# CHOCOLATE RESEARCH PROTOCOL

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***Protocol committee***

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**Acute CHOlecystitis in high risk patients: percutaneous ChOlecystostomy versus LAparoscopic cholecysTEctomy**; *a randomized controlled, open, parallel, superiority multicenter trial*

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## LIST OF ABBREVIATIONS AND RELEVANT DEFINITIONS

| | |
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| **ABR** | **ABR form, General Assessment and Registration form, is the application form that is required for submission to the accredited Ethics Committee (In Dutch, ABR = Algemene Beoordeling en Registratie)** |
| **ACC** | **Acute Calculous Cholecystitis** |
| **AE** | **Adverse Event** |
| **AR** | **Adverse Reaction** |
| **ASA** | **American Society of Anaesthesiologists** |
| **CA** | **Competent Authority** |
| **CCMO** | **Central Committee on Research Involving Human Subjects; in Dutch: Centrale Commissie Mensgebonden Onderzoek** |
| **CRP** | **C-Reactive Protein** |
| **CV** | **Curriculum Vitae** |
| **DSMB** | **Data Safety Monitoring Board** |
| **EU** | **European Union** |
| **EudraCT** | **European drug regulatory affairs Clinical Trials** |
| **GCP** | **Good Clinical Practice** |
| **IB** | **Investigator's Brochure** |
| **IC** | **Informed Consent** |
| **ILC** | **Interval Laparoscopic Cholecystectomy** |
| **IMP** | **Investigational Medicinal Product** |
| **IMPD** | **Investigational Medicinal Product Dossier** |
| **LC** | **Laparoscopic Cholecystectomy** |
| **METC** | **Medical research ethics committee (MREC); in Dutch: medisch ethische toetsing commissie (METC)** |
| **PC** | **Percutaneous Cholecystostomy** |
| **PD** | **Percutaneous Drainage** |
| **(S)AE** | **(Serious) Adverse Event** |
| **SPC** | **Summary of Product Characteristics (in Dutch: officiële productinfomatie 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.** |

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| **SUSAR** | **Suspected Unexpected Serious Adverse Reaction** |
| **Wbp** | **Personal Data Protection Act (in Dutch: Wet Bescherming Persoonsgevens)** |
| **WMO** | **Medical Research Involving Human Subjects Act (in Dutch: Wet Medisch-wetenschappelijk Onderzoek met Mensen** |

## SUMMARY

**Rationale** Acute calculous cholecystitis is a frequently encountered problem in the surgical practice and laparoscopic cholecystectomy (LC) is still the standard treatment for patients without significant comorbidity and therefore low-moderate risks on intervention. Acute cholecystitis is not a disease confined to this population, and in elderly patients or patients with significant comorbidity, surgery in general is associated with higher complication rates and even mortality, and there is no consensus in the general surgical practice if LC actually is the treatment of choice in this patient category. In addition, LC for acute cholecystitis can be a more difficult procedure than elective LC for cholelithiasis and is associated with increased operating time, higher conversion rate and more post-operative complications in any patient category, especially in elderly patients or patients with comorbidity. Percutaneous cholecystostomy (PC) may be a more preferable method, and in the current surgical practice many surgeons prefer this method over LC in acute calculous cholecystitis in patients with increased risks. Because the gallbladder remains in situ, the infection can worsen mandating an emergency LC which can be even more difficult, and there is always the risk of recurrence. There is some evidence in the current literature regarding the safety, success rate and procedure specific technique of this procedure, but the question whether there is a place for PC in the treatment of acute calculous cholecystitis, remains unanswered.

**Objective**: To determine superiority of the laparoscopic cholecystectomy over percutaneous drainage in the treatment of acute cholecystitis in patients with increased risk

**Study design:** Multi centre randomized controlled trial

**Study population:** Patients with acute calculous cholecystitis with increased risk (defined as APACHE II score ≥7 AND ≤14)

**Intervention (if applicable)**: Laparoscopic cholecystectomy (with or without conversion to open cholecystectomy)

**Control group:** Percutaneous, ultrasound- or CT- guided cholecystostomy (drainage)

**Main study parameters/endpoints:** Combined endpoint of all procedure related major morbidity, need for re-intervention and mortality

**Nature and extent of the burden and risks associated with participation, benefit and group relatedness:**

Risks of participation are no greater or different from the general treatment of acute calculous cholecystitis.

Burden of participation is a total of 11 follow up phone calls that would normally not take place.

Benefit of participation is treatment within 24 hours, and, when assigned to the LC-arm surgery by a specialised GI-surgeon.

## 1. INTRODUCTION AND RATIONALE

Acute calculous cholecystitis (ACC) is a frequently encountered disease in the general surgical practice. In the general population without significant comorbidity urgent laparoscopic cholecystectomy (LC) is the treatment of choice. In elderly patients or patients with significant comorbidity urgent LC carries the risk of serious morbidity (up to 41%) and mortality (around 4.5%)[1-7], alternative treatment options should be considered. Studies focusing on the treatment of ACC in the elderly or high risk population are mostly outdated and compare results to the open cholecystectomy. Most authors conclude that in elderly patients who are fit for surgery LC remains the preferred treatment; conservative therapy (intravenous antibiotics) in these patients is not recommended, because results are unpredictable and clinicaldeterioration might go unnoticed due to different pathophysiological responses in the elderly patient. And if cholecystectomy is indicated after several days of conservative management, this might prove to be far more difficult than emergency surgery , leading to an increased risk of complications and mortality[8,9].

