TMF 3.1

Study Protocol:

A prospective, observational study to examine the effects of ageing on the clinical outcomes of people living with HIV in England and Ireland.

POPPY – 'Pharmacokinetic and Clinical Observations in People over Fifty'

POPPY

Pharmacokinetic and clinical observations in people over 50

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1.0 Synopsis

Title	A prospective, observational study to examine the effects of ageing on the clinical outcomes of people living with HIV in England and Ireland.
Study name	POPPY – 'Pharmacokinetic and Clinical Observations in People over Fifty'
Study aims:	1. To analyse the incidence and outcomes of co-morbidities in older-HIV-positive people and their relationship with demographic/clinical factors. 2. To evaluate associations between antiretroviral drug concentrations and age, and to assess the potential impact of age on drug efficacy, drug-drug interactions and co-morbidities. 3. To contribute to the development and implementation of evidence-based recommendations for the clinical monitoring of older HIV-positive patients.
Target Population (summary)	**Older HIV-positive cohort (n=1000):** • documented HIV infection • age ≥50 years at study entry • self defined white or black African ethnicity • likely route of HIV acquisition via sexual exposure Either by male to male exposure if white or by heterosexual exposure if white or black African • able to comprehend study patient information leaflet **Younger HIV-positive cohort (n=500):** • documented HIV infection • age <50 at study entry • self defined white or black African ethnicity • likely route of HIV acquisition via sexual exposure Either by male to male exposure if white or by heterosexual exposure if white or black African • able to comprehend study patient information leaflet **HIV-negative cohort (n=500):** • documented negative HIV test in past 6 months or documented at screening • age ≥50 years at study entry • self defined white or black African ethnicity
Design	Multicentre, prospective, observational study over 3 years
Study visits	**The study will comprise of four study visits:** 1. Screening 2. Visit 1 (Baseline visit) 3. Visit 2 (1st year follow up visit) – HIV infected cohorts only

	Phone visit 2 (1st year follow up visit) – HIV negative cohorts only 4. Visit 3 (2nd year follow up visit) **The study visits are expected to take 1-2 hours to complete and will include the following assessments** (see main protocol for full description) • Baseline demographics. • Socio-economic status. • Anthropometrics. • Lifestyle factors. • Quality of life assessment. • Full clinical history: to include history of non-AIDS co-morbidities • Menstrual and reproductive history (women) • Family medical history. • Current and recent antiretroviral use (over past 12 months). • Duration of HIV infection and date of HIV-seroconversion if known • Adherence assessment. • Use of any other medications. • Neurocognitive function assessment. • Pain assessment. • DXA scan A full body where available for bone mineral density, otherwise simple a scan of spine and hips will be performed. • Falls risk, Fracture risk, Frailty assessment • Most recent routine laboratory tests will be recorded and will be assessed in the HIV-negative cohort • Blood (serum, plasma, and PBMC) and urine samples stored Blood (plasma) will be collected for pharmacokinetic analysis (including but not limited to antiretroviral drug exposure)
Sample Size	Our choice of sample size is largely pragmatic, reflecting the number of older patients receiving care and the proportion that are expected to participate. Detailed sample size calculations are difficult given the wide range of topics and methodological approaches proposed. However, power calculations for some exemplar projects are provided.

1.1 Table of contents.

2.0 Schedule of Visits

Study Visit	Screening	Baseline	Follow up visits	
	Within 60 days of baseline	Visit 1	Visit 2 (12 months after visit 1) HIV positive cohorts only	Visit 3 (24 months after visit 1)
Informed Consent	x			
Review Eligibility	x	x		
Detailed medical history as per protocol		x	x	x
Study Questionnaire		x	x	x
Respiratory questionnaire				x
Neurocognitive assessment		x		x
DXA scan		x		x
Blood sampling		x		x
Phone contact			x (HIV negative cohort)	

3.0 Introduction

3.1 Background – The HIV epidemic in the UK and Ireland

Despite the availability of combination antiretroviral therapy (cART), HIV continues to place a major burden on the NHS. During 2009, 60,240 HIV-positive individuals received care for HIV in England, with 6,630 new diagnoses that year [1]. The lifetime costs of HIV infection (with a projected life expectancy of 26.4 years) have been estimated at £17,000 per year [2].

The pattern of the HIV epidemic has undergone dramatic change over the last decade, most notably in terms of the ageing of the HIV-positive population. Of those receiving care for HIV in England in 2009, 18.4% were aged ≥50 years, an increase from 11.0% in 2000 [1]. This is largely due to the use of cART which has led to increased life expectancy [3]. However, older individuals continue to be newly diagnosed with HIV (12.9% of those newly diagnosed in 2009 were aged ≥50 years). Projections from the UK CHIC Study suggest that by 2015, 27% of those seen for care will be aged ≥50 years. Whilst an age of 50 would not normally be considered as old, this cut-off reflects the fact that prior to cART few people were expected to survive to this age.

Across the UK, those of white or black African ethnicity, and those acquiring HIV via sexual routes accounted for 84% of older people receiving care for HIV in 2009 [A Brown, personal communication]. The clinics that will participate in the POPPY study have provided care for >27,000 HIV-positive individual since 1996. Of the patients seen for care at these clinics in 2008/9, 12,620 fell into one of these target groups of whom around 19% were aged >50 years at their most recent visit (Table 1).

Table 1: Characteristics of patients seen at participating clinics in 2008/09

		Age at most recent visit in 2008/09	
		16-49 years	>50 years
Number of patients		10202	2418
Age (years)	Median	39	55
Gender	Male	78%	90%
	Female	22%	10%
Sexual orientation	Homosexual	66%	77%
	Heterosexual	32%	22%
Ethnicity	White	73%	87%
	Black African	26%	13%
Receiving cART		74%	90%
CD4 count (cells/mm^3)	Median	480	450
Prior AIDS diagnosis		16%	30%

3.2 Clinical manifestations of ageing in HIV

Bone manifestations

Older HIV-positive people experience significantly more medical co-morbidities than younger individuals [4,5]. In particular, low bone mineral density (BMD) and osteoporosis are prevalent, with HIV-positive patients being over six times as likely to have decreased BMD and four times as likely to have osteoporosis than HIV-negative counterparts [6]. The main clinical consequence of osteoporosis is fractures, which arise from poor bone health (osteoporosis) and increased falls (due to increased fragility or instability). In the general population, fracture rates increase dramatically in those aged >70 years; in HIV-positive people, fractures are more frequent and occur at a younger age [7]. High rates of vitamin D deficiency, of particular importance for bone health, have been observed in HIV-positive patients [8] and the initiation of cART is associated with further BMD loss and increased bone turnover [9]. As the HIV-positive population ages, it is important to determine the contributions of low BMD,

hypovitaminosis D, cART exposure and fragility to fracture incidence, to identify the age at which fracture risk starts to increase, and the extent to which existing risk prediction tools (e.g. FRAX [10]) accurately predict fracture risk in these patients.

Cerebral function

High rates of neurocognitive (NC) function impairment have been reported in HIV positive subjects on successful cART [11,12]. Prior to cART, HIV-associated brain disease often presented as a frank dementia process (HIV-associated dementia, HAD) with a high associated mortality [13]. In recent years, a milder form of this process (HIV-related NCI) is more often observed; this is associated with progression to HAD [14], poor adherence to cART, and difficulties in obtaining employment. An understanding of the factors associated with the development and progression of NC impairment is essential for the successful, long-term management of this population. Older age, viral hepatitis C co-infection and treatment with antiretroviral drugs lacking penetration into the CNS have been implicated as risk factors for HIV-related NC impairment. Although cognitive decline is part of the normal ageing process, differences in the patterns of cognitive decline have been reported between age-related and HIV-related cognitive decline [15].

Renal function

Chronic kidney disease has been reported in 17% of HIV positive patients, and increasing age is an independent risk factor [16]. Glomerular filtration rate declines with age, and people over 60 years have 20–30% lower GFR than those under 50 years [17]. Age-related decline in renal function is associated with co-morbidities including hypertension, diabetes mellitus, and atherosclerotic, cardiovascular and urological disease [18]. Serum phosphate levels decline with age as a result of impaired tubular phosphate reabsorption [19] and declining muscle mass results in lower serum creatinine concentrations. Elderly patients often use multiple medications, many of which are excreted via the kidney. Altered body composition and impaired renal function contribute to altered pharmacokinetics and pharmacodynamics in older patients, and may lead to an increased incidence of nephrotoxicity and systemic side effects. In addition, renal failure and altered renal tubular function may affect bone mineralisation.

