TAILoR – (TelmisArtan and InsuLin Resistance in HIV): A Dose-Ranging Phase II Randomised Open-Labelled Trial of Telmisartan as a strategy for the Reduction of Insulin Resistance in HIV-Positive Individuals on Combination Antiretroviral Therapy (cART)

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General Information
This document describes the TAILoR trial and provides information about procedures for entering patients into it. The protocol should not be used as an aide-memoir or guide for the treatment of other patients; every care was taken in its drafting, but corrections or amendments may be necessary. These will be circulated to the registered investigators in the trial, but centres entering patients for the first time are advised to contact the coordinating centre (Clinical Trials Research Centre, University of Liverpool) to confirm they have the most up to date version. Clinical problems relating to this trial should be referred to the relevant Chief Investigator via the CTRC.

This protocol defines the participant characteristics required for study entry and the schedule of treatment and follow-up. Participant recruitment will be undertaken in compliance with this document and applicable regulatory and governance requirements and waivers to authorise non-compliance are not permitted.

Incidence of protocol non-compliance, whether reported prospectively (e.g. where a treatment cannot be administered on a scheduled date as a result of public holidays) or retrospectively noted (e.g. as a result of central monitoring) are recorded as protocol deviations, the incidence of which are monitored and reported to trial oversight committees.

Statement of Compliance
This study will be carried out in accordance with the World Medical Association Declaration of Helsinki (1964) and the Tokyo (1975), Venice (1983), Hong Kong (1989) and South Africa (1996) amendments and will be conducted in compliance with the protocol, CTRC Standard Operating Procedures and EU Directive 2001/20/EC, transposed into UK law as the UK Statutory Instrument 2004 No 1031: Medicines for Human Use (Clinical Trials) Regulations 2004 as amended.

Relationship Statements
The UK Clinical Research Collaboration (UKCRC; www.ukcrc.org) is a partnership organisation working to establish the UK as a world leader in clinical research. Following a review by an international panel, the Clinical Trials Research Centre (CTRC) at the University of Liverpool has been assessed as reaching the highest quality standard required by the UKCRC and achieved full UKCRC registration.

The CTRC encompasses clinical trials activity in areas including medicines for children (The Medicines for Children Research Network Clinical Trials Unit; MCRN CTU), cancer (The Liverpool Cancer Trials Unit; LCTU), epilepsy, oral health and obstetrics and gynaecology (http://www.ctrc.org.uk/). All CTRC activities are underpinned by methodological rigour, a modern data management system, similar technical requirements and a common set of standard operating procedures. The NIHR Medicines for Children Research Network and National Cancer Research Network is part of the National Institute for Health Research Clinical Research Network.

The Wolfson Centre for Personalised Medicine is part of the Department of Molecular and Clinical Pharmacology in the Institute of Translational Medicine, University of Liverpool and undertakes research in various aspects of drug safety using *in vitro*, *in vivo* and clinical models. The Wolfson Centre will work with the CTRC for the efficient conduct of the trial.

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Glossary

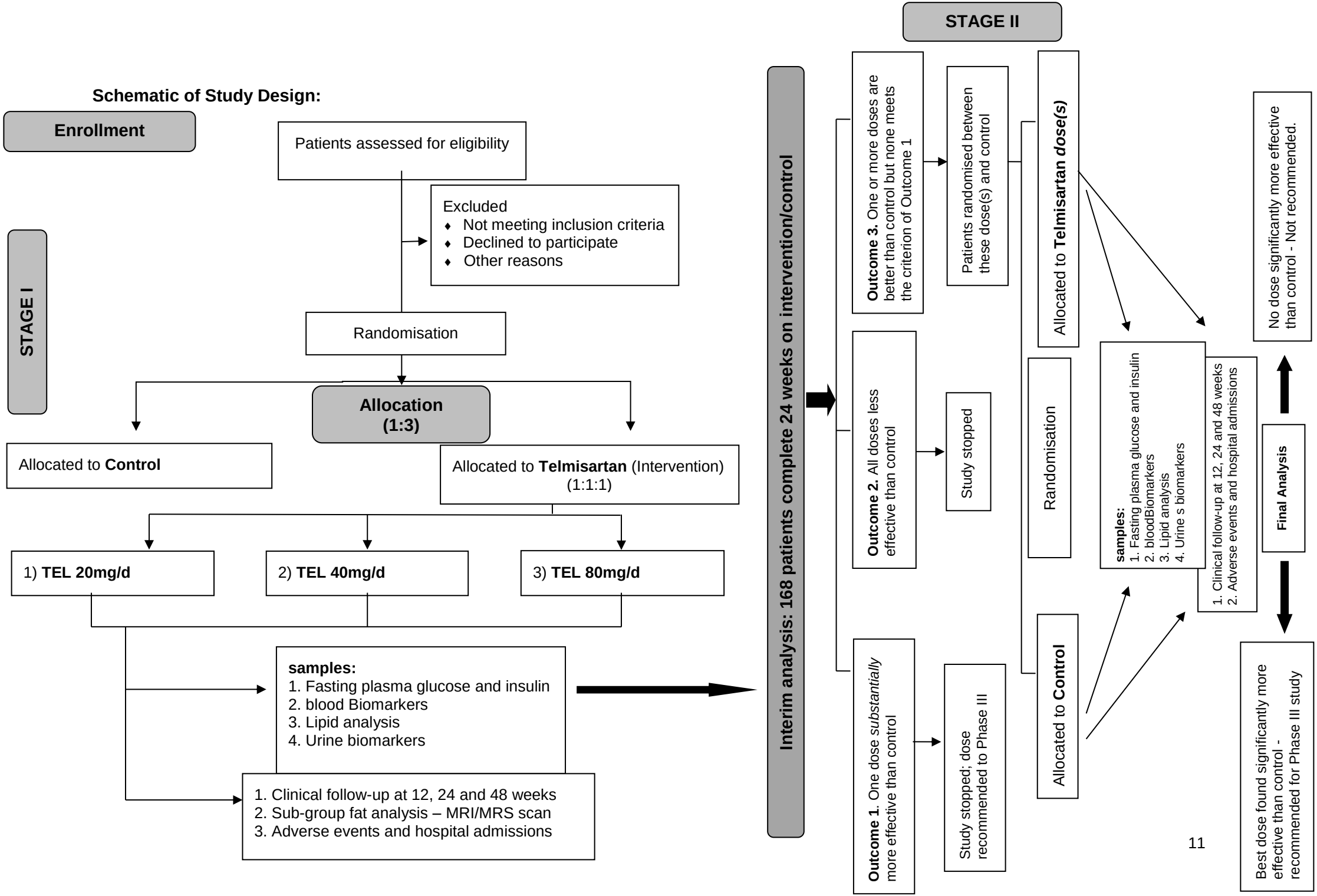
ACE	Angiotensin Converting Enzyme
AE	Adverse Event
AR	Adverse Reaction
ARBs	Angiotensin Receptor Blockers
cART	Combination Antiretroviral Therapy
CCRN	Comprehensive Clinical Research Network
CI	Chief Investigator
CRF	Case Report Form
CR-UK LCTU	Cancer Research UK Liverpool Cancer Trials Unit
CTIMP	Clinical Trial of Investigational Medicinal Product
CTRC	Clinical Trials Research Centre
CVD	Cardiovascular Disease
eGFR	Estimated Glomerular Filtration Rate
GCP	Good Clinical Practice
GP	General Practitioner
HOMA-IR	Homeostatic Model Assessment – by Insulin Resistance
HIV	Human Immunodeficiency Virus
HIVLD	HIV associated lipodystrophy
hs-CRP	High sensitivity- C Reactive Protein
IB	Investigator's Brochure
IDSMC	Independent Data and Safety and Monitoring Committee
IEC	Independent Ethical Committee
IL-6	Interleukin-6
IMP	Investigational Medicinal Product
LCL	Liverpool Clinical Laboratories
MARIARC	Magnetic Resonance and Image Analysis Research Centre
MCRN CTU	Medicines for Children Research Network Clinical Trials Unit
MREC	Multi-centre Research Ethics Committee
MRI	Magnetic Resonance Imaging
MRS	Magnetic Resonance Scanning
MS	Metabolic Syndrome
NIHR CRN	National Institute for Health Research Clinical Research Network
NRTI	Nucleoside Reverse Transcriptase Inhibitors
N(t)RTI	Nucleotide Reverse Transcriptase Inhibitors
PI	Principal Investigator
PPAR	Peroxisome Proliferator Activated Receptor
R&D	Research & Development
REC	Research Ethics Committee
RN	Research Nurse When RN is referred to in this protocol it means either the research nurse or someone who has been delegated that duty
RLH	Royal Liverpool Hospital
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SDV	Source Data Verification
SPC	Summary of Product Characteristics
SUSAR	Suspected Unexpected Serious Adverse Reaction
T2DM	Type 2 Diabetes
TMG	Trial Management Group
TNF	Tumour Necrosis Factor
TSC	Trial Steering Committee
UAR	Unexpected Adverse Reaction

1 PROTOCOL SUMMARY

Title:	TAILoR (TelmisArtan and InsuLin Resistance in HIV): A Dose-Ranging Phase II Randomised Open-Labelled Trial of Telmisartan as a Strategy for the Reduction of Insulin Resistance in HIV-Positive Individuals on Combination Antiretroviral Therapy (cART)
Phase:	II
Study Design:	Multi-centre randomised, open-labelled, phase II dose-ranging trial of telmisartan in HIV-positive individuals over a period of 48 weeks using an adaptive trial design.
Population:	All adult HIV-positive individuals receiving antiretroviral therapy containing a boosted protease inhibitor and/or efavirenz, for at least 6 months and fulfil the inclusion criteria.
Criteria for Inclusion:	1. Adult (age 18 or above) HIV-positive individuals receiving antiretroviral therapy containing • a boosted protease inhibitor (lopinavir/ritonavir, atazanavir/ritonavir, darunavir/ritonavir, fosamprenavir/ritonavir, saquinavir/ritonavir) • and/or efavirenz, rilpivirine, or etravirine for at least 6 months. The backbone can be based on N(t)RTI, raltegravir or maraviroc. Patients on protease inhibitor monotherapy will be included if they meet other criteria. Patients on nevirapine- or dolutegravir regimens, without concomitant boosted PIs, should not be included. Additionally, patients on Elvitegravir which is administered in combination with cobicistat (as Stribild) should not be recruited. 2. Ability to give informed consent. 3. Willingness to comply with all study requirements.
Criteria for Exclusion:	1. Pre-existing diagnosis of type 1 or 2 diabetes (Fasting glucose > 7.2mmol/L or HbA1c ≥ 6.5% [48 mmol/mol] or abnormal OGTT or random plasma glucose ≥ 11mmol/l) 2. Patients who consistently show low blood pressure (pre-existing hypotension; A reading below a threshold of 100/60 mm Hg on three separate occasions 3. Patients with renal disease (eGFR<60 in the 6 months preceding randomisation) 4. Patients with known untreated renal artery stenosis 5. Patients with cholestasis, biliary obstructive disorders or severe hepatic impairment 6. Patients with evidence of active, chronic hepatitis C infection (a previously cleared infection is not an exclusion) 7. Patients who are on unboosted atazanavir 8. Patients who are on/ have been on hormone therapy (eg. growth hormone), anabolics (eg. testosterone) and insulin sensitisers (eg. Metformin) within 6 months preceding randomisation. Patients who are on hormonal contraception are eligible. 9. Patients who are already on/ have been on other ARBs, ACE inhibitors, or direct renin inhibitors e.g. aliskiren within 4 weeks preceding randomisation. 10. Those with suspected poor compliance 11. Pregnant or lactating women 12. Women of childbearing age unless using reliable contraception (e.g. coil, barrier method, hormonal contraception) that does not interact with their antiretroviral therapy 13. Co-enrolment in other drug trials 14. Patients who have participated in a trial of an IMP likely to influence

	insulin sensitivity, plasma insulin, glucose levels or plasma lipid levels within 6 months preceding randomisation. For the sub-cohort of patients undergoing MRI/MRS, normal MR exclusion criteria will apply.
Study Centres and Distribution:	Specialist HIV treatment centres in the UK
Study Duration:	47 months
Description of Agent/ Intervention:	Oral Telmisartan. In the initial stage, the trial will involve an adaptive design and will use 20mg, 40mg and 80mg doses with appropriate dose titration.
Number of participants to be enrolled:	Original aim: 370 patients after accounting for a 10% loss to follow-up. In the first stage, the study will recruit 168 evaluable patients who are randomised to each of the trial arms. Upon interim analysis, a further maximum of 168 evaluable patients will be recruited, but this number may vary according to the results from the interim analysis. Post-interim analysis: As a result of the interim analysis, the maximum number of patients to be randomised has been increased to 377.
Primary Objective:	This trial will determine the effect of telmisartan on insulin resistance (as measured by HOMA-IR) in HIV-positive individuals on cART.
Secondary Objective/s:	1. To define the optimal dose of telmisartan that can significantly reduce insulin resistance. 2. To measure HOMA-IR values at the baseline and at 12, 24 and 48 weeks to provide data on time to, and sustainability of reduction in HOMA-IR. 3. To evaluate the tolerability of telmisartan in this patient group. 4. To mechanistically evaluate whether telmisartan modulates the plasma concentrations of both beneficial and adverse biomarkers. 5. To determine whether telmisartan improves general lipid homeostasis and reduces visceral fat accumulation in HIV-positive individuals on cART. 6. To determine whether ^{1}H MRS-assessed intrahepatic and intramyocellular triglyceride content are reduced by telmisartan. 7. To determine whether telmisartan reduces renal toxicity in HIV-positive individuals on cART. 8. To utilise alternate indices of insulin resistance (QUICKI and revised QUICKI) to determine the effect of telmisartan on insulin resistance.

Schematic of Study Design:



2 BACKGROUND INFORMATION

2.1 Introduction

Combination antiretroviral therapy (cART) is the mainstay for treatment of HIV and has dramatically improved the morbidity and mortality associated with HIV, turning it into a chronic disease. However, cART, together with the virus itself, can lead to various metabolic complications, leading to type 2 diabetes (T2DM) and an increased risk of cardiovascular disease (CVD). These metabolic complications associated with cART may occur with HIV lipodystrophy (HIVLD; also called fat redistribution syndrome), a clustering of morphologic and metabolic abnormalities comprising peripheral fat loss (lipoatrophy), visceral lipid hypertrophy, insulin resistance and dyslipidemia[1]. HIVLD is a predictor of metabolic syndrome (MS) and associated CVD risk[2]. MS itself is a known risk factor for T2DM and CVD[3]. The prevalence of MS is high in cART treated HIV+ patients (17-25%)[4,5]; the HIV DAD cohort (n=33,347) found the prevalence of MS to increase from 19.4% to 41.6% over a 6-year period[6]. Moreover, patients with MS had a 4-fold increase in the incidence of T2DM and a 2-3 fold increased risk of developing CVD. These results have been confirmed by the Multicenter AIDS Cohort Study (n=1278)[7] and a more recent analysis of the DAD cohort[8]. Cumulative exposure to cART also results in an increased risk of CVD in HIV-infected patients. The DAD study reported a linear increase in the incidence of myocardial infarction with long term cART exposure, with both protease inhibitors[9] and nucleoside reverse transcriptase inhibitors[10] (NRTIs). Long term use of cART also results in intima-media thickness and an increase in the prevalence of carotid lesions making it a risk factor for subclinical atherosclerosis[11]. It is therefore clear that cART treated HIV+ patients are at an increased risk of cardiometabolic problems.

Insulin resistance, a key feature of HIVLD and MS, has been described as central to cardiometabolic disease and is considered to be an important link between features of MS, obesity, dyslipidemia, T2DM and CVD[12]. *In vitro* studies[13] and single drug studies in healthy individuals[14] and HIV+ patients[15,16] have shown that PIs and NRTIs cause insulin resistance. The prevalence of insulin resistance in cART-treated HIV+ patients ranges from 10-37%[15,16,17] indicating a significant role for cART in its development. In the Fat Redistribution and Metabolic Change in HIV Infection (FRAM) study (n=926), a cross-sectional analysis showed the prevalence of insulin resistance to be 37%[17]. Several mechanisms have been suggested to be responsible for cART-induced insulin resistance; these include cART-induced inhibition of adipocyte differentiation[18], increased secretion of adipokines such as IL-6 and TNF-α[19], and impairment of insulin signalling pathway[13].

