



**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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**Study Sponsor(s):**

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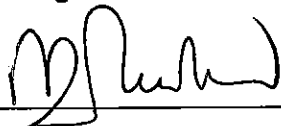
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Date: \_\_\_\_\_

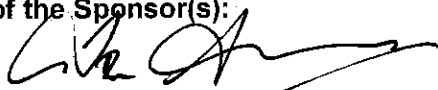
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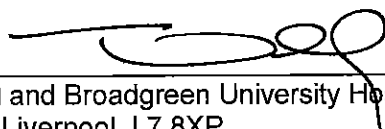
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## **General Information**

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](http://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.ctrcl.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

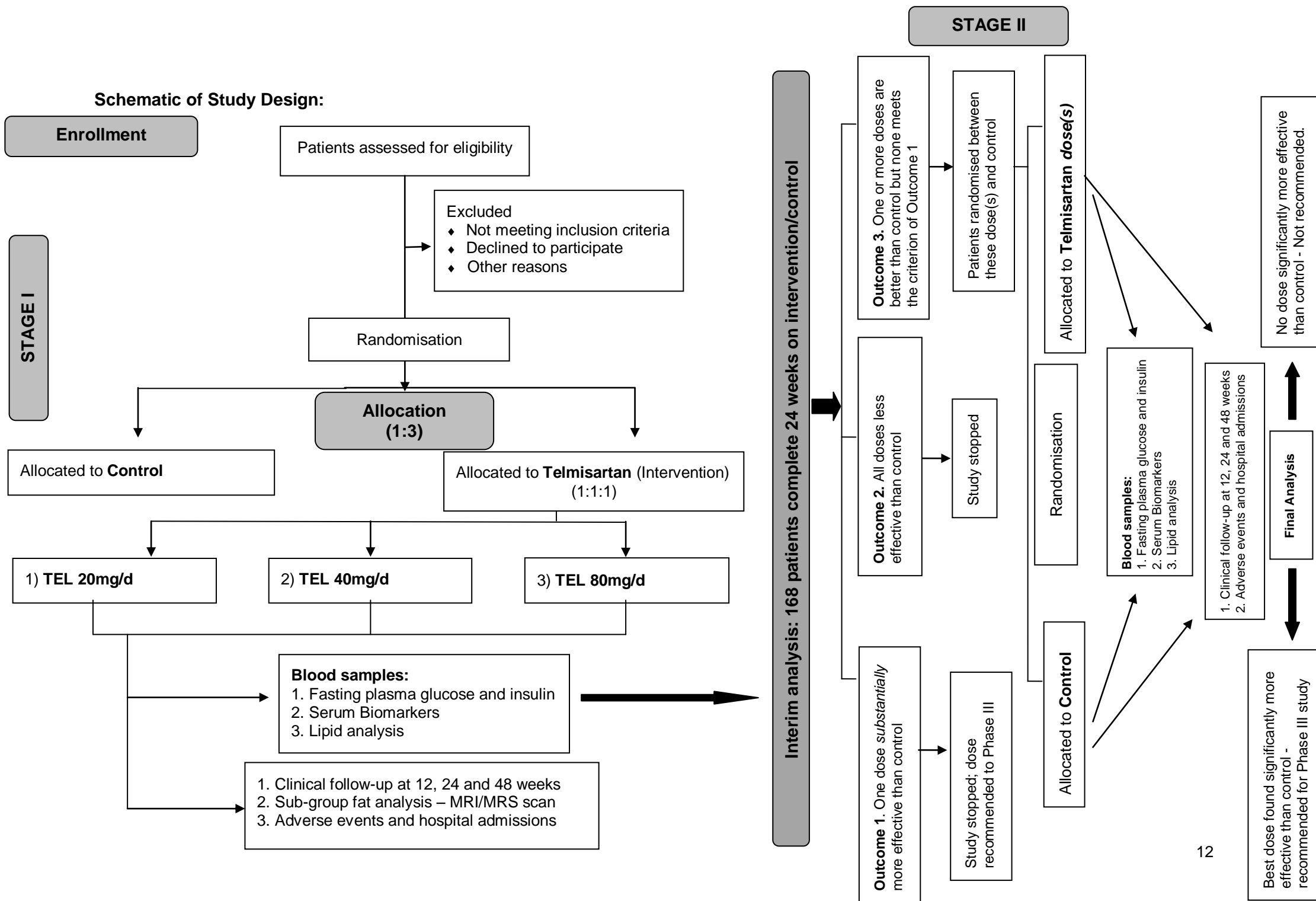
ACE	Angiotensin Converting Enzyme
AE	Adverse Event
AR	Adverse Reaction
ARBs	Angiotensin Receptor Blockers
cART	Combination Antiretroviral Therapy
CCRN	Comprehensive Clinical Research Network
CI	Chief Investigator
CRF	Case Report Form
CR-UK LCTU	Cancer Research UK Liverpool Cancer Trials Unit
CTIMP	Clinical 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
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

<b>Title:</b>	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)
<b>Phase:</b>	II
<b>Study Design:</b>	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.
<b>Population:</b>	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.
<b>Criteria for Inclusion:</b>	<p>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, for at least 6 months.</p> <p>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.</p> <p>2. Ability to give informed consent.</p> <p>3. Willingness to comply with all study requirements.</p>
<b>Criteria for Exclusion:</b>	<p>1. Pre-existing diagnosis of type 1 or 2 diabetes (Fasting glucose &gt; 7.2mmol/L or HbA1c ≥ 6.5% [48 mmol/ml] or abnormal OGTT or random plasma glucose ≥ 11mmol/l)</p> <p>2. Patients who consistently show low blood pressure (pre-existing hypotension; below a threshold of 100/60 mm Hg)</p> <p>3. Patients with renal disease (eGFR&lt;60 in the 6 months preceding randomisation)</p> <p>4. Patients with known untreated renal artery stenosis</p> <p>5. Patients with cholestasis, biliary obstructive disorders or severe hepatic impairment</p> <p>6. Patients with prior diagnosis of Hepatitis C (a positive PCR result in the 6 months preceding randomisation)</p> <p>7. Patients who are on unboosted atazanavir</p> <p>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.</p> <p>9. Patients who are already on/ have been on other ARBs and/or ACE inhibitors within 4 weeks preceding randomisation.</p> <p>10. Those with suspected poor compliance</p> <p>11. Pregnant or lactating women</p> <p>12. Women of childbearing age unless using non hormonal contraception</p> <p>13. Co-enrolment in other drug trials</p> <p>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.</p> <p>15. For the sub-cohort of patients undergoing MRI/MRS, normal MR exclusion criteria will apply.</p>
<b>Study Centres and Distribution:</b>	Specialist HIV treatment centres in the UK
<b>Study Duration:</b>	47 months
<b>Description of Agent/ Intervention:</b>	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.
<b>Number of participants to be enrolled:</b>	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.
<b>Primary Objective:</b>	This trial will determine the effect of telmisartan on insulin resistance (as measured by HOMA-IR) in HIV-positive individuals on cART.
<b>Secondary Objective/s:</b>	<ol style="list-style-type: none"> <li>1. To define the optimal dose of telmisartan that can significantly reduce insulin resistance.</li> <li>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.</li> <li>3. To evaluate the tolerability of telmisartan in this patient group.</li> <li>4. To mechanistically evaluate whether telmisartan modulates the plasma concentrations of both beneficial and adverse biomarkers.</li> <li>5. To determine whether telmisartan improves general lipid homeostasis and reduces visceral fat accumulation in HIV-positive individuals on cART.</li> <li>6. To determine whether <sup>1</sup>H MRS-assessed intrahepatic and intramyocellular triglyceride content are reduced by telmisartan.</li> </ol>

## 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<sup>1</sup>. HIVLD is a predictor of metabolic syndrome (MS) and associated CVD risk<sup>2</sup>. MS itself is a known risk factor for T2DM and CVD<sup>3</sup>. The prevalence of MS is high in cART treated HIV+ patients (17-25%)<sup>4,5</sup>; 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<sup>6</sup>. 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)<sup>7</sup> and a more recent analysis of the DAD cohort<sup>8</sup>. 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<sup>9</sup> and nucleoside reverse transcriptase inhibitors<sup>10</sup> (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<sup>11</sup>. 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<sup>12</sup>. *In vitro* studies<sup>13</sup> and single drug studies in healthy individuals<sup>14</sup> and HIV+ patients<sup>15,16</sup> have shown that PIs and NRTIs cause insulin resistance. The prevalence of insulin resistance in cART-treated HIV+ patients ranges from 10-37%<sup>15,16,17</sup> 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%<sup>17</sup>. Several mechanisms have been suggested to be responsible for cART-induced insulin resistance; these include cART-induced inhibition of adipocyte differentiation<sup>18</sup>, increased secretion of adipokines such as IL-6 and TNF- $\alpha$ <sup>19</sup>, and impairment of insulin signalling pathway<sup>13</sup>.

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<sup>20,21</sup>. Moreover, the associated adverse effects may limit their use in HIV+ patients<sup>22,23</sup>. 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 PPAR $\gamma$ , an important regulator of adipocyte function. Telmisartan shows maximal potency on PPAR $\gamma$  when compared to other ARBs and has been reported to reduce insulin resistance in several *in vitro*<sup>24,25</sup>, animal<sup>26,27</sup> and clinical studies<sup>28,29,30,31</sup>. 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<sup>28</sup>; (b) in a comparison with other ARBs in non-diabetic patients (n=151), telmisartan reduced HOMA-IR by 29% after 6 months

treatment<sup>29</sup>. Telmisartan also improves adiponectin levels, an important metabolic marker of insulin resistance and atherosclerotic disease; it improved lipid control in these patients<sup>28</sup>, and has favourable effects on fasting serum insulin and high sensitivity C-Reactive Protein<sup>28</sup> (hs-CRP; a marker of cardiovascular disease). Telmisartan has also been shown to reduce visceral, but not subcutaneous fat accumulation, in patients with MS<sup>32,33</sup>. 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<sup>34</sup>. 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<sup>31</sup>.

