Hernia reduction following laparotomy using small stitch abdominal wall closure with and without mesh augmentation (the HULC trial, DRKS00017517): Study protocol for a randomized controlled trial

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Abstract

Background Incisional hernias are among the most frequent complications following abdominal surgery and cause substantial morbidity, impaired health-related quality of life and costs. Despite improvements in abdominal wall closure techniques incisional hernia rates are reported to be between 10-30% following midline laparotomies. There have been two recent innovations with promising results to reduce hernia rates, namely the small stitches technique and the placement of a prophylactic mesh. So far, these two techniques have not been evaluated in combination.

Methods The HULC trial is a multicentre randomized controlled, observer and patient blinded surgical effectiveness trial with two parallel study groups. A total of 812 patients scheduled for elective abdominal surgery via a midline laparotomy will be randomized in 12 centres after informed consent. Patients will be randomly assigned to the control group receiving closure of the midline incision with a slowly absorbable monofilament suture in small stitches technique or to the intervention group that will receive a small stitches closure followed by augmentation with a light-weight polypropylen mesh in onlay technique. The primary endpoint will be the occurrence of incisional hernias as defined by the European Hernia Society within 24 months after surgery. Further perioperative parameters, as well as patient-reported outcomes, will be analysed as secondary outcomes.

Discussion The HULC trial will address the yet unanswered question whether a combination of small stitched fascial closure and onlay mesh augmentation after elective midline laparotomies reduces the rate of incisional hernias. The HULC trial marks the logical and innovative next step in the development of a safe abdominal closure technique.
Background

Incisional hernias (IHs) are among the most frequent complications following open abdominal surgery (1). IHs cause substantial morbidity, costs and reduce health-related quality of life (HRQoL) (2). In recent years several randomized controlled trials (RCTs) have been conducted comparing different techniques of abdominal wall closure. These trials have shown convincingly that abdominal wall closure with a continuous running suture is superior to interrupted suture techniques at least in the elective setting (3-6). Similarly, slowly absorbable suture material creates less IHs than rapidly absorbable sutures (3, 4, 7, 8). These results were summarized in a meta-analysis (9). Despite these advances IH rates of 10-30% are regularly reported in RCTs following abdominal wall closure (3-6, 10) and rise up to 36% in certain subgroups (11-14). Furthermore, IH rates increase with extended time of follow-up (15).

Since the INLINE meta-analysis in 2010 (9), there have been two recent innovations in the field of abdominal wall closure aiming at a reduction of incisional hernias: the small stitches technique (SST) (10, 16) and prophylactic mesh placement (17, 18). SST abdominal closure using a slowly absorbable suture and an increased suture-length to wound-length ratio of $\geq 4$ significantly reduced IH in a pseudo-randomized trial by Millbourn et al. (10). A recent multicentre RCT has verified the superiority of this technique in terms of reduced IH frequency in comparison to standard abdominal wall closure (1). However, even under these optimized conditions 13% of patients developed an IH after 12 months (1).

Regarding prophylactic mesh placement, several RCTs have been performed in specific subsets of patients with encouraging results (11, 19-23). A meta-analysis confirmed a significantly lower rate of IHs in the mesh group (17). Most importantly, other wound complications like surgical site infections (SSI) were not increased in the mesh groups
(17). This is in line with the results of a multicentre RCT comparing prophylactic mesh placement to primary closure (PRIMA trial) that confirmed the superiority of prophylactic mesh placement (18, 24). PRIMA compared onlay mesh augmentation (OMA) or sublay mesh augmentation (SMA) vs. primary suture closure of the abdominal incision in high-risk patients and identified significantly less patients with an IH in the OMA group (13%) than in the primary suture group (30%) after 2 years (OR 0.37; 95%-CI: 0.27 to 0.77; p = 0.0016). Comparing the SMA group with primary suture the results just failed statistical significance (SMA vs. primary suture 18% vs. 30%; OR 0.55; 95%-CI: 0.30 to 1.00; p = 0.05).

However, in none of these trials prophylactic mesh placement has been combined with SST. A combination of these two techniques, which showed effectiveness as single interventions, is considered to be the logic consequence and may either result in an additional reduction of IH formation.

Methods / Design

Trial rationale

The objective of the HULC trial is to investigate whether prophylactic OMA in addition to abdominal wall closure in SST reduces the rate of IH formation in patients undergoing elective midline laparotomy compared to SST alone.

