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Randomised clinical trial for the cost–utility evaluation of two strategies of perineal reconstruction after abdominoperineal resection in the context of anorectal carcinoma: biological mesh repair versus primary perineal wound closure, study protocol for the GRECCAR 9 Study

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ABSTRACT

Introduction Abdominoperineal resections performed for anorectal tumours leave a large pelvic and perineal defect causing a high rate of morbidity of the perineal wound (40%–60%). Biological meshes offer possibilities for new standards of perineal wound reconstruction. Perineal fillings with biological mesh are expected to increase quality of life by reducing perineal morbidity.

Methods and analysis This is a multicentre, randomised and single-blinded study with a blinded endpoint evaluation, the experimental arm of which uses a biological mesh and the control arm of which is defined by the primary closure after abdominoperineal resection for cancer. Patients eligible for inclusion are patients with a proven history of rectal adenocarcinoma and anal canal epidermoid carcinoma for whom abdominoperineal resection was indicated after a multidisciplinary team discussion. All patients must have social security insurance or equivalent social protection. The main objective is to assess the incremental cost–utility ratio (ICUR) of two strategies of perineal closure after an abdominoperineal resection performed for anorectal cancer treatment: perineal filling with biological mesh versus primary perineal closure (70 patient in each arm). The secondary objectives focus on quality of life and morbidity data during a 1-year follow-up. Deterministic and probabilistic sensitivity analyses will be performed in order to estimate the uncertainty surrounding the ICUR. CIs will be constructed using the non-parametric bootstrap approach. A cost-effectiveness acceptability curve will be built so as to estimate the probability of efficiency of the biological meshes given a collective willingness-to-pay threshold.

Ethics and dissemination The study was approved by the Regional Ethical Review Board of 'Nord Ouest 1' (protocol reference number: 20.05.14.60714; national number: 2020-A01169-30).
The results will be disseminated through conventional scientific channels.

Trial registration number ClinicalTrials.gov Registry (NCT02841293).

Strengths and limitations of this study

- This is a randomised controlled trial, ensuring minimal confounding.
- This is the first study of cost–utility evaluation comparing primary and mesh closure after extralevator abdominoperineal resection.
- The collection of costs will be exhaustive (eg, direct cost from the National Insurance Database and indirect costs from loss of productivity evaluation questionnaire).
- Perineal wound healing and quality of life evaluation will be double blinded.
- The expected sample size is adequate to evaluate the assessment of the incremental cost–utility ratio at 1 year but might be inadequate for secondary analyses.

BACKGROUND

Perineal wound problems after abdominoperineal resection (APR) in the context of cancer are frequent.[1] These types of resection problems occur because of wound complications caused by large perineal defects. Indeed, perineal wound complications, perineal

abscess, wound dehiscences, chronic fistulas and sinuses lengthen the hospital stays. Furthermore, the standardisation of the surgery since the late 2000s and the extralevator technique lead to a larger defect and increase in perineal complication.[2]

Several strategies are used to decrease the complication rate. Closure by direct approximation of the pelvic muscles leads to a rate of major complication up to 57% depending on the series.[3] Musculocutaneous flaps help to reduce this rate (16%–65%)[4] but they generate their own morbidity, require experience and increase the costs of care.[5 6] Finally, the use of biological meshes since the beginning of 2010 seems to have improve the healing process. However, results are still variable and the only randomised study comparing direct closure and mesh closure showed no significant results at 1 year.[7] Another ongoing randomised trial is comparing gluteus maximus flap to mesh closure and focusing on physical performances.[8]

This increase in postoperative complications and their consequences causes an increase in costs. In addition, they affect the patients' quality of life and lead to a loss of productivity. From an oncological point of view, perineal scarring problems can cause a delay in the adjuvant therapeutic sequence. Few studies have highlighted the efficiency of perineal wound complications, using cost-effectiveness analyses.[9] In order to clarify the best strategy comparing primary and mesh closure in term of cost-effectiveness on perineal healing after ELAPE (extralevator abdominoperineal excision), we designed this randomised controlled trial.

OBJECTIVES

Primary objective

The primary objective of this study is to assess the incremental cost–utility ratio (ICUR) at 12 months of two surgical strategies of pelvic reconstruction after ELAPE: biological mesh perineal reconstruction versus primary perineal closure in patients with proven rectal adenocarcinoma or anal canal epidermoid carcinoma, from the collective perspective.

Secondary objective

The secondary objectives are:

From a clinical perspective: to compare the effects of biological mesh perineal reconstruction versus primary perineal closure in patients with proven rectal adenocarcinoma or anal canal epidermoid carcinoma, with respect to the following: health-related quality of life, rate of perineal wound healing, healing time, perineal morbidity, pain intensity, pain medication, length of hospital stays, length of perineal nursing and time to initiation of first adjuvant therapy.