## 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<sup>18,19</sup>, reduce adiponectin secretion<sup>18,35</sup>, increase the secretion of detrimental cytokines, IL-6 and TNF- $\alpha$ <sup>18,19</sup> and impair GLUT-4 expression<sup>36</sup>, 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<sup>37</sup>. 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<sup>31</sup>. 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<sup>28,29</sup>.

## 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, TNF $\alpha$ , 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  $^1\text{H}$  MRS-assessed intrahepatic 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 steatosis and 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<sup>38,39</sup>. 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<sup>40</sup>. However, this meta-analysis has been heavily criticised<sup>41</sup>, and a new recent, more extensive meta-analysis<sup>42</sup> 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.

### **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- $\alpha$ , 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. Difference in expected and unexpected adverse events between different telmisartan treated dose arm(s) and the control arm.

## 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, 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.

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  $\geq$  6.5% [48 mmol/mol] or abnormal OGTT or random plasma glucose  $\geq$  11mmol/l)
2. Patients known to have consistently low blood pressure (pre-existing hypotension; below a threshold of 100/60 mm Hg)
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 prior diagnosis of Hepatitis C (a positive PCR result in the 6 months preceding randomisation)
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 and/or ACE inhibitors within 4 weeks preceding randomisation.
10. Those with suspected poor compliance
11. Pregnant or lactating women
12. Women of childbearing age unless using non hormonal contraception
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. Switching of therapy from protease inhibitors to EFV and viceversa.
- d. Unacceptable adverse effect of Grade3/4 which can be attributed to telmisartan (eg. Hypotension);
- e. Intercurrent illness preventing further treatment;
- f. Inability to attend regularly for treatment or assessment;
- g. Any change in the patient's condition that justifies the discontinuation of treatment in the clinician's opinion (eg. Acute Hep C);
- h. Failure to comply with the protocol requirements or cooperate with the investigator;
- i. The patient starts treatment with any disallowed medication without prior notification and consent of the investigators.

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 that the eligibility criteria are fulfilled;
2. Demographic details including age, gender, ethnicity;
3. Full medical 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 2 separate fasting blood samples from each patient.

Plasma will be extracted from both blood samples and stored at -20°C 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/](http://www.tailortrial.org.uk/rand/)**  
*If there are any problems with web randomisation,  
please contact the CTRC helpdesk on: 0845 68 00 951  
Or via email on [helpdesk@mcrnctu.org.uk](mailto:helpdesk@mcrnctu.org.uk) / [tailor@liverpool.ac.uk](mailto: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 (marketed as Micardis®; Boehringer Ingelheim Ltd) is indicated for clinical use as an antihypertensive agent. However, the current trial will use telmisartan outside the manufacturer's indication.

#### **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

### 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 and Composition of the Drug Product

##### **Telmisartan:**

Generic name – Telmisartan (Brand name: Micardis®).

Micardis® oral tablets contain telmisartan (20 mg, 40 mg, or 80 mg); 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.

Micardis® 20 mg tablets are white, round, 2.5 mm in diameter and engraved with the code number '50H' on one side and the company logo on the other side.

Micardis® 40 mg tablets are white, oblong-shaped, 3.8 mm in diameter and engraved with the code number '51H' on one side and the company logo on the other side.

Micardis® 80 mg tablets are white, oblong-shaped, 4.6 mm in diameter and engraved with the code number '52H' on one side and the company logo on the other side.

Micardis® tablets also contain povidone, meglumine, sodium hydroxide, sorbitol (E420) and magnesium stearate.

Micardis® is manufactured by Boehringer Ingelheim Ltd.

### **7.2.2 Packaging and Labelling**

Micardis is available in three different doses: 20 mg, 40 mg and 80 mg tablets. The tablets will be packaged in 28 tablet blister packs, with an aluminium foil top. Three blister packs will be packaged in an outer cardboard carton and 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 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. The 20 mg tablet has a shelf life of 3 years. The 40 mg and 80 mg tablets have a shelf life of 4 years.

## **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 can start immediately after randomisation. The PI or delegated other will issue a prescription based on the patient's randomisation status. The patient will be dispensed their first treatment pack by the respective pharmacy. 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).

Each treatment pack will contain 12 weeks (84 tablets) of trial medication, consisting of three blister packs (each blister pack containing 4 weeks treatment) of the IMP. 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, one 12 week treatment pack containing three 28 tablet blister packs of telmisartan 20 mg will be dispensed on receipt of a valid trial prescription.

#### **T+12 week study visit**

During this visit, the participants will be dispensed with one 12 week treatment pack containing three 28 tablet blister packs of telmisartan 20 mg on receipt of a valid trial prescription.

#### **T+24 week study visit**

During this visit, the participants will be dispensed with two 12 week treatment packs containing three 28 tablet blister packs of telmisartan 20 mg on receipt of a valid trial prescription. 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 a two week treatment pack of 20 mg telmisartan (14 tablets) 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 one 12 week treatment pack containing three 28 tablet blister packs 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 one 12 week treatment pack containing three 28 tablet blister packs 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 two 12 week treatment packs containing three 28 tablet blister packs of telmisartan 40 mg on receipt of a valid trial prescription. 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 a two week treatment pack of 20 mg telmisartan (14 tablets) 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 a two week treatment pack of 40 mg telmisartan (14 tablets) 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 one 12 week treatment pack containing three 28 tablet blister packs 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 one 12 week treatment pack containing three 28 tablet blister packs of telmisartan 80 mg on receipt of a valid trial prescription.

#### **T+24 week study visit**

During this visit, the participants will be dispensed two 12 week treatment packs containing three 28 tablet blister packs of telmisartan 80 mg on receipt of a valid trial prescription. 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, 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, to be taken in the morning 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 CTCRC:

- 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 (eg. Testosterone)
- 2) Other hormone supplements (eg. 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.

### 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. Wherever possible, all follow-up visits should be conducted no earlier than two weeks before the appropriate date (e.g. no earlier than 10 weeks after randomisation for T+12). When planning a visit which is later than the appropriate date, the research team should consider the participant's remaining trial medications and ensure they do not run out prior to the visit. Care should be taken to ensure that the 24 week and 48 week primary endpoint visits are arranged from the date that treatment started irrespective of earlier scheduled visit dates.

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		X						
Review of Medical History		X			X	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 blood sample 1 (fasting) - blood glucose & insulin RIA & Lipid profile to Clinical Chemistry		X			X	X	X	X
Collection of blood sample 2 (fasting) - Serum separated for biomarkers/WBC for DNA extraction		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		X				X		

(X) – As indicated/appropriate.

\*Baseline assessment and randomisation visit should be within 30 days of the patient giving consent.

### **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.

Two 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 will be extracted locally at each site and stored at -20°C. Batched samples will be couriered on dry ice to the 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 Department of Clinical Biochemistry and Metabolic Medicine, Royal Liverpool University Hospital, 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 a radioimmunoassay. 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 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 the Department of Clinical Biochemistry and Metabolic Medicine, RLH, for this purpose.

### **8.4.2 Assessment of hs-CRP**

High sensitivity C-Reactive Protein (hs-CRP) will be measured for T0 and T+12, T+24, and T+48 week visits; analysis will be carried out in the Department of Clinical Biochemistry and

Metabolic Medicine, RLH 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, lipin1, IL-6, TNF- $\alpha$  and resistin will be measured at T0 and T+12, T+24, and T+48 week visits. The biomarker levels will be measured using the second blood sample (see section 8.2.1) processed in the Wolfson Centre for Personalised Medicine, University of Liverpool, using Human Multiplex ELISA (Millipore) on a BioPlex 200 System (BioRad).

## **8.5 Sub studies – 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/ $^1\text{H}$  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/ $^1\text{H}$  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.

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  $^1\text{H}$  MRS (liver, limbs) undertaken at the MARIARC.

### **8.5.1 Exclusion Criteria**

For the sub-cohort of patients undergoing MRI/ $^1\text{H}$ 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 MARIARC.

MRI will be carried out both at T0 and at T+24 week visit<sup>44</sup> 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](http://www.vardisgroup.com)).



### **8.5.3 Assessment of Intrahepatic and Intramyocellular Lipid Content**

<sup>1</sup>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 <sup>1</sup>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<sup>44</sup>. Transverse MR images will be used to position three 20x20x20 mm voxels, avoiding blood vessels, gall bladder and fatty tissue. Skeletal muscle <sup>1</sup>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<sup>45</sup>. 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<sub>2</sub> relative to creatine signal<sup>45</sup>, and intrahepatic lipid as CH<sub>2</sub> relative to unsuppressed water.

### **8.6 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.

### **8.7 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 gender and ethnicity (African and Non-African).

### 9.3 Outcome Measures

See section 4.

### 9.4 Sample Size and Power Requirement

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,  $\sigma$ . 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  $\alpha$  if the effects of the treatments are identical ( $\alpha$  is the one-sided type I error rate), and with probability  $1 - \beta$  if the true treatment advantage takes some positive value ( $1 - \beta$  is the power of the study). Here we adopt a generalisation of this power requirement to multiple active treatments due to Dunnett<sup>46</sup>. If there is no difference between the mean response on any treatment and that on control, then a probability of  $\alpha = 0.05$  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  $\sigma$ . 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  $1 - \beta = 0.90$ . 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<sup>47</sup>, generalising the approach of Whitehead and Jaki<sup>48</sup>. 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 ( $0.178\sigma$ ) while the clinically relevant effect of 65% corresponds to a reduction of about half a standard deviation ( $0.545\sigma$ ). The standard deviation was reported to be around 5<sup>49,50</sup>. 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).

