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Collecting Biomarkers Using Trained Interviewers. Lessons Learned from a Pilot Study

Stephanie L. McFall[1], Anne Conolly[2], Jon Burton[1]

[1] Institute for Social and Economic Research
University of Essex

[2] NatCen Social Research

Understanding Society
THE UK HOUSEHOLD LONGITUDINAL STUDY

E·S·R·C ECONOMIC & SOCIAL RESEARCH COUNCIL

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Abstract

This paper reports the design and outcomes of a pilot study for the UK Household Longitudinal Study (UKHLS), Understanding Society to develop and test the collection of biomeasures by trained non-clinical interviewers. Additional objectives were to assess the data quality and reactions of participants. Biomeasures included anthropometrics, blood pressure, grip strength and collection of saliva and dried blood spots. We implemented measurement protocols, introduced training and certification, and collected data from 92 participants. The study produced information about time, participation and quality of blood samples. The pilot study informs design decisions about the biosocial component of Understanding Society.

Key words: biomarkers, survey design, data collection, dried blood spots

JEL Classifications: H10, C81, C83

Author contact details: smcfall@essex.ac.uk

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Collecting Biomarkers Using Trained Interviewers. Lessons Learned from a Pilot Study

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Non-technical summary

In this pilot study, we explored the collection of a core set of biomeasures by trained non-clinical interviewers. This is an alternative approach to the collection by nurses which was launched by Understanding Society in Wave 2 beginning in 2010. Biomeasures include a range of biological, functional, sensory, and body composition measures that tell us something about the body. Interviewer collection offers lower costs and some efficiency to the extent that survey interviewing and biomeasure collection could take place in the same visit. The pilot study was conducted to develop and test the feasibility of collection of biomeasures by trained non-clinical interviewers and to obtain information about the collection of biological samples using minimally invasive methods. Procedures for assessing body composition, blood pressure, hand strength, and collection of biological samples were adapted or developed. The biological samples were saliva, to obtain DNA for genetic studies, and small amounts of blood from a finger prick. Performance-based training methods were developed and implemented. Each interviewer was formally evaluated to standards for each measure. We recruited and trained ten interviewers; nine were evaluated to be ready to conduct the measures independently. Participants were drawn from the 2010 NatCen Omnibus sample who agreed to be re-contacted for interviews; 92 interviews were done in a four week field period in April and May 2011. Among 143 contacted persons, 64% participated and 36% refused. The completion of individual measures for participants ranged from 85% (blood) to 100% (height). The time required to conduct the measures was longer than planned, though there was improvement over time. The reaction of participants was positive, with more than 90% saying the interview was interesting or enjoyable. The quality of biological samples was satisfactory. Interviewers gave important feedback regarding the data collection process and measurement protocols. The pilot study has provided useful information about the feasibility and requirements for the collection of biomeasures by non-clinicians to inform design decisions for *Understanding Society*.

1. Background

The UK Household Longitudinal Study (UKHLS), *Understanding Society,* is a large longitudinal study with annual interviews of members of sampled households (Buck & McFall, 2012). The study is funded by the Economic and Social Research Council with scientific leadership from the University of Essex, University of Warwick and Institute of Education. The National Centre for Social Research (NatCen) is the survey research organisation for the study.

The design of *Understanding Society* is intended to support interdisciplinary biomedical and social research. The design and implementation of nurse collection of biomeasures launched in 2010 is described in a separate working paper (McFall, Booker, Burton, & Conolly, 2012). We use the term biomeasure to refer to a range of biological, anthropometric, functional, and sensory measures (Jaszczak, Lundeen, & Smith, 2009), while biological sample or specimen refers to the actual blood, urine or other biological material taken from the participant's body. Biomarker refers to an objectively measured indicator of normal or pathogenic processes or of response to treatment (Puntmann, 2009) , e.g., an assay such as glycated haemoglobin.

In this study, the biosocial component of *Understanding Society* tests the collection of biomeasures by trained non-clinical interviewers. Interviewer collection is expected to have cost and efficiency advantages by combining interviewing and biomeasure collection. Potentially, this could also reduce non-participation though a longer integrated interview plus assessment could adversely affect attrition. This paper reports a pilot study to test the feasibility of collection of biomeasures by trained non-clinical interviewers in *Understanding Society*.

The study took place in April – May 2011. Ethical approval was granted by Oxfordshire A REC "Understanding Society - UK Household Longitudinal Study: IBIO Pilot" (REC 10/H0604/70*).*

The biomeasures collected include:

- Anthropometrics – height, weight, waist circumference and percent body fat, using the Leicester portable stadiometer, Tanita BF-522 scales, and an insertion tape measure.
- Systolic and diastolic blood pressure and pulse using the Omron 907 monitor.
- Grip strength using the Smedley dynamometer.
- Saliva to obtain DNA using the Oragene 500 kit for collection, stabilization, transport, and purification of DNA.
- Capillary blood on Whatman #903 filter paper to prov*i*de these analytes: c-reactive protein, cholesterol, and glycated haemoglobin.

These measures overlapped substantially with those collected by the nurses (McFall, et al., 2012). The interviewers did not do spirometry to assess respiratory function. The procedures to collect biological samples differed. In the pilot study, interviewers obtained saliva samples using the Oragene 500 kit and collected capillary blood onto filter paper (dried blood spots, DBS) with a disposable lancet. Additional detail can be seen in the measurement protocols. The measurement protocols are available on request.

The development of measurement protocols built on those of other studies. For example, we used protocols for non-clinical interviewers to collect anthropometrics and saliva samples from the Health Survey for England (Craig & Hirani, 2010). The protocols for collection of blood spots, not previously used in U.K. surveys, were adapted from the U.S. Health and Retirement Survey (Crimmins, et al., 2008; Weir, 2008). The grip strength

and blood pressure protocols were adapted from those for nurses used in the English Longitudinal Study of Ageing (Marmot & Steptoe, 2008).

Section 2 describes features of the design of the pilot study including interviewer recruitment, training and certification, sampling, data collection, and transport and storage of biological samples. Section 3 reports on four major outcomes of the pilot study: recruitment and training of interviewers, data collection, participation and response rates, adequacy/quality of biological samples, and feedback from participation and interviewers. Section 4 summarizes the lessons learned from the pilot study.

2. Design and Methods

Important features of the survey design and implementation are the recruitment and training of interviewers, sampling and data collection and transport and storage of biological samples. We do not describe the measurement protocols here, but this information is available. (See Annex A.)

Interviewer recruitment and training

Recruitment

NatCen has substantial experience in conducting biosocial surveys. For example, its interviewer panel has collected physical measures such as height and weight. However, collection of biological samples, especially blood, introduced additional issues. Interviewers dealing with blood samples were required to be immunised against hepatitis B (as is standard for survey nurses). As these vaccinations take six months, only interviewers with an existing immunity were considered for the pilot. For recruitment, all interviewers were asked to respond in writing if they had previously been immunised against Hepatitis B; 85 interviewers reported vaccination within the required time frame. Interviewers with prior clinical training were excluded from working on the pilot study.

