Long Life Family Study Mortality Investigation

Background and Overview

In April 2014, the LLFS Steering Committee established the Morbidity and Mortality Committee as a new committee. The M and M committee was charged to develop the quality of the morbidity and mortality data in LLFS and to harmonize these outcomes with the Framingham Heart Study (FHS) and other cohort studies to replicate findings. The M and M committee reviewed the procedures in several studies including FHS and Health, Aging, and Body Composition Study and recommended several protocol changes that will increase the opportunities to review health outcome data.

It was determined that the study needed to establish the date, location and cause of death for all decedents. To confirm feasibility, a pilot was proposed at the University of Pittsburgh Field Site. While this was underway, the informed consent was modified to include the collection of medical records during the study. Also, three questionnaires were revised to obtain more detailed information about health events and allow event adjudication to occur at a future date, should resources be identified. These questionnaires were the Panel 5 medical history update, the Panel 16 annual telephone contact, and the Panel 18 Decedent Proxy Interview (DPI) which included a narrative from the proxy of the symptoms, sequence and details of the death.

The Steering Committee discussed the success of the pilot project at the February 2017 meeting. It was agreed that understanding cause of death in a study of exceptional longevity was important to the study, and to pursue the classification with the other US sites. All investigators (Study PIs) agreed to initiate the same type of investigation at the Boston and New York centers (collection of death certificates and medical records). Sites also agreed to complete a modified Decedent Proxy Interview with the families of the subjects dying prior to exam 2 to supplement information on diagnoses, symptoms, treatment, and circumstances of death which would add important information lacking in the pilot cases. In addition to developing the modified DPI, a death certificate abstraction form was created. A National Death Index search will validate deaths, and eventually provide a more complete list of decedents. Adjudication packets will include the death certificate, medical records from the most recent hospitalization or other treating facility, and the narrative interview from the family. The DPI will provide critical information necessary to adjudicate the deaths outside health care facilities (ie.at home) because a recent medical record will not be available, and a narrative will provide important details about the sequence of events. In addition, 30% of records requested in the pilot were unobtainable, and some records provide information that is insufficient to determine cause of death.

The M and M committee developed and piloted the **LLFS Underlying Cause of Death Adjudication Form** to have a standardized form to collect information on the cause of death on each participant. Forms from the Framingham Heart Study and Health Aging and Body Composition Study were reviewed. The form includes location of death, underlying cause, immediate cause, contributing cause, and conditions present at death. In addition, supporting documents present to the review panel were documented. The M and M committee empaneled an Adjudication Committee consisting of physician investigators from each site. The form was pilot tested using deaths from the Pittsburgh site and refined at a face-to-face adjudication committee meeting at the February 2017 Steering Committee meeting.

Procedures for Mortality Investigation

Identifying LLFS deaths at each site - The National Death Index (NDI) will be used to validate known deaths and identify deaths in lost-to-follow up subjects. The NDI application was submitted by the coordinating center (CC) in collaboration with the field centers and approved. The CC will submit lists of known deaths with identifiers to NDI, providing matches at varying levels of confidence. Spreadsheets of the NDI data of decedents including the identifiers will be distributed to the 3 US field centers with sufficient information to confirm the matches. The first submission to NDI was submitted in the spring 2017 which included deaths-only through 2015, because NDI data are approximately 2 years behind. Subsequent submissions will include lost-to-follow up subjects as well as all remaining subjects not identified in previous NDI searches. Subjects with contact by phone within the last year will not be included because of the lag time in NDI updates.

Obtaining death certificates with cause of death – When the NDI data were received, it was confirmed that location of death was not included, and therefore it would be necessary to obtain death certificates. Once field centers validate the NDI deaths matched to the LLFS participants, death certificates with cause of death will be obtained. Families may be asked to provide photocopies of death certificates. Death certificate requests standardly require full name, date of death, date of birth, county of death, and social security number, if available. Certificates range in price but average $10-$30 each, and non-certified copies are sufficient. Some states require applications for research while others are open access. Information to obtain death certificates from individual states can be found at https://www.cdc.gov/nchs/w2w/index.htm , or can be located by searching the web for 'vital records' in any specified state.

