CHOLENZ STUDY: Protocol for a multicentre, prospective cohort study of outcomes following cholecystectomy for benign gallbladder diseases in New Zealand

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Sponsor: Northland District Health Board

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2. Study Timeline

May 2021

- Provisional Protocol Finalised
- Locality and HDEC Assessment Submission
- Funding Application

June 2021

- Recruit Participating Centres
- Investigators Established

July 2021

- Participating sites to seek ethical approval
- Preparation for data collection

August - October 2021

- Data collection

November 2021

- 30-day follow up

December 2021-January 2022

- Data analysis
- Manuscript Writing

3. Synopsis

Study Title	Variation in practice of cholecystectomy across New Zealand: a multicentre, prospective cohort study.
Internal ref. no. / short title	CHOLENZ Study
Study Design	Multicentre prospective observational cohort study.
Study Population	Patients receiving an acute, elective, or delayed cholecystectomy at any centre in New Zealand.
Eligible Centres	All hospitals in New Zealand
Planned Cohort	3 months with 30-day follow-up
Objective	Measure the difference in all-cause readmission within 30-days of discharge following acute, elective, and delayed, cholecystectomies in New Zealand.
Primary outcomes of interest	• 30-day readmission rate
Secondary outcomes of interest	• 30-day all-cause postoperative complications (defined by Clavien-Dindo classification) • Bile leak • Bile duct injury • Conversion of operation • Duration of surgery • Length of stay
Follow Up	Participant's data will be collected during their index admission and 30-days after discharge.
Data Collection Period:	01 August 2021 – 30 October 2021 (+30 day follow up)

4. Background and Rationale

Cholecystectomy is one of the most commonly performed general surgical procedures in New Zealand. Approximately 7,782 acute, 21,269 elective, and 422 semi-acute cholecystectomies were performed between 2006 and 2010 (1). Management pathways for benign biliary disease can usually be categorised as follows: i) cholecystectomy performed acutely at the index admission for benign symptomatic biliary disease ii) elective cholecystectomy, often after outpatient referral; iii) other planned cholecystectomies performed on an elective operation list after previously having had an emergency surgical admission for benign symptomatic biliary disease.

The management of benign gallbladder disease, in particular whether patients have acute, elective or delayed surgery, varies significantly by surgeon and hospital (2,3). Population-based studies suggest cholecystectomy performed within 72-hours results in reduced intra-operative conversion, reduced complications and length of stay (4). There are high-quality randomized controlled trials which support the safety of acute laparoscopic cholecystectomy for biliary colic, cholecystitis, and gallstone pancreatitis (5–8). Population-based data is often variable suggesting outcomes may vary by hospital size and volume (2,9).

It is hypothesised that hospital readmission rates, complications and patient-outcomes are likely to vary based on whether patients had acute, elective or delayed cholecystectomy. These variations in the New Zealand setting remain unknown. It is also anticipated that readmission rates will also vary by hospital size and case volume (10). Reducing complications and hospital readmissions after cholecystectomy is likely to have significant impact on healthcare expenditure and improve patient-outcomes and patient-satisfaction (11).

The limited external validity of clinical trials conducted globally, and the anticipated variability in outcomes based on differences in hospital service provision, makes it difficult to understand variations in outcomes based on timing of cholecystectomy in Australasia. The CholeS study which investigated the clinical variation in practice of laparoscopic cholecystectomy and surgical outcomes in the United Kingdom (UK) through a multicentre, prospective, population-based cohort study found that readmissions and complications were common after cholecystectomy and increased with greater number of previous acute hospital admissions (12). This study also found significant variability between hospitals. While such data exists in the European setting, provided by the CholeS study (12), no such data is available for New Zealand and it is of interest to see if our rates of readmissions and complications follow similar patterns and hospital-based variability to that of the international literature.

This study is an adaption of the CholeS study in consultation with the CholeS Steering Group. Several variations in data points have been made to reflect the New Zealand healthcare context (12).

5. Aim

Primary Aim:

To measure the difference in all-cause readmissions within 30-days after discharge following acute, elective, and delayed cholecystectomies between hospitals in New Zealand.

