

PROTOCOL ‘ACTION STUDY’

CANCER AND ITS ECONOMIC IMPACT ON HOUSEHOLDS IN THE ASEAN COUNTRIES

Operations Group

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ASEAN Country participants

- 1. Cambodia**
- 2. Indonesia**
- 3. Laos**
- 4. Malaysia**
- 5. Myanmar**
- 6. Philippines**
- 7. Thailand**
- 8. Vietnam**

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1 Ethics and confidentiality

This study will be conducted in accordance with all relevant local, national and international regulations.

Approvals from institutional ethics committees and other regional or national regulatory bodies will be obtained prior to the initiation of the study in any centre. Written informed consent, complying with both these principles and local, regional and national requirements, will be obtained from all participants prior to entry into the study. The study will not commence in any centre until all the necessary documentation has been completed.

In obtaining informed consent, the research nurse will provide the potential participant with information about the purpose, methods, possible risks and benefits of participating in the study. All potential participants will have the opportunity to discuss the study with study staff. The participant and the person obtaining informed consent will each sign and date two copies of the consent form, one copy of which will be provided to the participant and the other copy of which will be stored in the participant's case record folder.

Participation in the study will be voluntary and all participants will be free to withdraw at any time, without consequence for their future care. For participants that are not able to read or sign the participant information sheet or consent form, a legal representative or other person approved by the relevant regulatory authorities may do so on their behalf.

All data generated by the study will remain strictly confidential and no report will contain any information that would allow an individual participant in the study to be identified. The privacy of the patient will be strictly protected.

2 Administrative structure

The ACTION (Asean CosTs In ONcology) study is conducted by ASEAN country-investigators and study sites together with the George Institute for Global Health, under the sponsorship of Roche Asia Pacific Regional Office.

Overall responsibility for the study will reside with the Operations Group. The study will be conducted in multiple sites from eight countries [Cambodia, Indonesia, Laos, Malaysia, Myanmar, the Philippines, Thailand and Vietnam]. The Executive Committee will consist of members of the Operations Group and one member of each country. Implementation and coordination of the project will be exercised between these countries and the George Institute via the support of Roche ASEAN affiliates headed by Roche Malaysia.

Data management will be provided by the George Institute and the principal means of data collection and data processing will be electronic, via Internet connection with the George Institute for Global Health. All forms will be entered locally in an online data base by the authorized study staff.

3 Background and rationale of study

Cancer has been cited as the leading cause of mortality globally, accounting for 13% (or 7.4 million) of all deaths annually (WHO, 2010) with 70% of these occurring in low and middle income countries. It is projected that mortality from cancer will increase significantly over the coming years with ~13 million deaths per year worldwide expected by 2030. The trend is even more striking in Asia where the number of deaths per year in 2002 of 3.5 million is expected to increase to 8.1 million by 2020 (Lancet, 2010).

As the availability of medical technologies and treatments expands across regions, the economic burden of cancer treatments, not only to health systems but to individuals and their households, will inevitably become more pronounced. These impacts will be felt most strongly in socioeconomically disadvantaged groups particularly (although not exclusively) those in low and middle income countries where social safety nets, such as universal health insurance, are less likely to be present. A consequence of this is that such illness, particularly through the costs associated with its treatment and its impact on people's ability to work, can be a major cause of poverty. The ACTION study will examine such economic impact of cancer on households across the ASEAN countries and assess the incidence of financial catastrophe and economic hardship associated with the illness. In addition it will examine the impact of cancer on quality of life of these patients, and the variations in the way in which patients within and across these countries are managed. It follows on from the phase 1 study in which data on cancer incidence and mortality in each of the ASEAN countries were used to estimate disease burden.

4 Research objectives

To assess the impact of different cancer types on quality of life and household income across ASEAN countries.

The main objectives are to assess in the ASEAN communities:

1. The economic impact of cancer on households
2. Variation in the management and the costs of hospital and non-hospital treatment for cancer
3. The impact of cancer on quality of life

5 Study design

5.1 Design

This is a longitudinal study of patients with a first time diagnosis of cancer in hospital. Patients will be followed throughout the first year after their cancer diagnosis.

