RESEARCH PROTOCOL

ICU-related Out of Pocket Expenses (ICOPE) – a multinational prospective study in African and Asian countries

Short title	Out of Pocket Expenses in Asian and African ICUs
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Steering Committee
Luigi Pisani, Mahidol Oxford Research Unit, Bangkok, Thailand*
Bharath K.T. Vijayaraghavan, Department of Critical Care Medicine, Apollo Hospitals, Chennai, India*
Diptesh Aryal, Nepal Mediciti, Nepal
Wangari Waweru Siika, Aga Khan University, Nairobi, Kenya
Rashan Haniffa, Mahidol Oxford Research Unit, Bangkok, Thailand*
Maryam Shamal, Afghanistan team, NICS-MORU collaboration, Kabul, Afghanistan
Aniruddha Ghose, Chattogram Medical Centre, Chattogram, Bangladesh
Swagata Tripathy, Department of Anaesthesia & Critical Care, All India Institute of Medical* Sciences, Bhubaneswar, India
Madiha Hashmi, Department of Critical Care, Ziauddin University, Karachi, Pakistan
Basri Nor, Department of Anaesthesiology and Intensive Care, Kulliyyah (School) of Medicine, International Islamic University Malaysia (IIUM)
Yen Lam Minh, Oxford University Clinical Research Unit, Ho Chi Minh City, Vietnam
Hem Paneru, Department of Critical Care Medicine, Tribhuvan University Teaching Hospital, Kathmandu, Nepal
Arishay Hussaini, Department of Critical Care, Ziauddin University, Karachi, Pakistan
Louise Thwaites, Oxford University Clinical Research Unit, Ho Chi Minh City, Vietnam*
Thuong Nguyen Thuy, Oxford University Clinical Research Unit, Ho Chi Minh City, Vietnam
Sutharshan Vengadasalam, Department of Surgery, Jaffna Teaching Hospital, Jaffna, Sri Lanka.
Iqbal Hussain, Pakistan Registry of Intensive Care (PRICE)
John Amuasi, Kumasi Center for Collaborative Research In Trop. Med., Ghana
Thomson David, University of Cape Town, Cape Town, South Africa
Adam Hewitt Smith, Mbale Hospital, Mbale, Uganda
Cornelius Sendagire, Makerere University College of Health Sciences, Kampala, Uganda
Arthur Kwizera, Makerere University College of Health Sciences, Kampala, Uganda
Abi Beane, CIR, University of Edinburgh, Scotland & Mahidol Oxford Research Unit, Bangkok, Thailand*
Ronnie Kaddu, Aga Khan Hospital, Mombasa, Kenya*
Jorge Salluh, D'Or Insitute (IDOR), Rio de janeiro, Brazil
Itimayee Panda, Indian Registry of IntenSive care, IRIS, Chennai, India & All India Institute of Medical Sciences, Bhubaneswar, India
Arjen Dondorp, Mahidol Oxford Research Unit, Bangkok, Thailand*
Statisticians
Mavuto Mukaka, Mahidol Oxford Research Unit, Bangkok, Thailand*
Atanu Bhattacharjee, Mahidol Oxford Research Unit, Bangkok, Thailand*
Health Economists
Abdur Sarker, Mahidol Oxford Research Unit, Bangkok, Thailand*
Yoel Lubell, Mahidol Oxford Research Unit, Bangkok, Thailand*
Hung Trinh Manh, Oxford University Clinical Research Unit, Ho Chi Minh City, Vietnam*

* Members of Protocol Writing group.

