Entrusted: The 60-Year Dialogue of Informed Consent

Presenters:
Greta Lee Splansky, Maggie Kelly-Hayes and Sue Blease

Framingham Heart Study
BUMC IRB
Protocol FHS-H-22762

January 16, 2008
Learning Objectives

• Describe evolution of consent process.

• Demonstrate the role of supplemental materials to inform in complex studies.

• Outline how we ensure proper use of data by tracking individual participants' consent choices.
Listening to the heartbeat of America

Framingham Heart Study's impact on a nation's lifestyle
Why Framingham

- In 1948, NIH in infancy
- 44% of deaths in US due to cardiovascular disease
- Primary focus of epidemiological studies was infectious disease
- Framingham participated in 1917 TB study
- New opportunity to study unbiased stable population sample over time
Noteworthy contributions from the FHS

- Risk factor determination
- Temporal trends in health conditions
- Lifetime risk of disease
Overview of the Framingham Heart Study

• Population-Based Observational Study
• Longitudinal Design
• Clinic and Off-site Exams
• 2 to 6 Year Exam Cycles
• Repeated and Novel Measures
• Six Cohorts
Framingham Heart Study
Intergeneration cohorts

Original cohort
N = 5,209 men and women (ages 28-62)
1644 spouse pairs, 596 extended families

Offspring study
N = 5,124 men & women (ages 5-70)
1576 spouse pairs, 3514 biological offspring

Third Generation study:
N = 4,095 men and women
OVERVIEW OF FRAMINGHAM COHORTS

Original Cohort
(n=5209)
Began in 1948

Offspring Study
(n=5124)
Began in 1971

New Offspring Spouses (NOS)
(n=103)
Began in 2002

Third Generation
(n=4095)
Began in 2002

2 Omni Cohorts
(n=917)
Began in 1994
Consent History at FHS

• **1948-1968** FHS under direct auspices of US Public Health Service, NIH, NHLBI with informal undocumented informed consent demonstrated by voluntary attendance at a series of examinations over 20 years.

• **1971-** FHS under auspices of BUMC, formal consent begins with 2 sentence document. Text is revised at every exam cycle and often mid-cycle. Over time, more details of the research are specified in consent forms several pages long.

• **2001-** Every FHS participant folder is reviewed to note all versions of consent forms signed by each individual participant starting in 1971.
CONSENT FOR INTERVIEW AND EXAMINATION

I have been fully informed of the nature of this study which includes a medical history, physical examination, blood tests and electrocardiogram and give my consent to be examined. I also authorize the Framingham study staff to secure pertinent medical information from my family, physicians, and/or hospital records for the purposes of this study.

Date_________________  Name______________________________

NIH – 1635-3 9-71  OMB 66-R1236 Expires Dec. 31, 1974
NAME:__________________

Voluntary Participation. You are free to withdraw your consent and to discontinue participation for any of the procedures in the Framingham Study at any time. You may choose to withdraw your samples at a future date and your sample will be destroyed at that time.

Please answer the following questions:

YES  NO  I agree to participate in the Physical Examination and Genetic Studies of factors contributing to heart, lung and blood diseases, stroke, dementia, osteoarthritis, osteoporosis, deafness, cancer, and other major diseases and health conditions.

☐  ☐  I agree to provide a blood sample from which a living tissue sample (cell line) will be made. This cell line will be stored at the BU/Framingham laboratories. The DNA will be extracted from it and will be made available to qualified scientists studying the diseases listed above.

09.21.01
Research Consent Form

Offspring Exam 8

Please check the appropriate box beside each statement you agree with:

1)  [ ] YES [ ] NO I agree to participate in the Framingham Heart Study examinations described above to study the frequency of and factors contributing to heart and blood vessel diseases, lung and blood diseases, stroke, memory loss, and other diseases and health conditions.

2)  [ ] YES [ ] NO I agree to provide a blood sample from which DNA and other components can be extracted. The DNA will be made available to researchers studying the diseases listed above.

3)  [ ] YES [ ] NO If a cell line has not already been collected, I agree to allow a cell line to be made from a sample of my blood to provide a renewable supply of DNA. (A cell line is a frozen sample of specially processed white cells from your blood that allows us to grow more white cells and get more DNA from them in the future as needed for research projects).

4)  [ ] YES [ ] NO I agree to participate in the genetic studies of factors contributing to heart and blood vessel diseases, lung and blood diseases, stroke, and memory loss.

5)  [ ] YES [ ] NO I agree to participate in genetic studies of other diseases and health conditions including but not limited to joint disease, bone loss, and cancer.

6)  [ ] YES [ ] NO I agree to participate in genetic studies of reproductive conditions and mental health conditions such as alcohol use and depressive symptoms.

