Gluteal turnover flap for closure of the perineal wound after abdominoperineal resection for rectal cancer.

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LIST OF ABBREVIATIONS AND RELEVANT DEFINITIONS

ABR	**General Assessment and Registration form (ABR form), the application form that is required for submission to the accredited Ethics Committee; in Dutch: Algemeen Beoordelings- en Registratieformulier (ABR-formulier)**
AE	**Adverse Event**
APR	**Abdominoperineal Resection**
Biomesh	**Biological Mesh**
eAPR	**Extralevator Abdominoperineal Resection**
iAPR	**Intersphincteric Abdominoperineal Resection**
CA	**Competent Authority**
CCMO	**Central Committee on Research Involving Human Subjects; in Dutch: Centrale Commissie Mensgebonden Onderzoek**
CRC	**Colorectal Cancer**
CRF	**Case Report Form**
CUA	**Cost Utility Analysis**
CV	**Curriculum Vitae**
DSMB	**Data Safety Monitoring Board**
EU	**European Union**
GCP	**Good Clinical Practice**
GDPR	**General Data Protection Regulation; in Dutch: Algemene Verordening Gegevensbescherming (AVG)**
GT flap	**Gluteal turnover flap**
IB	**Investigator's Brochure**
IC	**Informed Consent**
IGAP	**Inferior Gluteal Artery Perforator flap**
IMP	**Investigational Medicinal Product**
IMPD	**Investigational Medicinal Product Dossier**
METC	**Medical research ethics committee (MREC); in Dutch: medisch-ethische toetsingscommissie (METC)**
QALY	**Quality Adjusted Life-Year**
(S)AE	**(Serious) Adverse Event**
SGAP	**Superior Gluteal Artery Perforator flap**
SPC	**Summary of Product Characteristics; in Dutch: officiële productinformatie IB1-tekst**

Sponsor	**The sponsor is the party that commissions the organisation or performance of the research, for example a pharmaceutical company, academic hospital, scientific organisation or investigator. A party that provides funding for a study but does not commission it is not regarded as the sponsor, but referred to as a subsidising party.**
SUSAR	**Suspected Unexpected Serious Adverse Reaction**
TME	**Total Mesorectal Excision**
VRAM flap	**Verticus Rectus Abdominis flap**
Wbp	**Personal Data Protection Act; in Dutch: Wet bescherming Persoonsgegevens**
WMO	**Medical Research Involving Human Subjects Act; in Dutch: Wet Medisch-wetenschappelijk Onderzoek met Mensen**

SUMMARY

Rationale: Colorectal cancer (CRC) is one of the world's most common forms of cancer. Of which, about 700 patients per year undergo an abdominoperineal resection (APR) for distal rectal cancer (Dutch Colorectal Audit 2016). This procedure entails a radical resection of the rectum with en bloc resection of the anorectal sphincter complex and (part) of the levator muscle with lymphadenectomy according to the total mesorectal excision (TME) principle. Neo-adjuvant (chemo)radiotherapy is often used to further improve loco-regional control. Morbidity after APR is substantial and mainly consisting of perineal wound problems in about 35% of the patients. If primary healing of the perineal wound after APR does not occur, secondary healing can take up to one year, and there is even a small proportion of patients in whom a chronic perineal wound or fistula persists after one year. During this long period, intensive wound care is necessary. This results in a heavy burden on both patient and health care resources. The high morbidity rate of the perineal wound has resulted in a continuing discussion on how to close the perineal defect after APR. Our research group recently published the BIOPEX-study (NL42094.018.12), in which 104 patients were randomised between primary perineal wound closure and biological mesh closure of the pelvic floor after APR with preoperative radiotherapy for rectal cancer. Similar uncomplicated perineal wound healing rate at 30 days (Southampton wound score < 2) was found: 63% versus 66%, respectively. The hypothesis behind this negative trial result is related to the perineal dead space between the skin and the biological mesh. Fluid will accumulate in this dead space with the risk of secondary contamination and abscess formation, leading to wound dehiscence and purulent discharge. Autologous tissue flaps have been suggested to improve perineal wound healing based on several cohort studies, however conclusive evidence is lacking. For these reasons, primary perineal closure (control arm of BIOPEX) is still the standard of care in the Netherlands.

A gluteal turnover flap (GT flap) is a small transposition flap from the unilateral adjacent perineal skin and subcutaneous fat, which is flipped into the perineal dead space, and stitched with the de-epithelialized dermis to the contralateral pelvic floor remnant. Subsequently, the perineal subcutaneous fat and skin are closed over the flap in the midline, thereby not adding a donor site scar. A small pilot study from our group showed that this is a promising solution for routine perineal closure after APR, following the principle of filling perineal dead space

Objective: The aim of this study is to determine the additional value of a minimally invasive gluteal turnover flap for perineal wound healing after APR for rectal cancer in comparison to primary closure.

Study design: This is a multicentre study in which patients undergoing an APR are randomised between standard care using primary closure of the perineum and the experimental arm with assisted

closure using a GT flap.

Study population: Patients with a clinical diagnosis of primary or recurrent rectal cancer who are scheduled for APR. A total of 160 patients will be randomised.

Intervention: The intervention in the experimental arm consists of using a GT flap in the pelvic floor defect, followed by perineal closure similar to the control arm.

Main study parameters/endpoints: The primary endpoint is the percentage of uncomplicated perineal wound healing defined as a Southampton wound score of less than II at 30 days postoperatively.

Nature and extent of the burden and risks associated with participation, benefit and group relatedness: The potential benefit resulting from participation of the study in patients randomized for GT flap closure may be a higher chance of uncomplicated perineal wound healing and lower perineal hernia rate. The potential risks of a GT flap are experiencing more pain than usual after the operation. In addition, it may be that the GT flap does not heal and becomes necrotic after the operation. These previously mentioned complications usually do not require any major treatment. In exceptional cases, it may be necessary to remove the flap partially or completely. This will then be performed through a local operation. The use of a GT flap will not affect the strength or size of the buttocks.

1. INTRODUCTION AND RATIONALE

Problem

About 700 rectal cancer patients are yearly treated by an abdominoperineal resection (APR) in the Netherlands. This entails a radical resection of the rectum with the anorectal sphincter complex, (part of) the levator muscle, and lymph nodes according to the total mesorectal excision (TME) principle. A drawback of this procedure is the creation of a perineal defect, that results in wound healing problems in about 35% of the patients [1-4]. Radiotherapy is one of the major risk factors for perineal wound healing problems [4]. Although radiotherapy indication has been reduced in the Netherlands [5], it is still often indicated in distal rectal cancer because of the disappearing mesorectal fat towards the ano-rectal junction that often results in threatened margins. If primary healing of the perineal wound after APR does not take place, secondary wound healing of the defect can take up to one year, and there is even a small proportion of patients in whom a chronic perineal wound or fistula persists after one year [6]. Omentoplasty has been suggested to improve perineal wound healing, but this could not be confirmed in a recent large Dutch cross-sectional study [2]. Also Biomesh closure of the pelvic floor did not improve perineal wound healing, as shown in the BIOPEX study [3]. In contrast, it is consistently reported that autologous tissue flaps improve perineal wound healing, although no randomised trials have been performed [7]. But most flaps seem to be overtreatment if routinely used after APR for distal rectal cancer, because of the associated donor site morbidity in case of rectus abdominis or gluteus muscle flaps.

Solution

A gluteal turnover flap (GT flap) uses a small rim of de-epithelialized perineal skin and subcutaneous fat on a gluteal perforator of one side of the perineal incision, which is rotated into the perineal dead space, and the dermis is stitched to the contralateral levator remnant as pelvic floor closure. Compared to rectus abdominis or gluteus muscle flaps, it requires only limited additional dissection, and does not interfere with abdominal wall integrity. Furthermore, the perineal wound can be closed in the midline over the flap, without additional scar visible at the end of the procedure. The volume of transposed tissue appears to be adequate to fill the dead space in 'regular' APR procedures. The GT flap is thought to promote wound healing, and the de-epithelialized dermis to prevent herniation as an autologous biological mesh.