From an economic perspective: to assess, from the collective perspective, the cost-effectiveness at 12 months of the two surgical strategies; to assess, from the collective perspective, the budgetary impact of several scenarios of biological mesh perineal reconstruction diffusion; and to assess the production cost, from a hospital perspective, of the two surgical strategies with and without the use of meshes.

METHOD AND ANALYSING

Study design

This is a multicentre, two-arm parallel-group randomised (in a 1:1 ratio), single-blinded study (the patients are not aware of the treatment assignment) with blinded endpoint evaluation by an independent surgeon, assessing the ICUR after 12 months of biological mesh perineal reconstruction versus primary perineal closure in patients operated on for a low rectum carcinoma or an anal canal carcinoma by ELAPE. Seventeen French centres will contribute to the patient's recruitment during 24 months. Written informed consent and information will be obtained from patients before surgery by the referent surgeon.

Study population

Inclusion criteria

Patients must meet all the following criteria in order to be eligible to enrol in this study.

- Age ≥18 years.
- Eastern Cooperative Oncology Group performance status score of 2 or less.
- Proven history of rectal adenocarcinoma or anal canal epidermoid carcinoma.
- APR indicated after a multidisciplinary team discussion:
  - For rectal adenocarcinoma: circumferential MRI margin equal or less than 1 mm from the closest tumorous structure and a striated muscular layer (levator ani or external anal sphincter).
  - For epidermoid carcinoma: residual or recurrent tumour after chemoradiotherapy.
- Voluntary written informed consent.
- Patients with social security insurance or equivalent social protection.

Exclusion criteria

Any patient who meets the following criteria is not to be enrolled in this study:

- Tumour needing a surgical extensive resection with reconstruction by a musculocutaneous flap.
- Metastasis disease deemed unresectable with curative intent.
- Previous pelvic radiotherapy for another disease than the rectal or anal cancer.
- Immunosuppressive drug treatment.
- Uncontrolled diabetes (glycosylated haemoglobin >8% despite adequate therapy).
- Patient under juridical protection.
- Sensitivity to porcine-derived products.
- Enrolment in trial with overlapping primary endpoint.
- Pregnant women.
- Breastfeeding women.

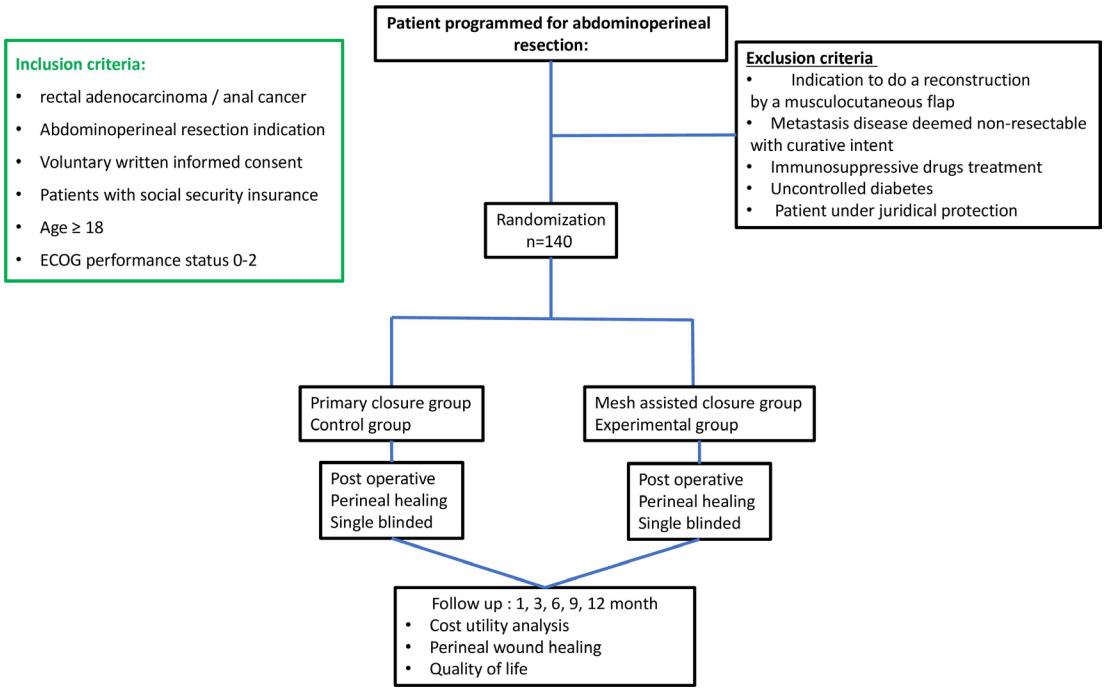

Figure 1 Study flow chart. ECOG, Eastern Cooperative Oncology Group.