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LIST OF ABBREVIATIONS

ICU, intensive care unit
OOPE, out of pocket expenses
CHE, catastrophic health expenditure
LMIC, low and middle income country
ACCCOS, African COVID-19 Critical Care Outcomes study
CRF, case report form
ICF, informed consent form
PIS, patient information sheet

1. STUDY SUMMARY

Title	ICU-related Out of Pocket Expenses (ICOPE) – a multinational prospective study in African and Asian countries		
Sponsor	Mahidol Oxford Tropical Research Unit Collaboration for Research, Implementation and Training in Critical Care in Asia and Africa (CCAA)		
Funder	Wellcome		
Trial design	Prospective observational study		
Trial Participants	All patients admitted to the participating ICUs during a predefined window of 14 days and expected to have a duration of stay >24 hours. Exclusion criteria is lack of informed consent.		
Sample size	at least 354 patients (at least 212 non-ventilated & 142 ventilated patients)		
Planned study period	Recruitment during 14 days Follow up until ICU discharge for each recruited patient, at 30 days after admission and 6 months after admission. Total study duration: 18 months		
Planned recruitment period	From 01 Dec 2023 to 30 June 2024		
	Objectives	Endpoints	Timepoint(s) of evaluation
Primary objective	To quantify ICU care related OOPE in African and Asian LMICs and the proportion of patients/families facing CHE, comparing patients receiving invasive ventilation to non-ventilated patients.	1.Costs per complete patient episode, as actually spent in US dollars and International dollars (purchasing power parity exchange rate) in ventilated versus non-ventilated groups. 2.Relative risk of CHE in ventilated versus non-ventilated groups.	During ICU stay, average 1 week
Secondary objectives	To identify risk factors for CHE.	Risk factors for CHE	Not applicable
	To identify coping strategies for OOPE and CHE	Frequency of different coping strategies for financial coverage of ICU costs	During ICU stay and follow up, 6 months

2. BACKGROUND AND JUSTIFICATION

2.1 Increasing availability and access to ICU care in LMICs

Availability and utilization of intensive care unit (ICU)-level care is increasing in low and middle income countries (LMICs). In parallel, there is a rise in the financial burden for service providers, but also for patients and their families. Even in LMIC healthcare systems which offer government funded healthcare, ICU is associated with considerable costs which impact patients' households. As such, stakeholders seeking to expand access to health services must consider the financial burden associated with critical care becoming routinely available. In fact, increasing health coverage is paradoxically associated with worsening out of pocket expenses.[1] Achieving universal health coverage, including financial risk protection, is a target of the 3rd Sustainable Development Goal.[2,3] Critical care relates both to acute conditions (injury, trauma, infection, etc.) and chronic diseases. Return on investment for these conditions may be different leading to cost-effectiveness considerations.

2.2 ICU costs

ICU admission is often unexpected, the treatment and interventions needed are usually unpredictable and length of stay frequently prolonged. In fact, a single ICU admission can cost from few hundreds to more than one hundred thousand US dollars.[4] Thus ICU care often results in spiraling costs, which if not absorbed by welfare or insurance systems, directly fall on the patient and family. Costs can be classified as direct and indirect costs, with direct cost further divided in 'medical' and 'non-medical' domains. *Direct* medical costs include any daily fixed costs for the ICU bed, consumables (eg. medications, laboratory tests, nutrition, fluids, bandaging, ventilation circuits) which often fall at the pocket of patients and families. Studies assessing ICU direct costs are available from LMICs such as Brazil, Thailand, Vietnam and India.[5–8] Direct non-medical costs include transportation and accommodation. In addition, *indirect costs* arise such as loss of income for patients, especially ones employed without sick leave cover. For families and caregivers, income loss and productivity loss are associated with time spent being at the hospital with their relatives.

2.3 Out of pocket and catastrophic health expenditure

ICU care in LMICs is mostly funded by a mixed system of public welfare, insurance coverage and out of pocket expenditure (OOPE). Insurance penetration and government support remains low in most LMICs. OOPE in healthcare is defined as any direct outlay by households, including gratuities and in-kind payments, where the primary intent is to contribute to the restoration or enhancement of an individual's health. OOPE can include direct medical and direct non-medical costs, but does not include pre-paid fees for health-related taxes or insurance.[2] OOPEs constitute around 60% of total health expenditure in India[9] and 67% in Bangladesh.[10] Yet, while some data is available on cost burden of specific conditions such as chronic liver failure[11] or organophosphorus poisoning,[12] data on ICU-related OOPE in LMICs remains extremely scarce.

