PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Global Evaluation and Outcomes of cholecystectomy: protocol for a multicentre, international, prospective cohort study (GlobalSurg 4)
AUTHORS	on Global Surgery, NIHR Global Health Research Unit; Harrison, Ewen; Kathir Kamarajah, Sivesh

VERSION 1 – REVIEW

REVIEWER	Haynes, Alex The University of Texas at Austin Dell Medical School, Surgery
REVIEW RETURNED	13-Nov-2023

GENERAL COMMENTS	The authors present their protocol for a large, international observational study of cholecystectomy outcomes. This is a tremendous undertaking and one of clear clinical importance, as well as an important evaluation of health systems. The manuscript is well-written. However, I have a number of queries that limit my ability to understand the proposed study. MAJOR QUERIES: 1. The primary outcome of the study is noted to be compliance to pre-, intra-, and postoperative audit standards. However, it is not clear exactly how this will be ascertained. Several of the standards listed in table 1 have non-prescriptive language (e.g. "...surgeons may use the Tokyo Guidelines 18." or "...intraoperative imaging... may help delineate relevant anatomy..." or "It is recommend (sic) knowing Strasberg's classification...). How will compliance to those standards be measured? How will this be incorporated into the primary outcomes? 2. Additionally, some of the standards are process measures which can be assessed on a patient level (e.g. obtaining the critical view of safety). However, others are aggregated outcomes (e.g. "...rates [of BDI] are 0.4% and 0.8%..." or "30-day readmission rate should be <10%"). How will these be adjudicated and incorporated into the outcomes measurement? Is the analysis on a patient level or a center level? 3. The time period of the study is defined as 8 two week periods. This is not described well, especially in the methods section. Are all centers participating in all eight periods? Do they choose? Please clarify both the study time and how centers may participate variably. 4. The methods are very superficial. The unit of analysis is not clear (patient versus center) and exactly what is being compared is also unclear.

	MINOR QUERIES 5. P5, lines 30-33. I'm not sure of the relevance of discussing litigation here. This is especially true for an international study including environments where the medicolegal environment is quite diverse. I would recommend focusing on the patient safety aspects. 6. Table 2, the second sentence under "return to theatre" is confusing and unclear. Please clarify 7. Appendix D there is a typo in spelling of "Anaesthesiologists" when describing the ASA classification. Overall, this is a worthwhile and exciting study. With some clarification the study can be protocol can be quite valuable as a first step to understanding this work. It would also serve the authors well to be a little more up front about limitations of this study.

REVIEWER	de Reuver, Philip Radboudumc
REVIEW RETURNED	16-Nov-2023

GENERAL COMMENTS	Thanks for the invitation to review. The surgical community is well aware this study is running and I would like to express my admiration for the approach, thorough communication, and enthusiasm of the research group as evident in their work. With interest, I have read the protocol of the study titled "Global Evaluation and Outcomes of Cholecystectomy: protocol for a multicentre, international, prospective cohort study (GlobalSurg 4)." Once again, it signifies a commendable collaboration to gather data from an international cohort of surgical patients. The research addresses a relevant question, given the existing significant practice variation in gallbladder surgery. Particularly, the subgroup of patients with cholecystitis will be of interest, as aspects such as percutaneous drainage, the timing of the operation, and antibiotic usage remain inadequately explored in an international cohort. There is ample room for improvement within the surgical community in this regard. It is transparent to publish the protocol before data analysis and manuscript writing. There are several aspects I would like to convey to the editor before deciding on potential publication: The inclusion period concludes in 3 days, which is evidently earlier than when this protocol will be published. The research heavily focuses on the surgical technical aspect of gallbladder surgery, while indications for surgery and patient-reported outcomes are insufficiently emphasized. Patient participation is discussed, but the input appears limited. Authorships and collaborative efforts are clearly described, but I would advise the group to organize a meeting post data collection to discuss the data with interested parties. It often happens that the final manuscript is sent or not sent to collaborators, leaving no room for further input. Other points to consider: The primary outcome is "compliance with cholecystectomy standards," which naturally includes the Common Variance Standard (CVS) but is also a secondary outcome.

	I assume data collection does not always occur based on surgical images but rather on reports. Whether CVS is achieved is often automatically included in operation reports, and thus, the method and quality of its achievement cannot be verified.