In patients with increased risk percutaneous cholecystostomy (PC) (with or without interval cholecystectomy (ILC)) has gained ground as an alternative treatment strategy. According to the Dutch guidelines for gallstone disease, PC can be a useful option in patients unfit for surgery but routine use has no additional value over antibiotic treatment in the treatment of ACC in the general population. There is little evidence to support this statement, and a number of questions remain regarding the efficacy and safety of this technique.

Winbladh et al conducted a systematic review in 2007, analyzing the safety and effectiveness of PC in elderly and critically ill patients[7]. At this time, there were no clinical trials comparing PC with LC. The review demonstrated a success rate of 91% in patients with confirmed calculous cholecystitis. Overall complication rate was 6.2%, however, a large number of papers did not mention an exact complication rate so a reliable complication rate is not available. 30-day mortality was 11.7% (0.4% PC-procedure-related).

4.5% of patients underwent emergency cholecystectomy after PC, and another 38.1% underwent elective interval cholecystectomy. Mortality rate of ILC was 1%, bringing the total mortality rate of patients treated with PC to 12.7%. In patients who primarily underwent urgent LC mortality was 4.5%. Of course selection bias might greatly be responsible for this difference in mortality.

The authors concluded that due to the high variability between the different studies, the many confounding factors and the low quality of the available studies a definite answer to the question whether elderly and critically ill patients with acute calculous cholecystitis should be treated with LC or PC could not be provided.

After publication of this review, only a handful relevant studies have been published on the safety and efficacy of PC in the elderly/critically ill patient. These studies report comparable figures. In a study by Ha et al[10] the success rate of PC in 57 ASA III/IV patients with ACC was 91%, with a mortality rate of 12.3%. Griniatsos et al[11] treated 24 ASA III/IV patients with PC, with a success rate of 96%, procedure related mortality of 4% and 12.4% overall mortality. Complications are not described in these papers.

Most studies available in current literature addressing PC as a therapeutic option in ACC in the elderly or critically ill are retrospective studies with limited population sizes. Success rates are fairly high, but mortality rates of PC (range 4-12.7%) are higher than those for LC (range 0.1-4.5%). This can most likely be partly attributed to selection bias, since it is to be expected that the patients treated with PC were in a worse condition than those treated with LC in the first place. Despite this, current literature does not provide us with evidence that PC is a better treatment option than LC in this patient group, but in the current surgical practice PC is chosen more and more frequently in these patients and many surgeons believe that it actually is a safer and better treatment option.

In our own clinic, we performed a retrospective review of all patients undergoing PC for acute calculous cholecystitis between January 2009 and June 2010. A total of 27 patients were included (M:F 15:12) with a median age of 83 years. PC was performed because of either comorbidity/age or duration of symptoms. Mean time to full recovery was eight days, the drain was in situ for a median period of 19 days (range 5-57). Relief of symptoms occurred in 26 patients; drain luxation occurred in nine patients, only in two patients with clinical consequences. Complication rate was 22.2% (N=6) Overall mortality rate was 14.8% (n=4). With a mean follow-up of eight weeks, four patients underwent interval cholecystectomy.

After a thorough search in current literature and evaluating the results in our own clinic it has become clear that the very high risk patients (APACHE II score >14) are probably best treated by PC and the very low risk patients (APACHE II <7) are probably best treated by LC. For the “middle group” (APACHE II 7-14) it remains unclear which strategy to choose and opinions among surgeons vary.

We initiated a randomized controlled clinical trial, comparing urgent laparoscopic cholecystectomy with percutaneous cholecystostomy in high risk patients. With this trial we hope to provide answers to these vital questions regarding the treatment of ACC in high risk patients.

## 2. OBJECTIVES

**Primary Objective:**

To demonstrate that primary LC as compared to PC is preferable with respect to morbidity and mortality in high risk patients (APACHE-II score 7-14) with acute calculous cholecystitis

*Argumentation APACHE-II score:*

*A number of imaginary case scenarios were presented to an expert panel of physicians. Patient characteristics varied between age, comorbidity, vital signs and laboratory findings on presentation, and the panel was asked whether either therapy (LC or PC) would be contra-indicated. Of all patients, APACHE-II scores were calculated after the panel gave their opinion. It was generally agreed upon, that patients scoring <7 should undergo emergency LC, and patients scoring >14 were to have PC. In patients scoring between 7 and 14, opinions differed, and no consensus was reached regarding which treatment was better. Therefore, this group of patients will be included in the trial.*

## 3. STUDY DESIGN

CHOCOLATE is a randomized controlled, open, parallel, superiority, multicenter trial

Expected inclusion will take two years with a follow up of one year resulting in a total study duration of 36 months.

CHOCOLATE is a multicenter trial conducted in university hospitals and greater volume non-university teaching hospitals.