Summary of literature

Several techniques have been described for the closure of the perineal wound after APR for rectal cancer. These techniques vary from primary closure to biological mesh closure[8]. Primary closure has resulted in high rate of immediate wound break down and long term perineal hernia formation, especially in patients receiving long courses of (chemo)radiotherapy[4,9,10]. These complications might

lead to chronic wounds and may jeopardize functional outcome after this operation. Therefore, other perineal closure methods, such as autologous tissue flap closures are increasingly being used. A number of musculocutaneous transposition flaps and fasciocutaneous perforator flaps can be used for perineal closure after APR. The rectus abdominis muscle flap, gracilis flap, lateral thigh flap and the gluteal flap have all been described for this purpose[11-16]. The vertical rectus abdominis muscle (VRAM) flap is one of the most often used flaps for closure of relatively large perineal defects. It is a well vascularised flap with sufficient vascular pedicle length and bulk, but disturbs the abdominal wall integrity. In the era of laparoscopic rectal cancer surgery, a VRAM flap for routine perineal closure seems to be too invasive with relatively high donor site morbidity. Furthermore, failure rates of a VRAM flap have been reported in up to 15%[11,17-18]. The gracilis flap can provide good coverage for the anterior perineal wound. However due the distal positioning of the vascular pedicle the mobility is restricted. According to the current literature, the lateral thigh flap can also pose as a good alternative for the reconstruction of the perineum. It is suitable for irradiated pelvis and may prevent perineal herniation due to the strong tensor fasciae latae[11]. Although promising, the literature on this topic is scarce, especially in oncological patients. In addition, the lateral thigh flap is most often performed by a plastic surgeon, has a difficult closure of the donor site, it may require an additional skin graft and the flap substantially increases surgery duration. Finally, a gluteal flap can be used for perineal closure after APR and can be performed as a myocutaneous flap or a perforator flap (IGAP/SGAP)[19]. The gluteal perforator flap lies outside the radiated field and transfers solely well vascularised skin and subcutaneous tissue into the perineal wound. Due to the transfer of only skin and subcutaneous tissue, patients experience less pain and morbidity at the donor site compared to the gluteal myocutaneous flap[20-21]. However, the gluteal myocutaneous flap has more bulk upon positioning in the pelvic wound, but due to the atrophy of the muscle the myocutaneous flap loses its size over time. The gluteal myocutaneous flap has less donor site morbidity compared to the VRAM flap by not disrupting the integrity of the abdominal wall, but still results in a big scar on the buttock with implications for daily life activities.

The perineal dead space after APR is often relatively limited and does not routinely require a large bulky tissue flap. A flap should therefore be relatively simple to perform, requiring only limited additional operative time, should be able to be combined with laparoscopic surgery, and should preferably not add additional scars. The gluteal turnover flap is a modified perforator flap which fulfills these criteria[22]. Recent meta-analysis of ten studies, including 8 studies using VRAM flap and 2 studies using gracilis flaps, found a significant reduction in perineal complications by flap reconstruction after APR compared to primary perineal wound closure (pooled perineal wound complication rate of 35% versus 52%, OR 2.17 (95% CI 1.49-3.15), heterogeneity I2=0%)[23]. Especially the major perineal wound complications were reduced (pooled proportions of 8% vs 25%, OR 3.64 (95% CI 1.70 - 7.79), I2=0%).

Results of own research

In our previous published systematic review with meta-analysis, a mean perineal wound complication rate up to 61% after APR was found (figure 1)[4]. The high morbidity rate after APR has resulted in a continuing discussion on how to close the perineal defect after extralevator abdominoperineal resection (eAPR). There is still no consensus on what should constitute the standard of care. We conducted a survey among Dutch colorectal surgeons, which revealed that 66% used primary closure exclusively. The remaining 34% of the responding surgeons reported the following clinical practices: routine biological mesh in 10% (3% of the whole group), selective use of biological mesh in 38% (13% of the whole group) and selective use of myocutaneous flap in 81% (28% of the whole group). An omentoplasty was routinely used if technically feasible in 71% and selectively used in 13%, while the remaining 16% never applied an omentoplasty [18].

Primary perineal closure is still considered routine practice in the Netherlands, with high inter-hospital variability in the use of an omentoplasty, and with a relatively limited use of primary flap repair or use of a biological mesh. In our published systematic review, a biological mesh seemed to reduce perineal wound complications [4]. This was the starting point to design and conduct a superiority trial on biological mesh reconstruction of the pelvic floor following APR, in which we decided to include only the highest risk group, namely those who underwent pre-operative radiotherapy. In this multicentre randomised trial (BIOPEX), rectal cancer patients undergoing APR after neo-adjuvant (chemo)radiotherapy were randomly assigned to primary perineal closure as a control arm and pelvic floor reconstruction using a biological mesh (Strattice 6x10cm) as the intervention arm [3]. Primary perineal closure was performed as a layered closure of the subcutaneous fat and perineal skin. The use of omentoplasty was at the discretion of the operating surgeon. Biomesh reconstruction was proctored in the participating centres, to ensure quality control of the intervention group. The primary endpoint, defined as perineal wound healing at 30 days (Southampton wound score <II), did not reveal a significant difference between the study arms (66% versus 63%, respectively (figure 2)). There was no difference at any point in time during 12 months of follow-up in perineal wound healing. The only difference between the two study arms was the proportion of perineal hernia after 12 months: 27% after primary closure versus 13% after biological mesh closure (figure 3; p=0.0316). Of these patients, only one patient in the primary closure group and one patient in the biological mesh group had a symptomatic perineal hernia. After a minimum of three years of follow-up, 56 patients were available for long-term outcome analysis. Any perineal hernia (both symptomatic and asymptomatic) was found in 28% after primary perineal wound closure and in 10% after perineal wound closure with a biological mesh (log rank p= 0.012) [Kaplan-Meier analysis, unpublished data]. The absolute reduction in perineal hernia rate is 18% after a minimum of 3 years of follow-up. Of these patients the majority are asymptomatic and do not need reconstructive surgery. If closure of a symptomatic perineal hernia is required, a synthetic mesh is used, because our group has shown that a biological mesh results in a high recurrent hernia rate [19]. The added mean duration of surgery due to the biological mesh place-

ment appeared to be 52 minutes, and increases direct medical costs. Therefore, the BIOPEX study did not change routine practice in the Netherlands, although there was a positive finding in one of the secondary endpoints. It is the feeling among most colorectal surgeons in the Netherlands that the added benefit of adding a Biomesh in all patients is too small to justify the routine use of an expensive mesh, especially because it does not have any positive influence on the most important clinical problem, which is non-healing of the perineal wound. Therefore, primary perineal wound closure remains the standard of care in the Netherlands.

It is hypothesised that the reason for not demonstrating any improvement in perineal wound healing by pelvic floor reconstruction using a biological mesh, is the perineal dead space between the perineal skin and the biological mesh. Fluid will accumulate in this dead space with the risk of secondary contamination and abscess formation, leading to wound dehiscence and purulent discharge. Other prophylactic measures to prevent perineal wound infections after APR, might be prophylactic antibiotics. However, for the antibiotics to be effective, a high antibiotic concentration at the designated site is warranted. Systemic or oral prophylactic antibiotics seem not to effect perineal wound infections. Local application of antibiotics can obtain higher local concentrations without systemic adverse reactions.

We performed a systematic review on the use of local gentamicin to improve perineal wound healing [20]. A total of four randomized trials were included. The overall perineal wound infection rate was not reduced by local gentamicin, neither superficial perineal wound infection rate and deep perineal wound infection rate. Based on this systematic review we concluded that current literature does not support routine application of local gentamycine for perineal closure after APR. In unplanned subgroup analysis of the BIOPEX-study, local application of gentamicin did also not significantly reduce perineal wound complications (p=0.539) [unpublished data].

