled in July 2013 All patients will be followed up until 36 months after surgery

1. INTRODUCTION

1.1 Rectal cancer

Colorectal cancer is the third most common malignancy in the Netherlands with every year around 9000 new patients of whom approximately 2300 have a rectal cancer.
In the Netherlands, the standard treatment for T2/3 rectal cancer is pre-operative short course radiotherapy followed by surgery. The addition of Total Mesorectal Resection (TME) (sharp nerve sparing dissection) instead of blunt resection reduced the 5 year recurrence rate from 22 % to less than 10% (1, 2). Moreover, the increased use of this nerve-sparing techniques may result in lower rates of sexual dysfunction and urinary incontinence (3). The addition of pre-operative radiotherapy to surgery resulted in a significant better local control for stage II-III rectal cancer. The 5-year local control rate using a short course (5x5Gy) of pre-operative radiotherapy was 6% compared to 11% after surgery alone (2, 4).
For patients with more advanced tumours a longer course of radiation treatment is usually performed. Two recent trials have demonstrated the benefit of additional chemotherapy leading to a higher complete response rate and a lower local recurrence rate after 5 years of follow-up (5, 6). In a German randomized trial, all patients undergoing preoperative chemo radiotherapy were evaluated for response to therapy, followed by radical excision 6 weeks after completing treatment. In this group, 10.3% of patients had a pathologic complete response with no viable tumour identified after resection (7). No patients with a complete pathologic response developed local recurrence of disease, and these patients experienced better disease-free survival than did those with a lesser response to preoperative therapy. Several other series report excellent outcomes for patients with a complete pathologic response after neoadjuvant chemo radiotherapy, and a number of case series demonstrate the association between response and survival (8, 9).

1.2 High dose chemo radiotherapy for low rectal cancer

The use of preoperative chemo radiotherapy may influence sphincter preservation. Tumour shrinkage associated with long-course preoperative treatment has the potential to facilitate surgical resection and increase the probability of resection with adequate margin. Numerous case series have demonstrated that response to chemo radiotherapy is associated with a high rate of sphincter preservation in low-lying rectal cancer (10, 11). The strongest evidence for the influence of preoperative chemo radiotherapy on sphincter preservation comes from the German Rectal Cancer Study Group (7). In this study, investigators determined at baseline whether an APR would likely be necessary for all patients enrolled. In the group that received preoperative therapy, 39% patients thought to need APR were actually able to undergo a sphincter-sparing procedure, whereas only 19% of patients in the postoperative therapy group thought to need APR had sphincter salvage at the time of operation. This difference was highly statistically significant, $P = 0.004$. However, it is interesting to note that the overall rate of sphincter preservation was no different between the randomization groups (69% in the group treated with preoperative therapy *v* 71% in the group treated with postoperative therapy), indicating no effect of preoperative therapy on overall rates of sphincter preservation.

1.3 Surgery

Although it is technically feasible to avoid a permanent stoma in the majority of patients with rectal cancer, functional disturbances in patients with low anastomoses are common, including bowel urgency, tenesmus, soiling, and faecal incontinence. In some cases, continence may be so severely affected that intestinal diversion is preferred. In terms of quality of life, the relative benefits of ultralow coloanal anastomosis versus APR are unclear and patients with stomas generally report high quality of life (12). An important disadvantage of the abdominal perineal resection is the complete resection of the anus and the definitive stoma that patients have after the operation. In addition to the need for permanent colostomy, the procedure is associated with significant short-term morbidity (13) and mortality (14). Because radical resection, even with restoration of intestinal continuity, is associated in many

cases with life-altering changes in function, there is active interest in applying less invasive methods for management of rectal cancer.
There are tumour factors that increase the difficulty of sphincter preservation, such as the presence of a bulky tumour and location within 5 cm of the anal verge, and factors that oncologically mandate an APR, such as direct involvement of the anal sphincter. Additionally, there are patient factors that increase the difficulty of sphincter preservation, such as male sex and obesity, and sphincter preservation is ill-advised in patients who have incontinence preoperatively(15). However, Population-based data suggest that the rate of abdominal perineal resection rate is higher (16) than could be obtained in expert centres (17).

1.4 Local excision

Historically, local excision was considered an alternative to radical resection for patients who were unfit for major surgery because of medical co-morbidities or those who required APR but refused colostomy. When local excision is performed, the patient avoids a major surgical procedure and avoids the need for a permanent stoma or difficulties associated with ultralow anastomosis. Recent studies have demonstrated that local excision leads to higher rates of local recurrence, and that survival may be compromised compared with radical surgery (15). The key to appropriate use of local excision for rectal cancer is patient selection; accurate preoperative staging and prediction of lymph node involvement is essential.
For detection of nodal disease, ERUS and MRI had similar sensitivity (67% *v* 66%) and specificity (78% *v* 76%); however, both examinations are highly operator dependent. MRI provides excellent imaging of the rectum, the mesorectum, the fascia propria of the rectum, and other pelvic structures, and is useful for determining the risk of circumferential margin involvement preoperatively; this, however, is not relevant to the early-stage patients considered for local excision (18). The risk of lymph node involvement increases with depth of wall penetration, but even in patients with only T1 invasion of the rectal wall, there can be lymph node involvement. The incidence of lymph node metastasis ranges from 6% to 14% for T1 tumours, 17% to 23% for T2 tumours, and 49% to 66% for T3 tumours (19). In addition, in T1 lesions, it appears that the depth of sub mucosal invasion is important. Those with T1 tumours invading the deepest part of the sub mucosa (SM3) might have a significantly higher rate of lymph node metastases than do those with T1 tumours with more superficial invasion (SM1 or SM2) (20).

1.5 Technical Considerations

TEM may be a useful alternative to transanal techniques, but is technically difficult and requires a significant investment in equipment and training for competent performance. The procedure may result in greater precision of resection and enables extension of local excision to tumours located in the upper rectum that are not amenable to removal by standard transanal techniques (21, 22). For the TEM technique, an operating rectoscope with a diameter of 4 cm and a length of 12 or 20 cm with a stereo-optic is used. Specially designed instruments are introduced through extra access port in the rectoscope, and the rectum is insufflated with CO_2, which maintains exposure.