Clinical intervention to arrest or reverse cART-associated insulin resistance has been suggested as a strategy to reduce the incidence of T2DM and CVD in HIV-positive patients. Insulin sensitizers such as thiazolidinediones and metformin have been trialled but results from randomised clinical trials in HIV+ patients have shown mixed results[20,21]. Moreover, the associated adverse effects may limit their use in HIV+ patients[22,23]. Therefore there is a need for novel clinical interventions with proven safety profile that can reduce cART-induced insulin resistance in HIV+ individuals.

Some angiotensin receptor blockers (ARBs) have a beneficial effect on insulin resistance and T2DM, owing to their partial agonistic activation of PPARγ, an important regulator of adipocyte function. Telmisartan shows maximal potency on PPARγ when compared to other ARBs and has been reported to reduce insulin resistance in several *in vitro*[24,25], animal[26,27] and clinical studies[28,29,30,31]. Prospective randomised clinical trials in patients with diabetes and those with MS have shown that telmisartan significantly reduces insulin resistance: (a) in 188 T2DM patients with MS, telmisartan significantly reduced HOMA-IR by 17% after 6 months treatment and by 29% after 12 months[28]; (b) in a comparison with other ARBs in non-diabetic patients (n=151), telmisartan reduced HOMA-IR by 29% after 6 months

treatment[29]. Telmisartan also improves adiponectin levels, an important metabolic marker of insulin resistance and atherosclerotic disease; it improved lipid control in these patients[28], and has favourable effects on fasting serum insulin and high sensitivity C-Reactive Protein[28] (hs-CRP; a marker of cardiovascular disease). Telmisartan has also been shown to reduce visceral, but not subcutaneous fat accumulation, in patients with MS[32,33]. Telmisartan reduced cardiovascular events in a broad group of at-risk patients; one of the largest ARB outcome trials (ONTARGET trial; 120,000 patient-years of follow-up) established telmisartan to confer similar cardiovascular protection as ramipril, but with better tolerance[34]. Importantly, the beneficial effects of telmisartan on insulin sensitivity have been observed at doses lower than those used for hypertension; 20mg/day telmisartan significantly reduced HOMA-IR after 20 months treatment in patients with non-alcoholic steatohepatitis[31]. Telmisartan also shows renoprotective effects[55]; it has been shown to significantly reduce microalbuminuria in HIV-positive patients[56] and therefore may have a positive impact on parameters of renal injury observed in cART-treated HIV-positive patients. The trial represents an opportunity to determine the effect of telmisartan on conventional and novel biomarkers of renal injury.

2.2 Rationale

There is already strong evidence for the beneficial effects of telmisartan on insulin resistance and other markers of glycemic control and cardiovascular health in non-HIV population. We and others have shown that antiretroviral drugs inhibit adipocyte differentiation[18,19], reduce adiponectin secretion[18,35], increase the secretion of detrimental cytokines, IL-6 and TNF-α[18,19] and impair GLUT-4 expression[36], all of which are suggested to contribute to the development of insulin resistance. We have recently shown that telmisartan partially reverses the anti-adipogenic effects of antiretrovirals *in vitro* (Pushpakom et al; unpublished). Telmisartan partially reversed antiretroviral drug-induced inhibition of adipocyte lipid accumulation and downregulation of adiponectin and lipin1. The beneficial effect of telmisartan on adipocyte function in the presence of antiretrovirals has also been shown by Capeau and co-workers[37]. However the clinical efficacy of telmisartan to reduce insulin resistance in cART-treated HIV+ patients has not been assessed; this study has been conceived and designed to address this.

Our *in vitro* study observed a non-monotone relationship of telmisartan on adiponectin and lipin1 secretion; a study in non-alcoholic steatohepatitis patients also observed that telmisartan improves insulin sensitivity at doses lower than those used for hypertension[31]. This indicates the need to carefully assess the dose-response relationship of telmisartan *in vivo;* hence the need for an adaptive trial design during the initial stage of the study. Three different doses of telmisartan (20mg, 40mg and 80mg) will be assessed for their effect on insulin resistance measured as HOMA-IR over a period of 24 weeks in the first stage of the study. An interim analysis will be conducted at the end of Stage I to eliminate ineffective doses and to take forward the most effective doses for further testing in Stage II. A treatment period of 24 weeks has been chosen for measuring the change in HOMA-IR both in Stage I and in Stage II based on existing literature which shows telmisartan results in significant reduction in HOMA-IR within this time-frame in non-HIV patient populations[28,29].

Alternate surrogate indices of insulin sensitivity such as Quantitative Insulin Sensitivity Check Index (QUICKI) and its revised version (Revised QUICKI, which incorporate non-esterified fatty acid levels) has been recently suggested to correlate better with the gold standard, hyperinsulinaemic–euglycaemic clamp, as compared to HOMA-IR[57] . The trial will also determine the effect of telmisartan on insulin resistance based on QUICKI and Revised QUICKI measures.

2.3 Objectives

Primary objective: To determine the effect of telmisartan on insulin resistance in HIV-positive individuals on cART using HOMA-IR as a measurable, validated surrogate marker of insulin resistance.

Secondary objectives:

1) To define the optimal dose of telmisartan that can significantly reduce insulin resistance; this dose will then be taken forward into phase III studies in the future.

2) To measure HOMA-IR values at the baseline (T0) and at 12, 24 and 48 weeks to provide data on time to, and sustainability of, reduction in HOMA-IR.
3) To evaluate the tolerability of telmisartan in this patient group.
4) To mechanistically evaluate whether telmisartan favourably modulates the plasma concentrations of both beneficial (adiponectin and lipin1) and adverse (IL-6, resistin, TNFα, hs-CRP) biomarkers, which may help in further stratifying telmisartan therapy in the future.
5) To determine whether telmisartan improves general lipid homeostasis and reduces visceral fat accumulation in HIV-positive individuals on cART over a 24-week period.
6) To determine whether ^{1}H MRS-assessedintrahepatic and intramyocellular triglyceride content, markers of hepatic steatosis and insulin resistance respectively, are reduced by telmisartan therapy. This will provide us with mechanistic insights into the ability of telmisartan to beneficially affect fat redistribution, hepatic staetosis and insulin resistance.
7) To determine whether telmisartan has an effect on urinary biomarkers (creatine, urea, total protein, novel biomarkers such as KIM-1, NGAL, and RBP) of renal injury in HIV-positive individuals on cART.
8) To utilise alternate indices of insulin resistance such as Quantitative Insulin Sensitivity Check Index (QUICKI) and revised QUICKI to determine the effect of telmisartan on insulin resistance.

A list of outcome measures is presented in Section 4.

2.4 Potential Risks and Benefits

The medications used in this study are subject to marketing authorisations and are to be prescribed in accordance with current clinical practice. The management of any symptoms or exacerbations will be in accordance with usual clinical practice and either the local principal investigator (PI) or delegated research staff, will be available throughout the study to discuss specific issues with individuals concerned. Any concerns, which cannot be satisfied at a local level, will be forwarded to the chief investigator (CI) via the TAILoR Trial Manager. Any participant can withdraw from the study at any time with no detriment to their future care. All ethical aspects of the study will be discussed when informed written consent is obtained. Appropriate information leaflets have been developed and are discussed at the screening consultation. Potential participants will be provided with a copy of the information sheets and their signed consent forms.

2.4.1 Potential Risks

There are few risks for patients entering this trial. Participation in this trial does not change existing HIV treatment protocols or have any impact on the viral control. Hypotension is clearly a potential adverse effect of telmisartan, it being an antihypertensive; but previous studies in normotensive individuals have shown that the prevalence of adverse effects on blood pressure is low[38,39]. This will be routinely monitored in all patients during the trial. There has been some recent publicity about telmisartan increasing the risk of cancer following the publication of a meta-analysis[40]. However, this meta-analysis has been heavily criticised[41], and a new recent, more extensive meta-analysis[42] has been more reassuring

with respect to the risk of cancer in patients on ARBs. There are no reported interactions between telmisartan and antiretrovirals.

One practical issue is the addition to the already existing pill burden in this group of patients; however, telmisartan is administered as a single oral tablet taken only once daily, and thus, likely to cause a minimal increase in the pill burden. There is no further additional burden to participants in the trial, apart from the need to undergo magnetic resonance imaging/spectroscopy (MRI/MRS) in a subset of patients recruited in Liverpool.

Telmisartan, and indeed any drug acting on the renin-angiotensin system, can lead to renal impairment in patients with known or undiagnosed renal artery stenosis. Known renal artery stenosis is an exclusion criterion for this trial; we have also excluded patients with an eGFR<60ml/min in the last 6 months. In the treatment of hypertension, some clinicians measure renal function 1-2 weeks after starting drugs acting on the rennin-angiotensin system. However, this is not a requirement in the SPC for telmisartan, and nor is it recommended by the NICE guidelines on hypertension in patients without known renal disease.

2.4.2 Known Potential Benefits

There are potential benefits if our hypothesis that telmisartan reduces insulin resistance in cART-treated HIV patients is proven. Other potential benefits include a beneficial effect on various biomarkers, lipid profile and visceral adiposity.

3 SELECTION OF CENTRES/CLINICIANS

Study centres will be initiated once all global (e.g. local R&D approval) and study-specific conditions (e.g. training requirements) have been met, and all necessary documents have been returned to CTRC. Initiation meetings will cover the requirements outlined in CTRC SOPs TM017 and TM018.

3.1 Centre/Clinician Inclusion Criteria

Each participating centre (and Principal Investigator; PI) has been identified on the basis of:

- Being a specialist HIV treatment centre
- Having at least one lead clinician with a specific interest in, and responsibility for supervision and management of patients with HIV
- Showing enthusiasm to participate in the study
- Ensuring that sufficient time, staff and adequate facilities are available for the trial
- Providing information to all supporting staff members involved with the trial or with other elements of patient management
- Identifying that they will be able to recruit the required number of patients
- Acknowledging and agreeing to conform to the administrative and ethical requirements and responsibility of the study including adhering to GCP and other regulatory documentation
- Other important criteria are:
  a. Local R&D approval
  b. Completion and return of 'Signature and Delegation Log' to CTRC
  c. Signed non-commercial agreement between centre and sponsor
  d. Receipt of evidence of completion of (a),(b) and (c) by CTRC

3.2 Centre/Clinician Exclusion Criteria

a. Not meeting the inclusion criteria listed above

4 TRIAL DESIGN

This study is a phase II, multi-centre, randomised, open-labelled, dose-ranging trial of telmisartan in HIV-positive individuals over a period of 48 weeks.

In the first stage of the study, an adaptive trial design with 3 different telmisartan dose arms and a non intervention (control) arm will be utilised. Patients will initially be randomised equally to receive 3 doses of telmisartan (20, 40 and 80mg) or no intervention (control). An interim analysis will be performed when half of the planned maximum of 336 patients has been followed up for at least 24 weeks. If one active dose group is substantially more effective than control then the study will be stopped and the corresponding dose will be taken directly into phase III. Any active dose groups showing insufficient promise at the interim analysis will be dropped and the study continued with the remaining doses and control. If no dose shows sufficient promise at the interim analysis, the study will be stopped. If some improvement over control is detected for at least one of the doses at interim analysis, that dose(s) will be followed up along with the control for a further 24 weeks (total: 48 weeks).

If at the final analysis, a large enough reduction in 24 week HOMA-IR score is found, the corresponding active dose will be recommended for phase III.

As the standard deviation of reductions in HOMA-IR in the patient group to be recruited is not well understood, a power requirement that does not depend on its value is used to construct the design. In the telmisartan 40mg and 80mg arms, dose titration will be undertaken over 2−4 weeks in order to step-up to the allocated dose (as per the SPC), or else the maximum tolerated dose if the target is not achieved.

4.1 Primary Outcome

Reduction in insulin resistance (as measured by HOMA-IR) in telmisartan treated arm(s) after 24 weeks of treatment in comparison with control. This is a pure efficacy outcome.

4.2 Secondary Outcome(s)

1. Change in lipid profile at T+12, T+24 and T+48 weeks (increase in HDL-c, reduction in total cholesterol, triglycerides and LDL-c) between telmisartan treated arm(s) and the control arm.

2. Change in body fat redistribution as measured by MRI/MRS at T+24 weeks between telmisartan treated arm(s) and control arm (reduction in visceral fat, change in intrahepatic fat, change in lower leg muscle fat) (See Section 8.5).

3. Change in plasma concentrations of biomarkers (adiponectin, lipin1, IL-6, TNF-α, Resistin and hs-CRP) at T+12, T+24 and T+48 weeks between telmisartan treated arm(s) and the control arm.

4. Change in insulin resistance, measured longitudinally, in telmisartan treated arm(s) in comparison with the control arm.

5. Change in urinary biomarker levels at T+12, T+24 and T+48 weeks between telmisartan treated arm(s) and the control arm.

6. Difference in expected and unexpected serious adverse events between different telmisartan treated dose arm(s) and the control arm.
7. Reduction in insulin resistance (as measured by QUICKI and Revised QUICKI) in telmisartan treated arm(s) after 24 weeks of treatment in comparison with control.

5 STUDY POPULATION

The study will recruit HIV-positive patients from HIV treatment centres in the UK.

5.1 Inclusion Criteria

1. Adult (age 18 or above) HIV-positive individuals receiving antiretroviral therapy containing
    - a boosted protease inhibitor (lopinavir/ritonavir, atazanavir/ritonavir, darunavir/ritonavir, fosamprenavir/ritonavir, saquinavir/ritonavir)
    - and/or efavirenz, rilpivirine, or etravirine for at least 6 months.

    The backbone can be based on N(t)RTI, raltegravir or maraviroc.
    Patients on protease inhibitor monotherapy will be included if they meet other criteria.

    Patients on nevirapine or dolutegravir regimens, without concomitant boosted PIs, should not be included. Additionally, patients on Elvitegravir which is administered in combination with cobicistat (as Stribild) should not be recruited.

2. Ability to give informed consent
3. Willingness to comply with all study requirements

5.2 Exclusion Criteria

1. Pre-existing diagnosis of type 1 or 2 diabetes (Fasting glucose > 7.2mmol/L or HbA1c ≥ 6.5% [48 mmol/mol] or abnormal OGTT or random plasma glucose ≥ 11mmol/l)
2. Patients known to have consistently low blood pressure (pre-existing hypotension; A reading below a threshold of 100/60 mm Hg on three separate occasions)
3. Patients with renal disease (eGFR<60 in the 6 months preceding randomisation)
4. Patients with known untreated renal artery stenosis
5. Patients with cholestasis, biliary obstructive disorders or severe hepatic impairment.
6. Patients with evidence of an active, chronic hepatitis C infection (a previously cleared infection is not an exclusion)
7. Patients who are on unboosted atazanavir
8. Patients who are on/ have been on hormone therapy (eg. growth hormone), anabolics (eg. testosterone) and insulin sensitisers (eg. Metformin) within 6 months preceding randomisation. Patients who are on hormonal contraception are eligible.
9. Patients who are already on/ have been on other ARBs, ACE inhibitors, or direct renin inhibitors (e.g. aliskiren) within 4 weeks preceding randomisation.
10. Those with suspected poor compliance
11. Pregnant or lactating women
12. Women of childbearing age unless using reliable contraception e.g. coil, barrier method, hormonal contraceptive that does not interact with their antiretroviral therapy
13. Co-enrolment in other drug trials
14. Patients who have participated in a trial of an IMP likely to influence insulin sensitivity, plasma insulin, glucose levels or plasma lipid levels within 6 months preceding randomisation.
15. For the sub-cohort of patients undergoing MRI/MRS, normal MR exclusion criteria will apply (See Section 8.5.1).

5.3 Patient Transfer and Withdrawal

In consenting to the trial, patients are consented to trial treatment, follow-up and data collection. If voluntary withdrawal occurs, the patient should be asked to allow continuation of scheduled evaluations, complete an end-of-study evaluation if appropriate and be given

appropriate care under medical supervision until the symptoms of any adverse event resolve or the patient's condition becomes stable.

Follow-up of these patients will be continued through the trial research nurses (RN) and the lead investigator at each centre unless the participant explicitly also withdraws consent for follow-up.

5.3.1 Patient Transfers

For patients moving from the area, every effort should be made for the patient to be followed-up at another participating trial centre if possible and for this trial centre to take over responsibility for the patient.

Participant transfer should not take place until the CTRC have confirmed that the transfer centre has received local approvals and has received the green light for recruitment onto the TAILoR study (see Section 3.1). Once the CTRC has confirmed the transfer centres participation in the TAILoR study, a copy of the patient CRFs should be provided to the new site. The patient will have to sign a new consent form at the new site, and until this occurs, the patient remains the responsibility of the original centre. The CTRC should be notified in writing of patient transfers.