Therefore, improvement in perineal wound healing can probably only be expected if the perineal dead space is filled with well vascularized tissue. Although an omentoplasty is often suggested to improve wound healing based on this mechanism, subgroup analysis of the BIOPEX study did not suggest any impact on perineal wound healing [2,3]. This was confirmed in a large collaborative snapshot research project, which was coordinated by our group. In this study, all rectal cancer resection that were registered in the Dutch Colorectal Audit in 2011 were included. Collaborators of the Dutch Snapshot Research Group completed this dataset with additional procedural data and long-term outcomes in 2015, resulting in a similar follow-up of approximately 4 years for all patients. Out of this dataset, 639 patients underwent APR, of which 477 were used to evaluate the impact of omentoplasty after APR with primary perineal wound closure. Although this was a cohort study, the value of the data forms the best available evidence because of 'pseudo randomisation' related to allocation to omentoplasty based on hospital variability, the size of the cohort, and the external validity by including both expert and non-expert centres. Non-healing of the perineal wound at 30-days was 47% after omentoplasty and 48% without omentoplasty, with a non-healing rate at end of follow-up of 9% and 5%, respectively. Pre-

sacral abscess developed in 12% and 13%, and re-intervention for small bowel obstruction was performed in 5% and 3%, respectively. Perineal hernia developed significantly more often after omentoplasty (13% vs. 7%; *P*=0.025), also by multivariate analysis (OR 2.61; 95%CI 1.271-5.364; *P*=0.009). This led us to conclude that routine use of omentoplasty should be questioned. More research is needed to determine whether omentoplasty might be of value in specific patient groups, for example in women with a wide pelvis that might have a significant posterior shift of the internal genital organs and bladder with functional implications. This is one of the topics of our current research.

Rationale for the BIOPEX-2 study

Present literature suggests that autologous tissue flaps might be the solution for perineal wound healing after APR. Because it is our feeling that the commonly used flaps are too invasive for routine use after APR for non-locally advanced rectal cancer, we have been looking for less invasive alternatives. Of the autologous tissue flaps, the GT flap is simple to perform, requires limited increase in operative time, does not add donor site morbidity or additional scars, and can be combined with laparoscopic surgery [21]. To evaluate the feasibility of the GT flap, we performed a pilot study at the Amsterdam University Medical Centre (location AMC) and Daniel den Hoed clinics [NL58380.018.16]. Rectal cancer patients were included and underwent a closure of the perineum after APR with a subcutaneous GT flap. The primary endpoint was the impact of the GT flap on perineal wound healing. Of the ten patients included, none of the GT flaps failed. There were no major wound complications within 30 days. Minor wound complications occurred in three patients, which consisted of a small wound dehiscence in two patients, and a small subcutaneous abscess with spontaneous drainage at one point.

2. OBJECTIVES

The primary objective of this study is to determine whether a GT flap closure of the perineum improves the rate of uncomplicated wound healing at 30 days compared to primary perineal closure, using the Southampton wound scoring system (score <II).

Secondary objectives of this study are:

1) Is Quality of Life and urogenital function after primary perineal closure and GT flap closure different? To what extent does complicated wound healing influence Quality of Life and urogenital function?
2) Is there a difference in the need for surgical re-intervention and need for re-admission between the two closure techniques?
3) What are specific procedure related complications of perineal closure using a GT flap, such as pain and seroma formation?
4) What are the incidences and severity of chronic (12 months p.o.) wound problems (perineal sinus, perineal fistula) after primary perineal closure and GT flap closure?
5) What is the incidence of perineal hernia after primary perineal closure and GT flap closure, both symptomatic and asymptomatic?

3. STUDY DESIGN

This is a multicentre single blinded study in which participating centres will perform standardized perineal dissection. The trial will be conducted in five Academic Medical Centres, six teaching hospitals and one non-teaching hospital, including a national referral centre for locally advanced rectal cancer. Eligible patients will be randomised between pelvic floor reconstruction using a GT flap (intervention arm) and primary closure of the perineal defect (standard arm). The allocation of treatment is blinded to the patient, only after the completion of the study the randomisation result will be announced Randomisation will be performed by a central automated randomisation using the trial website pre-operatively, with stratification for primary or recurrent rectal cancer and neo-adjuvant (chemo)radiation.

Colorectal cancer is one of the most common types of cancer worldwide. In the Netherlands about 2900 patients are being treated for rectal cancer each year, of which about 700 patients are treated by an abdominoperineal resection (APR) (Dutch Colorectal Audit 2016). Based on an estimated drop out of 5% due to unexpected death or withdrawal (www.cijfersoverkanker.nl), the estimated number of eligible patients for the BIOPEX II-study is about 665 each year. In daily practice, this number will appear to be much lower because of unfamiliarity with relevant trials and logistics in several Dutch hospitals. In addition, the use of the gluteal turnover flap will have to be performed by the surgeons of participating centres. To make it a uniform procedure the gluteal turnover flap will be learned and proctored by the project leader of the trial. This will take some time and therefore the participating hospitals will be opened in a phased fashion. However, the BIOPEX II study will be performed within existing trial collaboration, so the participating centres are familiar with performing randomized controlled trials. Because of the wide network of surgeons we have built during the BIOPEX study, it is expected that patient accrual in the BIOPEX II study can be completed in 34 months. The flow diagram of the study design is illustrated in Appendix 1.

The perineal wound healing will be evaluated at day 14 and 30 postoperatively using the Southampton wound scoring system (Appendix 2) by an independent observer not aware of the intervention to which the patient was allocated. In addition, full colour photographs will be taken from the perineal wound and assessed by an expert panel blinded for treatment allocation. During routine outpatient clinic visits for oncological follow-up at 3, 6 and 12 months, the perineal wound will be inspected and scored accordingly with respect to healing and herniation. In addition, CT scan of the pelvis as usually performed during oncological follow-up, will be reviewed with respect to pre-sacral or perineal sinuses and perineal herniation. Quality of Life and urogenital function questionnaires will be sent to the patients' home addresses at the start of the study and at 1, 3, 6 and 12 months after surgery. In the letter attached to the Quality of Life questionnaires, the patient will be asked to fill in the questionnaires (time duration: 15 minutes) and send them back to the hospital in the accompanied

return envelope (provided with postage stamps and the address of the hospital).

In addition, the nature and severity of any wound event, all medical or surgical interventions and re-operations will be collected.

4. STUDY POPULATION

4.1 Population (base)

The population will consist of patients with a clinical diagnosis of primary or recurrent rectal cancer who are scheduled for APR.

4.2 Inclusion criteria

In order to be eligible to participate in this study, a subject must meet all of the following criteria:

1) Resection of primary or recurrent rectal carcinoma by abdominoperineal resection.
2) Age of 18 years or older.
3) Ability to return for all scheduled and required study visits.
4) Written informed consent.

4.3 Exclusion criteria

A potential subject who meets any of the following criteria will be excluded from participation in this study:

1) The patient will undergo an intersphincteric abdminoperineal resection (iAPR).
2) Total pelvic exenteration or sacral resection above level S4/S5.
3) Severe systemic diseases affecting wound healing except diabetes (i.e. renal failure requiring dialysis, liver cirrhosis, and immune compromised status like HIV).
4) Collagen disorders (i.e. the syndrome of Marfan).
5) Enrolment in trials with overlapping primary endpoint.

4.4 Sample size calculation

The principal analysis will consist of an intention-to-treat comparison of the proportions of patients with primary uncomplicated perineal wound healing between both study arms. The hypothesis is to test superiority of the GT flap closure over primary closure of the perineum.

Our recent conducted pilot study showed promising results of the GT flap with a flap failure in zero patients of the ten patients included, and no Clavien Dindo complications of three or higher within 30 days of surgery. Among the ten patients, there were three minor complications and no major wound complications requiring re-intervention. The minor complications consisted of two wound dehiscences and a small subcutaneous abscess with spontaneous drainage at one point. A recent published case series of 13 patients undergoing an APR for rectal cancer showed no cases of flap loss and no donor site or major perineal morbidity after GT flap closure [22]. Combining these results with the recently published case series, results in an uncomplicated wound healing rate of 86% (19/22). In current literature an increase of uncomplicated perineal wound healing of ±20% is to be expected, when a muscle

flap is being used. However, the data were mostly derived from cohort series in which different kinds of flaps are being used with different definitions of complicated perineal wound healing. Therefore the currently available literature is difficult to interpret with regard to perineal wound healing. In our previously conducted randomized controlled trial (the BIOPEX-study), there was an uncomplicated perineal wound healing percentage of 66% after primary perineal wound closure. Extrapolating the reported improvement in perineal wound healing, a total number of 146 patients (73 per group) are needed to be able to detect a 20% increase in primary perineal wound healing by use of a GT flap from 65% to 85%, applying a Chi2-test with a two-sided 0.05 significance level and with 80% power. With an estimated drop-out of 10%, a total number of 160 patients are required (80 per group).