Musculoskeletal

Research into musculoskeletal manifestations and pain has been neglected in HIV-positive adults. A recent survey in Brighton of >850 respondents found a prevalence of current pain of 63%, with 80% of those with pain having had symptoms for >3 months and one in 4 of these patients meeting the criteria for chronic widespread pain [20]. In HIV-negative adults, chronic widespread pain is associated with an excess risk of mortality from cancers and cardiovascular disease [21]. Worldwide, osteoarthritis affects 60% of adults aged >65 years and is a major cause of disability; neither the prevalence nor impact of osteoarthritis have been assessed in HIV-positive adults.

Menopause

Around a third of those living with HIV in the UK are female. Whilst HIV appears to be associated with an earlier onset of the menopause [22], the clinical implications of this for cognitive function, BMD and fracture risk, cardiovascular disease and lipid/glucose metabolism [22] are unclear.

Antiretroviral drug use

Older individuals starting cART generally experience better virological responses but poorer immunological and clinical outcomes than their younger counterparts [23]. Laboratory abnormalities and temporary discontinuations of cART due to toxicities are common [23,24]. Detailed prospective studies on the pharmacokinetic characteristics of antiretroviral drugs are required to determine the optimal drug concentration and toxicity threshold in this population.

Older individuals experience changes in several elements of drug pharmacokinetics, including absorption, distribution, metabolism, and elimination. Furthermore, older HIV-positive people may be treated with several therapeutic agents that may interact with antiretroviral drugs [25]. Data from other drugs suggest that elderly patients require lower doses to achieve therapeutic efficacy but may experience adverse events at lower concentrations. Plasma concentrations of some HIV protease inhibitors are higher in those aged >40 years [25].

Transmembrane drug transporter (i.e. p-glycoprotein) expression and function increases with older age, which may contribute to altered drug effects, drug toxicity and drug-drug interactions. Finally, reduced glomerular filtration rate that may occur in older people may lead to impaired elimination of drugs undergoing renal excretion, resulting in increased potential for toxicity.

3.3 Justification for the study

Currently, there is no large study on HIV and the effects of ageing in the UK and Ireland. Internationally, several research groups have developed initiatives in this area, but most of these studies are either limited by size, or are still at the recruitment stage. For example, the Hawaii Aging with HIV (HAWH) cohort has been running for several years but includes only around 60 HIV-positive individuals. Furthermore, studies are often hampered by the lack of appropriately selected and matched control groups, which limits the conclusions that can be reached regarding any associations with age and/or HIV status.

3.4 Study team

The study will bring together a team of leading HIV clinicians and academic researchers with extensive experience in the conduct and analysis of longitudinal studies in the HIV setting. Most members of the research team have ongoing projects in this field. For example, Dr Winston has an established research programme on CNS toxicities in HIV-positive people. Professor Sabin has led a large international collaborative study on the effect of ageing on cART outcomes [26]. Dr Post has conducted several studies of the effects of antiretrovirals on renal function, phosphate and vitamin D homeostasis, bone turnover and BMD. Dr Boffito runs a multidisciplinary clinic for those aged ≥50 years. Dr Mallon's research focuses on the pathogenic mechanisms underlying long-term co-morbidities of HIV infection. Over the past five years, the team has co-authored >300 peer-reviewed publications, and has attracted >£20 million in research funding. Studies conducted by the group have contributed to guidelines to recommend cART for all HIV-positive patients with CD4 counts <350 cells/mm^3, and for the clinical monitoring of those living with HIV in the UK.

3.5 Summary

Our study, by enrolling both younger and older HIV-positive individuals with a matched HIV-negative control group, will be in the unique position to determine the effects of ageing and HIV status on chronic HIV-infection. In addition, results from this study will be well placed to assist in informing future HIV treatment guidelines on the monitoring of chronic HIV infection in older subjects and assisting in the design of future interventional studies for the treatment of age associated co-morbidities.

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4.0 Study Plan

Aim:

1. To analyse the incidence and outcomes of co-morbidities in older-HIV-positive people and their relationship with demographic/clinical factors.

2. To evaluate associations between antiretroviral drug concentrations and age, and to assess the potential impact of age on drug efficacy, drug-drug interactions and co-morbidities.

3. To contribute to the development and implementation of evidence-based recommendations for the clinical monitoring of older HIV-positive patients.

Design:

Multicentre, prospective, observational study over 3 years

Our study will describe the impact of advancing age on the experience of living with HIV in England and Ireland. To address this we will establish cohorts of HIV-positive people aged >50 and <50 years as well as demographically matched HIV-negative people aged >50 years.

4.1 Study population

Inclusion Criteria

Older HIV-positive cohort (n=1000):

- documented HIV infection
- age ≥50 years at study entry
- self defined white or black African ethnicity
- likely route of HIV acquisition via sexual exposure
  Either by male to male exposure if white or by heterosexual exposure if white or black African
- able to comprehend study patient information leaflet

Subjects with primary HIV infection are eligible and investigators are encouraged to recruit such subjects.

Our target population (those of white or black African ethnicity and those infected with HIV via sexual routes) has been chosen as these groups represent the vast majority of older HIV-positive individuals attending for care in the UK; analyses of other groups (e.g. injection drug users, those infected through blood/blood products and transgender individuals), who may have very different needs and outcomes, would likely be under-powered.

Younger HIV-positive cohort (n=500):

- documented HIV infection
- age <50 at study entry*
- self defined white or black African ethnicity
- likely route of HIV acquisition via sexual exposure
  Either by male to male exposure if white or by heterosexual exposure if white or black African.
- able to comprehend study patient information leaflet

* this group will comprise of at least 150 subjects in each of the following age groups: 20-29, 30-39, 40-49 years. Recruitment will be monitored by the Study Monitoring Team

HIV-negative cohort (n=500):

- documented negative HIV test at screening
- age ≥50 years at study entry
- self defined white or black African ethnicity
- registered with a General Practitioner and gives permission for contact with that GP.

Exclusion Criteria

- in the opinion of the investigator, those unable or unwilling to comply with the requirements of the study
- life expectancy less than 6 months

4.2 Setting

HIV-positive subjects will be recruited from eight clinics: St. Mary's Hospital; King's College Hospital; Chelsea and Westminster Hospital; Homerton University Hospital; Mortimer Market Centre; Brighton and Sussex University Hospital; Royal Free Hospital; and the Mater Misericordiae University Hospital Dublin. The seven UK clinics participate in the UK CHIC Study, providing annual downloads of data (demographics, AIDS events, deaths, laboratory tests, antiretroviral use, viral hepatitis co-infections) on patients seen for care. These data undergo extensive cleaning prior to inclusion in the dataset. Linkage to the UK CHIC Study will allow capture of historic HIV data for these patients thus allowing for efficiencies in data collection. Similar data extracts will be conducted from the Dublin HIV Cohort Database.

4.2.1 Recruitment of HIV-positive cohorts

A list of individuals eligible for the older HIV-positive cohort will be generated at each clinic by study co-ordinators in collaboration with the lead consultant at the clinic, thus ensuring no unnecessary transfer of patient identifiable data out of the clinic. Patients will be randomly sampled from the list, with black African heterosexual men and women, and white heterosexuals (men or women) being over-sampled so that the final cohort includes 100 participants in each of these three groups. Clinic lists of younger patients attending each clinic will be stratified by age, gender, ethnicity and sexual orientation; eligible patients will then be sampled from these lists at a rate determined by the demographic profile of the older patients at the clinic.

Recruitment targets at each clinic are shown below in table 2:

Table 2: Recruitment targets at each site

	Patients seen in 2008/09		Recruitment targets			Total
			HIV positive		HIV negative	
Centre	<50 years	>50 years	< 50 years	> 50 years	> 50 years	
St. Mary's Hospital	1406	317	60	120	60	**240**
King's College Hospital	1264	207	40	80	40	**160**
Chelsea & Westminster Hospital	3146	902	190	380	190	**760**
Homerton Hospital	445	73	15	30	15	**60**
Mortimer Market Centre	2246	468	90	180	90	**360**
Brighton and Sussex Hospital	1159	386	80	160	80	**320**
Mater Misericordiae University Hospital Dublin	536	65	25	50*	25	**100**
Total	10202	2418	500	1000	500	**2000**

**these subjects are already recruited into the Dublin HIV cohort study, therefore high rates of recruitment are considered feasible.*

The recruitment target for Royal Free Hospital, open for recruitment as of November 2015, is as follows: 25 patients > 50 years HIV-positive; 13 patients < 50 years HIV-positive; and 13 HIV-negative controls (total of 51).

