Chapter 1

Introduction and Visits

OVERVIEW

This is a manual of operations for the conduct of the Long Life Family Study (LLFS) which is a multi-center, research study sponsored by the National Institute on Aging, National Institutes of Health. The goal of this study is to identify the phenotypic measures associated with longevity and to determine the extent to which genetic factors play a role in exceptional survival.

The purpose of this manual is to provide guidance to insure the standardized collection of all data. While all encounters in clinical practice cannot be anticipated, we have attempted to provide a description of procedures for the most common situations, as well as for less frequent ones. Please feel free to contact study staff (see phone list at the end of this chapter) for additional information.

From time to time, we will prepare additions and amendments to this protocol. Please store these documents with the protocol and list them in the appropriate sections as designated on the table of contents.

A detailed description of each panel/survey is included. This manual is organized according to the order you will encounter the panels/surveys. We provide an introduction and overview to each form, summarizing its purpose and any special instructions about who may complete the panel/survey. We will review administration and scoring procedures especially in regard to the Spirometry, physical measures and neuropsychological assessments as well as the blood collection component of the study.

There are many details to conducting any study and we hope that this manual will provide a comprehensive source for such information.

PROTOCOL SYNOPSIS

Study Title: Long Life Family Study (LLFS)

Objective: To determine the familial aggregation and modes of transmission of Exceptional Survival (ES) within families, and to identify a large number of families across four Field Centers (Columbia University, Boston University, University of Pittsburgh, and University of Southern Denmark) that best characterizes the phenotypes associated with ES for eventual genetic linkage analysis.

Hypotheses: Exceptional Longevity (EL) and associated Exceptional Survival (ES) phenotypes are likely to be result of an interaction play between genetic and environmental factors, with genetic influences likely to play an important role. Given the likely familiality of EL and ES phenotypes, we hypothesize that there exist discernable familial patterns of transmission and aggregation of the EL and ES phenotypes. We also hypothesize that coping with age-related diseases in a manner that compresses disability towards the end of life is characteristic of EL.

Study Design: The three U.S. Field Centers will recruit the majority of the study sample from the Medicare 2004 Denominator file from The Center for Medicare and Medicaid Services (CMS). Additional study participants will be recruited from other research studies and from the general public through advertisements and mailers (i.e. brochures, newspaper and web-based ads, community presentations and radio announcements).

An initial pilot recruitment phase (Phase 1) will be designed to collect information on the sibship size of potential study participants, to gauge response rates and the proportion of people who may require additional follow-up, such as additional mailings or a follow-up telephone call. The pilot phase will consist of a brochure mailing with reply card to approximately 1,000 people per each of the three U.S. Field Centers over a 2-week period. Specific details and instructions regarding this phase can be found in the recruitment section of this document. Reply card returns will be carefully tracked and appropriate action will be taken for each response – willing participants will be interviewed by phone while those not responding or who reply by refusing to participate, will not be called. In the pilot phase of recruitment, attempts will be made to contact non-responders.

The telephone screening interview (as described in Chapter 2) consists of questions on family history of longevity. This screening information will include basic demographic information (age, race), parents' age at death, total number, vital and health status of all biological children and siblings. Data collected from this interview is needed to calculate a score utilizing the Family Longevity Scoring System (FLoSS) to rank eligible families according to their degree of clustering for longevity. With this FLOSS, the LLFS can then prioritize which families it will recruit for enrollment. Eligible and willing participants who meet the FLOSS requirements, will be asked to contact their family members who meet eligibility criteria to introduce the study and assess interest in participation. For those interested in participation, full names and contact information will be obtained and recorded on the Proband Relative Contact Information Form (TS2). These individuals will be contacted, and verbal consent will be obtained before the family members are screened as to their ability to participate. [Additional details regarding the recruitment and screening process can be obtained in Chapter 2 of the LLFS MOP]. In addition, the Proband and his/her sibling(s) will be asked to provide additional information about their parents, spouse(s), and children in order to collect the necessary information to construct a Family Pedigree. [Please refer to Chapter 14 of the LLFS MOP for additional details on the construction of the Family Pedigree.]

The pilot recruitment cycle will be repeated five times for a total of 15,000 addressees (for the 3 US Field Centers) over approximately 4 months. If the results of the pilot mailings indicate the feasibility of using the CMS address list for the recruitment of additional study participants, the study will proceed to a second recruitment phase, in which each of the three sites would contact a currently estimated 75,000 Medicare beneficiaries or until recruitment goals have been met. Among those subsequently enrolled in the LLFS, permission will be sought to obtain their Medicare and Minimum Data Set (MDS) (if the subject has been or is in nursing home) files in order to obtain medical history data.

At the end of the pilot phase, the proportion of non-responders (1) who are successfully contacted via follow-up telephone calls, and (2) non-responders whom we are unable to locate will be estimated along with the other mailing outcomes (refusals, enrolled, address unknown, etc.). Based on experience from the pilot phase, the study aims to adapt recruitment methods and eligibility criteria to improve recruitment success.

