ADVICE: Attenuation of D-dimer using Vorapaxar to target Inflammatory and Coagulation Endpoints

A double blind randomised comparison of vorapaxar versus placebo for the treatment of HIV associated inflammation and coagulopathy in patients with well controlled HIV replication

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Sponsor:
University of New South Wales
The Kirby Institute
University of NSW, New South Wales, Australia 2052
Email: advice@kirby.unsw.edu.au
Telephone: +61 2 9385 0900; Facsimile: +61 2 9385 0910

Coordinating Principal Investigator (CPI):
Professor Sean Emery
The Kirby Institute
The University of New South Wales
UNSW Medicine
University of NSW, New South Wales, Australia 2052
Email: semery@kirby.unsw.edu.au
Telephone: +61 2 9385 0900; Facsimile: +61 2 9385 0910

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1.0 Protocol Synopsis

Title	A double blind randomised comparison of vorapaxar versus placebo for the treatment of HIV associated inflammation and coagulopathy in patients with well controlled HIV replication
Protocol registration no,	NCT02394730
Background and rationale	**Clinical setting** Elevated expression of d-dimer (corresponding to coagulopathy) and hs-CRP/IL-6 (corresponding to immune activation/inflammation) are associated with increased risk of death and serious end-organ diseases among people with HIV infection[1-3]. While increased levels of these markers are driven by HIV replication, it is clear that even among people with well controlled HIV replication there is a consistent relationship between higher d-dimer levels and poorer clinical outcome. While combination antiretroviral therapy (cART) reduces levels of d-dimer, it does not result in normalisation[4]. Even among patients with suppressed HIV RNA replication, expression of these markers is higher among people with HIV infection than those observed in age matched populations without HIV infection[5]. Interventions to reduce either hypercoagulopathy and/or immune activation may permit a clearer understanding of the pathogenesis that underpins this presentation. Similarly, the interventions may also be consistent with improved prognosis that could be evaluated in additional studies. **Coagulation and immune activation** The relationship between coagulopathic disorder and immune activation is not clear. Data suggest that there is an evolutionary link between the immune system and the coagulation cascade. Tissue injury results in the release of tissue factor that promotes the coagulation cascade resulting in thrombus formation. T-cells differentially express receptors linked to this cascade and are activated at times when tissue injury has occurred. Recently, a novel observation was made suggesting that CD8+ T lymphocytes from HIV infected persons over-express Protease Activated Receptor-1 (PAR-1). This receptor is activated by thrombin and CD8+ cells expressing the receptor respond in a dose dependent fashion to exogenous thrombin[6]. In this setting CD8+ cell responses included expression of chemokines and cytokines. The sources of tissue injury, immune activation and hypercoagulopathy in people with well controlled HIV replication are not known. It is established that there are increased levels of tissue factor expression in monocytes from people with HIV-1 infection[9]. In the most comprehensive analysis of coagulation factors to date, mathematical modelling of thrombin generation indicated that the net effect of HIV replication was pro-coagulant. However, it was unclear from this investigation whether there were residual coagulation abnormalities after suppression of HIV replication[10]. As such it is plausible that tissue injury in the setting of HIV replication promotes thrombin formation and PAR-1 dependent signalling that in turn supports immune activation and inflammation. PAR-1 may mediate the intersection between these physiologic responses to injury and microbial threat. It is therefore a potential target for therapeutic manipulation in the setting of well controlled HIV infection.

	Vorapaxar Vorapaxar (Zontivity™) is an oral competitive PAR-1 antagonist that inhibits thrombin-induced platelet aggregation. Vorapaxar has recently been licensed as secondary prophylaxis for patients with a history of MI or peripheral arterial disease except ischemic stroke and was commercially available in the USA in July 2014 with other countries expected to follow.
Study objectives	To compare the safety and efficacy of vorapaxar versus placebo in reducing d-dimer expression and markers of cellular immune activation over a period of 12 weeks among people with HIV infection who are successfully treated with combination antiretroviral therapy that does not contain HIV protease inhibitors and/or NNRTIs (except rilpivirine). A secondary objective of the study will be to demonstrate that following cessation of vorapaxar in patients with suppressed plasma HIV viremia there will be an increase in the levels of d-dimer over a 6 week period. **Primary endpoint** • Differences between treatment groups in mean change from baseline log10 d-dimer at week 8 and week 12 **Secondary endpoints** Secondary endpoints to be measured during the two treatment phases will include, but not be limited to the following: *Virologic measures of interest* • Proportion of participants in each treatment group with plasma HIV-1 RNA <50 copies/mL at week 12 and week 18 *Immunologic measures of interest* • Differences between treatment groups in mean change from baseline in CD4+ cell counts at week 12 • Differences between treatment groups in mean change from baseline in CD4+ cell counts at week 18 • Differences between treatment groups in mean change from baseline in CD8+ cell counts at week 12 • Differences between treatment groups in mean change from baseline in CD8+ cell counts at week 18 *Activation/Coagulation measures of interest* • Percentage of patients in each treatment group with d-dimer <165ng/mL (0.165mg/L) at week 8 and week 12 • Percentage of patients in each treatment group with d-dimer >165ng/mL (0.165 mg/L) at week 18 • Differences between treatment groups in mean change from baseline log10 d-dimer at week 18 • Differences between treatment groups in mean change from baseline log10 hs-CRP at week 8 and week 12 • Differences between treatment groups in mean change from baseline log10 hs-CRP at week 18 • Differences between treatment groups in mean change from baseline log10 IL-6 at week 8 and week 12

- Differences between treatment groups in mean change from baseline log10 IL-6 at week 18

Safety endpoints

- Total number of participants in each treatment group with Type 1, 2, 3, 4 or 5 bleeding episodes (using BARC[16] criteria – see Appendix 2)
- Total number of participants in each treatment group with any Serious Adverse Event (SAE) and the cumulative incidence of SAEs.
- Total number of participants in each treatment group with any Adverse event (AE) and the cumulative incidence of AEs
- Changes from baseline in selected serum biochemical parameters, including changes in renal function measured by the CKD-EPI estimate of creatinine clearance

Exploratory analysis

During conduct of the study blood will be collected to support a range of exploratory laboratory analyses. If the primary endpoint of the trial is reached, the following measures of interest will be analysed:

Virologic measures

- Cell associated HIV RNA/DNA
- Ultrasensitive plasma viral load

Immunopathogenesis measures

- Plasma markers of monocyte activation (sCD14 and sCD163)
- Antibody function (ADCC)
- NK cell activation
- T cell activation markers (eg. CD38+ HLA+DR+ expression on CD4+/CD8+ cells)
- PAR-1 expression

Participant population

60 patients will be recruited from approximately 7 study centres in Australia and USA. Eligible patients will satisfy all of the following criteria within 14 days prior to randomisation:

Inclusion criteria

1. HIV-1 positive by licensed diagnostic test
2. aged ≥40 years
3. plasma HIV RNA <50 copies/mL for at least 24 weeks
4. screening CD4+ cell count > 50 cells/mm^3
5. treated for at least 12 weeks with a suppressive regimen of combination antiretroviral therapy that does not include HIV protease inhibitors and/or NNRTIs (except rilpivirine)
6. plasma d-dimer >200ng/mL (>0.2µg/mL or >0.2mg/L) fibrinogen equivalent units or >100ng/mL (>0.1 µg/mL or >0.1mg/L) d-dimer units in the absence of established cause (deep vein thrombosis/embolism)
7. provision of written informed consent

Exclusion criteria

1. Absolute neutrophil count (ANC) <1000 cells/µL
2. hemoglobin <10.0 g/dL
3. platelet count <75,000 cells/µL
4. AST and/or ALT >2.5 x ULN
5. estimated glomerular filtration rate<30mL/min/1.73m^2 using CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) equation
6. history of myocardial infarction or unstable atherosclerotic disease
7. history of ischemic stroke or transient ischaemic attack (TIA)
8. active peptic/duodenal ulcer or other bleeding disorder within the previous 12 months
9. intent to have surgery within the 6 month period after randomisation
10. current use of aspirin or P2Y12 antiplatelet therapy
11. current use of anticoagulants, (eg. heparin or warfarin), fibrinolytic therapy, chronic use (more than 5 consecutive days) of nonsteroidal anti-inflammatory drugs (NSAIDS), strong CYP3A4 inhibitors or inducers. See Manual of Operations for full list of medications to avoid.
12. participants unlikely to be able to remain in follow-up
13. pregnant or nursing mothers
14. in the clinical judgement of the investigator, participation in this trial is deemed inappropriate as this may conflict with the well-being of the participant.

Study design	This is an international, multi-centre, double-blind, randomised trial measuring the effects of vorapaxar versus placebo on inflammation and coagulopathy markers in patients with well controlled HIV infection. Randomisation will be stratified by clinical site.
Treatment of participants	Consenting participants will be screened and within 14 days randomly allocated to receive either vorapaxar sulphate (2.5mg) or matched placebo once daily for 12 weeks (phase 1). All patients will stop the study treatment at week 12 for a period of 6 weeks (phase 2) and have a final visit at week 18.

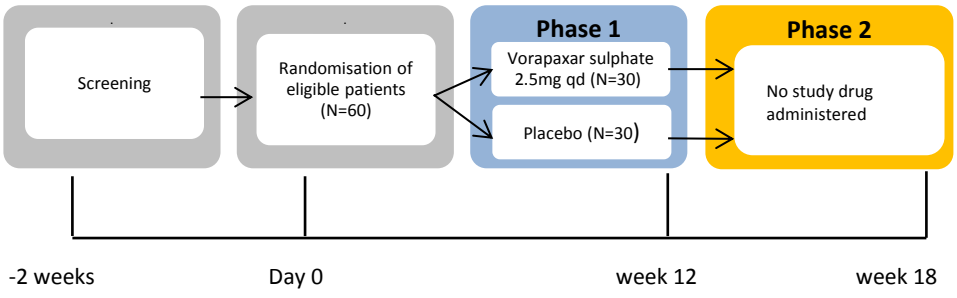

Figure 1. Study Design

Study procedures	Participants will be seen one week after randomisation and then at weeks 4, 8 and 12 (phase 1). At the week 12 visit, patients will not be dispensed any study treatment. In phase 2 all study treatment will stop for 6 weeks. At week 18 patients

will be seen for a final study visit.

Procedures include;

1. Informed consent
2. Medical and HIV history
3. Vital Signs (height, weight and sitting blood pressure)
4. Symptom directed physical exam
5. Blood sample collection for local laboratory analysis;
   - D-dimer (screening only for eligibility purposes)
   - Serum or urine pregnancy test
   - Virology: HIV-1 RNA measured using assays with lower limit of detection of at least 50 copies/mL
   - Haematology: full blood count
   - Fasted lipids
   - Biochemistry: Urea, Electrolytes, Creatinine, Liver Function Tests
   - Immunology: CD4+, CD8+ T cell count
6. Blood sample collection for storage and central laboratory analysis;
   - Coagulation / Immune Activation: D-dimer, IL-6, Hs-CRP
7. Blood sample collection for storage and central laboratory analysis (exploratory analyses);
   - Virology: cell associated HIV RNA/DNA, ultrasensitive HIV plasma viral load
   - Immunopathogenesis: ADCC Antibody, NK cell activation, T-cell activation markers, plasma markers of monocyte activation (sCD14, sCD163) and PAR-1 expression (PAR-1 to be analysed on fresh whole blood collected from a subset of participants from sites with capacity to perform this assay in real time)
8. Collection of AEs (including SAEs regardless of relationship to study drug)
9. Collection of concomitant medications

Statistics

Statistical analysis

Primary analyses will compare the two randomised arms in an intention to treat manner once all patients have completed follow up. Secondary analyses will exclude data in patients who cease study drug. There will be no adjustment of analyses for multiple comparisons.

The primary endpoint will be mean changes in log10 d-dimer levels from baseline at weeks 8 and 12. The proportion of patients with d-dimer<165ng/mL (0.165mg/L) will also be summarised.

Formal analyses will compare the randomised treatment arms in terms of mean differences in changes in log10 d-dimer at week 8 and week 12 using repeated

measures regression methods.

A focus of safety monitoring and analyses will be bleeding events assessed according to the Bleeding Academic Research Consortium (BARC)[16] criteria as BARC type 1, 2, 3, 4 or 5 bleeding events. Treatment arms will be compared in terms of proportions of patients with bleeding events using chi-square tests or Fisher's exact tests as appropriate.

Sample size

Using a repeated measures regression analysis at week 8 and 12, variability in change in log10 d-dimer =0.4, and correlation between these two time points as 0.5 (STEAL trial [14]), then a total sample size of 56 patients (2x28) gives 80% (90%) power to detect a mean difference of 0.26 (0.30) logs. A total of 60 patients gives some modest allowance for non-completion.

2.0 Study Flow Chart: Time and events schedule

Study Phase	Screening	Randomisation	Phase 1				Phase 2	
Study week number[c]	**SCRN[a]**	**0[b]**	**1**	**4**	**8**	**12**	**13-17** No study drug	**18**
Clinical Assessments								
Informed consent	•							
Medical and HIV history	•							
Interim history, AEs assessment and concomitant medication		•	•	•	•	•		•
Targeted physical examination (symptom directed)	•	•	•	•	•	•		•
Vital Signs[d]		•	•	•	•	•		•
Dispense study medication		•		•	•			
Real time local laboratory assessments								
Biochemistry[e]	•	•				•		•
Liver function[f]	•	•				•		•
Haematology[g]	•	•	•	•	•	•		•
Fasted lipids[h]		•						
CD4+ and CD8+ T cell (absolute and %)[i]	•	•	•	•	•	•		•
Virology: plasma HIV-1 RNA[j]	•	•	•	•	•	•		•
d-dimer	•							
Pregnancy test[k]	•	•		•	•	•		•
Storage samples for central laboratory analysis								
D-dimer		•	•	•	•	•		•
Hs-CRP		•	•	•	•	•		•
IL-6		•	•	•	•	•		•
Storage samples for central laboratory analysis (exploratory analysis)								
Ultrasensitive plasma viral load		•				•		•
T cell activation marker		•	•	•	•	•		•
ADCC Antibody/ NK cell function		•	•	•	•	•		•
PAR-1 expression[l]		•	•	•		•		•
Plasma markers of inflammation (sCD14, sCD163)		•				•		•

a All screening assessments are to be completed within 14 days prior to randomisation;
b All randomisation (week 0) assessments should be completed before the participant commences study drugs. Study drug should commence within 1 day of randomisation;
c Study Week Number: All efforts should be made to schedule visits in keeping with the proposed week numbers. Phase 1: week 1 to be conducted within 13 days of randomisation, weeks 4, 8 and 12 to be done +/- 2 weeks of scheduled visit date. Phase 2: week 18 to be conducted within + 2 weeks of scheduled visit date.
d Vital Signs: Sitting blood pressure (all visits), height (week 0 only) and weight (week 0 and week 18 only);
e Biochemistry: electrolytes (sodium, potassium, calcium, bicarbonate, chloride, phosphate), creatinine, urea;
f Liver Function test: ALT and AST;
g Haematology: haemoglobin, white blood cells, neutrophils, lymphocytes, platelets to be done (day 0 and week 12 to be done as standard of care). Haemoglobin to be tested at the time of any clinically significant bleeding event (clinical judgement to be used);
h Fasting lipid parameters includes: total cholesterol, HDL cholesterol, calculated LDL cholesterol and triglycerides;
i CD4+ and CD8+ cell counts: Day 0 and week 12 to be done as standard of care;
j HIV-1 RNA assays will be conducted at local laboratories with a lower limit of detection of at least 50 copies/mL plasma (day 0 and week 12 to be done as standard of care);
k Urine or serum pregnancy test if female and of child bearing potential;
l PAR-1 expression to be analysed on a subset of participants from selected sites with capacity to perform this assay in real time.

3.0 Background and rationale

3.1 Clinical setting

Elevated expression of d-dimer (corresponding to coagulopathy) and hs-CRP/IL-6 (corresponding to immune activation/inflammation) are associated with increased risk of death and serious end-organ diseases among people with HIV infection[1-3]. While increased levels of these markers are driven by HIV replication, it is clear that even among people with well controlled HIV replication there is a consistent relationship between higher d-dimer levels and poorer clinical outcome. While combination antiretroviral therapy (cART) reduces levels of d-dimer, it does not result in normalisation[4]. Even among patients with suppressed HIV RNA replication, expression of these markers is higher among people with HIV infection than those observed in age matched populations without HIV infection[5]. Interventions to reduce either hypercoagulopathy and/or immune activation may permit a clearer understanding of the pathogenesis that underpins this presentation. Similarly, the interventions may also be consistent with improved prognosis that could be evaluated in additional studies.

3.2 Coagulation and immune activation

The relationship between coagulopathic disorder and immune activation is not clear. Data suggest that there is an evolutionary link between the immune system and the coagulation cascade. Tissue injury results in the release of tissue factor that promotes the coagulation cascade resulting in thrombus formation. T-cells differentially express receptors linked to this cascade and are activated at times when tissue injury has occurred. Recently, a novel observation was made suggesting that CD8+ T lymphocytes from HIV infected persons over-express the Protease Activated Receptor-1 (PAR-1). This receptor is activated by thrombin and CD8+ cells expressing the receptor respond in a dose dependent fashion to exogenous thrombin[6]. In this setting CD8+ cell responses included expression of chemokines and cytokines. Furthermore, it is also known that natural polymorphisms in the PAR-1 gene that reduce PAR-1 expression are protective for thrombo-embolism in men[7, 8].

