

Chapter 1

Introduction and Visits

OVERVIEW

This is a manual of operations for the conduct of Visit 3 of the Long Life Family Study (LLFS), a multi-center, research study sponsored by the National Institute on Aging, National Institutes of Health. The goal of this study is to identify longitudinal Healthy Aging Phenotypes 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 email list at the end of this chapter) for additional information.

From time to time, the study may change procedures. The Data Management and Coordinating Center (DMCC) 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 to have a chapter for each broad area of data collected (sociodemographic, anthropometric, physical, cognitive, etc.), with its accompanying data collection form(s). We provide an introduction and overview to each form, and summarize its purpose along with any special instructions about who may complete the form/panel/survey. The procedure for calculating longitudinal changes, and how we anticipate harmonizing our phenotypes with Framingham Heart Study (FHS) are available in the Visit 2 MOP. We will review administration and scoring procedures especially in regard to the carotid ultrasound, spirometry, physical performance 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 Longevity (EL) and Healthy Aging Phenotypes (HAPs) 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 EL for eventual genetic linkage analysis.

Aims:

1. Exceptional Longevity (EL) and associated Healthy Aging Phenotypes (HAPs) are likely to be result of an interaction between genetic and environmental factors, with genetic influences likely to play an important role. Given the likely familiarity of EL and HAPs phenotypes, we hypothesize that there exist discernable familial patterns of transmission and aggregation of the EL and HAPs.
2. We also hypothesize that coping with age-related diseases in a manner that compresses disability towards the end of life is characteristic of EL. Visit 3 will be conducted to assess healthy aging longitudinally based upon the hypothesis that specific pathways likely determine healthy aging and ultimately, exceptional

longevity (EL). If true, then families achieving EL may differ in the relative degrees of influences of these pathways. If strongly heritable, these specific HAPs will be promising candidates for targeted association. We will identify Visit 1 HAPs predictive of subsequent survival and health span. We hypothesize that disease onset and mortality will be delayed in specific LLFS families, and that some HAPs measured at Visit 1 may be predictive of these. Telephone follow-up will continue to assess rates of disease in both generations, but because of the relatively younger ages in the offspring (mean 61.2 yrs. at enrollment) incident rates will be low for some events such as dementia.

3. We will also extend characterization of cross-sectional HAPs. We hypothesize that novel cross-sectional phenotypes will show patterns of heritability and identify useful GWAS and/or linkage signals. We will also look at the cross-sectional relationships of dietary choices, to be introduced into LLFS on Visit 3, with other measures and phenotypes.

4. We will extend our identification of composite phenotypes that may be powerful predictors of healthy survival. We have constructed two indices of healthy aging based on a priori knowledge of key factors that predict mortality. The first is the Healthy Aging Index, which uses tertile scores in five organ systems and identified individuals at very low mortality risk in the Cardiovascular Health Study (CHS) study (Sanders et al., 2013). Another is the Scale of Aging Vigor (SAVE) (Newman et al., 2012) that expands the scoring of the CHS frailty scale to identify the most vigorous participants. We have also conducted factor analyses (Matteini et al., 2010) to define composite traits and have found that pulmonary and physical function are linked, while other systems tend to fall within organ systems groupings. We will examine the extent to which these track over time, and explore the possibility of additional clusters, including multiple “longitudinal” HAPs. We have also extended the Survival Exceptionality Score concept (defined in Sebastiani et al., 2009) to other disease-free survival and quantitative HAPs, as Trait Exceptionality Scores (TEs). This approach puts all phenotypes on a log-probability scale using Framingham Heart Study (FHS) as the reference population to define percentiles. Principal components of these TEs have defined clusters of phenotypes showing co-variation, and demonstrate strong linkages, suggesting there may be pleiotropic variants to be discovered through sequencing.

5. Identify subgroups of LLFS families with exceptional HAPs. We demonstrated familial clustering of many exceptional cross-sectional HAPs (Matteini et al., 2010), and will extend this approach to identify subgroups of families with exceptional “longitudinal HAPs” (above). Subgroups of families with exceptional cross-sectional/longitudinal HAPs will be selected for linkage and sequencing studies.

6. Conduct Joint LLFS vs. FHS Analyses. FHS families were not selected for longevity and have been followed for far longer than the (proposed) LLFS thirteen-year follow-up. These features provide an opportunity for our planned collaborative studies to clarify several issues by jointly analyzing both.

