**Latin American Surgical Outcomes Study (LASOS)**

**Full Title** Observational cohort study of patient outcomes following surgery in Latin American countries

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1. **Glossary**

CI Chief Investigator

CRF Case Report Form

eCRF Electronic CRF

ICU Intensive Care Unit

LA Latin America

LMIC Low and middle-income country

HIC High-income country

GCP Good Clinical Practice

1. **Signature page**

**Co-Chief Investigator Agreement**

The study, as detailed within this Research Protocol, will be conducted in accordance with the principles of Good Clinical Practice, the UK Policy Framework for Health and Social Care Research, and the Declaration of Helsinki and any other applicable regulations. I delegate responsibility for the statistical analysis and oversight to a qualified statistician (see declaration below).

**Name: Ludhmila Abrahao Hajjar Luciana Cadore Stefani**

**Signature:  **

**Date:** **\_\_\_\_\_\_\_29 Sep 21\_ \_**  **29 Sep 21\_ \_\_\_**

**Statistician’s Agreement**

The study as detailed within this research protocol will be conducted in accordance with the current UK Policy Framework for Health and Social Care Research, the World Medical Association Declaration of Helsinki (1996), Principles of ICH E6-GCP, ICH E9 - Statistical principles for Clinical Trials and ICH E10 - Choice of Control Groups.

I take responsibility for the statistical work in this protocol is accurate and take responsibility for statistical analysis and oversight in this study.

**Statistician’s name:** **Akshaykumar Patel**

**Signature: A picture containing shape

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**Date:** **04 Oct 2021\_\_\_\_\_\_\_\_\_\_\_**

1. **Summary and synopsis**

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| **Short title** | LASOS |
| **Methodology** | International, seven-day observational cohort study of complications following elective or emergency surgery. |
| **Objectives** | To provide detailed data describing post-operative complications and associated mortality. |
| **Number of participants** | Our aim is to recruit as many patients from as many hospitals as possible in Latin American nations. |
| **Eligible countries for participation** | Countries and dependencies in Latin America that are situated in the area stretching from the northern border of Mexico to the southern tip of South America, including the Caribbean.  No participants will be recruited in the UK. |
| **Inclusion and exclusion criteria** | Inclusion criteria: all adult patients aged 18 years or older undergoing elective or emergency surgery during the seven-day study period with a planned overnight stay.  Exclusion criteria: patients who are undergoing planned day-case surgery or radiological procedures. |
| **Statistical methodology and analysis (if applicable)** | Single and multi-level logistic regression models will be constructed to identify factors independently associated with these outcomes and to adjust for differences in confounding factors. A single final analysis is planned at the end of the study. A pre-defined analysis will focus on outcomes of patients who have undergone caesarean section. |
| **Study duration** | Each nation will select a 7-day period, which will fall within between the 1st April and 31th October 2022. |

1. **Introduction**

More than 310 million patients undergo surgery worldwide each year with reported hospital mortality between 1 and 4%.1–4 Recent estimates suggest that 4.2 million deaths occur within 30 days of surgery, and half of these occur in low and middle-income countries (LMIC).5 Complications are more common and are a leading cause of long term morbidity and mortality.4,6 Patients who develop complications but survive to leave hospital often suffer reductions in functional independence and long-term survival. With the high volumes of surgery performed, there is increasing recognition of the massive potential impact of even small improvements in perioperative care.7

The International Surgical Outcomes Study (ISOS) confirmed the association between complications and death after surgery at a global scale, but predominantly included high-income nations.4 More recently, the African Surgical Outcomes Study (ASOS) found that patients undergoing surgery in African nations were twice as likely to die than those in high-income countries (HIC), despite being younger with fewer co-morbid diseases.8,9 While there is a global drive to improve access to surgery in LMICs there is a need to implement this safely.

Latin America describes a geographic area including 25 nations, and countries within the region have some of the highest income disparity worldwide.10 Rapid demographic and societal changes have led to an increasing burden of non-communicable disease. Provision of healthcare varies widely within Latin America, with a mix of private, social and government funded schemes. A recent report highlighted marked variation within and between countries of surgical provision in LA.11 Given the disparity in socioeconomic status and care models this is perhaps unsurprising. However, it is unclear how these disparities relate to outcomes for individual patients.12 Extrapolating the findings from high-income settings with a high burden of similar diseases (such as ISOS) is inappropriate, as is extrapolating the findings of ASOS, where communicable disease dominates healthcare need. Our aim is to conduct a seven-day cohort study of adults undergoing in-patient surgery in Latin America to provide detailed data describing post-operative complications and associated mortality.