5. TREATMENT OF SUBJECTS

5.1 Standard care of the control arm

Surgery can start with the abdominal or the perineal phase. The abdominal phase of the APR can be performed via either laparoscopic or open surgery.
The perineal phase of the APR will be performed according to the principles of a complete or limited eAPR, which means that the levator muscles will be transected laterally in order to leave a muscular cuff around the resection specimen or only at the site of the tumour. The coccyx will not be routinely resected, but only if indicated based on surgical exposure or oncological principles. The extent of excision of perineal skin will be as limited as oncologically justified. The APR specimens will be classified according to Phil Quirke classification.
Standard practice in the Netherlands and the participating centre in the UK is simple primary closure of the perineum, with selective use of an omentoplasty. For the purpose of this trial and in accordance to most recent evidence, we decided to recommend only highly selective application of omentoplasty, for example in a female patients with a wide pelvis, especially after hysterectomy, to preserve anatomical position of the vagina and bladder. A transabdominal drain will be placed. Closure of the perineum in the control arm consists of stitching the perineal ischioanal fat together using interrupted 2.0 Vicryl sutures. Afterwards, the subcutaneous fat will be closed using interrupted 2.0 Vicryl sutures. A Redon drain (CH10) will standardly be placed between these layers and removed after 14 days or when the production is beneath the 10cc/24hours. Subsequently, the skin will be closed using interrupted Vycril 3.0 sutures.
Dry gauze will be placed against the wound and will be changed two times a day.
Postoperatively the ERAS protocol will be followed and the sutures will be removed after 14 days at the outpatient clinic. The abdominal drain will be removed after 4 days or if the drain production is beneath 100cc/hours. The perineal redon drain will be removed after 14 days or when the production is beneath the 10cc/24hours.

5.2 Investigational product/treatment

Surgery can start with the abdominal or the perineal phase. The abdominal phase of the APR can be performed via either laparoscopic or open surgery.
The perineal phase of the APR will be performed according to the principles of a complete or limited eAPR, which means that the levator muscles will be transected laterally in order to leave a muscular cuff around the resection specimen or only at the site of the tumour. The coccyx will not be routinely resected, but only if indicated based on surgical exposure or oncological principles. The extent of excision of perineal skin will be as limited as oncologically justified. An omentoplasty will not be stand-

ardly being performed. A transabdominal drain will be placed and removed after 4 days or when the drain production is beneath 100cc/24hours.
Perineal closure will be performed by a surgeon experienced with the GT flap. When this experience is not sufficiently present at the local participating hospital, an experienced (plastic) surgeon from the study group will perform or supervise the perineal phase at the local participating hospital. The patient will be positioned either in prone or lithotomy position as preferred by the operating surgeon. A shallow semicircular incision is made in the right or left gluteal skin with a maximum distance of about 2.5 centimetre from the adjacent perineal defect. The half-moon shaped skin island is de-epithelialized. The subcutaneous fat is transected lateral from the perforator(s) down to the gluteal fascia in a 45-degree angle. Gluteal perforators will not be selectively dissected, and for this reason there is no need for preoperative doppler identification of perforators, which simplifies the procedure. Thereafter, the subcutaneous flap is placed into the perineal defect and the de-epithelialized dermis is fixed to the contralateral pelvic floor remnant with Vycril 2.0 sutures. Afterwards, the subcutaneous fat will be closed using interrupted 2.0 Vicryl sutures over the GT flap. A Redon drain (CH10) will standardly be placed between the flap and the subcutaneous fat and removed after 14 days or when the production is beneath the 10cc/24hours. Subsequently, the skin will be closed using interrupted Vycril 3.0 sutures. Dry gauze will be placed against the wound and will be changed two times a day. Postoperatively the ERAS protocol will be followed and the sutures will be removed after 14 days at the outpatient clinic.

6. METHODS

6.1 Study parameters/endpoints

6.1.1 Main study parameter/endpoint

The primary endpoint of the study is the percentage of uncomplicated perineal wound healing defined as a Southampton wound score of less than II at 30 days postoperatively.

6.1.2 Secondary study parameters/endpoints

1) Surgery characteristics (duration of surgery, complications)
2) Effect of neo-adjuvant treatment on GT flap healing
3) Perineal wound healing according to the Southampton wound grading at 14 days, 3, 6 and 12 months postoperatively.
4) Cosmetic outcome and satisfaction with result.
5) Incidence of persistent perineal or pre-sacral sinuses, both clinically and by imaging (routine follow-up CT).
6) Need for re-intervention or re-admission related to pre-sacral abscess or other perineal wound problems.
7) Length of hospital stay.
8) Incidence of symptomatic and asymptomatic perineal hernia during follow-up.
9) Quality of life (EQ 5D-5L, EORTC-QLQ-C30-QL2, EORTC-QLQ-CR29, SF36) and urogenital function (UDI-6, IIQ-7, IIEF, FSFI, FSDS-R).
10) Postoperative pain score and duration.
11) Serious adverse events rate.

6.2 Randomisation, blinding and treatment allocation

Inclusion procedure

The study will be conducted in accordance to Good Clinical Practice. Suitable patients will be approached for entry into the study at the outpatient visit before surgery. The rationale for the study is explained to the patient. A written patient information sheet is provided and patients will be given the opportunity to ask questions. After a 3 day reflection period, the willing patients are asked to sign the consent form before the surgical procedure is planned. When consent has been obtained, the original form is kept in the study file and a copy is given to the patient. Baseline data as well as baseline questionnaires are collected. (Appendix 3)

Randomisation will take place before the APR is planned. Eligible patients will be randomized in a 1:1 ratio between primary closure of the wound or the use of a gluteal turnover flap and stratified for pri-

mary or recurrent rectal cancer and neo-adjuvant (chemo)radiation. Randomization will be performed by the patient's surgeon. Randomization will be performed by a central automated randomization using the trial website. The allocated treatment will remain unknown to the patient. In case the patient's surgeon is unfamiliar with the use of a gluteal turnover flap, a dedicated surgeon from the study group will be present during the operation and supervise the wound closure using the gluteal turnover flap. In addition, with the secure augmented reality platform 'Proximie' the dedicated surgeon is able to supervise the wound closure at a distance. Randomised patients will be assigned a sequential subject number. A log of the assigned subject numbers will be maintained by each site.

6.3 Study procedures

Standard care and the intervention of the experimental arm are described in paragraph 5. During the operative procedure, information about the surgical procedure will be collected.

Postoperatively, perineal wound healing will be evaluated at day 14 and 30 using the Southampton wound scoring system (appendix 2) by an independent observer not aware of the intervention to which the patient was allocated. In addition, full colour photographs will be taken from the perineal wound and assessed by an expert panel blinded for treatment allocation. Information regarding the duration of pre- and postoperative hospitalization and inpatient resource utilization will be collected. During the entire postoperative period, concomitant medications, adverse events, procedures and adjuvant therapies will be reviewed and documented.

During routine outpatient clinic visits for oncological follow-up at 3, 6 and 12 months, the perineal wound will be inspected and scored accordingly with respect to healing and herniation. In addition, CT scan of the pelvis as usually performed during oncological follow-up, will be reviewed with respect to pre- sacral or perineal sinuses and perineal herniation. Assessment of perineal hernia will be made with the patient in the standing position. Quality of Life and urogenital questionnaires will be administered to the patient at each follow-up interval. In addition, the nature and severity of any wound event, all medical or surgical interventions and or re-operations, local wound therapies like aspiration of seroma or hematoma or any procedure to treat an adverse event will be collected. The data collected are displayed in appendix 3.

Questionnaires

To measure Quality of Life and urogenital function, several questionnaires will be used. These questionnaires will be sent to the patients' home addresses at the start of the study and at 1, 3, 6 and 12 months after surgery. In the letter attached to the Quality of Life and urogenital questionnaires, the patient will be asked to fill in the questionnaires (time duration: 15 minutes) and send them back to the hospital in the accompanied return envelope (provided with postage stamps and the address of the hospital).