Secondary Aims:

- Describe variations in practice of preoperative management and intraoperative technique
- Describe preoperative patient demographics, admission types, indication for cholecystectomy, diagnostic tests and interventions applied for benign gallbladder disease
- Describe perioperative aspects of management of benign gallbladder disease such as the surgical approach, conversion from laparoscopy to open, use of intraoperative cholangiogram, and complications
- To describe the postoperative course of benign gallbladder disease such as the length of stay and 30-day postoperative complication rates.

6. Outcomes

6.1 Primary Outcomes

- All-cause 30-day readmission rate

6.2 Secondary Outcomes

- 30-day all cause postoperative complications
- Bile leak (incidence and grade)
- Bile duct injury
- Conversion of operation
- Duration of surgery
- Length of stay

7. Methods

7.1 Study Design

National, multicentre, prospective observational cohort study.

All New Zealand hospitals that perform cholecystectomies will be invited to contribute to this study to maximise patient numbers and increase the applicability of the study to all New Zealand patients.

7.2 Data Collection

An investigator at each contributing hospital will be appointed to be responsible for data collection of all appropriate patients. Patients undergoing cholecystectomy may be admitted under multiple teams, it is the hospital lead's responsibility to capture all cholecystectomies that occur during the study inclusion period.

Each investigator will be provided access to a REDCap database with a pre-specified data fields to ensure standardised data collection across hospitals. Data will be collected prospectively from patient notes and electronic records.

Data from contributing hospitals will be prospectively collected from the 01 August 2021 to 30 October 2021 with 30-day follow up till 30 November 2021.

All hospital leads will also be required to complete a hospital-survey which assess hospital-related variables (**Appendix F**).

7.3 Eligibility Criteria

Inclusion Criteria

- All patients ≥18 years old who are undergoing a cholecystectomy in New Zealand

Exclusion Criteria

- Age less than 18
- Patients having a cholecystectomy for known GB cancer, or as a part of another surgical procedure for example, Whipple's procedure, bariatric, anti-reflux or transplant operations

7.4 Required Data

Definitions

- **Acute**: cholecystectomy performed in same index admission to acute presentation
- **Elective**: cholecystectomy performed from an outpatient or GP referral with no previous acute admissions
    - *Patients seen/discharged from an emergency department will be included in the **elective** group.*
- **Delayed**: cholecystectomy performed after a preceding acute admission for benign symptomatic biliary disease at any point

Primary Outcomes

Outcomes	Outcome Measures
All-cause 30-day readmissions	• All-cause 30-day readmission defined as any admission following discharge which requires an overnight stay (this standard and definition is based on the Royal College of Surgeons (RCS) and the Association of Upper Gastrointestinal Surgeons (AUGIS) of Great Britain and Ireland guidance which states that the audit standard of less than 10% 30-day readmission rate should be reached by hospitals performing cholecystectomies (13).
Reason for readmission	Free-text reason for readmission for further analyses

Secondary Outcomes

Outcomes	Outcome Measures
30-day all cause postoperative complications	• As described by the Clavien-Dindo classification of postoperative complications (14). Specifically, bile leak, CBD injury, wound infection, intra-abdominal collection, pancreatitis, CBD stones, ICU/HDU readmissions will be collected, as will non-surgical complications such as cardiac, respiratory, urinary, and other 30-day complications

Bile leak	• Y/N
	• Graded:
	  • A – bile leak which requires little or no change in patient's management and resolves with conservative management within 7-days.
	  • B – bile leak or collection which requires additional diagnostic or interventional procedures, such as ERCP or re-laparoscopy or Grade A which lasts >7-days.
	  • C – bile leak or collection which requires relaparotomy

Bile duct injury	• Y/N

	• Any injury to the main biliary tree and will be classified using the Stewart-Way Classification System (15): 1. Defined as incomplete injury to the CBD with no loss of duct 2. Defined as lateral damage to the CHD with either structure formation or fistula (bile leak) 3. Defined as transection of the CBD with excision of a variable portion of the CBD and cystic duct/common duct junction 4. Defined as injury to the right hepatic duct with or without injury to the right hepatic artery
Conversion to operation	• Laparoscopic approach converted to an open incision operation, or in which an abdominal incision to assist the procedure was needed
Duration of surgery	• Time in minutes from skin incision to the end of skin closure
Length of stay	• Calculated from date of admission to date of discharge

CBD, common bile duct; CHD, common hepatic duct; ERCP, endoscopic retrograde cholangiopancreatography; HDY, high dependency unit; ICU, intensive care unit.