4.2.2 Recruitment of HIV-negative cohort

HIV-negative subjects will be recruited through HIV/genitourinary medicine clinics, the HIV/gay/African press, community organisations, internet sites and churches, by the study coordinator and steering committee members; several members of the steering committee have substantial experience of recruiting gay men and black African men/women to research studies from community sites, and have developed successful strategies to identify and recruit HIV-negative volunteers that match the demographic profile of our target groups.

4.3 Study Objectives

Clinical manifestations

- To describe the incidence and presenting features of serious medical conditions (such as cardiovascular, liver, renal disease, cancer and fragility fractures) in the three cohorts.
- To describe the outcomes of serious medical conditions (including time to recovery/resolution, where applicable, the incidence of complications and use of health-care).
- To compare NC function in the three cohorts, and to identify predictors of NC function.
- To compare the levels of musculoskeletal pain in the three cohorts, to identify predictors of this and to describe the health-care needs of those affected.
- Among women, to assess the effects of menopausal status on cardiovascular disease, BMD and lipid/glucose metabolism.

Antiretroviral pharmacokinetics and drug interactions

- To describe plasma (or, where appropriate, intracellular) concentrations of antiretroviral agents (tenofovir, non-nucleoside reverse transcriptase, protease, integrase and entry inhibitors) at baseline in the older HIV-positive cohort, and to compare these to those seen in younger HIV-positive patients.
- To describe the incidence of toxicities/drug discontinuations and immunological/virological responses to cART in the HIV-positive cohorts and to assess correlations between these events and plasma drug concentrations.
- To describe the level of poly-pharmacy in the older HIV-positive cohort and thus the potential for/prevalence of unwanted drug-drug interactions.
- To determine whether accumulation of renally-excreted antiretroviral drugs (e.g. tenofovir) increases their potential to cause renal injury in older HIV-positive people.

5.0 Study visits

5.1 Screening

Each subject must sign an Informed Consent Form prior to the conduct of any screening procedures.

The purpose of the screening visit is to evaluate that the subject meets study inclusion/exclusion criteria. HIV antibody testing will be undertaken for subjects undergoing screening for the HIV-negative cohort.

5.2 Visit 1 (Baseline visit)

The baseline visit will perform evaluations as per schedule of visits (2.0).
The baseline visit is expected to take 1-2 hours; if possible the subject should attend fasted. The following information will be collected:

- Baseline demographics: age; sex; ethnic group; sexual orientation; country of birth; education.
- Socio-economic status: immigration status; employment; household dependents; household income; housing.
- Quality of life questionnaire.

- Anthropometrics: height; weight; body mass index; waist circumference.
- Lifestyle factors: current/past cigarette smoking; alcohol use; recreational drug use.
- Full clinical history: to include cardiovascular events (hypertension, myocardial infarction, angina or acute coronary syndromes, cardiogenic arrhythmias, coronary artery stenting/bypass grafting, peripheral vascular disease), renal failure, liver failure, diabetes, malignancies, falls, fractures, joint disease or joint replacements.
- Measurement of hand grip strength using an automated device.
- Simple measurement of walking speed over a distance of 15 feet (457 cms).
- Blood pressure will be estimated using an automated device.
- Menstrual and reproductive history (women), including menopausal status
- Family medical history: to include any cardiovascular disease, type 2 diabetes mellitus, malignancies, mental illness, dementia or Alzheimer's disease, parental hip fractures.
- Current and recent (over past 12 months) antiretroviral use: type of antiretroviral; start/stop dates; dose; frequency of dosing; side effects; reasons for prior changes/discontinuations.
- Duration of HIV infection and date of HIV-seroconversion if known
- Adherence assessment (see study questionnaire in appendix 1)
- Use of any other medications (including, but not limited to, anti-hypertensives, anti-depressants, vitamin D and/or calcium replacement therapy, lipid-lowering drugs, regular use of analgesics, herbal remedies, other over-the-counter drugs): type of drug; start/stop dates; dose; frequency of dosing; side effects.
- Neurocognitive function: specific memory and cognitive testing assessing cortical and sub-cortical function.
- Pain assessment: regional and widespread pain collected using a validated mannequin; nature of onset; duration; intensity; resulting disability (see study questionnaire in appendix 1)
- DXA scan for bone mineral density (full body DXA where available). These should be performed within 30 days of the clinic appointment.
- Falls risk (see study questionnaire in appendix 1)
- Fracture risk (see study questionnaire in appendix 1)
- Frailty assessment (see study questionnaire in appendix 1)
- Most recent laboratory tests will be recorded (assessed in the HIV-negative cohort): renal, liver, lipid and bone profiles, glucose, full blood count, sexual health screen, hepatitis C serology. These tests should have been performed within a year of the clinic visit.
- Blood (serum, plasma, and PBMC) and urine samples: stored for subsequent projects of the potential pathogenic mechanisms underlying age-related diseases. This will include assessment of vitamin-D and PTH
- Blood (plasma) will be collected for pharmacokinetic analysis (including but not limited to antiretroviral drug exposure)

5.3 Visit 2 (1st year follow up visit)

This follow up visit will be performed as per schedule of visits (2.0).
Only HIV-positive cohorts will be invited to undertake this visit with this visit expected to take 1 hour.
The following will be assessed:

- Changes to lifestyle and socio-economic status over the past year.
- Significant clinical events occurring over the past year: dates of onset and resolution, use of medical services, changes to antiretroviral and other medications, and resulting ongoing health concerns.
- Blood pressure will be estimated using an automated device.
- Details of access to health care services over the past year: visits to the general practitioner, hospital, counselors, psychiatrists, psychologists and medical investigations performed (information obtained by direct questioning and through HIV note review). Permission will be sought to contact the patient's general practitioner and/or hospital for further details.

- Most recent laboratory tests will be recorded: renal, liver, lipid and bone profiles, glucose, full blood count, sexual health screen, hepatitis C serology (Within the past year)
- Concomitant medications: start/stop dates; dose; dosing frequency; side effects.
- Fracture occurrence and fracture risk (see study questionnaire in appendix 1)
- Regional and widespread pain.

5.3a Visit 2 (1st year follow up visit) for HIV negative participants.

These participants will be contacted by telephone by arrangement with the study nurse. They may be asked to attend the clinic in order to facilitate this visit.
Details of any changes in circumstances or illnesses and medication will be documented.

5.4 Visit 3 (2nd year follow up visit)

This follow up visit will be performed as per schedule of visits (2.0).
This visit is expected to take 1-2 hours; if possible the subject should attend fasted. The following information will be collected:

- Changes to lifestyle and socio-economic status over the past year.
- Significant clinical events occurring over the past year: dates of onset and resolution, use of medical services, treatments, and resulting ongoing health concerns.
- Details of access to health care services over the past year: visits to the general practitioner, hospital, counselors, psychiatrists, psychologists and medical investigations performed (information obtained by direct questioning and through HIV note review). Permission will be sought to contact the patient's general practitioner and/or hospital for further details.
- Measurement of hand grip strength using an automated device.
- Simple measurement of walking speed over a distance of 15 feet (457 cms).
- Blood pressure will be estimated using an automated device.
- Concomitant medications: start/stop dates; dose; dosing frequency; side effects.
- Fracture occurrence and fracture risk (see study questionnaire in appendix 1).
- DXA scan for bone mineral density (full body DXA where available) (within 30 days of clinic appointment)
- Neurocognitive function: specific memory and cognitive testing assessing cortical and sub-cortical function.
- Respiratory questionnaire
- Regional and widespread pain.
- Quality of life questionnaire.
- Most recent laboratory tests will be recorded (assessed in the HIV-negative cohort): renal, liver, lipid and bone profiles, glucose, full blood count, sexual health screen, hepatitis C serology (within the previous year)
- Blood (serum, plasma, and PBMC) and urine samples: stored for subsequent projects of the potential pathogenic mechanisms underlying age-related diseases. This will included assessment of vitamin-D and PTH
- Blood (plasma) will be collected for pharmacokinetic analysis (including but not limited to antiretroviral drug exposure)

5.5 Withdrawal of subjects from study

Subjects are allowed to decline further participation in the study at any time. This will not affect their future care.