Trial design

HULC is a multicentre randomized controlled, observer and patient blinded surgical effectiveness trial with two parallel study groups.

Patients and trial centres

To enrol the required number of patients in the planned recruitment period, 12 trial sites of the Clinical Trials Network of the German Surgical Society (CHIR-Net) will participate in
The centers will be high-volume centres committing to include at least 50 patients each.

**Patient inclusion criteria**

All patients scheduled for elective clean or clean-contaminated (25) abdominal surgery as defined by the Centers for Disease Control and Prevention (CDC) via a midline laparotomy for any indication will be screened consecutively for eligibility and will be informed about the HULC trial. All subjects must be able to understand the nature and extent of the trial and only adult patients (> 18 years of age) with a life expectancy of at least two years who provide written informed consent will be included in the trial.

**Patient exclusion criteria**

Patients with planned relaparotomy via the midline incision within 2 years after trial intervention, midline laparotomy within the last 60 days prior to trial intervention or previous IHs or fascial dehiscences will be excluded from the trial. Moreover, patients with concurrent abdominal wall infections will not be included in the trial, in order to reduce the risk of SSI and potential mesh infections. Furthermore, patients with an ASA grade > 3 according to the American Society of Anesthesiologists (ASA) classification, pregnant or lactating women and patients that participate in another intervention-trial with interference of the intervention and/or outcome of the HULC trial will be excluded.

**Patient withdrawal criteria**

Patients are free to stop their trial participation at any time and without giving reasons for their decision. When a trial participant withdraws his/her informed consent, he/she is asked to decide whether his/her data captured so far may be analysed or if it should be discarded. In addition, if, in the surgeon’s opinion at the end of the operation, the trial intervention will be detrimental to the subject’s well-being, the trial participation can be stopped for this patient. In this case, the patient will not be randomized and the reason
for screening failure must be recorded in the screening log. All randomized patients, including those with premature trial termination, will be included in the final analysis.

**Control intervention**

Patients in both groups will receive closure of the midline incision with a slowly absorbable monofilament suture (USP 2–0, PDS Plus, Ethicon, Somerville, NJ, USA) in SST as in previous trials (1, 10). Tissue bites of 5mm and intersuture spacing of 5mm are applied exclusively to the fascia within the linea alba (omitting subcutaneous fat and muscle tissue). Suturing will be initiated at both ends of the median laparotomy towards the centre. An overlap of up to 2 cm may be created. Both sutures should be knotted independently. The suture length to wound length ratio (SL:WL) must be ≥ 4:1. The SL:WL ratio is recorded intraoperatively and is calculated as follows (16):

\[
\text{SL:WL} = \frac{A-(B+C)}{D}
\]

(A = total length of suture used (in cm); B = Length of suture remnants at starting knots (in cm); C = Length of suture remnants at finishing knots (in cm); D = Length of fascial incision (in cm))

**Experimental intervention**

In the experimental group, but not in the control group, the abdominal wall closure is augmented with a light-weight polypropylene mesh in onlay technique (OMA). To this end an anterior plane will be created between the anterior rectus fascia and the subcutis. The mesh should overlap the fascial midline incision by 3–4 cm on all sides (18, 24) and must be fixed to the fascia tension-free with USP 2–0 Prolene single knots (Ethicon, Somerville, NJ, USA). The mesh material will be standardized and an Optilene® Mesh (B. Braun, Melsungen, Germany) will be used. The interventional procedure will prolong the operation by approximately 20 minutes.

Materials and surgical technique will be standardized. HULC will use the same materials and surgical technique as the previous PRIMA and STITCH trials (1, 24) to ensure
comparability of results and to avoid potential bias.

Closure technique of the skin and the subcutaneous tissue will be the same in both groups and will be standardized to reduce dead space and seroma formation. The subcutaneous tissue should be closed with mono- or polyfilament absorbable sutures. No subcutaneous drains should be placed. The subcutaneous sutures in the experimental group will include the mesh in the midline in order to reduce seroma formation as the latter was increased in previous OMA trials without subcutaneous sutures (18, 24), but not in OMA trials with subcutaneous sutures (19). The skin will be closed using staples.