#### **9.4.1 Sample Size for the MRI/<sup>1</sup>H MRS Sub study**

To explore the secondary objective of using MRI/<sup>1</sup>H MRS 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<sup>32,33</sup> 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  $10\text{cm}^2/20\text{mg}$  with a 80% power at the 5% significance level, assuming a within-group standard deviation of visceral fat reduction,  $\sigma = 27\text{cm}^2$ . Even if deviations from the sample standard deviation  $\sigma = 27\text{cm}^2$  occur (e.g.,  $\sigma$  increases to  $40\text{cm}^2$ ), the sample size proposed would still be sufficient to detect a linear reduction in visceral distribution equal to or greater than  $15\text{cm}^2/20\text{mg}$  (nQuery, ANOVA).

### **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.

### **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<sup>51,52</sup> accounting for informative loss to follow up or censoring. Structural equation models<sup>53</sup> will be used to assess the inter-relationship between multiple biomarkers over effect of treatment while accounting for time-varying confounders.

### **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.

## 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 CTIRC 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 CTIRC 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**  
**CTIRC**  
**Fax: 00 44 (0) 151 794 5059**

## 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 CTSC 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
<b>Unrelated</b>	There is no evidence of any causal relationship. N.B. An alternative cause for the AE should be given
<b>Unlikely</b>	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).
<b>Possibly</b>	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).
<b>Probably</b>	There is evidence to suggest a causal relationship and the influence of other factors is unlikely.
<b>Almost certainly</b>	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

All adverse events 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 CTCR in the first instance. All 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.

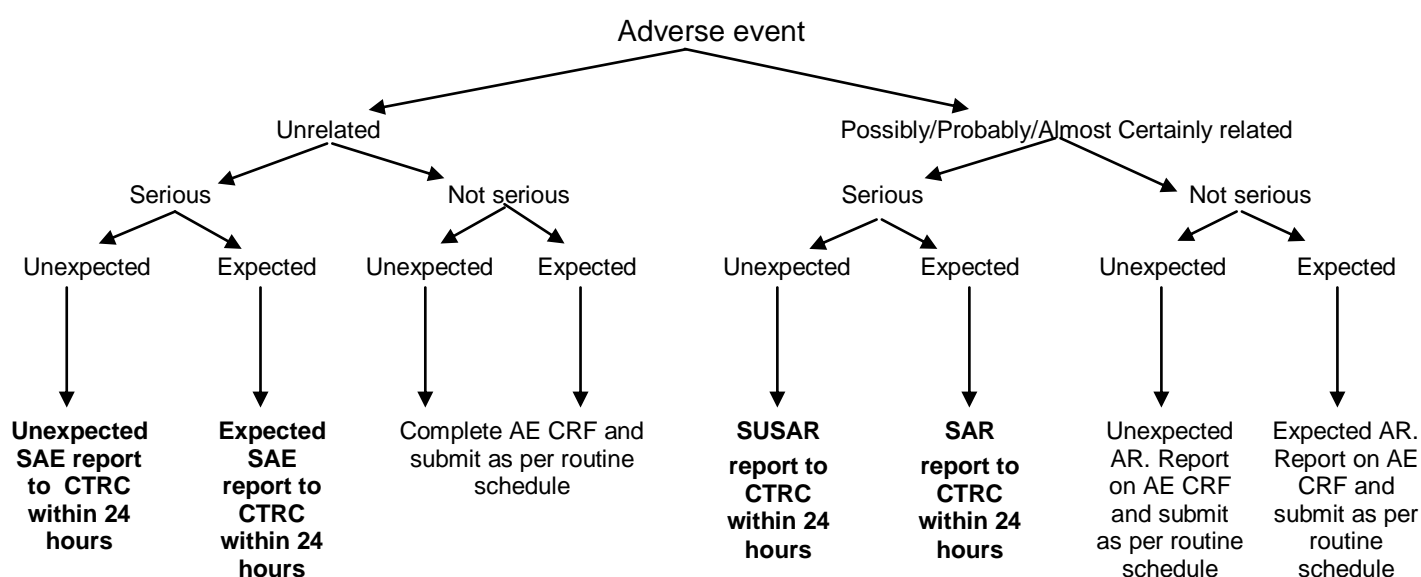
### 10.8.1 Non serious ARs/AEs

All such events, whether expected or not, should be recorded on an Adverse Event Form, which should be transmitted to the CTCR within seven days of the form being updated.

### 10.8.2 Serious ARs/AEs/SUSARs

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 CTCR 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 AEs that are 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 on telephone number **0151 795 5404** 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**

**Fax: 0151 794 5059**
- 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 specified in the protocol) 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.

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<sup>38,39</sup>. 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.

### **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. However, there is no further travel involved since the scans will be done at the MARIARC, University of Liverpool, which is located within walking distance of the RLH.

## **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 given to the participant. One final copy of the consent form should be sent to the CTRC.

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<sup>54</sup> 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)

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) 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 and 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.

### **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'

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## **20 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)

**APPENDIX A: DIVISION OF AIDS TABLE**  
for Grading the Severity of Adult and Pediatric Adverse Events Version 1.0 (2009)

# DIVISION OF AIDS TABLE FOR GRADING THE SEVERITY OF ADULT AND PEDIATRIC ADVERSE EVENTS VERSION 1.0, DECEMBER, 2004; CLARIFICATION AUGUST 2009

The Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events ("DAIDS AE Grading Table") is a descriptive terminology which can be utilized for Adverse Event (AE) reporting. A grading (severity) scale is provided for each AE term.

This clarification of the DAIDS Table for Grading the Severity of Adult and Pediatric AE's provides additional explanation of the DAIDS AE Grading Table and clarifies some of the parameters.

## I. Instructions and Clarifications

### Grading Adult and Pediatric AEs

The DAIDS AE Grading Table includes parameters for grading both Adult and Pediatric AEs. When a single set of parameters is not appropriate for grading specific types of AEs for both Adult and Pediatric populations, separate sets of parameters for Adult and/or Pediatric populations (with specified respective age ranges) are given in the Table. If there is no distinction in the Table between Adult and Pediatric values for a type of AE, then the single set of parameters listed is to be used for grading the severity of both Adult and Pediatric events of that type.

**Note:** In the classification of adverse events, the term "**severe**" is not the same as "**serious**." Severity is an indication of the intensity of a specific event (as in mild, moderate, or severe chest pain). The term "**serious**" relates to a participant/event outcome or action criteria, usually associated with events that pose a threat to a participant's life or functioning.

### Addenda 1-3 Grading Tables for Microbicide Studies

For protocols involving topical application of products to the female genital tract, male genital area or rectum, strong consideration should be given to using Appendices I-III as the primary grading scales for these areas. The protocol would need to specifically state that one or more of the Appendices would be primary (and thus take precedence over the main Grading Table) for items that are listed in both the Appendix and the main Grading Table.

- Addendum 1 - Female Genital Grading Table for Use in Microbicide Studies - [PDF](#)
- Addendum 2 - Male Genital Grading Table for Use in Microbicide Studies - [PDF](#)
- Addendum 3 - Rectal Grading Table for Use in Microbicide Studies - [PDF](#)

### Grade 5

For any AE where the outcome is death, the severity of the AE is classified as Grade 5.

### Estimating Severity Grade for Parameters Not Identified in the Table

In order to grade a clinical AE that is not identified in the DAIDS AE grading table, use the category "Estimating Severity Grade" located on Page 3.

### Determining Severity Grade for Parameters "Between Grades"

If the severity of a clinical AE could fall under either one of two grades (e.g., the severity of an AE could be either Grade 2 or Grade 3), select the higher of the two grades for the AE. If a laboratory value that is graded as a multiple of the ULN or LLN falls between two grades, select the higher of the two grades for the AE. For example, Grade 1 is 2.5 x ULN and Grade 2 is 2.6 x ULN for a parameter. If the lab value is 2.53 x ULN (which is between the two grades), the severity of this AE would be Grade 2, the higher of the two grades.

### Values Below Grade 1

Any laboratory value that is between either the LLN or ULN and Grade 1 should not be graded.

**DIVISION OF AIDS TABLE FOR GRADING THE SEVERITY OF  
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Determining Severity Grade when Local Laboratory Normal Values Overlap with Grade 1 Ranges

In these situations, the severity grading is based on the ranges in the DAIDS AE Grading Table, even when there is a reference to the local lab LLN.

*For example: Phosphate, Serum, Low, Adult and Pediatric > 14 years (Page 20) Grade 1 range is 2.50 mg/dL - < LLN. A particular laboratory's normal range for Phosphate is 2.1 – 3.8 mg/dL. A participant's actual lab value is 2.5. In this case, the value of 2.5 exceeds the LLN for the local lab, but will be graded as Grade 1 per DAIDS AE Grading Table.*

**II. Definitions of terms used in the Table:**

Basic Self-care Functions	<u>Adult</u> Activities such as bathing, dressing, toileting, transfer/movement, continence, and feeding.
	<u>Young Children</u> Activities that are age and culturally appropriate (e.g., feeding self with culturally appropriate eating implement).
LLN	Lower limit of normal
Medical Intervention	Use of pharmacologic or biologic agent(s) for treatment of an AE.
NA	Not Applicable
Operative Intervention	Surgical OR other invasive mechanical procedures.
ULN	Upper limit of normal
Usual Social & Functional Activities	<u>Adult</u> Adaptive tasks and desirable activities, such as going to work, shopping, cooking, use of transportation, pursuing a hobby, etc.
	<u>Young Children</u> Activities that are age and culturally appropriate (e.g., social interactions, play activities, learning tasks, etc.).