The following questionnaires will be used:
EQ 5D-5L (Euroqol): This questionnaire is a simple, generic instrument for describing and valuing health related quality of life. It includes 5 items (mobility, personal care, daily activities, pain, and anxiety-depression) that are answered on a 3-point scale ranging from no problems (level 1) to extreme problems (level 3).
Global quality of life (EORTC-QLQ-C30-QL2): This sub questionnaire contains the 2 items of the global quality of life dimension of the EORTC-QLQ-C30 questionnaire.
Global quality of life (EORTC-QLQ-CR29): This questionnaire is developed to assess the quality of life in colorectal patients.
Health and Labour questionnaire (adapted to the study setting): This questionnaire is designed to collect quantitative data on the impact of (treatment for) illness and resource utilization and absenteeism from work.
Quality of Life questionnaire (SF36): This questionnaire measures the relationship between a client's quality of life and other behaviours or affliction.Urogenital Distress Inventory (UDI-6): This questionnaire is used to determine the genitourinary symptoms and the discomfort they experience.
Incontinence Impact Questionnaire (IIQ): This questionnaire examines the influence of incontinence on activities and participation and makes physical, social and emotional functioning visible.
International Index of Erectile Function (IIEF): This questionnaire is used to measure various aspects of erectile performance.
Female Sexual Function Index (FSFI): This questionnaire evaluates and monitors woman sexual functioning as well as the level of dysfunction.
Female Sexual Distress Scale (FSDS-R): This questionnaire is multi-dimensional and measures female sexual dissatisfaction.

6.4 Withdrawal of individual subjects

Subjects can leave the study at any time for any reason if they wish to do so without any consequences. The investigator can decide to withdraw a subject from the study for urgent medical reasons.

6.5 Follow-up of subjects withdrawn from treatment

Patients whom have withdrawn from the study but are still willing in participating in the follow-up will be followed according to the specifications of the patient.

6.6 Premature termination of the study

At 6 weeks after inclusion of these patients the trial's safety data will be evaluated. The steering committee will be supplied with the number of (serious) adverse events in both groups at this time point. If there is a skewed distribution of the number of (serious) adverse events between the two groups an efficacy analysis can be performed at the discretion of the steering committee. Following these interim analyses, the steering committee will advise upon continuation of the trial.

7. SAFETY REPORTING

7.1 Temporary halt for reasons of subject safety

In accordance to section 10, subsection 4, of the WMO, the sponsor will suspend the study if there is sufficient ground that continuation of the study will jeopardise subject health or safety. The sponsor will notify the accredited METC without undue delay of a temporary halt including the reason for such an action. The study will be suspended pending a further positive decision by the accredited METC. The investigator will take care that all subjects are kept informed.

7.2 AEs, SAEs and SUSARs

7.2.1 Adverse events (AEs)

Adverse events are defined as any undesirable experience occurring to a subject during the study, whether or not considered related to the GT flap. All adverse events reported spontaneously by the subject or observed by the investigator or his staff will be recorded.

7.2.2 Serious adverse events (SAEs)

A serious adverse event is any untoward medical occurrence or effect that

- results in death;
- is life threatening (at the time of the event);
- requires hospitalisation or prolongation of existing inpatients' hospitalisation;
- results in persistent or significant disability or incapacity;
- any other important medical event that may not result in death, be life threatening, or require hospitalization, may be considered a serious adverse experience when, based upon appropriate medical judgement, the event may jeopardize the subject or may require an intervention to prevent one of the outcomes listed above.

The clinical course of each event should be followed until resolution, stabilisation or until it has been determined that study treatment or participation is not the cause. SAEs, which are still ongoing at the end of the study period, must be followed up to determine the final outcome.

The sponsor will report the SAEs through the web portal '*ToetsingOnline'* to the accredited METC that approved the protocol, within 7 days of first knowledge for SAEs that result in death or are life threatening followed by a period of maximum of 8 days to complete the initial

preliminary report. All other SAEs will be reported within a period of maximum 15 days after the sponsor has first knowledge of the serious adverse events.

A predefined list of SAE's will be reported periodically instead of individually using the CCMO-module *'ToetsingOnline'*. SAE's that will be listed and reported periodically are the following:

- SAE's related to postoperative complications
- SAE's related to wound healing problems
- SAE's that are classified by the steering group as 'not related to the trial'

7.3 Follow-up of adverse events

All AEs will be followed until they have abated, or until a stable situation has been reached. Depending on the event, follow up may require additional tests or medical procedures as indicated, and/or referral to the general physician or a medical specialist. SAEs need to be reported till end of study within the Netherlands and UK, as defined in the protocol.

Information on all AEs / SAEs will be recorded in the CRF. Furthermore, the investigators of the participating centres will report SAEs to the investigator via e-mail, fax or telephone. (P.J.Tanis@amsterdamumc.nl, G.D.Musters@amsterdamumc.nl, S.Sharabiany@amsterdamumc.nl, fax: +31 20 566 6569, telephone: +31 20 566 9111) upon occurrence.

7.4 Data Safety Monitoring Board (DSMB)

For this trial an independent DSMB committee will be established to perform ongoing safety surveillance and to perform interim analyses on the safety data. The DSMB is composed of two independent clinicians (prof. dr. M.G.H. Besselink and prof. dr. P. Fockens) and one independent epidemiologist (prof. dr. M.G.W. Dijkgraaf), each member has no conflict of interest with the sponsor of the study. The DSMB members should be familiar with the protocol and other documents related to the study; they are obliged to review, approve and sign the DSMB charter.
The specific responsibilities of the DSMB are to:

- Monitor safety data to guide recommendation for continuation of the study or early termination because of clear harm.
- Monitor efficacy data to guide recommendations for continuation of the study.
- Evaluate the overall conduct of the trial, including
  - monitoring of compliance with the protocol by participants and investigators
  - monitoring of recruitment figures and losses to follow-up
  - monitoring planned sample size assumptions
  - reports on data quality

- reports on completeness of data
- monitoring of continuing appropriateness of patient information

• During the first DSMB meeting, criteria for early termination of the study will be decided together with the DSMB team, after which the METC will be kept informed by an amendment.

The justifications for a recommendation to terminate the study due to clear harm will be based on data showing a notably increase of (serious) adverse events in the intervention group.

In addition, efficacy data of the perineal tumover flap will be kept. Interim analyses of efficacy data are presented only when planned in advance and appropriate statistical criteria for assessing evidence of efficacy have been clearly addressed. If an exception has been made to provide the Closed Session Report to non-voting members, the reasons and recipients will be clearly explained. Further information regarding efficacy data is written in the DSM Charter (Version 1.1, 25 April 2019).

The advice(s) of the DSMB will only be sent to the sponsor of the study. Should the sponsor decide not to fully implement the advice of the DSMB, the sponsor will send the advice to the reviewing METC, including a note to substantiate why (part of) the advice of the DSMB will not be followed.

Working hours of the DSMB members will be financially compensated to a maximum of €1320 per member.

8. STATISTICAL ANALYSIS

The primary endpoint, the percentage of uncomplicated wound healing defined as a Southampton wound score of less than II at 30 days postoperatively, will be compared between the two study groups (perineal closure using a GT flap/primary perineal closure). Using a two-sided Chi-square test with a significance level of 0.05 on an intention to treat basis. The primary endpoint will be further explored by comparing wound scores as categorical variable using the Mann Whitney U test. Furthermore, differences in time to healing between the two groups will be analysed as a censored continuous variable using Kaplan-Meier survival analysis. Statistical analyses will be performed using SPSS software for Windows version 26.

8.1 Secondary study parameter(s)

Treatment effects will be expressed as a relative risk with 95% confidence interval. Any binary secondary outcome measures (e.g. hernia rate, re-operation rate, infection rates, etc.) will be analysed in the same way as the primary outcome. Quality of life (e.g. EORTC-QLQ-C30- QL2) and urogenital data (e.g. UDI-6, IIQ-7, IIEF, FSFI, FSDS-R) will be graphically represented across all time points and analysed using a repeated measures analysis of variance. All analyses will be intention to treat, whereby patients will be analysed according to the treatment group to which they were randomised regardless of whether they complied with this treatment. All p-values will be two-tailed and a p-value of <0.05 will be considered statistically significant. Subgroup analyses will employ a test of interaction to explore whether there is evidence that the treatment effects differ across subgroups. As with all subgroups analyses these will be interpreted with caution, and will be considered hypothesis generating.

Analysis of quality of life and urogenital data

Quality of life and urogenital function data will be graphically represented across all time points and analysed according to the manuals and will presented as domain and summarized scores. Questionnaire outcome comparisons will be analysed using linear mixed models. All analyses will be according to the intention to treat principle, whereby patients will be analysed according to the treatment group to which they were randomized regardless of whether they complied with this treatment.

9. ETHICAL CONSIDERATIONS

9.1 Regulation statement

This study will be conducted according to the principles of the Declaration of Helsinki 64, October 2013) and in accordance with the Medical Research Involving Human Subjects Act (WMO) and other guidelines, regulations and Acts.