The sources of tissue injury, immune activation and hypercoagulopathy in people with well controlled HIV replication are not known. It is established that there are increased levels of tissue factor expression in monocytes from people with HIV-1 infection[9]. In the most comprehensive analysis of coagulation factors to date, mathematical modelling of thrombin generation indicated that the net effect of HIV replication was pro-coagulant. However, it was unclear from this investigation whether there were residual coagulation abnormalities after suppression of HIV replication[10]. As such it is plausible that tissue injury in the setting of HIV replication promotes thrombin formation and PAR-1 dependent signalling that in turn supports immune activation and inflammation. PAR-1 may mediate the intersection between these physiologic responses to injury and microbial threat. It is therefore a potential target for therapeutic manipulation in the setting of well controlled HIV infection.

3.3 Vorapaxar

Vorapaxar sulphate (Zontivity™) is a first in class, tricyclic himbacine-derived selective inhibitor of platelet aggregation mediated by PAR-1.

Vorapaxar has been developed in a number of primary and secondary care settings for cardiovascular diseases. In the setting of acute coronary syndromes vorapaxar did not affect a composite primary endpoint that included death, MI, stroke, recurrent ischemia or coronary revascularisation but did significantly

increase the risk of major bleeding including intracranial haemorrhage[11]. In a further study that followed 26,449 patients with a history of MI, cerebral stroke or peripheral arterial disease, vorapaxar significantly reduced the risk of cardiovascular disease mortality and ischemic events among patients with stable atherosclerosis while also increasing the risk of moderate to severe bleeding including intracranial haemorrhage[12]. This study identified the risk of severe bleeding among patients with a history of stroke – which would now be regarded as contraindicated for treatment with vorapaxar and therefore participation in this study. Importantly, the findings arose among a patient group who were also receiving standard secondary prophylaxis for CVD (88% receiving aspirin and 78% receiving thienopyridine) and so the effects reflect adjunctive use to already potent anti-thrombotic therapy. The hazard ratio (95% CI) for vorapaxar recipients relative to placebo recipients for the primary endpoint (fatal CV event, MI or stroke) was 0.87 (0.80-0.94; p<0.001). A total of 2204 patients experienced a primary event over three years, 1028 (9.3%) vorapaxar recipients and 1176 (10.5%) of placebo recipients. Moderate or severe bleeding occurred in 4.2% of patients who received vorapaxar and 2.5% of patients who received placebo (HR, 1.66; 95% CI 1.43–1.93: p<0.001).

Vorapaxar has now been licensed in the USA as secondary prophylaxis for patients with a history of MI or peripheral arterial disease except ischemic stroke.

4.0 Hypotheses

In patients with well controlled HIV disease treated with a suppressive cART regimen that does not contain HIV protease inhibitors and/or NNRTIs (except rilpivirine) who have relatively high levels of d-dimer, the use of vorapaxar will reduce d-dimer levels.

5.0 Study objectives

To compare the safety and efficacy of anti-platelet therapy with the PAR-1 antagonist vorapaxar versus placebo in reducing d-dimer expression and markers of cellular immune activation among people with HIV infection who are successfully treated with combination antiretroviral therapy that does not contain HIV protease inhibitors and/or NNRTIs (except rilpivirine).

5.1 Primary objective

To determine whether vorapaxar reduces d-dimer levels compared to placebo over a 12 week period.

5.2 Secondary objective

To demonstrate that following cessation of vorapaxar in patients with well controlled HIV replication there will be an increase in the levels of d-dimer over a 6 week period.

5.3 Exploratory objectives

To analyse the effect of vorapaxar on a range of virological, immunological and coagulation measures including cell associated HIV RNA/DNA, ultra-sensitive plasma HIV levels, T cell and NK cell function, monocyte activation, antibody function and PAR-1 expression.

5.4 Primary endpoint

Differences between treatment groups in mean change from baseline log10 d-dimer at weeks 8 and week 12

5.5 Secondary endpoints

Secondary endpoints to be measured during the two treatment phases will include, but not be limited to the following:

Virologic measures of interest

- Proportion of participants in each treatment group with plasma HIV-1 RNA <50 copies/mL at week 12 and week 18

Immunologic measures of interest

- Differences between treatment groups in mean change from baseline in CD4+ cell counts at week 12
- Differences between treatment groups in mean change from baseline in CD4+ cell counts at week 18
- Differences between treatment groups in mean change from baseline in CD8+ cell counts at week 12
- Differences between treatment groups in mean change from baseline in CD8+ cell counts at week 18

Activation/Coagulation measures of interest

- Percentage of patients in each treatment group with d-dimer <165ng/mL (0.165mg/L) at week 8 and week 12
- Percentage of patients in each treatment group with d-dimer >165ng/mL (0.165mg/L) at week 18
- Differences between treatment groups in mean change from baseline log10 d-dimer at week 18
- Differences between treatment groups in mean change from baseline log10 hs-CRP at week 8 and week 12
- Differences between treatment groups in mean change from baseline log10 hs-CRP at week 18
- Differences between treatment groups in mean change from baseline log10 IL-6 at week 8 and week 12
- Differences between treatment groups in mean change from baseline log10 IL-6 at week 18

Safety endpoints

- Total number of participants in each treatment group with Type 1, 2, 3, 4 or 5 bleeding episodes (using BARC[16] criteria – see Appendix 2)
- Total number of participants in each treatment group with any Serious Adverse Event (SAE) and the cumulative incidence of SAEs.
- Total number of participants in each treatment group with any Adverse event (AE) and the cumulative incidence of AEs
- Changes from baseline in selected serum biochemical parameters, including changes in renal function measured by the CKD-EPI estimate of creatinine clearance

5.6 Exploratory endpoints

During conduct of the study blood will be collected to support a range of exploratory laboratory analyses. If the primary endpoint of the trial is reached, the following measures of interest will be analysed:

Virological measures

- Cell associated HIV RNA/DNA
- Ultrasensitive plasma viral load

Immunopathogenesis measures

- Plasma markers of monocyte activation (sCD14 and sCD163)
- Antibody function (ADCC)
- NK cell activation
- T cell activation markers (e.g. CD38+ HLA+DR+ expression on CD4+/CD8+ cells)
- PAR-1 expression (to be analysed on fresh whole blood collected from a subset of participants at participating sites with the capacity to perform this assay in real time)

6.0 Study design & Statistics

This is an international, multi-centre, double-blind, placebo controlled trial. Randomisation will be stratified by clinical site.

Consenting participants will be screened and within 14 days randomly allocated to receive either vorapaxar sulphate (2.5mg qd) or matched placebo once daily for 12 weeks (phase 1). At the week 12 visit, all study treatment will stop for 6 weeks (phase 2). Patients will be seen for a final visit at week 18.

The study designed is summarised in Figure 1.

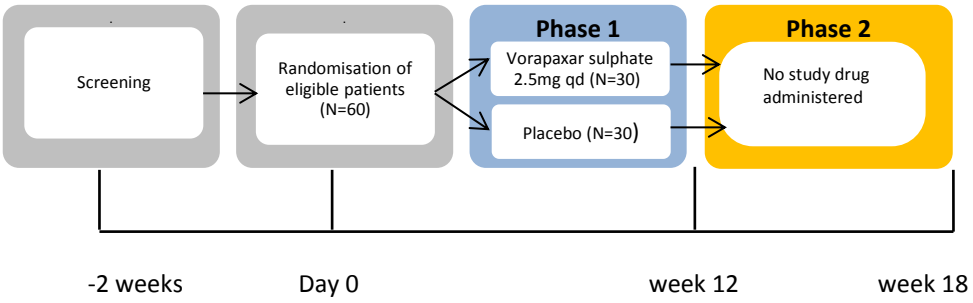

Figure 1. Study Design

60 participants will be randomised from approximately 7 selected centres in Australia and the USA and followed for a total of 18 weeks. It is anticipated that approximately 120 patients will need to be screened to randomise 60 participants. It is expected that the majority of ineligible participants through screening will be those with low d-dimer levels.

6.1 Sample size determination

Assumptions are based on data from the STEAL trial[14]. Excluding patients with d-dimer<200ng/mL, the standard deviation in change in log10 d-dimer is 0.356 at week 12 and 0.414 at week 24. The correlation of these two endpoints is 0.5726.

Using a repeated measures regression analysis at week 8 and 12, variability in change in log10 d-dimer =0.4, and correlation between these two time points as 0.5 (STEAL trial [14]), then a total sample size of 56 patients (2x28) gives 80% (90%) power to detect a mean difference of 0.26 (0.30) logs. A total of 60 patients gives some modest allowance for non-completion.

Mean baseline d-dimer in STEAL[15] (excluding patients with d-dimer<200 ng/mL at baseline) was 430ng/mL. Mean log10 decrease in STEAL was 0.07logs, which corresponds to about a 15% decrease – i.e. in the control arm we might expect a decrease from 430 to about 370ng/mL. We are powered to detect log differences of the order of 0.26, so in total in the vorapaxar arm we expect a 0.33log decrease – i.e. a decrease from 430 to about 200 ng/mL. In absolute terms we have 80% power to detect a difference in d-dimer changes of around 170 ng/mL.

These are quite large effect sizes, both compared with the expected variability (0.75 standard deviations), and in absolute terms (differences in d-dimer changes of around 170 ng/mL from expected baseline mean of 430 ng/mL. However, we believe that such large effects would be clinically significant, and will be required to justify expanded studies of vorapaxar treatment in HIV-positive individuals.

6.2 Analysis Plan

6.2.1 Statistical analysis

Baseline characteristics will be summarised by randomised group. Patients failing to complete study drug will be listed, with accompanying reasons. The primary endpoint will be mean changes in log10 d-dimer levels from baseline at weeks 8 and 12. The proportion of patients with d-dimer<165ng/mL will also be summarised.

Mean or median changes, or percentages, as appropriate, in primary and secondary endpoints will be plotted by study week.

Formal analyses will compare the randomised treatment arms in terms of mean differences in changes in log10 d-dimer at week 8 and week 12 using repeated measures regression methods. Models will be fitted using maximum likelihood methods using robust standard errors. Simple unadjusted models will initially be used to estimate the difference between randomised treatment arms in mean changes in log10 d-dimer. Models adjusted for key baseline covariates will also be fitted. If there is overall evidence of a difference between randomised treatment arms at $2p<0.05$, then further sensitivity analyses will also be performed using simple two-sample (t-test or rank-sum test) applied to the mean change in log10d-dimer at weeks 8 and 12.

Similar longitudinal methods will also be used to analyse mean changes from baseline in, or proportions of, secondary endpoints at weeks 8 and 12.

Differences between randomised treatment arms in mean changes in, or proportions of, all endpoints at week 18 will be investigated using linear regression or logistic regression methods.

6.2.2 Safety analysis

The proportion of participants with all DAIDS (Division of AIDS) grade adverse events and DAIDS grade 3/4 adverse events (see Appendix 1) will be summarised by randomised treatment group, by severity and by relation to study drug for all subjects treated with study drug. Serious adverse events will be summarised for all enrolled subjects. The analysis of safety variables will be done according to a per protocol approach.

A particular focus of safety analyses will be bleeding events. These will be solicited adverse events, and classified according to Bleeding Academic Research Consortium (BARC) criteria[16] (see Appendix 2) as BARC Type 1, 2, 3, 4 or 5 bleeding events. Bleeding events reported as unsolicited adverse events or serious adverse events will also be summarised. The proportions of patients with bleeding events will be compared between treatment arms using chi-square tests. If numbers of events are small, some bleeding events may be aggregated.

6.3 Schedule of Analyses

Primary analyses will compare the two randomised arms in an intention to treat manner once all patients have completed follow up (week 18). Secondary analyses will exclude data in patients who cease study drug. There will be no adjustment of analyses for multiple comparisons.

7.0 Participant population

Eligible participants will satisfy all the following inclusion and exclusion criteria within 14 days prior to randomisation. No waivers will be issued.

7.1 Eligibility criteria

Inclusion criteria

1. HIV-1 positive by licensed diagnostic test
2. aged ≥40 years
3. plasma HIV RNA <50 copies/mL for at least 24 weeks
4. screening CD4+ cell count >50 cells/mm^3
5. treated for at least 12 weeks with a suppressive regimen of combination antiretroviral therapy that does not include HIV protease inhibitors and/or NNRTIs (except rilpivirine)
6. plasma d-dimer >200ng/mL mL (>0.2µg/mL or >0.2mg/L) fibrinogen equivalent units or >100ng/mL (>0.1 µg/mL or >0.1mg/L) d-dimer units in the absence of established cause (deep vein thrombosis/embolism)
7. provision of written informed consent

Exclusion criteria

1. Absolute neutrophil count (ANC) <1000 cells/µL
2. haemoglobin <10.0 g/dL
3. platelet count <75,000 cells/µL
4. AST and/or ALT >2.5 x ULN
5. estimated glomerular filtration rate<30mL/min/1.73m^2) using CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) equation
6. history of myocardial infarction or unstable atherosclerotic disease
7. history of ischemic stroke or transient ischaemic attack (TIA)
8. active peptic/duodenal ulcer or other bleeding disorder within the previous 12 months

9. intent to have surgery within the 6 month period after randomisation
10. current use of aspirin or P2Y12 antiplatelet therapy
11. current use of anticoagulants, (e.g. heparin or warfarin), fibrinolytic therapy, chronic (more than 5 consecutive days) nonsteroidal anti-inflammatory drugs (NSAIDS), strong CYP3A4 inhibitors or inducers. See Manual of Operations for full list of medications to avoid.
12. participants unlikely to be able to remain in follow-up
13. pregnant or nursing mothers
14. in the clinical judgement of the investigator, participation in this trial is deemed inappropriate as this may conflict with the well-being of the participant

8.0 Treatment of participants

Eligible participants will be randomised in equal proportions to receive either:

I. vorapaxar sulphate (2.5mg qd) for 12 weeks
II. matched placebo for 12 weeks

All participants will stop study treatment at the week 12 visit and then be seen for a final visit at week 18. All participants will stop taking the study medication at the week 12 visit, even if having undergone a period of study drug interruption. The treatment period will not be extended to account for the missing days.

Randomisation will be conducted via the electronic case report form. Specific details regarding randomisation will be provided in the study Manual of Operations (MOOP). Randomisation will be stratified by centre on a 1:1 basis.

8.1 Vorapaxar

Vorapaxar sulphate is an oral competitive PAR-1 antagonist that inhibits thrombin-induced platelet aggregation. Vorapaxar is eliminated primarily by metabolism with contributions from CYP3A4 and CYP2J2. The primary route of elimination is through the faeces and to a lesser degree in urine. It has an effective half-life of 3-4 days and an apparent terminal elimination half-life of 8 days (range 5-13 days).

One vorapaxar sulphate encapsulated tablet (2.5mg) or matching placebo should be taken orally, once daily with or without food. A one month supply of vorapaxar or matching placebo will be provided at each dispensing visit (weeks 0, 4 and 8). Study drug will be dispensed from local pharmacies in a bottle containing a desiccant packet to protect the drug from moisture. The bottles must be stored at 20-25°C (68-77°F). Temperature monitoring logs will be kept at each pharmacy and checked during monitoring visits. All details regarding supply and dispensing of study treatment will be outlined in the MOOP.

8.2 Prior and concomitant medications

Given the involvement of CYP3A4 and CYP2J2 in the metabolism of vorapaxar, participants with HIV infection whose ART therapy includes ritonavir or cobicistat boosted PIs or NNRTIs (apart from rilpivirine) will not be enrolled into the study. Vorapaxar can increase the risk of bleeding in proportion to a participant's underlying bleeding risk. To this end, participants who have a history of bleeding disorders, active bleeding or are planning to undergo an elective surgical procedure within the 6 month period following randomisation will be excluded from the study. Certain concomitant medications are also known to increase the risk of

bleeding. As such, participants taking anticoagulants, (e.g. heparin or warfarin), fibrinolytic therapy or chronic (more than 5 consecutive days) nonsteroidal anti-inflammatory drugs (NSAIDS) will also be excluded from the study. A list of medications to avoid will be listed in the MOOP.

If during the course of the study, a participant needs treatment with a potent CYP3A4 inhibitor or inducer or other medication listed above, study treatment must be discontinued immediately. In the case of a potent CYP3A4 inhibitor or inducer, where possible, an alternative treatment should be given to avoid participants coming off study medication unnecessarily. Study treatment should recommence as soon as clinically possible with the safety and well-being of the participant paramount. It is important that the treating physician is informed that vorapaxar results in residual platelet aggregation activity 4 weeks after stopping and appropriate clinical decisions are made. Whilst there is no known antedote for vorapaxar, monkey data suggest that platelet transfusions of sufficient quantity (a full pheresis pack or two) have the potential to transiently (a few hours) reverse the antiplatelet activity of vorapaxar. It is the investigator's responsibility to inform the treating physician of this.

In this protocol all concomitant medications including over the counter medicines and natural supplements will be recorded.

8.3 ART Regimen

Participants will continue to have their ART regimen managed as directed by their treating physician in accordance with national and international guidelines. Modifications to the ART regimen can be made if required. However, ritonavir boosted PIs, elvitegravir+cobicistat (Stribild™ Genvoya™) or NNRTIs (apart from rilpivirine), should not be prescribed as they are potent inhibitors or inducers of CYP3A4. Rilpivirine is permitted as it is not a potent CYP3A4 inducer. At the recommended dose of 25mg daily, rilpivirine is not expected to have a clinically significant effect on vorapaxar exposure. Similarly, maraviroc is not expected to have a clinically significant effect on vorapaxar exposure as it does not inhibit any of the major CYP isoforms. Conversely vorapaxar is not expected to have a clinically significant effect on rilpivirine or maraviroc.

Warnings and precautions regarding medications to avoid whilst taking vorapaxar can be found in the FDA approved product information and Investigator Brochure. For ART medications Investigators can refer to the respective product information or www.HIV-druginteractions.org.