5.6 Study timelines

Recruitment and baseline visits (visit 1) will take place from months 1-12, with annual visits from months 13-24 (visit 2) and 25-36 (visit 3)

5.7 Sub-Study

- A sub-study will be conducted at the St Mary's Hospital site for participants equal to and over the age of 50 both HIV +ve and HIV –ve.

The protocol for this sub-study is entitled "The POPPY St. Mary's MRI Sub-study".

- Participants may be invited to participate in linked sub-studies that have been approved by the steering committee. Separate protocols, information sheets and consents would be produced for each sub-study.

5.8 End of trial definition

The end of the trial will be the last data capture for the last patient recruited to the POPPY study.

6.0 Study Specific Procedures

6.1 DEXA scanning

All study subjects will undergo a regional (hip and spine) and whole body DXA scan where available (only if urinary βhcg is negative in female subjects under the age of 50). Total and regional bone mineral density Z and T scores will be estimated and total and regional fat and lean mass calculated. All scans will be performed by medical staff and reported by a consultant radiologist and should be performed within 30 days of the clinic visit.
The reports of the scans will be sent to the patients GPs where permission for contact is in place. In the cases where no permission is granted for GP contact, the results will be sent to the health care professional in charge of that patient within the clinic. In all cases any abnormalities detected will therefore be actioned.

6.2 Blood sampling

Pharmacokinetic sampling

Prior to blood taking for pharmacokinetic sampling, time of food intake nearest last dose prior to sampling and food content will be recorded (fasting, light snack, heavy meal). Time of last dose and time of sampling will be recorded.

Efforts will allow for blood sample collection at least 5 hours after the drug dose is administered in order to ensure the sample is post-absorption and to enable the modeling of sparse data.

Blood sample (4-5 mL in EDTA or lithium heparin) collections for the determination of the plasma concentrations of tenofovir and the third agent (i.e. a non-nucleoside reverse transcriptase, protease, entry or integrase inhibitor) in the patient's regimen will be drawn at steady-state. Samples will be processed to isolate plasma and stored at -20°C until shipment to the central laboratory at the University of Liverpool for analysis.

Blood for storage

Blood (serum and plasma,) and urine samples will be collected at visits 1 and 3 stored for subsequent projects of the potential pathogenic mechanisms underlying age-related diseases. This will include assessment of vitamin-D and PTH and probably DNA analysis. Approximately 20mls of blood will be taken. These samples will be stored in a designated central repository for the POPPY study. The analyses will be instigated only by the steering

committee of this trial and will not be for general Biobank access. Specific permission will be sought from all participants for this storage and also for any DNA analysis.

6.3 Neurocognitive testing

At baseline, study subjects are asked questions about their level of education and about their current occupational attainment. The National adult reading test will be undertaken providing an estimate of pre-morbid cognitive ability, (see study questionnaire in appendix 1).

During all study visits the following are assessed:

1. A short patient questionnaire, (see study questionnaire in appendix 1)
2. Staff administered neurocognitive testing
3. Computerised cognitive testing

These assessments are detailed below:

Patient questionnaire:

- A short questionnaire assesses patient's own perception of cognitive abilities.
- Difficulties in coping with complex activities of daily living are investigated with Lawton's questionnaire of Instrumental Activities of Daily Living.

Computerised cognitive testing

The computerised assessment will be performed on a desktop computer and will comprise of 8 tasks. This battery will require approximately 20 minutes to complete. The tasks are in the form of card games and specifically assess the following cognitive functions:

- simple and choice reaction time
- choice reaction time
- complex reaction time
- continuous performance
- one-back working memory
- matching
- incidental learning
- associate learning
- executive function
- verbal fluency and semantic memory

Subjects will be advised to consume no alcohol for at least 24 hours prior to this visit.

6.4 Respiratory Questionnaire

A respiratory questionnaire will be completed at visit 3 by the participant, with the aid of a member of the research study team, to assess patient's own perception of whether or not they have any breathing troubles and if so, whether it affects their daily life (see study questionnaire in appendix 1).

7.0 Study Management

Imperial College London will act as the nominated sponsor for this study. All project documentation will be submitted to the sponsor for approval prior to submission to regulatory bodies such as a Research Ethics Committee (REC).

The study will comply with the requirements of The Research Governance Framework (2nd Edition) and the ethical principles described in the current revision of the Declaration of Helsinki. The study will also be carried out in keeping with local legal and regulatory requirements.

Before the first subject is enrolled into the study all ethical and legal requirements must be met and ethics and R&D approval should have been obtained.

The REC and R&D offices and sponsor will be informed of all subsequent protocol amendments. Amendments will be evaluated to determine whether or not they are substantial and therefore if formal approval must be sought and whether the informed consent documents should also be revised.

The study will be coordinated from the Imperial Clinical Trials Unit (ICTU), which holds provisional registration as a UKCRC Trials Unit. An experienced study co-ordinator, based in the ICTU and working under the supervision of Dr Winston, will manage the day-to-day running of the study. Statistical support will be provided by a statistician working at UCL under the supervision of Professor Sabin.

This study will not open to recruitment until appropriate approvals and authorisations have been obtained from an independent ethical committee. Recruitment will not commence at an individual participating site until local NHS Management approval has been obtained and all local documentation is in place and all requirements have been fulfilled according to ICTU Standard Operating Procedures (SOPs).

7.1 Adverse Events

Adverse event reporting for this study will be as follows:
All Adverse Events (AE) that are related to any of the study procedures outlined in the protocol (eg during blood testing, during DXA scanning) will be reported to the sponsor
All Serious Adverse Events (SAE) will be reported to the sponsor (both those related to study procedures and those which may not be related to study procedures)

All study-related adverse events, however minor, will be documented. An adverse event is any untoward medical occurrence in a subject administered a pharmaceutical product or, in the case of this study, in a subject undergoing a study procedure (including events that do not necessarily have a causal relationship with the study procedure). Adverse events observed by the Investigator, or reported by the subject, and any remedial action taken, will be recorded in the subject's CRF and should be verifiable in the subject's notes throughout the study. The nature of each event, time of onset (if known), after undergoing a study procedure will be documented together with in the Investigator's opinion of the causal relationship to the study procedure (unrelated, unlikely, possible, probable, definite and not assessable). All subjects experiencing adverse events, whether considered associated with study procedures or not, must be monitored until the symptoms subside.

Severity should be recorded and graded according to the AIDS Clinical Trial Group (ACTG) Grading Scale.
Moreover, adverse events should be assessed in relation to their intensity, defined as follows:
MILD: the adverse event does not interfere with subject's usual function
MODERATE: the adverse event interferes to some extent with subject's usual function
SEVERE: the adverse event interferes significantly with subject's usual function

7.1.2 Serious Adverse Events (SAE)

A SAE is any untoward medical occurrence or effect that:

- **Results in death**
- **Is life-threatening** – *refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe*
- **Requires hospitalisation, or prolongation of existing inpatients' hospitalisation**
- **Results in persistent or significant disability or incapacity** – *there is a substantial disruption of a person's ability to carry out normal life functions*
- **Is a congenital abnormality or birth defect**

An SAE form should be completed and faxed to ICTU for all SAEs within 24 hours of notification about the event. The ICTU will inform the following individuals within 24 hours of receiving notice of them:

1. The Sponsor (JRO, Imperial College London)

2. Funders where contractually agreed
3. The Chief Investigators (Dr Alan Winston and Professor Caroline Sabin)

Given the observational and non-interventional nature of this study, no additional information on SAEs will be captured.

At the study baseline visit, any SAEs occurring during the one year period leading up to entering the study will be assessed. Thereafter, at each yearly visit, SAEs occurring over the past year will be recorded.

All SAEs and AEs will be recorded on the annual study reports that are sent to the MHRA and REC.

Also, given the observational and non-interventional nature of this study, no serious, unexpected adverse drug reactions (SUSARs) reporting will be undertaken. As all subjects continue with their general clinical care, which is unaltered during the course of this study, the 'yellow card' reporting will be unaffected.

7.2 Monitoring

The Quality Assurance (QA) Manager will conduct a risk assessment with the assistance of the CI and Project Manager to assess the requirements for monitoring. A Monitoring Plan will be written accordingly. Monitors will be employed, trained and supervised by ICTU according to their SOP's. Monitoring will be implemented accordingly under the supervision of the Study Manager. Oversight of the trial will be conducted on a day-to-day basis by the QA Manager and the Director of Operations.