1.6 Results of Transanal Excision

Studies evaluating the results of local excision of rectal cancer are difficult to interpret because most studies are retrospective and based on the experience in a single institution, and the studies vary in terms of patient selection and surgical technique. Morbidity and mortality after local excision are lower than after radical resection; in a study of 5,305 patients with early-stage rectal cancer 30-day mortality after local excision was found to be 0.5% compared with 2.4% in patients undergoing radical resection ($P = 0.008$). Morbidity within 30 days of surgery was 4.4% in the local excision group versus 12.7% in the radical resection group ($P < 0.001$) (23)
A number of series reporting on the long-term results of transanal excision have been published during the last 10 years, and the findings have been alarming. Although patients included in these studies generally had favourable cancers, the local recurrence rates range

from 5% to 28% for T1 lesions, and from 11% to 45% for T2 lesions. (24, 25) Although there are no prospective randomized trials of local excision versus radical resection, these rates of recurrence seemed to be higher than would be expected for cancers treated with radical resection.

1.7 TEM after preoperative chemo radiation therapy

Reported series of patients treated in this manner include patients with T2 and even T3 cancers are small and involve single institutions (26-32) Given the advanced T stage of disease, the reported recurrence rates in these series were comparatively low (4% to 10%). Lezoche et al (26) conducted a small randomized trial (n = 40) comparing TEM to laparoscopic radical resection for patients with T2N0 rectal cancer after neoadjuvant chemo radiotherapy. After a median follow-up of almost 5 years, local recurrence rate was 5% in both arms. Although these findings are promising, patients with T2N0 would generally not be considered for adjuvant therapy after radical resection. Therefore, although this approach may decrease the morbidity and long-term functional effect of surgery, the morbidity and long-term functional effects of chemotherapy and irradiation are added.
The preferred strategy, however, depends on the degree of aversion to colostomy (local excision remains the preferred strategy at higher local recurrence rates if there is a high degree of aversion to colostomy) or degree of aversion to local recurrence (local excision would be the preferred strategy at only low local recurrence rates in this case).

1.8 The study drug: Capecitabine

Capecitabine is an oral fluoropyrimidine. It is rapidly and extensively absorbed as an intact molecule. Thereafter it is metabolized to 5-FU in three steps. The final step is catalysed by thymidine phosphorylase and takes place to a higher extent in the tumour cells. Thus capecitabine offers a potential reduction of the systemic exposure to 5-FU with an increased 5FU concentration in the tumour tissue. Dunst et al. performed a phase I study with 825 mg/m^2 capecitabine twice daily for 6 weeks in combination with a radiotherapy dose of 50.4 Gy. In 12 patients, no dose limiting toxicities (DLT) occurred (33). Kim et al. (34) treated 45 patients with 825 mg/m^2 capecitabine twice daily (plus leucovorin 20 mg/m^2 once a day) during 2 cycles of 2 weeks in combination with 50.4 Gy(34, 35). In Rotterdam we have treated patients with locally advanced rectal cancer with 825 mg/m2 during radiotherapy days and have experienced a complete response rate of 13% and minimal morbidity (36).

2. OBJECTIVES OF THE STUDY

Primary end-point:
The primary objective of the study is to determine the number of patients with minimal residual disease (ypT0-1) after neoadjuvant chemo radiation followed by TEM surgery. The resection specimen should be complete (> 2 mm margin) without evidence of nodal metastases (if nodes are found).

Secondary end-points:

- **Quality of Life**
  Determine the faecal continence and QOL in all patients.

- **Local recurrence**
  Careful follow-up will determine the local recurrence rate of patients treated with TEM or TME surgery.

- **Treatment related toxicity:**
  To determine the toxicity of the preoperative treatment with chemoradiation and postoperative complications. Not only from the patients who undergo TEM surgery, but also the TME surgery patients.

Other important issues that will be registered and analysed:

- **Number of positive lymph nodes**
  The number of positive lymph nodes in the TME patients will be assessed. This will give valuable information on the preoperative imaging modalities.

- **Number of sphincter saving TME procedures**
  The number of low anterior procedures in the TME patients will be assessed. The ratio sphincter saving surgery versus amputation of the rectum is important to analyse.

3. TREATMENT SCHEDULE AND PLANNING

3.1 Trial design and statistical analysis

This study is a non-randomized feasibility trial to determine whether radiotherapy, combined with capecitabine followed by organ sparing surgery using Transanal Endoscopic Microsurgery is feasible to consider as possible new treatment in distal rectal cancer. The radiotherapy dose is 2 Gy per fraction per day with a total dose of 50 Gy. The patients will receive 5 treatments a week, one on each working day. The chemotherapy will consist of continuous capecitabine 825 mg/m^2 bid use on radiotherapy days *and* during weekends.

Sample size
A total of 55 patients will be included in this study. The study treatment protocol is considered successful if 30% or more of the included patients will finish chemo radiation and undergo TEM surgery with complete resection of the ypT0-1 tumour. This means a resection with >2mm resection margins. A response of 15% or less will be considered a failure of this treatment modality. A three-step model for phase II cancer clinical trials will be used for calculating patient numbers with an alpha and beta of 0.1 (37). An evaluation will be planned after 20 patients, to ensure that at least 3 patients have successfully completed the treatment protocol (i.e. chemo radiation + TEM surgery with complete resection of the ypT0-1 tumour). Protocol on hold en CMO and DSMB will be informed. If the study continues another evaluation will be planned after 33 patients to ensure that at least 6 patients have successfully completed the treatment protocol. If 12 or more patients have completed the

protocol when 55 patients are treated, this is considered a feasible treatment modality and needs further evaluation in a phase III trial.