Field Area Managers nominated 32 interviewers who were likely to be competent and available. After mapping their locations onto the sample points for the pilot, 22 interviewers were actually approached to work on the pilot. Ten interviewers were not available during the relevant period, and two had no immunity to Hepatitis B, following a blood test. The remaining ten interviewers all agreed to work on the study.

Training program

The training of interviewers is fundamental to successful biomeasure collection. Interviewers were trained to take accurate and consistent measurements, collect high-quality biological samples and follow labelling and dispatch protocols. It was considered crucial that interviewers feel confident and competent to carry out the measurements and take biological samples. The structure and content of the training program was influenced by that used in the U.S. Health and Retirement Survey.

While much of the training focused the specific measurement protocols, there were additional major themes. These included:

- The importance of accurate and reliable measurement
- Care and calibration of equipment
- The ability to explain each procedure and get agreement about whether the participant is willing and able to do it
- Knowledge and skills to conduct procedures with safety for themselves and participants.
- Certification of interviewer performance to ensure quality and safety

The training team was a Briefing Manager (an experienced field supervisor), the Field Training Manager, the *Understanding Society* bio-social research team, and NatCen's Nurse Advisor. The Nurse Advisor provided clinical input into the development of collection procedures and training. Interviewer training took place over three days in April 2011.

The training used multiple modes of presentation and learning (Jaszczak, et al., 2009). These included written measurement protocols, recorded lectures, and in-person and recorded demonstrations. Finally, practice by paired interviewers, with feedback from the instructors was important to develop self-efficacy or mastery of interviewers. Table 1 summarises the topics and schedule of the training.

Table 1. Description of the training sessions

Schedule	Major Topics
Day 1	All measurement protocols using a combination of DVD presentations, demonstrations and practice sessions with feedback. Optional evening practice session
Day 2	Sample and fieldwork structure Mock interview with volunteer respondents Procedures for biological sample collection (e.g. obtaining informed consents for measurements and samples, labelling and dispatching samples, respondent feedback and the role of the Survey Doctor) Certification
Day 3	Health & safety Addressing respondent concerns Research findings from bio-social research. Review and summary and review Additional re-certification attempts

Certification

Interviewers were certified based on an objective assessment of performance of each procedure, their overall accuracy of recording, and labelling of biological samples. Certification was required in order to work on the study to ensure that protocols were being carried out in an accurate, consistent and, above all, safe way. The assessor scored the performance of major and minor criteria for each procedure using a checklist. One major

error or four minor errors was considered inadequate and required recertification in the specific procedure. Inadequate performance on four or more procedures required a full recertification. Interviewers could make one additional attempt to be certified.

Certified interviewers were accompanied by a Nurse Supervisor on their first few visits. The supervisor assessed the interviewer's performance of protocols using a checklist. After demonstrating competence in actual field conditions, interviewers were permitted to work independently. The Survey Doctor was available by telephone to provide clinical backup.

Data collection

This section describes the sampling and fieldwork procedures used in the pilot study. It also describes the transport of biological samples to the storage facility.

Sample

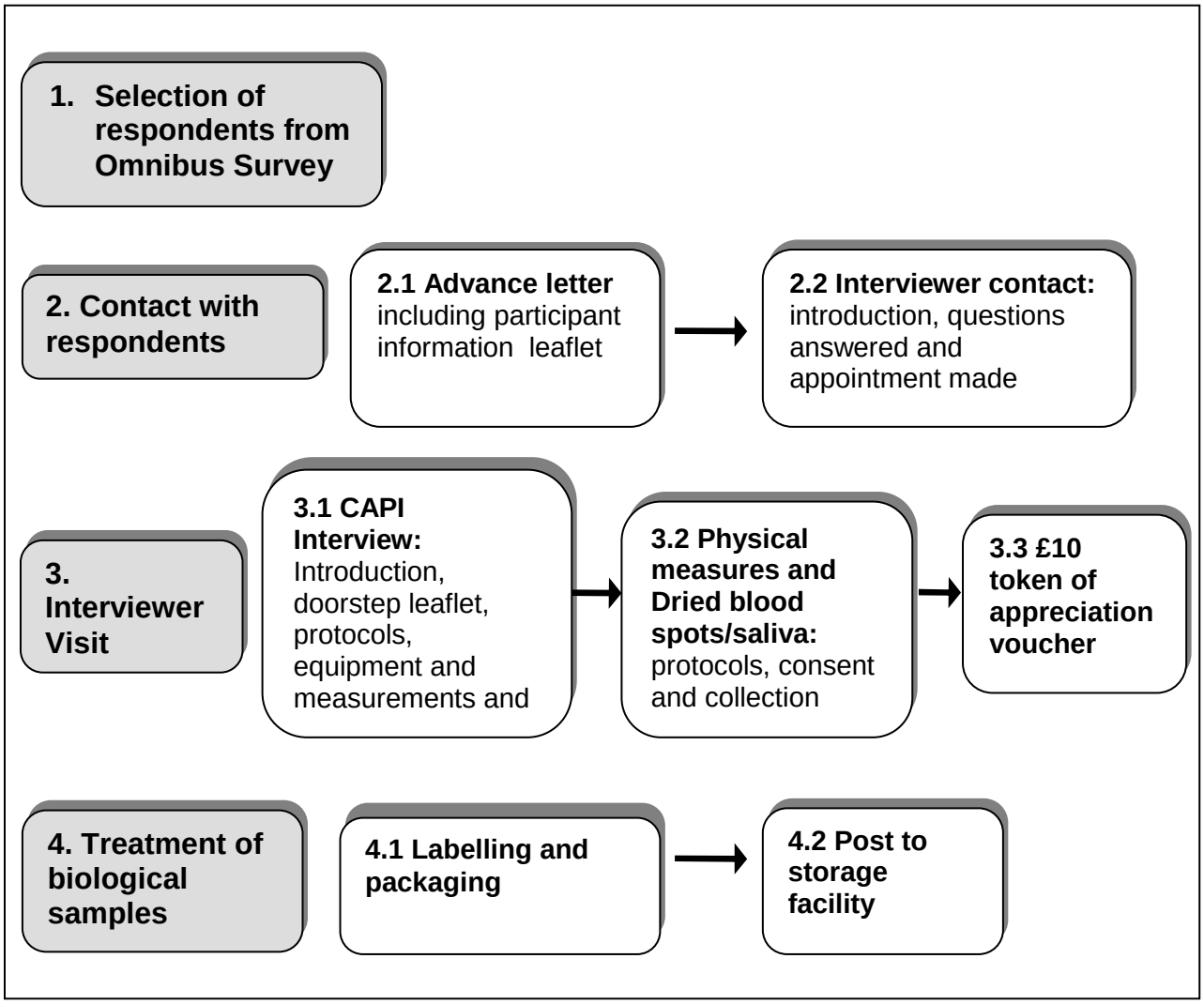
Pilot study participants were not *Understanding Society* sample members, but were drawn from the 2010 NatCen Omnibus sample who agreed to be re-contacted for interviews. The Omnibus study selects a random sample of addresses in Britain and interviews one adult (aged 16 or older) per address. Sample points were selected based on proximity to the selected interviewers.