5.3.2 Withdrawal from Trial Intervention

Patients may be withdrawn from treatment for any of the following reasons:

a. Patient withdraws consent;
b. Switching of antiretroviral therapy away from protease inhibitors or EFV (Switching or addition or subtraction to the backbone is allowed)
c. Unacceptable adverse effect of Grade 3/4 which can be attributed to telmisartan (e.g. Hypotension);
d. Intercurrent illness preventing further treatment;
e. Inability to attend regularly for treatment or assessment;
f. Any change in the patient's condition that justifies the discontinuation of treatment in the clinician's opinion (eg. Acute Hep C);
g. Failure to comply with the protocol requirements or cooperate with the investigator;
h. The patient starts treatment with any disallowed medication without prior notification and the consent of the investigators
i. Pregnancy during trial treatment period

If a patient wishes to withdraw from trial treatment, centres should nevertheless explain the importance of remaining on trial follow-up, or failing this, of allowing routine follow-up data to be used for trial purposes. Generally, follow-up will continue unless the patient explicitly also withdraws consent for follow-up (see Section 5.3.3).

Patients who withdraw from trial treatment but are willing to allow further data collection must have a discussion with the investigator as to whether they will be able to attend subsequent follow-up assessments at specific time-points (12, 24 and 48 weeks) until the end of their 48 week follow-up period. The decision should be based on the patient's own preferences and the clinician.

5.3.3 Withdrawal from Trial Completely

Patients are free to withdraw consent at any time without providing a reason. Patients who wish to withdraw consent for the trial will have anonymised data collected up to the point of that withdrawal of consent included in the analyses. The patient will not contribute further data to the study and the CTRC should be informed in writing and a withdrawal CRF should

be completed. Patients will be asked if they would participate in an end of the study evaluation (See Premature withdrawal in Table 1, Section 8.1). Data up to the time of withdrawal will be included in the analyses unless the patient explicitly states that this is not their wish.

6 ENROLMENT AND RANDOMISATION

6.1 Recruitment

Patients who are eligible for inclusion into the trial will be identified and recruited through the HIV speciality centres participating in the study.

Participants will be identified by the clinical team at each centre via a search of the patient database/s either electronically or manually or clinic list review to find potentially eligible patients. At the routine clinic visit, the patient will be asked whether they would be willing to participate in the study. A Patient Information Sheet and instructions on how to proceed if they are interested in taking part or finding out more about the study and a telephone number to contact the RN if they need to discuss or need further information will be provided. All patients will be provided with a full explanation of the trial before obtaining informed written consent (see Section 11.3 for the consent procedure).

If the patient is willing to participate in the study, informed written consent will be obtained either on the same day or after they contact the RN expressing their interest.

6.2 Screening

A 'Screening Log' will be maintained of all the patients who undergo screening regardless of whether they decide to participate in the study or are found ineligible to participate. Reasons for not being eligible will be recorded. Reasons for declining to participate will be asked routinely but it will be made clear that they do not have to provide a reason unless happy to do so.

6.3 Baseline (T0)

Once informed consent has been obtained from the patient, they will be booked in for a baseline assessment visit within 30 days of giving consent. The patient will be advised to arrive fasting when reporting for the baseline assessment. The research team should conduct the baseline (T0) assessments and complete the eligibility and baseline case report form (CRF) during the baseline assessment visit. The baseline assessments include:

1. Verification, by a medically qualified person, that the eligibility criteria are fulfilled;
2. Demographic details including age, gender, ethnicity;
3. Full medical history (including collection of most recent blood test results for: urea and electrolytes, eGFR, liver function tests, full blood count, diabetes screening, hepatitis C, CD4 cell count, and HIV viral load) and drug history (including concomitant medications such as contraceptives, anabolics, hormone therapy, insulin sensitisers and other antihypertensives);
4. Body weight and vital signs (temperature, blood pressure, heart rate, and respiratory rate);
5. Pregnancy test for females of childbearing potential (urine) (refusal of a pregnancy test will not preclude trial entry);
6. Waist/thigh circumference;
7. Collection of 3 separate fasting blood samples from each patient.
8. Collection of one urine sample from each patient at the same time as the blood samples.

Plasma and serum will be extracted from these blood samples; together with the urine samples, these will be stored at -20ºC until posted to the Wolfson Centre for Personalised Medicine, Liverpool for laboratory analysis (see Section 8).

For additional assessments required for the sub-study refer to Section 8.5.

6.4 Randomisation

Participants will be randomised to receive telmisartan 20mg, 40mg, 80mg or control (no intervention) (in a 1:1:1:1 ratio) once:

1. Eligibility criteria have been fulfilled;
2. Fully informed written consent has been obtained;
3. Baseline assessments have been completed.

Participants will be randomised using a secure (24-hour) web based randomisation programme controlled centrally by the CTRC.

Participant treatment allocation will be displayed on a secure webpage and an automated email confirmation sent to the authorised randomiser, the PI and the trial manager (TM). It is the responsibility of the PI or delegated research staff to inform the pharmacy department at their centre prior to randomisation to ensure there is enough supply of the study drugs.

Randomisation: web access www.tailortrial.org.uk/rand/
If there are any problems with web randomisation, please contact the trial coordinator in the first instance

Or via email on helpdesk@mcrnctu.org.uk / tailor@liverpool.ac.uk (Note that the CTRC is open from 0900 – 1700, Monday – Friday, excluding public holidays)

Randomisation backup envelopes will be used in case of failure of the randomisation systems outside CTU working hours

Research staff will be trained to use the randomisation systems, following this they will be issued with usernames and passwords.

In the event of a randomisation system failure, the centre should contact the CTRC (Monday to Friday between 9:00 to 17:00 excluding bank holidays) to try to resolve the problem.

Centres will be provided with emergency back-up randomisation envelopes to be used in the event of a system failure that occurs outside CTRC office hours or when a system failure cannot be resolved in a reasonable timeframe. In the event that emergency back-up envelopes are required, the randomising person will select the next sequentially numbered, opaque, pressure-sealed envelope that will give the randomisation allocation. The envelope will be similar to those used for pay slips, which cannot be viewed without fully opening and their construction is resistant to accidental damage or tampering. Page 1 of the randomisation envelope containing information on the allocation should be returned to the coordinating centre in a pre-paid envelope, and pages 2 & 3 of the randomisation envelope can be inserted into the patient's medical records.

The RN will check to ensure that the correct number of randomisation envelopes is present, that they are intact and that the sequential numbering system is maintained. Any discrepancies should be immediately reported to the coordinating centre.

7 TRIAL TREATMENT/S

7.1 Introduction

Telmisartan is indicated for clinical use as an antihypertensive agent. However, the current trial will use telmisartan outside the licensed indications of the different manufacturers.

Stage I: 4-arm randomised dose-ranging trial design

Participants recruited into the study will be randomised to one of the following arms:

Arm A: Non intervention (Control) arm

Arm B: 24 weeks oral telmisartan 20 milligram (mg) dose, once daily

Arm C: 24 weeks oral telmisartan 40 mg dose, once daily.
The starting dose for patients in this arm will be 20 mg and dose titration to 40mg will be undertaken over a period of 2 weeks.

Arm D: 24 weeks oral telmisartan 80 mg dose, once daily.
The starting dose for patients in this arm will be 20 mg and dose titration to 80mg will be undertaken over a period of 4 weeks.

Stage II: The number of treatment arms during this stage will depend on the results of the interim analysis. The objective of Stage II is to compare the 'most efficacious' dose(s) of telmisartan from Stage I with the non-intervention (control) arm. Hypothetically, if only one dose of telmisartan was found to be the most efficacious in reducing insulin resistance following interim analysis, then the design of Stage II will have two arms:

Arm A: Non intervention (Control) arm

Arm B (this can be 20mg and/or 40mg and/or 80mg arm)**:** 24 weeks oral telmisartan, 'most efficacious' dose, once daily

NB Treatment will not be stopped between Stages I and II. Therefore, some participants may receive up to a maximum of 48 weeks trial treatment before the results of the interim analysis are known.

7.2 Formulation, Packaging, Labelling, Storage and Stability

The telmisartan used in the trial will be sourced via usual local NHS procurement arrangements once the sites have been initiated. The size of the procurement of investigational drug at each site will be pre-determined based on the patient recruitment target for that individual site. Recruitment will be monitored centrally and drug procurement will be tailored in liaison with the respective pharmacies to ensure that pharmacies always hold adequate supplies of trial treatment.

7.2.1 Description of the Drug Product

Telmisartan:

Generic name – Telmisartan

Telmisartan is an angiotensin receptor antagonist and is used to treat essential hypertension (high blood pressure). It is also used to reduce cardiovascular events in patients who are at risk. Telmisartan tablets are for once-daily oral administration and should be taken with liquid, with or without food. Telmisartan tablets are available in 20, 40, or 80mg doses. Every effort should be made to provide the participant their required dose in one tablet. However, if for any reason a high dose is unavailable in single formulation then two tablets of a lower dose may be prescribed (i.e. if 80mg dose cannot be sourced as one tablet then two 40mg tablets may be given or if the 40mg tablet is not available then two 20mg tablets may be dispensed). Please note that tablets cannot be split i.e. a 40mg tablet cannot be split in half to provide a 20mg dose.

The reference safety information referred to for telmisartan in this trial is the Micardis brand (Boehringer Ingelheim Ltd).

Telmisartan is available from a number of manufacturers, considered to be bioequivalent to the brand leader Micardis, and licensed within the EU. Those formulations considered to be appropriate for use by the Trial Management Group are those that have a safety profile in line with the reference safety information used for the trial (the trial coordinator should be contacted for a list of brands approved by the TMG for use in the trial).

The Case Report Forms will be used to record which brand has been dispensed to the participant.

7.2.2 Packaging and Labelling

Telmisartan is available in three different doses: 20 mg, 40 mg and 80 mg tablets. Telmisartan is available in blister packs of 14, 28, 56, 84 or 96 doses (availability of pack size will vary with the manufacturer). Packs may be split prior to dispensing, although it is recommended that packs are not split into less than 7 doses. The tablets will be labelled and dispensed for trial treatment in compliance with paragraph 26 of Annex 13.

7.2.3 Stability and Shelf life

Telmisartan should be stored as per the manufacturer's Summary of Product Characteristics (SPC). Please refer to the reference SPCs provided as a separate document to this protocol

The product should be stored in the original package to protect the tablets from moisture and should not be refrigerated or frozen.

7.3 Preparation, Dosage and Administration of Study Treatment/s

7.3.1 Dispensing

For each randomised patient, treatment will continue for a maximum period of 48 weeks. The trial treatment should be dispensed immediately following randomisation and can start immediately after randomisation. The PI or delegated other will issue a prescription based on the patient's randomisation status. For the three treatment arms, treatments will be dispensed at the appropriate doses mentioned in Section 7.1 throughout the trial, unless interruption or discontinuation is warranted (see sections 5.3.2 and 7.3.4). There is a two week attendance window either side of each of the follow up visits (T+12, T+24 and T+48) and a four day window either side of the titration visits. If the patient is attending at a later

date within these time windows, it is possible to prescribe enough treatment to last until the visit date.

The respective pharmacy will dispense the trial treatments labelled as described in section 7.2.2

The medications will be dispensed upon production of a valid, signed trial prescription to either the RN or directly to the patient as detailed below:

7.3.1.1 Dispensing for Arm A:

For patients randomised to Arm A, the non-intervention (control) arm, no prescription will be given.

Patients who are on the control arm will have follow-up visits at T+12, T+24 and T+48 weeks but will not be prescribed telmisartan.

7.3.1.2 Dispensing for Arm B: Oral telmisartan 20 mg, once daily

T0 study visit
The participant will be randomised at T0. For those who are randomised to Arm B, 12 weeks (or enough to last until date of next visit) of 20mg telmisartan will be dispensed on receipt of a valid trial prescription.

T+12 week study visit
During this visit, the participants will be dispensed with 12 weeks (or enough to last until date of next scheduled visit) of 20mg telmisartan on receipt of a valid trial prescription.

T+24 week study visit
During this visit, the participants will be dispensed with 24 weeks of 20mg telmisartan on receipt of a valid trial prescription. However, if the PI, or delegated other prescriber, wishes a smaller amount of trial treatment may be prescribed more frequently i.e. if routine clinic visits are 3 monthly, then as long as treatment is not interrupted, it may be deemed appropriate to prescribe 2 X 12 weeks of treatment instead of 1 X 24 weeks. The participants will be advised to continue on the respective doses until after the interim analysis is performed.

T+48 week study visit
This will be the final study visit. The administration of trial treatments will be stopped on this day. Unused medications will be returned to pharmacy for disposal via their local procedures.

7.3.1.3 Dispensing for Arm C: Oral telmisartan 40 mg, once daily

T0 study visit
The participant will be randomised at T0. Patients who are randomised to Arm C need to be dose-titrated to their final dose of 40 mg over a period of 2 weeks. At T0, this group of patients will be dispensed with 2 weeks of trial treatment (or enough to last until date of next scheduled dose-titration visit) of 20 mg telmisartan on receipt of a valid trial prescription.

T+2 week study visit
This is a dose titration visit limited only for those who are randomised to either Arm C or Arm D. During this visit, participants in Arm C will be dose-titrated to 40 mg telmisartan. They will

be dispensed with 10 weeks (or enough to last until date of next scheduled visit) of trial treatment consisting of 40 mg telmisartan on receipt of a valid trial prescription.

T+12 week study visit
During this visit, the participants in Arm C will be dispensed with 12 weeks (or enough to last until date of next scheduled visit) of telmisartan 40 mg on receipt of a valid trial prescription.

T+24 week study visit
During this visit, the participants will be dispensed with 24 weeks (or enough to last until date of next scheduled visit) of trial treatment of 40mg telmisartan on receipt of a valid trial prescription. However, if the PI, or delegated other prescriber, wishes a smaller amount of trial treatment may be prescribed more frequently i.e. if routine clinic visits are 3 monthly, then as long as treatment is not interrupted, it may be deemed appropriate to prescribe 2 X 12 weeks of treatment instead of 1 X 24 weeks. The participants will be advised to continue on the respective doses until after the interim analysis is performed.

T+48 week study visit
This will be the final study visit. The administration of trial treatments will be stopped on this day. Unused medications will be returned to pharmacy for disposal via their local procedures.

7.3.1.4 Dispensing for Arm D: Oral telmisartan 80 mg, once daily

T0 study visit
The participant will be randomised at T0. Patients who are randomised to Arm D need to be dose-titrated to their final dose of 80 mg over a period of 4 weeks. At T0, this group of patients will be dispensed with 2 weeks of trial treatment (or enough to last until date of next scheduled dose-titration visit) of 20 mg telmisartan (on receipt of a valid trial prescription.

T+2 week study visit
This is a dose titration visit. During this visit, participants in Arm D will be dose-titrated to 40 mg telmisartan. They will be dispensed with 2 weeks (or enough to last until date of next scheduled dose-titration visit) of 40 mg telmisartan on receipt of a valid trial prescription.

T+4 week study visit
This is a dose titration visit. During this visit, participants in Arm D will be dose-titrated to 80 mg telmisartan. They will be dispensed with 8 weeks (or enough to last until date of next scheduled visit) of trial treatment of 80 mg telmisartan on receipt of a valid trial prescription.

T+12 week study visit
During this visit, the participants in Arm D will be dispensed with 12 weeks (or enough to last until date of next scheduled visit) of trial treatment medication consisting of 80mg telmisartan on receipt of a valid trial prescription.

T+24 week study visit
During this visit, the participants will be dispensed 24 (or enough to last until date of next scheduled visit) weeks of trial treatment consisting of 80mg telmisartan on receipt of a valid trial prescription. However, if the PI, or delegated other prescriber, wishes a smaller amount of trial treatment may be prescribed more frequently i.e. if routine clinic visits are 3 monthly, then as long as treatment is not interrupted, it may be deemed appropriate to prescribe 2 X

12 weeks of treatment instead of 1 X 24 weeks.The participants will be advised to continue on the respective doses until after the interim analysis is performed.

T+48 week study visit
This will be the final study visit. The administration of trial treatments will be stopped on this day. Unused medications will be returned to pharmacy for disposal via their local procedures.

7.3.1.5 Dispensing after Interim analysis and at Stage II

The interim analysis will take place once the 24 week change in HOMA-IR score is available for at least 42 patients on each arm (n=168, which is half of the planned maximum of 336 patients).

