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Routines of organization of clinical tests and interviews in the ELSA-Brasil investigation center

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ABSTRACT

The ELSA-Brasil (*Estudo Longitudinal de Saúde do Adulto* – Brazilian Longitudinal Study for Adult Health) is a prospective cohort study with extensive assessments throughout time. This article describes the routine of clinical tests and interviews performed with participants and the structuring of the Research Center physical space and teams. The ELSA-Brasil assumes that participants will be present at the Research Center to have the tests and interviews performed, according to standard protocols developed by this study. Considering the multiplicity of activities involved, each with specific needs for standardization, several predetermined orders of clinical tests and interviews were created. This ensured a high standard of quality in data collection without harm to participants' comfort. Each participant was previously assigned to a specific sequence of clinical tests and interviews with a predefined arrival time, mean length of stay of five to six hours and departure time.

DESCRIPTORS: Cohort Studies. Data Collection, methods. Adult. Patient Selection. Medical History Taking. Diagnostic Techniques and Procedures. Interviews as Topic, utilization.

INTRODUCTION

One of the first cohort studies, the Framingham Heart Study, aimed to identify the incidence and factors associated with cardiovascular disease throughout time, since the baseline began in 1948. In that study, volunteers went to a research center with an adequate infrastructure to have clinical tests performed, questionnaires about life habits and clinical history applied, and biological material collected for these tests. This assessment routine was repeated every two years and adult children and grandchildren of original participants (2nd and 3rd generations) were maintained in the data collection.[6,20] Other cohort studies appeared subsequently, using a similar methodology, but including increasingly more complex procedures. Cohort studies such as the Atherosclerosis Risk in Communities (ARIC) included ultrasonography to determine the intima-media thickness (IMT) of carotid arteries,[17] retinography,[21] magnetic resonance imaging (MRI)[9] and sophisticated biochemical dosages.[15] The Multi-Ethnic Study of Atherosclerosis (MESA) included thoracic tomography with calcium score calculation and cardiac MRI with left ventricular function evaluation.[1]

The ELSA-Brasil (Longitudinal Study on Adult Health) has similar objectives and included comparable clinical tests and interviews in its protocol, which also required volunteers to visit a clinical research center. Considering the large number of volunteers required, the expected frequency of visits and the meaning of the headquarters to guarantee participants' adherence to the study, physical infrastructures referred to as ELSA Research Centers (ELSA-Brasil RC) in this study were created. The ELSA-Brasil RC is the structure of the ELSA Investigation Center where the interviews and tests were performed. In addition to the RC, the Investigation Center (IC) includes the Reading Centers, Data Center and local and central biobanks.

The amount of information sought in the baseline through interviews and tests led to the division of this step into two stages. Stage 1 (mean length of one hour and a half) occurred right after recruiting, when an interviewer explained about the study, aiming at the informed consent form. Next, an interview was performed and instructions for Stage 2 (lasting between five and six hours) were provided. The present study describes the RC structure and the operational organization of the activities and teams expected for data collection in the baseline.

PHYSICAL STRUCTURE OF RESEARCH CENTERS

Each of the six ELSA ICs built their own research area. The financial resources allocated for this purpose were used for the renovation or construction of new areas, often in an integrated way/as a joint venture with the RC of university hospitals included in the project, which are also part of the National Clinical Research Network. The total building areas ranged from 214 to 639 m^2. Figure 1 shows a sample building area for a center that aimed to include 2,000 participants.

The particularities of each IC required certain operational center-specific decisions. The BA IC, located outside the Federal University of Bahia campus, required a 24-hour surveillance service to be hired. The centers located in the states of São Paulo (SP), Minas Gerais (MG) and Rio Grande do Sul (RS) used hospital structure for uniform cleaning and physical structure cleaning and maintenance (University Hospital, Hospital Borges da Costa and Porto Alegre Clinical Hospital, respectively). In the state of Rio de Janeiro (RJ), disposable uniforms were used. In MG and RS, an advanced station was built to facilitate the recruitment of participants in more distant campuses. The RC of the state of Espírito Santo (ES) used a renovated area and constructed a new area. The RS RC is located in a new six-floor building (Porto Alegre Clinical Hospital Research Center), which delayed the beginning of its complete activities.