A total of 26 sample points containing 267 respondents were selected, although interviewers only attempted to contact 244 respondents in the fieldwork period. Each interviewer was issued with between 20 and 35 potential respondents and asked to conduct 10-12 interviews and to obtain at least 7 blood samples. Interviewers were also asked to attempt to conduct interviews with a variety of respondents (age; sex; employment status).

Data collection procedures

The flow sheet (Figure 1) summarizes communications with the participant and data collection activities. Sampled persons received an advance letter with a leaflet describing the study procedures. Participants were given more detailed information in the doorstep leaflet.

Figure 1. Flow Sheet of Communication and Data Collection Activities



Participants were told that the purpose of the study was to assess and improve methods for data collection. We obtained written consent for the saliva and blood samples. For the saliva sample, participants were informed that the sample would be sent to a secure storage facility, that DNA would be extracted from the sample and analysis would be conducted to assess the amount of DNA. For the blood spots, participants were told that the

specimen would be sent to a laboratory and that scientific analyses would be conducted. Oral consent was used for the other biomeasures. Annex A has advance materials and the consent forms.

Following the biomeasures sections, the interviewers asked several modules of questions about health and reactions to the data collection. The questions integrated assessment techniques and interviewing and also gave time for the blood spots to dry before transport (about 20 minutes). The modules related to eating habits, smoking, drinking, physical activity, physical work, hypertension, diabetes and use of health services.

The final questions asked participants about their reactions to the measurements. These questions concerned whether they would have liked more information about each procedure. They were also asked about the measurement card (feedback on the participant's height, weight, and blood pressure) and enjoyment of the interview. This section used computer-assisted self-interview (CASI).

Transport and storage of biological samples

Interviewers wore gloves, a standard universal precaution for handling biological substances, when handling saliva or blood samples. The DBS cards and the saliva collection tubes were labelled with the respondent's ID number and their date of birth immediately before sample collection. Interviewers wrote this information onto a label and checked the date of birth with the respondent.

Saliva collection used the Oragene (OG-500) collection kit. Interviewers added the preservative to the saliva, closed the lid and inverted the mixture 5 times. The tube was placed into a moulded plastic container lined with absorbent material. The packaging and transportation of biological specimens conformed to the International Air Transport Association (IATA) P650 Packaging Instructions. For the saliva (or any liquid biological substance), the primary and secondary packaging must be leak-proof, with rigid secondary

packaging. The secondary package must have enough absorbent material to absorb the entire contents of the primary receptacle.

For the dried blood spots, after the drying period, the DBS cards were closed and placed in foil zip-lock envelopes which contained a desiccant pack to help keep the sample as dry as possible. The saliva and blood samples were then placed, together, in a plastic biological substances envelope for dispatch to the storage facility by first class post.

Staff at the storage facility, Fisher Bioservices, located in Bishop's Stortford, logged in the samples and added a barcoded label. The barcodes are used in their sample retrieval system. The saliva samples were stored at -80°C. prior to DNA extraction. The blood spots were stored at ambient temperature and protected from moisture.

The blood samples were sent to the Institut fur Klinische Chemie, University of Mannheim, for analysis. The assays were for total cholesterol, glycated haemoglobin and c-reactive protein. The laboratory protocols are in Annex B. For each assay, the laboratory includes as internal quality controls specimens with known amounts of the analyte.

3. Results

The evaluation of the pilot study focuses on four topics: interviewer recruitment and training, issues related to data collection such as time requirements and participation, process and outcomes related to the blood spot measurements, and interviewer and participant reactions to the pilot collection of biomeasures.

Interviewer recruitment and training

The requirement for Hepatitis B vaccination had a major influence on recruitment of interviewers. Vaccinated female interviewers tended to have health care work experience and were therefore excluded. Eight male and two female interviewers were selected - an atypical gender composition for survey research. The *Understanding Society* interviewers are 55% female and 45% male, and over 99% of NatCen's nurse workforce is female.

All interviewers completed the training. Partial re-certification was required for three individual interviewers; two for the blood pressure module and two on labelling of samples. One full re-certification was carried out, which the interviewer did not successfully complete. Nine out of the ten interviewers were certified and given their assignments.

It is clear that interviewer selection will be an important consideration in scaling up for larger projects in the future. While we had high take-up of offers to work on the study, the pool of potential interviewers when excluding immunization status and availability was not large. Several additional factors could also contribute to interviewer decisions to work on biosocial surveys. These include lack of interest, concern about their ability to be certified in the biomeasures collection, the requirement to keep doing work of this type in order to maintain certification, deciding that the equipment is burdensome, and other features related to perceived difficulty. Disincentives may, of course, be offset by such factors as the pay rate set for interviewers in this type of study. More information about the comments and suggestions of the interviewers are below.

The pilot study supported the importance of certification. First, the detailed plans for training were helpful in the project's ethical review. As an objective evaluation, certification gave a firm basis for deciding when an interviewer was sufficiently competent. It was important for safety and quality assurance. From the perspective of the interviewers, certification focused their efforts during the training. They reported that successful certification enhanced their confidence in their abilities to conduct the assessments.

Participation

Interviewers were given four weeks to obtain completed interviews and blood samples. As a result, 40% of the issued cases were classified at the end of the period as non-contact or of unknown eligibility. Among contacted cases, 92 were interviewed (64%) and 51 refused (36%). We should view the refusal rate as the lower bound of refusal. It is higher than

participation in interviewer collection of biomeasures in the U.S. Health and Retirement Survey (Sakshaug, Couper, & Ofstedal, 2010) and slightly higher than the household level refusal to nurse visits in *Understanding Society* (McFall, et al., 2012). Participants were more likely to be female (63%) than male. The age range was from 18 to 91; 38% were aged 18-44, 36% were 45-64 and 26% were 65 or older.

Response to the individual biomeasures is shown in Table 2. There were high rates of participation for all measures. The lowest performance, for the blood sample, was much higher than for providing the whole blood sample by venepunture (64%) in the nurse component of *Understanding Society* (McFall, et al., 2012). There was some variation in the collection of biological samples by interviewer. The collection of DBS ranged from 100% of eligible respondents for two interviewers to 60%. Collection of saliva samples ranged from 100% to 70% of eligible respondents across the interviewers. However, these comparisons are based on small numbers of respondents per interviewer.

Table 2. Completion of Biosocial Measures

Measurement	% of interviews	% of eligible respondents
Height	100.0	100.0
Weight	95.7	97.8
Body Fat	93.5	95.6
Waist	97.8	98.9
Blood Pressure	95.7	96.7
Grip Strength	100.0	100.0
Blood sample	85.9	90.8
Saliva sample	92.4	93.5

Data collection time

The mean time for collection of the biomeasures was 59 minutes (SD 1.8), with a range from 25 to 114 minutes. The minimum time did not include collection of biological samples. The timings are affected by the behaviour of the interviewers who must activate them in the CAPI program. Some interviewers reported that they had been saving time by beginning the first few measurements (the anthropometrics) while their computers booted up, recording the results on the measurement card and entering it later in the CAPI program. This would reduce the time. For example 18 of 92 interviews had times of less than two minutes for the height module, the first biomeasure.