Sample Size: Each Study Center will aim to recruit approximately 200 families, each with at least two long-lived siblings, three offspring and one control (a spouse of an offspring). When available, the spouses of the long-lived siblings will also be recruited. Thus, the total number of subjects to be enrolled at each site will be approximately 1200 subjects over approximately 3 years. A pilot sample of 5 to 10 individuals will be invited to participate in a pretest of the study protocol prior to recruitment of the study sample.

Participant Selection Criteria: While the eligibility criteria will depend somewhat upon the recruitment and enrollment success in the pilot and formal recruitment phases, the basic criteria (minimum) for family eligibility will be that the family contains at least the following, all of whom must be willing to enroll in the study: a long-lived proband (age ≥80 years), at least one living sibling (age 80 or older) and at least one offspring of the proband or sibling. In addition, we will seek to enroll a spouse of one of the offspring (a

control subject). If available, the offspring's other parent will also be recruited. Once these criteria are met, a phone survey will be conducted with the potential Proband to determine whether s/he is part of an eligible family (FLoSS ≥ 8.0 based on preliminary data from our Danish collaborators). If this criterion is met, the proband will then be asked to contact potentially interested family members to introduce the study. Each subject must be able to participate in the consent process and provide informed consent, which will take place at the time of the first telephone interview. In addition, each subject must agree to donate 40 mL (approximately 2.5 tablespoons) of blood to the study. The Proband's and his/her sibling(s)' age must be validated with acceptable documentation such as a birth certificate or a combination of corroborating documents (e.g. old passport, driver's license, military record, marriage licenses, old census record, etc).

CMS will provide a recruitment list that excludes people who are enrolled in the end stage renal disease program or who are enrolled in the hospice program. Subjects will not be recruited who cannot participate in the informed consent process (e.g. they cannot indicate the purpose of the study after the study is explained to them) or who do not agree to donate blood.

Statistical Analysis: Although the LLFS is a family study, it can also be viewed as a cross sectional observational study of elderly individuals. One complication is that most standard statistical models (regression, logistic, proportional hazards, etc.) assume some kind of IID (independent identically distributed) structure (e.g. of the error terms). Family data are very much dependent--in fact, one or our primary goals is to understand the exact reasons for the dependencies (genes, common exposures, lifestyle, etc.). One approach we have successfully used incorporates sandwich estimators in the context of a mixed model, as implemented in PROC MIXED in SAS (e.g. Argyropoulos et al., 2003). A related approach we have used is the generalized estimating equations (GEE) one of PROC GENMOD (e.g. Knox et al., 2000). An alternative strategy uses the standard statistical models with a resampling technique to account for the family sampling design. A simple way to measure the degree of familiality of a disease trait (or its absence) is by the use of Family Risk Scores (FRS; Hunt et al., 1986). We compute, for each pedigree, a Z-score type statistic, that contrasts the observed number of events in that pedigree, O, with the number E_M expected from a predictive model, M that assumes disease risk is independent of family membership (e.g. the simplest model, M, might be a Kaplan-Meier curve predicting disease onset for different age/sex strata). We can calculate a different FRS scores for each disease type, and examine the correlations among these scores for different subsets of the families. Families which show familial clustering for being disease free for a number of conditions may be expected to have higher rates of EL members. We can use this approach to test the hypothesis that EL families are simply families with fewer than expected rates of all of the major causes of death by chance alone. For quantitative traits, we tend to use a ML approach as implemented in the program SEGPATH (Province et al., 2003) since it is easily generalized to complex pedigree structures, multiple phenotypes, longitudinal measures and more complex modeling. Measured covariates (age, sex, smoking history, diet, exercise, etc.) can either be estimated simultaneously in the ML family model, or the data can be pre-adjusted for any/all of these effects outside the ML model in a two stage estimation procedure (usually, the differences are negligible between the two approaches, and the two stage model is simpler). Heterogeneity among the Field Centers and/or between any sampling types can be investigated using this methodology. Segregation analysis of quantitative or qualitative phenotypes will be carried out using the unified mixed model as formulated and implemented in the computer programs SEGPATH (Province et al., 1995) and/or PAP (Hasstedt, 1993). Although there is no genotyping planned in this phase of LLFS, since the overall goal is to search for longevity genes, there will undoubtedly be future whole-genome linkage scans (to CIDR), linkage studies to selected candidate genes, and/or SNP/haplotype genotype-phenotype association analyses in subsets or all of the LLFS subjects. Washington University School of Medicine, in St. Louis, MO, has extensive experience in data management and QC as it relates to processing large amounts of microsatellite and SNP genotype data in pedigrees.

CONTENT OF IN-PERSON VISIT

Although content and order of visits will vary from participant to participant, overall there will be 2 types of visits: in-person (either home or clinic, and may include participant alone or participant with another person to assist in interviews) and telephone with participant. The optimal examination will include the following forms, questionnaires and instruments.