Stage 1, which was performed after volunteer recruitment, began by reading and signing the informed consent form and lasted approximately ten minutes on average. A standard interview was subsequently performed for nearly 40 minutes. The remaining time was spent on instructions for Stage 2 activities. Individuals were given specific instructions on the 12-hour urine collection and fasting on the night before the appointment booked for the RC. During this time, questions were also answered, such as whether medications should be suspended or not and the characteristics of certain tests. Next, appointments were set up for participants. Individuals with known diabetes or those with special physical needs were given priority and allocated the first hours of study.

Stage 1 was usually performed in the volunteers' workplace or in an advanced station located nearby. In RS, the proximity of two campuses enabled the majority of participants to perform Stage 1 in the RC itself (in the afternoon). This also occurred in SP, as the RC is close to several units of the main campus of the University
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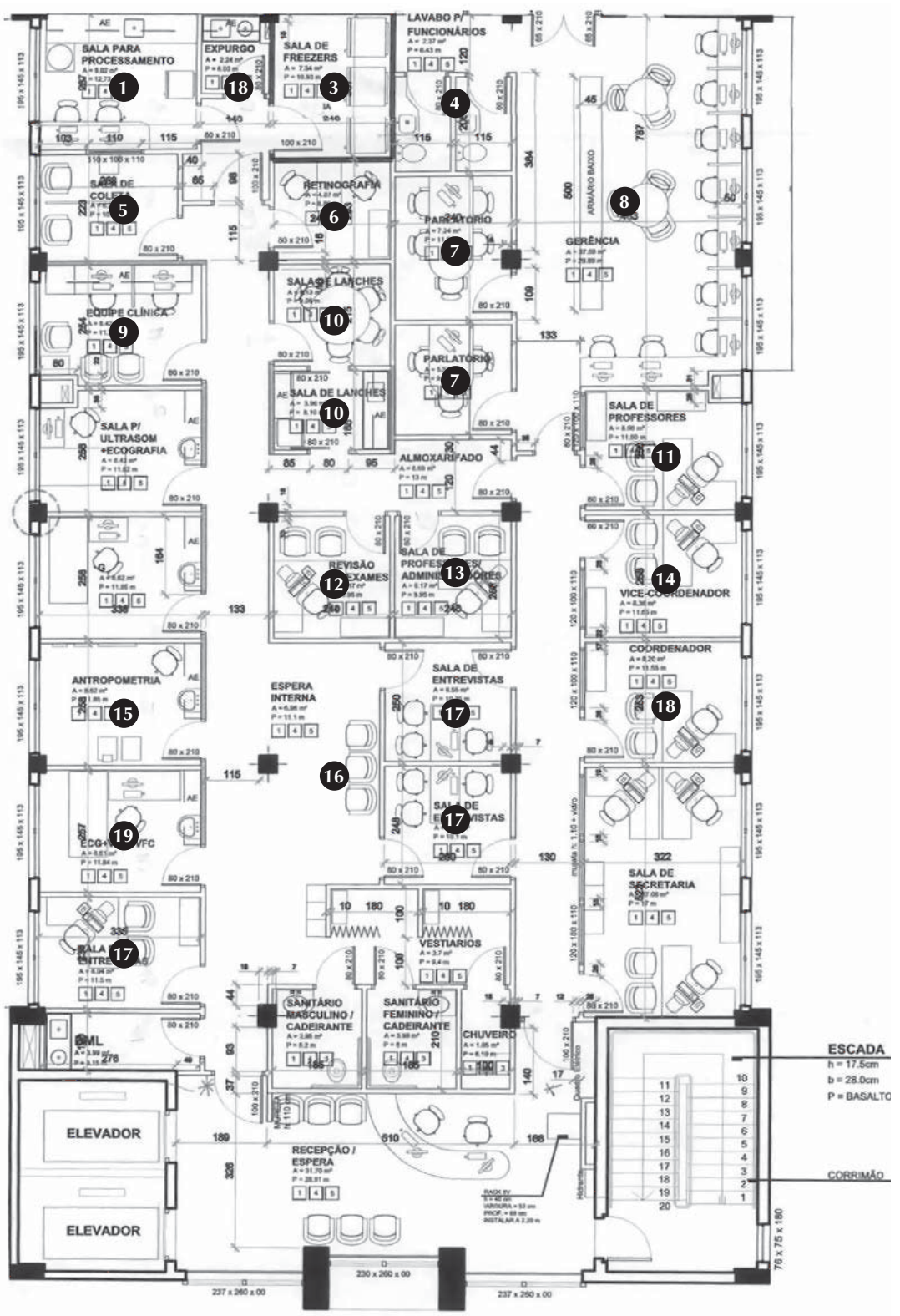