Randomisation

All eligible patients after completion of the screening visit procedures will be randomly assigned in a 1:1 ratio to receive either a pelvic floor reconstruction using a biological mesh followed by primary perineal closure (experimental arm) or primary perineal closure only (control arm) (figure 1).

The randomisation will be stratified according to the dose of preoperative radiation therapy (less or equal to 50 Gy, higher than 50 Gy).

The random assignment will be done centrally using a web-based randomisation system following a randomisation schedule using a random permuted block design generated before the start of the study.

The randomisation schedule will be generated confidentially by a member of the statistic unit not involved in the study, in conjunction with the biostatistician of the study. The biostatistician of the study will not be aware of the randomisation schedule nor have access to it. Specifications of the randomisation schedule and details of its generation and validation will be fully documented. The randomisation schedule and related documentation will be maintained in a secure place by the statistic unit throughout the course of the study until it is terminated.

Blinding

The study is single blinded (the patient will not be aware of the treatment assignment) with blinded endpoint evaluation by an independent surgeon. The assessments will be performed by a senior surgeon blinded to the treatment assignment.

Surgery strategy

To ensure surgical standardisation, the abdominal resection and reconstruction techniques have been discussed and approved by all the GRECCAR group members, during a dedicated scientific session. The procedure will be only performed by trained surgeons.

The perineal phase of the APR will be performed according to the extralevator approach's strategies. The levator muscles will be laterally transected in order to leave a muscular cuff around the tumour. The coccyx resection is left to the discretion of the operating surgeon (only if indicated, based on surgical exposure or oncological principles). The extent of excision of perineal skin and ischioanal fat will be as limited as oncologically justified. The specimen will be examined according to Quirke's classification and photographed. The patients' position (prone or supine), the surgical approach for the abdominal phase (open or laparoscopic) and the use of an omental plasty are left to the discretion of the operating surgeon.

Closure of the perineum in the control arm involves stitching the ischioanal and subcutaneous fat using interrupted Vicryl sutures in one or two layers. The skin will be closed using interrupted sutures as per local protocols. Placement of a transabdominal or transperineal drain will be performed as per local protocols.

Surgery in the experimental arm involves suturing an acellular biological mesh in the pelvic floor defect (Cellis prosthesis from Meccellis Biotech, reference C1015E size 10×15 cm). The mesh will be sutured at each side of the coccyx or distal sacrum with Prolene or polydioxanone sutures. Laterally, the mesh is attached to the remaining of the levator complex and, anteriorly, to the transverse

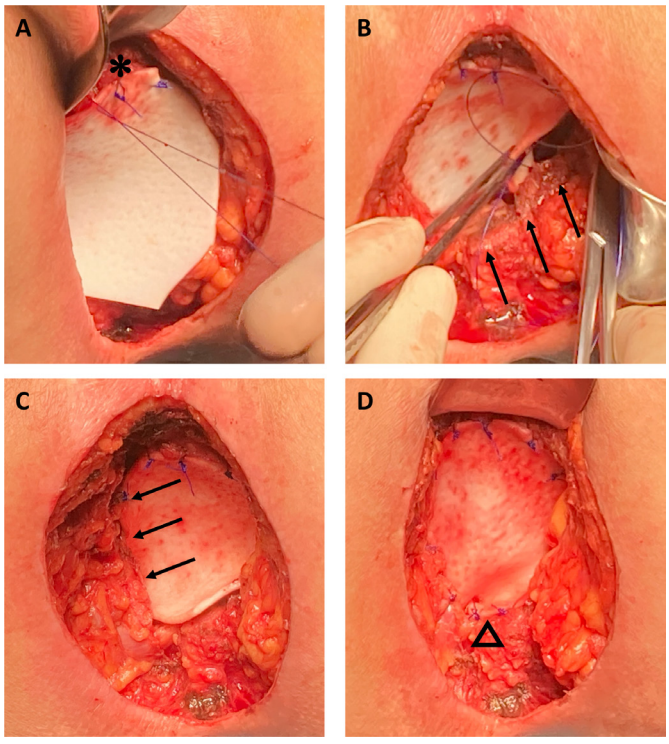

Figure 2 The pelvic floor seen from below during reconstruction with a Cellis biological mesh. The mesh is sutured anteriorly (A) to the transverse perineal muscle (*), laterally (B,C) the mesh is attached to the remaining of the levator complex (black arrows) and at each side of the coccyx or distal sacrum (Δ) with Prolene or polydioxanone sutures (D).

perineal muscle (figure 2). The perineal subcutaneous fat and skin will be subsequently closed in layers similar to the primary perineal closure, as performed in the standard arm. Placement of a transabdominal or transperineal drain will be performed as per local protocols.

Outcomes

Primary endpoint: ICUR

The primary endpoint in this study is based on the assessment of the ICUR at 1 year, from a collective perspective between biological mesh perineal reconstructions versus primary perineal closure in patients operated for an anorectal carcinoma with a proven rectal adenocarcinoma or an anal canal epidermoid carcinoma.