3.2 Radiology

All patients will prospectively enrol in the study with a routine imaging protocol of a CT scan of the thorax, abdomen, pelvis, and a MRI exam of the pelvis and endoanal ultrasound for staging. A second MRI exam of the pelvis, 6 weeks after the last radiotherapy treatment will be made for evaluation of response**.**

Sigmoidoscopy/rectoscopy and endoanal ultrasound:

All patients will undergo a sigmoidoscopy or rectoscopy before starting of the chemo radiation treatment to visualise the tumour. During this investigation, the borders of the tumour will be tattooed to enable visualisation of the original tumour location. In case of a (near) complete response, this marked area will be removed during TEM surgery. Afterwards, an endorectal ultrasound will be performed to assess the infiltration of the tumour. If the tumour is highly suspicious for a T4 tumour or enlarged lymph nodes are found, the patient will not be included in the study. Endorectal ultrasound will be performed in centres with experience with TEM surgery; usually this will be performed by the TEM surgeon.

CT scan:

A multidetector CT scan will be performed. Preferably, patients should fast 2-3 hours prior to the examination and 5 to 10 minutes before scanning patients should use 400 cc oral contrast media (Visipaque 320/ diluted with 20 parts water). Standard dose of 120 cc intravenous contrast media (Visipaque 320) will be administered intravenously at a rate of 2 cc/sec and a delay of 80 seconds. Patients will be scanned from the level of the neck till the perineum, to exclude lung, liver and peritoneal metastases.

MR Imaging:

MR imaging will be performed with a 1.5-T system. Preferably, the following sequences will be used in all patients: transverse, coronal and sagittal T2W (perpendicular on the tumour), The lower abdomen from the level of the anal canal up to the umbilicus is being imaged. Special attention will be paid to loco regional lymph nodes to assess features of lymphogenic tumour spread. Mesorectal, obturator or iliac lymph nodes > 5 mm or otherwise suspicious for metastases will exclude the patient for this treatment protocol.

3.3 Radiotherapy

Target definition

For all patients, a CT scan of the pelvis preferably with oral contrast to visualize the small bowel will be done. The oral contrast will be drunken 1 ½ to 2 hours before CT-scanning. Organs at risk (small and large bowel, bladder, anus) and the clinical target volume (CTV) will be contoured to derive dose volume histograms (DVH).

The CTV will be contoured as described in the article of Nuyttens et al (38): the CTV is defined as the rectum and perirectal tissues plus the regional lympatics. In the cranial-caudal dimension, contours of the lymphatic target begin at the inferior edge of L5 and ended at least 4 cm below the tumour or below the anus. The rectum is included at least 3 cm cranial and caudal to the tumour. Because the lymphatics follow vascular structures, the internal iliac arteries and veins are included plus a 3 to 5 mm margin, depending on the presence of bowel or bone. The posterior border of the perirectal tissues is defined by the posterior edge of the sacral foramina or the most anterior portion of the gluteus maximus. The lateral border is the ilium, piriformis, and obturator internus muscles. The anterior border is defined by the internal iliac vessels, sigmoid colon, bladder, vagina, prostate and small bowel. The small bowel is always excluded as much as possible.

Planning
The planning target volume (PTV) will include the CTV with a margin of 10 mm in all directions. If no on-line or off-line treatment set-up protocol is used the margins should be 15 mm. A CT-based treatment plan will be made and will consist of 3 fields (2 lateral, and 1 posterior-anterior) or a 4-field box technique. The PTV should receive the prescribed dose as described by the ICRU. The use of intensity modulated radiotherapy is allowed.

Treatment verification
Treatment verification should be done with an off-line treatment set-up protocol during the first 4 days of treatment. After the first 4 treatment controls, controls will be done once a week. If no off-line treatment set-up protocol is used, then portfilms should be taken on the first or second day of the treatment.

Radiotherapy side effects
With the standard treatment, radiation toxicity is limited to small bowel, bladder and skin problems. However, the combination of chemotherapy can lead to a higher incidence of diarrhoea, abdominal pain, cystitis, proctitis and anal pain.

3.4 Chemotherapy

Capecitabine
Capecitabine will be administered at a dose of 825 mg/m^2 bid during radiotherapy treatment and weekend days when patients do not undergo radiotherapy treatment.

Side effects
Nausea, vomiting and diarrhoea. Conventional treatment with anti-emetics and loperamide is seldom necessary.
Bone marrow suppression:leuco- and granulocytopenia; trombocytopenia, anaemia.
Skin toxicity: dry or red skin mainly on hands and feet (“hand-foot syndrome”).
For scoring of the toxicity the NCI CTC Toxicity Criteria version 3.0 will be used.

Dose modifications
If on the day of weekly blood sample analysis the ANC is < 1,5 x 109/l and/or platelets are < 100 x 109/l the chemotherapy will be postponed until recovery above these values. In case a patient experiences any grade 4 hematologic toxicity or a grade 3 hematologic toxicity complicated by neutropenic fever or bleeding, or a grade 2 hand-foot syndrome (e.g. peeling, blisters, bleeding, edema, or hyperkeratosis with pain; limiting instrumental ADL) the chemotherapy will be withheld until complete recovery. Thereafter chemotherapy can be restarted at 75% of the dose of capecitabine.
In case of any non-hematologic toxicity CTC-grade 3 or higher the chemotherapy will be interrupted until recovery to < grade 2. In these situations the radiotherapy can be continued.

Only in case of diarrhoea grade 3 the radiotherapy should be interrupted until recovery to < grade 2 diarrhoea.

3.5 Surgery

All patients undergo a MRI of the pelvis and a rectoscopy and endorectal ultrasound 6 weeks after chemo radiation. Patients who do not respond or clinically have a T3 tumour either on visual measurements or post therapy MRI or endoanal ultrasound will be operated on with a TME resection 8 - 10 weeks after the last chemo radiation treatment. Patients with a significant downsizing of the tumour (T0-T2) will be operated on by TEM surgery 8 -10 weeks after the last chemo radiation treatment.
After TEM surgery, pathological assessment will dictate further treatment. Conservative treatment with careful follow-up will be performed in patients with a complete resection of a ypT0-1 rectal tumour. Patients with lymphangioinvasion, an incomplete resected ypT1 (<2 mm margin), an ypT2 or ypT3 tumour after TEM will subsequently undergo TME surgery to remove the rectum within 4 weeks.