The interim analysis is also expected to identify which of the active dose(s) will go forward to Stage II (See Section 9 for details). The results of the interim analysis will therefore decide the design of the trial thereafter (See Section 9.6).

For those patients who are on a trial arm of which the dose is *NOT* taken forward to Stage II, they will be asked to *STOP* taking the medication completely. These patients will continue to be monitored for any adverse events for a period of 7 days (wash out period for telmisartan) after which they will no longer be part of the trial and will return to routine care. The unused medications will be returned to pharmacy for disposal via their local procedures.

For those who are on trial arms whose dose(s) are taken forward to Stage II, they will be asked to continue on the same dose for a further 24 weeks.
For patients recruited after the results of interim analysis are known, they will be randomised equally to the non-intervention (control) arm and the telmisartan dose arm(s). If randomised to the telmisartan dose arm(s), the respective dose of telmisartan will be dispensed as described in sections 7.3.1.2, 7.3.1.3 or 7.3.1.4.

7.3.2 Lost or Damaged Medications

In the event that a patient loses or damages the tablet pack they are currently using, they will move straight onto the next month's medication from the pack they were dispensed with at their last visit. The patient should contact the RN who will bring forward the date of the next visit to ensure that the patient can be dispensed their next prescription (if applicable) in sufficient time to ensure there is no break in medication. However, if the patient has no more dispensed medication, they should contact the RN immediately to discuss how to manage their treatment. If no arrangements can be put in place for the patient to collect their next medication pack from the pharmacy within an acceptable period of time (up to one week), the PI will withdraw the patient from trial treatment at that point. The patient will return to the routine care and will be followed up as per the follow-up schedule by the research team (see Section 8.1).

7.3.3 Administration

The patient will be instructed in the correct use of the medications dispensed. Further guidance will be provided throughout the remainder of the trial where necessary.

All trial treatments have only one route of administration:

Oral (telmisartan) - One tablet is to be administered daily, and should be taken with liquid, with or without food.

7.3.4 Dose Modifications

Dose modifications will be allowed in those who are randomised to a particular dose arm but do not tolerate that dose. The patient will be allowed to continue on the nearest dose tolerated. Those who show adverse effects as a result of the trial intervention or due to the HIV infection may be withdrawn from the trial treatment. The decision to withdraw the patient from trial treatment is based on the patient's current clinical presentation and the review of information on symptoms/exacerbations etc collected in the hand held record over the preceding weeks. The decision to interrupt or discontinue trial therapy is at the discretion of the treating physician using their informed clinical opinion. Doses may be interrupted or discontinued at any point during the trial period for reasons such as unacceptable adverse effects, intercurrent illness, development of serious disease or any change in the patient's condition that the physician believes warrants a change in medication. Any changes must be documented in the CRF along with the justification for those changes. Follow-up should be continued until the end of the trial as per the study visit schedule. If the patient is withdrawn from trial treatment, the dispensed medications will be returned to pharmacy for disposal via their local procedures.

7.4 Unblinding

Tailor is an open trial, therefore unblinding is not required.

7.5 Accountability Procedures for Study Treatment/s

As the telmisartan used in the trial will be sourced via usual NHS procurement arrangements, pharmacy will liaise with the local procurement department to ensure that the site has the following in place and will report any problems to the CTRC:

- A record of deliveries and dispensing of telmisartan - A system in place that allows for the retrieval if the manufacturer issues a recall - local procedures should be used
- Enough telmisartan within shelf life assigned to be used in the study (see Section 7.2.3).
- Telmisartan is used in compliance with the protocol requirements and accountability records are maintained

7.6 Assessment of Compliance with Study Treatment/s

Once the participant has been informed of their treatment allocation they should be given the appropriate treatment diary to record their daily treatment compliance. The PI or RN should explain how to complete the diaries before the participant leaves the hospital. Participants should be instructed to bring back copies of the treatment diary and any unused medication at their next scheduled visit to assess compliance with treatment.

Compliance with the study treatment will be ascertained by the following ways:

1) Participant completed treatment diaries to record their daily treatment routine.

2) At each follow-up visit, a member of the research team will go through the treatment diary to ascertain patient's compliance with the treatment regimen; if any data are missing, then

the patient will be asked about this and it will be recorded. If a participant has not returned their treatment diary they should be asked to bring this with them at the next follow-up visit for review.

3) Participants will be asked to retain all unused trial medications and packaging and bring them to each study visit from T+2–T+48. In conjunction with the treatment diary review the RN will count and record the number of pills remaining in the packs. If there are discrepancies between the participant treatment diary and the pill count, this should be discussed with the patient and the outcome of the conversation documented.

7.7 Concomitant Medications/Treatments

7.7.1 Medications Permitted

Details of concomitant medications will be collected at the screening visit (T0) and recorded on the CRF. They will be reviewed at all subsequent study visits (clinic visits until T+48). The trial treatment has very few adverse interactions with other medicinal products, therefore concomitant medications, with the exception of those listed in Section 7.7.2, are permissible at the discretion of the investigator.

7.7.2 Medications Not Permitted

The following are not permitted for the duration of the trial period:
1) Anabolic steroids (e.g. Testosterone)
2) Other hormone supplements (Growth hormone)
3) Insulin sensitisers (eg. Metformin)
4) Angiotensin II receptor blockers (ARBs) other than telmisartan
5) Angiotensin converting enzyme (ACE) inhibitors
6) Diuretics (including potassium sparing diuretics)
7) Lithium containing medications (used to treat depression)

7.7.3 Precautions required

Pregnancy: A pregnancy test should be offered to all women of child-bearing age at the time of enrolment to the study. Contraception must be *strongly* advised to all women of child-bearing age for the duration of the trial.

Pregnancy test should also be offered at T+12 and T+24 week visits.

Female participants will be advised to contact the site Research Team immediately if they discover that they are pregnant in between scheduled visits.

7.7.4 Data on Concomitant Medication

The dose and name of all concomitant medications should be documented on the CRF at T0. This will be reassessed at each trial visit by the PI/RN. Any new medications introduced or any changes to current medications should be documented on the CRF.

7.8 Co-enrolment Guidelines

To avoid potentially confounding issues, patients recruited into another CTIMP should not be enrolled in TAILoR. Individuals who have participated in a trial testing a medicinal product likely to influence insulin sensitivity, plasma insulin and glucose levels or plasma lipid levels within 6 months preceding randomisation will be ineligible for the TAILoR study. Where recruitment into another trial is considered to be appropriate and without having any detrimental effect on the TAILoR study, this must first be discussed with the CTRC who will contact the Chief Investigator (Prof Munir Pirmohamed).

8 ASSESSMENTS AND PROCEDURES

Participating centres will be expected to each maintain a file of essential trial documentation (Site File), which will be provided by the CTRC, and copies of all completed case report forms (CRFs) for the trial. Data collection will use a combination of paper CRFs and participant completed treatment diaries (see Section 13.3 for details on the data capture methods).

All paper CRFs should be completed as described in section 13.3.1 by personnel named on the delegation log as authorised to do so. The originals should be returned to the CTRC within 7 days of the time specified for completion, unless stated otherwise and copies of completed CRFs kept in the site file.

Participant details including name, initials and date of birth will be reported on the consent form, separate to clinical data. Once written informed consent has been obtained from the participant, the RN will collect the baseline characteristics and the participant will be randomised and followed-up in the trial. For screening, baseline and randomisation procedures refer to section 6. For details of procedures associated with trial treatments refer to section 7. At each follow-up visit, the participant should be instructed to bring back their Patient Diary, any un-used medication and the packaging of used medication. Treatment compliance should be recorded as described in section 7.6. Data similar to that collected at baseline (see section 6.3) should be recorded on the appropriate follow-up CRF.

8.1 Schedule for Follow-up

See schedule of study procedures, Table 1.

Scheduled study visits apart from the dose-titration visits for participants in Arm C and Arm D are designed to fit with routine hospital visits where possible. Follow-up visits should be conducted, when possible, as scheduled. However, as participants commitments may conflict with this schedule a two week window either side of the scheduled visit date is allowed; i.e. T+12 may occur at any time between T+10 and T+14. The titration visits have a four day window either side of the appointed day; i.e. T+ 2 may occur at any point between day 10 and day 18. When organising the date of each visit, the research team should take care to prescribe enough trial medication to last until the day the visit occurs. The dates of the visits should be scheduled based on the date of randomisation and baseline, not on the date of the last visit.

Participants withdrawn from trial treatment will be asked to continue with scheduled follow-up visits. If the participant misses the scheduled follow-up visit, the RN should conduct the follow-up at the earliest next visit. The RN should complete an un-scheduled CRF for this purpose. If a participant does not wish to continue in the study, a Withdrawal CRF will be completed to capture the date and reason for trial withdrawal as detailed in section 5.3.3.

TABLE 1: Schedule of Study Procedures

Time	Pre T0	T0	T+2 week	T+4 weeks	T+12 weeks	T+24 weeks	T+48 weeks	
	At each recruitment site	Randomisation/ Baseline*	Dose titration for 40/80mg arms (dose given 40mg)	Dose titration for 80mg arm (dose given 80mg)	Follow-up	Follow-up	End of treatment	Premature withdrawal of consent
Database search to identify potential participants or clinic list review	X							
Information sheet provided to patient	X							
Signed Informed consent		X						
Assessment of Eligibility Criteria by a medically qualified person		X						
Review of Medical History (including collection of most recent blood test results for Urea & electrolytes, eGFR, liver function, diabetes screening etc		X**					X	X
Review of Concomitant Medications		X	X	X	X	X	X	X
Urine pregnancy test		X			X	X		
Randomisation		X						
Study Intervention		X	X	X	X	X		
Compliance with study intervention - patient diaries & pill counting			X	X	X	X	X	
Physical Exam - Complete		X						
Physical Exam - Symptom-Directed			X	X	X	X	X	X
Height		X						
Weight		X			X	X	X	X
Waist/thigh circumference		X			X	X	X	X
Heart rate, blood pressure		X	X	X	X	X	X	X
Collection of 3 fasting blood samples for bioanalysis		X			X	X	X	X
Collection of urine sample for sub study 2		X			X	X	X	X
Assessment of Adverse Events			X	X	X	X	X	X
Consent for sub-study		X						
MRI/MRS scan for sub-study 1		X				X		

(X) – As indicated/appropriate.
*Baseline assessment and randomisation visit should be within 30 days of the patient giving consent.
** liver function and diabetes screening result only to be collected at baseline

8.1.1 Unscheduled Assessments

During the course of the trial, some participants may need to attend hospital for unscheduled study visits. In these instances, the PI or RN should complete the Unscheduled Visit CRF. If the unscheduled visit results in a change to the participants medication this should be recorded on the relevant CRF.

8.2 Procedures for Assessing Efficacy

Efficacy of trial treatments will be assessed throughout the period of the study using both objective and subjective measures.

8.2.1 Assessment of HOMA-IR

The objective measure of efficacy of trial treatment on insulin resistance will be provided by comparison of HOMA-IR values for the baseline and weeks 12, 24 and 48. HOMA-IR is a known surrogate marker to measure insulin resistance.

Three fasting blood samples will be collected from each participant at baseline (T0) and at follow-up visits during the T+12, T+24 and T+48 weeks at the respective sites. Plasma and serum will be extracted locally at each site, aliquoted and stored at -20ºC. Batched samples will be couriered on dry ice to the Wolfson Centre for Personalised Medicine, Department of Molecular and Clinical Pharmacology, University of Liverpool for subsequent analysis. HOMA-IR, lipid profile and hs-CRP estimation will be carried out in the Liverpool Clinical Laboratories (LCL),, whereas biomarker analysis and DNA extraction will be performed in the Wolfson Centre for Personalised Medicine, University of Liverpool. Fasting blood glucose will be measured by standard clinical methods and plasma insulin will be measured by an enzymatic immunoassay. HOMA-IR will be calculated using the equation: Fasting plasma insulin (mU/l) X fasting plasma glucose (mmol/l)/ 22.5.

8.3 Procedures for Assessing Safety

Adverse event reporting is detailed in Section 10 (Pharmacovigilance) and will occur from the point that the participant provides informed consent and throughout the trial treatment period up until seven days after the patient has taken the final dose of investigational medicinal product.

8.4 Other Assessments: Special Assays or Procedures

8.4.1 Assessment of Lipid Profile

Fasting serum lipid levels (total cholesterol, triglycerides, LDL-c and HDL-c) will be performed at T0 and T+12, T+24, and T+48 week visits. The blood sample mentioned above in Section 8.2.1 will be analysed in LCL , for this purpose.

8.4.2 Assessment of hs-CRP

High sensitivity C-Reactive Protein (hs-CRP) in the serum will be measured for T0 and T+12, T+24, and T+48 week visits; analysis will be carried out in LCL using the same blood sample as mentioned above (see section 8.4.1).

8.4.3 Assessment of Novel Biomarkers

The plasma concentration of five biomarkers: adiponectin, leptin ,IL6, TNF-α and resistin will be measured at T0 and T+12, T+24, and T+48 week visits. The biomarker analysis will be performed in the Wolfson Centre for Personalised Medicine, University of Liverpool, utilising human singleplex and multiplex kits using an electrochemiluminescence immunoassay technique (Meso Scale Discovery, Rockville, USA) as per manufacturer's protocol and analysed on a Meso Scale Discovery Sector Imager 2400A.

As with all laboratory biomarker analyses, strict quality control procedures to check on precision and accuracy will be employed. If an assay shows poor performance in that it does not match the performance characteristics detailed by the manufacturer, then alternative assays will need to utilised. Of importance here also is the llimit of quantification – if an analyte is not present in sufficient concentration and is consistently at or below the lower limit of quantitation, we will either use alternative assays (within the costings provided for the trial), or abandon the measurement of this biomarker as part of the secondary analysis (with full justification provided for not undertaking the analysis). The biomarker may be analysed in the future as new more sensitive assays become available, but this will be treated as a sub-study.Assessment of alternate indices of insulin resistance

8.4.3.1 QUICKI

Fasting glucose and insulin levels will be measured as stated in section 8.2.1. QUICKI will be calculated using the equation: 1 / [log(fasting insulin in µU/mL) + log(fasting glucose in mg/dL)].

8.4.3.2 – Revised QUICKI

Non-esterified fatty acids (NEFA) will be measured in serum samples at timepoints T0, T+12, T+24, and T+48. Serum NEFA analysis will be performed in the BRC GCP Laboratory, Royal Liverpool Hospital and will be measured using a colorimetric assay on a RX Daytona analyser (Randox Laboratories Limited, UK). Revised QUICKI will be calculated using the equation: 1/[log fasting insulin (µU/ml) + log fasting glucose (mg/dl) + log fasting NEFA (mmol/l)].

8.4.5 Abnormal Results

If any of the centrally performed assessments produce any clinically important observations, the results will be passed onto the patient's HIV clinical team (with their consent) so that any information can be acted upon.

8.5 Sub study 1 – Body Fat Redistribution Study

For patients recruited at the HIV-GU Medicine, RLH only, an additional assessment for the total body adipose content and intrahepatic and intramyocellular lipid content by MRI/^{1}H MRS will be conducted at T0 and T+24 weeks. In addition to the consent to take part in the trial, patients who are enrolled for the study at the RLH will be additionally asked for consent to participate in the MRI/^{1}H MRS sub-study (see section 11.3 for consent procedures).

Patients recruited at the RLH will be given a separate patient information sheet and consent form containing information on the sub study and requirements for MRI/MRS. As per section(s) 5.3.2 and 5.3.3 on withdrawal procedures participants are free to withdraw from the sub-study at anytime, if the participant wishes they may withdraw from the sub-study but remain in the main study. Staff at the RLH site will be trained to double check the consent and withdrawal forms for the sub-study prior to booking participants in for an MRI/MRS.

Those who consent (for taking part in the trial and undergoing MRI/MRS) and meet the relevant inclusion/exclusion criteria for performing MRI/MRS will be booked in for an MRI/MRS session by the RN at the MARIARC (Magnetic Resonance Imaging and Analysis Research Centre), University of Liverpool, at the time of their baseline visit. At T0, once the baseline assessments as described in Section 6.3 are completed, they will have an MRI (total body adipose content) and ^{1}H MRS (liver, limbs) undertaken at the MARIARC.

8.5.1 Exclusion Criteria

For the sub-cohort of patients undergoing MRI/^{1}H MRS, normal MR exclusion criteria will apply.

a. Pacemakers
b. Cochlear implants
c. Piercings
d. Metal in the head or elsewhere in the body
e. Claustrophobia

8.5.2 Assessment of Total Body Adipose Content

MRI of the total body adipose content (total body subcutaneous, total internal, subcutaneous abdominal, and intra-abdominal adipose tissue volumes) will be undertaken at the MARIARC on the Siemens 1.5T Symphony scanner (Siemens, Erlangen Germany), using well-established methods used at the MARIARC.