**Assignment of intervention and randomization**

In order to ensure equal distribution of patient characteristics randomization will be used. Allocation of treatments will be performed using a web-based randomization tool (www.randomizer.at) by means of block-wise randomization. Randomization will be performed intraoperatively at the end of surgery, after closure of the fascia. This prevents potential bias by different intraoperative techniques. Before randomization, the surgeon needs to confirm a clean or clean-contaminated operation according to CDC definition (25). Randomization will be stratified by centre and by IH risk (low vs. high risk patients, defined as patients with BMI ≥ 27 and/or surgery for abdominal aortic aneurysm). The surgeon who will perform the closing technique must be chosen before abdominal wall closure.

**Blinding**

Patients and observers will be blinded to the intervention in order to guarantee unbiased assessment of the primary outcome. The person performing randomization and the surgical team conducting the control/experimental intervention (“unblinded” study members) will be documented and will not be part of further outcome assessment. Moreover, neither the operation report nor the discharge letter will contain information
regarding group allocation.

Other methods against bias

To minimize performance bias, the intervention will be standardized in both groups and the suture-to-wound length ratio must be recorded intra-operatively and will be monitored. Furthermore, to minimize training effects all participating surgeons must pass an obligatory eLearning tutorial demonstrating the SST before participation in the trial. Only surgeons having performed a minimum of 10 SST abdominal wall closures are allowed to perform interventions in the HULC trial. In addition, only centres committing to include at least 50 patients will participate in the trial.

Primary endpoint

Primary outcome measure of the trial will be the occurrence of IHs within 24 months after surgery as defined by the European Hernia Society (EHS) (26). Consequently, “any abdominal wall gap with or without a bulge in the area of a postoperative scar perceptible or palpable by clinical examination or imaging” is regarded as an IH. Occurrence of a burst abdomen will not be counted as primary endpoint, but as a secondary endpoint by consensus (1,3). Follow-up time will be 24 months as has been recommended by the EHS (26) since IH rates increase over time (15). Patients will be assessed for the primary endpoint at 6, 12, and 24 months after trial intervention. At these time points patients will be examined by a clinician blinded for the trial intervention and by a radiologic examination performed by a blinded assessor. Radiologic exams allowed in the trial are sonography, CT or MRI scans. In case of conflicting results between clinical and radiologic exams, the radiologic imaging is decisive to increase sensitivity (26). If only one of the two examinations is performed (i.e. either clinical or imaging) the result of this assessment will be used for analysis. Possible results are listed in table 1. For patients who are unable or unwilling to attend the follow-up visits a telephone follow-up is
incorporated. The patient-reported outcome questionnaire developed by Jairam et al. (27) will be used as it exhibits a high reliability. It will be used as a screening tool, i.e. patients who are suspected to have an IH based on the questionnaire, might be convinced to attend an outpatient visit even if they were reluctant to do so before.

**Primary estimand**

In the recently released addendum to the ICH E9 guideline (draft version) (28), the estimands framework is recommended as clear and transparent definition of “what needs to be estimated to address a specific scientific question of interest”. Such an estimand can be defined through the population of interest, variable of interest, specification of how intercurrent events are handled, and summary measure. The specification of how intercurrent events are handled is referred to as intervention effect in the following.

**Population:** The population is defined as all patients fulfilling the in- and exclusion criteria.

**Variable:** The variable is the occurrence of IHs as defined by the European Hernia Society (EHS) within 24 months after intervention.

**Intervention effect:** Possible intercurrent events and the strategies to handle them are as follows: missing values due to death, drop-out, loss to follow-up and re-laparotomy will be replaced by using multiple imputation. Since re-laparotomy changes the probability of occurrence of an IH, information of occurrence or non-occurrence of IH after re-laparotomy will not be considered for primary analysis. This represents a hypothetical strategy for the post randomization events re-laparotomy, drop-out, loss to follow-up, and death. Besides these events, other post randomization events will not be considered, thus reflecting a treatment policy approach, which means that the effect of randomized treatment is estimated irrespectively of other post-randomization events not captured in the primary
Summary Measure: The summary measure is the odds ratio. The odds ratio will be calculated by a two-level binary logistic regression analysis including the fixed factors treatment group and IH risk (low vs. high), the latter being deemed as the by far most important confounder and being also used for stratification in the randomization procedure, and the random factor centre. Confounding by other less important prognostic and predictive factors can assumed to be controlled by the randomized study design. The model will be fitted using the variance-components covariance matrix. The level of significance is set to 5% (two-sided). The p-value for judging the primary hypothesis will result from the two-level binary logistic regression model, where the coefficient of the factor treatment effect is tested against zero using the Wald test.