VERSION 1 – AUTHOR RESPONSE

Reviewer 1:

1. The authors present their protocol for a large, international observational study of cholecystectomy outcomes. This is a tremendous undertaking and one of clear clinical importance, as well as an important evaluation of health systems. The manuscript is well-written. However, I have a number of queries that limit my ability to understand the proposed study.

RESPONSE: Many thanks for the positive review and support for the study. We have addressed your following comments below.

MAJOR QUERIES

2. The primary outcome of the study is noted to be compliance to pre-, intra-, and postoperative audit standards. However, it is not clear exactly how this will be ascertained. Several of the standards listed in table 1 have non-prescriptive language (e.g. "...surgeons may use the Tokyo Guidelines 18." or "...intraoperative imaging... may help delineate relevant anatomy..." or "It is recommend (sic) knowing Strasberg's classification...). How will compliance to those standards be measured? How will this be incorporated into the primary outcomes?

RESPONSE: Many thanks for the comment. This is an important one. The current guidelines that we have used across the United Kingdom, United States and world society lack clarity on the level of implementation. However, we have included these standards to ensure we capture this in the data collection forms. These standards will be reported in the primary paper and secondary analysis will seek to explore role of these standards on quality of cholecystectomy.

3. Additionally, some of the standards are process measures which can be assessed on a patient level (e.g. obtaining the critical view of safety). However, others are aggregated outcomes (e.g. "...rates [of BDI] are 0.4% and 0.8%..." or "30-day readmission rate should be <10%"). How will these be adjudicated and incorporated into the outcomes measurement? Is the analysis on a patient level or a center level?

RESPONSE: As mentioned above, we will evaluate the process measures and associations with outcomes which we are collecting at a patient-level. We will also incorporate centre-level factors derived from the survey data into the primary patient-level analysis to understand the quality of cholecystectomy done globally.

4. The time period of the study is defined as 8 two week periods. This is not described well, especially in the methods section. Are all centers participating in all eight periods? Do they choose? Please clarify both the study time and how centers may participate variably.

RESPONSE: Many thanks, we have clarified this in the methods as below:

"The study period includes eight two-weeks data collection periods. Mini teams of up to five collaborators per two-week data collection period will prospectively collect data at each participating centre. Centres may choose to collect data for on selected or all data collection periods. There are no restrictions to the centre participation."

5. The methods are very superficial. The unit of analysis is not clear (patient versus center) and exactly what is being compared is also unclear.

RESPONSE: The study will be reported at patient level and the main exposure or explanatory variable being the country income defined as high-, middle-, lower middle-, and low income. We have expanded the methods section to ensure they are clear.

MINOR QUERIES

6. P5, lines 30-33. I'm not sure of the relevance of discussing litigation here. This is especially true for an international study including environments where the medicolegal environment is quite diverse. I would recommend focusing on the patient safety aspects.

RESPONSE: Many thanks for the point. We have corrected this.

7. Table 2, the second sentence under "return to theatre" is confusing and unclear. Please clarify

RESPONSE: We have clarified this better. Any patient who has a cholecystectomy during a second operation following index operation should not be included. This likely reflects cholecystectomy because of a complication from the initial operation.

8. Appendix D there is a typo in spelling of "Anaesthesiologists" when describing the ASA classification.

RESPONSE: This has been updated.

9. Overall, this is a worthwhile and exciting study. With some clarification the study can be protocol can be quite valuable as a first step to understanding this work. It would also serve the authors well to be a little more up front about limitations of this study.

RESPONSE: Many thanks for the positive review and supporting the study.

Reviewer 2.

1. Thanks for the invitation to review. The surgical community is well aware this study is running and I would like to express my admiration for the approach, thorough communication, and

enthusiasm of the research group as evident in their work. With interest, I have read the protocol of the study titled "Global Evaluation and Outcomes of Cholecystectomy: protocol for a multicentre, international, prospective cohort study (GlobalSurg 4)." Once again, it signifies a commendable collaboration to gather data from an international cohort of surgical patients. The research addresses a relevant question, given the existing significant practice variation in gallbladder surgery. Particularly, the subgroup of patients with cholecystitis will be of interest, as aspects such as percutaneous drainage, the timing of the operation, and antibiotic usage remain inadequately explored in an international cohort. There is ample room for improvement within the surgical community in this regard.It is transparent to publish the protocol before data analysis and manuscript writing. There are several aspects I would like to convey to the editor before deciding on potential publication:

RESPONSE: Many thanks for the great review and support towards the study.