1. **Study objectives**

**Primary objective**

To confirm the incidence of 30-day in-hospital complications following elective or emergency in-patient surgery

**Secondary objective**

* To confirm the 30-day in-hospital mortality associated with these complications
* To describe the length of hospital stay
* To describe the pattern of post-operative critical care use
* To describe the effect of post-operative complications on duration of hospital stay

**Primary outcome measure**

In-hospital post-operative complications of any cause, censored at 30 days following surgery for patients who remain in hospital

**Secondary outcome measures**

* In-hospital all-cause mortality censored at 30 days following surgery for patients who remain in hospital
* Duration of hospital stay after surgery, censored at 30 days following surgery for patients who remain in hospital
* Admission to critical care within 30 days of surgery during the index admission

1. **Study design**

LASOS is an international, observational seven-day cohort study. Data will be collected over a four-month period, each national lead will select seven days over which participating sites within their nation will collect data. The study will take place in Latin American countries and dependencies defined as an area that stretches from the northern border of Mexico to the southern tip of South America, including the Caribbean. All countries and dependencies listed on the page ‘Latin America’ on Wikipedia as of 16th of September 2019 are eligible to take part.13 Eligible nations are listed in Section 20. All data collected will be that which is used for routine clinical care in hospital. There will be no additional patient contact.

1. **Study population**

Each national group will select a single seven-day period for patient recruitment between 1st April and 31st October 2022. Patients will be identified by the participating sites by review of elective theatre lists, theatre logbooks, handover sheets, emergency admissions and ward lists. All patients undergoing surgery over this period at a hospital taking part in the study will be eligible for inclusion provided they meet the following criteria.

**Inclusion criteria**

All adult patients (aged 18 years or older) undergoing elective or emergency surgery with a planned overnight stay.

Surgery is defined as a procedure where a deliberate access to the body is gained via an incision or percutaneous puncture, and where instrumentation is used in addition to the puncture needle, or instrumentation via a natural orifice.14

**Exclusion criteria**

Patients who are undergoing planned day-case surgery or radiological procedures.

1. **Risks and benefits**

**Risks**

There are no safety considerations relating to the LASOS study. There is no risk of harm to either patients or investigators. The risk of an information governance breach is negligible because no patient identifiable data is collected outside each participating hospital.

**Benefits**

There has been no regional study of outcomes after surgery in Latin America describing the outcomes patients experience would have three key benefits:

1. Be the driver for improved care at a policy level in Latin American countries
2. Provide a clear evidence base for further research in the region
3. Provide insights into surgical outcomes that may be applicable to other LMIC settings

1. **Study procedures**

**Consent procedures**

Very similar studies have been successfully performed in more than 80 countries. The majority of nations participating in these in prior studies waived the need for informed patient consent, given the dataset includes only those documented as part of routine clinical care and that the data is collected in a fully anonymised format.

Given this precedence, we anticipate that informed consent and ethical approval will not be required for LASOS. The need for consent at each centre will be determined by local co-ordinators, and a site agreement will be requested from each site lead confirming that data is collected in accordance with local requirements.

**Study data**

Data will be collected on all eligible patients who undergo surgery during the study week for that country. Case record forms (CRFs) are included in sections 21 & 22. Centre specific data will be collected at the start of the study period. Only routine clinical data will be included and where this is unavailable the domain will be left blank e.g. patients who do not require blood tests. Standard definitions for all outcomes will be provided to all centres, as outlined in the enclosed outcome definitions document. All relevant study documents will be translated into Spanish, French and Portuguese, and data entry will be available in those languages. A check for accuracy will be performed by native speakers.

**Data collection**

Centre specific data will be collected once for each hospital including: university or non-university hospital, number of hospital beds, number of operating rooms, number and level of critical care beds, details about the reimbursement status of the hospital, university hospital status, existence of residency programmes in anaesthesia, surgery, medicine or critical care, availability of a rapid response team, if the hospital holds valid accreditation (ONA, Qumentum or Joint Commission) and the ratio of nursing staff to hospital beds in post-operative care areas.

Data will be collected in individual hospitals on a paper CRF for each patient recruited. Paper CRFs will be stored within a locked office in each centre. This will include identifiable patient data in order to allow follow-up of clinical outcomes. The CRF will be completed for all participants, with separate data collection for patients having a caesarean section (please see section 22). Units for the two blood test results (haemoglobin and creatinine) will be determined by the local co-ordinator at each hospital at the start of the study. These units will be used for all records at that site.