7.3 Quality assurance

The plans for the Governance of this study include the involvement of the ICTU QA Manager. The QA Manager will oversee the creation of all essential documentation to be used in this trial, which will be written with reference to the ICTU SOPs to ensure they comply with all ethical and regulatory requirements and are fit for purpose. The QA manager will also conduct a Risk Assessment on the study to ensure the development of an appropriate monitoring plan, which takes into account the particular requirements of this study.

7.4 Data management

Data will be collected via the Inform system. Inform is an Electronic Data Capture (EDC) tool that is used to collect subject information in an electronic case report form (eCRF). The system has a full audit trail built in via a secure internet interface as well as query and alert functionality, electronic signing of case books can be used at multiple sites and has multiple roles and functionality as well as workflow and reporting elements.

8.0 Statistical Considerations

8.1 Methods and planned analysis clinical manifestations

Detailed information on clinical events will be collected at baseline and at each visit. As we currently have very little data on the incidence, presenting features or outcomes of these events in older HIV-positive individuals, many of the analyses will be descriptive. We will describe the proportion of individuals in the three cohorts who have already experienced each event at baseline (prevalence) and the proportions who develop a new (or re-current) event over follow-up (incidence). Confidence intervals will be generated for these proportions. Statistical comparisons of the prevalence/incidence of each event (where numbers are sufficiently large) will be performed using logistic/Poisson regression.

Sample size and power

The sample sizes for baseline analyses will be 1000, 500 and 500 respectively.

Based on data from Goulet *et al* [5], we expect baseline prevalence rates of liver/renal disease of around 14.0%/4.6% among those aged >50 years versus 5%/1% in younger HIV-positive patients and 3.1%/2.3% in HIV-negative patients. Our study will have 70-100% power to detect similarly-sized differences between the three cohorts. Serious medical conditions are, however, expected to be rare, even in the older groups. For example, based on the limited data that exist (from various sources), we may see at most only 17, 20, and 7 cases of myocardial infarction, malignancy and liver failure, respectively, in the HIV-positive groups combined; analyses of incidence of these events will therefore be descriptive. Incident fractures and chronic kidney disease may be more common (105 and 100, respectively), but these numbers will still limit multivariable analyses. NC function impairment and current pain are expected to be present in 40% (n=540) and 63% (n=850) of the HIV-positive subjects at baseline; we will therefore have >95% power (5% significance level) to detect differences of 10% between the proportions with each event in the older HIV-positive and other cohorts; these sample sizes will also permit multivariable analyses of predictive factors. Among the older women (130 or so in the white/black African groups combined), we estimate that 70 (54%) will have already experienced the menopause at baseline; our analyses will be limited to simple comparisons of biomarkers in the two groups.

8.2 Methods and planned analysis for pharmacokinetic analyses

Plasma drug concentrations from the older HIV-positive cohort will be compared with suggested minimally effective concentrations of each drug and to data from a large sample of historical HIV-positive controls obtained from a large therapeutic drug monitoring database held by the University of Liverpool. As plasma drug concentrations have a skewed distribution, non-parametric methods (e.g. Mann-Whitney tests) will be used. Proportional hazards regression will be used to investigate the impact of drug concentrations on time to virological failure (defined as two consecutive viral loads >50 copies/ml whilst remaining on treatment) after controlling for other confounders and adherence. All co-medications and drug doses, regardless of the prescriber, will be documented and the potential for drug-drug interactions investigated. Drug interactions will be defined as clinically significant (severe – drugs should not be co administered / potential interaction where dose adjustment may be necessary) or minor, and associations determined with any side effects reported.

Sample size

Based on current treatment guidelines, we anticipate that around 90% of older HIV-positive participants (n=810) will be receiving cART, with 60% of these patients (n=486) receiving tenofovir. These sample sizes are in excess of those generally used for other published studies of antiretroviral pharmacokinetics, providing further scope for multivariable analyses

8.3 Analysis plan

Cross-sectional analyses of clinical manifestations and therapeutic drug concentrations, and their association with patient factors, will be undertaken at the start of the project once baseline visits are complete; analyses of associations with outcomes will be performed in the following years.

8.4 Study management groups

Study Steering Committee (SSC)

The SSC will include all co-applicants, as well as a patient representative and the study co-ordinator. The SSC will meet twice-yearly. The SSC will have responsibility for the overall progress of the study, and providing scientific oversight.

Study Management Team (SMT)

A SMT will be set up to facilitate the efficient coordination of the programme of work. This group will include members of the SSC as well as the study coordinator, the study research nurses, and a community representative. The roles of this group will be to: develop the full study protocol; coordinate ethics approval of the study; develop information sheets for potential participants; over-see the development of all data collection tools; work with local consultants to generate lists of eligible HIV-positive subjects at each clinic; develop strategies and materials

for the recruitment of HIV-negative subjects; monitor patient recruitment and identify potential problems with this at an early stage of the study; and monitor participant retention in the project and develop strategies for maximizing this.

The SMT will meet monthly, either face-to-face or by teleconference.

8.5 Dissemination of study findings

Study results will be published in peer-reviewed journals from 2013 and will be presented at national and international meetings. Members of the team contribute to the development of management guidelines for those with HIV through BHIVA, the Infectious Diseases Society of Ireland (IDSI)) and the European AIDS Clinical Society (EACS). Through these groups, we will ensure that all relevant stakeholders receive information on study outcomes. Full anonymity of subject's details will be maintained throughout and no individual patient data will be presented.

Through the involvement in the study of Ms Sachikonye, information will be actively disseminated to the HIV patient community; we anticipate that this will involve a combination of workshops/presentations at UK-CAB meetings, the development of posters and short reports of study findings written specifically for the HIV community and to be displayed in hospital waiting areas, and the development of web-based reports accessible through the i-Base website. Subjects wanting to see the results of the study will also be able to request a copy of any study publications from the investigators once they have been published.

A full publication policy, including timelines for receipt of feedback and guidelines for authorship, will be established by the SSC at the start of the study.

8.6 Data sharing policy

We will be proactive in ensuring that this valuable resource is used to its full potential. The SSC will welcome proposals for collaborations from other academic groups as well as the study funders. Those potentially interested should submit a proposal to the SSC containing information about the project, analysis plan and data requirements. Proposals will then be discussed by the SSC and will be approved if it is felt to be scientifically valid with appropriate methodology.

8.7 Role of funders

Funders will also receive an annual report that will include key findings from the study over the past year. The funders will not have any input in the decision to publish findings from the study nor in the content or wording of any submitted manuscripts.
Funders will be allowed to submit scientific research proposals utilising the study data and/or stored samples (potentially requiring further funding) through the channel described above (section 8.6).

APPENDIX 1 TO PROTOCOL
Study questionnaires

The Lawton Instrumental Activities of Daily Living Scale

Ability to Use Telephone

1. Operates telephone on own initiative; looks up and dials numbers 1
2. Dials a few well-known numbers 1
3. Answers telephone, but does not dial 1
4. Does not use telephone at all 0

Shopping

1. Takes care of all shopping needs independently 1
2. Shops independently for small purchases 0
3. Needs to be accompanied on any shopping trip 0
4. Completely unable to shop 0

Food Preparation

1. Plans, prepares, and serves adequate meals independently 1
2. Prepares adequate meals if supplied with ingredients 0
3. Heats and serves prepared meals or prepares meals but does not maintain adequate diet 0
4. Needs to have meals prepared and served 0

Housekeeping

1. Maintains house alone with occasion assistance (heavy work) 1
2. Performs light daily tasks such as dishwashing, bed making 1
3. Performs light daily tasks, but cannot maintain acceptable level of cleanliness 1
4. Needs help with all home maintenance tasks 1
5. Does not participate in any housekeeping tasks 0

Laundry

1. Does personal laundry completely 1
2. Launders small items, rinses socks, stockings, etc 1
3. All laundry must be done by others 0

Mode of Transportation

1. Travels independently on public transportation or drives own car 1
2. Arranges own travel via taxi, but does not otherwise use public transportation 1
3. Travels on public transportation when assisted or accompanied by another 1
4. Travel limited to taxi or automobile with assistance of another 0
5. Does not travel at all 0

Responsibility for Own Medications

1. Is responsible for taking medication in correct dosages at correct time 1
2. Takes responsibility if medication is prepared in advance in separate dosages 0
3. Is not capable of dispensing own medication 0

Ability to Handle Finances

1. Manages financial matters independently (budgets, writes checks, pays rent and bills, goes to bank); collects and keeps track of income 1
2. Manages day-to-day purchases, but needs help with banking, major purchases, etc 1
3. Incapable of handling money 0

Scoring: For each category, circle the item description that most closely resembles the client's highest functional level (either 0 or 1).