Additionally, sensitivity and supplementary estimands will be considered, but not described in further detail in this publication.

Key secondary endpoints

The secondary measurements chosen in the HULC trial have been proposed by international guidelines (26). For an adequate evaluation of the secondary endpoints follow-up visits on postoperative day 5 to 7, 10 to 14 and 30 to 35 will be performed (see table 2) in addition to the follow-up visits for the primary endpoint described above (at 6, 12 and 24 months postoperatively). The key secondary endpoints are as follows:

1. Occurrence of superficial and deep surgical site infections (SSIs) within one year in both groups (25). SSIs will be assessed by clinical examination as defined by the CDC (25). Organ-space SSIs are excluded in this measurement as they are independent of abdominal wall closure technique, but rather depend on the underlying surgery. Consequently, organ-space SSIs will be recorded in the overall complication rate and as serious adverse events
if applicable. Follow-up for SSI is one year in line with CDC guidelines as patients in the experimental group undergo implantation of alloplastic material (mesh).

2. Postoperative 30-day morbidity. Complications will be recorded and classified according to the Dindo-Clavien classification (29).

3. Occurrence of non-infectious wound complications (hematoma, seroma) within 30 days. Seroma is defined as a collection of serous fluid in a dead space, which can either be in situ or leaking through a wound. Hematoma is defined as an accumulation of blood in the wound area, which warrants (bedside) surgical exploration and intervention.

4. Occurrence of postoperative burst abdomen within 30 days. Postoperative burst abdomen will be defined as missing continuity of the fascia in combination with wound dehiscence with consecutive re-operation.

5. Postoperative wound pain at rest and during movement. Assessment will be performed using the well-established numeric pain rating scale. Pain is an important patient-reported outcome measure and is influenced by hernia occurrence and by surgery. Pain will be assessed as visits 3–5 (see table 2).

6. HRQoL measured with the SF–36 and EQ–5D questionnaires. As HRQoL is an important patient-reported outcome measure and is influenced by hernia occurrence and by surgery (2), it will be recorded both preoperatively (visit 1) and during follow-up (visit 6–8) (see table 2).

7. Length of primary hospital stay in days from index operation.

Patient timeline and trial visits

Patients scheduled for elective abdominal surgery via a midline incision are screened preoperatively at day 0 (visit 1). Patients are enrolled given their ability to understand the extent and nature of the trial as well as their written informed consent after detailed
patient information. All inclusion criteria and no exclusion criteria must be fulfilled.

Baseline data are collected during the screening/baseline visit. The duration of visit 1 will be approximately 25 minutes. Included patients are randomized during surgery (visit 2) after closure of the fascia in SST. Follow-up visits will be on postoperative day 5 to 7, 10 to 14 and 30 to 35 (visits 3–5) for evaluation of secondary endpoints (time expenditure approximately 15 minutes). In addition, 6, 12 and 24 months (visits 6–8) after surgery patients are planned for follow-up to evaluate primary and secondary outcome parameters. The expenditure of time for each visit will be approximately 30 minutes per patient. An overview of trial visits and items captured during the trial visits is presented in table 2 according to the guidelines of the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) (30).

Data management

All protocol-required information collected during the trial must be entered by the investigator, or designated representative, in an electronic case report form (eCRF) implemented in the REDCap™ system (31) (www.project-redcap.org). An explanation should be given for all missing data. The completed eCRF must be reviewed and signed by the investigator named in the trial protocol or by a designated sub-investigator. The Institute of Medical Biometry and Informatics of the University of Heidelberg (IMBI) is responsible for the data management within the trial. To assure a safe and secure environment for data acquired, data transmission is encrypted with secure socket layer (SSL) technology. Only authorized users are able to enter or edit data, the access is restricted to patients’ data in the respective centre. All changes to data are logged with a computerized timestamp in an audit trail. All data will be pseudonymized. Completeness, validity and plausibility of data will be checked in time of data entry (edit-checks) and using validating programs, which will generate queries. If no further corrections are to be
made in the database, eCRF data will be locked. All data management procedures will be conducted according to written defined standard operating procedures (SOPs) of the IMBI that guarantee an efficient conduct complying with good clinical practice (GCP).