Covariates

Outcomes	Outcome Measures
Patients' details	• Age (years), sex, ethnicity, BMI (underweight, normal, overweight, moderate obesity, severe obesity, very severe obesity), smoking history (current, ex-smoker >1-month, ex-smoker <1 month, lifetime non-smoker), ASA score, admission date, discharge date, previous abdominal surgery, Charlson Comorbidity Index (16).
Operative timing	• Operation date, timing of surgery (acute; elective or delayed), planned day-case (Yes – defined as patients who are planned to be admitted and discharged on the same day as the operation/No), date decision made to operate (for elective cases this will be the date the patient was seen in the outpatient clinic; for delayed cases this is the date the patient was last discharged from hospital with biliary

	disease; for acute cases this should be the date the decision was made to perform an acute cholecystectomy in that emergency admission)
Preoperative	Preoperative indication: • Biliary colic – presence of colicky right upper quadrant pain associated with gallstones or sludge on an USS, but no signs of acute cholecystitis) • Acute or chronic cholecystitis – current or previous clinical or ultrasound evidence of cholecystitis (thick-walled GB and/or pericholecystsitis, or USS tenderness over the GB, the presence of gallstones). Graded based on Tokyo Severity Grade (17). • Gallstone pancreatitis - pancreatitis secondary to gallstones diagnosed according to the Atlanta guidelines which state the diagnosis of acute pancreatitis requires 2/3 of: 1) abdominal pain consistent with acute pancreatitis (acute onset of a persistent, severe, epigastric pain often radiating to the back), 2) serum lipase activity (or amylase activity) at least 3x upper limit of normal; and 3) characteristic findings of acute pancreatitis on contrast-enhanced CT (18). • CBD stones – confirmed by preoperative imaging, that may or may not have been removed preoperatively • GB polyps – hyperechoic lesions on USS imaging which have no acoustic shadowing and do not move with positional changes (and have no features of overt malignancy) • Dyskinesia – biliary-like abdominal pain, occurring in normal appearing GB with functional HIDA scan showing an abnormal GB ejection fraction of less than 40% • Acalculous cholecystitis (clinical or ultrasound evidence (thick-walled GV and/or pericholecystitis, USS tenderness over the GB, the absence of gallstones) • Surgical admissions with biliary symptoms in the previous 24 months – number of surgical admissions with biliary symptoms in the previous 24 months: 0, 1, 2, 3, 4, 5, >6;

	and total number of days spent in hospital as a result; date of last discharge
Investigations	• USS • CT • MR cholangiopancreatography • ERCP • Endoscopic USS Functional scan • Bloods (Hb, WCC, CRP, Platelets, ALP, ALT, Bilirubin, INR) – most recent blood test to procedure (e.g., pre-assessment clinic for elective cases, or from acute admission for acute cases)
Seniority of surgeons	• Non-SET trainee • SET trainee • Fellow • Medical officer of specialist scale (MOSS) • Consultant
Perioperative care	• Perioperative antibiotics Y/N • Preoperative cholecystostomy or interventional radiology drainage (Y/N)

Operative	• Method of operation (laparoscopic, laparoscopic converted to open, open cholecystectomy, SILS)
	• Degree of difficulty – Nassar scale of difficulty for cholecystectomy graded 1, 2, 3, 4 (19)
	  • Grade 1 – floppy, non-adherent gallbladder; clear, thin cystic pedicle, simple adhesions to neck and Hartmann's pouch only
	  • Grade 2 – Mucocele; packed with stones gallbladder; fat-laden cystic pedicle; simple adhesions, up to the body of gallbladder
	  • Grade 3 – deep fossa; acute cholecystitis; contracted, fibrous Hartmann's pouch adherent to CBD or with stone impaction; abnormal anatomy; cystic duct short,

	dilated, or obscured; dense adhesions, up to the fundus; involving hepatic flexure or duodenum • Grade 4 – completely obscured gallbladder; empyema/gangrene; or mass; impossible to clarify cystic pedicle dense, fibrous adhesions wrapping the GB. Duodenum or hepatic flexure difficult to separate.