Obtaining medical records from health care facilities (acute care hospital, nursing home, and hospice) - Based on the location of death listed on the death certificate, field centers will request copies of 1) discharge/death summary, and 2) admission history and physical exam, from the medical records department of the facility where the subjects died, or from the hospitalization prior to death if subjects died at home. Since an authorization to release medical records to the study was not obtained from subjects during the early period prior to exam 2, the HIPAA regulations for the "Partial Waiver for Deceased Subjects" may be used (see appendix). This permits providers/facilities to release medical records on research subjects if the research is dependent on those records to complete the scope of work. A copy of the field center IRB approval letter for study should accompany the request along with specifying the name and date of birth of the subject, the date of admission/discharge/death, and the two documents being requested (see appendix). For medical records requested for subjects signing an authorization to release records to the study (at the time of exam 2), the release should be included with the request for records. A copy of the death certificate should also be included to confirm the subject is deceased, and therefore the request falls under the 'Partial Waiver' criteria. Each field center will develop a system for tracking requested and received records, and pursue those that are not completed. This can be done by adding a column(s) to the spreadsheets indicating dates requests were made and responses by facilities.

Some field centers included in their informed consent an option for subjects to agree to allow the study access to medical records. For those participants opting out/refusing to allow LLFS access to medical records, there should be no attempt to collect medical records from a health care facility. Death certificates may be obtained and, if a willing proxy is available, supplemental DPI information may be collected with a narrative.

Decedent Proxy Interview – The Decedent Proxy Interview (DPI) has been modified to include more details about hospitalizations prior to death, and an open field to collect a narrative to capture information surrounding the death from the family member's perspective. The expanded DPI was implemented at the start of visit 2. Cognitive decline and dementia are often not well documented in hospital records, and this subjective detail will supplement the clinical information especially for deaths at home. Each site will determine if their IRBs should review the process of recontacting families if an earlier version of the DPI was collected. A merged version of the old and expanded DPI questions will be produced for deaths pre-exam 2, while the post exam 2 deaths have already incorporated the expanded questions in the DPI. For pre-exam 2 recalls, sites should prioritize the calls based on the location of death as follows:

1. Deaths at home
2. Deaths for which location of death was not determined (ex. death certificate could not be obtained)
3. Deaths in nursing homes and hospices
4. Deaths in acute care hospitals

For deaths at home or where location of death could not be determined (ex. no death certificate), information from the DPI should be used to obtain a medical record, as described in the previous step.

Preparing adjudication packets – Field centers will create a packet for each decedent including:

1. Completed cover page indicating ID, acrostic, date of death, and checklist of attachments.
2. Death certificate with cause of death
3. Medical record from last treatment facility
4. DPI including narrative interview

The 'comment' field on the cover page may be used to provide additional information, explain missing information, or anything useful to the adjudicators. Field centers should scan each packet as ".pdf", and label every page with study ID and acrostic. The file name should be the same as the label on each page using the ID and acrostic (ex. 312345679_JONEP). Identifiers must be redacted using Adobe Acrobat Pro or other similar software, and uploaded to LLFS secured server. Identifiers include names of patient and family, personal phone numbers, addresses, emails, day and month of birth, identifying numbers such as social security, insurance and medical record numbers. Do not redact subject age, hospital or physician names, and dates of admission, discharge, tests or treatments, as these are relevant to adjudication of the events. For death certificates, location of death should not be redacted if it includes the name of a medical facility, but it must be redacted if the death was at a residence and the address of the home is in this field. Detailed information on redaction may be found at: https://privacyruleandresearch.nih.gov/pr_08.asp

Procedures for uploading packets:

Any persons wishing to upload the files should contact the DMCC Project Manager, LeAnne Kniepkamp (l.kniepkamp@wustl.edu) with the name and email address of the new user. LeAnne will then add the person's email to WUSTL BOX. The requesting person should then receive an invitation to join WUSTL BOX. If you do not already have a BOX account, you will be prompted to create one. You will need to log completely out and then log in again with your new credentials

To upload a packet, log into BOX.com with the credentials you have created. Open the folder ”LLFS M&M Uploaded Records. Click on “Upload” in the upper right hand corner. Choose “file”, then you may drag and drop your filed from your local folder to the BOX folder. Box saves automatically. Once you are done with your uploads you may close the BOX website. Please email LeAnne (l.kniepkamp@wustl.edu) verifying your upload. Please include the IDs for the cases you have uploaded so that she may verify they are accessible.

Once packet upload has been verified, LeAnne will send credentials to the adjudicators and their assistants the day prior to our call to access the specific BOX folder for each meeting

BOX Organization- Uploaded records to be adjudicated will be stored in the folder “LLFS M&M Uploaded Records”. Once a meeting has been scheduled and the number of records to be adjudicated determined, LeAnne will sort the records by most recent death, She will then collate the records to be adjudicated into a folder dated with the Adjudication date. The dated adjudication folder will have all of the records as well as the agenda and specific folders for each physician where their folders will be separated by primary and secondary records.