Data will be anonymised by generating a unique numeric code (‘LASOS ID’) and transcribed by local investigators onto an internet based electronic CRF. Patients will only be identified on the electronic CRF by their LASOS ID. Thus the co-ordinating study team cannot trace data back to an individual patient without contact with the local team. A patient list will be used in each centre to match the LASOS ID to individual patients in order to record clinical outcomes and supply any missing data points. The patient list will be destroyed once the follow up has been completed and the data is submitted on the database making the data permanently anonymised. Once the local co-ordinator confirms data entry is complete for their hospital they will receive a spreadsheet of raw (un-cleaned) data, allowing further checks for data completeness and accuracy.

**Study group organisation**

LASOS will be led by the study management group who will be responsible for study administration, communication between project partners, data collation and data management. National co-ordinators will lead the project in each nation and:

* Identify local co-ordinators in participating hospitals
* Assist with translation of study paperwork as required
* Ensure distribution of study paperwork and other materials
* Ensure necessary regulatory approvals are in place prior to the start date
* Ensure good communication with the participating sites in his/her nation

Local co-ordinators in individual institutions will have the following responsibilities:

* Provide leadership for the study in their institution
* Ensure all relevant regulatory approvals are in place for their institution
* Ensure adequate training of all relevant staff prior to data collection
* Supervise daily data collection and assist with problem solving
* Act as guarantor for the integrity and quality of data collected
* Ensure timely completion of eCRFs by supervising local data entry
* Communicate with the relevant national co-ordinator
* Review and sign data sharing agreement at time of site opening.

**End of study definition**

The end of the study is defined as the end of the 30-day follow-up for the last patient included. Data analysis will follow this.

1. **Statistical considerations**

**Sample size**

As many centres as possible will be recruited in participating nations. All eligible patients during the recruitment period will be included. A minimum of ten centres from any country will be required for participation. We do not have a specific sample size and statistical models will be adapted to the event rate provided by the sample recruited.

**Statistical analysis**

No comparison will be made between individual nations and all national and institutional level data will be anonymised prior to publication. Categorical variables will be described as proportions. Continuous variables will be described as mean and standard deviation, if normally distributed, or median and inter-quartile range, if not normally distributed.

Univariate analysis will be performed to test factors associated with post-operative complications, admission to critical care and in-hospital death. Single-level and hierarchical multi-level logistic regression models will be constructed to identify factors independently associated with these outcomes and to adjust for differences in confounding factors. Factors will be entered into the models based on biological plausibility and low rate of missing data. Results of logistic regression will be reported as adjusted odds ratios (OR) with 95% confidence intervals. The models will be assessed in sensitivity analyses to explore possible interacting factors and examine any effect on the results. Imputation will be considered for important missing variables. A single final analysis is planned at the end of the study.

A pre-specified, separate analysis will be performed restricted to patients undergoing caesarean section as this group have previously been identified as having very poor outcomes compared to mothers in HIC.

1. **Ethics**

It is anticipated that requirements at participating nations will vary. This will vary by nation and the study will be conducted in line with local legal and regulatory requirements. In prior studies of this design across more than 80 countries, the vast majority of nations have been happy to proceed without individual patient level consent. It is the national and local investigators responsibility to clarify the need for ethics or other regulatory approvals, and for ensuring these are in place prior to data collection. Centres will not be permitted to record data without providing confirmation that the necessary ethics or other regulatory approvals are in place.

We will ensure that this study is conducted in accordance with the Principles of the Declaration of Helsinki as amended in Tokyo (1975), Venice (1983), Hong Kong (1989), South Africa (1996), Edinburgh (2000), Washington DC (2002), Tokyo (2004), Seoul (2008) and Fortaleza (2013) as described at the following internet site: https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects. The study will fully adhere to the principles outlined in the Guidelines for Good Clinical Practice ICH Tripartite Guideline (January 1997).

1. **Data handling and record keeping**

**Data management**

Data will be recorded on paper CRFs and uploaded onto the study database where only anonymised data is collected. Each centre will also maintain an investigator site file including a protocol, local investigator delegation log, CRFs, documentation of the relevant regulatory approvals if applicable, screening log and patient list. The study specific documents will be available to download on the LASOS study website. LASOS CRFs will be stored securely in a locked cupboard and handled only by clinical staff familiar with handling personal data.

**Source data**

Since only routine clinical data is collected, the study CRFs will be completed based on the hospital medical records, which are considered as source data for this study.

