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# ELSA-Brasil strategies for outcome identification, investigation and ascertainment

## ABSTRACT

**OBJECTIVE:** The article describes the strategies adopted by the Brazilian Longitudinal Study for Adult Health (ELSA-Brasil) for participation and retention of subjects. This is key to ensure internal validity of longitudinal studies, and to identify, investigate, and ascertain outcomes of interest.

**METHODS:** The follow-up strategies include annual telephone contacts with new assessments and interviews every three to four years this approach aims to identify transient outcomes (reversible or not), permanent outcomes as well as complications related to the progression of major diseases – cardiovascular diseases and diabetes – to be studied.

**RESULTS:** Telephone interviews are designed to monitor subjects' health status and to identify potential health-related events such as hospital admissions, medical visits or pre-selected medical procedures. Subjects are also encouraged to report to the ELSA-Brasil team any new health-related events. When a potential event is identified, a thorough investigation is carried out to collect relevant information about that event from medical records. All data are blinded and reviewed and analyzed by a medical expert committee. Incident outcome ascertainment follows well-established international criteria to ensure data comparability and avoid misclassification. In addition to these strategies, the occurrence of health-related events is also investigated through linkage of secondary databases, such as national mortality and hospital admission databases.

**CONCLUSIONS:** Accurate identification of outcomes will allow to estimating their incidence in the study cohort and to investigate the effect of the exposures studied in the ELSA-Brasil at baseline and at its subsequent waves.

**DESCRIPTORS:** Cardiovascular Diseases, epidemiology. Cardiovascular Diseases classification. Cardiovascular Diseases, complications. Diagnostic Techniques, Cardiovascular, utilization. Diabetes Mellitus, epidemiology. Diabetes Complications. Multicenter Studies as Topic, methods. Cohort Studies. ELSA-Brasil.

## INTRODUCTION

Retention of study subjects is a major challenge in cohort studies. Adequate follow-up is required to ensure that reliable sufficient information is obtained for identification and categorization of incident outcomes of interest.

High rates of losses to follow-up due to study withdrawal, difficulty of contacting subjects or other reasons may seriously affect internal validity and thus the study findings. Several cohort studies<sup>11</sup> have shown that outcome-related characteristics differ in subjects lost to follow-up and those who remain in the study.<sup>8,18</sup> A meta-analysis by Radon et al<sup>20</sup> showed that among follow-up losses there are often a higher proportion of individuals with poor sociodemographic characteristics or risk factors relevant to the study. It is also likely that those who remain in the study may differ from others in aspects directly related to the very event studied. For example, in a population-based longitudinal study on cognitive function, those who refused to participate in a second wave had lower cognitive abilities.<sup>15</sup>

### Prevention of loss to follow-up

Like any longitudinal study, the Longitudinal Study for Adult Health (ELSA-Brasil)<sup>4</sup> has a “zero loss” goal, i.e., it will make every effort to retain all subjects in the study. A systematic review of subject retention strategies in longitudinal studies have shown that cohorts that combine different strategies either directly or indirectly related to data collection have lower follow-up loss.<sup>22</sup>

It is crucial to clearly define loss to follow-up so that actual losses will not be overestimated. It has been shown in cohort studies (e.g., the French GAZEL study) that subject withdrawal may be reversed and to consider a single non-response as non-participation may be a hasty conclusion.<sup>10</sup> In a Finnish cohort study of young adults 50% of losses returned to the study in subsequent waves.<sup>13</sup>

For example, a subject cannot be contacted in a given year due to temporarily moving to another city or country or even because she/he refused to participate in a telephone interview, and then she/he may be reached the next year and accept to participate in interviews/assessments at the investigation center. In other words, a loss should be defined as temporary until it is proven otherwise. It implies that the analyses for a given year may include individuals who were temporary losses in the preceding year.

ELSA-Brasil’s goal is to prevent any losses, albeit temporary, regardless whether these losses are reversible or not. The main reasons for loss to follow-up include address changes (street, city or country); job changes in occupational cohorts; withdrawal from the study; and death.<sup>24</sup> In the Cornella study, almost two thirds of subjects who did not take follow-up interviews had died or moved to another city.<sup>9</sup> The ELSA-Brasil subjects have stable jobs, they are permanent employees of higher education and research institutions where this study is being conducted, which reduces the likelihood of loss to follow-up, especially while the subject is active.

During the first contact with prospective study subjects they are informed about the longitudinal design of the study and are asked to sign an informed consent form. They commit to attend all study visits over the years, agree and are willing to participate in all telephone interviews between study visits and to report hospital admissions and medical procedures. They also agree to the research teams’ blind review of their medical records kept at health facilities and at their attending physician’s office. To facilitate future contacts subject contact information (address and home, work, and cell phone numbers) was collected at the baseline visit along with contact information of family, friends, and colleagues who could provide information about the subject’s health. Information on their physician (name) and health care facility they usually attend was also collected. Contact information for follow-up is regularly updated as it may change over time.

