STUDY SYNOPSIS

Title of study	A randomized clinical trial comparing laparoscopic or robot-assisted radical/simple hysterectomy versus abdominal radical/simple hysterectomy in patients with early-stage cervical cancer
Short term	G-LACC (German-funded Laparoscopic Approach to Cervical Cancer)
Responsible investigator	Prof. Dr. Peter Hillemanns Hannover Medical School Department of Gynecology and Obstetrics Carl-Neuberg-Straße 1 30625 Hannover Germany [redacted]
Study design	Interventional, multicenter, open-label, randomized, controlled non-inferiority trial
Subject population	Female patients with operable early-stage cervical cancer: International Federation of Gynecology and Obstetrics (FIGO) stage IA2 - IB2 < 4cm and a histologic subtype of squamous-cell carcinoma, adenocarcinoma, or adenosquamous carcinoma
Participating study sites	20–30 trial sites in Germany and other countries
Number of subjects	To be enrolled: n = 756 women (378 women per treatment arm) The study is event-driven, at least 45 primary endpoint events need to be observed to demonstrate the non-inferiority of laparoscopic or robot-assisted radical/simple hysterectomy compared to abdominal radical/simple hysterectomy with regard to disease-free survival (DFS) using a pre-defined non-inferiority margin of 2.3 for the hazard ratio (HR). To be assessed for eligibility: n = 2100 women
Objectives	<u>Primary Objective</u> To investigate the oncologic safety of laparoscopic or robot-assisted radical/simple hysterectomy compared to abdominal radical/simple hysterectomy using pre-specified surgical techniques and qualitative standards and to demonstrate the non-inferiority with a non-inferiority margin of 2.3 for the hazard ratio (HR) for disease free survival (DFS), defined as the time from randomization to disease recurrence or death from any cause (whichever occurs first). <u>Secondary Objectives</u>

	To evaluate overall survival, disease recurrence, quality of life, complications and treatment-associated morbidity, treatment costs and cost effectiveness.
Inclusion and exclusion criteria	<u>Inclusion criteria</u> • Histologically confirmed primary adenocarcinoma, squamous cell carcinoma or adenosquamous carcinoma of the uterine cervix • Patients with FIGO stage IA2, IB1 or IB2 disease (< 4 cm) • Patients undergoing radical hysterectomy according either to Type II or III (Piver Classification) or to Type B or C (Querleu and Morrow classification) OR Simple hysterectomy can be considered for patients with low-risk early-stage cervical cancer (SHAPE criteria: tumor < 2cm, < 10 mm depth of stromal invasion (LEEP/cone). Simple hysterectomy has to be performed as extrafascial hysterectomy and the preparation of a max. 5mm vaginal cuff is required to ensure negative margins. • Performance status of Eastern Cooperative Oncology Group (ECOG) 0–1 • Patient must be suitable candidates for surgery with for instance preoperative Magnetic Resonance Imaging (MRI) and available for assessment of serious adverse events up to 3 or 6 months post-surgery • Patients who have signed an approved Informed Consent • Patients with a prior malignancy only if > 5 years previous with no evidence of disease • Females, aged 18 years or older <u>Exclusion criteria</u> • Any histology other than an adenocarcinoma, squamous cell carcinoma or adenosquamous carcinoma of the uterine cervix • Tumor size 4 cm and greater, estimated by either magnetic resonance imaging (MRI) or clinical examination • FIGO stage IB3 - IV • Patients with a history of pelvic or abdominal radiotherapy • Patients with evidence of metastatic disease by conventional imaging studies, enlarged pelvic or aortic lymph nodes > 2 cm, or histologically positive lymph nodes • Serious concomitant systemic disorders incompatible with the study (at the discretion of the investigator)

	• Patients unable to withstand prolonged lithotomy and steep Trendelenburg position • Patient compliance and geographic proximity that do not allow adequate follow-up • Women who are pregnant • Patients with contraindications to surgery • Patients with secondary invasive neoplasm in the last 5 years (except non-melanoma skin cancer, breast cancer T1 N0 M0 grade 1 or 2 without any signs of recurrence or activity)
Investigational Treatment	Laparoscopic or robot-assisted radical/simple hysterectomy or abdominal radical/simple hysterectomy
Interventions	Experimental intervention: Laparoscopic or robot-assisted, radical or in case of SHAPE criteria simple hysterectomy. Control intervention: Abdominal, radical or in case of SHAPE criteria simple hysterectomy Duration of treatment: Between 150 and 300 minutes (surgical procedure)
Trial duration	Recruitment: 48 months Study duration per subject: a minimum of 60 months (5 years) The duration of the surgical intervention per participant depends on individual circumstances and will take between 150 and 300 minutes followed by a follow-up period of at least 60 Months (5 years). Duration of the entire trial (first subject in to last subject out): 108 months The study is event-driven and can be terminated after 45 primary endpoint events have been observed.
Randomization	Permuted block randomization with randomly selected block sizes stratified by: • tumor size (< 2 cm vs 2 - < 4 cm) • sentinel node mapping only (Yes vs No) • radical vs simple hysterectomy (SHAPE criteria) • anticipated type of minimally invasive surgery (laparoscopic vs robot-assisted) • center The type of laparoscopic surgery, whether conventional or robotic, is determined by the surgeon based on the surgeon's experience and preference. Patients will be allocated to both treatment arms in a 1:1 ratio. Patients will be randomized using

	the electronic randomization tool provided within the electronic case report form (eCRF)/electronic data capture (EDC) system.
Endpoints/outcomes	Primary endpoint: • Disease-free survival (DFS) Secondary endpoints: • Overall survival (OS) • Disease recurrence • Quality of life including lymphatic side effects • Complications and treatment-associated morbidity • Health care costs
Statistical analysis	Primary endpoints: The primary endpoint disease-free survival (DFS) will be primarily analyzed according to the intention-to-treat (ITT) principle which includes all patients as randomized. The DFS curves will be estimated using the Kaplan-Meier method. A Cox proportional hazards model adjusted for the stratification factors for the randomization will be used for the comparison of minimally invasive and open surgery. Non-inferiority of minimally invasive as compared to open surgery will be declared if the upper boundary of the two-sided 95% confidence interval (CI) for the hazard ratio (minimally invasive/open) is below the predefined non-inferiority margin of 2.3. A sensitivity analysis will be performed according to the per-protocol (PP) principle which includes all randomized patients where surgery has been performed according to the initial randomization. Consistency between results in the ITT and PP analysis is needed to draw meaningful conclusion regarding differences in DFS. Secondary endpoints: Overall survival (OS) will be analyzed in line with the primary analysis of the primary endpoint. Data for other secondary endpoints will be summarized by treatment groups, compared with appropriate statistical tests adjusted in line with the primary analysis of the primary endpoint. Absolute and relative frequencies of serious adverse events (SAEs) will be displayed for the whole population and separately for each treatment group and comparisons between groups using Chi-squared tests will be performed and assessed descriptively. Analyses of DFS and OS in relevant subgroups will also be performed.