MRI will be carried out both at T0 and at T+24 week visit[44] using T1 weighted MR images (TR 705 ms, TE 12 ms) in 10 contiguous blocks of 1cm slices with 1cm gap. A validated semiautomatic program is used to segment the images into total body subcutaneous, total internal, subcutaneous, abdominal, and intra-abdominal adipose tissue volumes; this will be outsourced to a commercial analysis service (www.vardisgroup.com).

8.5.3 Assessment of Intrahepatic and Intramyocellular Lipid Content

^{1}H MRS of the liver and skeletal muscle will be performed in the same sub-cohort of patients recruited from RLH at T0 and at T+24 weeks. Liver ^{1}H MR spectra will be acquired with the Siemens body coil, using PRESS (TR 1500 ms/ TE 135 ms) without water saturation, 64 signal averages[44]. Transverse MR images will be used to position three 20x20x20 mm voxels, avoiding blood vessels, gall bladder and fatty tissue. Skeletal muscle ^{1}H MR spectra will be acquired with the Siemens CP extremity coil, using PRESS (TR 1500 ms/ TE 135 ms) without water saturation, 64 signal averages[45]. Transverse MR images will be used to position a 20x20x20 mm voxel in each of soleus and tibialis anterior. Spectra will be analysed in the time domain using the AMARES algorithm in the jMRUI 3.0 software package. Intramyocellular lipid is expressed as CH_2 relative to creatine signal[45], and intrahepatic lipid as CH_2 relative to unsuppressed water.

8.5.4 Abnormal Results

If the scans reveal any unexpected abnormalities that are medically significant, the HIV clinician for the patient will be informed (with consent of the patient).

8.6 Sub Study 2 – Assessment of renal biomarkers

8.6.1 Eligibility Criteria

The same inclusion/exclusion criteria to main study will apply.

8.6.2 Assessment of renal biomarkers

For all patients urine samples will be collected at T0 and T+12, T+24, and T+48 week visits for assessment of renal safety biomarkers (creatinine, albumin, total protein, novel markers such as KIM-1, NGAL and RBP). Urine samples will be stored at -20 ºC locally at each site and batched samples will be couriered on dry ice to the Wolfson Centre for Personalised Medicine, University of Liverpool for subsequent analysis. The main study PISC covers consent to this sub study.

8.6.3 Timing of analysis

The assessment of renal safety biomarkers wil not take place as part of the main study assessments, and will not be included in the final report to the TAILoR funder. This analysis will take place at a later date, when a source of funding has been identified.

8.6.4 Abnormal Results

If the laboratory tests for renal biomarkers show any unexpected abnormalities that are medically significant, the HIV clinician for the patient will be informed (with consent of the patient).

8.7 Loss to Follow-up

If any of the trial patients are lost to follow up, contact will be attempted through the RN and lead investigator at each centre. Wherever possible, information on the reason for loss to follow-up will be recorded.

8.8 Trial Closure

The end of the trial is defined to be the date on which data for all participants is frozen and data entry privileges are withdrawn from the trial database. However the trial may be closed prematurely by the Trial Steering Committee (TSC), on the recommendation of the Independent Data and Safety Monitoring Committee (IDSMC).

9 STATISTICAL CONSIDERATIONS

9.1 Introduction

A separate and full statistical analysis plan (SAP) will be developed prior to the final analysis of the trial. The SAP will be agreed by the TSC before being sent to the IDSMC for comment and approval. The main features of these planned statistical analyses are included here in the main protocol.

9.2 Method of Randomisation

Participants will be randomised using a secure (24-hour) web based randomisation programme controlled centrally by the CTRC. Randomisation lists will be generated in a 1:1:1:1 ratio using simple block randomisation with random variable block length.

For each recruiting centre, randomisation will be stratified by ethnicity (Black and Non-Black) Ethnicity will be determined by self-categorisation using the NHS ethnicity codes. For stratification, those of mixed ethnicity (e.g. White and Black Caribbean, White and Black African) will be categorised as Black.

9.3 Outcome Measures

See section 4.

9.4 Sample Size and Power Requirement

Original aim: The maximum total sample size of the study will be 336 patients. The primary response from each patient is the difference between the baseline HOMA-IR score and their HOMA-IR score at 24 weeks (so that positive values indicate improvement). The design has been constructed under the assumption that for all patients this response is normally distributed with a common standard deviation, σ. The sample size calculation is based on a one-sided type I error of 5% and a power of 90%.

In a conventional comparison of one active treatment against a control treatment, a criterion is set so that if the measure of advantage of the active over the control exceeds some critical value, the outcome is declared positive. It is required that a positive outcome should occur with probability α if the effects of the treatments are identical (α is the one-sided type I error rate), and with probability 1 – β if the true treatment advantage takes some positive value (1 – β is the power of the study). Here we adopt a generalisation of this power requirement to multiple active treatments due to Dunnett[46]. If there is no difference between the mean response on any treatment and that on control, then a probability of α = 0.05 is set for the risk of erroneously ending the study with a recommendation that any treatment be tested further. To fix a power requirement, effect sizes are specified in terms of the percentage chance of a patient on active treatment achieving a greater reduction in HOMA-IR score than a patient on control; as such a specification does not require knowledge of the value of the common standard deviation σ. The requirement is that, if a patient on the best of the active doses has a 65% chance of showing a better response than a patient on control, while patients on either of the other two active treatments have a 55% chance of showing a better response than a patient on control, then the best active dose should be recommended for further testing with probability 1 – β = 0.90. This condition demands a high power of making the correct choice if one active dose is substantially better than control while the others show some advantage, but not enough to be recommended for use. The critical values for recommending that a treatment is taken to further testing at the interim and final analyses

(2.782 and 2.086), have been chosen to guarantee these properties using a method described by Magirr et al[47], generalising the approach of Whitehead and Jaki[48]. These properties pertain to the whole 2-stage testing procedure.

A 55% chance of achieving a better response on active dose relative to control corresponds to a reduction in mean HOMA-IR score of about a sixth of a standard deviation (0.178σ) while the clinically relevant effect of 65% corresponds to a reduction of about half a standard deviation (0.545σ). The standard deviation was reported to be around 5[49,50]. Although this value is not felt to be sufficiently reliable to base the design, were it to be true, and if the changes in HOMA-IR were normally distributed, then the 55% and 65% chances of better outcomes correspond to mean changes in HOMA-IR of 0.890 and 2.725, respectively.

The maximum sample size of this study is 336 evaluable patients, although the use of the interim analysis may reduce both the sample size and the study duration as outlined in Section 9.6. The study will recruit additional patients to ensure that the target number of 24 week responses is achieved in the presence of an anticipated 10% drop-out rate (in which case, the sample number would be 370).

Post-interim analysis: Interim analysis has shown that there was a higher than anticipated rate of withdrawals and/or missing primary outcome data. In order to have the required number of patients for final analysis a total of 377 patients will now be required.

9.4.1 Sample Size for the Sub study 1 (MRI/^{1}H MRS)

To explore the secondary objective of using MRI/^{1}HMRS in a subset of patients to identify the effect of telmisartan on visceral fat distribution and hepatic and muscle fat, we will select 48 patients (12 each in telmisartan dose arms and 12 in the control arm) recruited locally to undergo whole body MRI scans and liver and calf MRS at baseline and at 24 weeks. There is limited information[32,33] on the effect of telmisartan on visceral fat distribution for the dose groups considered and no reliable estimates of the within-group variance are available to carry out a formal power calculation. A sample size of 10 patients per group will provide enough data for a reliable estimate of the within-group variance (sample size increased to 12 to account for 10% drop-out). To put this in context, the proposed sample size would allow the detection of a linear reduction in visceral fat of at least 10cm^2/20mg with a 80% power at the 5% significance level, assuming a within-group standard deviation of visceral fat reduction, σ = 27cm^2. Even if deviations from the sample standard deviation σ = 27cm^2 occur (e.g., σ increases to 40cm^2), the sample size proposed would still be sufficient to detect a linear reduction in visceral distribution equal to or greater than 15cm^2/20mg (nQuery, ANOVA).

9.4.2 Sample Size for Sub study 2 (renal biomarkers)

To explore the secondary objective of whether there is change in urinary biomarker levels at T+12, T+24 and T+48 weeks between telmisartan treated arm(s) and the control arm, we use the same samples as for the main study.

9.5 Interim Monitoring and Analyses

The study will be monitored by an Independent Data and Safety Monitoring Committee (IDSMC) (see section 16.3). The IDSMC will be responsible for reviewing and assessing

recruitment, interim monitoring of safety and effectiveness, trial conduct and external data. Missing data will be monitored and strategies developed to minimise its occurrence.

Interim analysis will take place once the 24 week change in HOMA-IR score is available for at least 42 patients on each arm (n=168, which is half of the planned maximum of 336 patients). The sample standard deviation pooled across all four arms will be used to construct test statistics expressing the advantage of each of the three active treatments over control. The analysis will be proceeding as follows:

i. If the largest of these statistics exceeds a critical value (equal to 2.782), this would mean that one active dose group shows a substantially higher mean reduction of 24 week HOMA-IR score than control group, and therefore the study will be stopped and the corresponding dose will be recommended for further testing.
ii. If any active dose showing no improvement over control (i.e. has a negative measure of advantage) that active dose will be dropped from the second stage
iii. If all three active doses satisfy this criterion, then the study will be stopped and no significant improvement over control will be claimed for any of the active doses.
iv. If some improvement over control is detected for at least one of the doses (i.e. if at least one test statistic is between 0 and 2.782), the study will progress to the second stage.

After the interim analysis, if arms are dropped, randomisation will continue to be in an equal ratio i.e. 1:1 or 1:1:1.

9.5.1 Effect of Interim Analysis on the Sample size and Study duration

At the interim analysis, doses may be dropped from the trial, or the trial may be stopped altogether. Consequently, the sample size when the decision is reached could be smaller than the maximum stated number of 336 patients. Due to the structure of the design, the values 168 (if the study is stopped following interim analysis), 252 (if one active dose arm is promoted to the second stage), 294 (if two active dose arms are promoted to second stage) and 336 (if all three active dose arms are promoted to second stage) are possible. Under the situation in which one treatment has a 65% of giving a better outcome than control, while the others achieve 55%, the four sample sizes occur with probabilities 0.40, 0.08, 0.19 and 0.33 respectively. In this same situation, the probability of dropping the best treatment at the interim analysis is 0.006 and it is even smaller for treatments with larger effects. The reduced sample sizes of 168, 252 and 294 mentioned above refer to the numbers of patients with 24 week HOMA-IR scores which are included in the analysis. There will be additional patients who have been recruited and treated during the 24 weeks prior to extracting the data for interim analysis and during the time when the analysis take place, and their number will depend on the recruitment rate achieved. Nevertheless, taking these patients into account, it can be deduced that the impact of the interim analysis will be to shorten the study duration by about 12 months if the conclusion is clear-cut and to reduce the sample size by an expected 40 patients (this figure is calculated by taking into account the number of patients recruited during the conduct of interim analysis from months 24-26, and therefore not actually contribute to the analysis).

The IDSMC will be asked to give advice on whether the accumulated data from the interim analysis justifies continuing recruitment of further patients and further follow-up. If a decision is made to continue, the IDSMC will advise on the frequency of future reviews of the data on the basis of accrual and event rates. The IDSMC will make recommendations to the Trial Steering Committee (TSC, see Section 16) as to the continuation of the trial. A decision to discontinue recruitment, in all patients or in selected subgroups, will be made on the basis of results from the interim analysis, by the IDSMC.

9.6 Analysis Plan

9.6.1 Primary Outcome Analysis

In order to satisfy the primary objective, as explained in the Trial Design (Section 4), we will evaluate three different doses against control in the first stage of the study and conduct an interim analysis that will allow ineffective doses to be eliminated quickly while a dose showing a positive effect can be taken forward. At the interim analysis, the sample standard deviation pooled across all four arms will be determined and used to construct test statistics expressing the advantage of each of the three active treatments over control. These statistics will be adjusted for the stratification factors (gender and ethnicity). The largest of these test statistics will be compared to the interim critical value (2.782). Exceeding this value would correspond to a significant improvement in HOMA-IR score for the corresponding dose over control and would lead to this dose being immediately taken forward for further study, and to the trial being stopped. Any dose corresponding to a negative test statistic would be dropped, and if all doses were dropped, the trial would be stopped. If some improvement over control is detected for at least one of the active doses (i.e. test statistic between 0 and 2.782), then the study continues after the interim analysis. At the final analysis, if the largest comparative test statistic exceeds the final critical value (2.086) then this dose would be recommended for further study. Adjustments can be made to allow for any discrepancies between target and actual sample sizes while still preserving the one-sided type I error rate at 0.05.

9.6.2 Secondary Outcome Analysis

9.6.2.1 Biomarker analysis

To explore the secondary objective of identifying change in the expression of biomarkers in telmisartan treated arm(s) in comparison to controls, linear mixed effect models will be used to fully exploit the serial nature of these outcomes. These models can estimate the effect of treatment and the timing of any effect on each biomarker while accounting for variability within patients of the various biomarkers. We will then be able to assess which biomarker has the largest and/or earliest change in response to treatment. The evaluation of beneficial and adverse biomarkers in relation to insulin resistance will be examined using joint modelling approach[51,52] accounting for informative loss to follow up or censoring.

9.6.2.2 Analysis of changes in body fat redistribution and intrahepatic and intramyocellular lipid content

The aim of this analysis is to identify the effect of telmisartan on visceral fat distribution and hepatic and muscle fat. The change in visceral fat in 24 weeks will be compared across the 3 treatment groups and controls using multiple linear regression. The multiple linear regression model will be examined to explore the differences in visceral fat change between the treatment groups while accounting for potential confounders. The standard error of each estimator of the model coefficients, p-values, as well as the 95% confidence intervals for the coefficient parameters will be provided. A similar strategy will be adopted for the analysis of liver and calf MRS data.

9.6.2.3 Evaluation of alternative methods of Insulin Resistance (QUICKI and revised QUICKI)

The aim of this analysis is to see if telmisartan show a similar direction of change in insulin resistance measured by QUICKI and revised QUICKI to what is observed with HOMA-IR. We use the same analysis as in section 9.6.1 for the two alternative measures

9.6.2.4 Renal biomarker analysis

To explore the secondary objective of identifying change in the expression of biomarkers in telmisartan treated arm(s) in comparison to controls, joint models will be used to fully exploit the serial nature of these outcomes adjusting for the informative lost to follow-up/censoring (see section 9.6.2.1 for further details).

10 PHARMACOVIGILANCE

10.1 Terms and Definitions

The Medicines for Human Use (Clinical Trials) Regulations 2004 (SI 2004/1031) definitions:

Adverse Event (AE)
Any untoward medical occurrence in a subject to whom a medicinal product has been administered, including occurrences which are not necessarily caused by or related to that product.

Adverse Reaction (AR)
Any untoward and unintended response in a subject to an investigational medicinal product which is related to any dose administered to that subject.

Unexpected Adverse Reaction (UAR)
An adverse reaction the nature and severity of which is not consistent with the information about the medicinal product in question set out in:
In the case of a product with a marketing authorization, in the summary of product characteristics for that product
In the case of any other investigational medicinal product, in the investigator's brochure relating to the trial in question.