**Confidentiality**

All identifiable data collected, processed and stored for the purposes of the project will remain confidential at all times and comply with Data Protection Act, the General Data Protection Regulation (GDPR), NHS Caldecott Principles, the UK Policy Framework for Health and Social Care Research. Data will be collected by the patients’ direct care team and will be anonymised prior to transfer to the LASOS study management group. Access to the data entry system will be protected by username and password, delivered during the registration process for individual local investigators. All electronic data transfer between participating centres and the co-ordinating centre will be encrypted using the SSL 3.0 protocol (HTTPS). Desktop and laptop security will be maintained through user names and passwords. The datacentre facilities are accredited to robust international standards that are standard for transfer of healthcare data: ISO 27001, ISO 9001, ISO 14001 and PCI DSS. At time of registration on the database entry portal, all users will review an information governance document and electronically sign to confirm they will abide by it. Individual site data sharing agreements will be requested from the local co-ordinator.

**Record retention and archiving**

All trial documentation and data will be stored for two years after the main study findings are publicly reported, and then archived or destroyed by participating hospitals according to local hospital policies. Electronic data sets will be stored indefinitely.

**Data management and ownership**

In line with the principles of data preservation and sharing, the steering committee will, after publication of the overall dataset, consider all reasonable requests to conduct secondary analyses. The primary consideration for such decisions will be the quality and validity of any proposed analysis. Only summary data will be presented publicly and all national, institutional and patient level data will be strictly anonymised. Individual patient data provided by participating hospitals remain the property of the respective institution. Once each local co-ordinator has confirmed the data provided from their hospital are both complete and accurate, they will be provided with a spreadsheet of the raw (un-cleaned) data for their hospital. The complete LASOS dataset, anonymised with respect to participating patients, hospitals and nations, will be made freely and publicly available two years following publication of the main scientific report. Prior to this, the steering committee is not under any obligation to release data to any collaborator or third party if they believe this is not in keeping with the wider aims of the LASOS project.

1. **Safety reporting**

The trial involves negligible risks to patients and investigators, as it involves only collection of anonymised routinely collected data. Adverse events will not be monitored or reported.

1. **Study committees**

**LASOS steering committee**

The trial steering committee will be made up of the following members, there is no role for a data monitoring committee:

Ludhmila Abrahao Hajjar (Co-Chief investigator; Brazil)

Luciana Cadore Stefani (Co-Chief investigator; Brazil)

Adrian Alvarez (Argentina)

Antonio Ramos De La Medina (Mexico)

Martha Delgado (Colombia)

Maria Jose Carmona (Brazil)

Greg Padmore (Barbados)

Rupert Pearse (UK)

**LASOS steering committee Independent Members**

Bruce Biccard (Chair; South Africa)

Duminda Wijeysundera (Canada)

Sean Bagshaw (Canada)

1. **Finance and funding**

There will be no funding from the coordinating centre for the study. The study will be financed with existing resources in the institutions taking part in data collection.

1. **Dissemination of research findings**

The steering committee will appoint a writing committee to draft the scientific report(s) of this investigation, which will be disseminated in a timely manner. It is anticipated that a number of secondary analyses will be performed. LASOS investigators will be given priority to lead such analyses and are encouraged to do so. Participation and authorship opportunities will be based on contribution to the primary study. The steering committee will consider the scientific validity and the possible effect on the anonymity of participating centres prior to granting any such requests. Where necessary, a prior written agreement will set out the terms of such collaborations. The steering committee must approve the final version of all manuscripts including LASOS data prior to submission. In the event of disagreement within the steering committee, the chief investigator will make a ruling. Any analysis incorporating LASOS data from two or more study sites will be considered a secondary analysis and subject to these rules.

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1. **List of Latin American countries**

The study will take place in Latin American countries and dependencies defined as an area that stretches from the northern border of Mexico to the southern tip of South America, including the Caribbean. All countries and dependencies listed on the page ‘Latin America’ on Wikipedia as of 16th of September 2019 are eligible to take part.

* Argentina
* Bolivia
* Brazil
* Chile
* Colombia
* Costa Rica
* Cuba
* Dominican Republic
* Ecuador
* El Salvador
* French Guiana\*
* Guadeloupe\*
* Guatemala
* Haiti
* Honduras
* Martinique\*
* Mexico
* Nicaragua
* Panama
* Paraquay
* Peru
* Peurto Rico\*
* Saint Barthélemy\*
* Saint Martin\*
* Saint Pierre and Miquelon\*
* Uruguay
* Venezuela

\*Not a sovereign state