1) Processing Room; 2) Sluice Room; 3) Freezer Room; 4) Employees' Restrooms; 5) Collection Room; 6) Retinography Room; 7) Meeting Room; 8) Management Room; 9) Clinical Team Room; 10) Snack Room; 11) Professors' Room 12) Test Review Room; 13) Professors' and Managers' Room; 14) Vice-Coordinator Room; 15) Anthropometry Room; 16) Inner Waiting Room; 17) Interview Room; 18) Coordinator's Room; 19) ECG+PWV+HRV Room.

Figure 1. Blueprint of an ELSA Research Center, where interviews and clinical tests were performed.

Table. Procedures performed on the appointment day at the Investigation Center, according to the need for fasting or not.

While fasting
Anthropometry: weight and height measurements, sitting height, waist and hip measurements, neck circumference measurement.[2,10]
Blood pressure measurement A total of three measurements with an interval of one minute, after five minutes of rest, using an automatic oscillometric sphygmomanometer (Omron HEM 705CP).[11,19]
First blood collection
Without fasting
Second blood collection – 120 minutes after consumption of 50% glucose solution in non-diabetic participants (16-18) or standard snack in diabetic participants.[3-5,8]
Pulse wave velocity estimation Measured using a non-invasive validated device (Complior SP, Artech Medicale France).[7]
Electrocardiogram 12-lead ECG with a 2-minute layout print in an Atria device (Burdick, Cardiac Science Corporation). The layout reading followed the Minnesota ECG Coding.
Heart rate variability Determination of time and rate indices in the spectral analysis of a 10-minute layout obtained from a 2-lead electrocardiographer at 250 Hz (Micromed, Brazil) using dedicated software (WinCardio, Brazil).[16]
Ankle-brachial index Calculation of the relationship between the systolic blood pressure measurement of the right and left ankles and the highest systolic blood pressure measurement of the right arm. Measurements were obtained with an automatic oscillometric sphygmomanometer (Omron 765CP).[14]
Blood pressure assessment after postural maneuver After 15 minutes of rest, participants got up quickly (with help if necessary) and immediately touched their feet on the floor. Blood pressure was measured with a device in 2, 3 and 5 minutes. Measurements were obtained with an automatic oscillometric sphygmomanometer (Omron HEM 705CP).[13]
Intima-media thickness index (IMT) measurement Ultrasonography of right and left carotid arteries obtained with a linear transducer (7.5 MHz) - Toshiba, SSA-770A - APLIO® (Tokyo, Japan) with an axial resolution of 0.10 mm. Images were measured in a workstation with the IMAGE ARENA –TOM TEC software®.[18]
Hepatic steatosis assessment obtained from a wide-band convex transducer (PVT - 375BT), with a central frequency of 3.5 MHz (2.5 – 5.5 MHz) – Toshiba, SSA-770A - APLIO® (Tokyo, Japan). Images were measured in a workstation with the IMAGE ARENA –TOM TEC software®.[23]
Abdominal wall thickness assessment with minimum and maximum subcutaneous fat measurement; and pre-peritoneal fat obtained with a wide-band convex transducer (PVT - 375BT), with a central frequency of 3.5 MHz (2.5 – 5.5 MHz) – Toshiba, SSA-770A - APLIO® (Tokyo, Japan). Images were analyzed in a workstation with the Medical Imaging Applications (MIA) software® and the maximum subcutaneous fat layer thickness was measured with the IMAGE ARENA –TOM TEC software®.
Echocardiography Images obtained with an ultrasonography machine with a transducer of 2.0 to 3.5 MHz Toshiba, SSA-770A - APLIO® (Tokyo, Japan)
Retinography Images centered on the macula and optical disk of the right and left eyes were obtained with a Canon CR-1 machine, using a system that did not require mydriasis with an EOS 40D digital camera® (10 megapixel).