Adjudication In Person – LeAnne will send a link to the BOX folder where records to be adjudicated can be found. This link should be password protected for HIPPA purposes. This link will be sent to both the Physician and their assistant. The assistant should prefill the adjudication forms for the physicians (ID, acrostic, DOD, Location of Death, Support Documents, Adjudicator ID [physicians initials] and date of review, so that as the physicians adjudicate, they need only fill out the table. Physicians should do their adjudication prior to the meeting and bring their completed adjudication forms to the meeting. As the physicians adjudicate, the primary doctor will take notes on their adjudication form. Each primary doctor will give the completed forms to their assistant after the meeting. The Assistant will then scan the completed adjudication forms as pdf and upload BOX in the folder designated for that dated meeting. The Ras will enter the adjudicated data in REDCap under “Adjudication”. Assistants should have access to all field sites data so that they may enter data for any participant regardless of originating Field Center.

Adjudication via Zoom- LeAnne will send a link to the BOX folder where records to be adjudicated can be found. This link should be password protected for HIPPA purposes. This link will be sent to both the Physician and their assistant. The assistant should prefill the adjudication forms for the physicians (ID, acrostic, DOD, Location of Death, Support Documents, Adjudicator ID [physicians initials] and date of review, so that as the physicians adjudicate, they need only fill out the table. Physicians should complete their adjudication prior to the zoom and have their completed adjudication forms ready for the zoom. As the physicians adjudicate, the primary doctor will take notes on their adjudication form. Each primary doctor will give the completed forms to their assistant after the meeting. The Assistant will then scan the completed adjudication forms as pdf and upload BOX in the folder designated for that dated meeting. The Assistant will then enter the adjudicated data in REDCap under “Adjudication”. Assistants should have access to all field sites data so that they may enter data for any participant regardless of originating Field Center.

1. Myocardial Infarction Recent or acute myocardial infarction (MI) is designated when there were at least two of three findings: 1) symptoms indicative of ischemia; 2) changes in

biomarkers of myocardial necrosis; 3) serial changes in the electrocardiograms indicating the evolution of an infarction, including the loss of initial QRS potentials (that is, development of “pathologic” Qwaves of 0.04 second duration or greater).

An old or remote myocardial infarction is considered to be present when the electrocardiogram shows a stable pattern including a pathologic Q-wave of 0.04 second or greater or loss of initial QRS potential R-wave in those leads in which this would not be expected to occur. Also, an interim unrecognized MI is indicated when changes from a previous tracing show development of loss of R-wave potential or appearance of pathologic Q-waves not otherwise explained, in persons in whom neither the patient nor his physician considered the possibility of MI. If the patient was asymptomatic for chest pain or upper abdominal pain during the interval at which the unrecognized MI occurred, the event is classified as silent, unrecognized. More weight is given to this finding if a T-wave abnormality is also associated with Q-wave abnormality. An autopsy report showing an acute, new, or recent infarction of the myocardium is accepted as evidence of an incident myocardial infarction. Because it is not possible to date an old infarction found on autopsy, such evidence is not used in the clinical diagnosis of a new event, unless there was an interim clinical event suspected of being an infarction.

Heart Disease Death Death from coronary heart disease is diagnosed as either sudden or nonsudden. For a detailed description of these diagnoses, see 4 below.

2 Stroke The diagnosis of cerebrovascular disease is based on the occurrence of a clinically evident stroke documented by clinical records reviewed by at least two neurologists. Stroke is defined as the sudden or rapid onset of a focal neurologic deficit persisting for greater than 24 hours. Stroke is further categorized into infarction or hemorrhage.

Hemorrhagic Stroke The diagnosis of subarachnoid hemorrhage is based on a history suggestive of this process such as abrupt onset headache, with or without change in the level of consciousness, and signs of meningeal irritation with or without other localizing neurological deficits. Intracerebral hemorrhage is diagnosed clinically by the occurrence of abrupt focal neurologic deficit, often with altered level of consciousness and symptoms of increased intracranial pressure. Hemorrhages are confirmed by imaging.