5.2 Participants

Inclusion criteria:

- 18 years and older
- With a first time cancer diagnosis received in the last 6 weeks
- Aware of their new cancer diagnosis
- Conscious and with sufficient cognitive capacity to give consent and complete an interview
- Willing to participate in the baseline and two follow-up interviews

Exclusion criteria

- Participating in a clinical trial

5.3 Sites

A cross-section of public and private hospitals as well as cancer centers across the ASEAN countries will participate.

5.4 Sample size

The initial target for patient recruitment is between 1000 and 2500 per country, with a maximum of 10,000 patients in total. Countries will recruit a sample of consecutive patients who are newly diagnosed with cancer.

A screening log will capture sex, age and cancer site information of all eligible patients, whether they consent to participate or not.

A sample of 10,000 patients allows us to reliably estimate (within a maximum of $\pm 1\%$ error) the prevalence of financial catastrophe, poverty induced illness, clinically relevant decrease in quality of life, depression and anxiety, across the region.

Similarly, for the country-specific analyses, a sample of at least 1000 patients per country allows us to estimate the prevalence of financial catastrophe and all secondary outcome measures with acceptable errors (i.e. a maximum of $\pm 3\%$ error).

6 Outcomes

6.1 Primary outcome

Incidence of financial catastrophe following treatment for cancer: Financial catastrophe is defined as out-of-pocket direct health care expenditure at 12 months exceeding 30% of household income as assessed over the 12 months of follow-up.

6.2 Secondary outcomes

Poverty induced illness: This will be assessed by a change reported in household income which brings a household from initially above the prevailing poverty line (country specific) at baseline to below that line at 12 months.

Quality of life (QoL) (generic): This will be assessed on the basis of change in health utilities over a 12 months period, as measured by the EQ-5D.

Quality of life (QoL) (cancer specific): This will be assessed by a change in quality of life over a 12 months period, as assessed by EORTC QLQ-C30.

Psychological distress: The presence of psychological distress (anxiety and depression) at baseline, 3 months and 12 months will be assessed using the HADS.

Hospital costs: These are the costs of hospitalization and hospital treatment incurred by patients in the 12 months after primary diagnosis. These costs will be assessed by examining the patient's medical file at 3 and 12 months, as well as information provided by the patient in the follow-up interviews.

Non-hospital health care costs: These are the health care costs which are incurred in the 12 months after primary diagnosis outside of hospital by patients. These costs will be assessed during the interviews. The patient is given a cost diary that can assist in answering the health care utilization questions.

Out-of pocket costs: These represent the hospital and non-hospital health care costs which are directly incurred by patients at point of delivery and not reimbursed by insurance. These

costs will be assessed during the interviews. The patient is given a cost diary that can assist in estimating out-of-pocket expenses.

Indirect costs: This is a measure of the change in household income in the 12 months of the study, as assessed in the suite of questionnaires.

Economic hardship: Assessed as the inability to make necessary household payments such as housing costs, energy, food and health care costs, as assessed in the suite of questionnaires.

Disease status: Response to treatment (i.e. complete response, partial response; stable disease, progressive disease) is assessed at 12 months.

Survival status: Vital status of the patient will be collected at both follow-up assessments. When a patient has died the cause of death will be determined, if possible.

A log-frame structuring the main elements of the study is presented in table 1.

Table 1. Log-frame ACTION study

Narrative summary	Indicators	Means of Verification	Assumption
To identify the economic impact of cancer on households	Financial catastrophe: relative burden of out-of-pocket expenditures for cancer on household income Per household expenditure for the cancer treatment Change in household income Failure to make necessary household payments	Baseline and follow-up surveys Patient cost diary	At least 500 participants per country with a reasonable distribution among cancer sites Active use of cost diary
To identify hospital and non-hospital costs of the management of cancer	Average costs of cancer treatment and one year follow-up, per cancer site, per country.	Medical information form Patient surveys	Data is available on cost prices of cancer related procedures and treatments, for all countries
To identify the impact of cancer on QoL	Change in QoL (physical functioning, emotional function, levels of anxiety, etc). Presence of anxiety and depression.	QoL and psychological distress questions in baseline and follow-up surveys	Completion of at least 2 interviews

7 Questionnaires

A suite of questionnaires will be administered at baseline and both follow-up visits. Demographic information will only be elicited at baseline. Table 2 provides the domains of the questionnaires and the source from which the questions are drawn, and when they will be administered.