# 4. STUDY POPULATION

## 4.1 Population (base)

All patients with APACHE-II score ≥ 7 AND ≤ 14, with acute calculous cholecystitis.

All patients with confirmed acute calculous cholecystitis who are not eligible for randomisation will be registered anonymously. This way an accurate overview of all patients with an acute calculous cholecystitis will be acquired and it will demonstrate the exact percentage of ACC patients defined as high risk.

## 4.2 Inclusion criteria

- APACHE-II score ≥ 7 AND ≤ 14
- Acute calculous cholecystitis, defined according to Tokyo Guidelines:
  - A. Local signs of inflammation etc.: (1) Murphy's sign, (2) RUQ mass/pain/ tenderness
  - B. Systemic signs of inflammation etc.: (1) Fever, (2) elevated CRP, (3) elevated WBC count
  - C. Imaging findings: imaging findings characteristic of acute cholecystitis
  - Definite diagnosis
  - (1) One item in A and one item in B are positive
  - (2) C confirms the diagnosis when acute cholecystitis is suspected clinically
- Written informed consent

## 4.3 Exclusion criteria

- < 18 years of age
- Onset of symptoms ≥7 days before first presentation
- Already admitted to ICU
- Pregnancy
- APACHE-II score ≤ 6 OR ≥15
- Acalculous cholecystitis
- Decompensated liver cirrhosis
- Mental illness prohibiting informed consent

## 4.4 Sample size calculation

The rates for the primary endpoint: major morbidity, need for re-intervention and mortality for PC were 6.2, 13.1 and 12.7% respectively in the review. In our own retrospective data this was 22.2, 18.5 and 14.8%. For morbidity the mean of the two values was used: 14.2%.

Mortality rates are reported to be about 4.5% in current literature. In our own series the complication rate was 13.6% and the mortality rate was 4.3%.

It is to be expected that most patients who die will also have a major complication, so mortality cannot be simply added to the other group(s). To ensure that no cases of mortality are missed, a hypothetic value of 1% will be added to both treatment arms.

A decrease of the primary endpoint from 28.3% (PC group) to 14.6% (LC group) with power 80%, alpha two-sided 5%, Fisher exact, two proportions, 1:1 randomization can be demonstrated by randomizing 2x140 patients (PS Power and Sample Size Calculations, version 2.1.30, February 2003). With an expected loss to follow up of 1%, a total of 284 patients will have to be included in the trial.

*Argumentation sample size calculation*
*Sample size calculations are preferably made based on data from previous studies especially randomised controlled trials or at least prospective cohort studies. Since these studies are not available regarding percutaneous drainage, numbers to be used in the sample size calculation were derived from Winbladh's review[8] and data from our own retrospective study. Since these are still not the most reliable rates to base our sample size on, an estimation has to be made.*

*We decided to use the mean value of the complication rate from the review and our own data for the PC group since the review is probably an underestimation and our own results are, due to the retrospective nature and possible selection bias, probably an overestimation. The mean value, 14.2%, could very well approach the actual complication rate. Reinterventions were described accurately thus the rate of 13.1% seems the most reliable to use. Adding one percent for mortality results in an overall morbidity rate of 28.3%.*

*In the LC group, a complication rate of 13.6 is reliable since this is derived from a large database containing all cholecystectomies over an eight year time period in our own hospital and are therefore used for the control group and added up with mortality results in an overall morbidity rate of 14.6%.*
*Reinterventions are much less frequent in LC than PC patients and are generally related to a complication whereas in PC renewed drainage due to luxation of the drain or recurrent cholecystitis is encountered more often. It was therefore decided not to include a separate rate for reinterventions in the LC group.*

*Feasibility*:

On a yearly basis, on average, a total of 40 patients with acute calculous cholecystitis are admitted to a large Dutch teaching hospital. Approximately 40% of these patients are aged 75 years of older, or otherwise carry a higher risk. (St. Antonius hospital in 2009: 43 ACC, 17 with APACHE 7-14)) Assuming that 90% of patients will give informed consent for randomization, 15 patients a year will be included in the trial.

If 10 high volume teaching hospitals participate in the trial, the needed number of patients will be included within two years time. Every 4 months the number of included patients will be analyzed, in case of too little patients, additional hospitals will join the study group.

# 5. TREATMENT OF SUBJECTS

## 5.1 Investigational product/treatment

The investigational treatments are laparoscopic cholecystectomy and percutaneous drainage. Specific details are provided in section 6.3.

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## 5.2 Use of co-intervention (if applicable)

Use of antibiotics is allowed only if patients have a proven non-surgical infection (pneumonia, urinary tract) or a positive culture surgical site infection (wound infection, abscess).

In the surgical group, all patients will receive prophylactic antibiotics according to the local protocol in participating centers.

Patients are allowed to use their own prescription drugs, there are no dietary limitations.