The ELSA has adopted two different strategies to prevent losses due to address changes throughout the study. In addition to annual contacts for collecting information on subjects’ health status and illnesses, keeping subjects informed about the study and making courtesy contacts for congratulating them on birthdays and end-of-the-year holidays also improve retention in the cohort. Mailing letters between the study waves (visits to the investigation center) and newsletters about the study can help engendering a feeling of belonging among subjects.<sup>3</sup>

Information about the study is made public through a website, small publications and mass media.<sup>5</sup> Likewise, all contact opportunities are important for retention in the cohort. For example, the reporting of test results in person or by mail is an opportunity to reinforce the importance of their participation in the study and to remind them about annual phone calls they will be receiving and about the estimated time for their next visit to the investigation center, three to four years from their entry into the study.

<sup>3</sup> Hispanic Community Health Study/Study of Latinos. ¡Salud Sol! Newsletter. [cited 2011 Mar 4] Available from: [http://www.hchsnews.net/HCHSSOL\\_Newsletter\\_Vol1\\_Iss1\\_ENSP.pdf](http://www.hchsnews.net/HCHSSOL_Newsletter_Vol1_Iss1_ENSP.pdf)

Subjects' refusal to remain in the study may be because they have lost interest or are distrustful of or dissatisfied with the study. In ELSA-Brasil we accept and respect participants' choice, but any expressed desire to withdraw from the study is carefully examined to ascertain the reasons. In these circumstances, the clinical outcome supervisor or sometimes the site coordinator call the subject or schedule a face-to-face talk, as needed, to encourage him/her to remain in the study.

### Follow-up stages

Follow-up actions in the ELSA-Brasil include identification, investigation, and ascertainment of health-related events over time. These actions are coordinated by the Clinical Outcome Committee (COC). The COC comprises members of all investigation centers and is coordinated by the ELSA-Brasil Research Steering Committee (ERSC) member from ELSA MG.

The main objectives of the COC are to develop and monitor all follow-up actions and to identify, investigate, and ascertain health-related events. The main COC actions include:

- To develop and test data collection instruments, and to investigate and ascertain health-related events;
- To train and qualify interviewers and researchers;
- To monitor telephone follow-up calls and ensure timely follow-up contacts;
- To establish criteria for incident outcome ascertainment working together with the Committee on Disease Morbidity and Mortality composed of medical experts on cardiology, neurology, endocrinology, nephrology and oncology;
- To coordinate outcome ascertainment by the Committee on Disease Morbidity and Mortality;
- To identify issues and develop strategies to approach subjects expressing desire to withdraw from the study.

A follow-up approach was adopted in the ELSA-Brasil to identify transient outcomes (reversible or not), permanent outcomes as well as complications related to the progression of major diseases to be studied (Table). It includes a set of strategies of remote monitoring via telephone calls and visits to investigation center for information collection and new rounds of assessments similar to those performed at baseline. Furthermore, the study expects and encourages subjects to contact the investigation center to report health-related events.

Contacts via phone calls are made on an annual basis to monitor outcomes. Time intervals between these contacts

are anticipated to be 10 to 14 months following the initial visit to the investigation center or the last telephone interview. Many attempts are made to contact subjects to prevent losses. Family members or coworkers specified by the subject will be contacted as needed.

If a potential event is detected or reported several actions are put in place to verify and substantiate it so to be correctly ascertained by expert committees. These actions include: a) visits to health services to collect information from medical records; b) interviews with the subject or informants to gather additional information as needed; and, rarely, c) interviews with the subject's physician. Monitoring and investigation of events are shown in the Figure. By March 2012 potential events related to hospital admissions were ascertained in about 10% of contacts.

To collect information of a potential event occurring in a hospital or outpatient clinic setting one of the study investigators visits the facility with the purpose of reviewing this subject's medical records. Medical records contain confidential patient information and are under responsibility of medical providers and health institutions and information can be released only the patient authorizes its release. All subjects who signed the informed consent form were asked explicitly for permission to give access to their medical records and/or contact their attending physician or interview a close contact to gather health information when necessary. For that reason a copy of the signed informed consent is provided to the facility staff.

The investigation of a hospital admission requires a review of the patient discharge to confirm the date of the potential event and other related medical diagnoses. If an event of interest is evidenced (Table), the entire record is copied or photographed making sure that the facility, provider and patient names are blacked out. The patient record is identified with the ELSA-Brasil subject ID and then reviewed by outcome supervisors and the medical experts committee for event ascertainment and reporting.