7. Assess degree of exceptionality of differing HAPs in LLFS families. By comparing differing LLFS family and individual change trajectories with those in the FHS community-based population, we will gain a clearer idea of the degree of exceptionality of the LLFS population with regard to these longitudinal HAPs than we would from the Visit 1 cross sectional data alone. For instance, which subjects and families remain exceptional in Visits 2 and 3, and which “regress toward the mean?” Do some show even greater exceptionality longitudinally than they did from Visit 1 and Visit 2 information? Because all LLFS families are exceptional, we have a greater gradient of comparison if we use FHS (or other study) referent controls to contrast, rather than just the internal LLFS spouse controls.

8. Estimate long-term predictive relationships of differing HAPs to longevity and other outcomes, and possible cohort or secular factors influencing these relationships. Because many phenotypes measured by LLFS were assessed in FHS many years ago in persons who were of similar ages to the LLFS’ proband generation, and who have been followed since then, we can assess long-term predictive relationships of HAPs developed in LLFS to longevity and other outcomes in FHS and eventually in LLFS. For example,

we already have begun to evaluate the Healthy Aging Index (Sanders et al., 2013) for prediction of mortality and heritability in LLFS. Utilizing FHS' three-generation structure and long follow-up, we will also explore the effects of birth cohort and secular factors on these relationships. Multivariate survival analyses will be used to capture dependence among HAPs including correlated gamma-frailty models (Yashin, et al, 1999) and a stochastic process model for evaluating dynamic regularities of aging related changes in biomarkers and their effects on HAPs and longevity (Yashin et al., 2012a). Detecting influential factors of HAPs on longevity may improve predictive value.

9. Leveraging Demography. The LLFS participants were selected from families in which members of the proband generation survived demographic processes of intense mortality selection. Such a selection can induce a population structure that may impact on longevity-related traits and confound their association with genetic and non-genetic factors (Vaupel et al., 1979; Vaupel and Yashin, 1985; Yashin et al., 2013b). LLFS investigators have shown that the information about these demographic processes can be used to better model the marginal survival distribution (Yashin et al., 1999c; 2000; 2007c; 2013b; Arbeeve et al., 2011b) and such approaches will be tested in LLFS data.

Study Design: The three U.S. Field Centers recruited the majority of the proband sample from the Medicare 2004 Denominator file from The Center for Medicare and Medicaid Services (CMS). Additional study participants were 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).

Data Collection for Visit 3 (Aim 1) – Overview of protocol. We propose a third in-person visit in the surviving LLFS cohort. Longitudinal assessment will be used to characterize trajectories (patterns of change with age) in a variety of phenotypes, to define individuals and families with exceptional survival and its subphenotypes. We will change the order of exams to begin with families that harbor the oldest individuals and families contributing to the high LOD scores. Annual follow-up will continue during and after Visit 3 based on the anniversary of the first visit. During the three years of Visit 3, if a participant has their in person visit within ± 3 months of their Visit 1 anniversary date then Visit 3 data will also replace the participant's annual follow-up visit for that year. If the in person visit is not in the ± 3 month window of their Visit 1 anniversary date then the participant will have both an in person Visit 3 and an annual follow-up for that year. We will attempt to see all surviving members of the cohort, including spouses who may be widowed, separated or divorced. Should a family member who did not enroll at baseline wish to join the study, procedures will allow for capturing both baseline and follow-up exam data. The family pedigree will not be reassessed, though any new recruits will be included in the existing pedigree file. (See chapters 2) We will also continue annual follow-up telephone interviews to assess new health events and change in functional status. Additionally, we will be actively recruiting the grandchild generation of the probands during Visit 3.

Phenotypes, clinical panels, forms and manuals of procedures. Visit 3 is planned to begin early February, 2020. We have laid the groundwork with retention activities such as newsletters, holiday cards and discussion of long term follow-up on the phone interview. We will obtain data and blood samples on all participants, repeating key aspects of the baseline in-person visit protocol (detailed below).

Long distance examinations Approximately 30% of LLFS participants enrolled at Visit 2 required staff to travel overnight by car or air. The staff examined ~15-30 individuals on a single trip lasting several days to a week. Procedures have been established for travel planning, obtaining consent by an alternate Field Center team and travel reimbursement. We will conduct repeat exams at distant locations as needed in the next phase, but will also be able to cluster these examinations more efficiently than was possible during recruitment.