# 6. METHODS

## 6.1 Study parameters/endpoints

### 6.1.1 Main study parameter/endpoint

**Primary Endpoint:**

Procedure related major morbidity within 30 days, including the following items

- Bile duct injury, defined as all injuries of the intra- and extrahepatic biliary ducts including leakage of the biliary tree, according to the Amsterdam classification of bile duct injury[12].
- **Intra-abdominal abscess**, defined as fever, elevated infection parameters* and intra-abdominal fluid collection on CT-imaging or ultrasound, confirmed by drainage of pus after intervention
- **Bleeding**, defined as drop in haemoglobin level requiring transfusion, confirmed by imaging or reintervention
- **Pneumonia,** defined as coughing or dyspnoea, radiography with infiltrative abnormalities, elevated infection parameters, confirmed by positive sputum culture.
- **Myocardial infarction periprocedural**, defined as symptomatic elevated cardiac enzymes and abnormalities on electrocardiography or cardiac ultrasound.
- **Thromboembolic complications,** defined as symptomatic deep venous thrombosis or pulmonary embolism, radiologically proven.
- **Cerebrovascular accident periprocedural,** defined as (temporary) loss of function of any body part or sense caused by cerebral ischemia or bleeding, proven on cerebral CT imaging.
- **Need for re-intervention**, defined as relaparoscopy, laparotomy, ERCP, intervention radiology, readmission
- **Mortality** during follow-up

### 6.1.2 Secondary study parameters/endpoints (if applicable)

**Secondary Endpoints:**

- Individual components of composite endpoint
- Minor complications, including superficial wound infection, urinary tract infection, bleeding without need for PCS or re-intervention
- Difficulty of LC/PC (as scored by VAS 1-10)
- Total length of hospital stay
- Duration of recovery to full daily activities
- Emergency room visits for related medical problems
- Cost efficiency

All results will be analysed for the study group in total, but there will also be a stratified analysis for the individual centres participating in the trial.

### 6.1.3 Other study parameters (if applicable)

Possible confounders are

- Previous abdominal surgery
- Body mass index
- Previous ERCP with sphincterotomy

## 6.2 Randomization, blinding and treatment allocation

Randomization will be done online through the CHOCOLATE website (www.cholecystitis.nl) using the ALEA software program. Random block sizes are used to ensure objective randomization. After randomization LC or PC has to be performed within 24 hours. In case of significant clinical deterioration within the waiting time hours, the APACHE-II score needs to be re-calculated. The patient will not be excluded from the study but an actual APACHE-II score at the time of treatment needs to be documented.

Blinding is not possible due to the nature of the two interventions compared in the CHOCOLATE trial.

### 6.3 Study procedures

Patients will be randomized to receive LC or PC, either one to be performed within 24 hours after randomization. LC will be performed by a surgeon trained and experienced in laparoscopic surgery, defined as >100 laparoscopic procedures on a yearly basis. Transsection of the duct and artery will be done only after reaching the critical view of safety as described in the Dutch Guidelines for Gallstone disease. Since small-incision cholecystectomy and laparoscopic cholecystectomy are comparable in terms of complications, mortality and duration of recovery[13], small-incision cholecystectomy may be performed instead of LC when this is according to local hospital protocol.
According to local hospital protocol, patients may receive pre-operative prophylactic antibiotics.

Percutaneous cholecystostomy will be performed by ultrasound- or CT-guided percutaneous drainage using an 8.5 French mac lock drain, either transhepatic or transperitoneal, depending on the local hospital protocol. (In the literature there is no consensus which route is better. A higher incidence of biliary leakage using the transperitoneal route has been reported by some authors[14], but multiple other studies did not find any difference between both routes. The transhepatic route is described to be more painful and maturation of the drainage tract might take longer as compared to the transperitoneal route).

Bile cultures will be performed during LC and PC to evaluate the incidence and specifics of bactobilia in ACC.

Successful PC is defined as resolution of symptoms and fever and normalization of CRP and white blood count without the need for renewed intervention. Failure to thrive < 48 hours will lead to LC. The drain will remain in situ during a total period of three weeks after which contrast-imaging of the drain will be performed to assess whether the drain is still located inside the gallbladder and whether there is a competent cystitc duct, visualized by backflow of contrast into the duodenum.
After imaging of the drain, the drain can be removed on the subsequent visit in the outpatient clinic.

*Data collection during hospital admission:*

Each patient will receive an anonymous study number which will be used for the study case-record-forms and in the database.

Clinical data with regard to baseline characteristics (gender, date of birth, length, weight, admitting physician, speciality and ward, date of onset of pain, date of admission, date of randomization) and outcomes will be collected during hospital admission using paper case record forms. The case record forms will be filled out by the local treating physicians, nurses or study coordinators. All case record forms will be centrally collected and stored in the Datacenter of the study group. The study coordinators are allowed to correct wrongly entered data (such as miscalculated patient age or miscalculated disease severity scores). The case record forms will be checked with source data (unblinded admission and discharge letters, unblinded surgery report) that will also be centrally stored in a locked cabinet in the Datacenter. In the patient consent form it will be specifically stated that these data will be stored in the Datacenter. Only the study coordinators will have access to the unblinded source data.