Sample size calculation

The sample size calculation is based on the primary efficacy endpoint (IH rate) within 24 months after surgery. Based on the assumption that the percentage of patients developing an IH after midline laparotomy in a general surgical population closed with the SST is approximately 15% for the control group, we hypothesize a reduction of 7% in the intervention arm based on previous RCTs (13, 20). Consequently, a sample size per group of 325 patients is needed for the between-group comparison by the Chi-squared test to achieve 80% power in detecting this difference in IH rate at a two-sided level of significance of 5%. It is assumed that using a two-level logistic regression model adjusting for the random factor centre and the fixed factor IH risk (low risk vs. high risk patients: BMI ≥ 27 and/or surgery for abdominal aortic aneurysm) (20) in the primary analysis will lead to less unexplained variance and thus to an increased power. Assuming a drop-out rate of up to 20% based on previous trials (1, 3, 10, 18), a total of 812 patients (406 per group) will be randomized in the study (figure 1). The potential occurrence of missing values for the primary outcome is partially addressed by the predefined multiple imputation strategy. Due to the broad inclusion and limited number of exclusion criteria, no more than 100 patients are expected to be screened but not included resulting in a total number of 912 patients that need to be assessed for eligibility. Sample size calculation was performed using ADDPLAN v6.1.

Analysis variables and statistical methods

The primary efficacy analysis will be based on the full analysis set (FAS) built according to the intention-to-treat (ITT) principle thus reflecting the recommendations given in
guidelines (32). As a sensitivity analysis, an evaluation based on the per-protocol (PP) population (based on those patients without major protocol violation and excluding patients that receive a fascial closure not predefined in the randomization scheme) will be performed. IH rates will be analysed via a two-level binary logistic regression model including the fixed factors treatment group and IH risk (high vs. low), the latter being deemed as the by far most important confounder and being also used for stratification in the randomization procedure, and the random factor centre. Confounding by other less important prognostic and predictive factors can assumed to be controlled by the randomized study design. The model will be fitted using the variance-components covariance matrix. The level of significance is set to 5% (two-sided). All secondary outcomes will be evaluated descriptively, and descriptive p-values will be reported together with 95% confidence intervals for the corresponding effects.

Further analyses

Further sensitivity analyses will be performed with the per protocol set and the results will be compared with those of the ITT analysis. Moreover, for missing data in the ITT population set further sensitivity analyses will be conducted by a worst-case scenario for the intervention, a minimal and a maximal IH rate imputation and by another alternative method of dealing with missing data as described by Higgins et al. (33). Furthermore, a time-to-event analysis for the outcome “time from randomization to occurrence of IH” will be performed in the ITT population according to Kaplan-Meier. Additionally, pre-specified subgroup analyses will be performed in the ITT population for the rate of incisional hernias in the subgroups of different types of surgery (colorectal, small bowel, hepatobiliary-pancreatic, upper GI (oesophageal and gastric), vascular, others), adipose vs. non-adipose patients and the presence or absence of neoadjuvant therapy, previous laparotomy or chronic obstructive pulmonary disease. All secondary outcomes will be evaluated
descriptively, and descriptive p-values will be reported together with 95% confidence intervals for the corresponding effects.

**Safety analysis**

The assessment of safety will be based on the frequency of serious adverse events (SAEs) in both groups, which will be analysed via descriptive statistical methods in the study population. For comparisons of frequencies between groups the Chi-squared test will be used. All analyses will be done using SAS version 9.4 or higher.

**Clinical data monitoring**

Clinical monitoring will be performed by independent monitors of the SDGC according to its standard operating procedures in line with the ICH-GCP guideline (E6) (34). A risk-based monitoring strategy will be conducted based on patient safety, patient rights, protocol adherence and data. The frequency of monitoring visits will be determined depending on recruitment numbers and individual performance of each centre based on feedback from project and data management.

**Premature closure of the trial**

The trial may be prematurely closed by the coordinating investigator in consultation with the Steering Committee including the responsible biometrician. If the termination of the trial becomes necessary, the Steering Committee of the trial will discuss this issue with the independent Data Safety Monitoring Board (DSMB). Similarly, the DSMB can recommend closing the trial based on the safety reports; however, the decision remains with the Steering Committee. Reasons that may necessitate the termination of the trial include the following: The incidence or severity of SAEs, morbidity or complications in this trial indicate a potential health hazard caused by the study treatment. Furthermore, the trial should be terminated if it appears that patients’ enrolment is unsatisfactory with respect to quality and/or quantity or data recording is severely inaccurate and/or
incomplete. Another case in which termination of the trial is necessary is, if external
evidence demands a termination of the trial.