appointment day. On such calls, questions were answered and the need to bring medications and to check one's birth weight in records or with family members was emphasized. The greatest difficulty was in understanding the duration of fasting (10 to 14 hours) and 12-hour urine collection (for example, understanding that at the zero time the urine must be discarded and at the final time one must urinate in the cup).

Apart from all these cautions taken, an additional number of participants had appointments set up to guarantee a minimum number of daily assessments. The number of contacts made per participant to set up their appointment at the RC and make their participation in the study effective was limited to four, assuming that the lack of contacts represented a possible loss of interest in participating in the project.

ROUTINES IN THE ELSA RESEARCH CENTER

The Manual of Clinical Operations, part of the Manual of General Project Operations, defines the activities developed with participants in the RC.

Flow of activities: clinical tests and interviews

Initially, a flow was defined by ordering the activities to be performed by each participant, aiming to maintain the standard among RCs. However, due to the specific logistic needs among ICs – for example, four participants were evaluated per day on average in ES, whereas 16 to 18 participants were evaluated per day on average in SP –, limits of flow flexibility among the six ICs had to be established. Figure 2 shows an example of participants' flow organization to have the clinical tests and interviews performed.

Each participant was designated to a certain flow, with a predefined arrival time, length of stay and departure time in each room for procedures to be performed. The standard flow began with the clinical tests while fasting: anthropometry, sitting blood pressure measurement, and blood collection. Participants without a previous diagnosis of diabetes received 75 g of a glucose solution, according to the standard glucose tolerance test performed by the World Health Organization (WHO).[22] Participants who reported having diabetes received a standard snack.[3-5,8,12] Blood was collected again 120 minutes after the snack or glucose solution began to be consumed. The Table lists all tests and procedures performed in the RC and the protocol references on which they were based. The ordering of clinical tests varied to enable the equipment and rooms to be fully taken advantage of, always respecting the aspects defined by standardization.

The questionnaire was applied in three sections, following a predefined order, allowing tests to be interspersed with interviews and thus preventing participants from feeling tired. Additionally, modules that could not be interrupted for tests (cognition and mental health) to be performed and the module that should not be applied while participants were fasting (food frequency questionnaire) were defined. An example of such restrictions is the blood collection after 120 minutes, which could never be performed during the mental health or cognition module. Certain peculiarities in the flow definition should be emphasized. Tests where participants had to lie down (such as electrocardiogram, heart rate variability and pulse wave velocity estimation) were performed together in a room so that they could remain in this position (usually 30 minutes). Tests performed while fasting (anthropometry and blood pressure measurement) were grouped in a section and usually performed in the same room. The ankle-brachial index was also grouped with the postural maneuver to assess blood pressure in the same room.