ICU-related OOPEs may rapidly lead to household debt and for some families, cross the threshold into catastrophic health expenditure (**CHE**).[13,14] The incidence of catastrophic spending on health is reported on the basis of out-of-pocket expenditures exceeding conventional thresholds of 10% or 25% of household total *annual* income.[15] CHE thus refers to any expenditure for medical treatment that can pose a threat towards a household's financial ability to maintain its subsistence needs.[3] Across countries, the mean incidence of catastrophic out-of-pocket payments at (considering the 10% threshold) is 9.2%.[15] This incidence was already increasing before the COVID-19 pandemic, with more than one in ten care episodes resulting in catastrophic spending in South Asia in 2010.[16,17] At the global level in 2010 some 808 million people incurred CHE, with a great concentration in Asia and Africa.

CHE calculation allows to capture financial tensions in households that arise when OOPEs are compensated by selling or mortgaging households assets, borrowing money from lenders, banks, black market, friends or relatives during ICU care. Forty-seven percent of patients with septic shock incurred CHE in a Vietnam hospital, against 13% of patients admitted with dengue shock.[5] In an Indian neonatal ICU, 56% of families incurred CHE, with one out of five families spending more on a single neonatal ICU admission than their monthly income.[18]

2.4 Risk factors and coping mechanisms for OOPE and CHE

Coping mechanisms for critical care-related OOPE have been inadequately investigated and are largely unknown for adult ICU patients admitted to LMICs hospitals. Many studies focus on non-ICU populations, limit their scope to direct medical costs or are performed in high-income countries. A study on 3100 households in Dhaka, found that marital status, religion, source of care, access to safe water, income quintile and even the location of households had a significant relationship with OOPE.[10] In a study from Thailand performed on 897 ICU patients with severe sepsis or septic shock, age, nosocomial or ICU infection, admission from the emergency department, number of organ failures, ICU length of stay, and fluid balance the first 72 hours were independently associated with ICU costs, although OOPE were not analyzed.[19] Mechanical ventilation was found to be a factor increasing OOPEs in LMICs for pediatric[20] patients and total ICU costs in adult patients.[4,19] Yet, the influence of the initiation of invasive ventilation on CHE remains to be described.

2.5 Impact of costs on ICU care

Financial costs are a barrier to both access and continuation of critical care. In a survey of 1465 ICU physicians from 466 ICUs in 16 Asian countries, those from LMICs (notably China, the Philippines, and Bangladesh) reported as more likely to accede to families' requests to withdraw life sustaining treatments in a patient with an otherwise reasonable chance of survival, so as to avoid further medical bills, than those from high-income economies.[18] The large ACCCOS study on COVID-19 ICU African patients reported 9% of treatment limitation with 3% of withdrawal of therapy, although it was not assessed whether the limitation was influenced by financial motives.[21] A study in India suggested up to 9% of discharge against medical advice patients are due to financial constraints.[22]

2.6 The knowledge gap

In LMICs, where ICU care is increasingly available with limited financial risk protection, there remains limited robust quantitative data linked to OOPEs. Particularly, the actual burden that critical illness has on direct and indirect costs to the patients and their families is unknown. While some data on direct costs is starting to be available,[5–8] there is limited insight into the magnitude of OOPEs and rates of CHE. We also lack robust data on risk factors for CHE due to ICU admissions and coping mechanisms in terms of sources of funding for patient families. Organ support, and especially mechanical ventilation that affects almost one out of two patients in the ICU, may be a key driver of OOPEs and CHE rates.

2.7 The present project

This study seeks to to precisely quantify ICU care related OOPEs in several LMICs in both the private and public sector. Context-specific drivers of OOPEs and CHE rates will also be established, while defining coping mechanisms and sources of funding. The impact of organ support, especially invasive mechanical ventilation, will be analyzed as a key potential driver of CHE.