Health-related quality of life will be assessed using the EuroQol EQ-5D-5L questionnaire.[10 11] The questionnaire is designed to be self-administered. It should be administered before the patient sees the physician so that the interaction between the patient and the physician does not influence the patient's answers to the questions. EQ-5D-5L will be administered at six different time points: before surgery and at months 1, 3, 6, 9 and 12. Data will be collected from the Health Data National System (HDNS) (ie, Système National des Données de Santé) for direct medical and non-medical costs as well as for days of non-attendance. For other indirect costs, the data will be gathered using a specific questionnaire (figures 3 and 4).

Secondary endpoints

Specific perineal complications

Perineal wound healing, assessed at each visit during hospitalisation and at 1, 3, 6, 9 and 12 months after surgery by a senior surgeon blinded to the treatment assignment (figure 3). The local perineal wound complication will be classified according to the validated[12] Southampton Wound Assessment Scale[13] (table 1).

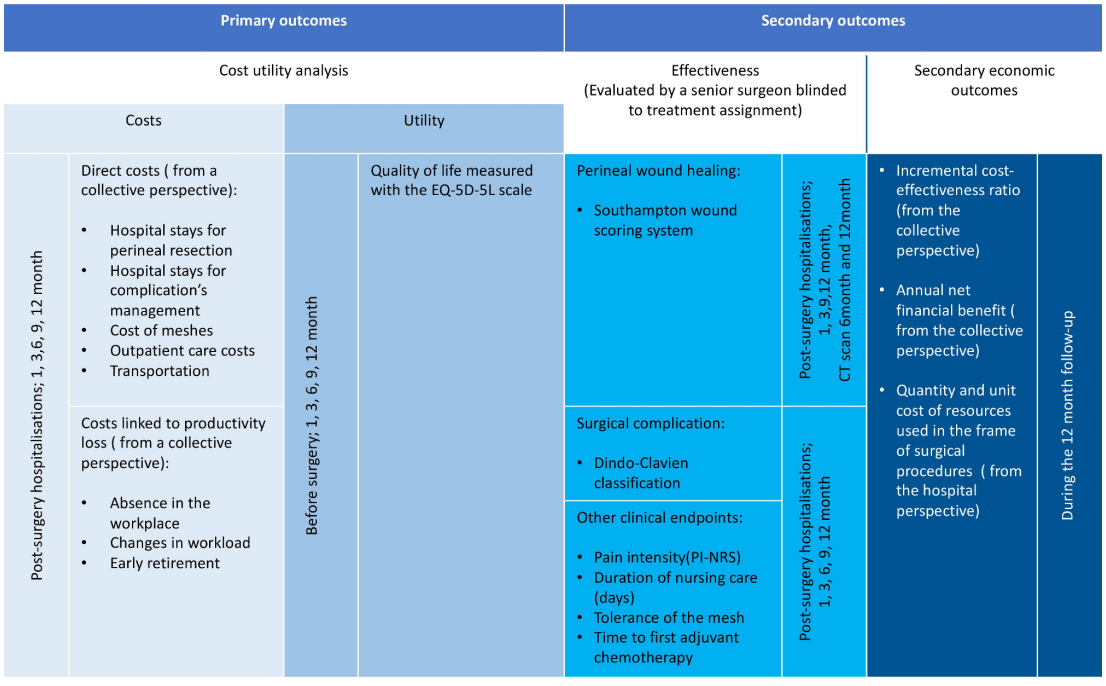

Figure 3 Outcomes summary. PI-NRS, Pain Intensity Numerical Rating Scale.