Serious Adverse Event (SAE), Serious Adverse Reaction (SAR) or Suspected Unexpected Serious Adverse Reaction (SUSAR)
Any adverse event, adverse reaction or unexpected adverse reaction, respectively, that:

- results in death
- is life-threatening* (subject at immediate risk of death)
- requires in-patient hospitalisation or prolongation of existing hospitalisation**
- results in persistent or significant disability or incapacity, or
- consists of a congenital anomaly or birth defect
- Other important medical events

*'life-threatening' in the definition of 'serious' refers to an event in which the patient 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.
**Hospitalisation is defined as an inpatient admission, regardless of length of stay, even if the hospitalisation is a precautionary measure for continued observation. Hospitalisations for a pre-existing condition, including elective procedures that have not worsened, do not constitute an SAE.
***Other important medical events that may not result in death, be life-threatening, or require hospitalisation may be considered a serious adverse event/experience when, based upon appropriate medical judgment, they may jeopardise the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition

10.2 Notes on Adverse Event Inclusions and Exclusions

10.2.1 Include

- An exacerbation of a pre-existing illness
- An increase in frequency or intensity of a pre-existing episodic event/condition
- A condition (even though it may have been present prior to the start of the trial) detected after trial drug administration
- Continuous persistent disease or symptoms present at baseline that worsens following the administration of the study/trial treatment

- Laboratory abnormalities that require clinical intervention or further investigation (unless they are associated with an already reported clinical event).
- Abnormalities in physiological testing or physical examination that require further investigation or clinical intervention

10.2.2 Do Not Include

- Medical or surgical procedures- the condition which leads to the procedure is the adverse event
- Pre-existing disease or conditions present before treatment that do not worsen
- Situations where an untoward medical occurrence has occurred e.g. cosmetic elective surgery
- Overdose of medication without signs or symptoms
- The disease being treated or associated symptoms/signs unless more severe than expected for the patient's condition

10.3 Reporting of Pregnancy

Study participants will be tested for pregnancy as part of the trial screening process and at T+12 weeks and T+24 weeks. Any pregnancy which occurs during the study should be reported as a SAE to the CTRC within 24 hours of the site becoming aware of its occurrence and the participant should be instructed immediately to stop taking study drugs. All pregnancies that occur during treatment need to be followed up until after the outcome using the SAE form. Consent to report information regarding these pregnancy outcomes should be obtained from the mother prior to completion and faxing of the SAE Form. Any SAE experienced during pregnancy must be reported on the SAE form.

The investigator should contact the participant to discuss the risks of continuing with the pregnancy and the possible effect to the foetus. Appropriate Obstetric care should be arranged.

The CTRC will report all pregnancies to the trial Sponsor, MHRA and MREC.

Pregnancies must be reported by faxing a completed SAE form within 24 hours of the PI becoming aware of the event to the CTRC

10.4 Notes on Severity / Grading of Adverse Events

The assignment of the severity/grading should be made by the investigator responsible for the care of the participant using the Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events Version 1.0 (2009) (Appendix 1) definitions below.
Regardless of the classification of an AE as serious or not, its severity must be assessed according to medical criteria alone using the following categories:

Grade 1 (Mild): Symptoms causing no or minimal interference with usual social & functional activities
Grade 2 (Moderate): Symptoms causing greater than minimal interference with usual social & functional activities
Grade 3 (Severe): Symptoms causing inability to perform usual social & functional activities

Grade 4 (Potentially life threatening): Symptoms causing inability to perform basic self-care functions OR Medical or operative intervention indicated to prevent permanent impairment, persistent disability, or death

A distinction is drawn between serious and severe AEs. Severity is a measure of intensity (see above) whereas seriousness is defined using the criteria in section 10.1, hence, a severe AE need not necessarily be a Serious Adverse Event.

10.5 Relationship to Trial Treatment

The assignment of the causality should be made by the investigator responsible for the care of the participant using the definitions in Table 2.

If any doubt about the causality exists the local investigator should inform the study CTRC who will notify the Chief Investigator. In the case of discrepant views on causality between the investigator and others, the MHRA will be informed of both points of view.

Table 2: Definitions of Causality

Relationship	Description
Unrelated	There is no evidence of any causal relationship. N.B. An alternative cause for the AE should be given
Unlikely	There is little evidence to suggest there is a causal relationship (e.g. the event did not occur within a reasonable time after administration of the trial medication). There is another reasonable explanation for the event (e.g. the participant's clinical condition, other concomitant treatment).
Possibly	There is some evidence to suggest a causal relationship (e.g. because the event occurs within a reasonable time after administration of the trial medication). However, the influence of other factors may have contributed to the event (e.g. the participant's clinical condition, other concomitant treatments).
Probably	There is evidence to suggest a causal relationship and the influence of other factors is unlikely.
Almost certainly	There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out.

10.6 Expectedness

An AE whose causal relationship to the study drug is assessed by the investigator as "possible", "probable", or "definite" is an Adverse Drug Reaction.All events judged by the designated investigator to be possibly, probably, or almost certainly related to the IMP, graded as serious and **unexpected** (see section 10.2 and SPC for list of Expected Adverse Events) should be reported as a SUSAR.

10.7 Follow-up After Adverse Events

All adverse events should be followed until satisfactory resolution or until the investigator responsible for the care of the participant deems the event to be chronic or the patient to be stable.

When reporting SAEs and SUSARs the investigator responsible for the care of the participant should apply the following criteria to provide information relating to event outcomes: resolved; resolved with sequelae (specifying with additional narrative); not resolved/ongoing; ongoing at final follow-up; fatal or unknown.

10.8 Reporting Procedures

Adverse reactions and all serious adverse events (regardless of causality) should be reported. Depending on the nature of the event the reporting procedures below should be followed. Any questions concerning adverse event reporting should be directed to the CTRC in the first instance. Adverse reactions and all serious adverse events will be reported and recorded from the point that the participant provides informed consent and throughout the trial treatment period up until seven days after the patient has taken the final dose of investigational medicinal product. A flowchart is given below to aid in determining reporting requirements.

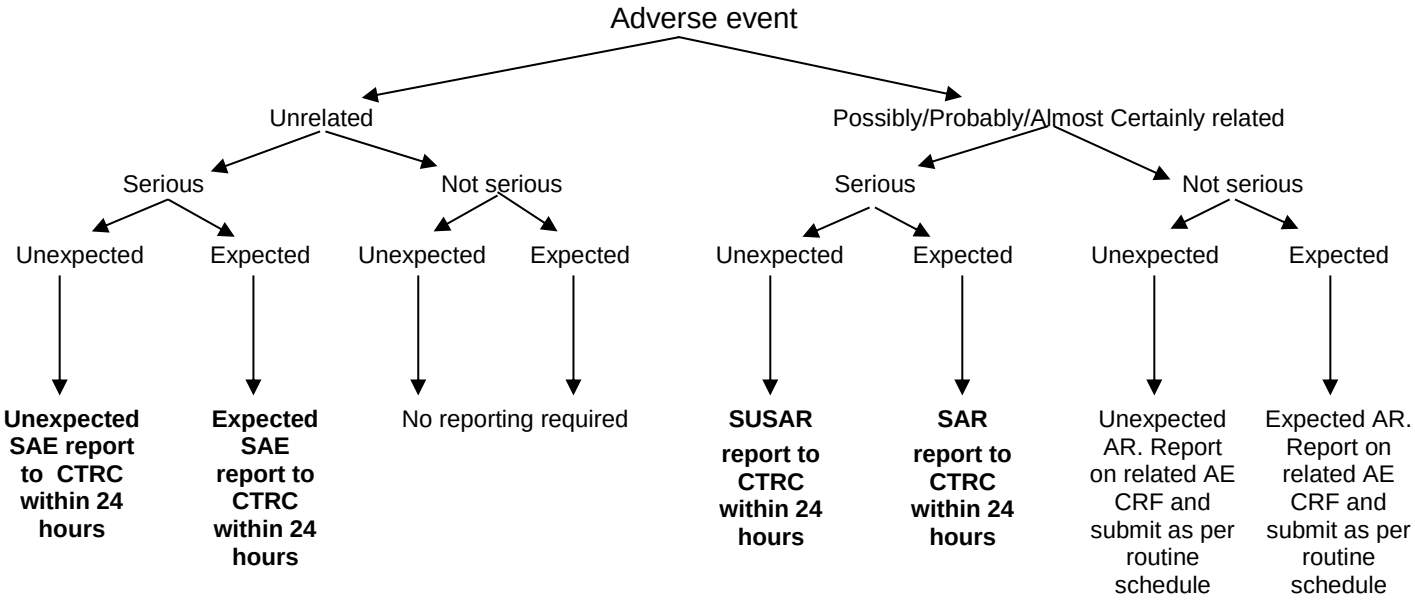
10.8.1 Non serious ARs

All adverse reactions (non-serious events suspected to be related to any dose administered of telmisartan) should be reported, whether expected or not. .Adverse reactions should be recorded on the Related Adverse Event Form, which should be transmitted to the CTRC within seven days of the form being updated. Non-serious adverse events do not need to be reported.

10.8.2 Serious ARs/AEs/SUSARs

All events that meet the serious criteria need to be reported (regardless of causality). SARs, SAEs and SUSARs should be reported within 24 hours of the local site becoming aware of the event. The SAE form asks for the nature of event, date of onset, severity, corrective therapies given, outcome and causality. The responsible investigator should sign the causality of the event. Additional information should be sent within 5 days if the reaction has not resolved at the time of reporting.

The CTRC will notify the MHRA and main REC of all SUSARs occurring during the study according to the following timelines; fatal and life-threatening within 7 days of notification and non-life threatening within 15 days. All investigators will be informed of all SUSARs occurring throughout the study. Local investigators should report any SUSARs and /or SAEs as required by their local Research & Development (R&D) Office.



10.9 Responsibilities – Investigator

The Investigator is responsible for reporting all ARs that are observed or reported during the study. The Investigator is also responsible for reporting all SAEs observed or reported during the study, regardless of their relationship to study product.
All SAEs must be reported immediately by the investigator to the CTRC on an SAE form unless the SAE is specified in the protocol as not requiring immediate reporting. All other adverse events should be reported on the regular progress/follow-up reports.

Minimum information required for reporting:

- Study identifier
- Study centre
- Patient number
- A description of the event
- Date of onset
- Current status
- Whether study treatment was discontinued
- The reason why the event is classified as serious
- Investigator assessment of the association between the event and study treatment

i. The SAE form should be completed by a designated investigator, a physician named on the 'signature list and delegation of responsibilities log' as responsible for reporting SAEs and making trial related medical decisions. The investigator should assess the SAE for the likelihood that it is a response to the investigational medicinal product. In the absence of the designated investigator the form should be completed and signed by an alternative member of the research site trial team and submitted to the CTRC. As soon as possible thereafter the responsible investigator should check the SAE form, make amendments as appropriate, sign and re-send to the CTRC. The initial report shall be followed by detailed reports as appropriate.

ii. When submitting an SAE to the CTRC research sites should also telephone the appropriate trial co-ordinator/data manager to advise that an SAE report has been submitted. (The CTRC trial team should ensure that the number to be used to report

SAEs in this way is manned during office hours, and is notified to research site personnel during the site initiation process.)

iii. Send the SAE form by fax (within 24 hours or next working day) to the CTRC:

Serious Adverse Events must be reported by faxing a completed SAE Form sent within 24 hours of becoming aware of the event to the CTRC

iv. The responsible investigator must **notify** their R&D department of the event (as per standard local governance procedures).

v. In the case of an SAE the subject must be followed-up until clinical recovery is complete and laboratory results have returned to normal, or until the event has stabilised. Follow-up may continue after completion of protocol treatment if necessary.

vi. Follow-up information is noted on another SAE form by ticking the box marked 'follow-up' and faxing to the CTRC as information becomes available. Extra, annotated information and/or copies of test results may be provided separately.

vii. The patient **must** be identified by trial number, date of birth and initials only. The patient's name **should not** be used on any correspondence.

10.10 Responsibilities – CTRC

The CTRC is undertaking duties delegated by the trial co-sponsors, The University of Liverpool and The Royal Liverpool and Broadgreen University Hospitals NHS Trust, and is responsible for the reporting of SUSARs and other SARs to the regulatory authorities (MHRA) and the main REC as follows:

- SUSARs which are fatal or life-threatening must be reported not later than 7 days after the CTRC is first aware of the reaction. Any additional relevant information must be reported within a further 8 days.
- SUSARs that are not fatal or life-threatening must be reported within 15 days of the CTRC first becoming aware of the reaction.
- A list of all SARs (expected and unexpected) must be reported annually.

It is recommended that the following safety issues should also be reported in an expedited fashion:

- An increase in the rate of occurrence or a qualitative change of an expected serious adverse reaction, which is judged to be clinically important;
- Post-study SUSARs that occur after the patient has completed a clinical trial and are notified by the investigator to the sponsor;
- New events related to the conduct of the trial or the development of the IMPs and likely to affect the safety of the subjects, such as:
    a. A SAE which could be associated with the trial procedures and which could modify the conduct of the trial;
    b. A significant hazard to the subject population, such as lack of efficacy of an IMP used for the treatment of a life-threatening disease;
    c. A major safety finding from a newly completed animal study (such as carcinogenicity).

d. Any anticipated end or temporary halt of a trial for safety reasons and conducted with the same IMP in another country by the same sponsor;

- Recommendations of the IDSMC, if any, where relevant for the safety of the subjects.

Staff at the CTRC will liaise with the Chief Investigator (or designated other, see table below)who will evaluate all SAEs received for seriousness, expectedness and causality. Investigator reports of suspected SARs will be reviewed immediately and those that are SUSARs identified and reported to regulatory authorities and MREC. The causality assessment given by the Local Investigator at the hospital cannot be overruled and in the case of disagreement, both opinions will be provided with the report.

Table 3: SAE Evaluator Contacts

Medical Expert who will evaluate SAE reports	**Role in trial**	**Address**	**Phone**	**email**
Prof. Munir Pirmohamed	Chief Investigator	The Wolfson Centre for Personalised Medicine Dept. Molecular and Clinical Pharmacology University of Liverpool Block A: Waterhouse Building 1-5 Brownlow St. Liverpool L69 3GL	0151 794 5549	munirp@liverpool.ac.uk
Prof. Saye Khoo	Principal Investigator (Royal Liverpool)	Block H: Waterhouse Building 70 Pembroke Place Liverpool L69 3GF	0151 794 5560	khoo@liverpool.ac.uk
Dr Mas Chaponda	Advisor/consultant	Infectious Diseases and Clinical Pharmacology Royal Liverpool Hospital, Prescot Street, Liverpool, L7 8XP		Chaponda@liverpool.ac.uk

The PIs at all institutions participating in the trial will be notified of any SUSARs.

Patient safety incidents that take place in the course of research should be reported to the National Patient Safety Agency (NPSA) by each participating NHS Trust in accordance with local reporting procedures.

10.11 Safety reports

Safety reports will be generated during the course of the trial which allows for monitoring of SAE and ADR reporting rates across sites. The CTRC will send developmental safety update reports containing a list of all SARS to regulatory authorities and MREC. Any concerns raised by the IDSMC or inconsistencies noted at a given site may prompt additional training at sites, with the potential for the CTRC to carry out site visits if there is suspicion of unreported AEs in patient case notes. Additional training will also be provided if unacceptable delay in safety reporting timelines. If any safety reports identify issues that have implications for the safety of trial participants, the PIs at all institutions participating in the trial will be notified.

11 ETHICAL CONSIDERATIONS

11.1 Ethical Considerations

We consider the specific ethical issues relating to participation in this trial to be:

11.1.1 Allocation of participants to control/ potentially less effective treatment arm(s)

In Stage I of the trial, a quarter of the patients will be allocated to the non-intervention control arm. These patients will not receive any investigational drug and therefore do not get any direct benefit of the intervention, if any; however such a non-intervention comparator arm is necessary for the identification of a positive drug effect in the treatment arm(s). However, this does not have any impact on the control of HIV infection since the intended use of telmisartan in this patient population is only as an adjuvant drug and not as the primary drug.

A percentage of the participants could also be on a treatment arm found to be less effective than control or other treatment arms during the interim analysis and hence, be dropped. Again, this does not have any impact on the control of HIV infection since the intended use of telmisartan in this patient population is only as an adjuvant drug and not as the primary drug.

11.1.2 Risk of hypotension

Telmisartan being an antihypertensive drug, there is a possibility that some of the participants randomised to the higher doses may experience hypotension. The eligibility criteria aim to exclude those who consistently show hypotension; moreover, the prevalence of telmisartan-induced hypotension in normotensive individuals was found to be rare in previous studies[38,39]. However, the trial will take adequate precautions to address this issue: all participants will be explained the potential risks involved prior to recruitment and those who take part will undergo routine screening for their vital parameters including blood pressure at both titration and follow-up visits.

11.1.3 Increase to existing pill burden to the participants

There will be further increase in the pill burden to the participants of this trial. However, we do not envisage this to be a major issue since the intervention is available as a single tablet that needs to be taken only once daily.

11.1.4 Contraception during the treatment period

For women of childbearing age, a pregnancy test will be performed before inclusion in the study and at T+12 weeks and T+24 weeks. Telmisartan is not recommended during early stages of pregnancy; therefore, for those who are on any of the treatment arms, contraception will be advised throughout the treatment period.

11.1.5 Additional visits required for the trial

For all participants, an additional visit (visits additional to routine clinical visits) is required for the baseline assessment which also includes collection of fasting blood samples.