List of In-Person Visit Procedures (Home or Clinic) (please see below for preferred Order of Exams):

- Informed Consent
- BP/HR/WT/HT & Waist Circumference
- Socio-demographics
- Physical Function and Activity
- Cognitive Assessment
- Mood and Personality
- Medical and Personal History
- Family Structure Review
- Performance Measures
- Spirometry
- Medication Inventory
- Phlebotomy

The following forms can be left at the home or mailed for self-administration:

- Physical function and activity
- Personal history
- Medical history
- Mood and Personality

ALTERNATIVES TO IN-PERSON VISIT

Telephone Visit - For family members who cannot participate in an in-person visit, the following components can be completed by telephone in this suggested order:

- Script for Waiver of Written Informed Consent of a Participant*
- Choose one-two panels as ice-breakers (Medical History and Personal History suggested)
- Cognitive Battery: TICS, First story, Digit Span, Verbal Fluency**
- Remainder of Panels (i.e. Socio-Demographics, Physical Function, Medication Inventory) not completed before the administration of the TICS.
- 2nd Story Recall
- Mood and Personality

*Please note, if the study participant on whom you plan to complete a telephone visit agrees to a remote blood draw, a waiver of informed consent will not suffice for the blood draw. A consent form must be sent to any participant agreeing to a remote blood draw and, before the specimen collection is arranged, the FC must first receive the signed consent form in the mail indicating the s/he has fully provided his/her consent to the blood sample collection.

** Examiners are encouraged to create a 20-30 minute delay without rearranging the assessments. The delay must be a minimum of 15 minutes.

Self-Administration – If self-administration is the only option for data collection, the following components may be self-administered:

- Physical function and activity
- Personal history
- Medical history
- Mood and Personality

IMPORTANT: If either of these alternatives is chosen to an in-person examination, please refer to the Remote Blood Collection Protocol outlined in Chapter 19. Regardless of the type of visit, examiners are **strongly** encouraged to make arrangements with the participant for remote collection of a blood sample. As stated on the previous page, the study participant must sign and mail back the consent form, indicating s/he has consented to the remote blood draw BEFORE any remote blood draw collection arrangements are made. Blood CANNOT be drawn without the signed consent form.

ORDER OF THE EXAMINATION

The sequence of procedures at a home visit is not mandated and may be administered at the discretion of the individual Field Centers in an order which would best build rapport with the participant. However, if there is any possibility that the participant may be too weak to complete the exam, collect the information according to scientific importance of the data:

Physical/Cognitive Measures

- BP/HR
- Phlebotomy (or on a separate visit)
- Performance Measures
- Cognitive Tests (with exception of long-term recall)
- WT/HT & Waist Circumference (please do as many of these measures as possible during the 40 minute wait for long term recall)
- Long-term recall
- Finish any WT/HT and Waist Circumference Measures not completed during 40 minute break
- Spirometry
- CES-D and NEO

Questionnaires/Other Instruments

- Socio-demographics
- Medical History
- Medications
- Family Structure Review
- Physical Function and Activity
- Personal History

The above list was ranked keeping in mind that some questionnaires can be administered over the telephone with the participant or left with the participant to complete and return mail to the Field Center. In some situations, the participant may be unable to complete some or all of the examinations due to either physical or mental impairment. In these cases, some of the forms may be administered to a proxy.

Because the blood sample must be fasting, it may be preferable to schedule the phlebotomy as a separate visit. **If so, the blood sample should be collected within four weeks AFTER the exam.** Do not arrange for the blood sample collection before the exam is completed because informed consent is part of the exam.

EQUIPMENT

1. Copies of Informed Consent and HIPAA Medical Release
2. Pens
3. Printed data collection forms
4. Laminated response forms
5. Automated blood pressure monitor and BP cuffs in 4 sizes
6. SECA 840 or 841 digital scale
7. Tape measure
8. Handi-stat measuring triangle
9. Steel/fiberglass tape calibrated in centimeters
10. Wooden pencils with eraser
11. Wrist watch
12. Several pieces of blank paper
13. Stopwatch or time piece with a second hand
14. Sliding scale caliper SECA 207
15. Jamar Dynamometer
16. Clipboard
17. Painter's tape
18. EasyOne™ spirometer
19. Spirettes™ disposable mouthpieces
20. Disposable gloves
21. Straight-back folding chair
22. 15 foot chain

Phlebotomy Supplies:

1. BD Safety-Lok Collection Set or equivalent (required for collection of PAXgene tube) – http://bd.com/vacutainer/products/venous/
2. Vacutainer Tube Holders
3. Alcohol swab
4. Tourniquet
5. Bandage or gauze and tape
6. Gloves
7. Biohazard containment system
8. Mailing/shipping supplies (including strapping tape to seal shipping box)
9. Smelling salts, ice packs, and washcloths should be readily available for patients who become faint during the blood draw
10. Centrifuge
11. Power Pack
12. Collection kit supplied by the Central Laboratory