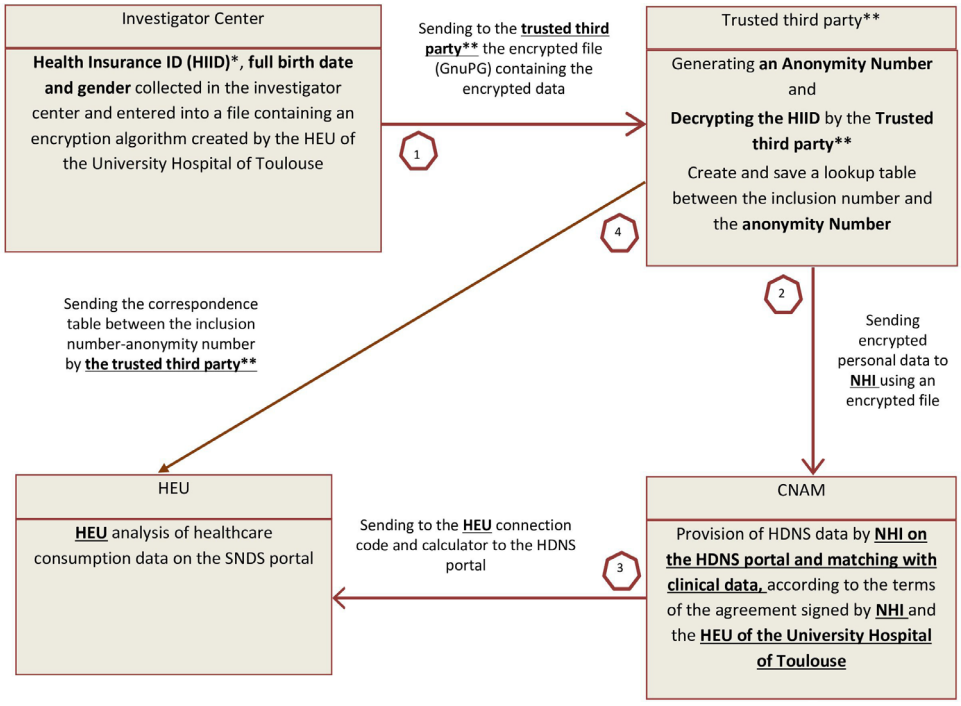

Figure 4 Flow chart for transmission of healthcare consumption data. *Health insurance ID or NIR for registration number to the listing. **Emergency Regional Observatory of Occitanie. ***Patients identified with their anonymity number. CNAM, Caisse Nationale de l'assurance Maladie et des travailleurs salariés; HDNS, Health Data National System; HEU, health economic unit; NHI, National Health Insurance; SNDS, Système National des Données de Santé.

Time to complete perineal healing is defined as the time from randomisation until complete healing. Complete healing will be assessed using the Southampton Wound Scoring System by an independent surgeon. A score of less than 2 will define complete healing.

Postoperative complications

Complications after surgery will be based on the Dindo-Clavien score.

Pain evaluation will be assessed on an 11-point Numerical Rating Scale at baseline before surgical procedure and at least three times a day during the hospital stay. Thereafter, patients will rate the intensity of their pain in a patient diary every day and immediately before each intake of pain medication. Pain medication will be summarised and reported by the study's team and from the patient daily diary at each patient visit.[14] The length of hospital stay is defined as the total number of consecutive days from randomisation to discharge after surgery. The number of days the patients stay at another unit for treatment of complications or comorbidities will be included in the calculation. The duration of the nursing care will be defined as the total number of days a nurse is required for perineal care as of discharge. Time to first adjuvant chemotherapy cycle defined as the time from randomisation up to the date of cycle 1 day 1 of first adjuvant treatment.

Table 1 Southampton Wound Assessment Scale

Grade	Definition
0	Normal healing
I	Normal healing with mild bruising or haematoma
II	Erythema plus other signs of inflammation
III	Clear or haemoserous discharge
IV	Pus
V	Deep or severe wound infection with or without tissue breakdown; haematoma requiring aspiration

From an economic perspective

We will evaluate:

- The incremental cost-effectiveness ratio (ICER), from a collective perspective at 12 months, is expressed as the cost per number of complications avoided between biological mesh perineal reconstructions versus primary perineal closure in patients operated for an anorectal carcinoma with a proven rectal adenocarcinoma or an anal canal epidermoid carcinoma.
- The annual net financial benefit over a cumulative 5-year period of systematic use of meshes in the frame of APR versus primary perineal closure in patients operated for anorectal carcinoma, from the collective perspective.
- Quantity and unit cost of resources used in the frame of surgical procedures with and without meshes as well as its impact on initial inpatient stay.

Sample size calculation

The primary objective of this protocol is to assess the ICUR at 12 months of two surgical procedures of pelvic

reconstruction. A difference of 0.5 SD for EQ-5D-5L between arm A and arm B will be considered clinically meaningful.[15] This effect size will be detected with at least 80% power, using a two-sided t-test with a 5% two-sided significance level and a drop-out rate of 10%.

Furthermore, based on the literature which indicates that the rate of early complications following conventional primary perineal wound closure may range between 35% and 65% (Foster colorectal disease 2012), a sample size of 140 patients will also provide at least 80% power assuming an absolute difference in complication rate of 25% (with the conventional arm response at 45%). The other parameters used in the calculation are a two-sided X^2 test with a two-sided significance level of 0.05, a drop-out rate of 10%.

Additionally, the sample size was calculated according to the ICUR using the Glick formula. ICUR will result in cost per quality-adjsted life-year (QALY).[16] According to a study conducted in 2012, the cost difference will be –€5704 (SD €8000) in favour of biological meshes.[5] According to a study assessing the significant minimum difference in terms of QALY, we estimate a difference of 0.06 (SD 0.20) in favour of biological meshes.[17] The correlation coefficient was estimated at –0.6 using an analysis of variance. The willingness-to-pay threshold has been set at €50 000. This effect size will be detected with at least 90% power, using a two-sided t-test with a 5% two-sided significance level. The drop-out rate has been set at 10%. The total sample size was evaluated at 132, in other words 66 patients to be recruited per arm.