Participant/proxy/study partner/LAR consent. At baseline, all participants were able to give informed consent. At Visit 3, family members with questionable capacity to provide informed consent may be enrolled via legally authorized representative consent, provided that the participant is determined to be unable to give consent but is able to express assent to be examined at the time of the examination. Additionally, proxy/study partner/LAR interviews will be obtained when there is concern about the participant's cognitive functioning, and therefore the accuracy of his or her self-report. All participants will be re-consented with new consent forms.

LLFS spouse controls and control families from the Framingham Heart Study (FHS). Married-in spouse controls will be included in the in-person examination as they were before. Married-in spouse controls of the grandchild generation will be included in the Visit 3 recruitment if they express interest. Additionally, the Framingham Heart Study will provide a large set of population control families, which should give us a wider gradient of odds ratios and effect sizes for analyses. There will be no additional examination of Framingham families, rather, we have added selected items to the LLFS examination to improve harmonization with the FHS exam and interview.

Forms and procedures. We will use the existing forms from Visit 1 and Visit 2 for those measures to be repeated. Questions will not be repeated where the answers would not change (e.g. birth date, years of education, etc.). Manuals of procedures (MOP) have been edited to reflect changes. Centralized training (built into the budget) will be organized and led by the project coordinators who conducted the baseline in-person and long distance visits, and will include interviews, all physical measures including spirometry and processing and shipping of blood specimens. Research assistants will be re-certified on all measures, with separate training sessions at the University of Pittsburgh for Carotid Ultrasound and Columbia University for cognitive testing. Training for physical performance measures will be conducted at both the University of Pittsburgh and Columbia University trainings, and we will train on the blood collection and processing and interview panels/surveys via online.

Examination/phenotypes and exposures. The protocol for the examination of LLFS participants was designed to be entirely portable to maximize complete data collection. All family members regardless of age will undergo as much of the same assessment as possible. We have developed study partner/proxy/LAR interview formats for individuals who may have become too ill to participate in part or all of the in-person examination. We are enhancing this examination by adding a dietary assessment, a measure of aerobic capacity (one-minute sit to stand) and a short neuromotor exam (see below). Selected measures, summarized in **Table 1**, were designed to assess aspects of exceptional longevity that 1) have significant heritability, 2) are related to longevity and active life expectancy, and 3) can be assessed in the home setting. For the Visit 3 examination, we will: repeat measures that are expected to change over time due to aging or to illness, update medical history and medications and repeat a blood draw. All interviews and examinations will be conducted via a standardized protocol by centrally trained and certified examiners, including the examiners from Denmark. The LLFS exceptional longevity phenotypes were organized into 3 major areas: 1) longevity, 2) physical and cognitive disability-free survival, and 3) disease-free survival. Within these major areas are several sub-phenotypes that were ascertained via multiple measures and either combined into clinically meaningful definitions of clinical and subclinical disease or examined as continuous traits.