Table 2. Questionnaire domains

Domain	Items	Source	Respondent	Baseline	3m	12m
Socio-demographic	Age, sex, education, insurance status, marital status, occupation	National Household Surveys (NHS)	Participant	X		
Medical information	Cancer site, tumour stage/grade, treatment plan, co morbidities	Developed within study	Research nurse		X	
Disease status	Response to treatment	Medical records	Research nurse	X		X
Vital status	Death	Named alternate respondent, death certificate or medical records	Research nurse		X	X
Quality of life	Global health, physical functioning, emotional functioning, utility	EORTC QLQ-C30 Aaronson (1993) EQ-5D (+ VAS) EuroQoL group	Participant	X	X	X
Mental health	Anxiety and depression	HAD Scale Zigmond (1983)	Participant	X	X	X
Socioeconomic	Economic hardship, household income	NHS, US Census, Heeley et al (2009), Hackett (2010)	Participant	X		X
Out-of-pocket costs initial hospitalization	Out of pocket costs not reimbursed by insurance, government etc	Developed within study	Participant		X	
Health care utilization and out-of-pocket costs	Hospital visits (excluding initial hospitalization), non-hospital based care, alternative medicines, etc	Wei et al (2010), Heeley et al (2009) Patient cost diary	Participant			X
Non-health out of pocket costs	Accommodation (nursing home), assistance (paid)	Developed within study	Participant			X
Hospital costs	Treatment, follow-up visits	Developed within study	Research nurse			X
Cost data form	Cost prices per site for health care services related to treatment	Developed within study	-	-	-	-

7.1 Specific questionnaires used

Household economic hardship is determined by a series of questions about failure to make household payments and whether there was help provided by any organization or individual to meet these payments. Similar questions have been successfully used in several studies conducted by the George Institute (e.g. Hackett et al (2010), Wei et al (2010), Heeley et al (2009), Essue et al (2011)).

Health care utilization and out-of-pocket costs will be assessed using a questionnaire developed within the study.

Treatment costs will be assessed by abstracting the following data from consented participant's medical files: hospitalization, consultations, treatment received. Cost prices will be collected in a separate cost data form to be filled out by each site.

Quality of life is assessed by the EORTC QLQ-C30 from the European Organisation for Research and Treatment of Cancer. The EORTC QLQ-C30 is a self-administered questionnaire specifically developed to assess the quality of life of cancer patients. The questionnaire consists of 30 items. After transformation, the EORTC QLQ-C30 has several multi-item functional subscales (e.g. physical, emotional functioning), multi-symptom scales (e.g. fatigue, pain), a global health subscale, and single items to assess symptoms (e.g. sleep disturbance). Scores on the functional and global health scales range from 0 to 100, where a higher scale score represents a higher level of functioning (Aaronson, 1993). The EORTC QLQ-C30 is available for all countries, except for Laos and Cambodia.

The EuroQol (EQ-5D) is a short self-reported generic health-related quality of life instrument that consists of two parts: a self-classifier and a Visual Analogue Scale (VAS). The self-classifier comprises five items relating to problems in the following domains: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each domain has three levels, namely, no problems, some problems and severe problems. Combinations of these categories define a total of 243 health states. An EQ-5D health state can be converted to a single summary index by applying a formula that essentially attaches weights to each of the levels in each dimension. Utility scores range between approximately -0.59 (for health states worse than death) and 1 (full health). The EQ-5D is available for all countries, except for Laos and Cambodia.

The Hospital Anxiety and Depression Scale (HADS) is used to collect information on psychological distress and more specifically the presence of depression and anxiety. The HADS is a self-report instrument designed for use with medically ill patients. Scores of 8 (possible range 0-21) or more on the depression or anxiety subscales are classified as 'depressed' or 'anxious', respectively (Zigmond, 1983). The HADS is available for Thailand, Malaysia, the Philippines and Indonesia (to be confirmed).

7.2 Translations

Questionnaires will be translated by each country using forward-translations and back-translations. Guidelines for this method can be found on the WHO website: (http://www.who.int/substance_abuse/research_tools/translation/en/).