The calculation of the number of subjects to be included in the study, using the Glick formula, was carried out based on conservative assumptions in terms of cost of care and utility. In fact, the cost difference was calculated using inflated costs (€2020) and all the complications avoided, thanks to biological meshes, those were not included in the cost calculation. Furthermore, concerning the significant minimum difference of QALY, the article by Walters *et al* proposes a mean of 0.074 and an SD of 0.10. We have chosen to include in our calculation an average difference of 0.06 and an SD of 0.2.

Data analysis

A Statistical Analysis Plan will be issued prior to database lock. The statistical analysis will be conducted at the Toulouse University Hospital within the Medico-Economic Evaluation Unit for the medico-economic evaluation criteria, and by a biostatistician in the Methodological Support Unit for Research for the other criteria. The analyses will be conducted using the SAS analysis software V.9.4 or later or using Stata V.14.2 or later.

Subject populations for analysis

The modified intent-to-treat (mITT) population is defined as all subjects who are randomised and who will undergo APR, whether they underwent or not the procedure under study (biological mesh). All the subjects in the population will be analysed according to the procedure they were randomised to receive and not according to what they actually received, if different.

The subjects' disposition, demographics, baseline characteristics and all analyses will be based on the mITT population.

The per-protocol population is the subset of patients in the mITT population who is characterised by the absence of any major deviation (ie, likely to affect the assessment of the procedure under study), such as compliance to procedure assignment, availability of measurements of the primary endpoint and no intake of prohibited concomitant treatment.

Demographic and baseline characteristics

All the study's variables will be presented by arms and on an overall basis, by using the appropriate descriptive statistics according to the type of variable.

- Continuous variables: number of non-missing observations, mean and SDs otherwise median and IQRs.
- Categorical variables: number of non-missing observations and percentages.

The comparability of treatment groups will be checked. Descriptive statistics will be used to tabulate the baseline characteristics. The number of patients who enrol, discontinue, complete the study and the reasons for early termination will be summarised per treatment group.

Cost–utility analysis

A cost–utility analysis will be performed. This study will establish a link between costs and medical consequences, expressed in QALY gained at 12 months between the two strategies. The ICUR between patients who receive the biological meshes and those who receive traditional care will be calculated. The cost differential will be reported into the utility differential between the two strategies.

Cost analysis

The conventional method for comparing average costs between the two groups of patients is the Student's t-test. This test is based on the assumption that data independence and the normality of the distributions of costs in each group are being compared. The latter is contrary to the nature of cost distributions, which in most cases is dispersed to the right. The assumption of distribution normality may in many cases not be respected. The Mann-Whitney U test could be used. Indeed, it makes no assumption on data distribution. However, it does not compare the mean costs but the median costs, and the results are sensitive to the heterogeneity of the group's variances. An alternative to these parametric and non-parametric methods for cost comparison between two groups of patients is the non-parametric bootstrap approach. This is the method we have chosen to implement.

Cost-effectiveness analysis

In addition, a cost-effectiveness analysis will be performed on the same model as the cost–utility analysis, except that medical consequences will be expressed in terms of avoided complications. The ICER between patients in the

two strategies will be calculated.[18] Differential costs will be reported to the differential effectiveness between the two strategies.

Data discounting

Data discounting will not be performed considering the short follow-up period. Discounting which consists of taking into consideration the preference of individuals for the present time is not justified because of the 12-month follow-up period.[18 19]

Sensitivity analyses

In order to test the robustness of the results, a multivariate sensitivity analysis will be performed. This analysis will measure the impact of the cost variation and the utility parameters on the ICUR and ICER.[20]

In addition, a probabilistic sensitivity analysis which estimates the uncertainty around the ICUR and ICER will be performed. CIs will be constructed using the non-parametric bootstrap method.[20]

Secondary medical endpoints

Health-related quality-of-life is assessed using the EQ-5D-5L questionnaire.

Analyses will be carried out on the subset of patients in the ITT population who have both baseline and at least one post-baseline EQ-5D-5L assessment.

The Health State Index score will be derived for the EQ-5D-5L descriptive system and the EuroQol Visual Analogue Scale score from the scoring procedure recommended by the EuroQol group, as described in the EQ-5D-5L User Guide V.3.0.

The scale's scores, values and changes from the baseline will be summarised at each scheduled assessment time point using the following descriptive statistics: mean, SD, first quartile, median, third quartile, minimum and maximum values. Furthermore, changes from baseline will be analysed on the basis of a likelihood-based mixed-effects model for repeated measures (MMRM), the model will include the main effects for the arms, assessment time points and stratification factors, the interaction terms per arm per assessment time point, and the baseline scale score value as a covariate.