TEM surgery

The procedure will only be performed in acknowledged TEM centres, which have performed more than 30 procedures in both benign and malignant disease. Briefly, the technique consists of a one-port rectoscope, a handle and a four-port working insert. It is introduced transanal and fixed to the operating table with a Martin arm allowing positioning in any conceivable position. A stereoscope with a documentation endoscope and a maximum of three instruments can be introduced in the working insert. An insufflator and specially developed TEM pump are connected via a tube system and take care of gas insufflations, pressure measurement, irrigation and suction. An electro surgery unit is used for cutting and coagulation. The system is airtight, which is necessary for creating a pneumorectum. Use of a multifunctional instrument is advocated to reduce the number of instruments. Marking dots are placed at a 1-2 cm margin around the tumour, followed by full thickness excision. The different layers of the rectal wall and the perirectal fat can be clearly identified. After removal of the specimen, the defect is closed transversally with a running suture. Clips are used as knots. The specimen is pinned on cork, fixed in formalin and sent to the pathologist (22).

TME surgery

Open and laparoscopic-assisted procedures are allowed to perform the mesorectal excision. The resection is carried out using sharp dissection to encompass the circumference of the mesorectum. The operation starts with the transection of the inferior mesenteric vessels below the left colic artery and continues in the avascular plane between the mesentery and the parietal structures thus preserving the pelvic plexus. In the male patients the anterior dissection is carried out in front of Denonvilliers' fascia. The dissection is carried out in the so-called "holy plane" and both the rectum and the mesentery are transected at least 2 cm below the tumour. When a safe distal margin can be obtained without the need of a perineal phase, and the residual rectal stump is too short to warrant continence with a colorectal anastomosis, the rectal stump is either closed or left open. This in fact is a modified Hartmann procedure. Depending on the size and distance to the anal verge a low anterior resection with colorectal or coloanal anastomosis or an abdominoperineal resection will be performed. When continuity is restored after low anterior resection, a diverting ileostomy is recommended including drainage of the pelvis with a non-suction drain.

3.6 Pathology

The TEM specimen should be adequately labelled (proximal and distal margins, and stretched under gentle tension, pinned to a corkboard and fixed in standard fixature for at least 48 hours. After fixation, the deep (lateral) resection margin should be inked, and the specimen is sliced as thinly as possible (preferably 3-4 mm). After inspection and photographic documentation, representative areas of the tumour should be sampled with a minimum of 5 samples) (including the area of the deepest tumour invasion). In addition, macroscopic normal rectal tissue should be sampled, for practical reasons, distal and/or proximal margins can be used.

Microscopic evaluation of the specimen should be performed using a standard protocol, including invasion depth, differentiation grade and presence of lymphangioinvasion. For invasion depth, the Japanese sub classification of the T1 tumours should be used:

- Sm1 (superficial sub mucosal invasion): <500µm
- Sm2 (invasion in the middle part of the sub mucosa)
- Sm3 (invasion in the deepest part of the sub mucosa)

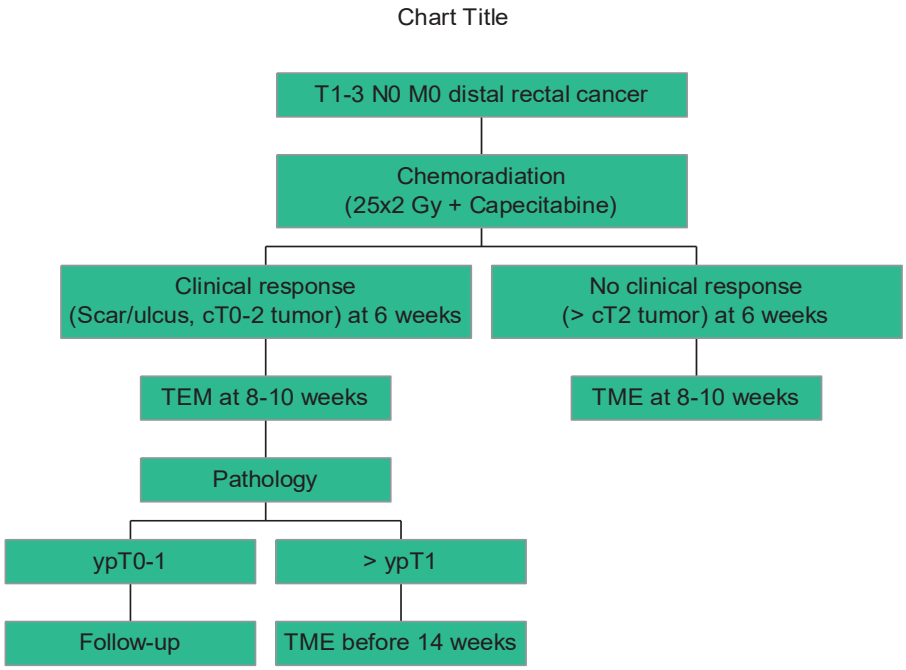
Margins should be carefully examined, all margins should be over 2 mm in order to declare the TEM procedure oncologically safe. Involved margins, invasion into the muscularis propria and/or lymphangioinvasion are reasons for TME surgery.
In addition to traditional histological factors, the presence of tumour regression should be examined, according to the national guidelines. A three-tiered system should be applied:

- Complete response
- Regression
- No regression

Criteria for determining a complete response (no viable tumour present) have been agreed upon internationally due to the importance of standardisation. Initially, at least 5 sections are taken from the tumour region. If no viable tumour is found, then the entire tumour region is embedded. If again no viable tumour is found, then the blocks are sectioned at three levels. If again no viable tumour is found, then it is considered a complete response. Presence of regression is noted when mucinous degeneration is present, or when fibrosis is present. Minor changes in the presence of profound changes in blood vessel architecture can also be counted as regression.

The TME specimen should be evaluated according to the national guidelines, including the tumour regression assessment as has been described before.
A central review of all reports, slides and photographs is part of the trial protocol and will be done by one pathologist (I.N.) in order to standardise the pathological assessment.