For participants who are randomised to the 40 mg (Arm C) or 80 mg telmisartan arms (Arm D), either one (for those in Arm C) or two (for those in Arm D) additional visits are required for dose titration. These participants will be informed well in advance about the additional visits and explained the need for dose titration. Travel expenses will be reimbursed to the value of £12.50 for one scheduled trial visit per patient outside of normal clinic visits, and additionally for each drug titration visit (1X titration Arm C, 2X titration Arm D).

11.1.6 MRI/MRS scans in a subset of patients

For a subset of patients recruited from RLH, separate consent will be obtained to conduct MRI/MRS scans during their T0 and T+24 visits. Even though these visits will coincide with their baseline and scheduled clinical visits, MRI/MRS scans may involve additional patient time.. Travel expenses will be reimbursed to the value of £16 per patient for each MRI visit (a total of £32 per patient for 2 scans).

11.2 Ethical Approval

The trial protocol will be submitted to a multi-centre Research Ethics Committee (MREC) and will also undergo independent review at the R&D offices at participating sites. The local R&D office should be sent the appropriate site specific information form complete with the necessary authorisation signatures, plus any other documentation requested for review. A copy of local Research & Development (R&D) approval should be forwarded to CTRC before the site is initiated and patients recruited.

Consent from the patient should be obtained prior to participation in the trial, after a full explanation has been given of the treatment options, including the conventional and generally accepted methods of treatment. Patient Information and Consent Forms (PISC) should also be implemented. The right of the patient to refuse consent to participate in the trial without giving reason must be respected. After the patient has entered the trial, the clinician must remain free to give alternative treatment to that specified in the protocol, at any stage, if he/she feels it to be in the best interest of the patient. However, the reason for doing so should be recorded and the patient will remain within the trial for the purpose of follow-up and data analysis according to the treatment option to which they have been allocated. Similarly, the patient remains free to withdraw at any time from the protocol treatment and trial follow-up without giving reasons and without prejudicing the further treatment.

11.3 Informed Consent Process

Informed consent is a process initiated prior to an individual agreeing to participate in a trial and continues throughout the individual's participation. Informed consent is required for all patients participating in CTRC coordinated trials. In obtaining and documenting informed consent, the investigator should comply with applicable regulatory requirements and should adhere to GCP and to the ethical principles that have their origin in the Declaration of Helsinki.

Discussion of objectives, risks and inconveniences of the trial and the conditions under which it is to be conducted are to be provided to patients by staff with experience in obtaining informed consent. For TAILoR, information sheets which outline the trial and possible risks and benefits will be given to the patient during their routine clinic visit once they are identified by the delegated clinical staff at respective recruitment centres to meet the eligibility criteria. This will enable the patients to go through relevant information pertaining to the trial and associated risks and benefits in advance. PISC describing in detail the trial interventions/products, trial procedures and risks will be approved by an independent ethical committee (IEC) and the patient will be asked to read and review the document.

At the patient's routine clinic visit, the designated member of the research team will explain the trial to the patient. This information will emphasise that participation in the trial is voluntary and that the participant may withdraw from the trial at any time and for any reason. They will discuss the objectives of the study and all potential benefits and inconveniences of taking part. They will clearly outline all of the responsibilities the patient will be expected to meet if they agree to participate, including attendance at study visits and compliance with trial medications. All participants will be given opportunity to ask any questions that may arise, should have the opportunity to discuss the study and time to consider the information prior to agreeing to participate. A contact point where further information about the trial may be obtained will be provided.

The patient will sign and date the informed consent document. Both the person taking consent and the participant must personally sign and date the form. A copy of the informed consent document will be given to the patient for their records. The original copy will be filed in the participant's notes and a further copy of the signed consent form will be stored in the Investigator Site File. One final copy of the consent form should be sent to the CTRC within 7 days of the participant consenting to the study.

The researcher delegated to obtain informed consent will be determined on a site by site basis, depending on the experience and knowledge of the individual staff at that site. Only personnel deemed competent to do so by the PI and delegated the duty on the site signatory and delegation log will be able to obtain informed consent. This can include PIs, other delegated investigators and RNs. Where informed consent is being obtained by a RN, the patient should have access to a clinician with expertise in HIV medicine if they have any concerns about participation or any further questions that the RN is unable to sufficiently answer.

Where the informed consent discussion is conducted through a translator (i.e. the patient is non-English speaking), the translator will also sign the consent form to confirm that a full and accurate account of the study information has been provided to the patient.

The participants in all recruiting sites will be asked to sign the consent form for participation in the TAILoR Study. In addition, the participants in RLH will also be invited on a first-to consent basis to take part in the Body Fat Redistribution sub study by MRI/MRS and will be asked to provide separate consent to participate in this study (Consent to participate in Body Fat Redistribution sub study by MRI/MRS).

Patients will be given sufficient time to consider their decision and consent to the trial.

The patient may, without being subject to any resulting detriment, withdraw from the trial at any time by revoking the informed consent. The rights and welfare of the patients will be protected by emphasising to them that the quality of medical care will not be adversely affected if they decline to participate in this study.

11.4 Study Discontinuation

In the event that the study is discontinued, participants will be treated according to standard clinical care. The process for participants who withdraw early from trial treatment or from the trial completely is described in Section 5.3.

12 REGULATORY APPROVAL

This trial fall within the remit of the EU Directive 2001/20/EC, transposed into UK law as the UK Statutory Instrument 2004 No 1031: Medicines for Human Use (Clinical Trials) Regulations 2004 as amended. This trial has been registered with the MHRA and has been granted a Clinical Trial Authorisation (CTA). The EUDRACT number is 2012-000935-18.

13 TRIAL MONITORING

"The determination of the extent and nature of monitoring should be based on considerations such as the objective, purpose, design, complexity, blinding, size and endpoints of the trial. In general there is a need for on-site monitoring, before, during and after the trial; however central monitoring in conjunction with procedures such as investigators' training and meetings and extensive written guidance can assure appropriate conduct of the trial in accordance with GCP. Statistically controlled sampling may be an acceptable method for selecting the data to be verified." (ICH GCP 5.18.3)

Trial monitoring is carried out to ensure that the rights and well-being of human participants are protected during the course of a clinical trial.

Trial Oversight Committees related to the monitoring of the trial are detailed in section 16.

13.1 Risk Assessment and Trial Monitoring Plan

A detailed risk assessment is performed for each trial coordinated by the CTRC to determine the level and type of monitoring required for specific hazards. The nature and extent of monitoring will be specific to the individual trial. Monitoring can take the form of on-site visits or central monitoring.

In accordance with the CTRC SOP TM005, the trial risk assessment is completed in partnership between:

- Representative/s of the Trial Sponsor
- Chief Investigator
- Trial Manager and supervising Trial Manager
- Trial Statistician and supervising Statistician
- Information Systems team
- Data management team
- CTRC Director

In conducting this risk assessment, the contributors consider potential patient, organisational and study hazards, the likelihood of their occurrence and resulting impact should they occur.

Monitoring of the TAILoR trial will be informed by the TAILoR risk assessment and will be conducted as per a detailed monitoring plan, which will describe who will conduct the monitoring, at what frequency monitoring will be done, and what level of detail monitoring will be conducted.

Guidance issued by the MRC, Department of Health and the MHRA on risk-adapted approaches to the management of CTIMPs[54] propose a three level categorisation for the potential risk associated with the IMP, assigned according to the following categories:

Type A *'no higher than that of standard medical care';*
Type B *'somewhat higher than that of standard medical care';*
Type C *'markedly higher than that of standard medical care'.*

Telmisartan is indicated for clinical use as an antihypertensive agent. However, as TAILoR will use telmisartan outside the manufacturer's indication, the IMP in the TAILoR trial is categorised as ***Type B 'somewhat higher than that of standard medical care'.*** This level

of risk informs the risk assessment, regulatory requirements, nature and extent of the monitoring, and the management processes used in the trial.

13.2 Source Documents

***Source data**: All information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents (original records or certified copies). (ICH E6, 1.51).*
***Source documents**: Original documents, data, and records (e.g., hospital records, clinical and office charts, laboratory notes, memoranda, subjects diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate copies, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories and at medico-technical departments involved in the clinical trial). (ICH E6, 1.52).*

In order to resolve possible discrepancies between information appearing in the CRF and any other patient related documents, it is important to know what constitutes the source document and therefore the source data for all information in the CRF. The following data recorded in the CRF should be consistent and verifiable with source data in source documents *other* than the CRF (e.g. medical record, laboratory reports and nurses' notes).
Identified source documents other than the CRF for this trial are:

- Medical records
- Pharmacy records
- Participant treatment diaries
- Printouts from blood results (Plasma insulin, glucose, lipids, hs-CRP, other biomarkers)
- Printouts from urine analysis (creatinine, albumin, total protein and other biomarkers)

The following parameters that will be documented in the CRF are not source data:

- Relevant medical history and diagnosis (medical notes are source documents)
- Data for evaluation of eligibility criteria (medical notes are source documents)
- Physical examinations and assessments (medical notes are source documents).
- Concomitant medications (including changes) and diagnoses (medical notes are source documents)
- Dispensing of trial medication (pharmacy records are source documents)
- Adverse events (medical notes are source documents)

Therefore, for data where no prior record exists and which is recorded directly in the CRF, the CRF will be considered the **source document**, unless otherwise indicated by the investigator. All such exemptions should be identified prior to the clinical phase of the trial. In addition to the above, date(s) of conducting informed consent process including date of provision of patient information, randomisation number and the fact that the patient is participating in a clinical trial (including possible treatment arms) should be added to the patient's medical record chronologically, i.e. when treatment is allocated to the patient.

13.3 Data Capture Methods

13.3.1 Case Report Forms

The study case report form (CRF) is the primary data collection instrument for the study. All data requested on the CRF must be recorded. All missing data must be explained. If a space on the CRF is left blank because the procedure was not done or the question was not asked, write “N/D”. If the item is not applicable to the individual case, write “N/A”. Or if the data item is un-known, write “NK”. If a data item has not been recorded on source data then write ‘NR’. All entries should be printed legibly in black ink. If any entry error has been made, to correct such an error, draw a single straight line through the incorrect entry and enter the correct data above it. All such changes must be initialled and dated. DO NOT ERASE OR WHITE OUT ERRORS. For clarification of illegible or uncertain entries, print the clarification above the item, then initial and date it.

The original CRFs should be returned to the CTRC within 7 days of the time specified for completion, unless stated otherwise (copies of completed CRFs should be kept in the site file).

For the following CRFs, which are updated on an ongoing basis, photocopies should be forwarded to coordinating centre as and when changes have been made:

- Adverse Event,
- Medical History
- Concomitant medications

The final version of the original page(s) should only be sent to the CTRC when the patient has completed their time in the trial.

13.3.2 Participant completed treatment diaries

The participant initials and randomisation number should be clearly labelled on all documents. The ‘centre use only’ section on the front cover of the diaries should also be completed. This records the dates given/completed and the type of visit (if applicable).

13.3.3 Central laboratory data

The laboratory read-outs will be obtained for bloods (plasma insulin, plasma glucose, hs-CRP, lipids, other biomarkers), urine (creatinine, albumin, total protein and other biomarkers) and for the body fat redistribution sub-study from automated equipments. These will be either in the form of/ populated into a MS Excel document and uploaded securely to the central trial database.

13.4 Central Monitoring

Data stored at CTRC will be checked for missing or unusual values (range checks) and checked for consistency within participants over time. Any suspect data will be returned to the site in the form of data queries. Data query forms will be produced at the CTRC from the trial database and sent either electronically or through the post to a named individual (as listed on the site delegation log). Sites will respond to the queries providing an explanation/resolution to the discrepancies and return the data query forms to CTRC. The forms will then be filed along with the appropriate CRFs and the appropriate corrections made on the database. There are a number of monitoring features in place at the CTRC to ensure reliability and validity of the trial data, to be detailed in the trial monitoring plan.

13.5 Clinical Site Monitoring

In order to perform their role effectively, the trial manager (or monitor) and persons involved in Quality Assurance and Inspection may need direct access to primary data, e.g. patient records, laboratory reports, appointment books, etc. Since this affects the patient's confidentiality, this fact is included on the PISC.

13.6 Confidentiality

Individual participant medical information obtained as a result of this study is considered confidential and disclosure to third parties is prohibited with the exceptions noted below.
CRFs will be labelled with the patient's initials and unique trial screening and/or randomisation number. Medical information may be given to the participant's medical team and all appropriate medical personnel responsible for the participant's welfare.

The CTRC will be undertaking activities requiring the transfer of identifiable data:
Verification that appropriate informed consent is obtained will be enabled by the provision of copies of participant's signed informed consent/assent forms being supplied to the CTRC by recruiting centres, which requires that name data will be transferred to the CTRC.

This transfer of identifiable data is disclosed in the PISC. The CTRC will preserve the confidentiality of participants taking part in the study and The University of Liverpool is registered as a Data Controller with the Information Commissioners Office.

13.7 Quality Assurance and Control

QA includes all the planned and systematic actions established to ensure the trial is performed and data generated, documented/recorded and reported in compliance with applicable regulatory requirements. QC includes the operational techniques and activities done within the QA system to verify that the requirements for quality of the trial-related activities are fulfilled. In accordance with the monitoring plan, site visits will be conducted and source verification performed if indicated to be required as a result of central monitoring processes. To this end:

- The PI and RN from each centre will attend site initiation training, coordinated by the CTRC, which will incorporate elements of trial-specific training necessary to fulfil the requirements of the protocol
- The Trial Manager is to verify appropriate approvals are in place prior to initiation of a site and the relevant personnel have attended trial specific training;
- The Trial Manager is to check safety reporting rates between centres;
- The Trial Manager is to monitor screening, recruitment and drop-out rates between centres;
- The Trial Manager is to conduct data entry consistency checks and follow-up data queries;
- Independent oversight of the trial will be provided by the Independent Data and Safety Monitoring Committee and independent members of the Trial Steering Committee.

13.8 Records Retention

(ICH GCP 4.9.5) "Essential documents should be retained until at least 2 years after last approval of a marketing application in an ICH region and until there are no ending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the Investigational Product. These documents should be retained for a longer period however if required by applicable

regulatory requirements or by an agreement with the Sponsor. It is the responsibility of the Sponsor to inform the investigator/institution as to when these documents no longer need to be retained".

The investigator at each investigational site must make arrangements to store the essential trial documents, (as defined in Essential Documents for the Conduct of a Clinical Trial (ICH E6, Guideline for Good Clinical Practice)) including the Investigator Site File and Pharmacy Site File, until the CTRC informs the investigator that the documents are no longer to be retained, or for a maximum period of 15 years (whichever is soonest).
In addition, the investigator is responsible for archiving of all relevant source documents so that the trial data can be compared against source data after completion of the trial (e.g. in case of inspection from authorities). The investigator is required to ensure the continued storage of the documents, even if the investigator, for example, leaves the clinic/practice or retires before the end of required storage period. Delegation must be documented in writing.

The CTRC undertakes to store originally completed CRFs, except for source documents pertaining to the individual investigational site, which are kept by the investigator only. The CTRC will archive the documents in compliance with ICH GCP utilising the Records Management Service of the University of Liverpool. All electronic CRFs and trial data will be archived onto an appropriate media for long term accessible storage. Hard copies of data will be boxed and transferred to specially renovated, secure, premises where unique reference numbers are applied to enable confidentiality, tracking and retrieval.

14 INDEMNITY

TAILoR Study is sponsored by The University of Liverpool and The Royal Liverpool and Broadgreen University Hospitals NHS Trust and co-ordinated by the CTRC in the University of Liverpool. The University of Liverpool has clinical trial insurance and professional indemnities in place to cover its liabilities in regards to any work undertaken by its staff in the course of their employment at the University. As this is an investigator-initiated study, the Association of the British Pharmaceutical Industry (ABPI) guidelines for patient compensation by the pharmaceutical industry do not apply.

The Royal Liverpool and Broadgreen University Hospitals NHS Trust does not hold insurance against claims for compensation for injury caused by participation in a clinical trial and they cannot offer any indemnity. As this is an investigator-initiated study, The Association of the British Pharmaceutical Industry (ABPI) guidelines for patient compensation by the pharmaceutical industry do not apply. However, in terms of liability, NHS Trust and Non-Trust Hospitals have a duty of care to patients treated, whether or not the patient is taking part in a clinical trial, and they are legally liable for the negligent acts and omission of their employees. Compensation is therefore available in the event of clinical negligence being proven.