9.2 Recruitment and consent

The information offered to the patient or representative contains:

-a statement that the trial involves research

-a full explanation of the procedure to be followed

-a full explanation of the nature, expected duration, and purpose of the study

-a description of any reasonable foreseeable risks or discomfort to the patient

-a description of any benefits which may reasonably be expected

-a statement that patient data will be handled with care and confidentiality

-a statement that participation is voluntary, that refusal to participate will involve no penalty or loss of benefits to which the patient is otherwise entitled, and that the patient may discontinue participation at any time without penalty or loss of benefits, in which case the patient will receive standard treatment with the same degree of care

9.3 Objection by minors or incapacitated subjects

Minors and legally incompetent adults are excluded from the trial.

9.4 Compensation for injury

The AMC Medical Research BV has insurance, which is in accordance with the legal requirements in The Netherlands (Article 7 WMO and the Measure regarding Compulsory Insurance for Clinical Research in Humans of July 1st, 2015). This insurance provides cover for damage to research subjects through injury or death caused by the trial:

- € 650.000,-- (i.e. six hundred and fifty thousand Euro) for death or injury for each subject who participates in the research;
- € 5.000.000,-- (i.e. five million Euro) for death or injury for all subjects who participate in the research;
- € 7.500.000,-- (i.e. seven million five hundred thousand Euro) for the total damage incurred by the organization for all damage disclosed by scientific research for the AMC as ‘Sponsor (verrichter)’ in the meaning of said Act in each year of insurance coverage. The

insurance applies to the damage that becomes apparent during the study or within 4 years after the end of the study.
For UK participants NHS indemnity will apply.

9.5 Incentives

Enrolled patients will not receive any special incentives, compensation or treatment through participation in this trial.

10. ADMINISTRATIVE ASPECTS, MONITORING AND PUBLICATION

10.1 Handling and storage of data and documents

Every randomised patient will be assigned a three digit study number. Communication occurs only with this number. The full name and birth date of the patient will only be recorded on the informed consent form.

A study coordinator coordinates the study, monitors patient inclusion and protocol steps, data collection, data entry, preparation and performs analyses and will report the data. Continuous data monitoring, and data collection on a CRF will guarantee complete and real-time prospective recording of data. Data will be collected and stored at the AMC in a separate, closed room

10.2 Monitoring and Quality Assurance

No monitoring was being performed in the initial BIOPEX-study. In this study a biological mesh closure was used for the closure of the perineal wound and compared to the standard primary wound closure. Closure of the perineal wound with a flap is being performed all over the world and is considered a common technique [7].

Because it is a common technique, the risk assessment of the initial BIOPEX-study was negligible, and because the risk assessment of the BIOPEX II-study is also considered negligible no monitoring will be necessary (Appendix 5).

Description of work

The execution of central data management will be performed by a PhD-student. In addition, the local data management will be performed by the local investigator and monitored by the PhD-student. The continuous data monitoring and data collection based on high quality eCRFs guarantees complete and timely recording, handling and storage of data and documents. The PhD- student will also be responsible for collecting the Quality of Life and urogenital questionnaires.

Central Data management

The central data manager will maintain quality of documentation by local data managers in the eCRF, and clarify mistakes where necessary. The central data manager develops the eCRFs, adds participating hospitals to the database, tests the database, and informs the local data managers about how to use the database. Furthermore, the central data manager keeps the Trial Master File according to GCP guidelines. In case of uncertainties or questions in the eCRF, additional queries for the local data managers may be formulated by the central data manager.

Local Data management

Data is registered by the treating physician in the patient file, and registered in the eCRF by the local data manager.

10.3 Amendments

Amendments are changes made to the research after a favourable opinion by the accredited METC has been given. All amendments will be notified to the METC that gave a favourable opinion.
All substantial amendments will be notified to the METC and to the competent authority.
Non-substantial amendments will not be notified to the accredited METC and the competent authority, but will be recorded and filed by the sponsor.

A 'substantial amendment' is defined as an amendment to the terms of the METC application, or to the protocol or any other supporting documentation, that is likely to affect to a significant degree:

- the safety or physical or mental integrity of the subjects of the trial;
- the scientific value of the trial;
- the conduct or management of the trial; or
- the quality or safety of any intervention used in the trial.

10.4 Annual progress report

The investigator/sponsor will submit a summary of the progress of the trial to the accredited METC once a year. Information will be provided on the date of inclusion of the first subject, numbers of subjects included and numbers of subjects that have completed the trial, serious adverse events/ serious adverse reactions, other problems, and amendments.

10.5 Temporary halt and (prematurely) end of study report

The investigator/sponsor will notify the accredited METC of the end of the study within a period of 8 weeks. The end of the study is defined as the last patient's last visit.
The sponsor will notify the METC immediately of a temporary halt of the study, including the reason of such an action.

In case the study is ended prematurely, the sponsor will notify the accredited METC within 15 days, including the reasons for the premature termination.

Within one year after the end of the study, the investigator/sponsor will submit a final study report with the results of the study, including any publications/abstracts of the study, to the accredited METC.

10.6 Public disclosure and publication policy

Patients are entitled to public disclosure of the results of the trial on the basis of their participation in it. The results of research will be submitted for publication to peer-reviewed scientific journals. Agreements with respect to participation in publication will be made before the start of the trial. Only participating doctors from other centres will participate in publication if a substantial contribution to the trial (e.g. patient accrual, full completion of CRF or intellectual input) is made.

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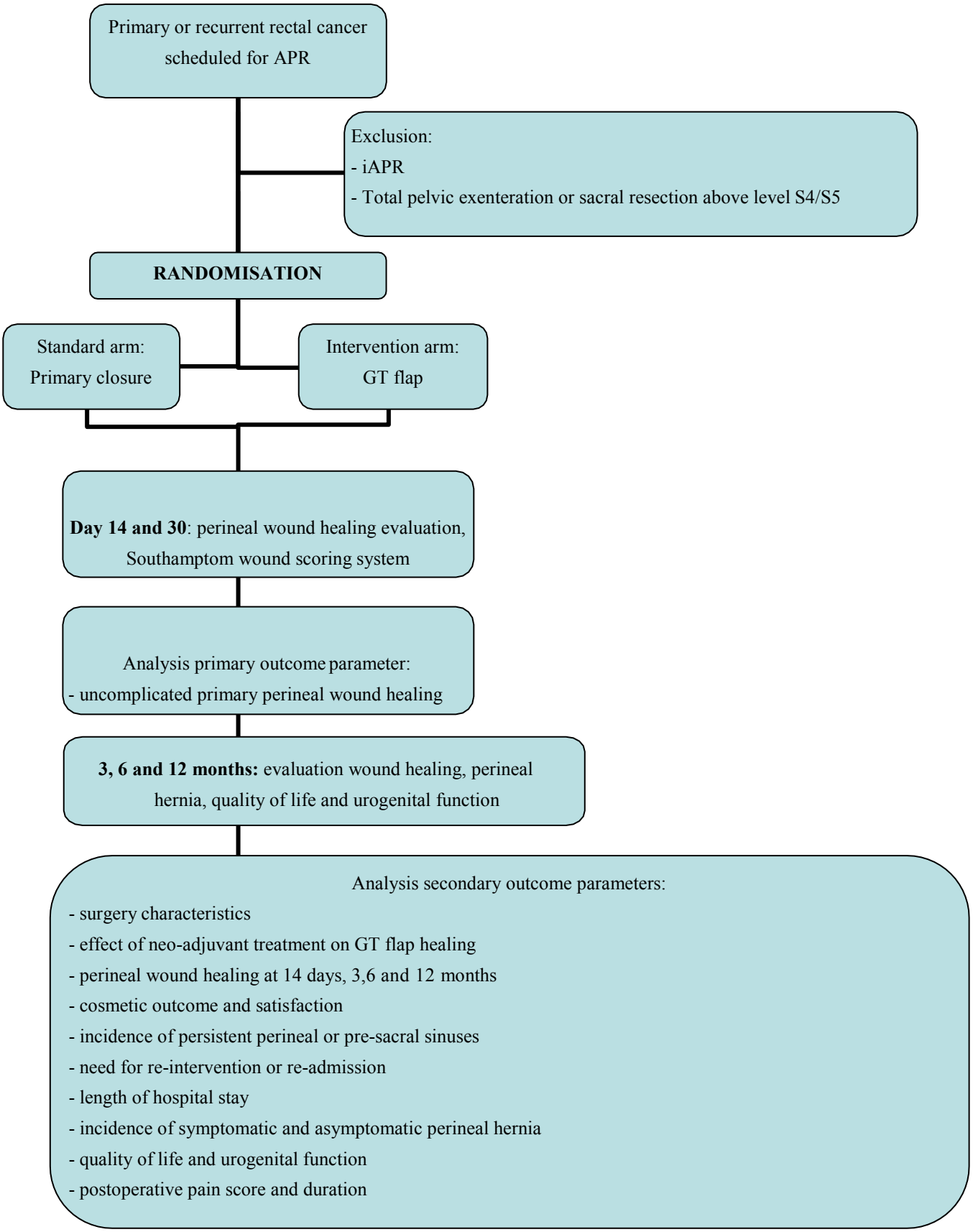
12. APPENDICES