3. STUDY AIMS AND HYPOTHESIS

3.1 Aims

The OOPE study has the following aims:

1. To **quantify** ICU care related OOPE in African and Asian LMICs and the proportion of patients/families facing CHE, comparing patients receiving invasive ventilation to non-ventilated patients.
2. To identify **risk factors** for CHE.
3. To identify **coping strategies** for OOPE and CHE

3.2 Hypothesis

The following exploratory hypothesis are formulated:

- Mechanical ventilation has a doubling effect on CHE incidence.
- The risk of CHE and magnitude of OOPE can be predicted by distinct patient-, disease-, household- and organizational-related factors.
- Distress financing by borrowing from family members is the most frequent coping mechanism both in Asia and Africa.

4. METHODS

4.1 Study design and duration

Observational prospective cohort study.
The recruitment period for each site will be consecutive 14-30 days, based on site feasibility. Daily follow up until death or ICU discharge.

4.2 Population

All patients admitted to the participating ICUs during a predefined window of 14 days and expected to have a duration of stay >24 hours will be eligible for the study. Exclusion criteria is lack of informed consent. For unconscious or unwell patients the primary caregiver will be approached to answer the interview questions.

4.3 Sample size calculation

Anticipating the following assumptions:

- an expected proportion of ventilated patients of 40% in the study cohort, derived from the aggregate proportion of ventilated patients across CCAA registries in 6 Asian countries (64327 patients across Pakistan, India, Nepal, Malaysia, Vietnam and Bangladesh – of 40.4% and the proportion of ventilated patients in Kenya in 2021-22 (47%, unpublished data).
- expected CHE incidence among ventilated patients of 30%
- expected CHE incidence among non-ventilated patients of 15% (i.e. relative risk of CHE of 0.50)

A sample size of at least 307 patients (at least 184 non ventilated and at least 123 ventilated patients) is needed to verify the expected difference in CHE incidence. Considering a 15% loss to follow-up or incomplete patient episodes, we intend to recruit a total of at least **354 patients** (at least 212 non-ventilated and at least 142 ventilated patients). Assuming each ICU will recruit an average of 12 patients, we seek to enroll at least **30 ICUs in the study, from at least 5 different countries.**

4.4 Study parameters/endpoints

Primary endpoints:

- Costs per complete patient episode, as actually spent in US dollars and International dollars (purchasing power parity exchange rate) in ventilated versus non-ventilated groups.
- Relative risk of CHE in ventilated versus non-ventilated groups.

Secondary endpoints:

- Risk factors for CHE (presumptive list in section 4.6)
- Frequency of different coping strategies for financial coverage of ICU costs

Tertiary endpoints

- Proportion of direct medical versus direct non-medical costs in the total OOPEs
- Patient family socio-economic status (SES) or income
- Paying structures, models by country.

4.5 Study procedures

Screening

Initial screening of study participants will be done by the research assistant on patients admitted to the ICU. Expectation of a length of stay >24 hours will be discussed with the treating team. If a patient fulfills inclusion criteria the research assistant will perform the consenting procedure with the patient or with the primary caregiver in case the patient is unconscious or unwell. After informed written consent is obtained from the patient or primary caregiver, the patient will be recruited in ICOPE.

Recruitment

Once eligibility is confirmed, the study will be explained to the patient or their primary caregiver. The research assistant will then conduct the consent procedure, which involves providing information about the study through the participant information sheet and obtaining written informed consent. Any reasons for exclusion, such as refusal to provide informed consent, will be recorded in the 'Screening and Enrolment Log'. After obtaining consent, the patient will be enrolled in the study.