Participants will receive their ART medication in the usual manner and this will not be provided by the study.

9.0 Study procedures

9.1 Initial screening period

Potentially eligible individuals can be screened within 14 days before the randomisation visit and all results from screening must be available for randomisation. All subjects should be given adequate information about the trial including the Participant Information Sheet and be given an opportunity to ask questions about the trial. Written consent for the trial should be obtained at the screening visit before any protocol specified assessments are performed. The following evaluations will be performed within 14 days prior to randomisation:

9.1.1 Clinical assessments at screening

- Informed consent
- Complete medical history to include; non-HIV related diagnosis including liver disease, renal disease, cardiovascular disease, bleeding disorders, race and gender at birth, surgical history and concomitant medications
- Full HIV history to include: mode of transmission, duration of HIV infection, ART history and current ART regimen, current stage of HIV disease (CDC classification – refer Appendix 3)
- Symptom directed physical examination

9.1.2 Laboratory assessments at screening

- If the patient is female and is of child bearing potential, she must have a urine or blood sample pregnancy test
- Serum chemistries and liver function tests: electrolytes (sodium, potassium, bicarbonate, chloride, phosphate), urea, creatinine and LFTs (ALT and AST only)
- Assessment of renal function will be undertaken with derivation of creatinine clearance using the CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) equation:

Estimated GFR = $141 \times \min(SCR/\kappa,1)^{\alpha} \times \max(SCR/\kappa,1)^{-1.209} \times 0.993^{Age}$ x (1.018 if female x (1.159 if black)

- Haematology: full blood count (haemoglobin, white cells, neutrophils, lymphocytes, platelets)
- Plasma HIV-RNA analysis
- Immunology: CD4 and CD8 (% and absolute)
- Plasma d-dimer

9.1.3 Rescreening

Rescreening is not permitted, including those participants with abnormal laboratory results. All screen failures must be documented on the site screening and randomisation log.

9.2 Randomisation visit

To proceed to the randomisation visit, all participants must have fulfilled the eligibility criteria by the results of evaluations at screening. All randomisation evaluations must be completed prior to the commencement of study drug

9.2.1 Clinical assessments at week 0 (prior to randomisation)

- Targeted physical examination (symptom directed). Symptoms reported by the subject will be reviewed by the clinician at each visit and recorded on the CRFs as adverse events
- Vital Signs: height, weight and sitting blood pressure
- Information required for Framingham risk[17] equation (smoking and diabetes)
- Concomitant medication information

9.2.2 Laboratory assessments at week 0 (prior to randomisation)

- If the patient is female and is of child bearing potential, she must have a urine or blood sample pregnancy test
- Serum chemistries and liver function tests: electrolytes (sodium, potassium, bicarbonate, chloride, phosphate), urea, creatinine and LFTs (ALT and AST only)
- Haematology: full blood count (haemoglobin, white cells, neutrophils, lymphocytes, platelets)
- Fasted lipids
- Plasma HIV-RNA levels
- Immunology: CD4 and CD8 (% and absolute)
- PAR-1 (to be analysed in a subset of participants from selected sites with capacity to perform this assay in real time)
- Plasma storage for central laboratory testing of d-dimer, Hs-CRP, IL-6
- Plasma, PBMC and serum storage for possible exploratory analysis of ultra-sensitive plasma viral load, T cell activation, NK cell function, ADCC antibody and markers of inflammation (sCD14, sCD163)

9.2.3 Randomisation and Drug Supply

After completion of all randomisation study visit assessments the participant will be randomised online via the web based CRF. Eligibility must be confirmed and the participant will then be automatically randomised to commence either vorapaxar sulphate (2.5mg) or matching placebo once daily. A Participant Identification (PID) number will be provided.

The treatment assignment will be stratified according to clinical site.

The investigator should complete a prescription and the participant should fill the prescription that same day or the next. Therefore, the study drug should be commenced within 1 day of randomisation.

9.3 Follow Up Visits

The scheduled date of study visits will be calculated from the date of randomisation (day 0, week 0). A schedule of the dates for study visits will be provided for each participant, once randomisation has been completed. Guidance for site staff will also be detailed in the MOOP.

The window period for each study visit is continuous so that all data collected may be used. The window period for: week 1 is between day 1 and day 13 from randomisation (inclusive); week 4, 8 and 12 visits in each treatment phase should be conducted 2 weeks before or after the scheduled visit date. Week 18 to be conducted no later than 2 weeks after the scheduled visit date.

9.3.1 Clinical assessments at weeks 1, 4, 8, 12, 18

- Targeted physical examination (symptom directed) [weeks 1, 4, 8, 12, 18]
- Symptoms reported by the subject or symptoms identified after examination will be reviewed by the clinician at each visit and recorded on the CRFs as adverse events [weeks 1, 4, 8, 12, 18]
- Updated medical history including changes or additions to diagnoses, diseases, or any change in antiretroviral drugs, prescribed concomitant medications [weeks 1, 4, 8, 12, 18]
- Sitting blood pressure [weeks 1, 4, 8, 12, 18]
- Weight [week 18 only]
- Dispense study medication [weeks 4 and 8 only]

9.3.2 Laboratory assessments at weeks 1, 4, 8, 12, 18

- If the participant is female and is of child bearing potential, she must have a urine or blood sample pregnancy test [weeks 4, 8, 12, 18]
- Haematology: full blood count (haemoglobin, white cells, neutrophils, lymphocytes, platelets) [weeks 1, 4, 8, 12, 18]
- Blood sample for haemoglobin measurement to be taken if the participant experiences a clinically significant bleeding event (clinical judgement to be used)
- Plasma HIV-RNA levels [weeks 1, 4, 8, 12, 18]
- Immunology: CD4 and CD8 (% and absolute) [weeks 1, 4, 8, 12, 18]
- Serum chemistries and liver function tests: electrolytes (sodium, potassium, bicarbonate, chloride, phosphate), urea, creatinine and LFTs (ALT and AST only) [weeks 12 and 18 only]
- PAR-1 (to be analysed in a subset of participants from selected sites with capacity to perform this assay in real time) [weeks 1, 4, 12, 18]
- Plasma storage for central laboratory testing of d-dimer, Hs-CRP, IL-6 [weeks 1, 4, 8, 12, 18]
- Plasma, PBMC and serum storage for possible exploratory analysis of T cell activation, NK cell function and ADCC antibody [weeks 1, 4, 8, 12, 18]
- Plasma storage for possible exploratory analysis of markers of inflammation (sCD14, sCD163) and ultra-sensitive plasma viral load [weeks 12 and 18 only]

9.4 Missed visits and missed assessments

All efforts should be made to schedule visits in keeping with the proposed week numbers and to carry out all required assessments at these visits. Any missed study visits or missed assessments should be indicated as such on the eCRF. If a scheduled visit is conducted after the window period has ceased for that specific visit, it will be counted as the next visit, and the previous visit should be documented as "missed". DO NOT conduct a second routine visit in the same window period.

9.5 Withdrawal of study participants

In general terms, all randomised study participants should remain in follow-up for the duration of the study, regardless of whether or not they continue to take randomly assigned therapy. All study participants should continue to attend all study visits and complete all study-mandated assessments as per protocol. No participants will be replaced if there is a withdrawal.

The reasons for premature study discontinuation and withdrawal of participants from the study include the following criteria:

- Termination of the study by the Protocol Steering Committee
- Withdrawal of consent - participants may revoke consent for follow-up without jeopardising their relationship with either their doctor or the Sponsor. If a participant revokes consent then, if possible, all assessments scheduled for the final visit should be completed. The date of the withdrawal of consent must be documented in the participant's medical notes. See MOOP for more details.

10.0 Clinical & Toxicity Management Guidelines

10.1 Clinical and Toxicity Management Guidelines

Investigators and study sites are encouraged to keep participants enrolled within the protocol regardless of whether they continue on their original randomised study treatment. For the purposes of uniform assessment of adverse events (including toxicities) this protocol employs the current DAIDS Common Toxicity Grading Scale (see Appendix 1). In this protocol bleeding events will be graded according to the Bleeding Academic Research Consortium (BARC) definitions for bleeding (see Appendix 2). Any neurological event should be investigated to rule out bleeding as an underlying cause. Any event with neurological symptoms and signs that is linked to bleeding of the central nervous system will be graded according to the BARC scale and managed as outlined in section 10.3.2. Neurological events without bleeding should be graded using the DAIDS scale and managed as clinically indicated.

This systematic approach is intended to also provide a framework for clinical management of emergent adverse events after randomisation as described in 10.2 below. These recommendations are guidelines that do not override sound and qualified clinical judgement.

10.2 Dose modifications

No vorapaxar dose modifications should be made in response to observed toxicities. If vorapaxar is suspected in the etiology of a significant adverse event then dosing should cease immediately. This could apply if an event unrelated to vorapaxar could be worsened as a consequence of continued exposure to the study drug. Rechallenge can occur if or when clinically appropriate.

10.2.1 DAIDS Grade 1 or 2 adverse events

Participants who develop a Grade 1 or 2 adverse event or toxicity may continue the study drug without modification. Participants experiencing Grade 1 or 2 adverse events who choose to discontinue the study drug should remain on study and continue to undergo protocol-mandated evaluations and assessments.

10.2.2 DAIDS Grade 3 adverse events

If the investigator has compelling evidence that the adverse event has NOT been caused by the study drug, dosing may continue. Participants who develop a Grade 3 adverse event or toxicity considered to be possibly, probably or definitely related to the study drug (including raised AST/ALT levels in the presence of clinical symptoms) should have study drug withheld, at the investigator's discretion. The participant should be re-evaluated regularly until the adverse event returns to Grade $\leq$2, at which time the study drug may be reintroduced at the discretion of the investigator or according to standard practice.

If the same Grade 3 adverse event recurs within four weeks, study drug must be permanently discontinued if the investigator considers the adverse event related to study drug. However, if the same Grade 3 adverse event recurs after four weeks, the management scheme outlined above may be repeated.

Participants experiencing Grade 3 adverse events requiring permanent discontinuation of study drug therapy should be followed regularly (weekly is suggested) until resolution of the adverse event. Participants should remain in follow-up and continue to attend for protocol-mandated assessments and evaluations.

10.2.3 DAIDS Grade 4 adverse events

Participants who develop a Grade 4 adverse event or toxicity considered to be possibly, probably or definitely related to the study drug will have the study drug temporarily discontinued. The AE should be resolved before any decision is made to rechallenge the subject with the study drug. Participants experiencing Grade 4 AEs requiring permanent discontinuation of study drug therapy should be followed regularly (weekly is suggested) until resolution of the adverse event. The patient should remain on study and continue to undergo protocol-specified evaluations and assessments.

Participants with Grade 4 asymptomatic or non-significant laboratory abnormalities may continue study drug therapy if the investigator has compelling evidence that the toxicity is NOT related to the study drug(s). However, if a participant develops a Grade 4 AST/ALT adverse event, without clinical symptoms, must have their study drug permanently discontinued. The participant should remain in follow-up and continue to attend for protocol-mandated assessments and evaluations.

10.2.4 Monitoring of Renal Function

There is no dose adjustment required in patients with renal impairment. However, routine assessment of renal function will be undertaken with derivation of creatinine clearance using the CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) equation[13]:

Estimated GFR = $141 \times \min(SCR/\kappa,1)^{\alpha} \times \max(SCR/\kappa,1)^{-1.209} \times 0.993^{Age}$ x (1.018 if female x (1.159 if black)

$\kappa = 0.7$ if female
$\kappa = 0.9$ if male

$\alpha = -0.329$ if female
$\alpha = -0.411$ if male

min = the minimum of Scr/κ or 1
max = the maximum of Scr/κ or 1

Scr = serum creatinine (mg/dL)

Dosing of all medications in a patient's regimen should be critically reviewed if the eGFR falls below 60ml/min/1.73m^2. It is recommended that Investigators follow the current local guidelines for the management of renal impairment in HIV-1-infected patients and/or reference the current EACS guidelines at: (Europeanaidsclinicalsociety.org/guidelinespdf/2_Non_Infectious_Co_Morbidities_in_HIV.pdf. Accessed 01Dec2010)

10.3 Protocol-specific toxicity management guidelines

10.3.1 Vorapaxar Side Effect Profile

The most common AEs associated with the use of vorapaxar sulphate (2.5mg) given once daily in patients with a history of cardiovascular disease are bleeding (including intracerebral bleeding), anaemia, depression and rash, retinal disorder and diplopia/oculomotor disturbance. The most clinically relevant are summarised below.

10.3.2 Bleeding

In the phase 3 TRA 2°P TIMI 50 (Thrombin Receptor Antagonist in Secondary Prevention of Atherothrombotic Ischemic Events) study[12] (Morrow et al), vorapaxar sulphate (2.5mg) given once daily in patients with a history of myocardial infarction or peripheral vascular disease with no history of ischaemic stroke or transient ischaemic attack saw an increase in GUSTO moderate or severe bleeding by 55% compared to the placebo arm. (GUSTO: Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Arteries). These bleeding events were assessed as being non-CABG related bleeds. GUSTO moderate to severe bleeding was defined as bleeding requiring transfusion of whole blood or packed red blood cells with or without haemodynamic compromise, intracranial haemorrhage or fatal bleeding.

To minimise the occurrence of bleeding events, participants with a high risk of bleeding will be excluded from this study. See section 7.1 for details.

Adverse events involving bleeding will be assessed according to the BARC definitions (see Appendix 2) for bleeding. If participants are suspected of having a clinically significant bleeding event, then a blood sample should be taken to monitor haemoglobin levels in order to classify the event according to the BARC criteria. Participants will be managed as outlined below.

10.3.2.1 BARC Type 1 Bleeding

Participants who develop a BARC type 1 adverse bleeding event should continue with the study drug. Participants experience a BARC type 1 adverse bleeding event who choose to discontinue the study drug should remain on study and continue to undergo protocol-mandated evaluations and assessments.

10.3.2.2 BARC Type 2 Bleeding

Participants who develop a BARC type 2 adverse bleeding event that requires nonsurgical, medical intervention by a healthcare professional or leads to hospitalisation or increased level of care, should discontinue study drug but remain on study and continue to undergo protocol mandated evaluations and assessments. The participant should be monitored as frequently as clinically required for the particular bleeding event. At least weekly is recommended. The appropriateness of whether to re-challenge the participant with the study drug will be left to the investigator's clinical judgement but the long half-life of vorapaxar must be taken into account.

10.3.2.3 BARC Type 3 Bleeding

Participants who develop a BARC type 3a, 3b or 3c (intracranial or intraocular) bleeding event will have the study drug permanently discontinued. Participants experiencing BARC type 3a or 3b AEs must be followed regularly (at least 4-5 times per week is suggested) until resolution of the adverse event. Participants experiencing a BARC Type 3c event (intracranial or intraocular bleed) must be followed on a daily basis until the resolution of the event. The patient should remain on study and continue to undergo protocol-specified evaluations and assessments. A BARC type 3 event would trigger an 'out of session' meeting of the Data Safety Monitoring Board to review the event in an unblinded manner.

10.3.2.4 BARC Type 4 Bleeding

Any participant who is planning to undergo any planned surgical procedure 6 months after the planned randomisation should not be enrolled into the study. If there is a need for a participant to undergo an emergency CABG or any other surgical procedure during the course of the study, the study drug should be immediately and permanently discontinued. If deemed necessary, unblinding procedures could be initiated but attention to how best do this will be given to avoid site staff becoming aware of the treatment allocation.

It is important that the treating physician is informed that vorapaxar results in residual platelet aggregation activity 4 weeks after stopping and appropriate clinical decisions are made. There is no known antedote for vorapaxar. It is the investigator's responsibility to inform the treating physician of this.

10.3.2.5 BARC Type 5 Bleeding

If any participant suffers a fatal bleed the blind for that participant will be broken. If the participant was taking vorapaxar at the time of the event, the trial will be temporarily stopped whilst the Data Safety Monitoring Board (DSMB) reviews the event in light of other clinical safety information for the study. Please see section 18.0 for details on DSMB.

10.3.3 Other Adverse Reactions

Pooling the adverse event data from the TRA 2°P TIMI 50 study[12] (13,186 patients) and TRA●CER (Thrombin Receptor Antagonist for Clinical Event Reduction in Acute Coronary Syndrome) study[11] (6,446 patients), the incidence of the adverse events was as shown in Table 1.

Table 1. Percentage of patients reporting non-haemorrhagic adverse events

	Vorapaxar N= 19,632	**Placebo N= 19,607**
Anemia	5%	4%
Depression	2.4%	2.1%
Rashes, Eruptions and Exanthemas	2.2%	2.0%

Less common adverse reactions (occurred at a rate of less than 2% in those patients taking vorapaxar but at least 40% greater rate than placebo) were iron deficiency, retinopathy or retinal disorder and diplopia / oculomotor disturbance.

10.4 Discontinuation of study treatment

In general terms, all randomised study participants should aim to take the study treatment as per protocol. However, reasons for either temporarily or permanently ceasing study treatment include:

- Disease progression requiring medical intervention
- Surgical intervention
- Administration of prohibited therapy
- Investigator or participant wish to stop therapy
- Occurrence of unacceptable adverse drug reactions

Participants MUST be discontinued from study treatment if there is any clinical adverse event, laboratory abnormality or intercurrent illness that in the opinion of the investigator indicates that continued treatment with study therapy is not in the best interest of the participant.

11.0 Adverse Event Recording & Reporting

11.1 Adverse Events

The definition of an adverse event is any untoward medical occurrence in a participant administered with a pharmaceutical product which does not necessarily have a causal relationship with the product. Where adverse events are related to the drug, they may be referred to as Adverse Drug Reactions.