The biological samples are the last of the biomeasures and would not have been influenced by the interviewer short cut. The average time for the 79 persons providing a blood sample was 16.6 minutes (SD 5.7), with a range from 5.4 to 35.6 minutes. The saliva samples required 10.7 minutes (SD 5.3) for the 85 persons who gave a saliva sample.

Interviewers reported getting faster over the course of the study. We compared times for the biological samples for April and May. The blood samples decreased from 16.3 minutes to 12.8 minutes, and the saliva samples from 11.1 minutes to 8.7 minutes. These are both substantial improvements. The May times should be viewed as better estimates of the time demands.

Blood samples

Lack of experience with the collection of blood via fingerpricks and analysis of the dried blood spots was a major motivator for the pilot study. We look at several process and outcome indicators related to the blood samples, including transport time, the quality of the blood spots, and the distribution of analyte values. From 92 participants, five were not eligible because they had a clotting disorder and one for taking a medication which can delay

clotting. Six people were not willing to provide a blood sample. Of 80 people who agreed to give a blood sample, 79 provided a sample.

Transport time

Analytes from the dried blood spots have been found to be stable at ambient temperatures and when frozen, with the period varying by analyte and storage temperature (McDade, Williams, & Snodgrass, 2007). However, researchers may be interested in transport time as an indicator of quality. Interviewers were instructed to mail the packages the same day if possible. The staff at the storage facility was available to log in and store the samples from Monday through Saturday.

Figure 3 plots the time of transport by days following the interview for the 79 blood samples. The modal transport time is one day (37%). Cumulatively, about half arrived within two days, and more than two-thirds within four days of the interview. Almost all arrived (97%) within six days of the interview. Two samples took 12 days.

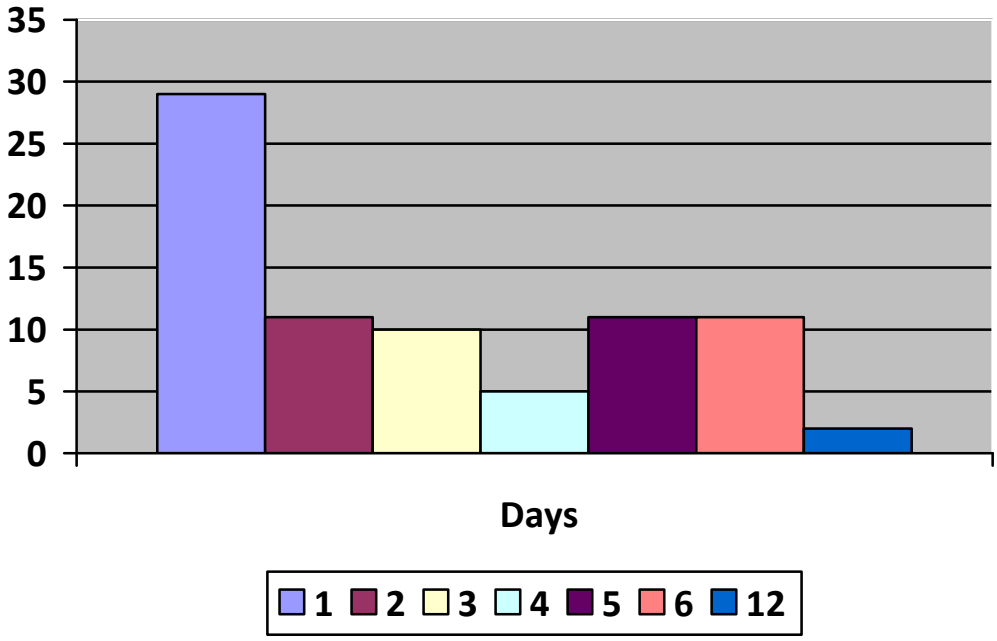


Figure 3. Transport time for blood samples (percent)

Quality of blood spots

Two issues shaping the quality of the blood samples are the amount and the extent to which spots are made less useful by smearing or double spots. When the spots are smeared or doubled, the analyte is not evenly distributed over the paper (Williams & McDade, 2009) and so the spot may not be usable. We used educational materials from the U.S. Centers for Disease Control & Prevention as reference material for evaluating whether spots were satisfactory and unsatisfactory (Mei, 2010).

Filter paper had five pre-printed circles of ½ inch diameter. The interviewers collected up to five spots to test the feasibility of collecting a volume similar to that used by the HRS and other surveys. We planned to conduct analysis for three commonly assessed DBS analytes.

We visually inspected the blood spots using an approach suggested by Williams and McDade (2009). Spots were counted and classified as large or small. We also noted whether spots were blotted, smeared, or double dropped. We classified one in four cards (n=19) as being of highest quality: five large spots with no blots or smears. A similar number had one or more smear or double spot (n=22). The number of large spots was:

5 spots	22
3 or 4 spots	24
1 or 2 spots	15
0 spots	16.

Generally, if there were zero large spots, there were five small ones. Based on the laboratory protocols, the three assays required two large spots or the equivalent amount from smaller spots. Thus, all cards provided sufficient material from either large or small spots to conduct the assays. Larger quantities provide more material for additional assays if a participant's consent has been framed to support additional research.

Blood spot analysis

We selected three assays relevant to risk of cardiovascular disease for which there were established laboratory protocols for analysis using dried blood spots. We cannot report on the agreement of results of assays for whole blood and the dried blood spots. However, we will present results from published information from the Health Survey for England and other literature concerning comparability of DBS and whole blood assays. Annex B has the laboratory protocols for the three assays.

Cholesterol is associated with the development of atherosclerosis and positively associated with cardiovascular disease (CVD). The assay for total cholesterol used the peroxidase method, adapted from Quraishi (2007) and Ramakrishnan et al. (2001). We converted the results from mg/dl to mmol/L, the units more commonly used in the UK. The mean for total cholesterol was 5.4 (SD .8) for all participants providing a blood sample (see Table 3). This is similar to the values reported in the 2006 Health Survey for England, 5.3 mmol/L. for men and 5.4 mmol/L for women (Craig & Mindell, 2008). While laboratory results from different laboratories and methods cannot be directly compared, studies correlating results from dried blood spots and from serum have reported correlations ranging from .78 to .98 (Lakshmy, Gupta, Prabhakaran, Snehi, & Reddy, 2010; Ramakrishnan, et al., 2001).

Table 3. Summary statistics for total cholesterol (mmol/L.)

Age	Range	Mean	Standard Deviation
18-44	4.0 – 6.6	5.29	.69
45-64	3.4 – 7.2	5.69	.91
65 +	3.9 – 7.2	5.35	.93
Total	3.4 – 7.2	5.45	.85
N=79			

Glycated haemoglobin (HbA1c) assesses the amount of blood sugar that is bound to haemoglobin over a period of two to three months. HbA1c is a measure of glycemic control in persons with diabetes, a risk factor for CVD, and has been used to screen for diabetes. The laboratory protocol used mass spectrometry with the International Federation of Clinical Chemistry (IFCC) method (Jeppsson, et al., 2002). The distribution of HbA1c in pilot study participants by age category, combining genders, is shown in Table 4.