2. The inclusion period concludes in 3 days, which is evidently earlier than when this protocol will be published.

RESPONSE: The protocol was submitted early in September 2023 to ensure transparency of the study.

3. The research heavily focuses on the surgical technical aspect of gallbladder surgery, while indications for surgery and patient-reported outcomes are insufficiently emphasized.

RESPONSE: The study is broader than technical aspects of gallbladder surgery. Our aims and objectives include access and quality of gallbladder surgery and sustainable practice.

4. Patient participation is discussed, but the input appears limited.

RESPONSE: We have expanded the section on patient and public involvement.

5. Authorships and collaborative efforts are clearly described, but I would advise the group to organize a meeting post data collection to discuss the data with interested parties. It often happens that the final manuscript is sent or not sent to collaborators, leaving no room for further input.

RESPONSE: Many thanks for the comment. We are planning to disseminate the final manuscript for transparency.

6. The primary outcome is "compliance with cholecystectomy standards," which naturally includes the Common Variance Standard (CVS) but is also a secondary outcome.

RESPONSE: Many thanks for pointing this out. We have updated this.

7. I assume data collection does not always occur based on surgical images but rather on reports. Whether CVS is achieved is often automatically included in operation reports, and thus, the method and quality of its achievement cannot be verified.

RESPONSE: Data collection will be based on collaborators being present in operating theatres and verifying operating notes to ensure they are accurately recorded. We will also perform data validation for data accuracy.

VERSION 2 – REVIEW

REVIEWER	Haynes, Alex The University of Texas at Austin Dell Medical School, Surgery
REVIEW RETURNED	18-Jan-2024

GENERAL COMMENTS	The authors have revised this protocol paper and have clarified many points. However, there remain some questions that limit my ability to understand the protocol. 1. Most importantly, I remain unclear how the audit standards on table 1 will actually be assessed for purposes of the study and reported in a manuscript. I will enumerate my lack of understanding below: - Timing of surgery - Will this be reported as <48 hrs or <10 days as both are stated? Will this be a binary outcome? Or proportion at a centre level? -BDI - will the rates be calculated from this study? How will adherence to this standard be counted? Proportion of centres with BDI rates below the specified? Or binary for an individual patient (proportion of patients having cholecystectomy at a centre with the rates)? Also should add "<" to each of the rates. It is also very unclear to me how 6c ("knowing Strasberg's classification") will be adjudicated for the purpose of this study. - Critical care - does access to these beds mean at the facility where surgery is performed or a pathway to these? Also, "level 2 and level 3" are not universally used terms. Overall I will comment that Table 1 reads more like a summary of guidelines than part of a study protocol and the pathway from patient enrolment to the data collection instrument to reporting on these variables remains unclear to me. I'm sure that the authors have a plan, but I cannot understand it from this protocol publication. 2. Finally, the authors need to discuss some limitations of this study. While this is likely to be a very powerful observational study of cholecystectomy, like all studies it will have limitations. Some suggestions to discuss: lack of visibility around cholecystectomy performed outside of the hospital setting (in the United States and some other countries, cholecystectomy is often performed at a freestanding ambulatory surgical center which may or may not be affiliated with a hospital), questions about ascertainment of some standards (e.g. critical view of safety which is reported to have been obtained more frequently than it actually is), potential limitations on long term followup. None of these diminish the value of this study, but ought to be acknowledged in the manuscript. 3. Finally, the brief mention in the introduction of the idea of "safe cholecystectomy as one that is 'safe for both the patient and the operating surgeon.'" is intriguing, but not well elaborated. The reference to litigation was removed, but are there other elements

	of lack of safety to surgeon that are being assessed in this? Ergonomics? Psychological safety? Well-being? It might be best to omit this line or elaborate, but as it is seems like a bit of a non sequitur, without corresponding data points in the study that anchor on this definition.

VERSION 2 – AUTHOR RESPONSE

]Reviewer 1:

1. The authors have revised this protocol paper and have clarified many points. However, there remain some questions that limit my ability to understand the protocol.

RESPONSE: Many thanks for the review and we hope the following comments and changes addresses the points below.

2. Most importantly, I remain unclear how the audit standards on table 1 will actually be assessed for purposes of the study and reported in a manuscript. I will enumerate my lack of understanding below:

a. Timing of surgery - Will this be reported as <48 hrs or <10 days as both are stated? Will this be a binary outcome? Or proportion at a centre level?