7)  [ ] YES [ ] NO I agree to allow researchers from private companies to have access to my DNA and genetic data which may be used to develop diagnostic lab tests or pharmaceutical therapies that could benefit many people. (Note: You or your heirs will not benefit financially from this, nor will your DNA be sold to anyone.)

8)  [ ] YES [ ] NO I agree to allow the Framingham Heart Study to release the findings from non-genetic tests and examinations to my physician, clinic, or hospital.

9)  [ ] YES [ ] NO If a genetic condition is identified that may have potentially important health and treatment implications for me, I agree to allow the Framingham Heart Study to notify me and with my permission to notify my physician.

Offspring Exam 8
Result
Key Aspects of Informed Consent in Observational Research

• Data Collection – What happens in the examination cycle? Burden, Risk, Benefit, **Consent with Options**

• Data Access - **Repositories** of FHS GWS and phenotypic data, Security, Staff Training & Certification

• Reporting Results – Scientific Publications, Standard Measures, **Incidental Findings, Novel Biomarkers and Genetic Associations**

(*Current Challenges*)

INFORMED CONSENT IS A TWO WAY PROCESS
The National Institutes of Health (NIH) is ramping up efforts to find genes involved in common diseases. A wave of new projects will take advantage of reduced costs to search for disease genes in people who are already enrolled in existing studies, including the famed Framingham Heart Study. The data will be freely available to other scientists. Genetic studies on large groups aren't new. But few have searched the entire genomes of participants for common genetic markers called single nucleotide polymorphisms (SNPs)...Using new technologies and the HapMap, a map of human genetic variation completed last year that allows gene hunters to use fewer markers, the cost of such "whole genome association" studies has dropped 30-fold, says Francis Collins, director of the National Human Genome Research Institute.
CONSENT FOR INTERVIEW AND EXAMINATION

I have been fully informed of the nature of this study which includes a medical history, physical examination, blood tests and electrocardiogram and given my consent to be examined. I also authorize the Framingham study staff to secure pertinent medical information from my family, physician, and/or hospital records for the purposes of this study.

DATE


NAME
# Consent Form Permission for Release of Genetic Samples and Data Through April 30, 2007

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*’For-Profit Use’ not established for consents before July 2001. The consents have no opt in/out check box for use by Private Company.*
Supplementary Sources of Information for Participants

- Recruitment calls, admitting interview, consent interview
- Explanation of procedures at examination stations
- Exit interview
- Access to Investigators and staff
- Media coverage
- Newsletters, Brochures
- Routine Result reports
- Special letters
- Web site http://www.framinghamheartstudy.org
- Focus groups and Advisory Boards
# Gen 3 Exam 1: Consent for Genetic Research (2002-2005)

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<td>13 (0.3%)</td>
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**Not included in Gen 3 Exam 1 consent process:**

Consent for genetic studies of particular health conditions

Consent to receive genetic results if a potentially important health risk is identified and treatment is available
## Offspring Exam 8: Consent for Genetic Research

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<td>Studies of other diseases including joint disease, bone loss, &amp; cancer.</td>
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Abstracting Consent Data from FHS Consent Form Text and Checkboxes (1971-2001)

- Every version of FHS consent forms is assigned a version number.
- Every participant’s FHS folder is reviewed and version numbers of all FHS consent forms are recorded in a data file for every individual including check box selections.
- All restrictions to consent are coded by version number. Restrictions may be imbedded in text of consent form, displayed as check boxes at the end of the consent form or, rarely, initiated *ad lib* by participants.
- Records of consent form versions and check box options are used programmatically with the associated restriction codes to indicate how the research data from individual participant may be accessed. The permissions and restrictions of the most recent consent form supersedes earlier versions for each individual. *Ad lib* communications are added and are effective until a later consent form is available.
### Restrictions by Version to Research in FHS Consent Forms

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<td>7A.3</td>
<td>25</td>
<td>0.5</td>
<td>5091</td>
<td>99.4 res4=0</td>
<td>NO</td>
<td>Assumption made, nothing in the body of the consent nor check box 1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>OSTEO1</td>
<td>3</td>
<td>0.1</td>
<td>5094</td>
<td>99.4 res4=1</td>
<td>YES</td>
<td>Language written in the body of consent also restricts cell line 2</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>OSTEO2</td>
<td>6</td>
<td>0.1</td>
<td>5100</td>
<td>99.5 res4=1</td>
<td>YES</td>
<td>Language written in the body of consent also restricts cell line 2</td>
<td>2</td>
<td></td>
</tr>
</tbody>
</table>
Challenge: To map participant choices from consent versions, into a simple dataset, that indicates distribution for data and samples