Published studies show strong correlation between values from DBS and whole blood, though values from DBS are positively biased by about 8% (Jones, Warber, & Roberts, 2010). If we multiply the mean value for the pilot study by .92, it is 5.79, not very different from the 5.7% for men and 5.6% for women (Craig & Hirani, 2010) reported in the 2009 Health Survey for England.

Table 4. Summary statistics for glycated haemoglobin %

	Range	Mean	Standard Deviation
Age category			
18-44	5.2 – 8.2	6.07	.57
45-64	5.3 – 7.7	6.42	.58
65 +	5.3 – 7.6	6.45	.53
Total	5.2 – 8.2	6.30	.59
N=79			

C-reactive protein (CRP) is a marker of inflammation expressed in the acute phase. In addition to being a marker of immune activation, it is a risk factor for cardiovascular disease. The laboratory used enzyme linked immunosorbent assay (ELISA). The distribution of CRP in pilot study participants by age and body mass index (BMI) category, combining genders, is shown in Table 5.

The distribution of CRP is skewed and a log transformation is often used in analysis. Table 5 has descriptive information about CRP by age and BMI category. An increase in CRP by age and BMI is shown, consistent with several studies (Ford, Giles, Myers, & Mannino, 2003; Rifai & Ridker, 2003).

Multiple studies have found a strong correlation of DBS and whole blood values (range .96-.97) and that the DBS values are lower than those from whole blood (Brindle, Fujita, Shofer, & O'Connor, 2010; McDade, Burhop, & Dohnal, 2004). Brindle and associates report DBS values are .69 of serum values, while McDade and associates reported they were .72 (Brindle, et al., 2010; McDade, et al., 2004). Dividing the pilot study median by .69 gives .83. We compare this to the median value (1.6 mg/L.) reported for 1,940 men aged 20 or older in the National Health and Nutrition Examination Study (Ford, et al., 2003). Another comparison is with 22,403 participants in the Physicians' Health Study (PHS), the Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS), the Women's Health Initiative (WHI), and the Women's Health Study (WHS) for which the median was 1.5 mg/L. for men and 1.52 for women. The 2006 Health Survey for England only reported mean values: 5.3 mg/L for men and 5.4 mg/L for women (Craig & Mindell, 2008) and they are not close to those reported for the pilot study or either of the U.S. studies. A closer comparison should be made to comparison of laboratory and statistical methods of analysis.

Table 5. Summary statistics for c-reactive protein (mg/L)					
Age Category	Range	Mean	Standard Deviation	Median	N
18-44	.2 – 2.7	.76	.69	.45	30
45-64	.1 – 4.2	.92	1.03	.5	29
65 +	.3 – 4.5	1.26	1.07	1.0	20
BMI category					
Normal 18.5 – 25	.2 – 3.5	.68	.76	.4	28
Overweight	.1 – 4.2	.86	.80	.65	28
Obese	.2 – 4.5	1.36	1.16	1.00	23
Total	.1 – 4.5	.94	.94	.6	79

Reactions of interview participants

As part of the interview, respondents were asked to complete a short self-completion questionnaire on the computer (CASI) about the data collection process. The three topics presented are items related to informed consent, reactions to obtaining the biological samples, and overall satisfaction with the interview. Nearly all the respondents completed the self-completion (89 out of 92).

Table 6 classifies whether respondents read all or part of the advance communication materials: the advance letter or leaflet. This item is relevant to the issue of informed consent for participation in the study.

Table 6. Percent reading the advance letter or leaflet		
	Letter	Leaflet
	%	%
Read all	74	56
Read some	14	29
Received, did not read	7	7
Did not receive	9	9
N= 89		

Most said they had enough information about the measures. Sixteen percent wanted more information about the body fat measure, blood pressure or the use of the saliva sample and 8% wanted more information about the use of the blood sample

Concerning the biological samples, 2/3 said it was very easy (N=19) or fairly easy (N=36) to provide a saliva sample. However, 1/3 reported the saliva sample was fairly difficult (N=20) or very difficult (N=6). Participants who gave a blood sample and had prior experience with venepuncture were asked which of the two methods they would prefer if giving a blood sample in the future. Two-thirds preferred a finger prick, and 20% said they would be willing to do either. However, 10% (N=7) preferred venepuncture, and one individual would not give a blood sample in the future.

All but one person said the interview was interesting or enjoyable. It was rated as very interesting or enjoyable by 52% and quite interesting or enjoyable by 46%. More than ¾ said they would be willing to do another interview with health measurements and samples in the future.

Reactions of interviewers

After the fieldwork period, interviewers attended a one day de-briefing session. This section summarises general feedback from interviewers and concludes with comments and suggestions related to specific measures.

Interviewers were surprised by the high level of co-operation among respondents. It is, however, important to bear in mind that the selected sample had taken part in previous survey research and had agreed to be re-contacted in the future. Interviewers commented that refusals tended to be firm, where people had decided that this type of thing definitely "wasn't for them" and were not open to persuasion.

The interview took longer than had been estimated (and as had been suggested to respondents in the advanced materials). Interviewers described adapting by explaining that the interview was likely to take about 90 minutes. Interviewers also reported they sped up over the fieldwork period.

With respect to the training, most interviewers felt that it should be a slightly longer course, with additional time to practice. They also suggested that the Health & Safety section should be done at the outset. They valued the accompanied launch with Nurse Supervisors reporting that this final evaluation by a qualified nurse was "beneficial and necessary".

A summary of the interviewer comments for each measurement is provided in Table 7.

Table 7. Summary of Interviewer comments and suggestions for individual measures	
Measure	**Comments / suggestions**
Height	No suggestions. Respondents tend to be shorter than they expect.
Weight and Body Fat	Important to discuss the CAPI checks for unusually low or high measurements. Respondents often asked about "normal" body-fat ranges But were satisfied with the signpost to the website provided on the Measurement Record Card. Interviewers felt it would be useful have some information themselves.
Waist	Interviewers said that the navel is not an accurate pointer to the waist, particularly on larger respondents. Some also suggested that the respondent materials should refer to "middle" instead of "waist". The procedure was difficult, except on slim respondents; however, they did not perceive specific gender issues. The introduction to this measure on the CAPI was too wordy.
Blood Pressure	There were some problems with the Omron machine, mainly at the start of the fieldwork period. Interviewers suggested a CAPI help screen with a list of error messages and solutions. The 5-minute resting time felt long to both interviewers and participants. Providing a rationale for the length of the period in the introduction could help deal with respondents' impatience. Some interviewers felt that the preamble could be shortened.
Grip Strength	There were no problems with this measurement. Interviewers reported that it was important to convey their own motivation when doing the demonstration so respondents are more likely to try hard
DBS	Interviewers reported feeling confident with this measurement: "100% confident as a result of the training" and were surprised by how willing the respondents were to take part. Interviewers found that the length of time it took **varied hugely** depending on how easily the respondent bled. It is important to have a flat, firm surface (using a coffee table next to an armchair was fine though).