Discussion

Despite the rise of laparoscopic surgery, open abdominal surgery by a midline laparotomy
is still the most performed approach in abdominal surgery today (35). Regardless of
improvements in the surgical techniques of abdominal wall closure, IH rates remain high
and cause substantial morbidity and costs (24). In the United States approximately
348,000 IH repairs leading to more than 3.2 billion dollars healthcare expenditure are
performed annually (36). Similar per capita numbers have been reported in Germany,
where more than 51,000 IH repairs are performed each year making it one of the most
frequent operations (37). Total costs for IH repair were estimated to be 6,451 € per
patient in France (38). Thus, reducing the IH rate by 5% was calculated to result in an
annual cost saving of 4 million € (38). Furthermore, IH-related reduction of the HRQoL is
an important patient-reported outcome as has been shown in recent trials (2).

Primary prevention of IH is of utmost importance, since recurrence and re-recurrence
rates reach 40% (39, 40) and a considerable decrease of HRQoL (41). Thus, prevention of
IHs would have a significant impact on the patients well-being and the whole health care
system by reducing complications, avoiding additional interventions and increasing HRQoL
of affected patients.

Among earlier techniques to optimise the abdominal wall closure and therefore reduce the
occurrence of IHs, the SST and OMA are the two most recent and promising ones. So far
there has been no RCT combining these two techniques of abdominal wall closure. The
HULC trial will be the first RCT to fill this gap of evidence and will combine the usage of
SST and the prophylactic mesh augmentation. The strengths of the HULC trial will be its
randomized and blinded study design and the adhesion to the most recent evidence of
abdominal wall closure regarding the control and intervention techniques. The HULC trial will be a multicenter trial including 12 high-volume centers in abdominal surgery to minimize selection bias. All centers will be trained to standardize the surgical techniques and outcome assessment as much as possible leading to an expected low performance bias. Furthermore, as recommended recently (42), the HULC trial will perform blinding as far as practicable by blinding patients and outcome assessors to reduce performance and detection bias. For the control and intervention group of the HULC trial, the most promising techniques of recent studies will be used including a slowly absorbable suture material in continuous suture technique in SST in both groups (1). The intervention group will receive an additional non-absorbable mesh in onlay position as absorbable meshes have failed to show a reduction in IH rates (43) in contrast to non-absorbable ones and the technique of OMA has been identified as superior to SMA recently (24). For safety reasons regarding the development of SSI after receiving the OMA treatment in the intervention group, the HULC trial will perform continuous follow-up visits including the evaluation of SSI during the first year after surgery according to the recommendations of the CDC (25). As earlier trials (6, 9) have shown an increase of IH rates even after 12 months and a minimum follow-up period of 24 months has been proposed by the EHS for future trials, the HULC trial will follow this recommendation. The trial will include a large sample size with an adequate drop-out rate measured by a properly conducted sample size calculation basing on the reliable results of earlier trials. The HULC trial will enable an adequate risk-benefit assessment due to secondary endpoints including all relevant intervention-related adverse events. And it will include an extensive HRQoL assessment as secondary outcome as the reduction in quality of life through IHs has been shown to be of great importance for patients (2).

In summary, the results of the HULC trial will
influence future guidelines and surgical practice concerning abdominal wall closure.

Trial Status

This manuscript was written according to the most current version of the study protocol (version 1.1, last updated on June 25th, 2019). Recruitment of patients for the HULC trial will start in August 2019. The clinical phase of the trial (last patient out) is expected to be completed in August 2023.

Abbreviations

ASA: American Society of Anesthesiologists
CDC: Centers for Disease Control and Prevention of Surgical Site Infections
DFG: German Research Foundation
DSMB: Data Safety Monitoring Board
eCRF: Electronic case report form
EHS: European Hernia Society
FAS: Full analysis set
GCP: Good clinical practice
HRQoL: Health-related quality of life
IEC: Independent ethics committee
IH Incisional hernia
IMBI: Institute of Medical Biometry and Informatics of the University of Heidelberg
ITT: Intention-to-treat
OMA: Onlay mesh augmentation
PP: Per-protocol
Declarations

Ethics approval and consent to participate

The HULC trial is conducted according to the Medical Association’s professional code (Berufsordnung der Bundesärztekammer) §15. To ensure patient’s rights and safety the responsible investigator will ensure that the trial will be conducted according to the ethical principles laid out in the declaration of Helsinki (44). Before participation in the HULC trial, written informed consent will be obtained from all study participants. This protocol is designed to ensure that the trial will be conducted and analyzed in accordance with ICH-GCP E6 (34). The protocol has already been approved by the IEC of the medical faculty of the University of Heidelberg and secondary approval of the corresponding ethical bodies of all other participating centres has been or will be obtained. The trial protocol has been formulated in accordance with the recommendations of the CONSORT and SPIRIT guidelines (30, 45).