The rate of success at this stage has varied from site to site because some health facilities are resistant to release patient information. This barrier is largely due to the fact that cohort studies do not traditionally apply this strategy of data collection in Brazil. In addition, other complicating factors include category of health facilities (public or private); non-affiliation to a research center; no institutional review board at the facility; and lack of clear specific regulations by Institutional Review Boards and the National Research Ethics Committee.

Another challenge is the analysis of data collected from hospital records because quality and completeness of information is quite variable. Brazilian studies have shown that medical records—that are supposedly

**Table.** Major distal clinical outcomes in the ELSA-Brasil and ascertainment criteria.

Health-related event	Source of information	Ascertainment criteria
Acute myocardial infarction	Hospital <sup>a</sup> , EU	AHA/ACC/ESC Criteria <sup>14</sup>
Unstable angina	Hospital, EU	Medical diagnosis based on symptoms, ECG findings <sup>c</sup> and tests <sup>14</sup>
Congestive heart failure (CHF)	Hospital, EU, self-reported diagnosis of CHF	Medical diagnosis and specific treatment for CHF and/or pulmonary edema in X-rays, and/or ventricular function on echocardiogram/ radionuclide scintigraphy or contrast ventriculography – AHA/ACC Criteria <sup>12,17,21</sup>
Peripheral arterial disease	Hospital, EU	Medical diagnosis based on symptoms, diagnostic procedure or therapeutic intervention
CABG	Hospital	Revascularization surgical procedure
Resuscitated sudden death	Hospital, EU	Medical diagnosis from medical records
Stroke	Hospital, EU	TOAST <sup>1</sup> /ASCO <sup>2</sup> Criteria
Transient ischemic attack	Hospital, EU	AHA/ASASC <sup>6</sup> Criteria
Incident diabetes	Self-reported diagnosis of diabetes; assessments (visits to SS-ELSA)	ADA Criteria 20103
Hospital admission due to complications of diabetes mellitus (ketoacidosis, severe hyperglycemia, diabetic foot)	Hospital, EU	Diagnosis from medical records
Chronic kidney disease	Hospital, EU, visits to SS-ELSA	KDOQI/CKD <sup>16</sup> Criteria
Cancer	Hospital, EU	Diagnosis from medical records and confirmatory tests

<sup>a</sup>Hospital – hospital stay  $\geq 24$ h

CABG: coronary artery bypass grafting

EU: emergency unit

ECC: electrocardiogram

SS: study site

AHA/ACC/ESC: American Heart Association/American College of Cardiology/European Society of Cardiology

TOAST/ASCO: Trial of Org 10172 in Acute Stroke Treatment

ASASC: American Stroke Association Stroke Council

ADA: American Diabetes Association

KDOQI CKD: Kidney Disease Outcome Quality Initiative/Chronic Kidney Disease

accurate, reliable inventory records of patient and procedure information during admissions – are sometimes a flawed source of data and may prevent correct ascertainment of events of interest in the ELSA-Brasil.<sup>23</sup>

In addition to the strategy mentioned before, outcomes can be further ascertained through linkage of secondary data. Death and hospital admission databases are sources of information from the Brazilian Ministry of Health, namely: the Mortality Database and Hospital Admission Database. Death information can also be ascertained from human resources records at the participating institutions.

### Distal outcomes

Correct identification of events of interest is key to ensure quality of the study. Considerable emphasis is put on the definition and standard ascertainment of events, especially because the ELSA-Brasil is a multicenter study.

The development of tools to identify health-related events require a multidisciplinary team and extensive testing to ensure that questions asked can identify what is being studied. Besides developing follow-up questionnaires, the team involved in monitoring outcomes has to be trained and qualified to apply the questionnaires in a standardized manner. Contact information of subjects and their informants are accessed online and consistently updated directly into ELSA-Brasil data entry system.<sup>7</sup> Annual follow-up interview questionnaires were also made available for online data entry and can be completed in real time while interviewing subjects or data can be entered later when completion is manual. The system facilitates the interview process by showing warnings when the interviewer is required to complete additional forms. Regular reports of the data entered into the system allow to monitoring advancement toward follow-up goals and potential inconsistencies. Outcome investigation and ascertainment forms accommodate the

variety of hospital records in Brazil. The features that are necessary to the system are established jointly by the COC and Data Center Operations.<sup>7</sup>

The flow chart of telephone contacts has several levels (Figure). The first reporting of a potential event initiates an investigation lead by a team especially trained to search and document information in health facilities (hospitals, emergency rooms, medical offices).