Treatment scheme



4.0 PATIENT SELECTION CRITERIA

4.1 Inclusion criteria

- Patients (aged >18 years) with histological proven adenocarcinoma of the distal part of the rectum (below 10 cm) without signs of distant metastases.
- T1-3 tumour without lymph nodes > 5 mm at CT, MRI and endoanal ultrasound.
- ANC > 1.5 x 10^9/l.
- Thrombocytes > 100 x 10^9/l.
- Creatinin clearance >50ml/min (according to the Cockcroft-Gault formula)
- Total serum bilirubin < 24 μmol/l or below <1.5 times the upper limit of the normal.
- ASAT,ALAT: up to 5 times the upper limit.
- Colonoscopy, colonography or virtual colonoscopy should exclude synchronous colorectal lesions in other parts of the colon.
- ECOG performance score 0-2.
- Fertile women should have adequate birth control during treatment.
- Mental/physical/geographical ability to undergo treatment and follow-up.
- Written informed consent (Dutch language).

4.2 Exclusion criteria

- Patients with Grade 1-2 T1 tumours (can be treated with TEM surgery without chemo radiation therapy)
- Patients with circular rectal tumour or tumours who are by other means unacceptable for TEM surgery (e.g. intra-analtumors).
- Patients with faecal incontinence **prior** to the diagnosis of rectal cancer (complaints of soiling due to the tumour will not be an exclusion criterion).
- Severe uncontrollable medical or neurological disease.
- Patients with secondary prognosis determining malignancies.
- Patients who have been treated with radiotherapy on the pelvis.
- Use of Vitamin K antagonists.
- Fenytoine and Allopurinol use.
- Known DPD deficiency
- Uncontrolled active infection, compromised immune status, psychosis, or CNS disease.
- Pregnant or lactating women.
- Clinically significant (i.e. active) cardiovascular disease for example cerebro vascular accidents (≤ 6 months prior to randomisation), myocardial infarction (≤ 6 months prior to randomisation), unstable angina, New York Heart Association (NYHA) grade II or greater congestive heart failure, serious cardiac arrhythmia requiring medication.
- Evidence of other disease, metabolic dysfunction, physical examination finding, or clinical laboratory finding giving reasonable suspicion of a disease or condition that contraindicates use of Capecitabine or patients at high risk for treatment complications. History or evidence upon physical examination of CNS disease unless adequately treated (e.g., seizure not controlled with standard medical therapy).

5.0 SCREENING PROCEDURE FOR STUDY ENTRY

5.1 The screening procedures consists of:

- **History**
  General medical history (previous disease, operations, allergies, drugs, other relevant factors).

- **Physical examination**
  Total body examination, weight and ECOG.

- **Special examinations**
- CT-scan of thorax, abdomen, pelvis before the start of the radiotherapy
- MRI of the pelvis before the start of the radiotherapy and 21-28days after the last radiotherapy treatment.
- Endoanal ultrasound
- Serum CEA
- Usual laboratory examinations (RBC, WBC, ANC, Platelets, alb, total protein, electrolytes (Na, K, Ca, Cl), liver enzymes (total bilirubin, LDH, Alkaline phosphatase, ASAT, ALAT, GGT, renal functional parameters (serum creatinin and/or creatine clearance)
- Fresh frozen sample of the tumour before treatment for further research.
- Serum sample before treatment, after (chemo)-radiation and after surgery for further research. This future research of both serum samples and tumor tissue is to be determined during or after all patients are included in the study. It will focus on analyzing prognostic factors for a (near) complete responses in order to predict which patients will benefit most from this type of treatment. Tissue and serum will not be used for other research projects without asking the Medical ethics committee for approval.

- **Quality of life**

Quality of life are checked according to EORTC-QLQC30 and 38. Before the start of treatment QOL questionnaire is filled out at the hospital, which will be continued during follow-up. For details information regarding urinary, defecation and sexual functions an additional questionnaire is given to the patients(39).

Screening procedures and study parameters in overview

	Pre-treatment	Weekly during CxRtx	6 weeks after CxRtx		Year 1				Year 2				Year 3	
# of months after surgery					3	6	9	12	15	18	21	24	30	36
History	#	#			#	#	#	#	#	#	#	#	#	#
Physical examination	#	#		S	#	#	#	#	#	#	#	#	#	#
Body weight (kg)	#	#		U	#	#	#	#	#	#	#	#	#	#
ECOG perf. scale	#	#		R	#	#	#	#		#		#		#
Quality of life Data form	#			G		#		#				#		#
RBC, ANC, platelets, Liver enzymes, creatinine	#	#		E	#	#	#	#		#		#		#
Serum sample	#		#	R										
CEA	#		#	Y	#	#	#	#	#	#	#	#	#	#
Colonoscopy, Colonography	#							#						
Rectoscopy and endoanal ultrasound *	#		#		#	#	#	#	#	#	#	#	#	#
MRI pelvis	#		#			#		#		#		#		#
CT-scan thorax & abdomen	#					#		#		#		#		#
Tumour sample	#			#										

= requested

* Rectoscopy and endoanal ultrasound will be performed in TEM treated patients only during follow-up

6.0 EFFICACY PARAMETERS

6.1 Primary Efficacy Parameter

Tumour assessment and measurement will be performed by sigmoidoscopy, endoanal ultrasound and MRI of the pelvis 6 weeks after the radiotherapy treatment. Accuracy of both endo-anal ultrasound as well as MRI is not known to be reliable after chemo radiation for locally advanced tumours (40, 41). Overstaging of the tumour-stage is often found, because it is difficult to differentiate between vital tumour tissue and fibrosis. However, the value of these imaging techniques in early rectal cancer is not assessed and both modalities will be used. Visual assessment during rectoscopy will be the gold standard for tumour response. Measurements of the tumour is made in millimetres of two perpendicular diameters of the marker lesions, applied at the widest portion of tumour.