Informed Consent

The participant or legally authorized person or primary caregiver must personally sign and date the latest approved version of the Informed Consent Form (ICF) before any study interview is performed. A written version of the Participant Information Sheet (PIS) and ICF will be presented and verbally explained to the patients, legal guardian or primary caregiver. Written Informed Consent will be obtained by means of participants (or witness if illiterate) dated signature (or thumb print plus dated signature of literate witness if legal guardian/primary caregiver unable to write) and a dated signature of the person who presented and obtained the Informed Consent. A copy of the signed Informed Consent will be given to the participant.

4.6 Data to be collected

CRF structure and timeline is detailed in **Table 1** and comprises sequential domains from A to F. Daily follow up will run until ICU discharge or death, whichever occurs first. An additional telephone follow up at 30 days and 6 months will be used in survivors.

Table 1. CRF structure and timepoints for data collection

	ICU Admission day	**Daily (max every 72h)**	**ICU Discharge**	**30 days**	**6 months**	**Responder**
A Socioeconomic status and admission costs	X					Patient or caregiver
B Relative Wealth tool	X					
C Costs form	X	X				
D Discharge form			X			
E Follow up form				☎	☎	Patient or caregiver (telephone)
F Clinical registry Admission form (core) Daily processes of care Discharge (core)	X	X	X			Extracted from patient file

*In some instances daily followup may not be feasible due to unavailability of family members or unwillingness to discuss the study. Therefore a maximum interval of 72h is granted between two daily forms.

#A. Socioeconomic status and admission costs

Absolute household estimated yearly and monthly income will be collected in order to calculate CHE. Household consumption expenditure (food and non-food expenditure) will also be collected in order to minimize recall bias and potential missing income data. This information on expenditure will be used as a proxy of income, in cases where the income information is missing.

The following potential risk factors for CHE will be investigated: household income status, patient occupation; marital status; religion; access to safe water; educational status; ownership and location of households (urban vs. rural vs. slum); female-headed households; household size and age/gender of members; geographical location.[10]

#B. Relative wealth

Relative wealth will be quantified using the Equity tool (www.equitytool.org), consisting of a short survey of 11-12 questions allowing to compare the wealth of the respondents to the national or urban population in over 60 countries.

#C. Costs form

Granularity on direct medical and non-medical costs will be sought. Family members (supported by research assistants) will be asked to provide information about expenditure on each visit to ICU. The data collection will ideally be daily, but time window is extended to maximum every 72h as we acknowledge several barriers to daily collection e.g. family members may not visit each day, the research assistant may face conflictual family meetings and some family members assisting a severe kin may not be comfortable with a daily visit. The form will be administered until patient discharge from ICU or death, whichever occurs

first. Direct medical and direct non-medical costs categories and operational definitions are defined in **Appendix 1.**

#D. Discharge form
The discharge form will comprise ICU and hospital discharge outcome and the MRC and EQ5D-3L functional outcome status. The EQ5D-3L is validated to monitor changes in self-reported health status through time in a given patient group.[23]

#E. Follow up form
The follow-up form to be collected by telephone outreach will contain the vital status, EQ5D-3L functional outcome status. The telephone version of EQ5D-3L will be used.[24]

#F. Registry variables
Patient characteristics, severity of illness, case-mix information and outcomes will be captured using the existing Critical Care Asia Africa (CCAA) network core registry data set. This dataset contains the following features on *admission*: demographics information, reason of admission, severity score on admission (eTROPICs and/or SOFA and/or APACHE II) and comorbidities. Clinical data points collected daily include variables used for the derivation of process-measures, organ support features and quality indicators. The following data will be collected:

- ventilation status and execution of spontaneous breathing trials;
- sedation status;
- use of renal replacement therapy;
- use of cardiovascular support such as vasopressors or inotropes;
- use of deep venous thrombosis prophylaxis and stress ulcer prophylaxis;
- infection and antimicrobial treatment status i.e. documented infections and number of antibiotics received during stay.