The rate of perineal wound healing, the number and percentages of patients with complete perineal wound healing will be summarised in each arm and at each time point and compared using a two-sided Cochran-Mantel-Haenszel test, stratified by the stratification factors.

For healing times, the duration of the hospital stay, the duration of the perineal nursing and the time of initiation of the first adjuvant therapy survival curves will be estimated using the non-parametric Kaplan-Meier method. Point estimates and corresponding two-sided 95% CI using the Greenwood's SE estimate will be provided at selected time points in each arm. Comparisons between the two arms will be made using a two-sided stratified log-rank test controlling for stratification factors. The effect size will be estimated using a multivariate Cox proportional hazards model adjusted to stratification factors. The adjusted HR along with the corresponding two-sided CI will be provided.

Perineal morbidity and postoperative complications: all complications will be summarised per primary system organ class and preferred term. The proportion of patients experiencing complications, grade 3–4 complications and complications leading to death (grade 5) will be summarised per arm and compared using a two-sided Fisher's exact test. The overall perineal morbidity will be calculated using the Comprehensive Complication Index and compared using a linear regression model adjusted to stratification factors.[21]

Pain intensity: rating of pain intensity will be averaged over 1 week during hospitalisation and over a 4-week period after discharge. These two distinct periods will be analysed separately. Change from baseline will be summarised using the following descriptive statistics: mean, SD, first quartile, median, third quartile, minimum and maximum values. Furthermore, changes from baseline will be analysed on the basis of a likelihood-based MMRM, the model will include main effects for the arms, assessment time points and stratification factors, the interaction terms per arm per assessment time point and the baseline scale score value as a covariate.

Pain medication: the number and percentage of patients who received pain medication will be summarised per arm according to the WHO Drug Dictionary anatomical main group and therapeutic subgroup. The percentages of patients free of pain medication will be summarised in each arm and at each time point and compared using a two-sided Cochran-Mantel-Haenszel test, stratified to stratification factors.

Patient and public involvement

Patients and/or the public were not involved in the development of this study, except the informed consent validated by a patient association.

DATA COLLECTION/MANAGEMENT

Clinical data

All the information required by the protocol must be entered in an electronic data capture system. The investigator will ensure the accuracy, completeness and timeliness of the reported data. A complete audit trail on all data changes will be maintained. The investigator or designee will cooperate with the monitor and the data manager for the periodic review of data in order to ensure the accuracy and completeness of the electronic data capture system at each scheduled monitoring visit and before any submission of results.

The data are collected on an electronic case report form.

All the information will be contained in the original documents, or in the authenticated copies of said documents; and relating to clinical examinations, observations or other activities conducted as part of a research study

and necessary for the reconstitution and evaluation of the research. The documents in which the source data are saved are called the source documents.

The source documents include medical files, results from original biological examinations, MRI examination reports, CT scan examination reports, EQ-5D-5L questionnaires filled out by the patients, pathological reports and patient diaries.

Healthcare consumption data will be recorded at a national level from the HDNS thanks to the French Health Insurance. The Health Insurance ID (HIID), generally used by health insurance agencies to identify patients, will be used as the identification key for the patients included in the study. This is allowed since the publication of the decree no. 2017-412 (27 March 2017) pertaining to the use of the HIID as a national health identifier. The HIID of each patient will be gathered in each participating centre. For the HIID, the confidentiality of identifying data (full birth date and gender), in accordance with the directives of the National Commission of Informatics and Liberties (ie, Comission Nationale Informatique et Libertés) will be respected through the use of a trusted third party, as shown in figure 4.

QUALITY CONTROL

A clinical researcher appointed by the sponsor will regularly visit each investigating centre during the implementation of the research, one or several times during the research phase according to the frequency of the inclusions and at the end of the research phase. During these visits and in accordance with the risk-based monitoring plan (participant, logistics, impact, resources), the following will be reviewed:

- Informed consent.
- Compliance with the research protocol and the procedures defined therein.
- Quality of the data collected in the electronic data capture system: accuracy, missing data, consistency of the data with the source documents (medical records, appointment books, originals of laboratory results and so on).
- Management of potential products.

All visits will be the subject of a written monitoring report.

ETHICS AND DISSEMINATION

Ethics and safety

This study will be conducted according to the principles of Good Clinical Practice or the ethical principles stated in the most recent version of the Declaration of Helsinki. The study was approved by the Regional Ethical Review Board of 'Nord Ouest 1' (protocol reference number: 20.05.14.60714; national number: 2020-A01169-30). The informed consent document (online supplemental file 1) with study information will be used to explain in simple terms to patients what participation in the study means for the patient.