- 36 years (1971-2007)
- ~229 consent versions
- 6 cohort groups
- 1-29 exams attended
Data Management
Consent Goals

Ensure that the participants’ choices are carried out with regards to use of their data and samples

- Document choices
- Communicate choices for release of data/samples
- Update choices
Tracking Participant Consent Forms

1. Capture consent in clinic or off-site
2. Enter data it into Clintrrial database
3. Create data set of all consents
4. Extract participants last choice from one or more consents
5. Reduce to a ‘use group’ dataset
1. Capturing Participant Choices

- Consent form
- Incidental comments
- Phone calls
- Letters

2. Entering Data in Clintrial
3. Create data set of all consents

NUMBER OF DOCUMENTED CONSENTS, FROM 1971 THROUGH JULY 31, 2007
(Paper consents were administered for the first time in 1971 N=68279)

<table>
<thead>
<tr>
<th>Cohort Group</th>
<th>Idtype</th>
<th>Frequency</th>
<th>Percent</th>
<th>Cumulative Frequency</th>
<th>Cumulative Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Original Cohort</td>
<td>0</td>
<td>30,151</td>
<td>44.16</td>
<td>30,151</td>
<td>44.16</td>
</tr>
<tr>
<td>Offspring</td>
<td>1</td>
<td>32,501</td>
<td>47.60</td>
<td>62,652</td>
<td>91.76</td>
</tr>
<tr>
<td>New Offspring Spouse</td>
<td>2</td>
<td>104</td>
<td>0.15</td>
<td>62,756</td>
<td>91.91</td>
</tr>
<tr>
<td>Generation 3</td>
<td>3</td>
<td>4,117</td>
<td>6.03</td>
<td>66,873</td>
<td>97.94</td>
</tr>
<tr>
<td>OMNI Generation 1</td>
<td>7</td>
<td>995</td>
<td>1.46</td>
<td>67,868</td>
<td>99.40</td>
</tr>
<tr>
<td>OMNI Generation 2</td>
<td>72</td>
<td>411</td>
<td>0.60</td>
<td>68,279</td>
<td>100.00</td>
</tr>
</tbody>
</table>
the Boston Medical Center IRB approved a continuation of the protocol for cognitively impaired original cohort allowing a waiver of consent. Original cohort with moderately or severe dementia determined by the Dementia Study will no longer be required to sign an informed consent form nor have a proxy sign a consent by substituted judgment form. If the original cohort patient is not known to have moderate or severe dementia as determined by the Dementia Study and a cognitive impairment is evident, the participant will sign an informed consent form to provide evidence of assent for the exam and a consent by substituted judgment form if needed. The appointment will be arranged with a family member according to established protocols. The family member will be informed regarding the content of exam but will not be required to provide verbal or written consent for the exam under the new waiver. Should the family member object to a Heart Study visit, this objection will be honored. Participants who do not sign a consent form and/or signed a consent but fall under the Waiver, this sheet will be completed by FHS and kept with the participant’s chart.

To Be Completed by Clinic Team

[ ] Draw Date: ___/___/___

[ ] Exam Number: ______

[ ] Participant Name: ____________________________

[ ] 0 = Clinic Exam  1 = NH  2 = Residence  3 = Blood draw only  4 = Other: __________

[ ] Ed Consent Status: ____

If IC Status = 3, send to Neurology Group

[ ] 1 = Consent, 2 = Waiver Only, 3 = Consent form signed may qualify for Waiver

[ ] Dementia Rating Scale (CDR): ______ on ___/___/___

[ ] Dementia Review Outcome/Severity Score *: ______ on ___/___/___

[ ] Status *: ______ on ___/___/___

[ ] Score: ______ at exam ______ on ___/___/___

[ ] Score: ______ at exam ______ on ___/___/___

[ ] Notes: ____________________________

_______________________________

______________________________

[ ] Neurology for Review: ___

[ ] 1 = Yes  2 = No

[ ] Need to Neurology: ___/___/___

[ ] Over ?