Intraoperative complications	• Bile spilt (intra-abdominal spillage of bile during the procedure, including when removing the GB from the abdominal cavity)
	• Stones spilt (intra-abdominal spillage of stones during the procedure, including when removing the GB from the abdominal cavity)
	• Bleeding (requiring haemostatic agents (e.g., Surgicel, Fibrillar, etc), extra clips, suturing or conversion to open procedure)
	• CBD injury - Y/N (will be defined as any injury to the main biliary tree and classified using the Stewart-Way Classification System (1, 2, 3, 4)).
	  • If Y: recognised intraoperatively or delayed recognition?
	  • If Y and reconstructed: immediate reconstruction or delayed reconstruction?

Intraoperative cholangiography	• Y/N
Intraoperative variables	• Full cholecystectomy or subtotal cholecystectomy • CBD exploration (Y/N) • Abdominal drain (Y/N)
Postoperative variables	• All-cause 30-day A&E attendance (Y/N) • All 30-day reinterventions and reimaging (Y/N) • 30-day mortality (Y/N)

BMI, body mass index; ERCP, endoscopic retrograde cholangiopancreatography, A&E, accident, and emergency department; ASA, American Society of Anesthesiologist; CBD, common bile duct; GB, gallbladder; HIDA, hepatobiliary iminodiacetic acid; SILS, single-incision laparoscopic surgery; USS, ultrasound scan.

Further details about the Charlson Comorbidity Index, Tokyo Guidelines, Atlanta guidelines and Nassar scale can be found in Appendix A-D.

7.5 Follow up

All patients will be followed for the period of their index admission and then at 30 days.

8. Ethical and Regulatory Considerations

8.1 Ethical considerations

This study will take the form of a prospective cohort study. There will be no change to the management of patients and no advice or guidelines given to the data collectors/clinical team. The aim will be to collect information on the routine practise of different hospitals around New Zealand. There is no foreseen impact on standard patient care and therefore no risk to patients involved in this study. There will be no contact with patients and follow-up data will be collected from routine clinical notes; NO phone calls will be made.

8.2 Ethical approval

An out of scope HDEC letter will be applied for. Rational for out of scope approval is as stated above. Each participating centre will be required to apply for locality ethical or audit approval as appropriate to their centre.

8.3 Data Handling and storage

Data will be collected and stored using the web application Research Electronic Data Capture (REDCap). It is encrypted with HIPAA-Security and compliant with guidelines in the United States and is widely used by academic institutions. Each collaborator will be given secure REDCap server login details, allowing secure data storage on the REDCap system. Collaborators will be unable to upload identifiable information to the REDCap database. All anonymous data will be held for a total of ten years, after which it will be permanently removed from the server space.

When creating an entry for a patient in REDCap a unique REDCap ID for each patient is created. Each collaborator will be asked to keep an spread sheet on a password protected hospital computer to store NHI and the corresponding REDCap ID. This will give investigators the opportunity to use the data in the future if required. Data will only be stored for a period of 10-years after which it will be permanently deleted.

All centres will be required to have locality approval prior to starting data collection.

8.4 Māori Health Directorate

Joy Panoho from the Whangārei Hospital Māori Health Directorate offered guidance and advice in the conceptualisation stages of this project. To date no New Zealand study has

reported on the effects of ethnicity on outcomes after acute, elective, and delayed cholecystectomy in the New Zealand setting. Ethnicity data will be collected and its impact on outcomes investigated. If a disparity in outcomes is found it will be imperative that this is reported with the aim of improving outcomes for our Māori patients. At the conclusion of the study anonymous information will be made available to each Māori Health directorate in all participating DHBs following analysis and prior to publication.

9. Funding

Application for funding will be made to Auckland Medical Research Foundation.

9. Statistical Analysis

The study will be reported in accordance to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement (20). Descriptive analysis will be performed where normal continuous variables will be compared via students t test, and non-normal continuous variables will be compared via Mann-Whitney U test; if >2 categories a one-way ANOVA or Kruskal-Wallis test will be used for normal and non-normal variables respectively, Chi-square tests will be used to detect differences between categorical variables. Multiple imputation may be used in the case of missing data.