Consent for publication
Not applicable

Availability of data and material
Not applicable

Competing interests
The authors declare that they have no competing interests

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Authors’ contribution
ALM, PH, MF, CDH, ST, and MKD are responsible for the study design, the definition of endpoints and the preparation of the protocol. JK, MF, and TB are the study’s statisticians and are responsible for the sample size calculation and statistical design of the study.

MWB, as the head of the surgical department provided general support from a clinical perspective and support concerning technical aspects. All authors revised the manuscript critically and all authors read and approved the final manuscript.

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Tables

Table 1: Definition of the primary endpoint for the HULC trial

| Clinical exam result | Imaging result | Primary endpoint for HULC |
|----------------------|---------------|--------------------------|
| Hernia               | Hernia        | Hernia                   |
| No hernia            | Hernia        | Hernia                   |
| Hernia               | No hernia     | No hernia                |
| No hernia            | No hernia     | No hernia                |
| Hernia               | Missing       | Hernia                   |
| No hernia            | Missing       | No hernia                |
| Missing              | Hernia        | Hernia                   |
| Missing              | No hernia     | No hernia                |

Table 2: Time table of the trial according to SPIRIT guidelines (30)
| Activity                                      | Visit 1 (screening) | Visit 2 (surgery, randomization) | Visit 3-5 (POD 5-7, 10-14, 30-35) | Visit 6-8 (postoperative months 6, 12, 24) |
|----------------------------------------------|---------------------|----------------------------------|-----------------------------------|-------------------------------------------|
| Inclusion/exclusion criteria                 | X                   |                                  |                                   |                                           |
| Informed consent                             | X                   |                                  |                                   |                                           |
| Medical history                              | X                   |                                  |                                   |                                           |
| Clinical examination                         | X                   | X                                | X                                 | X                                         |
| Surgery                                      |                     | X                                |                                   | X                                         |
| Randomization                                |                     | X                                |                                   |                                           |
| Incisional hernia assessment*                |                     |                                  |                                   | X                                         |
| Assessment of SSI**                          |                     | X                                | X (not at 24)                     |                                           |
| Assessment of postoperative morbidity***     |                     | X                                |                                   |                                           |
| Assessment of non-infectious wound complications |                   | X                                | X                                 |                                           |
| Assessment of burst abdomen                  |                     | X                                |                                   |                                           |
| Quality of life assessment *                 | X                   |                                  |                                   | X                                         |
| Length of hospital stay                      |                     | X                                |                                   |                                           |
| Assessment of wound pain§                    |                     | X                                |                                   |                                           |
| Assessment of reoperations                   |                     | X                                | X                                 | X                                         |
| Assessment of SAE                            |                     | X                                | X                                 | X                                         |

* via blinded assessor: clinical and radiologic assessment;  
** via blinded assessor according to CDC Definition (25);  
*** according to Dindo-Clavien;  
# according to SF-36 and EQ-5D questionnaires, using a numeric pain rating scale (NRS 1-10);  
§ as defined by the Centers for Disease Control CDC: “follow-up should be 30 days after the operation if no implant is left in place or 1 year if implant is in place” (25).  
POD: postoperative day; SAE: serious adverse event; SSI: surgical site infection.
Figures

Visit 1

Screening (n=512)
n=50 fulfilling exclusion criteria
n=25 not compliant
n=25 no informed consent

Visit 2

Enrolment / informed consent

Surgery

Randomization (n=612)

Visit 3-5
(day 5-7,10-14,30-35)

Intervention (n=406)

Control (n=406)

Follow-up

Visit 6-8
(month 6,12,24)

Postop. evaluation of secondary endpoints

Blinded evaluation of primary+ secondary endpoints

Analysis

to be analyzed (n=406)

to be analyzed (n=406)
n=81 lost to F/U

Figure 1

Trial flow chart

Supplementary Files

This is a list of supplementary files associated with the primary manuscript. Click to download.

SPIRIT-Checklist.doc