Appendices content

Appendix 1: Flow diagram of the study design
Appendix 2: Southampton Wound Scoring System
Appendix 3: Data to be collected
Appendix 4: Timeline study
Appendix 5: Risk assessment
Appendix 6: Inclusion scheme

Appendix 1: Flow diagram of the study design



Appendix 2: Southampton Wound Scoring System

Class	Grade	Description	Appearance
Normal wound healing	**0**		Normal healing
	I	**Normal healing with mild bruising or erythema**	
		A	Some bruising
		B	Considerable bruising
		C	Mild erythema
Minor wound complications	**II**	**Erythema plus other signs of inflammation**	
		A	At one point
		B	Around sutures
		C	Along wound
		D	Around wound
	III	**Clear of haemoserous discharge**	
		A	At one point only (<2cm)
		B	Along wound (>2cm)
		C	Large volume
		D	Prolonged (>3days)
Wound Infection	**IV**	**Pus**	
		A	At one point only (<2cm)
		B	Along wound (>2cm)
Major wound complication	**V**	**Deep or severe wound infection with or without tissue breakdown, haematoma requiring aspiration**	

Appendix 3: Data to be collected

Baseline

- Demographics, length and weight
- Medical History
- Family history
- Current drug use
- ASA- classification
- Symptoms
- Tumour characteristics
- Pre-operative imaging
- Pre-operative pathology
- Neo-adjuvant treatment

Day of surgery

- Open / laparoscopic procedure / conversion
- Positioning of patient during perineal phase
- Change in tumour stage (i.e. peritoneal metastases)
- Additional resections (i.e. coccyx, vagina wall or prostate)
- Operation details (extralevatoric approach, omental plasty, drain use)
- Intraoperative complications (e.g. bleeding, urethral injury, tumour perforation)
- Suture materials
- Total operation time, separate time use for GT flap

Pathology of resected tumour

- Qualtiy of the resected specimen (Phill Quirke, colour photographs)
- Size of the tumour
- Resection margins
- TNM-stage

14 day's post operatively

- Southamptom wound score
- If applicable herniation specifications
- Colour photographs
- Post-operative complications
- Serious adverse events

1, 3, 6 and 12 months post operatively

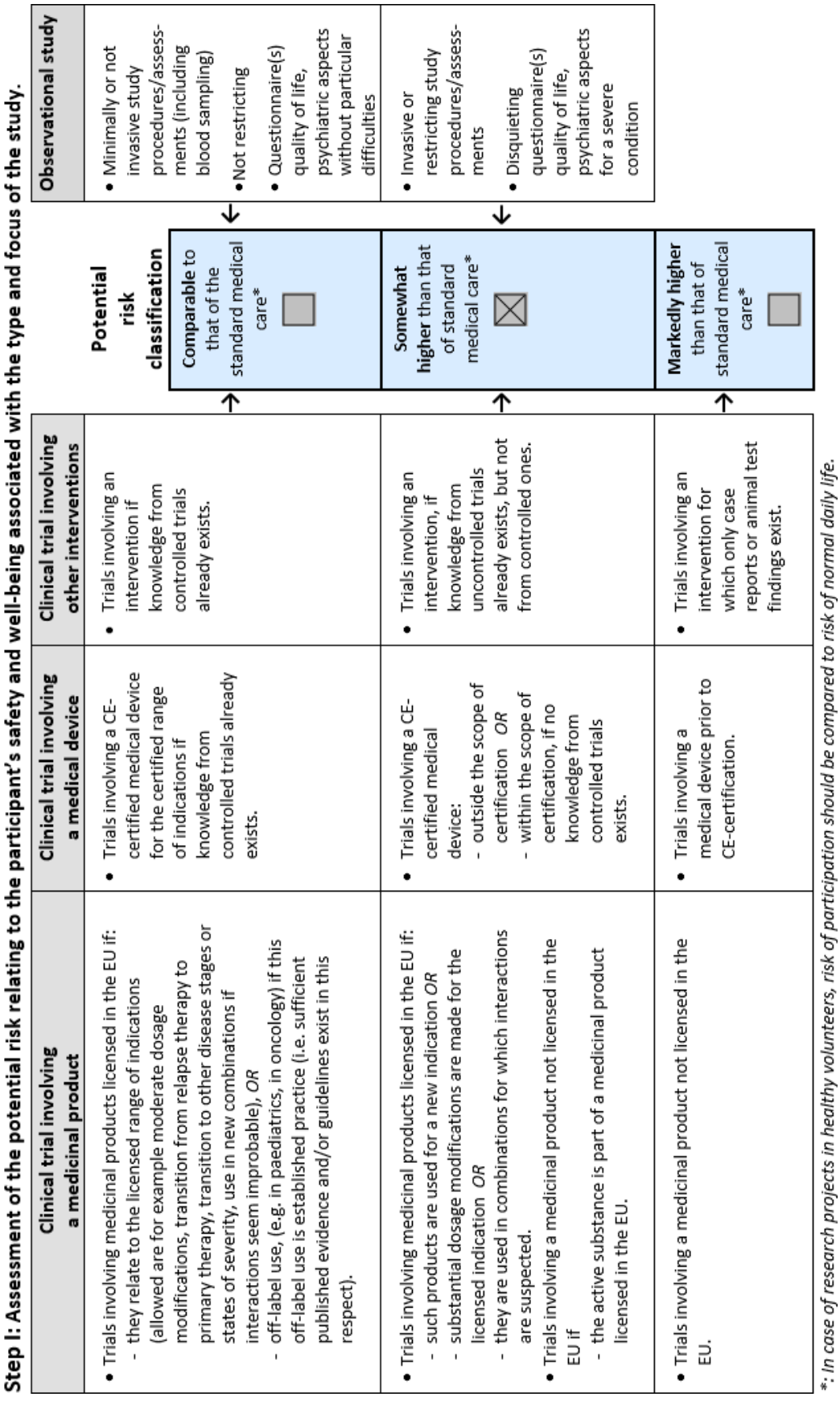
- Southamptom wound score
- Total in-hospital stay (including re-admissions/ nursing home stay)
- If applicable herniation specifications
- Colour photographs
- Re-operation / re-intervention related to perineal wound healing
- Imaging (CT as cancer surveillance)
- Serious adverse events

End of study

- Reason for the termination of the study
- Serious adverse event

Appendix 4: Timeline study	Screening Visit / Day before surgery	APR Surgery (DOS)	14 days p.o.	30 days p.o.	3 months p.o.	6 and 12 months p.o.
Informed Consent	X					
Baseline case record form	X					
Pre-operative case record form	X					
Adverse Events		X	X	X	X	X
Intervention case record form		X				
Perineal wound assessment /Southampton Wound Scoring / color photos			X	X	X	X
Perineal hernia assessment			X	X	X	X
CRF corresponding with time interval from surgery			X	X	X	X
CT (as normal cancer surveillance)						X
EQ 5D-5L (Euroqol)	X			X	X	X
Global quality of life (EORTC-QLQ-C30-QL):	X			X	X	X
Global quality of life (EORTC-QLQ-CR29):				X	X	X
Quality of Life questionnaire (SF36)	X				X	
Health and Labor questionnaire	X			X	X	X
Urogenital Distress Inventory (UDI-6)	X			X	X	X
Incontinence Impact Questionnaire (IIQ)	X			X	X	X
International Index of Erectile Function (IIEF)	X			X	X	X
Female Sexual Function Index (FSFI)	X			X	X	X
Female Sexual Distress Scale (FSDS-R)	X			X	X	X

Appendix 5: Risk assessment



Step II: Identification of further study specific factors.