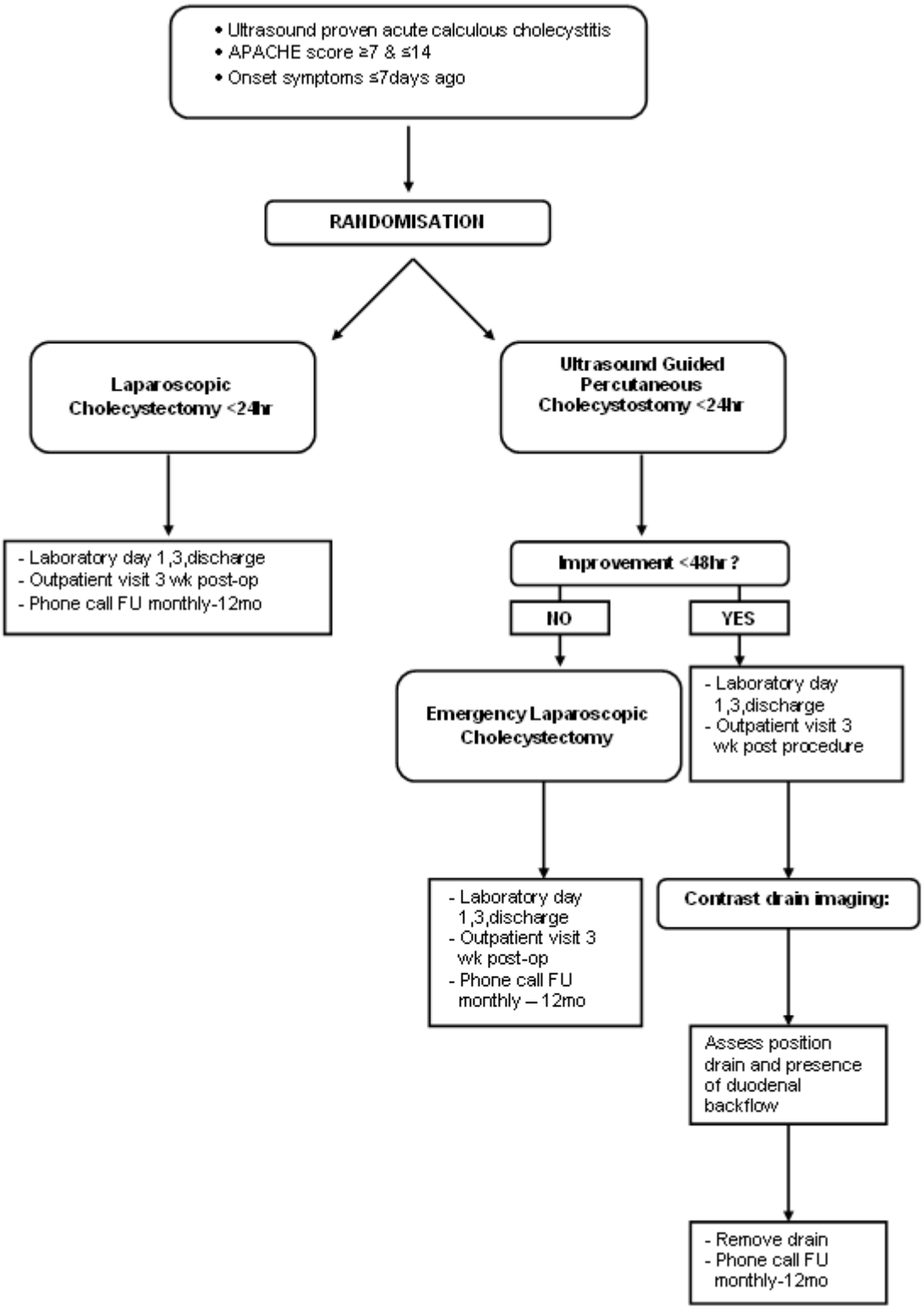


Figure 1. Flowchart of study outline for included patients

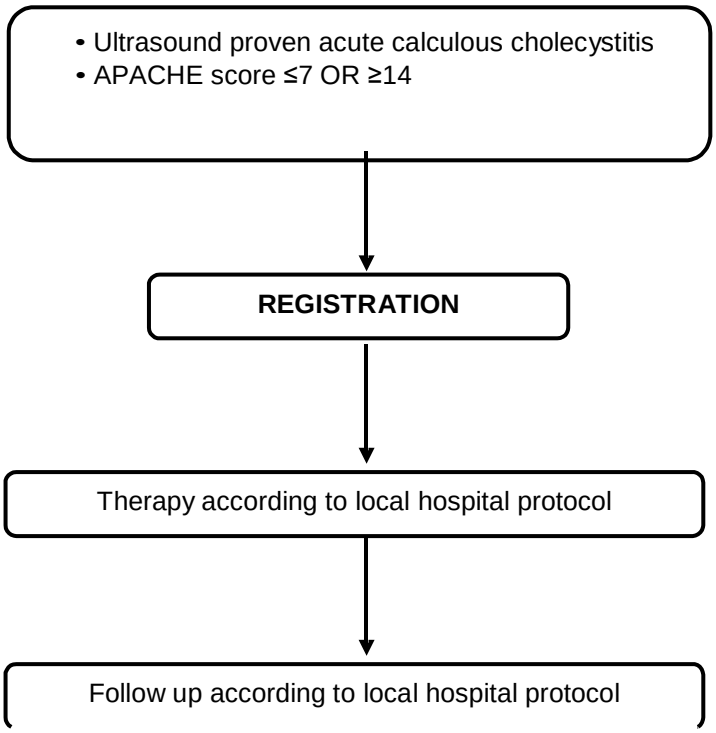


Figure 2. Flowchart of study outline for registered patients

## 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. Follow-up in terms of primary outcome of those participants will be performed as usual.