RESPONSE: We will capture the proportion of patients with acute cholecystitis who have a cholecystectomy as follows: within 48 hours of admission, 48 hours - 10 days, and >10 days. As such this will be a three-level categorical outcome. This has been clarified.

b. BDI - will the rates be calculated from this study? How will adherence to this standard be counted? Proportion of centres with BDI rates below the specified? Or binary for an individual patient (proportion of patients having cholecystectomy at a centre with the rates)? Also should add "<" to each of the rates. It is also very unclear to me how 6c ("knowing Strasberg's classification") will be adjudicated for the purpose of this study.

RESPONSE: We will determine bile duct injury on an individual patient basis. This will be used for further analyses at the hospital, country, and World Bank Income Group level. We will identify the overall reporting of the Strasberg classification as recorded in the patient's notes / case report form, but will not adjudicate whether the classification is correct. This has been clarified in the text.

c. Critical care - does access to these beds mean at the facility where surgery is performed or a pathway to these? Also, "level 2 and level 3" are not universally used terms.

RESPONSE: This refers to access to critical care facility which is stated in the guidelines. We have removed the option on Level 2 and Level 3 to improve clarity. The Table 1 has been improved to for clarity.

d. Overall I will comment that Table 1 reads more like a summary of guidelines than part of a study protocol and the pathway from patient enrolment to the data collection instrument to reporting on

these variables remains unclear to me. I'm sure that the authors have a plan, but I cannot understand it from this protocol publication.

RESPONSE: We have made it clearer that indeed table 1 is a summary of audit standards used as part of this study. The point is well made that guidelines often provide insufficient information about how a particular audit standard should be best measured and reported. We have made edits to make it clearer how each audit standard will be assessed, and will present the proportion of patients achieving each individual audit standard globally.

3. Finally, the authors need to discuss some limitations of this study. While this is likely to be a very powerful observational study of cholecystectomy, like all studies it will have limitations. Some suggestions to discuss: lack of visibility around cholecystectomy performed outside of the hospital setting (in the United States and some other countries, cholecystectomy is often performed at a freestanding ambulatory surgical center which may or may not be affiliated with a hospital), questions about ascertainment of some standards (e.g. critical view of safety which is reported to have been obtained more frequently than it actually is), potential limitations on long term followup. None of these diminish the value of this study, but ought to be acknowledged in the manuscript.

RESPONSE: Many thanks for this important comment. This has been clarified in the in the discussion (text) as below:

“However, this study has limitations which need to be acknowledged. Firstly, selection bias will exist in the cholecystectomies captured in the cohort; for instance, there is an expected bias towards central hospitals at the expense of district hospitals and ambulatory care facilities, across high-, middle-, and low--income settings. Secondly, ascertainment of certain standards such as critical view of safety is inherently difficult, and we for some we are reliant on clinician reporting rather than an objective measure. Thirdly, due to the observational nature of the study, it will not be possible to determine a causative link between laparoscopic surgery and complications and therefore comparisons of incidence and risk factors across different Human Development Index settings will be hypothesis generating only. Finally, delivering long-term follow-up is likely to be challenging, particularly in health systems where there is low availability of health records.”

4. Finally, the brief mention in the introduction of the idea of ''safe cholecystectomy as one that is 'safe for both the patient and the operating surgeon.'" is intriguing, but not well elaborated. The reference to litigation was removed, but are there other elements of lack of safety to surgeon that are being assessed in this? Ergonomics? Psychological safety? Well-being? It might be best to omit this line or elaborate, but as it is seems like a bit of a non sequitur, without corresponding data points in the study that anchor on this definition.

RESPONSE: Many thanks for highlighting this. We are not collecting data around ergonomics, psychological safety or wellbeing which are beyond the scope of the study. We have removed this sentence as advised.

VERSION 3 – REVIEW

REVIEWER	Haynes, Alex The University of Texas at Austin Dell Medical School, Surgery

REVIEW RETURNED	20-May-2024

GENERAL COMMENTS	The revisions have made the protocol much clearer and precise. I look forward to seeing the results of this undertaking

VERSION 3 – AUTHOR RESPONSE

Reviewer 1:
1. The revisions have made the protocol much clearer and precise. I look forward to seeing the results of this undertaking.
Response: Many thanks for the review and thank you for the suggestions to improve the paper.