Tumour response will be defined according to the criteria as described in WHO handbook for Reporting Results of Cancer Treatment:

a) Complete response (CR): Disappearance of all clinically detectable disease.
b) Partial response (PR): 50% or greater reduction in the sum of the products of the two greatest perpendicular diameters of all measurable lesions.
c) No change (NO) or stable disease (SD): a <25% increase or <50% decrease in tumour size as defined above throughout the period of treatment. No new lesions may have developed
d) Progressive disease (PD): An increase of greater than or equal to 25% in measurable disease or appearance of new lesions.

Tumours that are clinically assessed as T0-2 are scheduled for organ-sparing TEM surgery. Tumours with obvious signs of progression or invasion through the muscularis propria (T3 tumour) are treated with standard TME surgery. After surgery (either TEM or TME) resection specimen are send to pathology for tumour regression analysis.

6.2 Secondary Efficacy Parameters

Quality of Life:
Determine the faecal continence and QOL after treatment with TEM surgery will be compared with TME treated patients.

Local recurrence:
Careful follow-up will determine the local recurrence rate of patients treated with TEM and TME surgery. This will be standard colorectal cancer follow-up with additional endo-anal endography and MRI for patients treated with TEM surgery during the first two years.

6.3 Other Efficacy Parameters

Toxicity:
Regional and systemic Toxicity/Side effects will be recorded according to the CTC-Toxicity Grading system, CTC-NCIC Toxicity Criteria v. 3.0. (See appendix).
Surgical and postoperative complications will be collected and assessed during interim analysis.

Number of positive nodes in TME treated patients:
The number of patients with positive lymph nodes after chemo radiation is expected to be less than 20%, this will carefully be monitored.

Number of sphincter saving operations:
Patients who fail the initial treatment and finally undergo TME surgery who can be treated with a sphincter saving operation will be monitored.

7.0 REGULATORY AFFAIRS

Registration procedure
Prior to registration and study entry, all patients must have given written informed consent and must have completed the pre-treatment evaluations according to the flow chart. All patients will be registered at the Radboud UMC Nijmegen IKO trials office.

Case Record Forms (CRF)
For each patient enrolled a CRF must be completed and signed by the principal investigator (J.H.W. de Wilt) or co-investigator in a reasonable time period after data collection. This also applies to records for those patients who fail to complete the study. If a patient is withdrawn of the study the reason must be clearly noted in the CRF. Data Management will be performed by the data managers of the comprehensive cancer centres.

Safety Reporting and DSMB
The chemo radiation treatment protocol is an accepted, standard treatment protocol that is used in most hospitals in the Netherlands treating locally advanced rectal cancer patients. Serious adverse events are therefore not suspected to be related to the chemotherapy or radiation treatment. If, despite this anything occurs on the basis of which it appears that the disadvantages of participation may be significantly greater than was foreseen in the research proposal, one of the principal investigator will be informed. The study will be suspended pending further review by the accredited METC.
A data and safety monitoring board (DSMB) will monitor any reported serious adverse event (SAE) and the data quality 2 times during the study and more frequent when necessary. Reponse data of all patients treated with chemoradiation will be presented during this analysis. This enables the DSMB to evaluate not only the patients who respond after chemoradation, but also if any patient will encounter progression of the rectal tumor. Problems will be discussed with the principal investigators, who will take appropriate measures. If it appears that the disadvantages of participation may be significantly greater than was foreseen in the research proposal, the study will be suspended pending further review by the accredited METC.

The DSMB consist of:

- Prof. Dr. W. Bemelman, surgeon, Amsterdam Medical Center
- Dr. T. Rozema, radiotherapist, Verbeten Instituut Tilburg

Stopping rules for the study
The study will be evaluated according to the three-step model for phase II cancer clinical trials. When too less patients have successfully completed the treatment protocol (i.e. chemo radiation + TEM surgery with complete resection of the ypT0-1 tumour) the study will be stopped. This evaluation is after the first 20 patients and 3 patients should have completed the protocol successfully. After 33 patients 6 should be treated successfully.
These data will be presented to the DSMB as well as all SUSARs and SAEs. The DSMB can decide that this study should be stopped when patient safety is at risk.

GCP
The study will be conducted in accordance with the W.M.O. (Wet Medisch-wetenschappelijk Onderzoek met mensen), the principles of Good Clinical Practice and in accordance with the latest version of the Declaration of Helsinki.

Independent physician
In accordance with the W.M.O. an independent physician has been assigned to this study in each participating centre. This will be mentioned in the patient information sheet.

Insurance
In accordance with Dutch law and the W.M.O., an insurance policy, covering all participating patients, has been effected.

Informed consent
Patients are to be informed of the standard institutional treatment in this situation as an alternative to this study. Before recruitment, enrolment into the study, each prospective candidate will be given a full explanation of the study (see informed consent form). No patient should be obliged to participate in the trial. Patients must be given ample opportunity to inquire about details for the trial. The information must make clear that refusal to participate or withdrawal from the trial at any stage is without any disadvantage for the patient's subsequent care. When the essential information has been provided to the patient and when the investigator has checked that the patient has understood the implications of participating in the study, the patient will be asked to give written informed consent. All relevant elements relating to the study have to be clearly explained to the candidate in an understandable form. In all cases the notation that informed consent has been obtained, will be made on the subjects case report form.

Ethical Review Board
The study will be submitted to the 'Commissie Mensgebonden Onderzoek regio Arnhem en Nijmegen'of for the approval process in accordance with the Dutch law W.M.O.
A participating centre will not submit patients to any study related activity before the centre has received the written approval from the Ethical Review Board of the participating hospital to start the study.

Publication policy
One of the principal investigators will be first author of papers based on this study, unless they all agree that a member of the writing committee qualifies for first authorship. Members of the writing committee and investigators not from Erasmus MC or Radboud UMCN who have entered at least 10 percent of the patients in the study qualify for co-authorship.

Reporting serious adverse events

Definitions
As per the International Conference of Harmonization (ICH) guideline for Good Clinical Practice (GCP), an **Adverse Event (AE)** is any untoward medical occurrence or experience in a patient or clinical investigation subject which occurs during or following treatment regardless of the causal relationship.
This can include any unfavourable and unintended signs (such as rash or enlarged liver), or symptoms (such as nausea or chest pain), an abnormal laboratory finding (including blood tests, x-rays or scans) or a disease temporarily associated with the treatment.