4.7 *CRF testing and refining*
The case report forms (including expenditure categories) were reviewed by a stakeholder group with representation from participating registries. The stakeholders were asked to contextualize the categories with examples relevant for their healthcare setting and to agree on operational definitions for spending as described above, including relevant source data documents. Expenditure will be recorded in local currency and then converted to USD using a single time point exchange rate (xe converter, xe.com).

4.8 Statistical analysis
Normally distributed continuous variables will be summarized using means and standard deviations while ordinal variables and skewed continuous data will be expressed as median with interquartile range. For categorical variables, percentages will be calculated and tests of significance between categorical variables will be done using a Fisher's exact or a Chi-square test as appropriate. Student's t-test will be used to compare normally distributed numerical variables between factors and a linear regression model will be fitted where applicable. Mann Whitney U-tests and Kruskal-Wallis tests will be used to compare numerical variables when normality cannot be assumed.

Analysis of the primary endpoint

a. Quantification of ICU OOPEs

The primary endpoint will be summarized by reporting overall income group quintiles. Information on direct medical costs, including ICU bed charges, laboratory costs, medication

costs, procedure costs, consumables, medical nutrition, and other related costs will be obtained and summarized.

b. Calculation of CHE

The best method for CHE calculation for single patient episodes is debated in the literature. For the purpose of this study ICU episodes causing CHE will be defined as the calculated total episode OOPE divided by total *yearly* household income exceeding **10%**.[2]
Other applicable definitions that are justified in literature will also be considered and clearly documented in the Statistical Analysis Plan prior to statistical analysis.

c. CHE Sensitivity analysis

The primary analysis regarding CHE will be repeated using a variety of other considerations as a form of sensitivity analysis. These sensitivity analyses will be clearly outlined in the Statistical Analysis Plan prior to database lock and statistical analysis.

Analysis of risk factors for CHE

We will use mixed effects logistic regression models to investigate the relationship between risk factors and CHE. The multivariable mixed effects logistic regression model will then be used to simultaneously estimate the effects of multiple explanatory variables on CHE while controlling for the effects of other covariates. The mixed-effects models will help to account for clustering of the patient level, ICU level and country level data. Tests of significance will be performed at 5 % significance level. Where appropriate, the 95% confidence intervals will be calculated and reported. A detailed Statistical Analysis Plan will be developed for the primary and the secondary outcomes. The Statistical Analysis Plan will be finalized and signed by key investigators after database lock prior to statistical analyses.

5. DATA MANAGEMENT

5.1 Data management

All patients will be identified with a unique study identification code. A logbook with the matching between patient number and name will be stored in the study site. The logbook will be the only document containing patient identifier information. Data will be stored an additional 10 years after the study's completion.

5.2 Data capture

Data will be collected from patients or caregivers interviews, or from the patient's medical chart and transcribed onto an Internet–based electronic CRF. Access to the data–entry system is protected by a personalized username and password. Patients are identified with a study identification code.

5.3 Data sharing

After publication of the primary results, on request a FAIR-compliant pooled dataset will be available for secondary analysis, after judgment and approval of scientific quality and validity of the proposed analysis by the CCAA Data Access Committee (email: dac@nicslk.com).

6. PROJECT MANAGEMENT

6.1 Dissemination of results and publication policy

The results of this study will be published in a peer–reviewed medical journal. We have no restrictions in publication of outcomes of this study.

6.2 Timeline of project

Ethical Clearance: Sep 23 - Nov 23
Data Collection period: Dec 23 - Jun 24

Data analysis: Jun 24- Aug 24
Preliminary results: Sep 24
Final report: Dec 24

7. ETHICS AND INFORMED CONSENT

7.1 Regulation statement

This study will be conducted according to the principles of the Declaration of Helsinki (revision Fortaleza, Brazil, October 2013). Approval to carry out this study will be sought from the relevant National and local Ethical Review Boards, as mandated by the country legislation. Ethical review will be requested from the Oxford Tropical Research Ethics Committee (OxTREC) and from relevant National Ethics bodies and Institutional review boards, as mandated by national and site regulations.