**DIVISION OF AIDS TABLE FOR GRADING THE SEVERITY OF  
ADULT AND PEDIATRIC ADVERSE EVENTS  
VERSION 1.0, DECEMBER, 2004; CLARIFICATION AUGUST 2009**

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
<b>ESTIMATING SEVERITY GRADE</b>				
Clinical adverse event NOT identified elsewhere in this DAIDS AE Grading Table	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	Symptoms causing inability to perform basic self-care functions OR Medical or operative intervention indicated to prevent permanent impairment, persistent disability, or death
<b>SYSTEMIC</b>				
Acute systemic allergic reaction	Localized urticaria (wheals) with no medical intervention indicated	Localized urticaria with medical intervention indicated OR Mild angioedema with no medical intervention indicated	Generalized urticaria OR Angioedema with medical intervention indicated OR Symptomatic mild bronchospasm	Acute anaphylaxis OR Life-threatening bronchospasm OR laryngeal edema
Chills	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	NA
Fatigue Malaise	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	Incapacitating fatigue/ malaise symptoms causing inability to perform basic self-care functions
Fever (nonaxillary)	37.7 – 38.6°C	38.7 – 39.3°C	39.4 – 40.5°C	> 40.5°C
Pain (indicate body site) DO NOT use for pain due to injection (See Injection Site Reactions: Injection site pain) See also Headache, Arthralgia, and Myalgia	Pain causing no or minimal interference with usual social & functional activities	Pain causing greater than minimal interference with usual social & functional activities	Pain causing inability to perform usual social & functional activities	Disabling pain causing inability to perform basic self-care functions OR Hospitalization (other than emergency room visit) indicated

**Basic Self-care Functions – Adult:** Activities such as bathing, dressing, toileting, transfer/movement, continence, and feeding.

**Basic Self-care Functions – Young Children:** Activities that are age and culturally appropriate (e.g., feeding self with culturally appropriate eating implement).

**Usual Social & Functional Activities – Adult:** Adaptive tasks and desirable activities, such as going to work, shopping, cooking, use of transportation, pursuing a hobby, etc.

**Usual Social & Functional Activities – Young Children:** Activities that are age and culturally appropriate (e.g., social interactions, play activities, learning tasks, etc.).

**DIVISION OF AIDS TABLE FOR GRADING THE SEVERITY OF  
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PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Unintentional weight loss	NA	5 – 9% loss in body weight from baseline	10 – 19% loss in body weight from baseline	≥ 20% loss in body weight from baseline OR Aggressive intervention indicated [e.g., tube feeding or total parenteral nutrition (TPN)]
<b>INFECTION</b>				
Infection (any other than HIV infection)	Localized, no systemic antimicrobial treatment indicated AND Symptoms causing no or minimal interference with usual social & functional activities	Systemic antimicrobial treatment indicated OR Symptoms causing greater than minimal interference with usual social & functional activities	Systemic antimicrobial treatment indicated AND Symptoms causing inability to perform usual social & functional activities OR Operative intervention (other than simple incision and drainage) indicated	Life-threatening consequences (e.g., septic shock)
<b>INJECTION SITE REACTIONS</b>				
Injection site pain (pain without touching) Or Tenderness (pain when area is touched)	Pain/tenderness causing no or minimal limitation of use of limb	Pain/tenderness limiting use of limb OR Pain/tenderness causing greater than minimal interference with usual social & functional activities	Pain/tenderness causing inability to perform usual social & functional activities	Pain/tenderness causing inability to perform basic self-care function OR Hospitalization (other than emergency room visit) indicated for management of pain/tenderness
Injection site reaction (localized)				
<b>Adult &gt; 15 years</b>	Erythema OR Induration of 5x5 cm – 9x9 cm (or 25 cm <sup>2</sup> – 81cm <sup>2</sup> )	Erythema OR Induration OR Edema > 9 cm any diameter (or > 81 cm <sup>2</sup> )	Ulceration OR Secondary infection OR Phlebitis OR Sterile abscess OR Drainage	Necrosis (involving dermis and deeper tissue)
<b>Pediatric ≤ 15 years</b>	Erythema OR Induration OR Edema present but ≤ 2.5 cm diameter	Erythema OR Induration OR Edema > 2.5 cm diameter but < 50% surface area of the extremity segment (e.g., upper arm/thigh)	Erythema OR Induration OR Edema involving ≥ 50% surface area of the extremity segment (e.g., upper arm/thigh) OR Ulceration OR Secondary infection OR Phlebitis OR Sterile abscess OR Drainage	Necrosis (involving dermis and deeper tissue)

**Basic Self-care Functions – Adult:** Activities such as bathing, dressing, toileting, transfer/movement, continence, and feeding.

**Basic Self-care Functions – Young Children:** Activities that are age and culturally appropriate (e.g., feeding self with culturally appropriate eating implement).

**Usual Social & Functional Activities – Adult:** Adaptive tasks and desirable activities, such as going to work, shopping, cooking, use of transportation, pursuing a hobby, etc.

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**DIVISION OF AIDS TABLE FOR GRADING THE SEVERITY OF  
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PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Pruritis associated with injection See also Skin: Pruritis (itching - no skin lesions)	Itching localized to injection site AND Relieved spontaneously or with < 48 hours treatment	Itching beyond the injection site but not generalized OR Itching localized to injection site requiring ≥ 48 hours treatment	Generalized itching causing inability to perform usual social & functional activities	NA
<b>SKIN – DERMATOLOGICAL</b>				
Alopecia	Thinning detectable by study participant (or by caregiver for young children and disabled adults)	Thinning or patchy hair loss detectable by health care provider	Complete hair loss	NA
Cutaneous reaction – rash	Localized macular rash	Diffuse macular, maculopapular, or morbilliform rash OR Target lesions	Diffuse macular, maculopapular, or morbilliform rash with vesicles or limited number of bullae OR Superficial ulcerations of mucous membrane limited to one site	Extensive or generalized bullous lesions OR Stevens-Johnson syndrome OR Ulceration of mucous membrane involving two or more distinct mucosal sites OR Toxic epidermal necrolysis (TEN)
Hyperpigmentation	Slight or localized	Marked or generalized	NA	NA
Hypopigmentation	Slight or localized	Marked or generalized	NA	NA
Pruritis (itching – no skin lesions) (See also Injection Site Reactions: Pruritis associated with injection)	Itching causing no or minimal interference with usual social & functional activities	Itching causing greater than minimal interference with usual social & functional activities	Itching causing inability to perform usual social & functional activities	NA
<b>CARDIOVASCULAR</b>				
Cardiac arrhythmia (general) (By ECG or physical exam)	Asymptomatic AND No intervention indicated	Asymptomatic AND Non-urgent medical intervention indicated	Symptomatic, non-life-threatening AND Non-urgent medical intervention indicated	Life-threatening arrhythmia OR Urgent intervention indicated
Cardiac-ischemia/infarction	NA	NA	Symptomatic ischemia (stable angina) OR Testing consistent with ischemia	Unstable angina OR Acute myocardial infarction

**Basic Self-care Functions – Adult:** Activities such as bathing, dressing, toileting, transfer/movement, continence, and feeding.

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**Usual Social & Functional Activities – Adult:** Adaptive tasks and desirable activities, such as going to work, shopping, cooking, use of transportation, pursuing a hobby, etc.

**Usual Social & Functional Activities – Young Children:** Activities that are age and culturally appropriate (e.g., social interactions, play activities, learning tasks, etc.).

**DIVISION OF AIDS TABLE FOR GRADING THE SEVERITY OF  
ADULT AND PEDIATRIC ADVERSE EVENTS**  
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PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Hemorrhage (significant acute blood loss)	NA	Symptomatic AND No transfusion indicated	Symptomatic AND Transfusion of $\leq 2$ units packed RBCs (for children $\leq 10$ cc/kg) indicated	Life-threatening hypotension OR Transfusion of $> 2$ units packed RBCs (for children $> 10$ cc/kg) indicated
Hypertension				
<b>Adult &gt; 17 years</b> (with repeat testing at same visit)	140 – 159 mmHg systolic OR 90 – 99 mmHg diastolic	160 – 179 mmHg systolic OR 100 – 109 mmHg diastolic	$\geq 180$ mmHg systolic OR $\geq 110$ mmHg diastolic	Life-threatening consequences (e.g., malignant hypertension) OR Hospitalization indicated (other than emergency room visit)
<b>Correction:</b> in Grade 2 to 160 - 179 from $> 160$ -179 (systolic) and to $\geq 100$ -109 from $> 100$ -109 (diastolic) and in Grade 3 to $\geq 180$ from $> 180$ (systolic) and to $\geq 110$ from $> 110$ (diastolic).				
<b>Pediatric <math>\leq 17</math> years</b> (with repeat testing at same visit)	NA	91 <sup>st</sup> – 94 <sup>th</sup> percentile adjusted for age, height, and gender (systolic and/or diastolic)	$\geq 95^{\text{th}}$ percentile adjusted for age, height, and gender (systolic and/or diastolic)	Life-threatening consequences (e.g., malignant hypertension) OR Hospitalization indicated (other than emergency room visit)
Hypotension	NA	Symptomatic, corrected with oral fluid replacement	Symptomatic, IV fluids indicated	Shock requiring use of vasopressors or mechanical assistance to maintain blood pressure
Pericardial effusion	Asymptomatic, small effusion requiring no intervention	Asymptomatic, moderate or larger effusion requiring no intervention	Effusion with non-life threatening physiologic consequences OR Effusion with non-urgent intervention indicated	Life-threatening consequences (e.g., tamponade) OR Urgent intervention indicated
Prolonged PR interval				
<b>Adult &gt; 16 years</b>	PR interval 0.21 – 0.25 sec	PR interval $> 0.25$ sec	Type II 2 <sup>nd</sup> degree AV block OR Ventricular pause $> 3.0$ sec	Complete AV block
<b>Pediatric <math>\leq 16</math> years</b>	1 <sup>st</sup> degree AV block (PR $>$ normal for age and rate)	Type I 2 <sup>nd</sup> degree AV block	Type II 2 <sup>nd</sup> degree AV block	Complete AV block