Dissemination

Study information will be publicly available at www.clinicaltrials.gov. The results of this trial will be submitted for publication in relevant peer-reviewed publications and the key findings presented at national and international conferences. Dissemination will be done under the responsibility of the study's coordinating investigator with the agreement of the principal investigators. The coauthors of the report and the publications will be the investigators and clinicians involved, on a pro rata basis of their contribution in the study as well as the statistician, methodologist and economic researcher.

Sharing of data generated by this project is an essential part of our proposed activities and will be carried out in several different ways. We would wish to make our results available both to the community of scientists interested in colorectal disease to avoid unintentional duplication of research and improve the current standard of care.

Our plan includes the following:

- Presentations at national and international scientific meetings.
- Biannual meeting of the interest group: presentation of the data is planned all along the project to the cooperator group GRECCAR, this is an opportunity to discuss things with the participant investigator of the project.
- Publication: the generated results/data will be shared through public publications as soon as the results analysed are available.

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REFERENCES

1 Blok RD, Hagemans JAW, Klaver CEL, *et al*. A systematic review and meta-analysis on omentoplasty for the management of abdominoperineal defects in patients treated for cancer. *Ann Surg* 2020;271:654–62.
2 West NP, Anderin C, Smith KJE, *et al*. Multicentre experience with extralevator abdominoperineal excision for low rectal cancer. *Br J Surg* 2010;97:588–99.
3 Musters GD, Buskens CJ, Bemelman WA. Perineal wound healing after abdominoperineal resection for rectal cancer: a systematic review and meta-analysis. *Dis Colon Rectum* 2014;57:1129–39.
4 Devulapalli C, ATJ W, Dibiagio JR. Primary versus flap closure of perineal defects following oncologic resection: a systematic review and meta-analysis. *Plast Reconstr Surg* 2016;137:1602–13.
5 Peacock O, Pandya H, Sharp T, *et al*. Biological mesh reconstruction of perineal wounds following enhanced abdominoperineal excision of rectum (APER). *Int J Colorectal Dis* 2012;27:475–82.
6 Woodfield J, Hulme-Moir M, Ly J. A comparison of the cost of primary closure or rectus abdominis myocutaneous flap closure of the perineum after abdominoperineal excision. *Colorectal Dis* 2017;19:934–41.
7 Musters GD, Klaver CEL, Bosker RJI. Biological mesh closure of the pelvic floor after extralevator abdominoperineal resection for rectal cancer: a multicenter randomized controlled trial (the BIOPEX-study). *Ann Surg* 2017;265:1074–81.
8 Rutegård M, Rutegård J, Haapamäki MM. Multicentre, randomised trial comparing acellular porcine collagen implant versus gluteus maximus myocutaneous flap for reconstruction of the pelvic floor after extended abdominoperineal excision of rectum: study protocol for the Nordic extended abdominoperineal excision (NEAPE) study. *BMJ Open* 2019;9:e027255.
9 Billig J, Hsu J, Zhong L. Comparison of effective cost and complications after abdominoperineal resection: primary closure versus flap reconstruction. *Plast Reconstr Surg* 2019;144.
10 Chevalier J, de Pouvourville G. Valuing EQ-5D using time trade-off in France. *Eur J Health Econ* 2013;14:57–66.
11 Essink-Bot M-L, Stouthard MEA, Bonsel GJ. Generalizability of valuations on health states collected with the EuroQolc-questionnaire. *Health Econ* 1993;2:237–46.
12 Karran SJ, Karran SE, Toyn K, *et al*. Antibiotic prophylaxis in clean surgical cases and the role of community surveillance. *Eur J Surg Suppl* 1992:31–2.
13 Bailey IS, Karran SE, Toyn K, *et al*. Community surveillance of complications after hernia surgery. *BMJ* 1992;304:469–71.
14 Dindo D, Demartines N, Clavien P-A. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. *Ann Surg* 2004;240:205–13.
15 Norman GR, Sloan JA, Wyrwich KW. Interpretation of changes in health-related quality of life: the remarkable universality of half a standard deviation. *Med Care* 2003;41:582–92.
16 Glick HA. Sample size and power for cost-effectiveness analysis (Part 2): the effect of maximum willingness to pay. *Pharmacoeconomics* 2011;29:287–96.
17 Walters SJ, Brazier JE. Comparison of the minimally important difference for two health state utility measures: EQ-5D and SF-6D. *Qual Life Res* 2005;14:1523–32.
18 Drummond MF, Drummond MF, O'brien BJ. *Méthodes d'évaluation économique des programmes de santé*. Paris: Economica, 1998.
19 Santé HAdela. Guide des choix méthodologiques pour l'évaluation médico-économique. *Octobre* 2011.
20 Jo C. Cost-of-Illness studies: concepts, scopes, and methods. *Clin Mol Hepatol* 2014;20:327–37.
21 Slankamenac K, Graf R, Barkun J, *et al*. The comprehensive complication index: a novel continuous scale to measure surgical morbidity. *Ann Surg* 2013;258:1–7.