Binary logistic regression modelling will be used. Multivariable models will be built to produce odds rations (OR) to account of the impact of predictive variables when assessing primary and secondary outcomes. A multilevel model, using the patient at the fixed effect level 1 and the hospital as the random effect level 2 (using the R lmer package) will be performed. A one level, fixed effect binary logistic regression model using a pooled dataset from 5 multiply imputed datasets will also be used in the event of substantial missing data.

Variable selection will be based on statistically significant univariable analysis and those variables deemed clinically significant. Fixed, forced entry will be used to adjust the main outcome measure, The effect of interaction, and sequential removal of non-significant variables will be assessed using changes in Akaike information criteria for multilevel models, and p-values for multiple imputed fixed models.

Risk-adjusted funnel plots will be produced to test the performance of individual, anonymised centres for normal rates of primary and selected secondary outcomes.

11. Study Completion

11.1 Completion

The study will be deemed complete after 4 months (3 months of recruitment and 1 month of follow up) of prospective data collection. The data will then be pooled and analysed by the chief investigator.

11.2 Publication

The manuscript will be prepared by a writing committee. Prior to publication all hospital leads will be invited to be involved in reviewing drafts of the manuscripts, abstracts, press releases and any other publications arising from the study. All investigators and collaborators in mini-teams including supervising consultant(s) will be acknowledged as PubMed-citable co-authors using a corporate authorship model. Collaborators will have the responsibility of registering this study at their locality, acquiring appropriate approvals, identifying patients, collecting data and completing 30-day follow-up. Where hospital leads fail to submit complete data, or if a hospital's data is removed, collaborators at that hospital will be excluded from the authorship list; if substantially incomplete data is submitted, the writing committee may decide to exclude that unit from further analysis. Authors will acknowledge the study funding sources and other contributors.

Appendix A – Charlson Comorbidity Index(16)

Comorbdiity	Scoring
Age	0 points (<50 years) 1 point (50 – 59 years) 2 points (60 – 69 years) 3 points (70 – 79 years) 4 points (≥ 80 Years)
Previous myocardial infarction (MI)	1 point
Congestive heart failure (CHF)	1 point
Peripheral vascular disease	1 point
Previous cerebrovascular accident (CVA) or transient ischaemic attach (TIA)	1 point
Dementia	1 point
COPD	1 point
Connective Tissue Disease	1 point
Peptic ulcer disease	1 point
Liver disease	1 point (Mild) 3 points (moderate to severe)
Diabetes mellitus	0 point (none or diet-controlled) 1 point (uncomplicated) 2 points (end-organ damage)
Hemiplegia	2 points
Moderate to severe chronic kidney disease (*Moderate = creatinine >3 mg/dL (0.27 mmol/L), Severe = on dialysis, status post kidney transplant, uraemia)*	2 points
Solid tumour	0 point (none) 2 points (localised) 6 points (metastatic)
Leukaemia	2 points
Lymphoma	2 points
Acquired immunodeficiency syndrome (AIDS)	6 points
Total Charlson Comorbidity Index (Max score = 37 point)	

Appendix B – Tokyo Guidelines 2018 for Severity Grading of Acute Cholecystitis(17)

Grade I (mild): No organ dysfunction and mild inflammatory changes in the gallbladder

Grade II (moderate): Associated with any one of the following conditions: (1) Elevated WBC count (>18,000/mm3)
(2) Palpable tender mass in RUQ
(3) Duration >72h

(4) Marked local inflammation (gangrenous/emphysematous cholecystitis, pericholecystic/hepatic abscess, biliary peritonitis)

Grade III (severe): Associated with dysfunction of any one of the following organs/systems:
(1) Cardiovascular: hypotension requiring treatment with vasopressors
(2) Neurological: decreased level of consciousness

(3) Respiratory: PaO2/FiO2ratio <300
(4) Renal dysfunction: oliguria, creatinine >2.0 mg/dl (5) Hepatic dysfunction: PT-INR >1.5
(6) Haematology

Appendix C – Atlanta Guidelines(18)

Severity	Definition
Mild acute pancreatitis	Absence of organ failure Absence of local complications
Moderately severe acute pancreatitis	1. Local complications AND/OR 2. Transient organ failure (<48 h)
Severe acute pancreatitis	3. Persistent organ failure >48 h

Organ failure defined as a Modified Marshall score >2:

Organ system	0	1	2	3	4
Respiratory (PaO2/FiO2)	>400	301-400	201-300	101-200	<101
Renal (serum creatinine, umol/l)*	<134	134-169	170-310	311-439	>439
Cardiovascular (systolic blood pressure, mm Hg) †	>90	<90, fluid response	<90, not fluid responsive	<90, pH <7.3	<90, pH <7.2

A score of 2 or more in any system defines the presence of organ failure.