Ischemic Stroke A diagnosis of cerebral embolism is made when an established source for embolus including atrial fibrillation, rheumatic heart disease with mitral stenosis, recent myocardial infarction, bacterial endocarditis or other known source is determined. A clinical course consistent with embolic infarction or evidence of other systemic embolism may be present. Symptoms are usually rapid with maximal severity at onset. Antherothrombotic brain infarction is defined as the sudden onset of a focal neurologic deficit lasting longer than 24 hours, in the absence of: 1) known source of embolism (atrial fibrillation, rheumatic heart disease with mitral stenosis, myocardial infarction within preceding six months, bacterial endocarditis); 2) intracranial hemorrhage (intracerebral or subarachnoid); 3) known hypercoagulable states; 4) other disease processes causing focal neurologic deficits (brain tumor, subdural hematoma, hypoglycemia). Confirmatory imaging supports the diagnosis. Silent stroke may be documented at the stroke review sessions when a stroke event is determined and an incidental infarct is seen on brain imaging in the absence of a reported clinical event.

Stroke Death Death attributed to stroke is designated when a documented focal neurologic deficit of greater than 24 hours duration preceded death and was responsible for the fatality.

3. Congestive heart failure A definite diagnosis of congestive heart failure requires that a minimum of two major or one major and two minor criteria be present concurrently. The presence of other conditions capable of producing the symptoms and signs are considered in evaluating the findings.

Major Criteria:
1) Paroxysmal nocturnal dyspnea or orthopnea;
2) Distended neck veins (in other than the supine position);
3) Rales;
4) Increasing heart size by x-ray;
5) Acute pulmonary edema on chest x-ray;
6) Ventricular S(3) gallop;
7) Increased venous pressure > 16 cm H20;
8) Hepatojugular reflux;
9) Pulmonary edema, visceral congestion, cardiomegaly shown on autopsy;
10) Weight loss on CHF Rx: 10 lbs./5days.

Minor Criteria:
1) Bilateral ankle edema;
2) Night cough;
3) Dyspnea on ordinary exertion;
4) Hepatomegaly;
5) Pleural effusion by x-ray;
6) Decrease in vital capacity by one-third from maximum record;
7) Tachycardia (120 beats per minute or more);
8) Pulmonary vascular engorgement on chest x-ray.

4 Coronary heart disease death Death from coronary heart disease is diagnosed as either sudden or nonsudden.

Nonsudden death from CHD If the terminal episode lasted longer than one hour, if the available information implies that the cause of death was probably CHD, and if no other cause can be ascribed, this is called nonsudden death from CHD. In making this diagnosis, the review panel uses prior clinical information as well as information concerning the final illness.

Sudden death from CHD If a subject, apparently well, was observed to have died within a few minutes (operationally documented as under one hour) from onset of symptoms and if the cause of death cannot reasonably be attributed on the basis of the full clinical information and the information concerning death to some potentially lethal disease other than coronary heart disease, this is called sudden death and is attributed to coronary heart disease.

5. Cardiovascular disease death This cause of death is designated when any disease of the heart or blood vessels is considered responsible.

All-cause mortality The fact of death is supported by a death certificate. Additional information is obtained from records supplied by hospital, nursing home, attending physician, pathologist, medical examiner, or family. The Framingham Endpoint Review Committee comprised of three senior investigators reviews all evidence to arrive at the cause of death.
Causes of death include: Coronary heart disease, stroke, cancer, other causes, cause unknown.

Appendix A

Partial Waiver of Consent

Reference: http://www.cga.ct.gov/2013/rpt/2013-R-0124.htm

Permitted Disclosures

....The privacy rule also permits disclosure of protected health information without the patient's authorization, subject to various conditions and limitations, for 12 national priority purposes — categories where disclosure is permitted due to the important uses for such information in contexts outside of health care. Such categories include, among other things, (1) disclosures required by law, (2) public health activities, (3) health oversight activities, (4) judicial and administrative proceedings, (5) law enforcement purposes, **(6) research**, and (7) serious threats to health or safety (45 C.F.R. § 164.512).

...The privacy rule establishes various conditions for researchers who seek protected health information. For example, if someone requests a deceased person's protected health information for research purposes without the personal representative's authorization, the researcher must provide the covered entity with representations that the (1) use or disclosure being sought is solely for research on the protected health information of decedents and (2) information being sought is necessary for the research. The researcher must also provide documentation of the person's death if the covered entity requests it (45 C.F.R. § 164.512(i)(1)(iii)). HHS's website has more information on requirements for researchers: http://www.hhs.gov/ocr/privacy/hipaa/understanding/coveredentities/research.html.