8 Reporting of study outcomes and deaths

Information about the occurrence of all study outcomes as defined above (section 6) as well as study withdrawal and death will be sought at each of the scheduled visits and captured on the participant's case record form. Cause of death will be determined by the research nurse.

9 Analysis

Initial descriptive analyses will be produced with outcomes reported for each country. Analyses will be undertaken to investigate associations between demographic, socioeconomic and cancer specific factors and each of the key outcomes (see section 6). Country-specific and pooled analyses will be undertaken.

The analyses will allow us to provide evidence in the ASEAN countries of:

- the impact of different cancer types on quality of life, household economic and social outcomes across countries
- the influence of insurance status, hospital type, region and socioeconomic status on these outcomes

- an analysis of the variations in costs and treatment for cancer across hospitals and countries
- an analysis of non hospital direct costs, non-health care costs, indirect costs and out-of-pocket costs incurred by patients with cancer

10 Logistics and consent

10.1 Recruitment and consent

At each site, consecutive patients receiving a new diagnosis of cancer, fulfilling the inclusion criteria, will be approached to participate in the study. The treating physician will identify eligible patients and provides the patient with the patient information sheet (PIS) and patient informed consent (PIC) form. The research nurse/officer will contact the patient and seeks consent for participation. This would entail participation in the baseline interview and two follow-up interviews (at approximately 3 and 12 months after the baseline interview) and consent to examine their individual patient files (see figure 1).

A screening log will be completed by the research nurse(s)/officer(s) at each participating site, with details of all patients approached to participate. Age, sex, type of cancer and area code of home town (optional) will be collected from non-responders.

10.2 Data collection and data entry

Data will be collected through conducting structured interviews by a trained researcher at a place of the participant's convenience. All research nurses will be specifically trained for this study. The first interview will be held at the hospital, after the patient has given informed consent to participate in the study, and before start of treatment. In addition, the patient is provided with a cost diary that is kept for the duration of the study, assisting in capturing health service use and out of pocket costs.

At approximately 2 to 3 months after inclusion, the research nurse will fill out the medical information form, capturing information on the type of cancer, cancer stage and treatment plan, etc.

A follow up interview will be carried out at 3 and 12 months after the baseline interview (see section 7 table 2, for details of the contents of the interviews). To minimize loss to follow-up and optimize the validity of responses, the 3 and 12 months interviews will be held (in order of preference): 1) at the patient's home, 2) by post and telephone and 3) in the clinic during a follow-up visit. If, due to disease progression, a patient is unable to undergo the interview, another member of the household, identified by the participant at baseline, may do the interview on their behalf. In this case, the quality of life questions will be left out of the assessment.

Research nurses will attend a two-day training prior to the start of the study. This training will cover the following topics: general research methods, study-specific content and data entry. The training will enable individuals to recruit study participants, employ the research tools to conduct interviews and to manage the data collection and data storage processes in their country. The overall goal is to capture reliable, unbiased data, which truly represents the overall population.

Research nurses are required to enter the data onto electronic case report forms (eCRFs) and uploaded to a secure centralized database. Data will be entered once, with several automated quality checks incorporated in the database system.