Adverse events and adverse drug reactions may occur in the course of this study and within the specified follow-up period. These events may also occur in screened participants during the screening period prior to

randomisation as a result of protocol-specified interventions. All such events will be recorded at each study visit on the adverse event case report form.

In this study we will be collecting all grade (grade 1-4) clinical adverse events. As a general rule, isolated laboratory abnormalities in the absence of clinical symptoms and/or signs should not be captured as adverse events. If the laboratory event becomes clinically significant, then the resulting clinical event should be reported as an adverse event (e.g. low haemoglobin should be reported as anaemia).

Pre-existing conditions or diseases that occur during the study (e.g. seasonal allergies, asthma or recurrent headaches) should not be considered as adverse events unless they change in frequency or severity. In this study we will be collecting all grade (grade 1-4) clinical adverse events. If known, the diagnosis of the underlying illness or disorder should be recorded, rather than its individual symptoms.

11.1.1 Reporting of Adverse Events

Timely and complete reporting of all AEs assists in identifying any untoward medical occurrence, thereby allowing: (1) protection of safety of study subjects; (2) a greater understanding of the overall safety profile of the study drugs; (3) recognition of dose-related study drug toxicity; (4) appropriate modification of study protocols; (5) improvements in study design or procedures; and (6) adherence to worldwide regulatory requirements.

The collection of non-serious AE information should begin at initiation of study drugs. AEs may be either spontaneously reported or elicited during questioning and examination of a participant. All identified AEs must be recorded in the participant's medical notes immediately and entered on the AE page of the eCRF within 1 week of the study visit at which they were reported. If known, the diagnosis of the underlying illness or disorder should be recorded, rather than its individual signs or symptoms.

Participants experiencing AEs that cause interruption or discontinuation of study drugs, or those experiencing AEs that are present at the end of their participation in the study should receive follow-up as appropriate. If possible, report the outcome of any AE that caused permanent discontinuation or that was present at the end of the study particularly if the AE was considered by the investigator to be certainly, probably, or possibly related to the study drugs.

Non-serious AEs should be followed to resolution or stabilisation at or until the end of the study, and reported as SAEs should they become serious.

11.2 Serious Adverse Event (SAE)

The definition of a SAE is any untoward medical occurrence that at any dose:

- results in death,
- is life-threatening,
  (Note: the term "life-threatening" in the definition of "serious" refers to an event/reaction in which the participant was at risk of death at the time of event/reaction; it does not refer to an event/reaction which hypothetically might have caused death if it were more severe)
- requires in-patient hospitalisation (≥ 24 hours) or prolongation of existing hospitalisation,
- results in persistent or significant disability/incapacity,
- is a congenital anomaly/birth defect
  or
- is a medically important event or reaction

Medical and scientific judgment should be exercised in deciding whether other situations should be considered serious e.g. important medical events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the participant or may require intervention to prevent one of the outcomes listed in the definition above. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsion that does not result in hospitalisation, or development of drug dependency or drug abuse.

Where SAEs are related to the drug, they may be referred to as Serious Adverse Drug Reactions.

11.2.1 Reporting Serious Adverse Events

SAEs should be collected following the participant's written consent to participate in the study. All serious adverse events (SAEs) must be reported within 24 working hours after the SAE occurs or from the time when the study investigator first becomes aware of the SAE whether or not there is a suspected causal relationship to the study drug.

SAEs must be reported to the Kirby Institute by telephone, email or fax. The appropriate Serious Event form should be used. The Project team in conjunction with the Medical Officer will review all SAEs for completion and accuracy. Immediate reports should be followed promptly by detailed, written follow-up reports when all information is not included in the initial report. The immediate and follow up reports should identify participants by unique code numbers assigned to study participants rather than personal identification. Such reports must be supported by copies of de-identified relevant laboratory and diagnostic tests and further information as it becomes available. Copies of all x-rays and other imaging related to the event must be sent to the Sponsor, as well as all discharge summaries should the participant have been hospitalised. For deaths, the Principal Investigator will supply the sponsor and the IRB/IEC with any additional requested information (e.g. death certificate, autopsy reports and medical reports).

Line listings of SAEs occurring during the study will be distributed to all sites by the Kirby Institute on a quarterly basis. Study treatment group will not be provided.

The investigator must also comply with all applicable ethical and regulatory requirement/s relating to the reporting of serious adverse events.

Any serious adverse event that is ongoing at the post-study follow-up visit must be followed until resolution or until the event stabilises (for those events that will not resolve).

11.3 Suspected Unexpected Serious Adverse Reaction (SUSAR)

A SUSAR is a serious adverse event which is both suspected as being related to the drug (i.e. has a reasonable suspected causal relationship and is unexpected) and where the nature and severity is not consistent with known information (e.g. the Investigator's Brochure for an unapproved investigational product or Product Information for an approved product) about the drug in question.

11.3.1 Reporting of SUSARs

The Project Team in collaboration with the Medical Officer will review and identify all serious events which fit the criteria of a SUSAR and require expedited reporting to relevant parties. The event will be designated as unexpected if it is not reported in the Investigator Brochure or Product Information or if the event is of greater frequency, specificity or severity.

The Sponsor must expedite the reporting of all suspected unexpected and certainly, probably, possibly, or of undetermined relationship to the study drug to all concerned investigators/institutions, IRB/IEC/s, and regulatory authorities within 7 days if it is life-threatening or fatal or within 15 days if not. Reports must comply with the applicable regulatory requirements and ICH Guideline for Clinical Safety Data Management: Definitions and Standards for Expedited Reporting.

Researchers must inform the IRB/IEC and regulatory authorities of all serious or unexpected AEs that occur during the study which may affect the conduct of the study or the safety of the participants and/or their willingness to continue participation in the study.

11.4 Serious Non-AIDS events (SNAEs) and AIDS events

SNAEs are defined as fatal and non-fatal diagnoses in the following categories (see Appendix 4 for details):

- Acute myocardial infarction
- Coronary artery disease requiring drug treatment
- Stroke
- Coronary revascularisation
- Congestive heart failure
- Deep vein thrombosis
- Peripheral arterial disease
- Pulmonary embolism
- End stage renal disease
- Decompensated liver disease
- Non-AIDS defining malignancy (except non-invasive basal cell carcinoma or squamous cell carcinoma)
- Diabetes mellitus

- AIDS events (CDC Category C 1993 Definition – see Appendix 3):
    - Candidiasis of bronchi, trachea, or lungs
    - Candidiasis, oesophageal
    - Cervical cancer, invasive
    - Coccidioidomycosis, disseminated or extrapulmonary
    - Cryptococcosis, extrapulmonary
    - Cryptosporidiosis, chronic intestinal (> 1 month's duration)
    - CMV disease (other than liver, spleen, or nodes)
    - CMV retinitis (with loss of vision)
    - Encephalopathy, HIV-related (including AIDS Dementia Complex)
    - Herpes simplex, chronic ulcers (> 1 month's duration); or bronchitis, pneumonitis, or esophagitis
    - Histoplasmosis, disseminated or extrapulmonary
    - Isosporiasis, chronic intestinal (> 1 month's duration)
    - Kaposi's sarcoma (mucocutaneous or visceral)
    - Lymphoma , Burkitt's (or equivalent term)
    - Lymphoma, primary, of brain
    - Mycobacterium avium complex or M. kansasii, disseminated or extrapulmonary
    - M. tuberculosis, any site (pulmonary or extrapulmonary)
    - Mycobacterium, other species or unidentified species, disseminated or extrapulmonary
    - Pneumocystis carinii (jiroveci) pneumonia
    - Pneumonia, recurrent bacterial (2 documented episodes within 1 year of each other following randomisation)
    - Progressive multifocal leukoencephalopathy
    - Salmonella septicaemia, recurrent (2 documented episodes within 1 year of each other following randomisation)
    - Toxoplasmosis of brain
    - Wasting syndrome due to HIV
    - Aspergillosis, invasive
    - Bartonellosis
    - Chagas disease (American trypanosomiasis) of the CNS
    - Herpes zoster, multi-dermatomal (≥10 lesions in a non-contiguous site)
    - Leishmaniasis, visceral (kala-azar)
    - Lymphoma, Hodgkin's
    - Lymphoma, non-Hodgkin's, all cell types
    - Microsporidiosis (> 1 month's duration)
    - Nocardiosis
    - Penicillium marneffii, disseminated
    - Pneumocystis carinii (jiroveci), extrapulmonary
    - Rhodococcus equi disease

11.4.1 Reporting of SNAEs and AIDS defining illnesses

All SNAEs and AIDS defining illnesses must be reported to the Kirby Institute as per SAE reporting outlined in section 11.2.1. Details of how to report these will be outlined in the MOOP.

11.5 Reporting of pregnancy

There are no clinical studies in the use of vorapaxar in pregnant women. Studies in rats and rabbits showed no embryo/foetal toxicities, malformations or maternal toxicities when exposed to high doses of vorapaxar during gestation.

As there is a paucity of data on voraxapar in pregnancy, sexually active women of childbearing potential must use an effective method of birth control during the course of the study, in a manner such that risk of pregnancy is minimised. Women will undergo a urine dipstick or serum pregnancy test at each visit (except week 1) and if found to be pregnant during follow-up should be managed in keeping with prevailing national or international guidelines. At a minimum, women must immediately cease study medication.

All pregnancies on study are subject to expedited reporting and therefore the serious event form will need to be completed and submitted to The Kirby Institute within 24 hours (one working day) of becoming aware of the pregnancy. In addition, it is requested that information from any pregnancy on study be recorded on the appropriate page of the eCRF. It is the responsibility of investigators or their designees to report any pregnancy in a subject/patient (spontaneously reported to them) which occurs during the study (from screening until the week 18 visit). All subjects/participants who become pregnant must be followed to the completion/termination of the pregnancy. If the pregnancy continues to term, the outcome (health of infant) must also be reported to The Kirby Institute.

It is requested that information from any pregnancy on study be recorded on the appropriate page of the electronic CRF. Anonymised data from these forms will then be transmitted by the Kirby Institute to the Antiretroviral Pregnancy Register, an international register making a systematic attempt to collect data on pregnancy, ART and outcomes. Submission of data to the registry is encouraged, but not mandated by the study and a participant may choose not to have their data submitted. The scientific conduct and analysis of the Registry are overseen by an Advisory Committee consisting of members from the Centers for Disease Control and Prevention (CDC), Food and Drug Administration (FDA), the National Institutes of Health (NIH) as well as the private sector (http://www.apregistry.com/).

11.6 Definition and reporting of an overdose

In previous studies, vorapaxar has been given in single doses up to 120mg and daily doses of 5mg for up to 4 weeks without identification of a specific risk or dose related adverse events. However, for the purposes of this study, an overdose of vorapaxar is defined as 3 doses (7.5mg) or more within 24 hours. Any overdose, whether or not associated with an adverse reaction, must be reported within 24 hours on the paper SAE form to the Kirby Institute and the participant monitored closely for signs and symptoms of adverse reactions and appropriate clinical care given

There is no known treatment to reverse the antiplatelet effect of vorapaxar. Dialysis or platelet infusion is not expected to be beneficial if bleeding occurs after an overdose. Monkey data suggest that platelet transfusions of sufficient quantity (a full pheresis pack or two) have the potential to transiently (a few hours) reverse the antiplatelet activity of vorapaxar. There is no standard test available to assess the risk of bleeding in case of an overdose.

11.7 Unblinding

The necessity to unblind the participant's randomisation prior to reporting Serious Events will be considered on a case-by-case basis by the Medical Officer, site Principal Investigator and the expertise of members of the

Protocol Steering Committee. Where unblinding is authorised by the Project Leader, it will be undertaken by a statistician. If the Project Leader does not authorise unblinding, the Serious Event reporting form should indicate that the study is blinded and that the participant may be on placebo or vorapaxar.

In case of emergency, the Principal Investigator should contact the Kirby Institute to request unblinding where it is essential to know what treatment the participant is on to decide on the medical interventions required. Access to the code break procedures must be available on a 24-hour basis.

At the conclusion of the study, after the clinical database is locked, treatment allocation information will be given to participating centres.

12.0 Packaging, labelling, storage and accountability of clinical trial supplies

12.1 Drug packaging, labelling and distribution

Study drug will be sent to nominated pharmacies at study sites in accordance with the random allocation, following receipt of orders from recognised study staff. A designated person at the pharmacy must receive investigational drug supplies. The designated person must check that the supplies are in good condition and are complete as per the shipping records. Investigational drugs must be stored in a secure location with limited access and according to the drug requirements and local regulations.

Further detailed information on the packaging, labelling and distribution of the study drug will be outlined in the MOOP and dealt with in detail during the site initiation process. Distribution and receipt of the study drugs will be at no cost to study sites.

12.2 Handling and dispensing of study drugs

Study drugs must only be dispensed according to the protocol and MOOP. It is the responsibility of the Investigator to ensure that study drug is only dispensed to study participants and only dispensed by suitably trained, authorised personnel according to local regulations at recognised hospital and clinic pharmacies.

Study drugs should only be dispensed on receipt of a prescription written by the Principal Investigator or designee at the site. This prescription must contain the unique participant identification number.
The participant must be instructed to take the study drug tablets whole and to store all medication safely out of sight and reach of children.

Once the participant has been randomised, a one month blinded supply of vorapaxar or placebo will be dispensed to the participant from clinical supplies stored at the study site. At each subsequent visit, participants will be required to return empty, partially used and unused study drug containers that will be retained at the site for later destruction at the approval of the Sponsor. Records must be kept of unreturned study drug and/or containers. No drugs will be returned to the Sponsor.

At each dispensing, participants should be counselled on adherence issues. All participants should be counselled regularly on the need for maintaining strict adherence with the allocated study regimens. The objective should be 100% adherence at all times during follow-up. The site Principal Investigator is responsible for assessing adherence with all aspects of the study including use of study drugs and attendance at protocol-mandated clinical visits and assessments.

The Investigator must be satisfied that the participant has returned or accounted for all unused study drug before additional medication is dispensed. If the number of encapsulated tablets recorded as used is substantially different from the number prescribed, the participant must be counselled on how study drugs should be taken. If such deviations persist, the Investigator may consider discontinuing the regimen for non-adherence. If this occurs, the participant must remain in follow-up and undergo the protocol-specified assessments and evaluations.

12.3 Study drug accountability records at investigational site(s)

It is the responsibility of the Principal Investigator to ensure that a current record of study drug disposition is maintained at each study site where they are inventoried and disposed. Records and/or logs must comply with applicable regulations and guidelines, and should include:

- Amount received from the sponsor and placed in storage area (temperature logs to be kept to document appropriate storage conditions)
- Label ID number or batch number
- Amount dispensed to and returned by each participant, including unique participant identifiers
- Non-study disposition (e.g. lost, wasted, broken)
- Amount destroyed at study site (with Sponsor authorisation), as applicable.
- Dates and initials of person responsible for each investigational product inventory entry/movement

The Kirby Institute will provide forms to facilitate inventory control. Please refer to the MOOP for further details.

12.4 Destruction of study drug

Study drugs will not be returned to the Kirby Institute for destruction. Instead, it will be destroyed at site after reconciliation has been conducted by the study monitor. For further details of destruction of study medications, please refer to the MOOP.

12.5 Post study drug supply

The Sponsor will not provide vorapaxar to study participants beyond the duration of the study.

13.0 Biological samples

13.1 Blood collection

It is important that the handling of blood samples is undertaken according to local guidelines and regulations for handling infectious substances. The blood tubes required to be used for each test should be as per local laboratory guidelines. Storage samples will be collected for d-dimer, IL-6 and Hs-CRP analysis at a central laboratory as well as other exploratory analyses. This includes plasma, serum and PBMC. The blood tubes required for storage samples will be outlined in the MOOP. These samples will be processed locally and then shipped to central laboratories for storage and analysis.

Any unused plasma, serum or PBMC samples (unused back up samples or if exploratory analyses are not conducted due to failure to reach the primary endpoint) will be kept for possible future HIV related research.

Ethics approval would need to be granted for any future HIV research on these samples prior to these samples being released.

The following details can be found in the laboratory MOOP:

- Types and quantities of specimens
- Collection schedule
- Methods for processing laboratory samples prior to analysis
- Shipping and storage

Only the laboratory supplies as described in the clinical trial agreement with sites are to be provided by the Sponsor. It is strongly recommended that the blood is collected on the date of the actual study visit. However, if this cannot occur for some particular reason, a blood sample taken within 2-3 days of the actual visit date is acceptable. However, all blood samples for eligibility purposes must be taken at the screening visit.

13.2 Labelling of blood collection tubes

Blood collection tubes should be labelled accurately and legibly as outlined in the MOOP. The Sponsor can provide the site with specimen labels if needed. These labels are only to be used on the blood tubes to be sent to the local laboratory, not to be placed on the aliquot tubes for frozen storage. Aliquot tubes for storage must only be labelled with the participant's identification number.

13.3 Transportation of samples

It is important that during the transportation of blood samples precaution is taken according to local guidelines and regulations for handling infectious substances.

Sites will be required to set up the procedures for transporting the blood tubes to the local laboratory. It is important that the samples arrive at the laboratory within 3 hours of blood collection (this time frame is determined by need to process the plasma sample for d-dimer within 4 hours of collection).

It is the responsibility of the Principal Investigator at each site to ensure that all site staff handling, packaging, and/or shipping biological samples understand and comply with International Air Transport Association (IATA) regulations relating to the handling and shipping of hazardous goods and/or diagnostic specimens. Methods for packaging and shipping biological samples are detailed in the laboratory MOOP.