Review the research protocol to identify specific factors that are critical for the participants' safety and well-being and/or rights and/or the validity of the results.
Here again, for participant-related risks, the risks identified should be balanced against the risks a participant would run if treated outside a study protocol. For each risk identified, consider the appropriate study management and/or monitoring strategy.
For guidance for each specific factor see Addendum.

F1. Potentially vulnerable population?
a. Will a vulnerable population be included? ☐ YES: *Continue with b;* ☒ NO: *Continue with F2.*
b. Does it mean a higher risk? *(check all that apply)* ☐ YES, for participant's safety, well-being ☐ YES, for participant's rights ☐ YES, for data validity ☒ NO *If 'YES' was chosen at least once, continue with c and d;* *If 'NO' was chosen, continue with F2.*
c. Which study management measures will be taken to control this risk?
d. Could on-site monitoring independently contribute to risk management in conjunction with the above mentioned control measures? ☐ YES ☐ NO

F2. Emergency medical treatment?
a. Will trial participants be recruited within the scope of emergency medical treatment? ☐ YES: *Continue with b;* ☒ NO: *Continue with F3.*
b. Does it mean a higher risk? *(check all that apply)* ☐ YES, for participant's safety, well-being ☐ YES, for participant's rights ☐ YES, for data validity ☐ NO *If 'YES' was chosen at least once, continue with c and d;* *If 'NO' was chosen, continue with F3.*
c. Which study management measures will be taken to control this risk?
d. Could on-site monitoring independently contribute to risk management in conjunction with the above mentioned control measures? ☐ YES ☐ NO

F3. Eligibility criteria
a. Are there any critical eligibility criteria? ☐ YES: *Continue with b;* ☒ NO: *Continue with F4.*
b. Does it mean a higher risk? *(check all that apply)* ☐ YES, for participant's safety, well-being ☐ YES, for participant's rights ☐ YES, for data validity ☐ NO *If 'YES' was chosen at least once, continue with c and d;* *If 'NO' was chosen, continue with F4.*
c. Which study management measures will be taken to control this risk?
d. Could on-site monitoring independently contribute to risk management in conjunction with the above mentioned control measures? ☐ YES ☐ NO

F4. Additional prescription medication for concomitant diseases/symptoms
a. Is it likely that participants receive additional medication for concomitant diseases/symptoms? ☐ YES: *Continue with b;* ☒ NO: *Continue with F5.*
b. Does it mean a higher risk? *(check all that apply)* ☐ YES, for participant's safety, well-being ☐ YES, for participant's rights ☐ YES, for data validity ☐ NO *If 'YES' was chosen at least once, continue with c and d;* *If 'NO' was chosen, continue with F5.*
c. Which study management measures will be taken to control this risk?
d. Could on-site monitoring independently contribute to risk management in conjunction with the above mentioned control measures? ☐ YES ☐ NO

F5. Lack or limited knowledge about the (combination of) intervention(s)
a. Is there a lack of or only very limited knowledge about the (combination) of intervention(s) being investigated? ☐ YES: *Continue with b;* ☒ NO: *Continue with F6.*
b. Does it mean a higher risk? *(check all that apply)* ☐ YES, for participant's safety, well-being ☐ YES, for participant's rights ☐ YES, for data validity ☐ NO *If 'YES' was chosen at least once, continue with c and d;* *If 'NO' was chosen, continue with F6.*
c. Which study management measures will be taken to control this risk?
d. Could on-site monitoring independently contribute to risk management in conjunction with the above mentioned control measures? ☐ YES ☐ NO

F6. Risks due to other study related procedures
a. Are any additional study procedures performed that carry significant risk, i.e. other than the intervention(s) being tested, and that are not part of standard care? ☐ YES: *Continue with b;* ☒ NO: *Continue with F7.*
b. Does it mean a higher risk? *(check all that apply)* ☐ YES, for participant's safety, well-being ☐ YES, for participant's rights ☐ YES, for data validity ☐ NO *If 'YES' was chosen at least once, continue with c and d;* *If 'NO' was chosen, continue with F7.*
c. Which study management measures will be taken to control this risk?
d. Could on-site monitoring independently contribute to risk management in conjunction with the above mentioned control measures? ☐ YES ☐ NO

F7. Risks due to barriers to compliance with the study protocol
a. Is the study complex and/or unusual compared to standard medical care, so compliance to the study protocol may be difficult for the site and/or participant? And/or any other barriers for compliance? ☐ YES: *Continue with b;* ☒ NO: *Continue with F8.*
b. Does it mean a higher risk? *(check all that apply)* ☐ YES, for participant's safety, well-being ☐ YES, for participant's rights ☐ YES, for data validity ☐ NO *If 'YES' was chosen at least once, continue with c and d;* *If 'NO' was chosen, continue with F8.*
c. Which study management measures will be taken to control this risk?
d. Could on-site monitoring independently contribute to risk management in conjunction with the above mentioned control measures? ☐ YES ☐ NO

F8. Risks due to participating sites
a. Are sites included that introduce particular vulnerabilities, e.g. inexperienced/under- resourced sites/research teams? ☐ YES: *Continue with b;* ☒ NO: *Continue with F9.*
b. Does it mean a higher risk? *(check all that apply)* ☐ YES, for participant's safety, well-being ☐ YES, for participant's rights ☐ YES, for data validity ☐ NO *If 'YES' was chosen at least once, continue with c and d;* *If 'NO' was chosen, continue with F9.*
c. Which study management measures will be taken to control this risk?
d. Could on-site monitoring independently contribute to risk management in conjunction with the above mentioned control measures? ☐ YES ☐ NO

F9. Risks from data collection and handling methods
a. Are data collection and handling methods complex/under-resourced and/or are any particularly sensitive data being collected? ☐ YES: *Continue with b;* ☒ NO: *Continue with F10.*
b. Does it mean a higher risk? *(check all that apply)* ☐ YES, for participant's safety, well-being ☐ YES, for participant's rights ☐ YES, for data validity ☐ NO *If 'YES' was chosen at least once, continue with c and d;* *If 'NO' was chosen, continue with F10.*
c. Which study management measures will be taken to control this risk?
d. Could on-site monitoring independently contribute to risk management in conjunction with the other above mentioned measures? ☐ YES ☐ NO

F10. Risks to the AMC organisation
a/b. Will the study concern aspects that carry a risk to the AMC organisation for the reputation and/or liability and/or financials? *(check all that apply)* ☐ YES, for the reputation ☐ YES, for liability ☐ YES, for financials ☒ NO *If 'YES' was chosen at least once, continue with c and d;* *If 'NO' was chosen, continue with F11 .*
c. Which study management measures will be taken to control this risk?
d. Could on-site monitoring independently contribute to risk management in conjunction with the above mentioned control measures? ☐ YES ☐ NO

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F11. Any other further risks
a/b. Are there any other further risks that could have a negative impact on participant's safety, well-being and/or participant's rights and/or data validity, that haven't been addressed adequately in the above factors? *(check all that apply)* ☐ YES, for participant's safety, well-being ☐ YES, for participant's rights ☐ YES, for data validity ☒ NO *If 'YES' was chosen at least once, continue with c and d;* *If 'NO' was chosen, continue with the summary.*
c. Which study management measures will be taken to control this risk?
d. Could on-site monitoring independently contribute to risk management in conjunction with the other above mentioned measures? ☐ YES ☐ NO

Summary of Step II further study specific risks:

Is at least one of the above questions (F1 – F 11) answered with 'YES'?

☐ **YES** ☒ **NO**

*If one or more further study specific factors are identified, that may significantly impact on the risk, consider to increase the potential risk classification of Step I, to arrive at the **final** risk classification.*

NOTE: If the potential risk level (Step I) is already classified as 'markedly higher' than standard medical care (or normal daily life for healthy volunteers), identification of further study specific risks (Step II) cannot further increase the risk classification. However, identification of these factors is relevant to consider escalation of study management and/or monitoring activities specifically focusing on these vulnerabilities.

Final risk classification, based on Step I and II:

☒ **negligible risk**
☐ **moderate risk**
☐ **high risk**

Approval

This document has been approved by:

Signature of Project Leader: _____ Date: 04-02-2019

Name: R. Nusters en Dr. Tonis

Appendix 6: Inclusion scheme