7.2 Recruitment and consent

Family members and primary caregivers will be invited to participate in the study and written consent obtained. If eligibility is confirmed, the study will be explained to the patient or patient relative/legal guardian, including detailed explanation of the participant information sheet and informed consent form.

7.3 Benefits and risks assessment

The participation in this observational study will not bring direct benefits to the patient or family. However the findings of the OOPE study will provide important information for policymakers on the burden of OOPE/CHE and potential solutions. No safety concerns are envisaged for this observational study based on information collected from patients or caregivers, with no influence on patient treatment or procedures.

8. FUNDING

The study will be supported by the Wellcome award, Collaboration for Research, Implementation and Training in Critical Care in Asia and Africa (Grant number: 224048/Z/21/Z).

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10. APPENDIX

Appendix 1. Operational definitions

Term	Definition
OOPE	Defined as the cost incurred by individuals or households at the time of receiving any healthcare services in the ICU, including the component of cost-sharing (the part not covered by a third party like, an insurer) and informal payments (e.g., tips and under-the-table payments), but excluding insurance premiums and any reimbursements from the third-party payers (e.g., the government, a health insurance fund or a private insurance company). OOPE includes direct medical and direct non-medical costs, but excludes indirect costs (such as income/productivity loss).
Catastrophic health expenditure (CHE):	For CHE incidence estimation, there is no single agreed threshold. In this study CHE will be defined as OOPEs exceeding 10% of the household budget (yearly income or consumption expenditure). In sensitivity analysis, we will apply the higher threshold level of 25%.
Direct costs	Direct costs are expressed as expenditure during ICU treatment by households and consist of two main categories: direct medical cost and direct non-medical cost.
Direct medical costs	Subcategory of 'direct costs' referring to direct payments made by individuals to healthcare providers at the time of service use. These include those costs that are consumed for healthcare resources during ICU care and will be classified across 7 categories. - Facility/provider fees, e.g. ICU bed charges, hospital daily rates, theater fees. - Laboratory costs - Medication costs e.g. drugs, fluids, nutrition solutions, bandages - Procedure costs e.g . diagnostic imaging procedures, mechanical ventilation, dyalisis - Consumables e.g. (ventilator circuits, infusion sets, ventilation masks, gloves, alcohol rub, etc.) - Medical nutrition - Other costs These *exclude* any prepayment for health services, for example in the form of taxes or specific insurance premiums or contributions and where possible, net of any reimbursement to the individual who made the payments.
Direct non-medical costs	Subcategory of 'direct costs' including transportation, lodging, food items, informal payments and tips, payments incurred by caregivers and family for helping the patients during treatment.
Yearly/ Annual Income	Annual income refers to the total amount of money earned by a household over the course of a year (i,.e. last 12 months preceding this survey time). This income can come from various sources, such as salary or wages from employment, profits from a business, rental income, investment income, land, or any other source of income received over the course of a year.
Yearly/ Annual Expenditure	Annual expenditure refers to the total amount of money spent by a household over the course of a year (i.e., last 12 months preceding this survey). This includes all expenses such as rent or mortgage payments, utilities, groceries,

	transportation costs, insurance, taxes, entertainment, food and any other expenses incurred during the year.
Family caregivers	Defined as any family member, relative, partner or friend of the ICU patient, who were caring for the patient while he or she stayed in the ICU with or without remuneration. - *Primary family caregiver:* is the family caregiver with the most patient contact. - *Secondary family caregivers:* defined as any other family member or friend over the age of 18 involved in patient care and listed along with their time commitment by the primary family care-giver.
Coping strategies	Any mechanisms for OOPE coverage by patient or family member, including: - Savings: own income. - Medical debt: defined as personal debt derived from healthcare expenditures or paying for medical OOPE by borrowing money from friends or family, institutional loans (banks, etc) or non institutional loans (borrowing from black market). - selling of personal property - limitation to procurement of medical services or drugs - other