Below is the federal law that is referenced in the highlighted paragraph (which details the legality of using an IRB-approved waiver of consent for release of PHI of decedents for research purposes):
http://www.law.cornell.edu/cfr/text/45/164.512

Title 45, CFR 46.116(d):
"...(d) An IRB may approve a consent procedure which does not include, or which alters, some or all of the elements of informed consent set forth in this section, or waive the requirements to obtain informed consent provided the IRB finds and documents that:
(1) The research involves no more than minimal risk to the subjects;
(2) The waiver or alteration will not adversely affect the rights and welfare of the subjects;
(3) The research could not practicably be carried out without the waiver or alteration; and
(4) Whenever appropriate, the subjects will be provided with additional pertinent information after participation."

LLFS Death Packet Cover Page

Study ID: __ __ __ __ __ __ __ __ Acrostic: __ __ __ __ __

Date of Death: __ __ / __ __ / __ __ __ __

Submitted by: _____ Upload Date: __ __ / __ __ / __ __ __ __

All pages should include ID number and acrostic, and should be redacted/sterilized for all identifiers (names of subject and family members, home addresses and phone numbers, social security numbers, month and day of birth, medical record and insurance numbers, etc.)

Attachments:

1. Death Certificate with cause of death:

   ☐ Attached

   ☐ Not attached – reason:

2. Medical record (last hospitalization including discharge/death summary and admitting history & physical exam. Final progress notes may be substituted if there is no summary. May also include outpatient clinical notes if detailed enough to reflect health status proximate to death.):

   ☐ Attached

   ☐ Not attached – reason:

3. DPI with narrative describing circumstances, symptoms, medical issues resulting in death (please type if illegible):

   ☐ Attached

   ☐ Not attached – reason:

Comments:

LLFS Death Certificate Abstraction Form

ID: _ _ _ _ _ _ _ _ _ _ _ _ Acrostic: _ _ _ _ _ _

Date of Death: _ _ / _ _ / _ _ _ _

Was the Death Certificate with cause of death obtained? ☐YES ☐NO

If No, provide reason (s): ☐State/county would not release

☐Family refused

☐ Other: _____(END)

State Where Death occurred (Dropdown with 50 states and 'other'):

Location of Death (categorical): ☐Inpatient Hospital ☐Emergency Room

☐DOA ☐ NH/SNF/Rehab ☐ Inpatient Hospice ☐Residence

☐Other _____

Autopsy: ☐YES ☐NO

Transcribe causes of death on certificate (do not abbreviate):

Part I.

1. _____
2. _____
3. _____
4. _____

Part II (Other significant conditions):

_____

_____

LLFS Underlying Cause of Death Adjudication Form

Participant Study ID: _____ Participant Acrostic: _____ Death Certificate Date of Death: ___ ___ / ___ ___ / ___ ___ ___ ___
D D M M Y Y Y Y

1. *Location* of death (choose only 1):
☐ [1] Hospital inpatient ☐ [2] Emergency room ☐ [3] NH, SNF, or ECF ☐ [4] Inpatient hospice ☐ [5] Residence ☐ [8] Other, Specify: _____

	2. *Underlying* Cause of Death ***(choose only 1)***	3. *Immediate* Cause of Death ***(choose only 1)***	4. Conditions *Contributing* to Death ***(mark all that apply)***	5. Medical History ***(mark all that apply)***
1. Coronary Heart Disease				
a. Sudden				
b. Non-sudden				
2. Stroke				
a. Infarct				
b. Hemorrhage				
c. Unknown				
3. Other CVD				
a. Atherosclerotic disease other than coronary or cerebrovascular disease (PAD, AAA, etc)				
a1. Specify				
b. Other CVD disease, not codable as 1, 2, or 3a (valvular heart disease, pulmonary embolism, endocarditis)				
b1. Specify				
4. Cancer				
a. Primary site/location				
b. Cell type				
5. COPD				
6. Dementia				
7. Parkinson's Disease				
8. GI bleed				
9. Liver failure				
10. Renal failure				
11. Sepsis or infection				
a. Pneumonia				
b. UTI				
c. Cellulitis				
d. Line Infection				
e. Other				
12. Diabetes	N/A	N/A		
13. Other				
14. Unknown				

6. Support documents used in adjudication (mark all that apply):
☐ [1] Death Certificate ☐ [2] Medical Record, hospital ☐ [3] Medical record, nursing home/SNF ☐ [4] Medical record, hospice
☐ [5] Narrative with Proxy ☐ [6] Obituary ☐ [7] NDI ☐ [8] Other, Specify: _____

Adjudicator ID: _____ Date of Review: _____
DD/MM/YYYY