Table 1. LLFS exceptional survival phenotypes and environmental exposure measures in Visit 1 and 2, the annual follow-up and the proposed Visit 3.				
LLFS Core Phenotypes	Interview; Physical Exam; Biospecimen repository performed in Visit 1 and Visit 2.	Annual Phone Follow-up. "Expanded" f/up performed each	Visit 3 Proposal	Measured in Framingham Heart Study
Age	Validated age or age at death, Family history of Longevity, Update vital status	Update vital status (Annual & Expanded)	Update vital status	age of death
Disability-free Survival				
Cognitive function	Medical History; Clinical Dementia Rating Scale, MMSE, Logical Memory – Immediate and Delayed, Digit Span Forward/Backward, Animal Fluency, Trail Making Test (A and B), Letter Fluency, Category Fluency, Digit Symbol, Hopkins Verbal Learning Test, Digital clock drawing (use of digital pen and digital voice recording)	Telephone Interview for Cognitive Status (TICS) and Dementia Questionnaire (DQ) (Expanded)	Same as V2, adding neuromotor test	MMSE
Physical function	IADL's, ADL's; Grip strength, gait speed, balance, chair stands, heart rate, Pittsburgh Fatigability Scale, Health Habits	ADLs (Annual & Expanded)	Same as visit 2, add One minute sit to stand	Grip, Gait speed
Disease-free Survival				
CVD	Medical history; Blood pressure (BP), ankle-brachial index (ABI) (ABI was performed in Visit 2 only for new enrollees), see labs below, Carotid Ultrasound	Medical History Update (Expanded)	V2 with ABI added back	Medical history, BP, ABI, carotid
Cancer	Medical history	Update (Expanded)	Update	similar
Lung Disease	Medical History; FEV1, FEV6 with portable spirometer	Medical History Update (Expanded)	Update	Medical history, FEV1
Diabetes	Medical history, medication use; fasting glucose and insulin, weight, waist circumference, height, knee height	Medical history, medication use Update (Expanded)	Update	Medical history, Weight, height, waist
Renal disease	Medical history; see labs below	Update (Expanded)	Update	Medical history,
Dementia	Same as for cognitive function (above)	TICS and DQ (Expanded)	Update	Medical history,
Depression/personality	CES-D, Neuroticism, Extraversion, Openness (NEO) 2 factors only.	Full 5-Factor NEO (Expanded once)	CES-D, NEO for new participants	
Environmental/Behavioral Exposures				
Social	Place of birth, education	Not needed	Update education	similar
Habits	Smoking, alcohol consumption, physical activity (current and historical)	Physical activity and Sleep habits (One follow-up) time	Update; sleep habits for new participants	similar
Health care	Utilization, classes of medications	Update (Annual and Expanded)	Update	similar
Nutrition	Weight history	Not collected	Update; add FFQ	similar
Reproduction	Parity, age of last pregnancy, age at menopause, hormone replacement therapy	Medication Update (Expanded)	Update if age<65	Age at menopause
Laboratory Studies				
Genetics	Leukocytes or buccal cells for DNA, future lymphoblastoid cell lines. Telomere studies.	None	Repeated	Genome-wide genotype data
Other	Fasting glucose, insulin, HbA1C, creatinine, cystatin C, total/HDL/LDL cholesterol, hemoglobin, leukocyte and platelet counts. Iron, TIBC, ferritin, IL6, heat shock protein 60 and 70. 10 aliquots serum + plasma for future analysis.	None	See below* (next page)	Fasting glucose, insulin, lipids

*Due to budget limitations, we are limiting the number of currently planned biochemical analyses of our specimens, so that we may prioritize decisions on which additional analytes to measure, pending consideration of other phenotype results and potential availability of additional funds in the future. Analyses currently planned to be performed for this second exam are fasting glucose, hemoglobin, HDL/LDL/Total Cholesterol, and telomere length.

Sample Size: Each Study Center will invite their Visit 1 and 2 participants who are still alive and have not withdrawn to participate in a third in home or clinic visit during a telephone call. All sites will also recruit the grandchild generation of the probands (estimate 826 grandchildren across all four sites). As of October 4, 2018, this is a sample size of 2,904 overall, 746 in Boston, 830 in Denmark, 640 in New York, and 688 in Pittsburgh. Due to attrition, particularly mortality, we estimate a final sample size for Visit 3, including grandchildren, of 3,149. Additionally, to promote good family relations, any relative who did not participate in Visit 1 or 2 but is interested in participating in Visit 3 will be accepted.

Participant Selection Criteria: All Visit 3 participants have to satisfy one of three conditions: 1) participated in Visit 1 or 2; 2) a family member of a Visit 1 or 2 participant who is interested in participating in LLFS; or 3) a grandchild of the proband generation (or grandchild spouse).

CONTENT OF VISITS

Although content and order of visits will vary from participant to participant, overall there will be 4 types of visits, listed in order of preferred offering to participant:

1. In-person (either home or clinic, and may include participant alone or participant with another person to assist in interviews); including a split visit
2. Telephone with participant (followed by biological specimen collection, either remote blood draw or mouthwash (saliva collection kit), if the participant agrees)
3. Telephone interview with no biological specimen
4. Refuse Visit 3 (in person, telephone, or study partner/proxy/LAR) but continue with annual follow-up.

Regardless of the visit type, a set of self-administered questionnaires can be mailed to participants (or their study partners/proxy/LAR) in advance of the in person visit. The optimal examination includes the forms, questionnaires and instruments described below.