The definition of the standardization of clinical tests was aimed at participants' comfort whenever possible. As an example, the electrocardiogram and heart rate variability were not performed while fasting. The time of their performance was standardized to occur 30 to 60 minutes after the consumption of glucose solution or a standard snack. The use of cell phones was not allowed during the tests, although magazines, television and the Internet were made available. Additionally, some smokers requested a break to smoke, which was permitted after the glucose tolerance test ended. Water was also available at all times, but neither coffee nor tea. Moreover, the flow of each participant took into consideration the previous knowledge of their clinical conditions (such as diabetes, special needs and smoking habit).

At the end of their visit, participants received the results of the anthropometry and blood pressure measurement. Before leaving, they either completed an anonymous questionnaire of satisfaction that quantified aspects associated with the quality of care in the RC, but which also included an open field for any comments or talked to a team member, who listened to possible suggestions that could improve the performance of procedures.

Specific situations

Procedures defined as minimum criteria to take part in the study – fasting blood glucose, blood pressure, electrocardiogram and certain interviews – were prioritized in the case of participants who reported dependence on nicotine or those who needed to leave earlier without completing the flow. A new date was set up to perform the remaining tests and interviews. The main cause for new appointment booking was that participants could not fast for 10 to 14 hours. Cases when fasting was lower than ten hours or longer than 14 hours were booked again, preferably in the same week.

Contingencies

The project defined mechanisms to provide service in the case of contingencies, which varied according to the center. The most frequent clinical contingencies were nausea and vomit associated with the consumption of glucose solution, persistent dizziness after postural maneuver to assess blood pressure, headache, high blood pressure, and suicidal ideation in the previous seven days, detected with the questionnaire of mental health. The RC physician who was present assessed the patient and instructed the team, recording occurrences in a specific form or field journal. The number of serious occurrences was small in this study and fewer than ten cases were referred to emergency services. The cause of referrals was not associated with the study protocol and resulted from the identification of changes in the results of the clinical tests performed, such as echocardiographic changes detected in asymptomatic patients or decompensation of diabetes in those with such disease. In all these cases, the RC team provided care and referred patients to referral services.

Figure 2. Continuation

	P1	P2	P3	P4	P5	P6	P7	P8	P9	P10	P11	P12	P13	P14	P15	P16
8:50																
8:55					Retina		Quest 25	Quest 25	ABI	ABI			Anthropo	Anthropo		
9:00			CV-Fisio	CV-Fisio		USG										

Delivery of test results

In the present study, certain warning signs requiring the results to be informed to participants, so they could seek adequate health care, were defined a priori. Altered results that indicated greater severity had their delivery prioritized. In the case of tests without important alterations, participants could choose to receive them in the RC itself, by mail or via the Internet. Patients with a type of referral to health services for cases of clinical warnings could receive care in the institution (SP), health plan of the institution (RJ) or health plan/ Brazilian Unified Unified Health System (RS, MG, BA and ES).

The delivery of results with alterations required a great effort from all centers. There were cases in which serious diseases were detected, such as heart failure with an ejection fraction of 35% and severe aortic valve stenosis, which required immediate referral to a cardiology service. In all centers, new cases of arterial hypertension, diabetes, dyslipidemia, thyroid disorders (hypothyroidism, hyperthyroidism), neoplasms, pancreatitis, anemia and Chagas disease were identified. The presence of certain alterations in retinography, echocardiography and electrocardiography tests led to immediate referrals for a more accurate diagnosis by specialists. The most frequent alterations in electrocardiograms requiring referrals were atrial fibrillation, ventricular arrhythmias and junctional rhythms, signs of acute or chronic ischemia, and presence of electrically inactive areas.