Serious Adverse Events (SAE) are defined as:
any undesirable experience occurring to a patient, whether or not considered related to the treatment. Adverse events which are considered as serious are those which result in:

- death
- a life-threatening event (i.e. the patient was at immediate risk of death at the time the reaction was observed)
- hospitalization or prolongation of hospitalization
- severe/permanent disability
- a congenital anomaly
- medically significant

Upon receiving a report of an SAE, the study coordination center will evaluate whether the SAE qualifies as a SUSAR (Suspected Unexpected Serious Adverse Reaction). The last

SmPC serves as a reference document. A copy of the submission will be send to the registration holder. The following information must be submitted in the following timelines:

- Within 7 days of the receiving the report by the investigator, if the SAE resulted in death or was life-threatening and was qualified as a SUSAR.

- Within 15 days of the receiving the report by the investigator, if the SAE was qualified as a SUSAR.

- After 20 patients, 33 patients and 55 patients list of all SAEs (lethal, life-threatening, unexpected and expected) will be supplied to the DSMB, the regulatory authorities (College ter Beoordeling van geneesmiddelen), the Ethics Committee and the registration holder.

- According to the Dutch Law (WMO 13o-13q) SUSARs and SSARs will be reported to CMO within the timelines specified in the law.

Timelines
SAEs must be reported within one working day of the investigator becoming aware of the event (expedited reporting). In circumstances where it is not possible to submit a complete report, an initial report may be made giving only the mandatory information. Initial reports must be followed-up by a complete report within a further 14 calendar days and sent to the TRIAL Centre. All SAE Reports must be dated and signed by the responsible investigator or one of his/her authorized staff members.
Causality is initially assessed by the investigator. For Serious Adverse Events, possible causes of the event are indicated by selecting one or more options (Underlying disease, Study drug treatment, Protocol-related procedure, other e.g. accident, new or intercurrent illness)
All SAEs will be reported up to **28 days after last intake of capecitabine**. Unexpected SAEs that are considered to be *possibly related to protocol treatment* must be reported at any time after the completion of protocol treatment.

Progression of underlying malignancy
If progression of underlying malignancy occurs, it is not reported as an adverse event if it is clearly consistent with the suspected progression of the underlying cancer as defined by RECIST criteria, or other criteria as determined by protocol. Hospitalisation due solely to the progression of underlying malignancy should NOT be reported as a serious adverse event. Clinical symptoms of progression may be reported as adverse events if the symptom cannot be determined as exclusively due to the progression of the underlying malignancy, or does not fit the expected pattern of progression for the disease under study.

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9.0 APPENDICES

Appendix 1: staging classification of colorectal cancer
(TNM UICC 5th edition 2004)

Primary tumor (T)
Tx Primary tumor cannot be assessed
T0 No evidence of primary tumor
Tis Carcinoma in situ
T1 Tumor invades submucosa
T2 Tumor invades muscularis propria
T3 Tumor invades through muscularis propria into subserosa or into non-peritonealized pericolic or perirectal tissues
T4 Tumor directly invades other organs or structures and/or perforates visceral peritoneum

Regional lymph nodes (N)
Nx Regional lymph nodes cannot be assessed
N0 No regional lymph node metastasis
N1 Metastasis in 1 to 3 regional lymph nodes
N2 Metastasis in 4 or more regional lymph nodes

Distant metastases (M)
Mx Distant metastasis cannot be assessed
M0 No distant metastasis
M1 Distant metastasis present

Appendix 2: ECOG PERFORMANCE STATUS SCORING SYSTEM

STATUS	ECOG PERFORMANCE STATUS SCORE
0	Fully active, a-symptomatic
1	Ambulatory; capable of carrying out work of a light or sedentary nature, e.g.: light house work, office work.
2	In bed < 50% of the time: capable of self-care but not work
3	In bed > 50% of the time: capable of only limited self-care
4	Completely bedridden; incapable of self-care

Appendix 3: Toxicity Grading

NCI CTC Toxicity scale Version 4.0

COMMON TOXICITY CRITERIA (NCI CTC)

See website: http://evs.nci.nih.gov/

Appendix 4: World Medical Association Declaration Of Helsinki

Ethical Principles for Medical Research Involving Human Subjects

Adopted by the 18th WMA General Assembly Helsinki, Finland, June 1964 and amended by the 29th WMA General Assembly, Tokyo, Japan, October 1975,
The 35th WMA General Assembly, Venice, Italy, October 1983,
The 41st WMA General Assembly, Hong Kong, September 1989,
The 48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996,
The 52nd WMA General Assembly, Edinburgh, Scotland, October 2000.

A. INTRODUCTION

1. The World Medical Association has developed the Declaration of Helsinki as a statement of ethical principles to provide guidance to physicians and other participants in medical research involving human subjects. Medical research involving human subjects includes research on identifiable human material or identifiable data.
2. It is the duty of the physician to promote and safeguard the health of the people. The physician's knowledge and conscience are dedicated to the fulfillment of this duty.
3. The Declaration of Geneva of the World Medical Association binds the physician with the words, "The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act only in the patient's interest when providing medical care which might have the effect of weakening the physical and mental condition of the patient."
4. Medical progress is based on research which ultimately must rest in part on experimentation involving human subjects.
5. In medical research on human subjects, considerations related to the well-being of the human subject should take precedence over the interests of science and society.
6. The primary purpose of medical research involving human subjects is to improve prophylactic, diagnostic and therapeutic procedures and the understanding of the aetiology and pathogenesis of disease. Even the best proven prophylactic, diagnostic, and therapeutic methods must continuously be challenged through research for their effectiveness, efficiency, accessibility and quality.
7. In current medical practice and in medical research, most prophylactic, diagnostic and therapeutic procedures involve risks and burdens.
8. Medical research is subject to ethical standards that promote respect for all human beings and protect their health and rights. Some research populations are vulnerable and need special protection. The particular needs of the economically and medically disadvantaged must be recognized. Special attention is also required for those who cannot give or refuse consent for themselves, for those who may be subject to giving consent under duress, for those who will not benefit personally from the research and for those for whom the research is combined with care.
9. Research Investigators should be aware of the ethical, legal and regulatory requirements for research on human subjects in their own countries as well as applicable international requirements. No national ethical, legal or regulatory requirement should be allowed to reduce or eliminate any of the protections for human subjects set forth in this Declaration.