13.4 Storage of samples

Plasma, serum and PBMC samples will be collected and processed at the local laboratory. The samples will be stored in the interim at local laboratories and then sent for central storage at St Vincent's Centre for Applied Medical Research laboratory (AMR) in Sydney at regular intervals throughout the study. Transport to AMR in Sydney will be organised by The Kirby Institute. The cost of processing and storage of bloods will be provided to the sites as per the clinical trial agreement. For more detailed information on the types of tubes and processing requirements please refer to the Manual of Operations.

13.5 Processing of samples

All blood samples for routine clinical care and safety monitoring will be analysed at the local laboratory. Analysis of d-dimer, IL-6 and Hs-CRP will be performed centrally at LEIDOS Biomedical Research Inc. in the USA on frozen plasma samples from each participant.

It is important that the handling of blood samples is undertaken according to local guidelines and regulations for handling infectious substances. The investigator may be contacted should the technical condition of the sample, absence of information or inconsistencies on the request form be such that the samples cannot be processed. Demographic errors (i.e. incomplete or inconsistent participant information) will be called through to the site and a faxed confirmation of correct information requested. Where such errors are noted after a report has been sent to the site, then a second corrected report will be reissued by the local laboratory.

13.6 Reporting of results

The blood results from routine clinical care and safety monitoring will be reported to the site as per local standard procedure. It is important that once these results are received they are entered into the eCRF and a hardcopy of the results are kept in the medical notes. If results are received electronically, the electronic format is adequate for source data verification.

13.7 Plasma d-dimer determination

Plasma d-dimer will be measured at the local laboratory for assessment of eligibility. Plasma samples at weeks 0, 1, 4, 8, 12 and 18 will be stored and sent to a central laboratory (LEIDOS Biomedical Research Inc. in the USA) for central assessment of d-dimer, IL-6 and Hs-CRP at the end of the study. These central results will be used for the analysis of the study. Results cannot be provided in real time to individual patients. Results will be provided at completion of the project.

14.0 Data collection, source documents and record retention

14.1 Records and reports

The Principal Investigator or designee is responsible for preparing and maintaining adequate and accurate case histories designed to record all observations and other data pertinent to the investigation on each individual treated with the investigational product. Data reported on the CRF that are derived from source documents must be consistent with the source documents or the discrepancies must be explained.

14.2 Source documents

Source documents include all recordings of observations or notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the study. Source documents include, but are not limited to, participant medical records, laboratory reports, ECG tracings, X-rays, radiologist reports, biopsy reports, ultrasound photographs, participant progress notes, pharmacy records and any other similar reports or records of procedures performed in accordance with the protocol. It is not acceptable for the CRF to be the only record of the participant's study participation and progress as these must also be recorded in the participant medical record. This is to ensure that anyone accessing the participant's medical record has adequate knowledge of their participation in a clinical study.

Any document that acts as a source document (the point of the initial recording of a piece of data) should be signed and dated by the person recording or reviewing the data for issues of medical significance (for example the review of laboratory reports). Persons signing the source documents must be listed, on the appropriate study documentation (site delegation log), as a site staff member.

14.3 Submission of data

Data will be collected for this study using an Electronic Data Capture system using a web-enabled password protected platform. Following each participant visit the designated site staff will complete the visit specific eCRF. The Principal Investigator is responsible for ensuring the data collected are complete, accurate and recorded in a timely manner. The confidentiality of records that could identify participants must be protected, respecting the privacy and confidentiality rules in accordance with the applicable regulatory requirement(s).

Once all of the information is received the eCRF will be completed. Sponsor staff will then monitor the data for completeness and accuracy. Any discrepancies either manual or automatic will be notified to the site staff for clarification. Corrections to eCRFs will only be possible by study personnel with sufficient authorisation to make changes. All changes will record time, date, computer ID and the name of the authorised person's access code.

14.4 Records retention and archiving

The Investigator must retain investigational product disposition records, copies of CRFs (or electronic files) and source documents for the maximum period required by applicable regulations and guidelines, or Institution procedures, or for 15 years, whichever is longer. The Investigator must contact the Sponsor prior to destroying any records associated with the study.

If a Principal Investigator withdraws from the study (e.g. relocation, retirement), the records will be transferred to a mutually agreed-upon designee or site (i.e. another Investigator or IRB). Notice of such transfer will be given in writing to the Sponsor.

14.5 Study monitoring

Representatives of the Kirby Institute or NIAID must be allowed to visit all study site locations periodically to assess the data, quality and study integrity. On site, Kirby Institute or NIAID representatives will review study records to directly compare them with source documents, discuss the conduct of the study with the Principal Investigator or their designee and verify that the facilities remain acceptable.

Monitoring visits will be scheduled in advance and with sufficient warning to allow arrangements of diaries and personnel as appropriate. The number of visits shall depend upon recruitment rate; however, the monitor shall conduct a minimum of two source data verification visits at each site during the study. These shall occur shortly after the study entry of the first participant(s) and at the end of the study once all study visits have been completed.

The Principal Investigator is responsible for retaining all essential documents listed in ICH Good Clinical Practice (GCP) guidelines. These must be organised in a comprehensive filing system that is accessible to study monitors and other relevant personnel.

14.6 Auditing

The study may be subject to audit by the Kirby Institute, NIAID, Merck, the ethics committee, relevant regulatory agencies or the relevant government authorities. Under such circumstances, the investigator must agree to allow access to study documents and relevant hospital/clinic records. Audit reports will be kept confidential between the site and the Sponsor.

The Principal Investigator must notify the Sponsor promptly of any inspections scheduled by regulatory authorities and forward copies of inspection reports to the Sponsor.

15.0 Ethics committee/regulatory approval and informed consent

15.1 Ethical conduct of the study

This study shall be conducted in accordance with the ethical principles laid out in the National Statement on Ethical Conduct in Research Involving Humans, the Declaration of Helsinki (most current version issued, available at www.wma.net) and will be consistent with GCP, and applicable regulatory requirements.

The rights, safety and wellbeing of the study participants are the most important considerations and should prevail over interests of science and society. All personnel involved in conducting this study will be qualified by education, training, and experience to perform their respective task(s).
The Sponsor is responsible for obtaining regulatory approval for the study. Before study initiation, the Investigator must have written and dated approval/favourable opinion from the IRB/IEC and local regulatory authorities for the protocol, consent form, participant recruitment materials/process (e.g. advertisements) and any other written information to be provided to participants. The approval must clearly identify all documents approved by the IRB/EC and regulatory authorities including version number and dates of the protocol and participant information/informed consent form. A copy of the approval must be sent to the study Sponsor.

The Principal Investigator must comply with all IRB/EC, and where relevant regulatory authorities, reporting requirements for all serious or unexpected AEs, annual updates and end of study reports and must agree to abide by any IRB/EC conditions of approval. Researchers must inform the IRB/IEC, and where relevant regulatory authorities, as soon as possible of any new information from other published or unpublished studies which may have an impact on the continued ethical acceptability of the study or which may indicate the need for amendments to the study protocol. In addition, the Principal Investigator should provide any updates or other information required by relevant parties in accordance with any local regulatory requirements or institution procedures.

This study will not use the services of study personnel where sanctions have been invoked or where there has been scientific misconduct or fraud (e.g. loss of medical licensure, debarment).
Monitoring systems with procedures to maximise the quality of every aspect of the study will be implemented.

15.2 Compliance with the protocol and protocol revisions

The study shall be conducted as described in this approved protocol. The protocol and any amendments and the participant information and consent will receive IRB/IEC approval prior to initiation of the study. This

study will be reviewed by the relevant local ethics committees and regulatory authorities, in accordance with current local guidelines. The Sponsor will assist in the process of approval as required by each individual site.

The Principal Investigator should not implement any deviation or change to the protocol without prior review and documented approval/favourable opinion from the IRB/IEC of an Amendment, except where necessary to eliminate an immediate hazard(s) to study participants. Any significant deviation must be documented and notified to the Sponsor.
If a deviation or change to a protocol is implemented to eliminate an immediate hazard(s) prior to obtaining IRB/IEC approval/favourable opinion, as soon as possible the deviation or change will be submitted to:

- IRB/IEC for review and approval/favourable opinion;
- The Sponsor;
- Regulatory Authority(ies), if required by local regulations.

Documentation of approval signed by the chairperson or designee of the IRB/IEC must be sent to the Sponsor along with other required documentation.

If the revision is an Administrative Letter, the Principal Investigator must inform their IRB/IEC.
If an Amendment substantially alters the study design or increases the potential risk to the participant: (1) the consent form must be revised and submitted to the IRB/IEC for review and approval/favourable opinion; (2) the revised approved form must be used to obtain consent from participants currently enrolled in the study if they are affected by the Amendment; and (3) the new approved form must be used to obtain consent from new participants prior to enrolment.

Preparation of the consent form is the responsibility of the Principal Investigator and must include all elements required by ICH-GCP and applicable regulatory requirements, and must adhere to GCP and to the ethical principles that have their origin in the Declaration of Helsinki. The consent form must also include a statement that the sponsor, Merck, the ethics committee, and regulatory authorities will have direct access to participant study records (See Appendix 5 for participant information and consent form template).

Prior to beginning the study, the Principal Investigator must have the IRB/IEC's written approval/favourable opinion of the written informed consent form and any other information to be provided to the participants.

The Principal Investigator should endeavour to provide the participant or legally authorised representative with a copy of the consent form and written information about the study in the language in which the participant is most proficient. The language must be non-technical and easily understood. The Principal Investigator should allow time necessary for participant or participant's legally authorised representative to inquire about the details of the study. The Principal Investigator must ensure that participants or their legally authorised representative are clearly and fully informed about the purpose, potential risks and other critical issues regarding clinical trials in which they volunteer to participate.

Freely given written informed consent must be obtained from every participant or his or her legally authorised representative prior to any protocol-specific procedures being conducted on that participant. Consent must be documented by the participant's dated signature on a consent form along with the dated signature of the person conducting the consent discussion.

If the participant is illiterate, an impartial witness should be present during the entire consent discussion. Once the discussion is complete, the participant must sign and date the informed consent form, if capable.

The impartial witness must also sign and date the informed consent form along with the person who conducted the consent discussion.

Should an ethics committee-approved informed consent form not be available in a participant's most proficient language, then a translator should be sought. This translator should act as a witness to the informed consent process and be asked to sign the informed consent form accordingly.
If the participant is legally incompetent (i.e. mentally incapacitated) the written consent of a parent, guardian or legally authorised representative must be obtained.
Imprisonment or the compulsory detention for treatment of either a psychiatric or physical (e.g. infectious disease) illness precludes enrolment in clinical trials.
When a participant may be in a dependent relationship with the investigator, a well-informed physician who is not engaged in the study and is completely independent of the relationship between the participant and investigator should obtain the participant's informed consent. This issue will be addressed within the site training process.

The participant or legally authorised representative should receive a copy of the signed and dated informed consent and any other written information provided prior to the participant's participation in the study.

15.4 Updates to the consent form

The informed consent and any other information provided to participants or the participant's legally authorised representative, should be revised whenever important new information becomes available that is relevant to the participant's consent. This information should receive IRB/IEC approval/favourable opinion prior to use, except if the safety of the participant is compromised. The Principal Investigator, or a person designated by the Principal Investigator, should fully inform the participant or the participant's legally authorised representative of all pertinent aspects of the study and of any new information relevant to the participant's willingness to continue participation in the study. This communication should be documented. During participation in the study, any updates to the consent form and/or the written information will be provided to the participant.

16.0 Confidentiality of data

16.1 Confidentiality of participant records

By signing the Clinical Trial Agreement, the site Principal Investigator agrees that the sponsor, IRB/EC or regulatory authorities may consult and/or copy study documents to verify information in the case report form. By signing the consent form the participant agrees to these processes.

Participant confidentiality will be maintained at all times and no documents containing the participant's name or other identifying information will be collected by the sponsor. It may be necessary for the sponsor's representatives, the IRB/EC and regulatory authority representatives to have direct access to the participant's medical records. If study documents need to be photocopied during the process of verifying case report form data, the participant will be identified by a unique code only; full names and other identifying information will be masked.

16.2 Confidentiality of study data

By signing the Clinical Trial Agreement, the site Principal Investigator affirms to the sponsor that information provided to them by the sponsor will be maintained in confidence and divulged only as necessary to the ethics committee and institution employees directly involved in the study. Both ethics committee members and employees must also understand the confidentiality requirements for any information divulged to them. The data generated by this study will be considered confidential, except where it is included in a publication as agreed in the publication policy of this protocol.

17.0 Governance

This international research protocol is funded by The National Health Medical & Research Council, Australia. The study intervention/clinical trial supplies will be provided by Merck. The study is sponsored by the University of New South Wales (UNSW) and coordinated through the Kirby Institute for infection and immunity in society. The Kirby Institute has established governance and implementation structures which use resources efficiently to deliver program objectives on schedule.

17.1 Protocol Steering Committee (PSC)

There will be a single PSC chaired by Professor Sean Emery. This group will comprise a representative from each participating site, representatives from UNSW and NIAID project teams and the project biostatistician. A representative from Merck will also be invited to join the PSC. The PSC will seek the expertise of other key opinion leaders as necessary. The PSC will be the primary management entity for the collaborative study group. This group will meet by teleconference, arranged as required and at least twice per year during the study follow up period. Decisions in this group will be reached by consensus among the designated membership. Routinely the views of other stakeholders will be sought at meetings of the PSC and this will allow others to attend meetings. The PSC, comprised of members from a range of internal and external stakeholders will guide the design, implementation and conduct of the study.

17.2 Project Team

Day-to-day management of the protocol will be undertaken by a dedicated project team based at The Kirby Institute at UNSW and NIAID and supported as required by contract service organisations. The Project Team is accountable to the PSC.

For contact details on the clinical trial sites, laboratories and pharmacies please refer to the MOOP.

18.0 Data Safety and Monitoring Board (DSMB)

The DSMB will be accountable to the PSC and will undertake independent review of protocol-specified and ad hoc interim analyses if required. The DSMB will be composed of individuals neither directly associated with the study nor employees of any of the organisations responsible for the conduct of the research. The study biostatistician will be an ex officio member of the DSMB. The primary focus of the reviews undertaken by the DSMB will be safety. The first scheduled review will take place after 20 patients have completed 6 weeks of treatment with further reviews scheduled every 8 weeks thereafter. For ad hoc reviews an interim analysis would be prompted when four (4) BARC type 2 events or one (1) BARC type 3 event are reported. During the ad hoc review and until the PSC has received and acted upon a DSMB recommendation, patient recruitment will be paused but randomised patients will continue study treatment. The terms of reference and operating

guidelines of the DSMB will be drafted by the study biostatistician (as documents separate to the Protocol) and finalised in collaboration with the DSMB prior to the commencement of the study.

19.0 Financing and insurance

The Principal Investigator should provide details of the study budget to the IRB/IEC, as required by the individual committee. In addition, any participant payments or reimbursement of expenses for participation in the study must be clearly stated in the participant information and consent form and must be approved by the IRB/IEC.

19.1 Indemnity and compensation

Indemnification for site personnel, investigators and institutions will be provided as required in keeping with the provisions as determined by the Medicines Australia guidelines through the UNSW for Australian sites. Details of this provision will be documented in separate agreements.

No-fault-compensation is available to study participants who experience injury as a result of their participation in this study. Details of the method of compensation will be provided in separate agreements between institutions.

20.0 Quality Control (QC) and Quality Assurance (QA)

By signing this protocol (Appendix 6), the sponsor agrees to be responsible for implementing and maintaining quality control and quality assurance systems with written standard operating procedures to ensure the study is conducted and data are generated, documented and reported in compliance with the protocol, Good Clinical Practice standards and all applicable local laws and regulations relating to the conduct of a clinical study.

21.0 Publication Policy

There will be one final written manuscript arising from the ADVICE protocol to describe the primary results as defined in the protocol. In the interests of collegiality and recognising that completion of this study will have resulted from the contribution of many people around the world the masthead authorship for this manuscript will be “The ADVICE Study Group”. The PSC will compose a writing committee for this primary manuscript who will be identified as such in an appendix. In addition, one person from each investigational site will be listed in a separate appendix as being part of the ADVICE Study Group. The PSC will determine if there is a need for additional appendices in which to identify others who have contributed in a significant way to the design AND conduct AND reporting of resultant study data. If the journal will not accept group authorship the writing committee will be listed as authors and be completed with the phrase ‘on behalf of the ADVICE Study Group’.

Additional manuscripts that are expected to report on the findings of any subsequent substudies should have named investigators and be completed with the phrase ‘on behalf of the ADVICE Study Group’. In these circumstances an appendix should contain the names of the PSC.

All proposed manuscripts should be submitted to the PSC 45 days before they are to be submitted to a journal for peer review.

Conference presentations should identify an authorship group consistent with those who have contributed to the data to be reported. All proposed conference presentations should be submitted to the PSC at least 20 days before submission of an abstract.