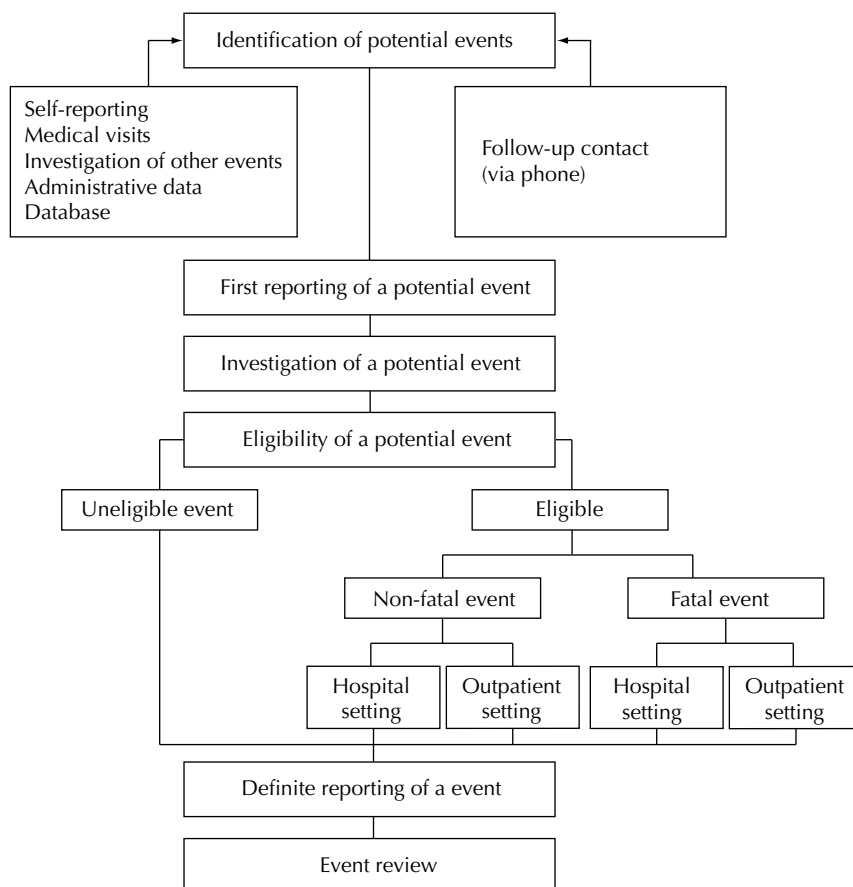
The criteria for event ascertainment were set in consensus meetings of medical experts (reviewers) based on internationally well-established ascertainment criteria available (Table). The study reviewers were trained and are qualified for the application of these criteria in the analysis of information available for each event of interest. They work in specialty subcommittees (cardiology, neurology, endocrinology, among others).

**Intermediate or subclinical outcomes**

In addition to distal outcomes, the ELSA-Brasil aims to identify and study subclinical changes, reversible or not, that can be detected before clinical manifestation

of diseases as well as changes in exposures that play a role in the natural history of a disease under study. These changes will be detected by comparing results of assessments, measurements and interviews that will be repeated for each new wave of visits at investigation centers.

Intermediate or subclinical outcomes include a wide range of events including arterial hypertension, cognitive function changes, significant variations in body mass index, dyslipidemia, renal function impairment and changes in carotid intima-media thickness. Some of these events have internationally recognized standard definitions, such as hypertension, hypercholesterolemia, obesity, and smoking cessation. Other changes, such as changes in cognitive function or carotid intima-media thickness, will be further explored using different cutoffs and definitions. Old and new intermediate markers will be investigated and explored in the study aiming to increasing knowledge about the natural history of the diseases of interest. Creating a repository of biological specimens from serum, plasma, and urine stored during the waves of the study will allow to investigating new markers in using, for example, a case-cohort strategy.<sup>19</sup>



**Figure 1.** Flowchart for identifying health-related events, ELSA-Brasil.

## FINAL CONSIDERATIONS

The ELSA-Brasil will study the association of a wide variety of exposures at baseline with multiple outcomes investigated during the study. The follow-up approach of this cohort study is a combination of several strategies so to prevent losses. In addition, interviews and standard assessments and procedures will allow the identification and ascertainment of events of interest, ensuring data validity and

comparability over time and with data from other relevant chronic disease studies in adults.

The ELSA-Brasil configuration encompassing a repository of biological specimens and DNA database will allow to conducting new analyses and tests in pre-stored samples after the occurrence of major outcomes. In addition to the study of sociodemographic and behavioral factors, it is a promising opportunity for genetic studies of diseases investigated in the ELSA-Brasil.

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