	Interviewers came up with their own preference for which finger/thumb to use and a comfortable hand position. It is important to quickly check the hand position before using the lancet. Some interviewers said they wanted more information about adequate blood spots at the training.
Saliva	Some respondents were self-conscious about giving a saliva sample. Interviewers sometimes allowed them to go elsewhere to do this. The length of time to provide the saliva sample varied. Interviewers were questioned about the use of the samples, and the explanation provided in CAPI was usually satisfactory. In a future study, interviewers would want to have more information about how DNA can be used for research. It was suggested that respondents, as well as interviewers, should clean their hands after the saliva sample as participants touched showcards and the laptop later in the interview.

4. Lessons learned and conclusions

Overall strengths and limitations of pilot study

The priorities for this pilot study were to test the feasibility of interviewer collection of multiple biomeasures and to gain experience with the collection and analysis of dried blood spots. As a preparatory step, there was major effort in developing and implementing interviewer training materials and methods. It is a major strength of the pilot study that it addressed several major dimensions of study design and implementation as described below.

The pilot study's limitations stem from the fact that it did not have a household panel design, like *Understanding Society*. Participants were from a study of individual adults who had completed a brief interview. So the pilot study does not have the same demands of collecting data from multiple household members. Interviewers were told that their priority was to get experience in collecting the biomeasures rather than in obtaining cooperation and fieldwork was stopped when sufficient cases had been obtained. It may be, therefore, that the

households who were easier to contact may differ from those who were never contacted, and consequently, we cannot generalize about whether the observed rate of cooperation will extend to a longer and more complex interview or to studies where the interviewers make every effort to maximise response rates. Additional limitations were not including a component validating and calibrating the assays for the DBS.

Lessons learned from interviewer recruitment and training

There were no major difficulties in recruitment of interviewers though the requirement for Hepatitis B immunity presented barriers. Because relatively few interviewers had been vaccinated, and the vaccine series takes four to six months to complete, the recruited interviewers were disproportionately likely to be male. Future studies will need to build in time for the immunization or review whether this safety precaution is necessary in light of experience gained with the safety lancet.

The implementation of the training should be viewed as a major component of the pilot study. This development work will readily contribute to future studies collecting these measures. Certification, a form of performance-based evaluation ensured accurate and safe implementation of the protocols. The interviewers also characterized certification as boosting their confidence in their skills.

Lessons learned about data collection

It is not possible to make definitive conclusions about the rate of response. However, the percentage refusing was not unusually high, and the participation in the individual measurement procedures was good. Participation in providing biological specimens was particularly noteworthy. While these measures had the lowest rates of participation, DBS collection was much higher than for the nurse collected blood samples using venepuncture. The saliva samples had the next lower level of participation, and we should note that the

participants found providing the saliva samples difficult. Invasiveness is only one dimension of burden for participants. Data collection plans should attempt to lessen the difficulty of producing the sample and to reduce the distaste for the task.

The data collection took longer than was expected, and longer than we think is good for the household panel design of *Understanding Society*. Other biosocial surveys have reported having to adjust their designs in relation to preliminary time information, for example, trimming measures and delivering different modules to random subsets of their sample in order to balance the collection of different biomeasures and their time requirements (Smith, et al., 2009). We will need to continue weighing the value of each measure and its time requirements.

The pilot study provided important information about collecting blood samples via finger prick. This approach has not been much used in social surveys in the UK where clinical laboratories are dominated by requirements of the NHS. This market does not support the development of small niches of specialisation so it was difficult to identify laboratories with wide spread expertise in the less standard methods of DBS analysis. Colleagues with the German component of SHARE referred us to the laboratory we used, Institut fur Klinische Chemie, University of Mannheim. This laboratory and chief scientist Peter Findeisen has a program of research in biomarker development and implementation.

There are significant challenges related to scientific and administrative issues for the laboratory analysis. While assays are becoming more available, the DBS analyses are not standard. The pilot study brought home the difficulty of comparing blood assays across methods, laboratories and even populations, as well as making use of clinical criteria or cutpoints. We regret that we could not conduct research comparing DBS and serum-based assays. Research validating, calibrating, and assessing stability is important for each assay

planned for the study. McDade and colleagues describe a general strategy to be followed in such a program of research (McDade, et al., 2007).

We are currently not inclined to adopt the collection of blood samples via DBS in *Understanding Society*, and not solely because we have implemented venepuncture by nurses for a major share of our adult sample. Even if we resolved some of the laboratory questions associated with the DBS approach, there are some remaining issues. The collection of blood samples was a major share of the time requirements for the biomeasures; this time demand would be multiplied in households with multiple interviews. In addition, the time required for training and certification related to the DBS is substantial. We think that biomeasures collection without the DBS could trim nearly a day from the time for training and make a major reduction in the time for data collection. Interviewer training is extremely important in addressing biosafety concerns and collecting and recording accurate data; however, the training program will be shaped by the breadth and complexity of the measures selected.

Conclusion

The design of *Understanding Society* calls for substantial health content. This pilot study supports innovation with an approach to collection of biomeasures using an approach contrasting to the nurse model (McFall, et al., 2012). We have gained experience in relation to training and certification of interviewers, and in the collection of biomeasures especially biological samples. These lessons will be important in the future when *Understanding Society*obtains resurces to introduce repeated measures of biomarkers. When such opportunities are presented, an integrated collection of biomeasures by interviewers will be a useful approach.

5. List of annexes

Annex A – Consent form and participant information sheet

Annex B – Laboratory protocols

6. References

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A study of health

We are inviting you to take part in a study which will pilot the collection of physical measurements from survey respondents. This pilot study will feed into a larger study called Understanding Society, which is now expanding in scope to gather physical and health information from participants.

What does it involve?

This study consists of a visit by a trained interviewer who will contact you in a couple of weeks.

When the interviewer visits, they will explain a bit more about the physical and health measurements, which are outlined on the adjacent page. Should you agree to take part they will then ask you a few questions about your health, and with your permission take each of the measurements. All elements of the study are optional.

As a thank you...

We hope you will agree to take part and we are offering you a £10 voucher as a token of our appreciation for your time.

The measurements...

Physical measurements:

These include blood pressure readings, height, weight, body fat percentage and waist measurements.

Why? High blood pressure can be a health problem. Waist and body fat measurements tell us about your body shape, which can be related to health.

Upper body strength:

This measurement involves gripping a handle which will provide a reading of grip strength.

Why? Grip strength is an indication of physical functioning.

A saliva measurement:

We would like to take a sample of saliva. This is collected by spitting into a specially designed container.

Why? The purpose is to test our processes for obtaining genetic material (DNA) from saliva.

A blood sample:

The interviewer will ask you if you would be willing to have your finger pricked in order to provide a very small blood sample.

Why? Your blood can tell us very important things about your health status.

If you don't want to do one of the above measurements then please just tell the interviewer when they visit. As with all surveys carried out by NatCen, we take great care to protect the confidentiality of all information and test results. The interviewer will give you another leaflet when she/he visits, which explains the different measurements in more detail.

Understanding Society: Physical measures pilot study

Any questions?

Our interviewer will try to answer any questions you may have. Or, if you like you can speak to someone on the NatCen research team on Freephone: 0800 526 397

Introduction

We all know how important our health is – it has an effect on many other parts of our lives, today and as we get older. Understanding Society, a study which looks at social trends and changes in the lives of people living in the UK over time, is expanding to incorporate a physical and health element to the research. This pilot study will help to decide which physical measures should be collected from respondents going forward.