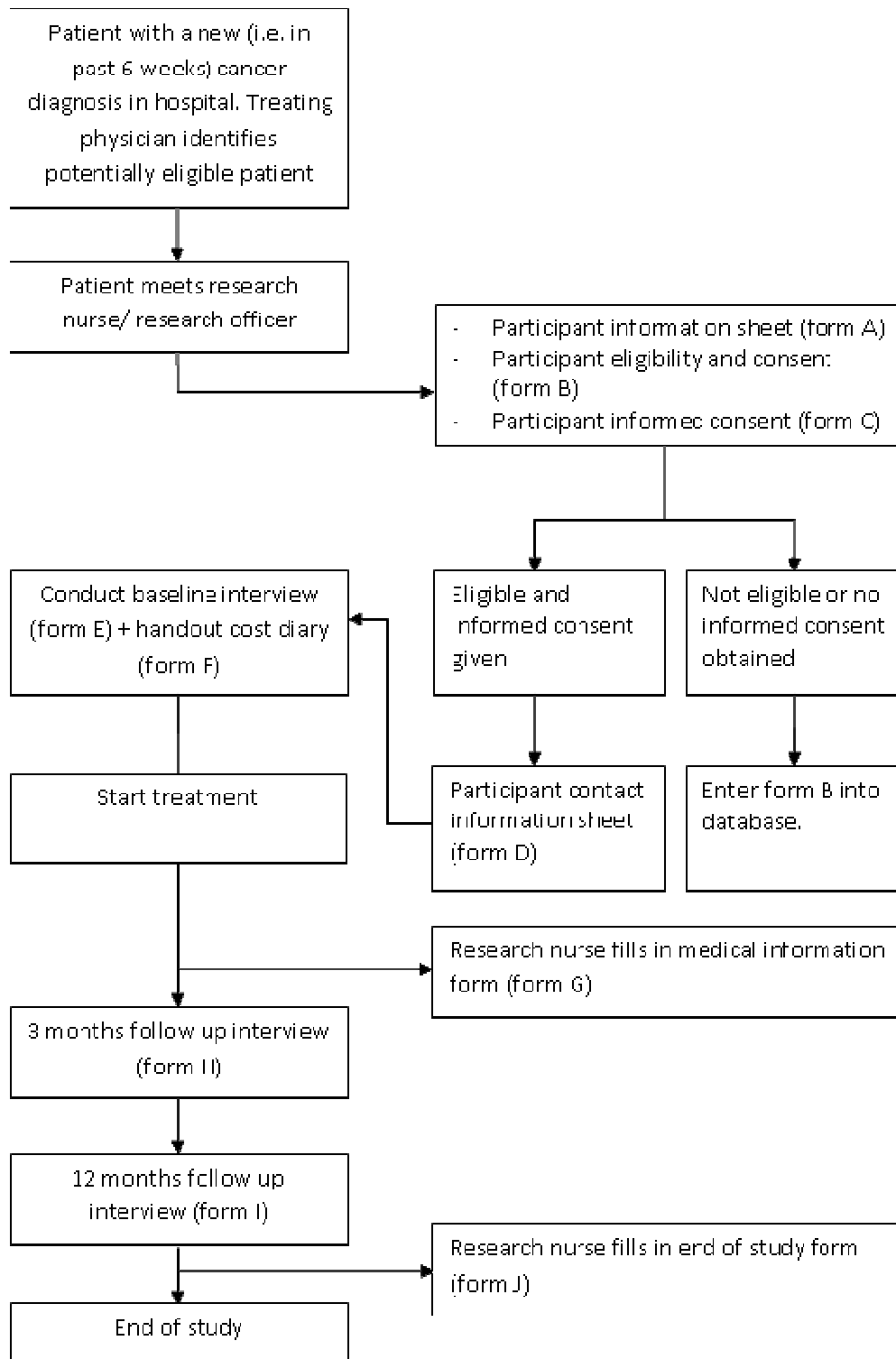


Figure 1. Interview flowchart

10.3 Registration

The original patient informed consent form will be included in the patient's medical file and a copy will be given to the patient. Each participating site will receive a unique site number at the start of the study from the George Institute. In addition, interviewers will be assigned an

interviewer letter. Research nurses will assign each participant a unique participant ID, consisting of a country code (1-8), the site-specific number, interviewer letter and then a consecutive number for the new patient.

Example: Myanmar (country code 5), hospital A (site number 02), interviewer (interviewer C) and first patient. Patient ID: 5-02-C-001

10.4 Time sheet

Table 3. Time sheet

	Aug-Sep11	Oct-Dec11	Jan-Jul12	Jul12-Jun 13	Jun-Sept13
Finalize protocol	X				
Ethics approval	X	X			
Train research nurses		X			
Start recruitment		X	X		
Baseline interviews		X	X		
Follow-up interviews			X	X	
Data analysis				X	X
Final report					X

11 Intellectual property and publication

All papers presenting results from the ACTION study will be published in the name of the project, listing all investigators. The papers will not have named authors, but a writing committee made up of all contributors to the paper.

In addition, each investigator team of each country may publish special interests not superseding the main report. The Executive Committee would like to be notified of manuscripts before submission.

12 Funding

This study is funded through an unrestricted educational grant from the Roche Asia Pacific Regional Office.

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Appendix A Signatures

I have read and approve this protocol.

Name (print) _____

Hospital/site _____

Signature _____

Date of Signature (dd/mmm/yyyy) _____