A. 1971 No check boxes

B. 1998 Two check boxes

C. 2005 Nine check boxes

D. 2004 Waiver, use previous consent(s)
4. Extract participants’ last choice

CHECK BOX
CB1-CB9

↓

RESTRICTION
RES1-RES12

↓

DISTRIBUTION
YES/NO

↓

USE GROUP
NO RELEASE/NON-PROFIT/FOR-PROFIT
Extract Check Box Value and Code Restriction for Distribution of Genetic Data and Samples

**Early Consent**

CB2 | YES | NO  Provide blood for DNA and Cell Line → Res1 Res3 → Dist y/n

**Recent Consent**

CB2 | YES | NO  Provide blood for DNA → Res3 → Dist y/n
CB3 | YES | NO  Provide blood for Cell Line → Res1 → Dist y/n
CB7 | YES | NO  Permission to private companies → Res4 → Use Group p/np
<table>
<thead>
<tr>
<th>Meaning of Check Box for Gen3 Consents</th>
<th>‘Nth’ Check Box on Consent Form</th>
<th>Check Box Code 1=Yes 0=No blank =Missing</th>
<th>Offspring Clinic Consent Frequency n=2585</th>
</tr>
</thead>
<tbody>
<tr>
<td>Agree to participate in the physical exam</td>
<td>1st</td>
<td>Yes</td>
<td>2,585</td>
</tr>
<tr>
<td></td>
<td></td>
<td>No</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Missing</td>
<td>0</td>
</tr>
<tr>
<td>Genetic research permitted (Restriction 3)</td>
<td>2nd</td>
<td>Yes</td>
<td>2,583</td>
</tr>
<tr>
<td></td>
<td></td>
<td>No</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Missing</td>
<td>0</td>
</tr>
<tr>
<td>Cell line permitted (Restriction 1)</td>
<td>3rd</td>
<td>Yes</td>
<td>2,579</td>
</tr>
<tr>
<td></td>
<td></td>
<td>No</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Missing</td>
<td>1</td>
</tr>
<tr>
<td>Genetic studies of heart, blood vessel, lung and blood vessel disease permitted (Restriction 10)</td>
<td>4th</td>
<td>Yes</td>
<td>2,583</td>
</tr>
<tr>
<td></td>
<td></td>
<td>No</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Missing</td>
<td>0</td>
</tr>
<tr>
<td>Genetic studies of other diseases not limited to joint, bone loss and cancer permitted (Restriction 11)</td>
<td>5th</td>
<td>Yes</td>
<td>2,581</td>
</tr>
<tr>
<td></td>
<td></td>
<td>No</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Missing</td>
<td>0</td>
</tr>
<tr>
<td>Genetic studies of reproductive, mental health and alcohol permitted (Restriction 12)</td>
<td>6th</td>
<td>Yes</td>
<td>2,577</td>
</tr>
<tr>
<td></td>
<td></td>
<td>No</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Missing</td>
<td>0</td>
</tr>
<tr>
<td>Commercial research permitted (Restriction 4)</td>
<td>7th</td>
<td>Yes</td>
<td>2,381</td>
</tr>
<tr>
<td></td>
<td></td>
<td>No</td>
<td>203</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Missing</td>
<td>1</td>
</tr>
</tbody>
</table>
5. Reduce to a ‘use group’ dataset

User Groups For Genetic Data and Samples

- Use Prohibited
- Non-Profit Use Only
- For-Profit Use Permitted
Breakdown of Last Documented Choice, for Cohort, Offspring, Gen3 and NOS Participants (Non-Profit Use Only, July, 2007)

No Release for any genetic studies  n=263

Release For Non-Profit Use  n=14,268

Total  n=14,531

If distribution is prohibited for genetic studies in general, it will always be prohibited for use by private (for-profit) companies.
Breakdown of Last Documented Choice, for Cohort, Offspring, Gen3 and NOS Participants (Non-Profit and For-Profit Use, July 2007)

User Status Group

1. General Research Use (P+NP) \( (n=7056) \)

2. Non-Profit Use Only \( (n=7212) \)

To construct “general research” and “non profit” user groups

General research user: “use_grp”=1 \( (n=7056) \)
Non profit user: “use_grp”=1 + “use_grp”=2 \( (n=14268) \)
Gen 3 Exam 2: Proposed Informed Consent
Check Boxes for Genetic Research

<table>
<thead>
<tr>
<th>I agree to provide a blood sample from which DNA and other components can be extracted.</th>
<th>(Res3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I agree to participate in the genetic studies of factors contributing to heart and blood vessel diseases, lung and blood diseases, stroke, memory loss and other diseases and health conditions</td>
<td>(Res10 + Res11)</td>
</tr>
<tr>
<td>I agree to participate in genetic studies of reproductive health and mental health conditions such as alcohol use and depressive symptoms</td>
<td>(Res12)</td>
</tr>
<tr>
<td>I agree to allow researchers from private for-profit companies to have access to my DNA and genetic data</td>
<td>(Res4)</td>
</tr>
<tr>
<td>If a genetic condition is identified that may have potentially important health and treatment implications for me, I agree to allow the Framingham Heart Study to notify me and with my permission to notify my physician</td>
<td></td>
</tr>
</tbody>
</table>
Informed Consent is a Two-Way Process

It is our duty at Framingham to ensure that the participants’ choices are updated and carried out