This survey is being carried out for the Economic and Social Research Council, by the Institute of Social and Economic Research at the University of Essex, with the National Centre for Social Research.

The interviewer visit

A trained interviewer will ask some general questions about your health and then ask permission to take some measurements. The measurements are described on the adjacent page. You need not have any measurements taken if you do not wish but we very much hope you will agree to them, as they are a valuable part of this study. If the study results are to be useful, we need information from all types of people in all states of health. As with information obtained in all NatCen studies, we take great care to protect the confidentiality of information and test results.

Is it compulsory?

No. In all our studies we rely on voluntary participation. The success of the study depends on the goodwill and co-operation of those asked to take part. The more people who do take part, the more useful the results will be. You are free to withdraw from the study at any time. However, we will not be able to remove individual information after the study results have been published.

Everything you say is confidential unless you tell us something that indicates that you or someone else is at risk of harm, or about illegal activity which could harm the public.

Who has reviewed the study?

The study has been looked at by an independent group of people called a Research Ethics Committee, to protect your safety, rights, wellbeing and dignity. This study has been given a favourable opinion by the Oxfordfordshire Research Ethics Committee A.

The measurements

Blood pressure

Blood pressure is measured using an inflatable cuff that goes around your upper arm. High blood pressure can be a health problem. A person's blood pressure is influenced by age and can vary from day to day with emotion, meals, tobacco, alcohol, medication, temperature and pain. The interviewer will tell you your blood pressure along with an indication of its meaning. However, a diagnosis cannot be made on measurements taken on a single occasion.

Height, weight, waist measurement, body fat percentage

Lately there has been much discussion about the relationship between weight and health. Your waist measurement is useful for assessing distribution of weight over the body. The body fat measurement is taken using scales that are similar to a set of bathroom scales, but they measure the amount of fat in the body.

Saliva sample

We would like to take a sample of saliva (spit). This simply involves spitting in to a specially designed collection tube. The interviewer will ask for your written permission before taking this sample. The purpose of the sample is to test our processes for obtaining genetic material (DNA) from saliva.

Blood sample

Analysis of blood samples will tell us a lot about the health of the population. This part of the survey involves a small quantity of blood being obtained by a finger prick and collected on a blood spot collection card. This sample will be analyzed for cholesterol (total cholesterol and HDL), blood sugar (glycated haemoglobin), C-Reactive protein, and Cystain-C.

We would be very grateful if you would agree to provide us with a small sample of blood. You are, of course, free to choose not to give a blood sample and the interviewer will ask for your written permission before a blood sample is taken.

FRONT PAGE

Physical and Health Measurements:

Information for Participants

Understanding Society

BACK PAGE

Frequently asked questions

What will happen to the blood and saliva samples I give?
The blood and saliva samples will be sent to a secure facility, and analysed as outlined in the previous section. The blood sample will also be stored for a period and analysed again for quality checking. Your name and address will not be attached to the samples and so your samples will remain confidential.

DNA will be extracted from the saliva sample and the amount will be measured. No other tests will be conducted with the DNA.

You can withdraw your consent to store your blood at any time, without giving any reason, by asking the investigators in writing for your blood to be removed from storage and destroyed (see contact details below). When the sample is tested for research, it will no longer be possible to link it to you, so you will not be told the results of the testing. It will not be possible to remove your results from reports, as the results cannot be linked to you.

Will any genetic tests be made?
The anonymous saliva samples will be destroyed after we examine how much genetic material is obtained. No genetic analyses will be conducted.

If I have any other questions?
We hope this leaflet answers the questions you may have, and that it shows the importance of the survey. If you have any other questions or concerns about the measurements, results or samples please do not hesitate to ring one of the contacts listed below. Your co-operation is very much appreciated.

Contacts

Lesley Mullender
National Centre for Social Research
Kings House 101 -131 Kings Road
Brentwood
Essex, CM14 4LX
Freephone: 0800 526 397

Dr Ian Forde
Dept Epidemiology and Public Health
UCL Medical School
1-19 Torrington Place
London, WC1E 6BT
Tel: 0207 679 5627

NatCen
National Centre *for* Social Research

Understanding Society – Physical Measures Pilot

CONSENT BOOKLET

Please use capital letters and write with a ballpoint pen

SERIAL NO. | | | | | | | | | | |

House / flat number (or name): _____

Postcode: | | | | | | | |

1. Interviewer number | | | | | | |

2. Date interview completed DD | | MM | | YYYY | | | | |

3. Full name (of person interviewed) _____

4. Sex

Male	1
Female	2

5. Date of birth DD | | MM | | YYYY | | | | |

6. Full name of parent/guardian (*if person under 18*) _____

7.

SUMMARY OF CONSENTS - RING CODE FOR EACH ITEM	YES	NO
a) Sample of blood to be taken, stored and analysed	01	02
b) Sample of saliva to be taken and DNA extracted	03	04

8. BLOOD/SALIVA DISPATCHED (if applicable): DD | | MM | | YYYY | | | | |

THIS PAGE CARBONATED

NatCen
National Centre *for* Social Research

SALIVA SAMPLE CONSENT

SERIAL NO. ☐ ☐☐ ☐☐☐ ☐☐ ☐ ☐

1. *I consent to a trained interviewer collecting a sample of my saliva on behalf of the Institute for Social and Economic Research/National Centre for Social Research.*

   a) *I have read and the Information for Participants leaflet and understand that I will be asked to provide a saliva sample collected by spitting into a small container that will then be sealed and packaged. This measurement will take approximately three (3) minutes to complete.*
   b) *The saliva sample will be sent to a secure storage facility wherein DNA will be extracted from the sample and analysis conducted to assess the amount obtained. I understand that:*
      i. *the DNA samples and related information will be coded to ensure that my personal identity is not revealed to researchers carrying out scientific analysis*
      ii. *links to my name and/or contact details will not be made at any time*
      iii. *that no personal test results from my DNA will be given to me*
      iv. *the data and samples will be owned by the Study and the ESRC. No samples or information will be sold.*
      v. *The DNA analyses will **not** be used for paternity analysis, life insurance, mortgage applications or police records.*
   c) *The interviewer has explained the procedure, and I have had an opportunity to discuss this with him/her.*
   d) *I also understand my right to withdraw consent for storing the saliva sample.*

Initial: _____

Print name (respondent): _____

Sign name (respondent): _____

Date: _____

Print name (interviewer): _____

Sign name (interviewer): _____

Date: _____

You can cancel this permission at any time in the future by writing to us at the following address:
Freepost RRXX-KEKJ-JGKS, Understanding Society,
University of Essex, Wivenhoe Park, Colchester, CO4 3SQ.