### 6.4.1 Specific criteria for withdrawal (if applicable)

Individuals 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 an individual from the study for any medical reason. In case of randomization for PC, a clinical response must be seen within 48 hours after start of treatment. If clinical improvement fails to occur within 48 hrs, patients may undergo emergent (laparoscopic) cholecystectomy.

## 6.5 Replacement of individual subjects after withdrawal

Once individual subjects are withdrawn from the study there will be no replacement. All patients will be analyzed according to the intention to treat principle.

### 6.6 Follow-up of subjects withdrawn from treatment

All patients randomized will be analyzed according to the intention to treat principle.

### 6.7 Premature termination of the study

After the first year of inclusion an interim analysis will be performed.

The trial will not be stopped for futility the reason being that this is the first randomized trial on this subject and treatment policy will be based on this trial.

To guarantee the safety of patients throughout the study an independent biostatistician follows the occurrence of all components of the composite endpoint between groups. The outcome of this analysis is only known to the independent biostatistician. Whenever a significant difference occurs, the DSMB, the METC and the investigators will be informed and the study will be put on hold until the results of a formal interim-analysis are discussed. Also see the paragraph on DSMB.

# 7. SAFETY REPORTING

## 7.1 Section 10 WMO event

In accordance to section 10, subsection 1, of the WMO, the investigator will inform the subjects and the reviewing accredited METC if anything occurs, on the basis of which it appears that the disadvantages of participation may be significantly greater than was foreseen in the research proposal. The study will be suspended pending further review by the accredited METC, except insofar as suspension would jeopardize the subjects' health. The investigator will take care that all subjects are kept informed.

## 7.2 Adverse and serious adverse events

Adverse events are defined as any undesirable experience occurring to a subject during the study, whether or not considered related to [the investigational product / the experimental treatment]. All adverse events reported spontaneously by the subject or observed by the investigator or his staff will be recorded.

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

- results in death;
- is life threatening (at the time of the event);
- requires hospitalization or prolongation of existing inpatients' hospitalization;
- results in persistent or significant disability or incapacity;
- is a congenital anomaly or birth defect;
- is a new event of the trial likely to affect the safety of the subjects, such as an unexpected outcome of an adverse reaction, lack of efficacy of an IMP used for the treatment of a life threatening disease, major safety finding from a newly completed animal study, etc.

Local investigators will report mortality within 24 hours to the study coordinator. The study coordinator will report mortality to the accredited central-METC via the "Toetsingonline" website of the website of the Central Committee on Research inv. Human Subjects (CCMO, ccmo.nl) within 7 days after the study coordinator has been made aware of this. All other SAE's have to be reported within 72 hours to the study coordinator. In all study meetings all participating physicians will be

reminded to report mortality and other SAE's to the study coordinator as soon as possible.

Data on mortality and all other SAE's/AE's will be collected per 30 randomized patients and presented to the DSMB and will at that time be listed in "Toetsingonline" The DSMB will discuss the SAE's and give advice to the trial steering-committee and the METC.

If in one patient multiple similar endpoints (e.g. intra-abdominal abscess and pulmonary infection) occur only the initial endpoint will be reported as a SAE/AE. The rationale for this being that in the final table made for the DSMB only one such endpoint will count per patient as is current 'best practice' in reporting of RCTs.

No annual safety report is drafted as during the study the DSMB will continuously be monitoring patient safety. The DSMB will be reporting directly to the METC.

### 7.3 Follow-up of adverse events

All adverse events 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.

### 7.4 Data Safety Monitoring Board (DSMB)

The DSMB will consist of three members: an epidemiologist/statistician, a surgeon and a radiologist. One of the three (the epidemiologist) will be the chairperson and another member will produce written short transcripts of the meeting that should include: data, location, participants, patient numbers that were discussed and decisions made. These transcripts will be send to the study coordinator and the METC.

Every six months, an analysis will be performed by the DSMB. The trial statistician will perform the analysis, using an unblinded database. The results of this analysis will be presented to the members of the DSMB who will discuss these and provide the primary investigator with an advise to either continue with or terminate the trial.

The primary endpoint will be monitored for benefit or harm using a restricted procedure (Whitehead, 1997), designed according to the sample size characteristics as described in the protocol (4.4).

Safety monitoring will be performed on the mortality outcome with a two-sided type I error α of 0.05 using a restricted procedure (Whitehead, 1997). A relative risk of 2 or larger will be considered reason to advice to stop the study.

Efficacy and safety monitoring will be performed using the PEST 4 software (PEST, 2000).

Formal statistical methods are more generally used as guidelines rather than absolute rules. This is because they generally only consider one dimension of the trial. Reasons should be recorded for disregarding a stopping guideline.