ADHERENCE QUESTIONNAIRE

ADHERENCE ASSESSMENT

'We would like to know how much of your HIV medication you have taken recently. We understand that many people on HIV medication find it very difficult to take it regularly and often miss doses so we won't be surprised if you have missed lots of doses as well. We need to know how many doses you have missed.

This questionnaire is completely confidential. Under no circumstance will your answers be shown to your doctor or anyone else involved with your care.'

QA How many doses of HIV medication did you miss yesterday?

O 0 O 1 O 2	O 3 O Don't know

QB How many doses of HIV medication did you miss the day before yesterday?

O 0 O 1 O 2	O 3 O Don't know

QC How many doses of HIV medication did you miss the day before that? (3 days ago)

O 0 O 1 O 2	O 3 O Don't know

QD How many doses of HIV medication have you missed in the last 2 weeks?

O 0 O 1 O 2 O 3-5 O 6-10	O 11-20 O 20-40 O More than 40 O All of them O Don't know

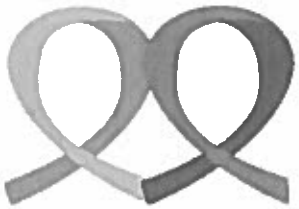
QE Put a cross on the line below at the point showing your best guess about how much HIV medication you have taken in the last month. We would be surprised if this was 100% for most people.

e.g. 0% means you have taken no HIV medication
50% means you have taken half your HIV medication
100% means you have taken every single dose of your HIV medication

QF When was the last time you missed a dose of HIV medication ?

O Today O Yesterday O Earlier this week O Last week	O Less than a month ago O More than a month ago O Never O Don't know

STUDY NUMBER:
PATIENT INITIALS:
DATE:
VISIT:



POPPY

Pharmacokinetic and clinical observations in people over 50

Questionnaire

Thank you for taking the time to fill in this questionnaire.

If you would like help with filling in the questionnaire, one of the study team will be happy to help you.

All information that you give will be treated as strictly confidential.

The nursing team will not assess your answers, they will we entered anonymously at Imperial College.

Take your time – it is not a competition.

Your answers are very important to the POPPY study.

They will give us a good idea how we may treat people as they get older.

The questions will take about 30 minutes to answer.

INSTRUCTIONS

Fill out your answers with a black pen provided – put a cross in the box which most fits your response. The boxes vary in size.

X

COGNITIVE COMPLAINTS		Never	Hardly ever	Yes, definitely
Q1	Do you experience frequent memory loss (for example, do you forget the occurrence of special events even the more recent ones, appointments etc.)?			

Q2	Do you feel that you are slower when reasoning, planning activities, or solving problems?			
Q3	Do you have difficulties paying attention (for example to a conversation, a book, or a movie)?			

IN GENERAL:

Q4	In general, would you say your health is:	Excellent	Very good	Good	Fair	Poor

Q5	Compared to one year ago, how would you rate your health in general now?	Much better now than one year ago	Somewhat better now than one year ago	About the same as one year ago	Somewhat worse now than one year ago	Much worse now than one year ago

SPECIFICALLY:

The following items are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much?				
		Yes, limited a lot	Yes, limited a little	No, limited not at all
Q6	Vigorous activities, such as running, lifting heavy objects, participating in strenuous sports			
Q7	Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf			
Q8	Lifting or carrying groceries			
Q9	Climbing several flights of stairs			
Q10	Climbing one flight of stairs			
Q11	Bending, kneeling or stooping			
Q12	Walking more than a mile			
Q13	Walking several blocks (say 150 yards)			

Q14	Walking one block (say 50 yards)			
Q15	Bathing or dressing yourself			

IN THE PAST 4 WEEKS:

During the past 4 weeks, have you had any of the following problems with your work or regular daily activities as a result of your physical health?		Yes	No
Q16	Cut down the amount of time you spent on work or other activities		
Q17	Accomplished less than you would like		
Q18	Were limited in the kind of work or other activities		
Q19	Had difficulty performing the work or other activities (for example, it took extra effort)		

FEELINGS OF ANXIETY OR DEPRESSION:

During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?		Yes	No
Q20	Cut down the amount of time you spent on work or other activities		
Q21	Accomplished less than you would like		
Q22	Didn't do work or other activities as carefully as usual		

Q23	During the past 4 weeks, to what extent have your physical health or emotional problems interfered with your normal social activities with family, friends, neighbours, or groups?	Not at all	Slightly	Moderately	Quite a bit	Extremely

PAINS:

Q24	How much bodily pain have you had during the past 4 weeks?	None	Very Mild	Mild	Moderate	Severe	Very severe
Q25	During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework)?	Not at all	slightly	moderate	Quite a bit	Extremely	

You have completed a third of the questions.
Well done!

HOW ARE YOU FEELING?

These questions are about how you feel and how things have been with you during the past 4 weeks. For each question please give the one answer that comes closest to the way you have been feeling:

		All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	None of the time
Q26	Did you feel full of pep (energy)?						
Q27	Have you been a very nervous person?						
Q28	Have you felt down in the dumps that nothing could cheer you up?						
Q29	Have you felt calm and peaceful?						
Q30	Did you have a lot of energy?						
Q31	Have you felt downhearted and blue?						
Q32	Did you feel worn out?						
Q33	Have you been a happy person?						
Q34	Did you feel tired?						

Q35. During the past 4 weeks, how much of the time have your health or emotional problems interfered with your social activities (like visiting with friends, relatives etc)?

		All of the time	Most of the time	Some of the time	A little of the time	None of the time

GENERAL HEALTH:

How TRUE or FALSE is each of the following statements to you?						
		Definitely true	Mostly true	Don't know	Mostly false	Definitely false
Q36	I seem to get sick a little easier than other people?					
Q37	I am as healthy as anybody I know					
Q38	I expect my health to get worse					
Q39	My health is excellent					

DEPRESSION:

During the past week

		Rarely or none of the time (less than 1 day	Some or a little of the time (1-2 days)	Occasionally or a moderate amount of time (3-4 days)	Most or all of the time (5-7 days)
Q40	I was bothered by things that usually don't bother me				
Q41	I did not feel like eating: my appetite was poor				
Q 42	I felt that I could not shake off the blues even with help from my family or friends				
Q43	I felt I was just as good as other people				
Q44	I had trouble keeping my mind on what I was doing				
Q45	I felt depressed				
Q46	I felt that everything I did was an effort				
Q47	I felt hopeful about the future				
Q48	I thought my life had been a failure				
Q49	I felt fearful				
Q50	My sleep was restless				
Q51	I was happy				

Q52	I talked less than usual				
Q53	I felt lonely				
Q54	People were unfriendly				
Q55	I enjoyed life				
Q56	I had crying spells				
Q56a	I felt sad				
Q57	I felt that people dislike me				
Q58	I could not get "going"				

Over the last 2 weeks, how often have you been bothered by

		Not at all	Several days	More than half the days	Nearly every day
Q59	Little interest or pleasure in doing things				
Q60	Feeling down, depressed or hopeless				
Q61	Trouble falling asleep, staying asleep, or sleeping too much				
Q62	Feeling tired or having little energy				
Q63	Poor appetite or overeating				
Q64	Feeling bad about yourself – or that you're a failure or have let yourself or your family down				
Q65	Trouble concentrating on things, such as reading the newspaper or watching television				
Q66	Moving or speaking so slowly that other people could have noticed. Or the opposite – being so fidgety or restless that you have been moving around a lot more than usual				
Q67	Thoughts that you would be better off dead, or of hurting yourself.				

RISK OF FALLING:

Q68	Over the past 28 days have you had any falls?	I have not fallen	Once	Twice	Three or more times

If you have had no falls please do not answer the next few questions and proceed to question 73, otherwise please answer the next question.

Where have you fallen?