Clinical negligence is defined as:
"A breach of duty of care by members of the health care professions employed by NHS bodies or by others consequent on decisions or judgments made by members of those professions acting in their professional capacity in the course of their employment, and which are admitted as negligent by the employer or are determined as such through the legal process".

15 FINANCIAL ARRANGEMENTS

This study is funded by the MRC-NIHR Efficacy and Mechanism Evaluation (EME) Board of the Department of Health. Contractual agreements will be in place between the sponsor and collaborating sites that will incorporate financial arrangements.

15.1 Participant Payment

Participants in TAILoR Study will not be paid to participate in the trial. The schedule of the study will be in line with routine standard care where possible. Travel expenses will be reimbursed to the value of £12.50 for one scheduled trial visit per patient outside of normal clinic visits, and additionally for each drug titration visit (1X titration Arm C, 2X titration Arm D). Also, participants in the sub study will be reimbursed travel expenses to the value of £16 for each MRI visit (up to £32 per patient for 2 scans). These are reimbursements and should in no way be considered payments for participating in the trial.

15.2 Collaborating Centre

Some tasks are to be undertaken during routinely scheduled clinic appointments that are directly related to the research and will impose a time demand on clinic staff, which is in addition to their usual clinical work. The EME has provided funding for per patient payments for each patient recruited and followed up. The exact amounts are detailed in the contract between the Sponsor and the Site.

Also, as the study is funded by the MRC-NIHR EME, it will be automatically adopted onto the NIHR portfolio, which will allow trusts to apply to their comprehensive local research network for service support costs as required.

16 TRIAL COMMITTEES

16.1 Trial Management Group (TMG)

A Trial Management Group (TMG) will be formed comprising the Chief Investigator, other lead investigators (clinical and non-clinical) and members of the CTRC.

The TMG will be responsible for the day-to-day running and management of the trial and will meet as a minimum approximately 3 times a year. Refer to the TMG terms of reference and Trial Oversight Committee Membership document for further details.

16.2 Trial Steering Committee (TSC)

The Trial Steering Committee will consist of an independent chairperson (a HIV clinician), two independent statisticians with expertise in adaptive trial design and medical statistics and a user representative. The TSC will also include the applicants and representatives of the research networks, sponsors and the funder (EME) and up to seven Principal Investigators.

The role of the TSC is to provide overall supervision for the trial and provide advice through its independent Chairman. The ultimate decision for the continuation of the trial lies with the TSC. Refer to the TSC terms of reference and trial oversight committee membership document for further details.

16.3 Independent Data and Safety Monitoring Committee (IDSMC)

The Independent Data and Safety Monitoring Committee (IDSMC) consist of an independent chairperson (with clinical expertise in HIV) and two independent members: one who is an expert in the field of HIV lipodystrophy, and one who is an expert in medical statistics and adaptive trial design.

The IDSMC will be responsible for reviewing and assessing recruitment, interim monitoring of safety and effectiveness, trial conduct and external data. The IDSMC will first convene prior to trial initiation prior to the start of recruitment and will then define frequency of subsequent meetings (at least annually). The IDSMC will provide a recommendation to the TSC concerning the continuation of the study. Refer to the IDSMC charter and trial oversight committee membership document for further details.

17 PUBLICATION

The results from different centres will be analysed together and published as soon as possible. Individual clinicians must undertake not to submit any part of their individual data for publication without the prior consent of the Trial Management Group.

The Trial Management Group will form the basis of the Writing Committee and advice on the nature of publications. The Uniform Requirements for Manuscripts Submitted to Biomedical Journals (http://www.icmje.org/) will be respected. All publications shall include a list of participating centres, and if there are named authors, these should include the trial's Chief Investigator(s), Statistician(s) and Trial Manager(s) involved at least. If there are no named authors (i.e. group authorship) then a writing committee will be identified that would usually include these people, at least. The ISRCTN allocated to this trial should be attached to any publications resulting from this trial.

The members of the TSC and IDSMC should be listed with their affiliations in the Acknowledgements/Appendix of the main publication.

18 PROTOCOL AMENDMENTS

Version 1.0 (29/02/2012)
Original Approved version.

Version 2.0 (14/06/2012)
Exclusion criteria amended in Page 18. An additional criterion was added:
'Patients with cholestasis, biliary obstructive disorders or severe hepatic impairment'

Version 3.0 (28/09/2012)
Section 14 - Indemnity statement amended to show that UoL holds Clinical Trial insurance

Section 8.5 – Body fat redistribution amended to reflect that participants are free to withdraw from the sub study and remain in the main study, if they so wish

Cover Page – the ISRCTN reference number has been added and the UoL sponsor reference number has been corrected

Contact details – Clinical laboratory changed from RLH to UHA, CTRC Sherrington address added

Section 1 – exclusion criteria number 12 'non hormonal contraception' replaced with 'reliable contraception'

Section 1 – point 7 added to 'secondary objectives'

Section 1 – mention of 'serum' removed

Section 2.1 – paragraph on possible renoprotective effects of Telmisartan added

Section 2.3 point 7 added to secondary objectives

Section 2.4.1 – paragraph on renal artery stenosis has been added

Section 4.2 – point 6 added to secondary outcomes

Section 5.2 – exclusion criteria number 12 'non hormonal contraception' replaced with 'reliable contraception'

Section 5.3.2 – point b – spelling mistake corrected

Section 5.3.2 – Inserted j – it is discovered that the patient is pregnant

Section 6.3 – point 7 – changed number of blood samples from 2 to 3

Section 6.3 – point 8 collection of urine sample added

Section 7.2.2 – changed packaging description

Section 7.3 – replaced phrase 'treatment pack' with 'trial treatment'

Section 7.7.3 – amended to state the female patients discovering they are pregnant should let the research team know immediately

Section 8.1 – table 1 – removed ‘collection of blood sample 1’ and collection of blood sample 2’ replaced with ‘collection of 3 blood samples for bioanalysis’

Section 8.1 – table 1 – inserted collection of urine sample

Section 8.2.1 – replaced mention of Department of Clinical Biochemistry, Royal Liverpool Hospital, with ClinicalClinical Laboratories, University Hospital Aintree

Section 8.2.1 – changed number of blood samples from ‘two’ to ‘three’

Section 8.2.1 – replaced ‘radioimmunoassay’ with enzymatic immunoassay’

Section 8.4.1– replaced mention of Department of Clinical Biochemistry, Royal Liverpool Hospital, with Clinical Laboratories, University Hospital Aintree

Section 8.4.2 – replaced mention of Department of Clinical Biochemistry, Royal Liverpool Hospital, with Clinical Laboratories, University Hospital Aintree

Section 8.4.4 – section inserted to describe assessment of renal biomarkers

Section 9.2 – Changed stratification details and added a sentence on ethnicity

Contact details: Institutions– Clinical Laboratory changed from Department of Clinical Biochemistry, Royal Liverpool Hospital, to Clinical Laboratories, University Hospital Aintree

Section 10.8– altered to reflect that adverse reactions and all serious events are to be recorded

Section 10.8.1– Altered to reflect Telmisartan related ARs only

Section 10.9 (– amended to read ‘all ARs that are observed or reported.....The investigator is also responsible for reporting all SAEs’

Section 10.9 i)– inserted ‘if a control (Arm A) patient has experienced an SAE the event does not need to be assessed for expectedness or relationship to study treatment, although the event should still be reported’

Section 10.9 ii)– amended phone number

Section 10.9 iii)– amended fax number

Version 4.0 (03/09/2013)

Contact details – these have been removed

Section 1 – point 2 clarified

Section 1 – point 6 clarified

Section 1 – point 9 addition of extra drug group due to changes in Summary of Product Characteristics
Section 4.2 – point 6 clarified

Section 5.2 – point 2 clarified

Section 5.2 – point 6 clarified

Section 5.2 – point 9 further drug group/class added due to change in Summary of Product Characteristics

Section 6.3 – point 3 further clarification of medical history

Section 6.4 – added trial coordinator to contacts if a problem with the randomisation system arises and removed helpdesk

Section 7.1 – statement inserted to clarify that treatment is not stopped between stage I and II

Section 7.3.1 – added statement of time windows for visits

Section 7.3.1.2 – clarification on time windows

Section 7.3.1.2 – change to dispensing guidelines to minimise drug wastage

Section 7.3.1.3 – clarification on time windows

Section 7.3.1.3 – change to dispensing guidelines to minimise drug wastage

Section 7.3.1.4 – clarification on time windows

Section 7.3.1.4 – change to dispensing guidelines to minimise drug wastage

Section 7.2 – clarification of ‘acceptable period of time

Section 8.1 – clarification on time windows

Section 8.1, table 1 – clarification on Medical History

Section 10.4 – removal of fax number

Section 10.9 – removal of fax number

Section 10.10 – insertion of table 3 @SAE Evaluator Contacts

Section 11.1.5 – insertion of statement on patient travel expenses

Section 15.1 – insertion of statement on travel expenses

Version 5.0 24/01/2014

Section 1 and section 5.2 – The units for the HbA1C value in exclusion criterion 1 have been corrected

Section 7 – removal of all mentions of ‘Micardis’ – a brand name of telmisartan

Section 7.2.1 – insertion of a statement on dispensing of telmisartan if a high dose is unavailable

Section 7.2.1 – insertion of statements on reference safety information and bioequivalence

Section 7.2.3 – insertion of word manufacturers

Version 6.0 16/06/2014

Section 1 and section 5.2 – the included and excluded drugs have been clarified

Section 6.3 – insertion of the phrase ‘by a medically qualified person’ to the verification of eligibility criteria

Section 7.3.3 – removal of the phrase ‘in the morning’ from the administration instructions

Table 1 – Insertion of ‘by a medically qualified person’ to assessment of eligibility criteria

Section 10.8.2 – Insertion of ‘All events that meet the serious criteria need to be reported (regardless of causality)’

Version 7.0 13/05/2015

Glossary – Addition of abbreviation for Liverpool Clinical Laboratories

Glossary – Deletion of University Hospitals Aintree

Section 1 – change to the number of participants to be enrolled

Section 8.2.1, 8.4.1, and 8.4.2 – replaced Clinical laboratories, University Hospitals Aintree with Liverpool Clinical Laboratories

Section 8.4.5 and 8.5.4 – insertion of statement(s) on the reporting of any clinically significant results

Section 9.4 – insertion of statement on what happens ‘post interim analysis’

Section 9.5 – insertion of statement that after interim analysis randomisation will continue in an equal ratio

Version 8.0 (28/07/2016)

Cover page – insertion of trial statistician signature

Protocol Summary – insertion of a further secondary objective

Section 2.2 – insertion of a statement on alternative surrogate indices of insulin sensitivity

Section 2.3 – insertion of a further secondary objective

Section 4.2 – insertion of a further secondary outcome

Section 8.4.3 – change to novel biomarkers

Section 8.4.3 – removal of assessment of renal biomarkers

Section 8.4.4 – addition of section on alternate measures of insulin resistance

Section 8.5 – changed to sub-study 1

Section 8.6 – Insertion of sub-study 2 (assessment of renal biomarkers)

Section 9.4.1 – changed to sub study 1

Section 9.4.2 – insertion of statement on sample size for sub study 2 (renal biomarkers)

Section 9.6.2.1 – removal of assessment by structural equation models

Section 9.6.2.3- insertion of statement on evaluation of alternate measures of insulin resistance

Section 9.6.2.4 – insertion of statement on renal biomarkers

References – addition of reference 57

REFERENCES

1. HIV Lipodystrophy Case Definition Study Group. Lancet. 2003;361:726-735.
2. Potthoff A et al, J Dtsch Dermatol Ges. 2010;8:92-8.
3. Lorenzo C et al, Diabetes Care. 2007;30:8-13.
4. Jericho C et al, Diabetes Care. 2005;28:144-149.
5. Jacobson DL et al, J Acquir Immune Defic Syndr. 2006;43:458-66.
6. Worm SW et al, AIDS. 2010; 24:427-35.
7. Brown TT et al, Arch Intern Med. 2005;165:1179-84.
8. De Wit S et al, Diabetes Care. 2008; 31:1224-9.
9. Friis-Møller N et al, N Engl J Med. 2007;356:1723-35.
10. Strategies for Management of Anti-Retroviral Therapy/INSIGHT; DAD Study Groups; AIDS. 2008;22:F17-24.
11. Lo J et al, AIDS. 2010;24:243-53.
12. Samaras K et al, J Acquir Immune Defic Syndr. 2009;50:499-505.
13. Djedaini M, Biochem Biophys Res Commun. 2009;386:96-100.
14. Lee GA et al, AIDS. 2007;21:2183-90.
15. Palacios R et al, Antivir Ther. 2006;11:529-35.
16. Bernal E et al. Med Clin (Barc). 2007;129:252-4.
17. Grunfeld C et al, J Acquir Immune Defic Syndr. 2007;46:283-90.
18. Jones SP et al, Antivir Ther. 2005;10:207-13.
19. Lagathu C et al, Antivir Ther. 2004;9:911-20.
20. Benavides S et al, Ann Pharmacother. 2004;38:448-57.
21. McGoldrick C et al, HIV Med. 2007;8:325-34.
22. Sheth SH et al, BMC Infect Dis. 2010;10:183.
23. Nissen SE et al, N Engl J Med. 2007;356:2457-71.
24. Benndorf RA et al, Metabolism. 2006;55:1159-64.
25. Younis F et al, Metabolism. 2010;59:1200-9.
26. Foryst-Ludwig A et al, Cardiovasc Diabetol. 2010;9:64.
27. Souza-Mello V et al, Clin Sci. 2010;119:239-50.
28. Derosa G et al, J Clin Pharm Ther. 2007;32:261-8.
29. Rizos CV et al, Clin Ther. 2010;32:492-505.
30. Makita S et al, Metabolism. 2008;57:1473-8.
31. Georgescu EF et al, World J Gastroenterol. 2009;15:942-54.
32. Chujo D et al, Hypertens Res. 2007 Dec;30:1205-10.
33. Shimabukuro M et al, J Hypertens. 2007;25:841-8.
34. ONTARGET Investigators, N Engl J Med. 2008;358:1547-59.
35. Lagathu C et al, Antivir Ther. 2007;12:489-500.
36. Koster JC et al, Diabetes. 2003;52:1695-700.
37. Boccara F et al, Antivir Ther. 2010;15:363-75.
38. Stangier J et al, J Int Med Res. 2000;28:149-67.
39. Stangier J et al, J Clin Pharmacol. 2000;40:1355-64.
40. Sipahi I et al, Lancet Oncol. 2010;11:627-36.
41. Kjeldsen SE et al, Blood Press. 2010;19:271-2.
42. Bangalore S et al, Lancet Oncol. 2010 Nov 29.
43. http://www.ct-toolkit.ac.uk/_db/_documents/Annex_13.pdf
44. Thomas EL et al, Gut. 2005;54;122-127.
45. Rico-Sanz, J et al, J Appl Physiol.1999;87: 2068–2072.
46. Dunnett C, Design of Experiments: Ranking and Selection (T. Santer and A. Tamhane, eds.), pp. 47-66, 1984.
47. Magirr D et al, Stat Med. 2010 (in press).
48. Whitehead J et al, Stat Med. 2009;28:828-47.
49. Hanefeld M et al, Curr Med Res Opin. 2007;23:1329-39.
50. Carrizo E et al, Schizophr Res. 2009;113:19-26.

51. Henderson R et al, Biostatistics. 2000;1:465-480.
52. Williamson PR et al, Statistics in Medicine. 2008; 27: 6426-6438
53. Emsley RA et al, *Stat Meth Med Res.* 2010;19:237-270.
54. MRC/DH/MHRA Joint Project: Risk-adapted approaches to the management of of Clinical Trials of Investigational Medicinal Products; 10 October 2011; http://www.mhra.gov.uk/home/groups/l-ctu/documents/websiteresources/con111784.pdf
55. Takagi H et al*, Int J Cardiol*. 2012.
56. Ucciferri C et al. *Eur Rev Med Pharmacol Sci*. 2012; 16: 491-8.
57. Otten J et al. Diabetologia. 2015;58(2):416-7.

19 DOCUMENTS SUPPLEMENTARY TO THE PROTOCOL

The following supplementary documents will accompany the protocol and are separately updated and version controlled:

- Patient information sheet and consent form
- Patient information sheet and consent form (including MRI/MRS sub-study)
- Summary of Product Characteristics (Telmisartan)

20 APPENDIX A: DIVISION OF AIDS TABLE

for Grading the Severity of Adult and Pediatric Adverse Events Version 1.0 (2009)