When the DSMB performs an analysis, the Peto approach will be followed meaning that the study will only be stopped for beneficial effects in case of a $P<0.001$[14]. For harm (higher incidence of the primary endpoint in either group) the Pocock approach will be followed, a P-value of 0.029 is required[15].

A clear relation should exist from the data that either treatment modality is indeed associated with harm. The interim-analysis is performed by the study coordinator and the trial epidemiologist/statistician together and then presented to the DSMB. Results of this analysis will be discussed in a private meeting with only the DSMB members present. Prior to this meeting the principal investigator and study coordinator may present additional data/studies/arguments that the DSMB should take into account but the DSMB gives the final advice to stop or continue the trial to the steering committee. This advice is sent to the study coordinator and principal investigator and the ethics committee will receive a direct copy of this advice.

# 8. STATISTICAL ANALYSIS

## 8.1 Descriptive statistics

Every six months, an interim analysis is performed to monitor the safety of the trial. Final analysis will be done after follow-up of the final patient is completed, a blinded adjudication committee will assess all primary endpoints according to the definitions listed in this protocol. The comparison of the primary endpoint will be expressed in terms of a relative risk and 95% confidence intervals. Subsequent analyses are directed at secondary endpoints. Data will be presented as mean ± SD and in case of skewed distributions as median and range. Values will be compared by the $\chi^2$ test, Fischer exact test or Mann-Whitney U as appropriate. A two-tailed $P < 0.05$ is considered statistically significant. All analysis will be according to the intention to treat principle.

*Costs*

All costs will be estimated based on the actual input in terms of resource use and personnel. For all cost-items such as ICU or regular hospital admission, operation, medication, diagnostic tests, rehabilitation, unit costs will be derived from the Dutch costing manual or with hospital administration. The use of in hospital cost-items will be recorded in CRFs. The use of medical resources outside hospital (e.g. general practitioner consultation, physiotherapy) will be recorded in patient diaries. The costs pertaining to the actual sick leave will be calculated by means of the friction cost method. Ninety days post-discharge the definite outcome can be determined regardless of the approach used. Accordingly neither costs nor effects will be discounted. Uncertainty regarding the incremental cost-effectiveness ratio (iCERs) will be assessed using bootstrap replicates of the original trial data.

*Economic evaluation:*

The analyses will initially focus on the iCER in terms of costs per primary endpoint avoided. Uncertainty with regard to the iCER will be evaluated by means of bootstrapping (500 replicates). By plotting incremental costs (y-axis) and incremental effects (x-axis) for each replicate uncertainty is depicted directly. Subsequently, costs per infectious complication and death avoided and per (QA)LY gained will be estimated, also based directly on the outcomes in the trial. Accordingly, uncertainty will also be evaluated using bootstrapping.

To document cumulative total costs for both treatment strategies, the use of resources will be assessed using hospital information systems and additional data collection in the case record forms. The tracking of resources will start at randomization. Unit prices will either be determined based on current guidelines for economic evaluations or, alternatively, if not existent or not applicable, they will be calculated during the study. Out of hospital resource use as well as data on direct non-medical and indirect costs will not be analyzed. Within the study, differences in treatment will be analyzed to detect potential limitations to the reproducibility of our findings.

# 9. ETHICAL CONSIDERATIONS

## 9.1 Regulation statement

The CHOCOLATE trial will be conducted according to the principles of the Declaration of Helsinki (version October 2008) and in accordance with the Medical Research Involving Human Subjects Act (WMO).

## 9.2 Recruitment and consent

All patients presenting to the emergency department or outpatient clinic meeting the inclusion criteria will be informed about the CHOCOLATE trial by the surgical doctor in charge (this can be either a resident, a fellow or attending surgeon).

Since there is no place for a wait-and-see approach in acute cholecystitis, patients will be asked to decide if they want to participate within 24 hours .

The patient information letter and informed consent form are attached as a separate document.

## 9.3 Objection by minors or incapacitated subjects (if applicable)

Not applicable.

## 9.4 Benefits and risks assessment, group relatedness

Current available evidence, although mostly retrospective and small populations, points out that is an alternative therapy for high risk patients with ACC. However, treatment takes longer, is associated with considerable morbidity and even mortality and cholecystitis may recur. LC in the same patient category is also associated with morbidity and mortality, but these figures seem to be lower.

Complications that may occur are: procedure related complications including infection (wound, drain site, intra-abdominal) and bleeding, as well as non surgical complications including urinary tract infections, pneumonia, cardiac complications and deep venous thrombosis.

It is therefore imperative to define the best treatment option for ACC in this specific patient category.

## 9.5 Compensation for injury

The investigator has a liability insurance which is in accordance with article 7, subsection 6 of the WMO. The investigator (also) has an insurance for the main participating center (St. Antonius Hospital) 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 23th June 2003). This insurance provides cover for damage to research subjects through injury or death caused by the study.

The other participating centers will have to provide for their own insurances.

- € 450.000,-- (i.e. four hundred and fifty thousand Euro) for death or injury for each subject who participates in the Research;
- € 3.500.000,-- (i.e. three million five hundred thousand Euro) for death or injury for all subjects who participate in the Research;
- € 5.000.000,-- (i.e. five million Euro) for the total damage incurred by the organisation for all damage disclosed by scientific research for the Sponsor as '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.