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23.0 Abbreviations List

ADVICE	Attenuation of d-dimer using vorapaxar to target inflammatory and coagulation endpoints	LFT	Liver function test
AE	Adverse event	MI	Myocardial infarction
AIDS	Acquired immune deficiency syndrome	MOOP	Manual of operations
ALP	Alkaline phosphatase	NIAID	National Institute of Allergy and Infectious Diseases
ALT	Alanine amino transferase	NHI	National Institutes of Health
ANC	Absolute neutrophil count	NNRTI	Non-nucleoside reverse transcriptase inhibitor
ART	Antiretroviral therapy	NRTI	Nucleoside reverse transcriptase inhibitor
AST	Aspartate amino transferase	NSAID	Non-steroidal anti-inflammatory drug
BARC	Bleeding Academic Research Consortium	PAR-1	Protease Activated Receptor-1
BID	Twice daily	PBMC	Peripheral blood mononuclear cell
CABG	Coronary artery bypass graft	PI	Protease inhibitor
CART	Combined antiretroviral therapy	PID	Patient Identification
CDC	Centres for disease control	QA	Quality assurance
CI	Confidence interval	QC	Quality control
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration	Qd	Once daily
CRF/eCRF	Case report form/electronic case report form	PI/r	Ritonavir-boosted protease inhibitor
CVD	Cardiovascular disease	PSC	Protocol Steering Committee
DAIDS	Division of AIDS	RNA	Ribonucleic acid
DNA	Deoxyribonucleic acid	SAE	Serious adverse event
DSMB	Data safety monitoring board	SD	Standard deviation
EACS	European AIDS Clinical Society	SNAE	Serious non-AIDS defining event
ECG	Electrocardiograph	STEAL	Simplification of antiretroviral therapy with tenofovir-emtricitabine or abacavir-lamivudine
FDA	Food and Drug Administration	SUSAR	Suspected unexpected serious adverse reaction
GCP	Good Clinical Practice	TIA	Transient ischaemic attack
GFR	Glomerular Filtration Rate		
GUSTO	Global utilization of streptokinase and tissue plasminogen activator for occluded arteries	TRACER	Thrombin receptor antagonist for clinical event reduction in acute coronary syndrome
HIV	Human Immunodeficiency Virus	TRA 2°P TIMI	Thrombin receptor antagonist in secondary prevention of atherothrombotic ischemic events study
Hs-CRP	High sensitivity c reative protein	ULN	Upper limit of normal
IATA	International Air Transport Association	UNSW	University of New South Wales

ICH	International Conference on Harmonisation	USA	United States of America
ID	Identification		
IEC	Institutional ethics committee		
IRB	Institutional review board		

Appendix 1: Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Paediatric Adverse Events (Version 2.0, November 2014)

General Instructions

The DAIDS Table provides descriptive terminology which can be utilized for Adverse Event (AE) reporting. A grading (severity) scale is provided for each AE term.

In the classification of AEs, 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.

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:

The functional table below should be used to grade the severity of an AE that is not specifically identified in the grading table. In addition, all deaths related to an AE are to be classified as grade 5.

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Clinical adverse event **NOT** identified elsewhere in the grading table	Mild symptoms causing no or minimal interference with usual social & functional activities with intervention not indicated	Moderate symptoms causing greater than minimal interference with usual social & functional activities with intervention indicated	Severe symptoms causing inability to perform usual social & functional activities with intervention or hospitalization indicated	Potentially life-threatening symptoms causing inability to perform basic self-care functions with intervention indicated to prevent permanent impairment, persistent disability, or death

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.

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, "Magnesium, Low" has a grade 1 range of 1.2 to < 1.4 mEq/L, while a particular laboratory's normal range for magnesium may be 1.3 to 2.8 mEq/L. If a study participant's magnesium laboratory value is 1.3 mEq/L, the laboratory value should be graded as grade 1.

Definitions of terms used in the Table:

AE	Adverse event; Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medical treatment or procedure regardless of whether it is considered related to the medical treatment or procedure.
ALT (SGPT)	Alanine aminotransferase (serum glutamic pyruvic transaminase)
ANC	Absolute neutrophil count
AST (SGOT) transaminase)	Aspartate aminotransferase (serum glutamic-oxaloacetic
AV	Atrioventricular
Basic Self-care Functions	Adult Activities such as bathing, dressing, toileting, transfer or movement, continence, and feeding. Young Children Activities that are age and culturally appropriate, such as feeding one's self with culturally appropriate eating implements.
BMI z-score	Body mass index z- score; A body reference norm. Specifically, the number of standard deviations a participant's BMI differs from the average BMI for their age, sex, and ethnicity.
BMD t-score	Bone mineral density t-score; The number of standard deviations above or below the mean bone mineral density of a healthy 30 year old adult of the same sex and ethnicity as the participant.
BMD z-score	Bone mineral density z-score; The number of standard deviations a participant's BMD differs from the average BMD for their age, sex, and ethnicity.
BPAP	Bilevel positive airway pressure; A mode used during noninvasive positive pressure ventilation.

Chemical Pregnancy	A pregnancy in which a positive pregnancy test is followed by a negative pregnancy test without evidence of a clinical pregnancy loss.
CNS	Central nervous system
CPAP	Continuous positive airway pressure
DAERS	DAIDS Adverse Experience Reporting System; An internet-based system developed for clinical research sites to report Expedited Adverse Events (EAEs) to DAIDS. It facilitates timely EAE report submission and serves as a centralized location for accessing and processing EAE information for reporting purposes.
Disability	A substantial disruption of a person's ability to conduct normal life functions.
ECG	Electrocardiogram
eGFR	Estimated glomerular filtration rate
Hospitalization	Does not include the following hospital admissions: under 24 hours, unrelated to an adverse event (e.g., for labor and delivery, cosmetic surgery, social or administrative for temporary placement [for lack of a place to sleep]), protocol-specified, and for diagnosis or therapy of a condition that existed before the receipt of a study agent and which has not increased in severity or frequency.
INR	International normalized ratio
Intervention	Medical, surgical, or other procedures recommended or provided by a healthcare professional for the treatment of an adverse event.
IV	Intravenous
IVIG	Intravenous immune globulin
LDL	Low density lipoprotein
LLN	Lower limit of normal
Life-threatening AE	Any adverse event that places the participant, in the view of the investigator, at immediate risk of death from the reaction when it occurred (i.e., it does not include a reaction that would have caused death if it had occurred in a more severe form).
NA	Not applicable
Participant ID	The identification number assigned to a study participant which is used to track study-related documentation, including any reported AEs.
PR Interval	The interval between the beginning of the P wave and the beginning of the QRS complex of an electrocardiogram that represents the time between the beginning of the contraction of the atria and the beginning of the contraction of the ventricles.
PT	Prothrombin time
PTT	Partial thromboplastin time

QTc Interval	The measure of time between the onset of ventricular depolarization and completion of ventricular repolarization corrected for ventricular rate.
RBC	Red blood cell
SI	Standard international unit
ULN	Upper limit of normal
Usual Social & Functional Activities	Activities which adults and children perform on a routine basis and those which are part of regular activities of daily living, for example: <u>Adults</u> Adaptive tasks and desirable activities, such as going to work, shopping, cooking, use of transportation, or pursuing a hobby. <u>Young Children</u> Activities that are age and culturally appropriate, such as social interactions, play activities, or learning tasks.
WBC	White blood cell
WHO	World Health Organization
WNL	Within normal limits

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Arrhythmia (by ECG or physical examination) *Specify type, if applicable*	No symptoms AND No intervention indicated	No symptoms AND Non-urgent intervention indicated	Non-life-threatening symptoms AND Non-urgent intervention indicated	Life-threatening arrhythmia OR Urgent intervention indicated
Blood Pressure Abnormalities[1] ***Hypertension*** *(with the lowest reading taken after repeat testing during a visit)* *≥ 18 years of age*	140 to < 160 mmHg systolic OR 90 to < 100 mmHg diastolic	≥ 160 to < 180 mmHg systolic OR ≥ 100 to < 110 mmHg diastolic	≥ 180 mmHg systolic OR ≥ 110 mmHg diastolic	Life-threatening consequences in a participant not previously diagnosed with hypertension (e.g., malignant hypertension) OR Hospitalization indicated
< 18 years of age	> 120/80 mmHg	≥ 95th to < 99th percentile + 5 mmHg adjusted for age, height, and gender (systolic and/or diastolic)	≥ 99th percentile + 5 mmHg adjusted for age, height, and gender (systolic and/or diastolic)	Life-threatening consequences in a participant not previously diagnosed with hypertension (e.g., malignant hypertension) OR Hospitalization indicated
Hypotension	No symptoms	Symptoms corrected with oral fluid replacement	Symptoms AND IV fluids indicated	Shock requiring use of vasopressors or mechanical assistance to maintain blood pressure
Cardiac Ischemia or Infarction *Report only one*	NA	NA	New symptoms with ischemia (stable angina) OR New testing consistent with ischemia	Unstable angina OR Acute myocardial infarction
Heart Failure	No symptoms AND Laboratory or cardiac imaging abnormalities	Symptoms with mild to moderate activity or exertion	Symptoms at rest or with minimal activity or exertion (e.g., hypoxemia) OR Intervention indicated (e.g., oxygen)	Life-threatening consequences OR Urgent intervention indicated (e.g., vasoactive medications, ventricular assist device, heart transplant)
Hemorrhage (with significant acute blood loss)	NA	Symptoms AND No transfusion indicated	Symptoms AND Transfusion of ≤ 2 units packed RBCs indicated	Life-threatening hypotension OR Transfusion of > 2 units packed RBCs (for children, packed RBCs > 10 cc/kg) indicated

[1] Blood pressure norms for children < 18 years of age can be found in: Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents. *Pediatrics* 2011;128;S213; originally published online November 14, 2011; DOI: 10.1542/peds.2009- 2107C.

Cardiovascular

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Prolonged PR Interval or AV Block *Report only one* *> 16 years of age*	PR interval 0.21 to < 0.25 seconds	PR interval ≥ 0.25 seconds OR Type I 2nd degree AV block	Type II 2nd degree AV block OR Ventricular pause ≥ 3.0 seconds	Complete AV block
≤ 16 years of age	1st degree AV block (PR interval > normal for age and rate)	Type I 2nd degree AV block	Type II 2nd degree AV block OR Ventricular pause ≥ 3.0 seconds	Complete AV block
Prolonged QTc Interval[2]	0.45 to 0.47 seconds	> 0.47 to 0.50 seconds	> 0.50 seconds OR ≥ 0.06 seconds above baseline	Life-threatening consequences (e.g., Torsade de pointes, other associated serious ventricular dysrhythmia)
Thrombosis or Embolism *Report only one*	NA	Symptoms AND No intervention indicated	Symptoms AND Intervention indicated	Life-threatening embolic event (e.g., pulmonary embolism, thrombus)

[2] As per Bazett's formula

Dermatologic

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Alopecia (scalp only)	Detectable by study participant, caregiver, or physician AND Causing no or minimal interference with usual social & functional activities	Obvious on visual inspection AND Causing greater than minimal interference with usual social & functional activities	NA	NA
Bruising	Localized to one area	Localized to more than one area	Generalized	NA
Cellulitis	NA	Non-parenteral treatment indicated (e.g., oral antibiotics, antifungals, antivirals)	IV treatment indicated (e.g., IV antibiotics, antifungals, antivirals)	Life-threatening consequences (e.g., sepsis, tissue necrosis)
Hyperpigmentation	Slight or localized causing no or minimal interference with usual social & functional activities	Marked or generalized causing greater than minimal interference with usual social & functional activities	NA	NA
Hypopigmentation	Slight or localized causing no or minimal interference with usual social & functional activities	Marked or generalized causing greater than minimal interference with usual social & functional activities	NA	NA
Petechiae	Localized to one area	Localized to more than one area	Generalized	NA
Pruritus[3] (without skin lesions)	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
Rash *Specify type, if applicable*	Localized rash	Diffuse rash OR Target lesions	Diffuse rash AND Vesicles or limited number of bullae or superficial ulcerations of mucous membrane limited to one site	Extensive or generalized bullous lesions OR Ulceration of mucous membrane involving two or more distinct mucosal sites OR Stevens-Johnson syndrome OR Toxic epidermal necrolysis

Endocrine and Metabolic

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Diabetes Mellitus	Controlled without medication	Controlled with medication OR Modification of current medication regimen	Uncontrolled despite treatment modification OR Hospitalization for immediate glucose control indicated	Life-threatening consequences (e.g., ketoacidosis, hyperosmolar non-ketotic coma, end organ failure)
Gynecomastia	Detectable by study participant, caregiver, or physician AND Causing no or minimal interference with usual social & functional activities	Obvious on visual inspection AND Causing pain with greater than minimal interference with usual social & functional activities	Disfiguring changes AND Symptoms requiring intervention or causing inability to perform usual social & functional activities	NA
Hyperthyroidism	No symptoms AND Abnormal laboratory value	Symptoms 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	No symptoms AND Abnormal laboratory value	Symptoms 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[4]	Detectable by study participant, caregiver, or physician AND Causing no or minimal interference with usual social & functional activities	Obvious on visual inspection AND Causing greater than minimal interference with usual social & functional activities	Disfiguring changes	NA
Lipohypertrophy[5]	Detectable by study participant, caregiver, or physician AND Causing no or minimal interference with usual social & functional activities	Obvious on visual inspection AND Causing greater than minimal interference with usual social & functional activities	Disfiguring changes	NA

[4] Definition: A disorder characterized by fat loss in the face, extremities, and buttocks.
[5] Definition: A disorder characterized by abnormal fat accumulation on the back of the neck, breasts, and abdomen.

Gastrointestinal

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
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, total parenteral nutrition)
Ascites	No symptoms	Symptoms AND Intervention indicated (e.g., diuretics, therapeutic paracentesis)	Symptoms recur or persist despite intervention	Life-threatening consequences
Bloating or Distension *Report only one*	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
Cholecystitis	NA	Symptoms AND Medical intervention indicated	Radiologic, endoscopic, or operative intervention indicated	Life-threatening consequences (e.g., sepsis, 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 *≥ 1 year of age*	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 to 6 stools over baseline per 24-hour period	Increase of ≥ 7 stools per 24-hour period OR IV fluid replacement indicated	Life-threatening consequences (e.g., hypotensive shock)
< 1 year of age	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	Life-threatening consequences (e.g., liquid stools resulting in severe dehydration, hypotensive shock)
Dysphagia or Odynophagia *Report only one and specify location*	Symptoms but able to eat usual diet	Symptoms causing altered dietary intake with no intervention indicated	Symptoms causing severely altered dietary intake with intervention indicated	Life-threatening reduction in oral intake
Gastrointestinal Bleeding	Not requiring intervention other than iron supplement	Endoscopic intervention indicated	Transfusion indicated	Life-threatening consequences (e.g., hypotensive shock)

[3] For pruritus associated with injections or infusions, see the *Site Reactions to Injections and Infusions* section (page 23).

Gastrointestinal

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Mucositis or Stomatitis *Report only one and specify location*	Mucosal erythema	Patchy pseudomembranes or ulcerations	Confluent pseudomembranes or ulcerations OR Mucosal bleeding with minor trauma	Life-threatening consequences (e.g., aspiration, choking) OR Tissue necrosis OR Diffuse spontaneous mucosal bleeding
Nausea	Transient (< 24 hours) or intermittent AND No or minimal interference with oral intake	Persistent nausea resulting in decreased oral intake for 24 to 48 hours	Persistent nausea resulting in minimal oral intake for > 48 hours OR Rehydration indicated (e.g., IV fluids)	Life-threatening consequences (e.g., hypotensive shock)
Pancreatitis	NA	Symptoms with hospitalization not indicated	Symptoms with hospitalization indicated	Life-threatening consequences (e.g., circulatory failure, hemorrhage, sepsis)
Perforation (colon or rectum)	NA	NA	Intervention indicated	Life-threatening consequences
Proctitis	Rectal discomfort with 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)
Rectal Discharge	Visible discharge	Discharge requiring the use of pads	NA	NA
Vomiting	Transient or intermittent AND No or minimal interference with oral intake	Frequent episodes 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)

Musculoskeletal

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Arthralgia	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	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
Myalgia (generalized)	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
Osteonecrosis	NA	No symptoms but with radiographic findings AND No operative intervention indicated	Bone pain with radiographic findings OR Operative intervention indicated	Disabling bone pain with radiographic findings causing inability to perform basic self-care functions
Osteopenia[6] *≥ 30 years of age*	BMD t-score -2.5 to -1	NA	NA	NA
< 30 years of age	BMD z-score -2 to -1	NA	NA	NA
Osteoporosis[6] *≥ 30 years of age*	NA	BMD t-score < -2.5	Pathologic fracture (e.g., compression fracture causing loss of vertebral height)	Pathologic fracture causing life-threatening consequences
< 30 years of age	NA	BMD z-score < -2	Pathologic fracture (e.g., compression fracture causing loss of vertebral height)	Pathologic fracture causing life-threatening consequences

[6] BMD t and z scores can be found in: Kanis JA on behalf of the World Health Organization Scientific Group (2007). Assessment of osteoporosis at the primary health-care level. Technical Report. World Health Organization Collaborating Centre for Metabolic Bone Diseases, University of Sheffield, UK. 2007: Printed by the University of Sheffield.