*A score for patients with pre-existing chronic renal failure depends on th extent of further deterioration of baseline renal function. No formal correction exists for a baseline serum creatinine >134 umol/l.

†Off inotropic support

For non-ventilated patients, FiO2 can be estimated from below:

Supplemental O2 (l/min)	FiO2 (%)
Room air	21
2	25
4	30
6-8	40
9-10	50

Appendix D – Nassar Scale(19)

Nassar grade	Gallbladder	Cystic pedicle	Adhesions
I	Floppy, nonadherent	Thin and clear	Simple up to the neck/Hartmann's pouch
II	Mucocele, packed with stones	Fat-laden	Simple up to the body
III	Deep fossa, acute cholecystitis, contracted, fibrosis, Hartman's adherent to CBD, impaction	Abnormal anatomy or cystic duct short, dilated, or obscured	Dense up to fundus; involving hepatic flexure or duodenum
IV	Completely obscured, empyema, gangrene, mass	Impossible to clarify	Dense, fibrosis, wrapping the gallbladder, duodenum, or hepatic flexure difficult to separate
V	Findings as in grade 4 + presence of either Mirizzi type 2 or higher, cholecystocutaenous or ch0lecystoenteric fistula		

CBD: common bile duct

Appendix E – Clavien-Dindo Grading of Surgical Complications(14)

Grade	Definition
Grade I	Any deviation from the normal post-operative course not requiring surgical, endoscopic or radiological intervention. This includes the need for certain drugs (e.g. antiemetics, antipyretics, analgesics, diuretics and electrolytes), treatment with physiotherapy and wound infections that are opened at the bedside
Grade II	Complications requiring drug treatments other than those allowed for Grade I complications; this includes blood transfusion and total parenteral nutrition (TPN)
Grade III	Complications requiring surgical, endoscopic or radiological intervention • Grade IIIa - intervention not under general anaesthetic • Grade IIIb - intervention under general anaesthetic
Grade IV	Life-threatening complications; this includes CNS complications (e.g. brain haemorrhage, ischaemic stroke, subarachnoid haemorrhage) which require intensive care, but excludes transient ischaemic attacks (TIAs) • Grade IVa - single-organ dysfunction (including dialysis) • Grade IVb - multi-organ dysfunction
Grade V	Death of the patient

Appendix F – Hospital Survey (adapted from CholeS)

Provision of emergency surgical services	
How many consultants are on the general surgery on-call rota?	
How many beds does your hospital have?	
Cholecystectomy and biliary services	
Does your hospital provide tertiary HPB services?	Yes / No
Does your hospital provide ERCP service?	Yes / No Availability – weekdays / weekends / out of hours
How many consultant surgeons offer laparoscopic cholecystectomy in your hospital?	
Does your hospital offer dedicated 'hot' gallbladder lists?	Yes / No
What consultant specialities are involved in performed laparoscopic cholecystectomy in your hospital (tick all that apply)	OG, HPB, Colorectal, Breast, Vascular, Endocrine, General, Other
Where are elective laparoscopic cholecystectomies performed in your hospital? (tick all that apply)	Main operating theatre Separate day case unit Onsite treatment centre Offsite treatment centre
Approximately how many cholecystectomies are performed annually in your hospital?	
Does your unit routinely offer day-case laparoscopic cholecystectomy	Yes / No
During working hours (0800-1800, weekdays), is acute laparoscopic cholecystectomy:	Routinely available; Only available if oncall consultant performs hot gallbladders ; Not available
During weekend days (0800-1800), is acute laparoscopic cholecystectomy:	Routinely available Only available if oncall consultant performs hot gallbladders Not available
At your centre, do you have a defined protocol to give prophylactic or therapeutic antibiotics during or after laparoscopic cholecystectomy?	Yes / No

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