B. BASIC PRINCIPLES FOR ALL MEDICAL RESEARCH

10. It is the duty of the physician in medical research to protect the life, health, privacy, and dignity of the human subject.

11. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and on adequate laboratory and, where appropriate, animal experimentation.

12. Appropriate caution must be exercised in the conduct of research which may affect the environment, and the welfare of animals used for research must be respected.

13. The design and performance of each experimental procedure involving human subjects should be clearly formulated in an experimental protocol. This protocol should be submitted for consideration, comment, guidance, and where appropriate, approval to a specially appointed ethical review committee, which must be independent of the investigator, the sponsor or any other kind of undue influence. This independent committee should be in conformity with the laws and regulations of the country in which the research experiment is performed. The committee has the right to monitor ongoing trials. The researcher has the obligation to provide monitoring information to the committee, especially any serious adverse events. The researcher should also submit to the committee, for review, information regarding funding, sponsors, institutional affiliations, other potential conflicts of interest and incentives for subjects.

14. The research protocol should always contain a statement of the ethical considerations involved and should indicate that there is compliance with the principles enunciated in this Declaration.

15. Medical research involving human subjects should be conducted only by scientifically qualified persons and under the supervision of a clinically competent medical person. The responsibility for the human subject must always rest with a medically qualified person and never rest on the subject of the research, even though the subject has given consent.

16. Every medical research project involving human subjects should be preceded by careful assessment of predictable risks and burdens in comparison with foreseeable benefits to the subject or to others. This does not preclude the participation of healthy volunteers in medical research. The design of all studies should be publicly available.

17. Physicians should abstain from engaging in research projects involving human subjects unless they are confident that the risks involved have been adequately assessed and can be satisfactorily managed. Physicians should cease any investigation if the risks are found to outweigh the potential benefits or if there is conclusive proof of positive and beneficial results.

18. Medical research involving human subjects should only be conducted if the importance of the objective outweighs the inherent risks and burdens to the subject. This is especially important when the human subjects are healthy volunteers.

19. Medical research is only justified if there is a reasonable likelihood that the populations in which the research is carried out stand to benefit from the results of the research.

20. The subjects must be volunteers and informed participants in the research project.

21. The right of research subjects to safeguard their integrity must always be respected. Every precaution should be taken to respect the privacy of the subject, the confidentiality of the patient's information and to minimize the impact of the study on the subject's physical and mental integrity and on the personality of the subject.

22. In any research on human beings, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail. The subject should be informed of the right to abstain from participation in the study or to withdraw consent to participate at any

time without reprisal. After ensuring that the subject has understood the information, the physician should then obtain the subject's freely-given informed consent, preferably in writing. If the consent cannot be obtained in writing, the non-written consent must be formally documented and witnessed.

23. When obtaining informed consent for the research project the physician should be particularly cautious if the subject is in a dependent relationship with the physician or may consent under duress. In that case the informed consent should be obtained by a well-informed physician who is not engaged in the investigation and who is completely independent of this relationship.

24. For a research subject who is legally incompetent, physically or mentally incapable of giving consent or is a legally incompetent minor, the investigator must obtain informed consent from the legally authorized representative in accordance with applicable law. These groups should not be included in research unless the research is necessary to promote the health of the population represented and this research cannot instead be performed on legally competent persons.

25. When a subject deemed legally incompetent, such as a minor child, is able to give assent to decisions about participation in research, the investigator must obtain that assent in addition to the consent of the legally authorized representative.

26. Research on individuals from whom it is not possible to obtain consent, including proxy or advance consent, should be done only if the physical/mental condition that prevents obtaining informed consent is a necessary characteristic of the research population. The specific reasons for involving research subjects with a condition that renders them unable to give informed consent should be stated in the experimental protocol for consideration and approval of the review committee. The protocol should state that consent to remain in the research should be obtained as soon as possible from the individual or a legally authorized surrogate.

27. Both authors and publishers have ethical obligations. In publication of the results of research, the investigators are obliged to preserve the accuracy of the results. Negative as well as positive results should be published or otherwise publicly available. Sources of funding, institutional affiliations and any possible conflicts of interest should be declared in the publication. Reports of experimentation not in accordance with the principles laid down in this Declaration should not be accepted for publication.

C. ADDITIONAL PRINCIPLES FOR MEDICAL RESEARCH COMBINED WITH MEDICAL CARE

28. The physician may combine medical research with medical care, only to the extent that the research is justified by its potential prophylactic, diagnostic or therapeutic value. When medical research is combined with medical care, additional standards apply to protect the patients who are research subjects.

29. The benefits, risks, burdens and effectiveness of a new method should be tested against those of the best current prophylactic, diagnostic, and therapeutic methods. This does not exclude the use of placebo, or no treatment, in studies where no proven prophylactic, diagnostic or therapeutic method exists.

30. At the conclusion of the study, every patient entered into the study should be assured of access to the best proven prophylactic, diagnostic and therapeutic methods identified by the study.

31. The physician should fully inform the patient which aspects of the care are related to the research. The refusal of a patient to participate in a study must never interfere with the patient-physician relationship.

32. In the treatment of a patient, where proven prophylactic, diagnostic and therapeutic methods do not exist or have been ineffective, the physician, with informed consent from the patient, must be free to use unproven or new prophylactic, diagnostic and therapeutic measures, if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. Where possible, these measures should be made the object of research, designed to evaluate their safety and efficacy. In all cases, new information should be recorded and, where appropriate, published. The other relevant guidelines of this Declaration should be followed.