Neurologic

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Acute CNS Ischemia	NA	NA	Transient ischemic attack	Cerebral vascular accident (e.g., stroke with neurological deficit)
Altered Mental Status (for Dementia, see *Cognitive, Behavioral, or Attentional Disturbance* below)	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	Symptoms causing no or minimal interference with usual social & functional activities OR No symptoms with ataxia detected on examination	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	Disabling symptoms causing inability to perform basic self-care functions
Cognitive, Behavioral, or Attentional Disturbance (includes dementia and attention deficit disorder) *Specify type, if applicable*	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
Developmental Delay *< 18 years of age* *Specify type, if applicable*	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 OR Headache with significant impairment of alertness or other neurologic function

Neurologic

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Neuromuscular Weakness (includes myopathy and neuropathy) *Specify type, if applicable*	Minimal muscle weakness causing no or minimal interference with usual social & functional activities OR No symptoms with decreased strength on examination	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
Neurosensory Alteration (includes paresthesia and painful neuropathy) *Specify type, if applicable*	Minimal paresthesia causing no or minimal interference with usual social & functional activities OR No symptoms with sensory alteration on examination	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
Seizures ***New Onset Seizure*** *≥ 18 years of age*	NA	NA	1 to 3 seizures	Prolonged and repetitive seizures (e.g., status epilepticus) OR Difficult to control (e.g., refractory epilepsy)
< 18 years of age (includes new or pre-existing febrile seizures)	Seizure lasting < 5 minutes with < 24 hours postictal state	Seizure lasting 5 to < 20 minutes with < 24 hours postictal state	Seizure lasting ≥ 20 minutes OR > 24 hours postictal state	Prolonged and repetitive seizures (e.g., status epilepticus) OR Difficult to control (e.g., refractory epilepsy)
Pre-existing Seizure	NA	Increased frequency from previous level of control without change in seizure character	Change in seizure character either in duration or quality (e.g., severity or focality)	Prolonged and repetitive seizures (e.g., status epilepticus) OR Difficult to control (e.g., refractory epilepsy)
Syncope	Near syncope without loss of consciousness (e.g., pre-syncope)	Loss of consciousness with no intervention indicated	Loss of consciousness AND Hospitalization or intervention required	NA

Pregnancy, Puerperium, and Perinatal

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Fetal Death or Stillbirth (report using mother's participant ID) *Report only one*	NA	NA	Fetal loss occurring at ≥ 20 weeks gestation	NA
Preterm Delivery[7] (report using mother's participant ID)	Delivery at 34 to < 37 weeks gestational age	Delivery at 28 to < 34 weeks gestational age	Delivery at 24 to < 28 weeks gestational age	Delivery at < 24 weeks gestational age
Spontaneous Abortion or Miscarriage[8] (report using mother's participant ID) *Report only one*	Chemical pregnancy	Uncomplicated spontaneous abortion or miscarriage	Complicated spontaneous abortion or miscarriage	NA

[7] Definition: A delivery of a live-born neonate occurring at ≥ 20 to < 37 weeks gestational age.
[8] Definition: A clinically recognized pregnancy occurring at < 20 weeks gestational age.

Psychiatric

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Insomnia	Mild difficulty falling asleep, staying asleep, or waking up early	Moderate difficulty falling asleep, staying asleep, or waking up early	Severe difficulty falling asleep, staying asleep, or waking up early	NA
Psychiatric Disorders (includes anxiety, depression, mania, and psychosis) *Specify disorder*	Symptoms with intervention not indicated OR Behavior causing no or minimal interference with usual social & functional activities	Symptoms with intervention indicated OR Behavior causing greater than minimal interference with usual social & functional activities	Symptoms with hospitalization indicated OR Behavior causing inability to perform usual social & functional activities	Threatens harm to self or others OR Acute psychosis OR Behavior causing inability to perform basic self-care functions
Suicidal Ideation or Attempt *Report only one*	Preoccupied with thoughts of death AND No wish to kill oneself	Preoccupied with thoughts of death AND Wish to kill oneself with no specific plan or intent	Thoughts of killing oneself with partial or complete plans but no attempt to do so OR Hospitalization indicated	Suicide attempted

Respiratory

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Acute Bronchospasm	Forced expiratory volume in 1 second or peak flow reduced to ≥ 70 to < 80% OR Mild symptoms with intervention not indicated	Forced expiratory volume in 1 second or peak flow 50 to < 70% OR Symptoms with intervention indicated OR Symptoms causing greater than minimal interference with usual social & functional activities	Forced expiratory volume in 1 second or peak flow 25 to < 50% OR Symptoms causing inability to perform usual social & functional activities	Forced expiratory volume in 1 second or peak flow < 25% OR Life-threatening respiratory or hemodynamic compromise OR Intubation
Dyspnea or Respiratory Distress *Report only one*	Dyspnea on exertion with no or minimal interference with usual social & functional activities OR Wheezing OR Minimal increase in respiratory rate for age	Dyspnea on exertion causing greater than minimal interference with usual social & functional activities OR Nasal flaring OR Intercostal retractions OR Pulse oximetry 90 to < 95%	Dyspnea at rest causing inability to perform usual social & functional activities OR Pulse oximetry < 90%	Respiratory failure with ventilator support indicated (e.g., CPAP, BPAP, intubation)

Sensory

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Hearing Loss *≥ 12 years of age*	NA	Hearing aid or intervention not indicated	Hearing aid or intervention indicated	Profound bilateral hearing loss (> 80 dB at 2 kHz and above) OR Non-serviceable hearing (i.e., >50 dB audiogram and <50% speech discrimination)
< 12 years of age (based on a 1, 2, 3, 4, 6 and 8 kHz audiogram)	> 20 dB hearing loss at ≤ 4 kHz	> 20 dB hearing loss at > 4 kHz	> 20 dB hearing loss at ≥ 3 kHz in one ear with additional speech language related services indicated (where available) OR Hearing loss sufficient to indicate therapeutic intervention, including hearing aids	Audiologic indication for cochlear implant and additional speech-language related services indicated (where available)
Tinnitus	Symptoms causing no or minimal interference with usual social & functional activities with intervention not indicated	Symptoms causing greater than minimal interference with usual social & functional activities with intervention indicated	Symptoms causing inability to perform usual social & functional activities	NA
Uveitis	No symptoms AND Detectable on examination	Anterior uveitis with symptoms OR Medicamylasal intervention indicated	Posterior or pan-uveitis OR Operative intervention indicated	Disabling visual loss in affected eye(s)
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
Visual Changes (assessed 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)

Systemic

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Acute Allergic Reaction	Localized urticaria (wheals) with no medical intervention indicated	Localized urticaria with intervention indicated OR Mild angioedema with no intervention indicated	Generalized urticaria OR Angioedema with intervention indicated OR Symptoms of 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
Cytokine Release Syndrome[9]	Mild signs and symptoms AND Therapy (i.e., antibody infusion) interruption not indicated	Therapy (i.e., antibody infusion) interruption indicated AND Responds promptly to symptomatic treatment OR Prophylactic medications indicated for ≤ 24 hours	Prolonged severe signs and symptoms OR Recurrence of symptoms following initial improvement	Life-threatening consequences (e.g., requiring pressor or ventilator support)
Fatigue or Malaise *Report only one*	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 symptoms of fatigue or malaise causing inability to perform basic self-care functions
Fever (non-axillary temperatures only)	38.0 to < 38.6°C or 100.4 to < 101.5°F	≥ 38.6 to < 39.3°C or ≥ 101.5 to < 102.7°F	≥ 39.3 to < 40.0°C or ≥ 102.7 to < 104.0°F	≥ 40.0°C or ≥ 104.0°F
Pain[10] (not associated with study agent injections and not specified elsewhere) *Specify location*	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 indicated
Serum Sickness[11]	Mild signs and symptoms	Moderate signs and symptoms AND Intervention indicated (e.g., antihistamines)	Severe signs and symptoms AND Higher level intervention indicated (e.g., steroids or IV fluids)	Life-threatening consequences (e.g., requiring pressor or ventilator support)

[9] Definition: A disorder characterized by nausea, headache, tachycardia, hypotension, rash, and/or shortness of breath.

[10] For pain associated with injections or infusions, see the *Site Reactions to Injections and Infusions* section (page 23).

[11] Definition: A disorder characterized by fever, arthralgia, myalgia, skin eruptions, lymphadenopathy, marked discomfort, and/or dyspnea.

Systemic

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Underweight[12] *> 5 to 19 years of age*	NA	WHO BMI z-score < -2 to ≤ -3	WHO BMI z-score < -3	WHO BMI z-score < -3 with life-threatening consequences
2 to 5 years of age	NA	WHO Weight-for-height z-score < -2 to ≤ -3	WHO Weight-for-height z-score < -3	WHO Weight-for-height z-score < -3 with life-threatening consequences
< 2 years of age	NA	WHO Weight-for-length z-score < -2 to ≤ -3	WHO Weight-for-length z-score < -3	WHO Weight-for-length z-score < -3 with life-threatening consequences
Weight Loss (excludes postpartum weight loss)	NA	5 to < 9% loss in body weight from baseline	≥ 9 to < 20% loss in body weight from baseline	≥ 20% loss in body weight from baseline OR Aggressive intervention indicated (e.g., tube feeding, total parenteral nutrition)

[12] WHO reference tables may be accesed by clicking the desired age range or by accessing the following URLs: http://www.who.int/growthref/who2007_bmi_for_age/en/ for participants > 5 to 19 years of age and http://www.who.int/childgrowth/standards/chart_catalogue/en/ for those ≤ 5 years of age.

Urinary

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Urinary Tract Obstruction	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

Site Reactions to Injections and Infusions

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Injection Site Pain or Tenderness *Report only one*	Pain or tenderness causing no or minimal limitation of use of limb	Pain or tenderness causing greater than minimal limitation of use of limb	Pain or tenderness causing inability to perform usual social & functional activities	Pain or tenderness causing inability to perform basic self-care function OR Hospitalization indicated
Injection Site Erythema or Redness[13] *Report only one* *> 15 years of age*	2.5 to < 5 cm in diameter OR 6.25 to < 25 cm^2 surface area AND Symptoms causing no or minimal interference with usual social & functional activities	≥ 5 to < 10 cm in diameter OR ≥ 25 to < 100 cm^2 surface area OR Symptoms causing greater than minimal interference with usual social & functional activities	≥ 10 cm in diameter OR ≥ 100 cm^2 surface area OR Ulceration OR Secondary infection OR Phlebitis OR Sterile abscess OR Drainage OR Symptoms causing inability to perform usual social & functional activities	Potentially life-threatening consequences (e.g., abscess, exfoliative dermatitis, necrosis involving dermis or deeper tissue)
≤ 15 years of age	≤ 2.5 cm in diameter	> 2.5 cm in diameter with < 50% surface area of the extremity segment involved (e.g., upper arm or thigh)	≥ 50% surface area of the extremity segment involved (e.g., upper arm or thigh) OR Ulceration OR Secondary infection OR Phlebitis OR Sterile abscess OR Drainage	Potentially life-threatening consequences (e.g., abscess, exfoliative dermatitis, necrosis involving dermis or deeper tissue)
Injection Site Induration or Swelling *Report only one* *> 15 years of age*	Same as for **Injection Site Erythema or Redness,** *> 15 years of age*	Same as for **Injection Site Erythema or Redness,** *> 15 years of age*	Same as for **Injection Site Erythema or Redness,** *> 15 years of age*	Same as for **Injection Site Erythema or Redness,** *> 15 years of age*
≤ 15 years of age	Same as for **Injection Site Erythema or Redness,** *≤ 15 years of age*	Same as for **Injection Site Erythema or Redness,** *≤ 15 years of age*	Same as for **Injection Site Erythema or Redness,** *≤ 15 years of age*	Same as for **Injection Site Erythema or Redness,** *≤ 15 years of age*
Injection Site Pruritus	Itching localized to the injection site that is relieved spontaneously or in < 48 hours of treatment	Itching beyond the injection site that is not generalized OR Itching localized to the injection site requiring ≥ 48 hours treatment	Generalized itching causing inability to perform usual social & functional activities	NA

[13] Injection Site Erythema or Redness should be evaluated and graded using the greatest single diameter or measured surface area.

Laboratory Values

Chemistries

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Acidosis	NA	pH ≥ 7.3 to < LLN	pH < 7.3 without life-threatening consequences	pH < 7.3 with life-threatening consequences
Albumin, Low (g/dL; *g/L*)	3.0 to < LLN *30 to < LLN*	≥ 2.0 to < 3.0 *≥ 20 to < 30*	< 2.0 *< 20*	NA
Alkaline Phosphatase, High	1.25 to < 2.5 x ULN	2.5 to < 5.0 x ULN	5.0 to < 10.0 x ULN	≥ 10.0 x ULN
Alkalosis	NA	pH > ULN to ≤ 7.5	pH > 7.5 without life-threatening consequences	pH > 7.5 with life-threatening consequences
ALT or SGPT, High *Report only one*	1.25 to < 2.5 x ULN	2.5 to < 5.0 x ULN	5.0 to < 10.0 x ULN	≥ 10.0 x ULN
Amylase (Pancreatic) or Amylase (Total), High *Report only one*	1.1 to < 1.5 x ULN	1.5 to < 3.0 x ULN	3.0 to < 5.0 x ULN	≥ 5.0 x ULN
AST or SGOT, High *Report only one*	1.25 to < 2.5 x ULN	2.5 to < 5.0 x ULN	5.0 to < 10.0 x ULN	≥ 10.0 x ULN
Bicarbonate, Low (mEq/L; *mmol/L*)	16.0 to < LLN *16.0 to < LLN*	11.0 to < 16.0 *11.0 to < 16.0*	8.0 to < 11.0 *8.0 to < 11.0*	< 8.0 *< 8.0*
Bilirubin ***Direct Bilirubin[14], High*** *> 28 days of age*	NA	NA	> ULN	> ULN with life-threatening consequences (e.g., signs and symptoms of liver failure)
≤ 28 days of age	ULN to ≤ 1 mg/dL	> 1 to ≤ 1.5 mg/dL	> 1.5 to ≤ 2 mg/dL	> 2 mg/dL
Total Bilirubin, High *> 28 days of age*	1.1 to < 1.6 x ULN	1.6 to < 2.6 x ULN	2.6 to < 5.0 x ULN	≥ 5.0 x ULN
≤ 28 days of age	See Appendix A. Total Bilirubin for Term and Preterm Neonates	See Appendix A. Total Bilirubin for Term and Preterm Neonates	See Appendix A. Total Bilirubin for Term and Preterm Neonates	See Appendix A. Total Bilirubin for Term and Preterm Neonates
Calcium, High (mg/dL; *mmol/L*) *≥ 7 days of age*	10.6 to < 11.5 *2.65 to < 2.88*	11.5 to < 12.5 *2.88 to < 3.13*	12.5 to < 13.5 *3.13 to < 3.38*	≥ 13.5 *≥ 3.38*
< 7 days of age	11.5 to < 12.4 *2.88 to < 3.10*	12.4 to < 12.9 *3.10 to < 3.23*	12.9 to < 13.5 *3.23 to < 3.38*	≥ 13.5 *≥ 3.38*

Chemistries

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Calcium (Ionized), High (mg/dL; *mmol/L*)	> ULN to < 6.0 *> ULN to < 1.5*	6.0 to < 6.4 *1.5 to < 1.6*	6.4 to < 7.2 *1.6 to < 1.8*	≥ 7.2 *≥ 1.8*
Calcium, Low (mg/dL; *mmol/L*) *≥ 7 days of age*	7.8 to < 8.4 *1.95 to < 2.10*	7.0 to < 7.8 *1.75 to < 1.95*	6.1 to < 7.0 *1.53 to < 1.75*	< 6.1 *< 1.53*
< 7 days of age	6.5 to < 7.5 *1.63 to < 1.88*	6.0 to < 6.5 *1.50 to < 1.63*	5.50 to < 6.0 *1.38 to < 1.50*	< 5.50 *< 1.38*
Calcium (Ionized), Low (mg/dL; *mmol/L*)	< LLN to 4.0 *< LLN to 1.0*	3.6 to < 4.0 *0.9 to < 1.0*	3.2 to < 3.6 *0.8 to < 0.9*	< 3.2 *< 0.8*
Cardiac Troponin I, High	NA	NA	NA	Levels consistent with myocardial infarction or unstable angina as defined by the local laboratory
Creatine Kinase, High	3 to < 6 x ULN	6 to < 10 x ULN	10 to < 20 x ULN	≥ 20 x ULN
Creatinine, High	1.1 to 1.3 x ULN	> 1.3 to 1.8 x ULN OR Increase of > 0.3 mg/dL above baseline	> 1.8 to < 3.5 x ULN OR Increase of 1.5 to < 2.0 x above baseline	≥ 3.5 x ULN OR Increase of ≥ 2.0 x above baseline
Creatinine Clearance[15] or eGFR, Low *Report only one*	NA	< 90 to 60 ml/min or ml/min/1.73 m^2 OR 10 to < 30% decrease from baseline	< 60 to 30 ml/min or ml/min/1.73 m^2 OR ≥ 30 to < 50% decrease from baseline	< 30 ml/min or ml/min/1.73 m^2 OR ≥ 50% decrease from baseline or dialysis needed
Glucose (mg/dL; *mmol/L*) ***Fasting, High***	110 to 125 *6.11 to < 6.95*	> 125 to 250 *6.95 to < 13.89*	> 250 to 500 *13.89 to < 27.75*	> 500 *≥ 27.75*
Nonfasting, High	116 to 160 *6.44 to < 8.89*	> 160 to 250 *8.89 to < 13.89*	> 250 to 500 *13.89 to < 27.75*	> 500 *≥ 27.75*
Glucose, Low (mg/dL; *mmol/L*) *≥ 1 month of age*	55 to 64 *3.05 to 3.55*	40 to < 55 *2.22 to < 3.05*	30 to < 40 *1.67 to < 2.22*	< 30 *< 1.67*
< 1 month of age	50 to 54 *2.78 to 3.00*	40 to < 50 *2.22 to < 2.78*	30 to < 40 *1.67 to < 2.22*	< 30 *< 1.67*
Lactate, High	ULN to < 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

[15] Use the applicable formula (i.e., Cockroft-Gault in mL/min or Schwatrz in mL/min/1.73m^2).