THIS PAGE CARBONATED

NatCen
National Centre *for* Social Research

BLOOD SAMPLE CONSENT

SERIAL NO. ☐ ☐☐ ☐☐☐ ☐☐ ☐ ☐

1. *I consent to a trained interviewer taking a small sample of my blood on behalf of the Institute for Social and Economic Research/National Centre for Social Research.*

   a) *I have read and understood the Information for Participants leaflet and understand that my finger will be pricked and blood will be collected on a blood spot collection card. This measurement will take approximately five (5) minutes to complete. The interviewer has explained the procedure, and I have had an opportunity to discuss this with him/her.*

   b) *The blood spot collection card will be sent to a laboratory where it will be stored and used in scientific research. I understand that all blood test results and related information will be coded so I cannot be identified. For purposes of scientific analyses, links to my name will be held separately and securely from any data collected. The sample will not be tested for HIV. I also understand my right to withdraw consent for storing the blood sample.*

Initial: _____

Print name (respondent): _____

Sign name (respondent): _____

Date: _____

Print name (interviewer): _____

Sign name (interviewer): _____

Date: _____

You can cancel this permission at any time in the future by writing to us at the following address:
Freepost RRXX-KEKJ-JGKS, Understanding Society,
University of Essex, Wivenhoe Park, Colchester, CO4 3SQ.

THIS PAGE CARBONATED

P3024 Pilot

DISPATCH NOTE FOR BLOOD AND SALIVA SAMPLES

Complete <u>all</u> sections CLEARLY and LEGIBLY.

1. SERIAL NO. ☐ ☐☐ ☐☐☐ ☐☐ ☐ ☐

2. SEX : Male 1
Female 2

3. DATE OF BIRTH: DD ☐☐ MM ☐☐ YYYY ☐☐☐☐

4. SALIVA SAMPLE COLLECTED: Yes 1 No 2

5. DNA CONSENT: Given 1 Not Given 2

6. TICK BLOOD SPOTS FILLED (INCLUDE PARTIALLY FILLED):

Spot 1 ☐ Spot 2 ☐ Spot 3 ☐ Spot 4 ☐ Spot 5 ☐ Spot 6 ☐

7. DATE SAMPLE(S) TAKEN: DD ☐☐ MM ☐☐ YYYY ☐☐☐☐

8. TIME SAMPLES TAKEN (24 HR CLOCK): ☐☐ : ☐☐

9. INTERVIEWER NO: ☐☐☐☐☐☐

LABELLING ON SAMPLE TUBES AND THIS FORM <u>MUST</u> CORRESPOND
CHECK ALL DETAILS ABOVE ARE CORRECT BEFORE POSTING

STORAGE FACILITY USE ONLY

TUBES ENCLOSED:	✓ if rec'd
Saliva	
BLOOD SPOTS FILLED:	✓ if filled
Spot 1	
Spot 2	
Spot 3	
Spot 4	
Spot 5	
Spot 6	

PROTOCOL

Total Cholesterol / DBS

adapted from (1, 2)

Reagents:

- Randox kit (CHOL; Cat.No. CH202)
- Methanol (Merck)

1. Add 120 µL methanol to an Eppendorf cup that contains 2 DBS punchs with 5 mm diameter
2. close cup and secure with parafilm
3. Vortex 350 rpm (2h, 37°C)
4. Centrifugation (1 min 13.000rpm, Eppendorf Microfuge)
5. Dispense 950µL of reagent (Randox kit, green cap) in microcuvette
6. Add 50 µl methanol-extract from patients specimens (supernatant) and mix well. Include quality controls and calibration standards in every run.
7. Incubate 15 min at 37°C
8. Measure at 500 nm within 60 minutes (Lange Photometer)

References:

1. Quraishi R, Lakshmy R, Prabhakaran D, Irshad M, Mukhopadhyay AK, Jailkhani BL. Effect of storage temperature on cholesterol measurement from dried blood. Indian J Med Res 2007;126:228-9.
2. Ramakrishnan L, Reddy KS, Jailkhani BL. Measurement of cholesterol and triglycerides in dried serum and the effect of storage. Clin Chem 2001;47:1113-5.

HbA1c / DBS

Reagents:

Haemolysis solution

- 275 ml Aqua dest.
- 275 ml Potassiumhydrogenphosphat buffer (0,05M, pH4)
- 100 ml Hämolysis reagent (Recipe)
- 25 ml Acetonitrile (Fluka)

Endoprotease Glu-C (#P2922, Sigma) solution

1mg/ml (0,02 M potassiumhydrogenphospaht buffer wit 3% Acetonitrile). 1 mg of enzyme is equivalent to 500-1000 units.

Trichloroacetic acid (TCA 10%, Fluka)

assay procedure

- Add 300 µl haemolysis solution to 1 DBS-punch (5mm diameter) and incubate 4h at room temperature. Include quality controls and calibration standard into any run.
- Add 10 µl endoprotease Glu-C solution and incubate at 37°C for 20h.
- Add 150 µl of TCA and incubate at 4°C for 30 min.
- Centrifuge 10 min at 13.000 rpm and 4°C (Microfuge Eppendorf)
- Transfer 20 µl of supernatant to HPLC

HPLC (Agilent 1100):

solid phase:	Agilent Technologies, Zorbac Eclipse XDB-C18, 5µm, 4.6x150mm
temperature :	65°C
mobile phase:	A : 4mM Ammoniumformiat
	B: 90% Methanol in 4mM Ammoniumformiat
elution:	0.375 ml/min, Elution per Gradient (6.4%B/min)

Mass spectrometry (AmazonSpeed, Bruker)

Extracted ions:(1)

HbA0	vhltpe	[M+H]+ 695.4 / 677.4
HbA1c	Gluc- vhltpe	[M+H]+ 857.4 / 839.4

1. Jeppsson JO, Kobold U, Barr J, Finke A, Hoelzel W, Hoshino T, et al. Approved IFCC reference method for the measurement of HbA1c in human blood. Clin Chem Lab Med 2002;40:78-89.

CRP / DBS

Reagents:

- hsCRP ELISA kit (BioChek #BC-1119)
- Extraction buffer (0,5M NaCl + 0,1% Tween 20)

assay procedure:

1. Add 200 µl CRP extraction buffer to 1 DBS-punch (5mm diameter) and incubate over night at 4°C with vortexing at 250 rpm. Include quality controls and calibration standard into any run.
2. Centrifugation at 10 000 rpm (Eppendorf Microfuge). Transfer 50 µl of the supernatant (CRP extract) to a microtiter plate and add 50 µl sample diluent (from CRP Kit).
3. Transfer 10 µl of the diluted specimens with the multichannel pipette to the ELISA microwell plate (CRP kit)
4. Dispense 100 µl of CRP Enzyme Conjugate Reagent (CRP Kit) to each well, thoroughly mix for 30 seconds and incubate for 45 min at room temperature.
5. Remove the incubation mixture by flicking the plate contents into a waste container. Rinse and flick the microtiter wells 5 times with deionized water.
6. Strike the wells sharply onto absorbent paper towels to remove residual water droplets.
7. Dispense 100 µl TMB solution (CRP-kit) into each well. Gently mix for 5 seconds.
8. incubate at room temperature for 20 minutes
9. Stop the reaction by adding 100 µl of stop solution to each well.
10. Gently mix for 30 seconds. It is important to make sure that all the blue colour changes to yellow colour completely.
11. Read absorbance at 450 nm with microtiter well reader (Viktor III, Perkin Elmer) within 15 minutes.