Q69			
	Inside You may tick more than one	On the one level	
		Getting out of bed	
		Getting out of a chair	
		Using the shower/bath	
		Using the toilet	
		Walking up or down stairs	
		Other	
	Home entrance or in the garden You may tick more than one	Walking up or down a step	
		On the one level (e.g path)	
		In the garden	
		Other	
	Away from home: You may tick more than one	On the footpath	
		On a kerb/gutter	
		In a public building	
		Getting out of a vehicle	
		In another person's home	
		Other	

Q70	How did you fall? Tick more than one if necessary						
I tripped	I slipped	I lost my balance	My legs gave way	I felt faint	I felt giddy/dizzy	I am not sure	Other

Q71	As a result of this fall or falls did you suffer any injuries?	Yes	No

Q72	If yes, what type of injuries did you suffer?					
Bruises	Cuts/grazes	Broken wrist	Broken hip	Broken ribs	Back pain	Other

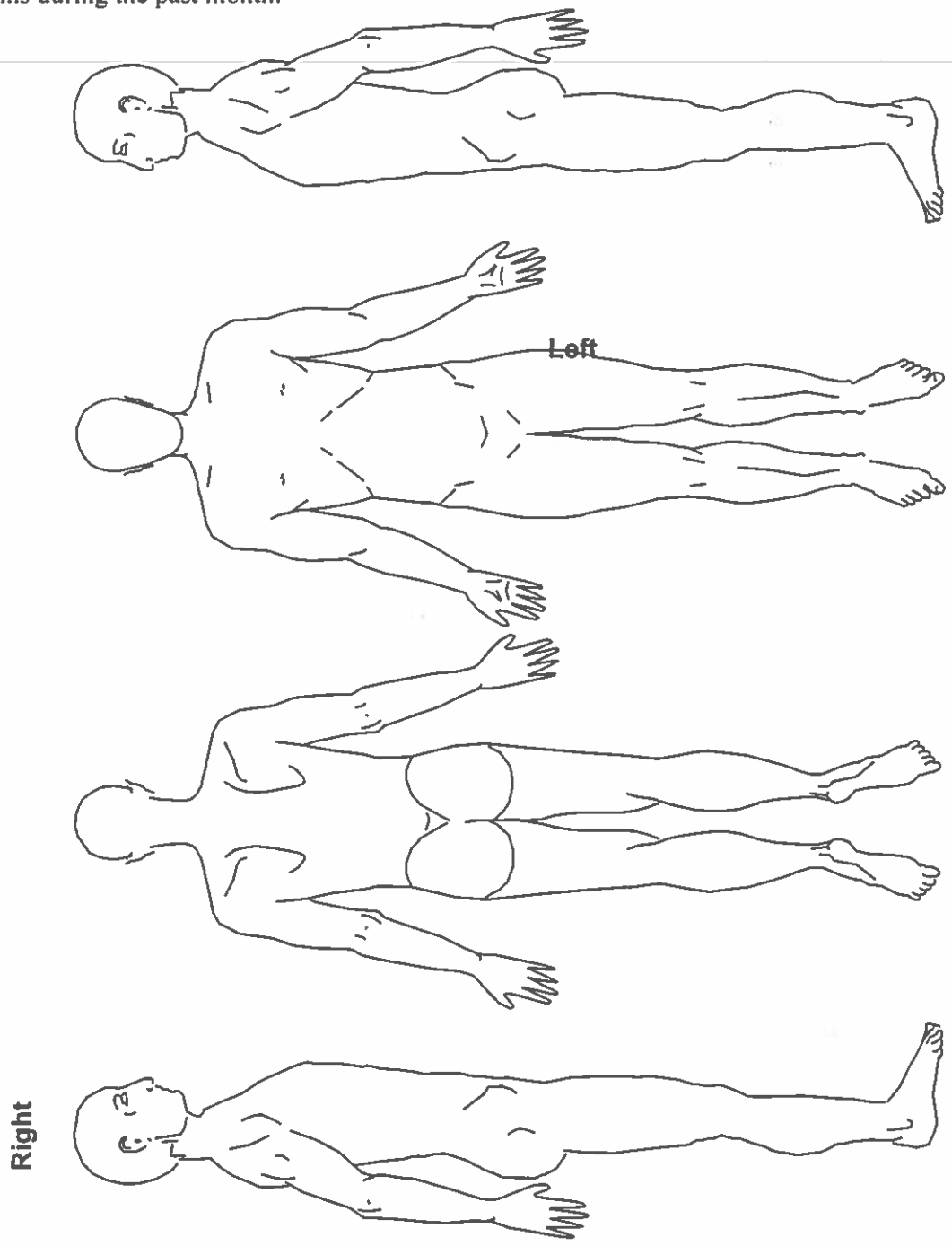
ACHES AND PAINS

Q73	During the past month have you had any aches or pains which have lasted for one day or longer?	Yes	No

if YES, please continue with question 74, otherwise go to question 78

		Yes	No
Q74	Do you have any such aches or pains today?		
Q75	If you work - did you miss any days in the past month from work because of aches or pains? *LEAVE BLANK IF YOU DO NOT WORK*		
Q 76	Have you previously consulted your family doctor because of these aches or pains?		

Q77 Please shade any area on the diagrams below where you feel, or have felt, aches and pains during the past month:



EMPLOYMENT, EDUCATION AND HOUSING

Q78	What is your current work situation?	*cross one square only*
Employed or self-employed FULL-TIME (at least 30 hours per week)		

Employed or self-employed PART-TIME (less than 30 hours per week)	
Full time student / education / training	
Unemployed and registered for benefits	
Unemployed, NOT registered for benefits	
Permanently sick / disabled (for 3 months or more)	
Temporarily sick / disabled (for less than 3 months)	
Looking after home / family / dependants full-time	
Retired	
Other (please specify)	
	Enter number below
If you work, or are a full time student, or you have been temporarily sick or disabled (for less than 3 months), how many days have you been off sick in the last year?	

Q79	What is your current housing situation?	*cross one square only*
Own my own home (including with mortgage / loan / shared ownership)		
Renting from the council or housing association		
Renting from private landlord		
Temporary accommodation (hostel, shelter, bed & breakfast, squat)		
Staying with partner / friend(s) / family		
Homeless		
Other (please specify)		

Q80	Do you have enough money to cover your basic needs? (e.g. food, heating)	*cross one square only*
Yes, all of the time		
Yes, most of the time		
Yes, some of the time		

No	

Q81	At what level did you COMPLETE your education? (Please tick ONE ONLY)	*cross one square only*
Finished education with no qualifications		
O levels / GCSEs (or equivalent qualifications at age 16)		
A levels (or equivalent qualifications at age 18)		
University degree or above		
Other qualifications (please specify)		

SEXUAL FUNCTION

Q82	Regarding your sexuality: which of the following options best describes how you think of yourself?	*cross one square only*
Gay or homosexual		
Bisexual		
Straight or heterosexual		
Any other term (please state)		
I don't usually use a term		

Q83	How often have you felt unsatisfied with your own sex life during the last 4 weeks?	*cross one square only*
Never		
Rarely		
Now and then		
Often		
Always		

Q84	How often have you worried about minimal sexual desire during the last 4 weeks?	*cross one square only*
Never		

Rarely	
Now and then	
Often	
Always	

IF YOU ARE MALE PLEASE ANSWER THE FOLLOWING QUESTION. **MALES ONLY PLEASE.**

Q85	How often could you develop an erection while being sexually active during the last 4 weeks?	*cross one square only*
I haven't been sexually active / not applicable		
Nearly always or always		
Most of the times (much more than half of the times)		
Sometimes (approximately half of the times)		
A few times (much less than half of the times)		
Almost never or never		

IF YOU ARE FEMALE PLEASE ANSWER THE FOLLOWING QUESTIONS. **FEMALES ONLY PLEASE.**

Q86	How often have you been satisfied about your sexual arousal during sexual activities or sexual intercourse during the last 4 weeks?	*cross one square only*
I haven't been sexually active / not applicable		
Nearly always or always		
Most of the times (much more than half of the times)		
Sometimes (approximately half of the times)		
A few times (much less than half of the times)		
Almost never or never		

Q87. Relating to women's periods.

Usually women's periods stop in their 40s or 50s. This is known as the **menopause** or **'the change'**. Some women experience physical and emotional symptoms as their periods begin to stop and for some time after. We want to ask a few questions to find out how this may affect you.