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PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Prolonged QTc				
<b>Adult &gt; 16 years</b>	Asymptomatic, QTc interval 0.45 – 0.47 sec OR Increase in interval < 0.03 sec above baseline	Asymptomatic, QTc interval 0.48 – 0.49 sec OR Increase in interval 0.03 – 0.05 sec above baseline	Asymptomatic, QTc interval ≥ 0.50 sec OR Increase in interval ≥ 0.06 sec above baseline	Life-threatening consequences, e.g. Torsade de pointes or other associated serious ventricular dysrhythmia
<b>Pediatric ≤ 16 years</b>	Asymptomatic, QTc interval 0.450 – 0.464 sec	Asymptomatic, QTc interval 0.465 – 0.479 sec	Asymptomatic, QTc interval ≥ 0.480 sec	Life-threatening consequences, e.g. Torsade de pointes or other associated serious ventricular dysrhythmia
Thrombosis/embolism	NA	Deep vein thrombosis AND No intervention indicated (e.g., anticoagulation, lysis filter, invasive procedure)	Deep vein thrombosis AND Intervention indicated (e.g., anticoagulation, lysis filter, invasive procedure)	Embolic event (e.g., pulmonary embolism, life-threatening thrombus)
Vasovagal episode (associated with a procedure of any kind)	Present without loss of consciousness	Present with transient loss of consciousness	NA	NA
Ventricular dysfunction (congestive heart failure)	NA	Asymptomatic diagnostic finding AND intervention indicated	New onset with symptoms OR Worsening symptomatic congestive heart failure	Life-threatening congestive heart failure
<b>GASTROINTESTINAL</b>				
Anorexia	Loss of appetite without decreased oral intake	Loss of appetite associated with decreased oral intake without significant weight loss	Loss of appetite associated with significant weight loss	Life-threatening consequences OR Aggressive intervention indicated [e.g., tube feeding or total parenteral nutrition (TPN)]
<b>Comment:</b> Please note that, while the grading scale provided for Unintentional Weight Loss may be used as a <a href="#">guideline</a> when grading anorexia, this is not a requirement and should not be used as a substitute for clinical judgment.				
Ascites	Asymptomatic	Symptomatic AND Intervention indicated (e.g., diuretics or therapeutic paracentesis)	Symptomatic despite intervention	Life-threatening consequences

**Basic Self-care Functions – Adult:** Activities such as bathing, dressing, toileting, transfer/movement, continence, and feeding.

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**Usual Social & Functional Activities – Adult:** Adaptive tasks and desirable activities, such as going to work, shopping, cooking, use of transportation, pursuing a hobby, etc.

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PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Cholecystitis	NA	Symptomatic AND Medical intervention indicated	Radiologic, endoscopic, or operative intervention indicated	Life-threatening consequences (e.g., sepsis or perforation)
Constipation	NA	Persistent constipation requiring regular use of dietary modifications, laxatives, or enemas	Obstipation with manual evacuation indicated	Life-threatening consequences (e.g., obstruction)
Diarrhea				
<b>Adult and Pediatric ≥ 1 year</b>	Transient or intermittent episodes of unformed stools OR Increase of ≤ 3 stools over baseline per 24-hour period	Persistent episodes of unformed to watery stools OR Increase of 4 – 6 stools over baseline per 24-hour period	Bloody diarrhea OR Increase of ≥ 7 stools per 24-hour period OR IV fluid replacement indicated	Life-threatening consequences (e.g., hypotensive shock)
<b>Pediatric &lt; 1 year</b>	Liquid stools (more unformed than usual) but usual number of stools	Liquid stools with increased number of stools OR Mild dehydration	Liquid stools with moderate dehydration	Liquid stools resulting in severe dehydration with aggressive rehydration indicated OR Hypotensive shock
Dysphagia- Odynophagia	Symptomatic but able to eat usual diet	Symptoms causing altered dietary intake without medical intervention indicated	Symptoms causing severely altered dietary intake with medical intervention indicated	Life-threatening reduction in oral intake
Mucositis/stomatitis (clinical exam) Indicate site (e.g., larynx, oral) See Genitourinary for Vulvovaginitis See also Dysphagia- Odynophagia and Proctitis	Erythema of the mucosa	Patchy pseudomembranes or ulcerations	Confluent pseudomembranes or ulcerations OR Mucosal bleeding with minor trauma	Tissue necrosis OR Diffuse spontaneous mucosal bleeding OR Life-threatening consequences (e.g., aspiration, choking)
Nausea	Transient (< 24 hours) or intermittent nausea with no or minimal interference with oral intake	Persistent nausea resulting in decreased oral intake for 24 – 48 hours	Persistent nausea resulting in minimal oral intake for > 48 hours OR Aggressive rehydration indicated (e.g., IV fluids)	Life-threatening consequences (e.g., hypotensive shock)

**Basic Self-care Functions – Adult:** Activities such as bathing, dressing, toileting, transfer/movement, continence, and feeding.

**Basic Self-care Functions – Young Children:** Activities that are age and culturally appropriate (e.g., feeding self with culturally appropriate eating implement).

**Usual Social & Functional Activities – Adult:** Adaptive tasks and desirable activities, such as going to work, shopping, cooking, use of transportation, pursuing a hobby, etc.

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**DIVISION OF AIDS TABLE FOR GRADING THE SEVERITY OF  
ADULT AND PEDIATRIC ADVERSE EVENTS  
VERSION 1.0, DECEMBER, 2004; CLARIFICATION AUGUST 2009**

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Pancreatitis	NA	Symptomatic AND Hospitalization not indicated (other than emergency room visit)	Symptomatic AND Hospitalization indicated (other than emergency room visit)	Life-threatening consequences (e.g., circulatory failure, hemorrhage, sepsis)
Proctitis ( <u>functional-symptomatic</u> ) Also see Mucositis/stomatitis for clinical exam	Rectal discomfort AND No intervention indicated	Symptoms causing greater than minimal interference with usual social & functional activities OR Medical intervention indicated	Symptoms causing inability to perform usual social & functional activities OR Operative intervention indicated	Life-threatening consequences (e.g., perforation)
Vomiting	Transient or intermittent vomiting with no or minimal interference with oral intake	Frequent episodes of vomiting with no or mild dehydration	Persistent vomiting resulting in orthostatic hypotension OR Aggressive rehydration indicated (e.g., IV fluids)	Life-threatening consequences (e.g., hypotensive shock)
<b>NEUROLOGIC</b>				
Alteration in personality-behavior or in mood (e.g., agitation, anxiety, depression, mania, psychosis)	Alteration causing no or minimal interference with usual social & functional activities	Alteration causing greater than minimal interference with usual social & functional activities	Alteration causing inability to perform usual social & functional activities	Behavior potentially harmful to self or others (e.g., suicidal and homicidal ideation or attempt, acute psychosis) OR Causing inability to perform basic self-care functions
Altered Mental Status For Dementia, see Cognitive and behavioral/attentional disturbance (including dementia and attention deficit disorder)	Changes causing no or minimal interference with usual social & functional activities	Mild lethargy or somnolence causing greater than minimal interference with usual social & functional activities	Confusion, memory impairment, lethargy, or somnolence causing inability to perform usual social & functional activities	Delirium OR obtundation, OR coma
Ataxia	Asymptomatic ataxia detectable on exam OR Minimal ataxia causing no or minimal interference with usual social & functional activities	Symptomatic ataxia causing greater than minimal interference with usual social & functional activities	Symptomatic ataxia causing inability to perform usual social & functional activities	Disabling ataxia causing inability to perform basic self-care functions

**Basic Self-care Functions – Adult:** Activities such as bathing, dressing, toileting, transfer/movement, continence, and feeding.

**Basic Self-care Functions – Young Children:** Activities that are age and culturally appropriate (e.g., feeding self with culturally appropriate eating implement).

**Usual Social & Functional Activities – Adult:** Adaptive tasks and desirable activities, such as going to work, shopping, cooking, use of transportation, pursuing a hobby, etc.

**Usual Social & Functional Activities – Young Children:** Activities that are age and culturally appropriate (e.g., social interactions, play activities, learning tasks, etc.).



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PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Cognitive and behavioral/attentional disturbance (including dementia and attention deficit disorder)	Disability causing no or minimal interference with usual social & functional activities OR Specialized resources not indicated	Disability causing greater than minimal interference with usual social & functional activities OR Specialized resources on part-time basis indicated	Disability causing inability to perform usual social & functional activities OR Specialized resources on a full-time basis indicated	Disability causing inability to perform basic self-care functions OR Institutionalization indicated
CNS ischemia (acute)	NA	NA	Transient ischemic attack	Cerebral vascular accident (CVA, stroke) with neurological deficit
Developmental delay – <b>Pediatric ≤ 16 years</b>	Mild developmental delay, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting	Moderate developmental delay, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting	Severe developmental delay, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting	Developmental regression, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting
Headache	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	Symptoms causing inability to perform basic self-care functions OR Hospitalization indicated (other than emergency room visit) OR Headache with significant impairment of alertness or other neurologic function
Insomnia	NA	Difficulty sleeping causing greater than minimal interference with usual social & functional activities	Difficulty sleeping causing inability to perform usual social & functional activities	Disabling insomnia causing inability to perform basic self-care functions
Neuromuscular weakness (including myopathy & neuropathy)	Asymptomatic with decreased strength on exam OR Minimal muscle weakness causing no or minimal interference with usual social & functional activities	Muscle weakness causing greater than minimal interference with usual social & functional activities	Muscle weakness causing inability to perform usual social & functional activities	Disabling muscle weakness causing inability to perform basic self-care functions OR Respiratory muscle weakness impairing ventilation