All participating centers are responsible for their own insurance.

# 10. ADMINISTRATIVE ASPECTS AND PUBLICATION

## 10.1 Handling and storage of data and documents

Patients will be coded by a numeric randomization code (anonymous) and the principal investigators will be the only ones to have access to this code. The main investigator/project coordinator will monitor all participating centers and guide the location coordinators in entering the data into the database. On inclusion of the first patients per center, the main investigator will be present to make sure data collection and entry is done accurately. The main investigator will perform a final check on all entries comparing source data with data entered into the database.

The source data will be kept by the project leader for 15 years.

## 10.2 Amendments

Amendments are changes made to the research after a favorable opinion by the accredited METC has been given. All amendments will be notified to the METC that gave a favorable 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.

## 10.3 Annual progress report

The sponsor/investigator 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.

## 10.4 End of study report

The investigator 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.

In case the study is ended prematurely, the investigator will notify the accredited METC, 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.

### 10.5 Public disclosure and publication policy

No arrangements have been made concerning public disclosure. The trial will be registered by Controlled-trials.com. The trials' results will be submitted to a peer-reviewed journal regardless of the outcome. Co-authorship will be based on the international guidelines. Clinicians that do not fulfill these criteria will be listed as 'collaborator' and the journal will be asked to present the names of all collaborators to be listed as well in Pubmed. The study coordinators will be first and second authors whereas the principal investigators will be the final authors. The further order of authors will be based primarily on scientific input and secondarily on the number of randomized patients to be judged by the principal investigators.

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APPENDIX I. APACHE-II score

**APACHE-II score**

Consists of three scoring tables, resulting in the addition of the three individual scores.

APACHE-II Score = Score 1 + Score 2 + Score 3

**1.** Clinical scoring items

| | **+4** | **+3** | **+2** | **+1** | **0** | **+1** | **+2** | **+3** | **+4** |
|---|---|---|---|---|---|---|---|---|---|
| Temperature | ≥41 | 39,0-40,9 | | 38,5-38,9 | 36-38,4 | 24-35,9 | 32-33,9 | 30-31,9 | ≤29,9 |
| MAP, mmHG | ≥160 | 130-159 | 110-129 | | 70-109 | | 50-69 | | ≤49 |
| Heart rate | ≥180 | 140-179 | 110-139 | | 70-109 | | 55-69 | 40-54 | ≤39 |
| Respiratory rate | ≥50 | 35-49 | | 25-34 | 12-24 | 10-11 | 6-9 | | ≤5 |
| PAo2-Pao2 (if Fi02>0,5)<br>Pa02 (if Fio2 < 0,5) | ≥500 | 350-499 | 200-349 | | <200<br>>70 | 61-70 | | 55-60 | ≤55 |
| PH (arterial) | ≥7,7 | 7,6-7,69 | | 7,5-7,59 | 7,33-7,49 | | 7,25-7,32 | 7,15-7,24 | ≤7,14 |
| Serum Na | ≥180 | 160-179 | 155-159 | 150-154 | 130-149 | | 120-129 | 111-119 | ≤110 |
| Serum K | ≥7 | 6,0-6,9 | | 5,5-5,9 | 3,5-5,4 | 3-3,4 | 2,5-2,9 | | ≤2,4 |
| Serum creatinine (umol/L, score x2 in case of acute kidney failure) | ≥302 | 169-301 | 125-168 | | 53-124 | | ≤52 | | |
| Haematocrit | ≥60 | | 50-59,9 | 46-49,9 | 30-45,9 | | 20-29,9 | | ≤19 |
| White blood count (in 1000/mm3) | ≥40 | | 20-39,9 | 15-19,9 | 3-14,9 | | 1-2,9 | | ≤0.9 |
| Glasgow coma scale | | | | | 15 min actual score | | | | |

| 2. Age | Score |
|---|---|
| <44 | 0 |
| 45-54 | 2 |
| 55-64 | 3 |
| 65-74 | 5 |

> 75 6

3. Comorbidity

The following defines "chronic organ insufficiency" and immunocompromise:

*0 Points if none of the below mentioned criteria are present*

*2 Points if the patients is eligible for surgery*

*5 Points if surgical intervention is not an option*

- Liver insufficiency
  - Biopsy proven cirrhosis
  - Documented portal hypertension
  - Episodes of past upper GI bleeding attributed to portal hypertension
  - Prior episodes of hepatic failure / encephalopathy / coma.
- Cardiovascular
  - New Heart Association Class IV Heart Failure
- Respiratory
  - Chronic restrictive, obstructive or vascular disease resulting in severe exercice restriction, i.e. unable to climb stairs or perform household duties.
  - Documented chronic hypoxia, hypercapnia, secondary polycythemia , severe pulmonary hypertension (> 40 mmHg), or respirator dependency.
- Renal
  - Receiving chronic dialysis
- Immunosuppression
  - The patient has received therapy that suppresses resistance to infection e.g. immuno-suppression, chemotherapy, radiation, long term or recent hight dose steroids, or has a disease that is sufficiently advanced to suppress resistance to infection, e.g. leukemia, lymphoma, AIDS.