Section A:
Factors affecting cycle. **(please tick the appropriate box)**

1. In the <u>past 6 months</u> have you used	Yes	No	Don't Know
The contraceptive implant (Nexplanon).			
The contraceptive injection (Depo or Depo-provera),			
The hormone coil (Mirena),			

The contraceptive pill?			
2. In the <u>past 12 months</u> have you been pregnant or breastfed?			
3. Are you currently having treatment for any type of cancer?			
If yes please give details of the cancer and any treatment.			
4. Have you had your ovaries and/or uterus (womb) removed?			

Section B: **Menstrual pattern.**	
1. When was your <u>last</u> period?	Month (if known)...../Year.....
2. Thinking about your periods, which of the following best applies to you (<u>tick one</u>):	

a. I have had regular periods in the past 3 months.	a
b. I have had periods in the past 3 months but they are irregular.	b
c. My last period was more than 3 months ago but less than 12 months ago.	c
d. I have not had a period for between one to two years.	d
e. I have not had a period for over two years.	e
f. Not relevant to me.	f

Section C:
1

Which of the following symptoms apply to you at this time? Please, mark the appropriate box for each symptom. For symptoms that do not apply, please mark 'none'.

Symptoms:	none	mild	moderate	severe	very severe
Score =	0	1	2	3	4
1. Hot flushes, sweating (episodes of sweating)	☐	☐	☐	☐	☐
2. Heart discomfort (unusual awareness of heart beat, heart skipping, heart racing, tightness)	☐	☐	☐	☐	☐
3. Sleep problems (difficulty in falling asleep, difficulty in sleeping through, waking up early)	☐	☐	☐	☐	☐
4. Depressive mood (feeling down, sad, on the verge of tears, lack of drive, mood swings)	☐	☐	☐	☐	☐
5. Irritability (feeling nervous, inner tension, feeling aggressive)	☐	☐	☐	☐	☐
6. Anxiety (inner restlessness, feeling panicky)	☐	☐	☐	☐	☐
7. Physical and mental exhaustion (general decrease in performance, impaired memory, decrease in concentration, forgetfulness)	☐	☐	☐	☐	☐
8. Sexual problems (change in sexual desire, in sexual activity and satisfaction)	☐	☐	☐	☐	☐
9. Bladder problems (difficulty in urinating, increased need to urinate, bladder incontinence)	☐	☐	☐	☐	☐
10. Dryness of vagina (sensation of dryness or burning in the vagina, difficulty with sexual intercourse)	☐	☐	☐	☐	☐
11. Joint and muscular discomfort (pain in the joints, rheumatoid complaints)	☐	☐	☐	☐	☐

Have you ever used hormone replacement therapy (HRT)? (tick one below)

a. Yes I am using it currently.	a
b. Yes I have used it in the past but not at the moment.	b
c. No.	c
d. I don't know what hormone replacement therapy (HRT) is.	d

2 If you have ever had any of the symptoms above, and thought that these might be due to the menopause, is there anything else you did to relieve your symptoms?

Please write below:

Finished!
Well done

Thank you for answering all these questions.
You answers are very important to the study

POPPY
Pharmacokinetic and clinical observations in people over 50

Visit 3 Respiratory Questionnaire

STUDY NUMBER:
PATIENT INITIALS:
DATE OF COMPLETION:

FOR RESEARCH STAFF:
Complete details above.
Ensure that all participants complete questions 1-6 and, if any symptoms are reported (indicated by an *), that they also complete the rest of the questionnaire.

FOR STUDY PARTICIPANT:
This questionnaire is designed to help us learn how your breathing may or may not be troubling you, and how your breathing may or may not affect your life.

We ask everyone to complete the first 6 questions.
We then only ask you to complete the rest of the questionnaire (questions 7 to 40) if you report some form of breathing difficulties in your answers to the first 6 questions.

Please read the instructions carefully and ask if you do not understand something. Do not spend too long deciding about your answers.

The following questions are about how much trouble you have with your breathing.

Please mark one box for each question:

1. I cough:
   1 ☐ Most days of the week*
   2 ☐ Several days of the week*
   3 ☐ Only with chest infections
   4 ☐ Not at all

2. I cough up phlegm (sputum):
   1 ☐ Most days of the week*
   2 ☐ Several days of the week*
   3 ☐ Only with chest infections
   4 ☐ Not at all

3. I am short of breath:
   1 ☐ Most days of the week*
   2 ☐ Several days of the week*
   3 ☐ Not at all

4. I have episodes or attacks of wheezing:

1 ☐ Most days of the week*
2 ☐ Several days of the week*
3 ☐ A few days a month*
4 ☐ Only with respiratory infections
5 ☐ Not at all

5. How many sudden shortness of breathing episodes did you have during the last year?

1 ☐ 3 or more episodes*
2 ☐ 1 or 2 episodes *
3 ☐ None

6. How often do you have good days (with few chest or breathing problems)?

1 ☐ No good days*
2 ☐ A few good days*
3 ☐ Most days are good
4 ☐ Every day is good

*If any answer with an *asterisk* has been selected, please complete the rest of the questionnaire. If you have not ticked any of the answers with an asterisk, please do not proceed. This is the end of the questionnaire.

Please mark one box for each question:

7. If you wheeze, is it worse when you get up in the morning?

1 ☐ No
2 ☐ Yes
3 ☐ Don't wheeze

8. How would you describe your chest problem(s)?

1 ☐ Cause me a lot of problems or are the most important physical problems I have
2 ☐ Cause me few problems
3 ☐ Cause no problems

For each of the following activities, please state whether the activity makes you feel breathless or not.

	For each statement please mark the box that applies to you these days	
	Yes	No
9. Washing or dressing yourself	1☐	2☐
10. Walking around the house	1☐	2☐
11. Walking outside on level ground	1☐	2☐
12. Walking up a flight of stairs	1☐	2☐
13. Walking up hills	1☐	2☐

Please say whether each of the statements applies to you or not.

	For each statement please mark the box that applies to you these days	
	Yes	No
14. Coughing hurts	1☐	2☐
15. Coughing makes me tired	1☐	2☐
16. I am short of breath when I talk	1☐	2☐
17. I am short of breath when I bend over	1☐	2☐
18. My coughing or breathing disturbs my sleep	1☐	2☐
19. I get exhausted easily	1☐	2☐

Please say whether each of the statements applies to you or not.

For each statement please mark the box that applies to you these days

	Yes	No
20. My cough or breathing is embarrassing in public	1☐	2☐
21. My chest problems are a nuisance to my family, friends or neighbours	1☐	2☐
22. I get afraid or panic when I cannot catch my breath	1☐	2☐
23. I feel that I am not in control of my chest problems	1☐	2☐
24. I have become frail or an invalid because of my chest problems	1☐	2☐
25. Exercise is not safe for me	1☐	2☐
26. Everything seems too much of an effort	1☐	2☐

Statements about how your activities might be affected by your chest problems.

For each statement please mark the box that applies to you these days

	True	False
27. I take a long time to get washed or dressed	1☐	2☐
28. I cannot take a bath or shower, or I take a long time to do it	1☐	2☐
29. I walk slower than other people my age, or I stop to rest	1☐	2☐
30. Jobs such as household chores take a long time, or I have to stop to rest	1☐	2☐
31. If I walk up one flight of stairs, I have to go slowly or stop	1☐	2☐
32. If I hurry or walk fast, I have to stop or slow down	1☐	2☐
33. My breathing makes it difficult to do things such as walk up hills, carry things up stairs, light gardening such as weeding, dance, bowl or play golf	1☐	2☐
34. My breathing makes it difficult to do things such as carry heavy loads, dig in the garden or shovel snow, jog or walk briskly (5 miles per hour or 8km/h), play tennis or swim	1☐	2☐

Statements about how your chest problems usually affect your daily life.

For each statement please mark the box that applies to you these days

	True	False
35. I cannot play sports or do other physical activities	1☐	2☐
36. I cannot go out for entertainment or recreation	1☐	2☐
37. I cannot go out of the house to do the shopping	1☐	2☐
38. I cannot do household chores	1☐	2☐
39. I cannot move far from my bed or chair	1☐	2☐

40. How do your chest problems affect you (please mark one box)?

1☐ They do not stop me from doing anything I would like to do

2☐ They stop me from doing one or two things I would like to do

3☐ They stop me from doing most of the things I would like to do

4☐ They stop me from doing everything I would like to do

Thank you for filling out this questionnaire

Before you finish would you please check to see that you have answered all the questions.