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PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Neurosensory alteration (including paresthesia and painful neuropathy)	Asymptomatic with sensory alteration on exam or minimal paresthesia causing no or minimal interference with usual social & functional activities	Sensory alteration or paresthesia causing greater than minimal interference with usual social & functional activities	Sensory alteration or paresthesia causing inability to perform usual social & functional activities	Disabling sensory alteration or paresthesia causing inability to perform basic self-care functions
Seizure: ( <u>new onset</u> ) – <b>Adult ≥ 18 years</b>  See also Seizure: (known pre-existing seizure disorder)	NA	1 seizure	2 – 4 seizures	Seizures of any kind which are prolonged, repetitive (e.g., status epilepticus), or difficult to control (e.g., refractory epilepsy)
Seizure: ( <u>known pre-existing seizure disorder</u> ) – <b>Adult ≥ 18 years</b>  For worsening of existing epilepsy the grades should be based on an increase from previous level of control to any of these levels.	NA	Increased frequency of pre-existing seizures (non-repetitive) without change in seizure character OR Infrequent break-through seizures while on stable medication in a previously controlled seizure disorder	Change in seizure character from baseline either in duration or quality (e.g., severity or focality)	Seizures of any kind which are prolonged, repetitive (e.g., status epilepticus), or difficult to control (e.g., refractory epilepsy)
Seizure – <b>Pediatric &lt; 18 years</b>	Seizure, generalized onset with or without secondary generalization, lasting < 5 minutes with < 24 hours post ictal state	Seizure, generalized onset with or without secondary generalization, lasting 5 – 20 minutes with < 24 hours post ictal state	Seizure, generalized onset with or without secondary generalization, lasting > 20 minutes	Seizure, generalized onset with or without secondary generalization, requiring intubation and sedation
Syncope (not associated with a procedure)	NA	Present	NA	NA
Vertigo	Vertigo causing no or minimal interference with usual social & functional activities	Vertigo causing greater than minimal interference with usual social & functional activities	Vertigo causing inability to perform usual social & functional activities	Disabling vertigo causing inability to perform basic self-care functions

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PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
<b>RESPIRATORY</b>				
Bronchospasm (acute)	FEV1 or peak flow reduced to 70 – 80%	FEV1 or peak flow 50 – 69%	FEV1 or peak flow 25 – 49%	Cyanosis OR FEV1 or peak flow < 25% OR Intubation
Dyspnea or respiratory distress				
<b>Adult ≥ 14 years</b>	Dyspnea on exertion with no or minimal interference with usual social & functional activities	Dyspnea on exertion causing greater than minimal interference with usual social & functional activities	Dyspnea at rest causing inability to perform usual social & functional activities	Respiratory failure with ventilatory support indicated
<b>Pediatric &lt; 14 years</b>	Wheezing OR minimal increase in respiratory rate for age	Nasal flaring OR Intercostal retractions OR Pulse oximetry 90 – 95%	Dyspnea at rest causing inability to perform usual social & functional activities OR Pulse oximetry < 90%	Respiratory failure with ventilatory support indicated
<b>MUSCULOSKELETAL</b>				
Arthralgia See also Arthritis	Joint pain causing no or minimal interference with usual social & functional activities	Joint pain causing greater than minimal interference with usual social & functional activities	Joint pain causing inability to perform usual social & functional activities	Disabling joint pain causing inability to perform basic self-care functions
Arthritis See also Arthralgia	Stiffness or joint swelling causing no or minimal interference with usual social & functional activities	Stiffness or joint swelling causing greater than minimal interference with usual social & functional activities	Stiffness or joint swelling causing inability to perform usual social & functional activities	Disabling joint stiffness or swelling causing inability to perform basic self-care functions
Bone Mineral Loss				
<b>Adult ≥ 21 years</b>	BMD t-score -2.5 to -1.0	BMD t-score < -2.5	Pathological fracture (including loss of vertebral height)	Pathologic fracture causing life-threatening consequences
<b>Pediatric &lt; 21 years</b>	BMD z-score -2.5 to -1.0	BMD z-score < -2.5	Pathological fracture (including loss of vertebral height)	Pathologic fracture causing life-threatening consequences
Myalgia (non-injection site)	Muscle pain causing no or minimal interference with usual social & functional activities	Muscle pain causing greater than minimal interference with usual social & functional activities	Muscle pain causing inability to perform usual social & functional activities	Disabling muscle pain causing inability to perform basic self-care functions

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Osteonecrosis	NA	Asymptomatic with radiographic findings AND No operative intervention indicated	Symptomatic bone pain with radiographic findings OR Operative intervention indicated	Disabling bone pain with radiographic findings causing inability to perform basic self-care functions
<b>GENITOURINARY</b>				
Cervicitis ( <u>symptoms</u> ) (For use in studies evaluating topical study agents) For other cervicitis see Infection: Infection (any other than HIV infection)	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	Symptoms causing inability to perform basic self-care functions
Cervicitis ( <u>clinical exam</u> ) (For use in studies evaluating topical study agents) For other cervicitis see Infection: Infection (any other than HIV infection)	Minimal cervical abnormalities on examination (erythema, mucopurulent discharge, or friability) OR Epithelial disruption < 25% of total surface	Moderate cervical abnormalities on examination (erythema, mucopurulent discharge, or friability) OR Epithelial disruption of 25 – 49% total surface	Severe cervical abnormalities on examination (erythema, mucopurulent discharge, or friability) OR Epithelial disruption 50 – 75% total surface	Epithelial disruption > 75% total surface
Inter-menstrual bleeding (IMB)	Spotting observed by participant OR Minimal blood observed during clinical or colposcopic examination	Inter-menstrual bleeding not greater in duration or amount than usual menstrual cycle	Inter-menstrual bleeding greater in duration or amount than usual menstrual cycle	Hemorrhage with life-threatening hypotension OR Operative intervention indicated
Urinary tract obstruction (e.g., stone)	NA	Signs or symptoms of urinary tract obstruction without hydronephrosis or renal dysfunction	Signs or symptoms of urinary tract obstruction with hydronephrosis or renal dysfunction	Obstruction causing life-threatening consequences

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Vulvovaginitis ( <u>symptoms</u> ) (Use in studies evaluating topical study agents) For other vulvovaginitis see Infection: Infection (any other than HIV infection)	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	Symptoms causing inability to perform basic self-care functions
Vulvovaginitis ( <u>clinical exam</u> ) (Use in studies evaluating topical study agents) For other vulvovaginitis see Infection: Infection (any other than HIV infection)	Minimal vaginal abnormalities on examination OR Epithelial disruption < 25% of total surface	Moderate vaginal abnormalities on examination OR Epithelial disruption of 25 - 49% total surface	Severe vaginal abnormalities on examination OR Epithelial disruption 50 - 75% total surface	Vaginal perforation OR Epithelial disruption > 75% total surface
<b>OCULAR/VISUAL</b>				
Uveitis	Asymptomatic but detectable on exam	Symptomatic anterior uveitis OR Medical intervention indicated	Posterior or pan-uveitis OR Operative intervention indicated	Disabling visual loss in affected eye(s)
Visual changes (from baseline)	Visual changes causing no or minimal interference with usual social & functional activities	Visual changes causing greater than minimal interference with usual social & functional activities	Visual changes causing inability to perform usual social & functional activities	Disabling visual loss in affected eye(s)
<b>ENDOCRINE/METABOLIC</b>				
Abnormal fat accumulation (e.g., back of neck, breasts, abdomen)	Detectable by study participant (or by caregiver for young children and disabled adults)	Detectable on physical exam by health care provider	Disfiguring OR Obvious changes on casual visual inspection	NA
Diabetes mellitus	NA	New onset without need to initiate medication OR Modification of current medications to regain glucose control	New onset with initiation of medication indicated OR Diabetes uncontrolled despite treatment modification	Life-threatening consequences (e.g., ketoacidosis, hyperosmolar non- ketotic coma)

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Gynecomastia	Detectable by study participant or caregiver (for young children and disabled adults)	Detectable on physical exam by health care provider	Disfiguring OR Obvious on casual visual inspection	NA
Hyperthyroidism	Asymptomatic	Symptomatic causing greater than minimal interference with usual social & functional activities OR Thyroid suppression therapy indicated	Symptoms causing inability to perform usual social & functional activities OR Uncontrolled despite treatment modification	Life-threatening consequences (e.g., thyroid storm)
Hypothyroidism	Asymptomatic	Symptomatic causing greater than minimal interference with usual social & functional activities OR Thyroid replacement therapy indicated	Symptoms causing inability to perform usual social & functional activities OR Uncontrolled despite treatment modification	Life-threatening consequences (e.g., myxedema coma)
Lipoatrophy (e.g., fat loss from the face, extremities, buttocks)	Detectable by study participant (or by caregiver for young children and disabled adults)	Detectable on physical exam by health care provider	Disfiguring OR Obvious on casual visual inspection	NA

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LABORATORY				
PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
<b>HEMATOLOGY</b> <i>Standard International Units are listed in italics</i>				
Absolute CD4+ count – <b>Adult and Pediatric</b> > 13 years (HIV <u>NEGATIVE</u> ONLY)	300 – 400/mm <sup>3</sup> <i>300 – 400/μL</i>	200 – 299/mm <sup>3</sup> <i>200 – 299/μL</i>	100 – 199/mm <sup>3</sup> <i>100 – 199/μL</i>	< 100/mm <sup>3</sup> <i>&lt; 100/μL</i>
Absolute lymphocyte count – <b>Adult and Pediatric</b> > 13 years (HIV <u>NEGATIVE</u> ONLY)	600 – 650/mm <sup>3</sup> <i>0.600 x 10<sup>9</sup> – 0.650 x 10<sup>9</sup>/L</i>	500 – 599/mm <sup>3</sup> <i>0.500 x 10<sup>9</sup> – 0.599 x 10<sup>9</sup>/L</i>	350 – 499/mm <sup>3</sup> <i>0.350 x 10<sup>9</sup> – 0.499 x 10<sup>9</sup>/L</i>	< 350/mm <sup>3</sup> <i>&lt; 0.350 x 10<sup>9</sup>/L</i>
<b>Comment:</b> Values in children ≤ 13 years are not given for the two parameters above because the absolute counts are variable.				
Absolute neutrophil count (ANC)				
<b>Adult and Pediatric, &gt; 7 days</b>	1,000 – 1,300/mm <sup>3</sup> <i>1.000 x 10<sup>9</sup> – 1.300 x 10<sup>9</sup>/L</i>	750 – 999/mm <sup>3</sup> <i>0.750 x 10<sup>9</sup> – 0.999 x 10<sup>9</sup>/L</i>	500 – 749/mm <sup>3</sup> <i>0.500 x 10<sup>9</sup> – 0.749 x 10<sup>9</sup>/L</i>	< 500/mm <sup>3</sup> <i>&lt; 0.500 x 10<sup>9</sup>/L</i>
<b>Infant*†, 2 – ≤ 7 days</b>	1,250 – 1,500/mm <sup>3</sup> <i>1.250 x 10<sup>9</sup> – 1.500 x 10<sup>9</sup>/L</i>	1,000 – 1,249/mm <sup>3</sup> <i>1.000 x 10<sup>9</sup> – 1.249 x 10<sup>9</sup>/L</i>	750 – 999/mm <sup>3</sup> <i>0.750 x 10<sup>9</sup> – 0.999 x 10<sup>9</sup>/L</i>	< 750/mm <sup>3</sup> <i>&lt; 0.750 x 10<sup>9</sup>/L</i>
<b>Infant*†, ≤1 day</b>	4,000 – 5,000/mm <sup>3</sup> <i>4.000 x 10<sup>9</sup> – 5.000 x 10<sup>9</sup>/L</i>	3,000 – 3,999/mm <sup>3</sup> <i>3.000 x 10<sup>9</sup> – 3.999 x 10<sup>9</sup>/L</i>	1,500 – 2,999/mm <sup>3</sup> <i>1.500 x 10<sup>9</sup> – 2.999 x 10<sup>9</sup>/L</i>	< 1,500/mm <sup>3</sup> <i>&lt; 1.500 x 10<sup>9</sup>/L</i>
<b>Comment:</b> Parameter changed from “Infant, < 1 day” to “Infant, ≤1 day”				
Fibrinogen, decreased	100 – 200 mg/dL <i>1.00 – 2.00 g/L</i> OR 0.75 – 0.99 x LLN	75 – 99 mg/dL <i>0.75 – 0.99 g/L</i> OR 0.50 – 0.74 x LLN	50 – 74 mg/dL <i>0.50 – 0.74 g/L</i> OR 0.25 – 0.49 x LLN	< 50 mg/dL <i>&lt; 0.50 g/L</i> OR < 0.25 x LLN OR Associated with gross bleeding