Team organization

The ELSA-Brasil relied on a trained and certified team, who was periodically re-certified, to perform study procedures and routines. Supervisors trained and certified on a central level provided training to local teams, aiming to guarantee uniformity in the standards of procedures performed in all RCs. Each clinical test adopted minimum criteria, based on international studies and included in specific ELSA-Brasil manuals, to assess whether an evaluator/interviewer is fit to perform tests. Throughout data collection, when members from the executing team needed to be replaced, new training programs/certifications were performed by supervisors. Aspects associated with selection, training and certification of ELSA-Brasil evaluators/interviewers are dealt with in specific articles of this supplement.

The team composition to perform Stage 2 was defined by study protocols, although there were changes among centers throughout data collection. Certain teams were multifunctional, i.e. trained to perform most of the expected activities. Others were trained to perform interviews or some tests exclusively. Advantages and disadvantages were observed with both forms of team organization. As expected, team members obtained a role in the job market during data collection, which led to the loss of some of these members and thus required new training programs. Centers that used multifunctional teams performed progressive training programs, enabling the immediate inclusion of new members as soon as a specific certification was achieved.

Teams were paid with scholarships from research support foundations or the *Conselho Nacional de Desenvolvimento Científico e Tecnológico* (CNPq – National Council for Scientific and Technological Development) or through paid undergraduate training programs. All members were trained to perform the procedures included in this study and certified through theoretical and practical tests, performance of several procedures under the observation of a supervisor and analysis of a minimum number of tests by the Reading Center responsible for the study procedure standardization.

In all centers, a coordinator or supervisor of clinical operations was in charge of team training, certification and re-certification; supervision of procedures; and organization of the flows of activities of all participants. Their task was to prevent a localized problem from affecting the flow of the remaining participants. Additionally, whenever a procedure was delayed and a participant was free, the coordinator adapted spaces that enabled privacy to apply the questionnaire.

Another important professional in the RC was the physician, who dealt with possible contingencies and answered the team's questions about the performance of a certain procedure, referral of participants and delivery of tests. All decisions made by the physician were based on the content and standardizations of the Manual of Clinical Operations, although their presence reduced the team's level of stress and facilitated decision-making. As an example, when one was not sure whether a participant should have the oral glucose tolerance test performed or not, or when it was necessary to refer participants with positive responses in certain items of the questionnaire of mental health.

Another complex logistic issue was the hiring of echocardiogram and ultrasonogram technicians to perform imaging tests. The reason for this is that the salary of these professionals is significantly higher than the value allowed for available scholarships. It was agreed among centers that echocardiography tests should be performed by a specialized physician, given the complexity of the procedure. In centers such as SP and RS, the measurements of intima-media thickness, hepatic parenchyma, and pre-peritoneal and abdominal wall thickness were successfully performed by technicians. In the beginning, in some centers, the echocardiogram technician performed the remaining ultrasonography procedures. However, after a brief trial period, all centers decided to use different professionals.

Another alternative used by certain centers (BA, SP and RJ ICs) was performing echocardiography and ultrasonography tests on a different day or at a different time than the main flow of tests and interviews (in the afternoon, when specialists arrived at specific times to perform tests for several participants). This strategy resulted in a higher number of absences, although it enabled the inclusion of such tests in the project. In the case of echocardiography, priority criteria were adopted, such as being aged older than 55 years and belonging to the cohort's random sample.

FINAL COMMENTS

The ELSA-Brasil is different from other ongoing studies in Brazil because it has been developed by researchers living in this country and funded on a public and national level. Therefore, this study is entirely aimed at the Brazilian reality. Due to these characteristics, the ELSA-Brasil had to develop unique strategies of implementation of procedures and training of teams with their own identity, in addition to a high standard of quality. This study is innovative as it shows that Brazil is capable of performing cohort studies without international funding or protocol. All procedures and routines in the RC have been recorded in specific manuals, accessible to other researchers who would like to develop similar projects. Aspects related to the integration between the ICs and Data Center and to the application of strategies that guarantee and control the quality of the ELSA-Brasil have been dealt with by specific articles of this supplement.

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