1. FORMS THAT CAN BE MAILED PRIOR TO IN-PERSON (OR TELEPHONE) VISIT

Certain forms can be completed by the participant (or a study partner/proxy/LAR) prior to the in-person assessment. Guidelines for determining whether forms should be completed by the participant or the study partner/proxy/LAR are outlined in Chapter 4 in the section titled, “Procedures for Study Partner/Proxy/LAR Interviews”.

The following forms can be sent from the field center, along with the appropriate cover letter (Chapter 5, Appendix 1), 2 weeks prior to the scheduled visit, with an expected arrival at the participants home 1 week prior to the visit. The cover letter will emphasize that participants (or their study partners/proxy) should complete these forms on their own, without help from anyone else.

- Socio-demographics – Panel 2
- Medical History – Panel 5
- Physical Function and Activity – Panel 3
- IADLs - Panel 20
- Health Habits – Panel 19 (new participants only)
- Personal History – Panel 4
- Dietary food frequency questionnaire – Panel 22

If the visit is telephone plus biologic specimen collection, or telephone only, the above forms will be administered to the participant over the telephone.

2. ORDER OF THE IN-PERSON EXAMINATION

The sequence of procedures at an in person 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.

Physical/Cognitive Measures

- BP/HR
- Phlebotomy (or on a separate visit)
- Performance Measures including sit to stand test
- 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
- Carotid ultrasound
- Ankle-brachial index
- Neuro-motor Exam
- Finish any WT/HT and Waist Circumference Measures not completed during 40 minute break, including additional measures for new enrollees
- Spirometry
- CDR and DQ

Questionnaires/Other Instruments – Interviewer Administered and Review Self-administered

- Medical History (interviewer administer and review)
- Medications (interviewer administer)
- CDR and DQ (interviewer administer, if applicable)
- CES-D (interviewer administer at the very end of the visit)
- Socio-demographics (review)
- Physical Function and Activity (review)
- IADL's (review)
- Personal History (review)
- Dietary Food Frequency Questionnaire (review)
- NEO (interviewer administer - new participants only)
- Health Habits (review - new participants only)

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 study partner/proxy. If the in person visit is a split visit, the order outlined above should also be followed.

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.

3. TELEPHONE VISIT - For family members who cannot participate in an in-person visit, the panels

that are typically mailed (see section 1 above) and returned by the participant. The following components that are administered in-person can also be administered over the telephone by the examiner in this suggested order:

- Script for Waiver of Written Informed Consent of a Participant*
- Choose one panel as an ice-breaker (Personal History suggested)
- Cognitive Battery: TICS, HVLIT Immediate, Logical Memory 1A, Number Span Test, Category Fluency – Animals, Letter Fluency**
- Remainder of Panels (i.e. Socio-Demographics, Medical History, Physical Function, Medication Inventory, FFQ, IADL form not completed before the administration of the TICS, etc (if forms were not mailed in advance).
- HVLIT Delay**, Logical Memory IIA***
- CES-D (done at the very end of the call)
- NEO (new participants only)
- Food frequency questionnaire
- CDR
- DQ (if needed)

*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. In lieu of a blood draw, we can also use a saliva collection kit to obtain DNA if the telephone visit participant consents.

**Do not administer unless at least 20 minutes has passed since the completion of the immediate condition of the test. If necessary, administer non-cognitive measures to fill the time and return to the delay condition after you have completed intervening measure(s) and 20 minutes has passed.

*** Do not administer unless at least 30 minutes have passed since the completion of the immediate condition of the test. If necessary, administer following tests to fill the time interval and return to the delay condition after you have completed intervening task(s) and 30 minutes have passed.

IMPORTANT: If either of these alternatives is chosen to an in-person examination, please refer to the Remote Blood Collection Protocol outlined in Chapter 7. 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. If a blood draw is unsuccessful, DNA can still be obtained using the saliva collection kit.

4. Refuse Visit 3 (in person, telephone, or study partner/proxy/LAR) but allow to continue with Annual Follow-Up

It is possible that participants may refuse the in person visit but are willing to continue with the annual follow-up. In this case, the usual annual follow-up forms will be administered at a time determined based on the Visit 1 anniversary date.

EQUIPMENT

(not exhaustive list, please refer to individual MOP chapters for needed 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 or 803 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. Portable ultrasound machine (GE Logiq e)
23. Electronic Pen and accompanying paper
24. Digital voice recorder

Phlebotomy Supplies:

(consult MOP chapter 7 for complete listing)

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

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