\* Values are for term infants. Preterm infants should be assessed using local normal ranges.

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PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Hemoglobin (Hgb)				
<b>Comment:</b> The Hgb values in mmol/L have changed because the conversion factor used to convert g/dL to mmol/L has been changed from 0.155 to 0.6206 (the most commonly used conversion factor). For grading Hgb results obtained by an analytic method with a conversion factor other than 0.6206, the result must be converted to g/dL using the appropriate conversion factor for that lab.				
<b>Adult and Pediatric ≥ 57 days (HIV <u>POSITIVE</u> ONLY)</b>	8.5 – 10.0 g/dL <b>5.24 – 6.23 mmol/L</b>	7.5 – 8.4 g/dL <b>4.62–5.23 mmol/L</b>	6.50 – 7.4 g/dL <b>4.03–4.61 mmol/L</b>	< 6.5 g/dL <b>&lt; 4.03 mmol/L</b>
<b>Adult and Pediatric ≥ 57 days (HIV <u>NEGATIVE</u> ONLY)</b>	10.0 – 10.9 g/dL <b>6.18 – 6.79 mmol/L</b> OR Any decrease 2.5 – 3.4 g/dL <b>1.58 – 2.13 mmol/L</b>	9.0 – 9.9 g/dL <b>5.55 - 6.17 mmol/L</b> OR Any decrease 3.5 – 4.4 g/dL <b>2.14 – 2.78 mmol/L</b>	7.0 – 8.9 g/dL <b>4.34 - 5.54 mmol/L</b> OR Any decrease ≥ 4.5 g/dL <b>&gt; 2.79 mmol/L</b>	< 7.0 g/dL <b>&lt; 4.34 mmol/L</b>
<b>Comment:</b> The decrease is a decrease from baseline				
<b>Infant<sup>†</sup>, 36 – 56 days (HIV <u>POSITIVE</u> OR <u>NEGATIVE</u>)</b>	8.5 – 9.4 g/dL <b>5.24 – 5.86 mmol/L</b>	7.0 – 8.4 g/dL <b>4.31 – 5.23 mmol/L</b>	6.0 – 6.9 g/dL <b>3.72 – 4.30 mmol/L</b>	< 6.00 g/dL <b>&lt; 3.72 mmol/L</b>
<b>Infant<sup>†</sup>, 22 – 35 days (HIV <u>POSITIVE</u> OR <u>NEGATIVE</u>)</b>	9.5 – 10.5 g/dL <b>5.87 - 6.54 mmol/L</b>	8.0 – 9.4 g/dL <b>4.93 – 5.86 mmol/L</b>	7.0 – 7.9 g/dL <b>4.34 – 4.92 mmol/L</b>	< 7.00 g/dL <b>&lt; 4.34 mmol/L</b>
<b>Infant<sup>†</sup>, ≤ 21 days (HIV <u>POSITIVE</u> OR <u>NEGATIVE</u>)</b>	12.0 – 13.0 g/dL <b>7.42 – 8.09 mmol/L</b>	10.0 – 11.9 g/dL <b>6.18 – 7.41 mmol/L</b>	9.0 – 9.9 g/dL <b>5.59- 6.17 mmol/L</b>	< 9.0 g/dL <b>&lt; 5.59 mmol/L</b>
<b>Correction:</b> Parameter changed from “Infant < 21 days” to “Infant ≤ 21 days”				
International Normalized Ratio of prothrombin time (INR)	1.1 – 1.5 x ULN	1.6 – 2.0 x ULN	2.1 – 3.0 x ULN	> 3.0 x ULN
Methemoglobin	5.0 – 10.0%	10.1 – 15.0%	15.1 – 20.0%	> 20.0%
Prothrombin Time (PT)	1.1 – 1.25 x ULN	1.26 – 1.50 x ULN	1.51 – 3.00 x ULN	> 3.00 x ULN
Partial Thromboplastin Time (PTT)	1.1 – 1.66 x ULN	1.67 – 2.33 x ULN	2.34 – 3.00 x ULN	> 3.00 x ULN
Platelets, decreased	100,000 – 124,999/mm <sup>3</sup> <b>100.000 x 10<sup>9</sup> – 124.999 x 10<sup>9</sup>/L</b>	50,000 – 99,999/mm <sup>3</sup> <b>50.000 x 10<sup>9</sup> – 99.999 x 10<sup>9</sup>/L</b>	25,000 – 49,999/mm <sup>3</sup> <b>25.000 x 10<sup>9</sup> – 49.999 x 10<sup>9</sup>/L</b>	< 25,000/mm <sup>3</sup> <b>&lt; 25.000 x 10<sup>9</sup>/L</b>
WBC, decreased	2,000 – 2,500/mm <sup>3</sup> <b>2.000 x 10<sup>9</sup> – 2.500 x 10<sup>9</sup>/L</b>	1,500 – 1,999/mm <sup>3</sup> <b>1.500 x 10<sup>9</sup> – 1.999 x 10<sup>9</sup>/L</b>	1,000 – 1,499/mm <sup>3</sup> <b>1.000 x 10<sup>9</sup> – 1.499 x 10<sup>9</sup>/L</b>	< 1,000/mm <sup>3</sup> <b>&lt; 1.000 x 10<sup>9</sup>/L</b>

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<b>CHEMISTRIES</b>	<i>Standard International Units are listed in italics</i>			
Acidosis	NA	pH < normal, but $\geq 7.3$	pH < 7.3 without life-threatening consequences	pH < 7.3 with life-threatening consequences
Albumin, serum, low	3.0 g/dL – < LLN 30 g/L – < LLN	2.0 – 2.9 g/dL 20 – 29 g/L	< 2.0 g/dL < 20 g/L	NA
Alkaline Phosphatase	1.25 – 2.5 x ULN <sup>†</sup>	2.6 – 5.0 x ULN <sup>†</sup>	5.1 – 10.0 x ULN <sup>†</sup>	> 10.0 x ULN <sup>†</sup>
Alkalosis	NA	pH > normal, but $\leq 7.5$	pH > 7.5 without life-threatening consequences	pH > 7.5 with life-threatening consequences
ALT (SGPT)	1.25 – 2.5 x ULN	2.6 – 5.0 x ULN	5.1 – 10.0 x ULN	> 10.0 x ULN
AST (SGOT)	1.25 – 2.5 x ULN	2.6 – 5.0 x ULN	5.1 – 10.0 x ULN	> 10.0 x ULN
Bicarbonate, serum, low	16.0 mEq/L – < LLN 16.0 mmol/L – < LLN	11.0 – 15.9 mEq/L 11.0 – 15.9 mmol/L	8.0 – 10.9 mEq/L 8.0 – 10.9 mmol/L	< 8.0 mEq/L < 8.0 mmol/L
<b>Comment:</b> Some laboratories will report this value as Bicarbonate (HCO <sub>3</sub> ) and others as Total Carbon Dioxide (CO <sub>2</sub> ). These are the same tests; values should be graded according to the ranges for Bicarbonate as listed above.				
Bilirubin (Total)				
<b>Adult and Pediatric &gt; 14 days</b>	1.1 – 1.5 x ULN	1.6 – 2.5 x ULN	2.6 – 5.0 x ULN	> 5.0 x ULN
<b>Infant*<sup>†</sup>, ≤ 14 days</b> (non-hemolytic)	NA	20.0 – 25.0 mg/dL 342 – 428 μmol/L	25.1 – 30.0 mg/dL 429 – 513 μmol/L	> 30.0 mg/dL > 513.0 μmol/L
<b>Infant*<sup>†</sup>, ≤ 14 days</b> (hemolytic)	NA	NA	20.0 – 25.0 mg/dL 342 – 428 μmol/L	> 25.0 mg/dL > 428 μmol/L
Calcium, serum, high				
<b>Adult and Pediatric ≥ 7 days</b>	10.6 – 11.5 mg/dL 2.65 – 2.88 mmol/L	11.6 – 12.5 mg/dL 2.89 – 3.13 mmol/L	12.6 – 13.5 mg/dL 3.14 – 3.38 mmol/L	> 13.5 mg/dL > 3.38 mmol/L
<b>Infant*<sup>†</sup>, &lt; 7 days</b>	11.5 – 12.4 mg/dL 2.88 – 3.10 mmol/L	12.5 – 12.9 mg/dL 3.11 – 3.23 mmol/L	13.0 – 13.5 mg/dL 3.245 – 3.38 mmol/L	> 13.5 mg/dL > 3.38 mmol/L
Calcium, serum, low				
<b>Adult and Pediatric ≥ 7 days</b>	7.8 – 8.4 mg/dL 1.95 – 2.10 mmol/L	7.0 – 7.7 mg/dL 1.75 – 1.94 mmol/L	6.1 – 6.9 mg/dL 1.53 – 1.74 mmol/L	< 6.1 mg/dL < 1.53 mmol/L
<b>Infant*<sup>†</sup>, &lt; 7 days</b>	6.5 – 7.5 mg/dL 1.63 – 1.88 mmol/L	6.0 – 6.4 mg/dL 1.50 – 1.62 mmol/L	5.50 – 5.90 mg/dL 1.38 – 1.51 mmol/L	< 5.50 mg/dL < 1.38 mmol/L
<b>Comment:</b> Do not adjust Calcium, serum, low or Calcium, serum, high for albumin				

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<sup>†</sup> Use age and sex appropriate values (e.g., bilirubin).



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ADULT AND PEDIATRIC ADVERSE EVENTS  
VERSION 1.0, DECEMBER, 2004; CLARIFICATION AUGUST 2009**

LABORATORY				
PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Cardiac troponin I (cTnI)	NA	NA	NA	Levels consistent with myocardial infarction or unstable angina as defined by the manufacturer
Cardiac troponin T (cTnT)	NA	NA	NA	≥ 0.20 ng/mL OR Levels consistent with myocardial infarction or unstable angina as defined by the manufacturer
Cholesterol (fasting)				
<b>Adult ≥ 18 years</b>	200 – 239 mg/dL 5.18 – 6.19 mmol/L	240 – 300 mg/dL 6.20 – 7.77 mmol/L	> 300 mg/dL > 7.77 mmol/L	NA
<b>Pediatric &lt; 18 years</b>	170 – 199 mg/dL 4.40 – 5.15 mmol/L	200 – 300 mg/dL 5.16 – 7.77 mmol/L	> 300 mg/dL > 7.77 mmol/L	NA
Creatine Kinase	3.0 – 5.9 x ULN <sup>†</sup>	6.0 – 9.9 x ULN <sup>†</sup>	10.0 – 19.9 x ULN <sup>†</sup>	≥ 20.0 x ULN <sup>†</sup>
Creatinine	1.1 – 1.3 x ULN <sup>†</sup>	1.4 – 1.8 x ULN <sup>†</sup>	1.9 – 3.4 x ULN <sup>†</sup>	≥ 3.5 x ULN <sup>†</sup>

LABORATORY				
PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Glucose, serum, high				
Nonfasting	116 – 160 mg/dL 6.44 – 8.88 mmol/L	161 – 250 mg/dL 8.89 – 13.88 mmol/L	251 – 500 mg/dL 13.89 – 27.75 mmol/L	> 500 mg/dL > 27.75 mmol/L
Fasting	110 – 125 mg/dL 6.11 – 6.94 mmol/L	126 – 250 mg/dL 6.95 – 13.88 mmol/L	251 – 500 mg/dL 13.89 – 27.75 mmol/L	> 500 mg/dL > 27.75 mmol/L
Glucose, serum, low				
<b>Adult and Pediatric ≥ 1 month</b>	55 – 64 mg/dL 3.05 – 3.55 mmol/L	40 – 54 mg/dL 2.22 – 3.06 mmol/L	30 – 39 mg/dL 1.67 – 2.23 mmol/L	< 30 mg/dL < 1.67 mmol/L
<b>Infant*<sup>†</sup>, &lt; 1 month</b>	50 – 54 mg/dL 2.78 – 3.00 mmol/L	40 – 49 mg/dL 2.22 – 2.77 mmol/L	30 – 39 mg/dL 1.67 – 2.21 mmol/L	< 30 mg/dL < 1.67 mmol/L
Lactate	ULN - < 2.0 x ULN without acidosis	≥ 2.0 x ULN without acidosis	Increased lactate with pH < 7.3 without life-threatening consequences	Increased lactate with pH < 7.3 with life-threatening consequences

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<sup>†</sup> Use age and sex appropriate values (e.g., bilirubin).

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Comment: Added ULN to Grade 1 parameter					
LDL cholesterol (fasting)					
	Adult ≥ 18 years	130 – 159 mg/dL 3.37 – 4.12 mmol/L	160 – 190 mg/dL 4.13 – 4.90 mmol/L	≥ 190 mg/dL ≥ 4.91 mmol/L	NA
	Pediatric > 2 - < 18 years	110 – 129 mg/dL 2.85 – 3.34 mmol/L	130 – 189 mg/dL 3.35 – 4.90 mmol/L	≥ 190 mg/dL ≥ 4.91 mmol/L	NA
Lipase		1.1 – 1.5 x ULN	1.6 – 3.0 x ULN	3.1 – 5.0 x ULN	> 5.0 x ULN
Magnesium, serum, low		1.2 – 1.4 mEq/L 0.60 – 0.70 mmol/L	0.9 – 1.1 mEq/L 0.45 – 0.59 mmol/L	0.6 – 0.8 mEq/L 0.30 – 0.44 mmol/L	< 0.60 mEq/L < 0.30 mmol/L
Pancreatic amylase		1.1 – 1.5 x ULN	1.6 – 2.0 x ULN	2.1 – 5.0 x ULN	> 5.0 x ULN
Phosphate, serum, low					
	Adult and Pediatric > 14 years	2.5 mg/dL – < LLN 0.81 mmol/L – < LLN	2.0 – 2.4 mg/dL 0.65 – 0.80 mmol/L	1.0 – 1.9 mg/dL 0.32 – 0.64 mmol/L	< 1.00 mg/dL < 0.32 mmol/L
	Pediatric 1 year – 14 years	3.0 – 3.5 mg/dL 0.97 – 1.13 mmol/L	2.5 – 2.9 mg/dL 0.81 – 0.96 mmol/L	1.5 – 2.4 mg/dL 0.48 – 0.80 mmol/L	< 1.50 mg/dL < 0.48 mmol/L
	Pediatric < 1 year	3.5 – 4.5 mg/dL 1.13 – 1.45 mmol/L	2.5 – 3.4 mg/dL 0.81 – 1.12 mmol/L	1.5 – 2.4 mg/dL 0.48 – 0.80 mmol/L	< 1.50 mg/dL < 0.48 mmol/L
Potassium, serum, high		5.6 – 6.0 mEq/L 5.6 – 6.0 mmol/L	6.1 – 6.5 mEq/L 6.1 – 6.5 mmol/L	6.6 – 7.0 mEq/L 6.6 – 7.0 mmol/L	> 7.0 mEq/L > 7.0 mmol/L
Potassium, serum, low		3.0 – 3.4 mEq/L 3.0 – 3.4 mmol/L	2.5 – 2.9 mEq/L 2.5 – 2.9 mmol/L	2.0 – 2.4 mEq/L 2.0 – 2.4 mmol/L	< 2.0 mEq/L < 2.0 mmol/L
Sodium, serum, high		146 – 150 mEq/L 146 – 150 mmol/L	151 – 154 mEq/L 151 – 154 mmol/L	155 – 159 mEq/L 155 – 159 mmol/L	≥ 160 mEq/L ≥ 160 mmol/L
Sodium, serum, low		130 – 135 mEq/L 130 – 135 mmol/L	125 – 129 mEq/L 125 – 129 mmol/L	121 – 124 mEq/L 121 – 124 mmol/L	≤ 120 mEq/L ≤ 120 mmol/L
Triglycerides (fasting)		NA	500 – 750 mg/dL 5.65 – 8.48 mmol/L	751 – 1,200 mg/dL 8.49 – 13.56 mmol/L	> 1,200 mg/dL > 13.56 mmol/L

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<b>LABORATORY</b>				
<b>PARAMETER</b>	<b>GRADE 1 MILD</b>	<b>GRADE 2 MODERATE</b>	<b>GRADE 3 SEVERE</b>	<b>GRADE 4 POTENTIALLY LIFE-THREATENING</b>
Uric acid	7.5 – 10.0 mg/dL <i>0.45 – 0.59 mmol/L</i>	10.1 – 12.0 mg/dL <i>0.60 – 0.71 mmol/L</i>	12.1 – 15.0 mg/dL <i>0.72 – 0.89 mmol/L</i>	> 15.0 mg/dL <i>&gt; 0.89 mmol/L</i>
<b>URINALYSIS</b> <i>Standard International Units are listed in italics</i>				
Hematuria (microscopic)	6 – 10 RBC/HPF	> 10 RBC/HPF	Gross, with or without clots OR with RBC casts	Transfusion indicated
Proteinuria, random collection	1 +	2 – 3 +	4 +	NA
Proteinuria, 24 hour collection				
<b>Adult and Pediatric ≥ 10 years</b>	200 – 999 mg/24 h <i>0.200 – 0.999 g/d</i>	1,000 – 1,999 mg/24 h <i>1.000 – 1.999 g/d</i>	2,000 – 3,500 mg/24 h <i>2.000 – 3.500 g/d</i>	> 3,500 mg/24 h <i>&gt; 3.500 g/d</i>
<b>Pediatric &gt; 3 mo - &lt; 10 years</b>	201 – 499 mg/m <sup>2</sup> /24 h <i>0.201 – 0.499 g/d</i>	500 – 799 mg/m <sup>2</sup> /24 h <i>0.500 – 0.799 g/d</i>	800 – 1,000 mg/m <sup>2</sup> /24 h <i>0.800 – 1.000 g/d</i>	> 1,000 mg/ m <sup>2</sup> /24 h <i>&gt; 1.000 g/d</i>

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† Use age and sex appropriate values (e.g., bilirubin).