Chemistries

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Lipase, High	1.1 to < 1.5 x ULN	1.5 to < 3.0 x ULN	3.0 to < 5.0 x ULN	≥ 5.0 x ULN
Lipid Disorders (mg/dL; *mmol/L*)				
Cholesterol, Fasting, High *≥ 18 years of age*	200 to < 240 *5.18 to < 6.19*	240 to < 300 *6.19 to < 7.77*	≥ 300 *≥ 7.77*	NA
< 18 years of age	170 to < 200 *4.40 to < 5.15*	200 to < 300 *5.15 to < 7.77*	≥ 300 *≥ 7.77*	NA
LDL, Fasting, High *≥ 18 years of age*	130 to < 160 *3.37 to < 4.12*	160 to < 190 *4.12 to < 4.90*	≥ 190 *≥4.90*	NA
> 2 to < 18 years of age	110 to < 130 *2.85 to < 3.34*	130 to < 190 *3.34 to < 4.90*	≥ 190 *≥ 4.90*	NA
Triglycerides, Fasting, High	150 to 300 *1.71 to 3.42*	>300 to 500 *>3.42 to 5.7*	>500 to < 1,000 *>5.7 to 11.4*	> 1,000 *> 11.4*
Magnesium[16], Low (mEq/L; *mmol/L*)	1.2 to < 1.4 *0.60 to < 0.70*	0.9 to < 1.2 *0.45 to < 0.60*	0.6 to < 0.9 *0.30 to < 0.45*	< 0.6 *< 0.30*
Phosphate, Low (mg/dL; *mmol/L*)				
> 14 years of age	2.0 to < LLN *0.81 to < LLN*	1.4 to < 2.0 *0.65 to < 0.81*	1.0 to < 1.4 *0.32 to < 0.65*	< 1.0 *< 0.32*
1 to 14 years of age	3.0 to < 3.5 *0.97 to < 1.13*	2.5 to < 3.0 *0.81 to < 0.97*	1.5 to < 2.5 *0.48 to < 0.81*	< 1.5 *< 0.48*
< 1 year of age	3.5 to < 4.5 *1.13 to < 1.45*	2.5 to < 3.5 *0.81 to < 1.13*	1.5 to < 2.5 *0.48 to < 0.81*	< 1.5 *< 0.48*
Potassium, High (mEq/L; *mmol/L*)	5.6 to < 6.0 *5.6 to < 6.0*	6.0 to < 6.5 *6.0 to < 6.5*	6.5 to < 7.0 *6.5 to < 7.0*	≥ 7.0 *≥ 7.0*
Potassium, Low (mEq/L; *mmol/L*)	3.0 to < 3.4 *3.0 to < 3.4*	2.5 to < 3.0 *2.5 to < 3.0*	2.0 to < 2.5 *2.0 to < 2.5*	< 2.0 *< 2.0*
Sodium, High (mEq/L; *mmol/L*)	146 to < 150 *146 to < 150*	150 to < 154 *150 to < 154*	154 to < 160 *154 to < 160*	≥ 160 *≥ 160*
Sodium, Low (mEq/L; *mmol/L*)	130 to < 135 *130 to < 135*	125 to < 130 *125 to < 135*	121 to < 125 *121 to < 125*	≤ 120 *≤ 120*
Uric Acid, High (mg/dL; *mmol/L*)	7.5 to < 10.0 *0.45 to < 0.59*	10.0 to < 12.0 *0.59 to < 0.71*	12.0 to < 15.0 *0.71 to < 0.89*	≥ 15.0 *≥ 0.89*

[16] To convert a magnesium value from mg/dL to mmol/L, laboratories should multiply by 0.4114.

Hematology

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Absolute CD4+ Count, Low (cell/mm^3; *cells/L*) *> 5 years of age (not HIV infected)*	300 to < 400 *300 to < 400*	200 to < 300 *200 to < 300*	100 to < 200 *100 to < 200*	< 100 *< 100*
Absolute Lymphocyte Count, Low (cell/mm^3; *cells/L*) *> 5 years of age (not HIV infected)*	600 to < 650 *0.600 x 10^9 to < 0.650 x 10^9*	500 to < 600 *0.500 x 10^9 to < 0.600 x 10^9*	350 to < 500 *0.350 x 10^9 to < 0.500 x 10^9*	< 350 *< 0.350 x 10^9*
Absolute Neutrophil Count (ANC), Low (cells/mm^3; *cells/L*) *> 7 days of age*	800 to 1,000 *0.800 x 10^9 to 1.000 x 10^9*	600 to 799 *0.600 x 10^9 to 0.799 x 10^9*	400 to 599 *0.400 x 10^9 to 0.599 x 10^9*	< 400 *< 0.400 x 10^9*
2 to 7 days of age	1,250 to 1,500 *1.250 x 10^9 to 1.500 x 10^9*	1,000 to 1,249 *1.000 x 10^9 to 1.249 x 10^9*	750 to 999 *0.750 x 10^9 to 0.999 x 10^9*	< 750 *< 0.750 x 10^9*
≤ 1 day of age	4,000 to 5,000 *4.000 x 10^9 to 5.000 x 10^9*	3,000 to 3,999 *3.000 x 10^9 to 3.999 x 10^9*	1,500 to 2,999 *1.500 x 10^9 to 2.999 x 10^9*	< 1,500 *< 1.500 x 10^9*
Fibrinogen, Decreased (mg/dL; *g/L*)	100 to < 200 *1.00 to < 2.00* OR 0.75 to < 1.00 x LLN	75 to < 100 *0.75 to < 1.00* OR ≥ 0.50 to < 0.75 x LLN	50 to < 75 *0.50 to < 0.75* OR 0.25 to < 0.50 x LLN	< 50 *< 0.50* OR < 0.25 x LLN OR Associated with gross bleeding
Hemoglobin[17], Low (g/dL; *mmol/L*)[18] *≥ 13 years of age (male only)*	10.0 to 10.9 *6.19 to 6.76*	9.0 to < 10.0 *5.57 to < 6.19*	7.0 to < 9.0 *4.34 to < 5.57*	< 7.0 *< 4.34*
≥ 13 years of age (female only)	9.5 to 10.4 *5.88 to 6.48*	8.5 to < 9.5 *5.25 to < 5.88*	6.5 to < 8.5 *4.03 to < 5.25*	< 6.5 *< 4.03*

[17] Male and female sex are defined as sex at birth.

[18] The conversion factor used to convert g/dL to mmol/L is 0.6206 and is the most commonly used conversion factor. For grading hemoglobin 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 the particular laboratory.

Hematology

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
57 days of age to < 13 years of age (male and female)	9.5 to 10.4 *5.88 to 6.48*	8.5 to < 9.5 *5.25 to < 5.88*	6.5 to < 8.5 *4.03 to < 5.25*	< 6.5 *< 4.03*
36 to 56 days of age (male and female)	8.5 to 9.6 *5.26 to 5.99*	7.0 to < 8.5 *4.32 to < 5.26*	6.0 to < 7.0 *3.72 to < 4.32*	< 6.0 *< 3.72*
22 to 35 days of age (male and female)	9.5 to 11.0 *5.88 to 6.86*	8.0 to < 9.5 *4.94 to < 5.88*	6.7 to < 8.0 *4.15 to < 4.94*	< 6.7 *< 4.15*
8 to ≤ 21 days of age (male and female)	11.0 to 13.0 *6.81 to 8.10*	9.0 to < 11.0 *5.57 to < 6.81*	8.0 to < 9.0 *4.96 to < 5.57*	< 8.0 *< 4.96*
≤ 7 days of age (male and female)	13.0 to 14.0 *8.05 to 8.72*	10.0 to < 13.0 *6.19 to < 8.05*	9.0 to < 10.0 *5.59 to < 6.19*	< 9.0 *< 5.59*
INR, High (not on anticoagulation therapy)	1.1 to < 1.5 x ULN	1.5 to < 2.0 x ULN	2.0 to < 3.0 x ULN	≥ 3.0 x ULN
Methemoglobin (% hemoglobin)	5.0 to < 10.0%	10.0 to < 15.0%	15.0 to < 20.0%	≥ 20.0%
PTT, High (not on anticoagulation therapy)	1.1 to < 1.66 x ULN	1.66 to < 2.33 x ULN	2.33 to < 3.00 x ULN	≥ 3.00 x ULN
Platelets, Decreased (cells/mm^3; *cells/L*)	100,000 to < 124,999 *100.000 x 10^9 to < 124.999 x 10^9*	50,000 to < 100,000 *50.000 x 10^9 to < 100.000 x 10^9*	25,000 to < 50,000 *25.000 x 10^9 to < 50.000 x 10^9*	< 25,000 *< 25.000 x 10^9*
PT, High (not on anticoagulation therapy	1.1 to < 1.25 x ULN	1.25 to < 1.50 x ULN	1.50 to < 3.00 x ULN	≥ 3.00 x ULN
WBC, Decreased (cells/mm^3; *cells/L*)				
> 7 days of age	2,000 to 2,499 *2.000 x 10^9 to 2.499 x 10^9*	1,500 to 1,999 *1.500 x 10^9 to 1.999 x 10^9*	1,000 to 1,499 *1.000 x 10^9 to 1.499 x 10^9*	< 1,000 *< 1.000 x 10^9*
≤ 7 days of age	5,500 to 6,999 *5.500 x 10^9 to 6.999 x 10^9*	4,000 to 5,499 *4.000 x 10^9 to 5.499 x 10^9*	2,500 to 3,999 *2.500 x 10^9 to 3.999 x 10^9*	< 2,500 *< 2.500 x 10^9*

Urinalysis

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Glycosuria (random collection tested by dipstick)	Trace to 1+ or ≤ 250 mg	2+ or > 250 to ≤ 500 mg	> 2+ or > 500 mg	NA
Hematuria (not to be reported based on dipstick findings or on blood believed to be of menstrual origin)	6 to < 10 RBCs per high power field	≥ 10 RBCs per high power field	Gross, with or without clots OR With RBC casts OR Intervention indicated	Life-threatening consequences
Proteinuria (random collection tested by dipstick)	1+	2+	3+ or higher	NA

Total Bilirubin Table for Term and Preterm Neonates

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Total Bilirubin[19], High (mg/dL; *µmol/L*)[20]				
Term Neonate[21] *< 24 hours of age*	4 to < 7 *68.4 to < 119.7*	7 to < 10 *119.7 to < 171*	10 to < 17 *171 to < 290.7*	≥ 17 *≥ 290.7*
24 to < 48 hours of age	5 to < 8 *85.5 to < 136.8*	8 to < 12 *136.8 to < 205.2*	12 to < 19 *205.2 to < 324.9*	≥ 19 *≥ 324.9*
48 to < 72 hours of age	8.5 to < 13 *145.35 to < 222.3*	13 to < 15 *222.3 to < 256.5*	15 to < 22 *256.5 to < 376.2*	≥ 22 *≥ 376.2*
72 hours to < 7 days of age	11 to < 16 *188.1 to < 273.6*	16 to < 18 *273.6 to < 307.8*	18 to < 24 *307.8 to < 410.4*	≥ 24 *≥ 410.4*
7 to 28 days of age (breast feeding)	5 to < 10 *85.5 to < 171*	10 to < 20 *171 to < 342*	20 to < 25 *342 to < 427.5*	≥ 25 *≥ 427.5*
7 to 28 days of age (not breast feeding)	1.1 to < 1.6 x ULN	1.6 to < 2.6 x ULN	2.6 to < 5.0 x ULN	≥ 5.0 x ULN
Preterm Neonate[20] *35 to < 37 weeks gestational age*	Same as for ***Total Bilirubin, High, Term Neonate*** (based on days of age).	Same as for ***Total Bilirubin, High, Term Neonate*** (based on days of age).	Same as for ***Total Bilirubin, High, Term Neonate*** (based on days of age).	Same as for ***Total Bilirubin, High, Term Neonate*** (based on days of age).
32 to < 35 weeks gestational age and < 7 days of age	NA	NA	10 to < 14 *171 to < 239.4*	≥ 14 *≥ 239.4*
28 to < 32 weeks gestational age and < 7 days of age	NA	NA	6 to < 10 *102.6 to < 171*	≥ 10 *≥ 171*
< 28 weeks gestational age and < 7 days of age	NA	NA	5 to < 8 *85.5 to < 136.8*	≥ 8 *≥ 136.8*
7 to 28 days of age (breast feeding)	5 to < 10 *85.5 to < 171*	10 to < 20 *171 to < 342*	20 to < 25 *342 to < 427.5*	≥ 25 *≥ 427.5*
7 to 28 days of age (not breast feeding)	1.1 to < 1.6 x ULN	1.6 to < 2.6 x ULN	2.6 to < 5.0 x ULN	≥ 5.0 x ULN

[19] Severity grading for total bilirubin in neonates is complex because of rapidly changing total bilirubin normal ranges in the first week of life followed by the benign phenomenon of breast milk jaundice after the first week of life. Severity grading in this appendix corresponds approximately to cut-offs for indications for phototherapy at grade 3 and for exchange transfusion at grade 4.

[20] A laboratory value of 1 mg/dL is equivalent to 17.1 µmol/L.

[21] Definitions: Term is defined as ≥ 37 weeks gestational age; near-term, as ≥ 35 weeks gestational age; preterm, as < 35 weeks gestational age; and neonate, as 0 to 28 days of age.

Appendix 2: Bleeding Academic Research Consortium (BARC) Definitions for Bleeding Events

Type 0	no bleeding
Type 1	bleeding that is not actionable and does not cause the patient to seek unscheduled performance of studies, hospitalization, or treatment by a healthcare professional; may include episodes leading to self-discontinuation of medical therapy by the patient without consulting a healthcare professional
Type 2	any overt, actionable sign of haemorrhage (eg, more bleeding than would be expected for a clinical circumstance, including bleeding found by imaging alone) that does not fit the criteria for type 3, 4, or 5 but does meet at least one of the following criteria: (1) requiring nonsurgical, medical intervention by a healthcare professional, (2) leading to hospitalization or increased level of care, or (3) prompting evaluation
Type 3	Type 3a • Overt bleeding plus hemoglobin drop of 3 to <5 g/dL* (provided hemoglobin drop is related to bleed) • Any transfusion with overt bleeding Type 3b • Overt bleeding plus hemoglobin drop ≥5 g/dL* (provided hemoglobin drop is related to bleed) • Cardiac tamponade • Bleeding requiring surgical intervention for control (excluding dental/nasal/skin/hemorrhoid) • Bleeding requiring intravenous vasoactive agents Type 3c • Intracranial hemorrhage (does not include microbleeds or hemorrhagic transformation, does include intraspinal) • Subcategories confirmed by autopsy or imaging or lumbar puncture • Intraocular bleed compromising vision
Type 4	CABG-related bleeding • Perioperative intracranial bleeding within 48 hrs • Reoperation after closure of sternotomy for the purpose of controlling bleeding • Transfusion of ≥5 U whole blood or packed red blood cells within a 48-hr period† • Chest tube output ≥2L within a 24hr period CABG indicates coronary artery bypass graft. Platelet transfusions should be recorded and reported but are not included in these definitions until further information is obtained about the relationship to outcomes. If a CABG-related bleed is not adjudicated as at least a type 3 severity event, it will be classified as not a bleeding event. If a bleeding event occurs with a clear temporal relationship to CABG (ie, within a 48-h time frame) but does not meet type 4 severity criteria, it will be classified as not a bleeding event. * Corrected for transfusion (1 U packed red blood cells or 1 U whole blood=1 g/dL hemoglobin). † Cell saver products are not counted.
Type 5	Fatal bleeding Type 5a • Probable fatal bleeding; no autopsy or imaging confirmation but clinically suspicious Type 5b • Definite fatal bleeding; overt bleeding or autopsy or imaging confirmation

Appendix 3: Definitions and Criteria for HIV Disease and AIDS Events

The following list encompass the CDC's 1993 surveillance case definition of AIDS (without the CD4+ criterion), with the addition of several diagnoses increasingly felt to be associated with severe immunosuppression in participants infected with HIV.

Modified CDC Category C 1993 Definition

- Candidiasis of bronchi, trachea or lungs
- Candidiasis, esophageal
- Cervical cancer, invasive
- Coccidioidomycosis, disseminated or extrapulmonary
- Cryptococcosis, extrapulmonary
- Cryptosporidiosis, chronic intestinal (> 1 month's duration)
- CMV disease (other than liver, spleen, or nodes)
- CMV retinitis (with loss of vision)
- Encephalopathy, HIV-related (including AIDS Dementia Complex)
- *Herpes simplex*, chronic ulcers (> 1 month's duration); or bronchitis, pneumonitis or esophagitis
- Histoplasmosis, disseminated or extrapulmonary
- Isosporiasis, chronic intestinal (> 1 month's duration)
- Kaposi's sarcoma (mucocutaneous or visceral)
- Lymphoma, Burkitt's (or equivalent term)
- Lymphoma, primary, of brain
- *Mycobacterium avium* complex or *M. kansasii*, disseminated or extrapulmonary
- *M. tuberculosis*, any site (pulmonary or extrapulmonary)
- *Mycobacterium*, other species or unidentified species, disseminated or extrapulmonary
- *Pneumocystis carinii* pneumonia (*pneumocystic jiroveci*)
- Pneumonia, recurrent bacterial (2 documented episodes within 1 year of each other following randomization)
- Progressive multifocal leukoencephalopathy
- *Salmonella* septicemia, recurrent (2 documented episodes within 1 year of each other following randomization)
- Toxoplasmosis of brain
- Wasting syndrome due to HIV

Additions to CDC Definition

- Aspergillosis, invasive
- Bartonellosis
- Chagas disease (American trypanosomiasis) of the CNS
- *Herpes zoster*, multi-dermatomal (≥10 lesions in a non-contiguous site)
- Leishmaniasis, visceral (kala-azar)
- Lymphoma, Hodgkin's
- Lymphoma, non-Hodgkin's, all cell types
- Microsporidiosis (> 1 month's duration)
- Nocardiosis
- *Penicillium marneffii*, disseminated
- *Pneumocystis carinii*, extrapulmonary
- *Rhodococcus equi* disease

	CONFIRMED	PROBABLE
CONSTITUTIONAL DISEASE		
HIV wasting syndrome	None	A plus B plus C: (A) unexplained, involuntary weight loss >10% from baseline, (B) persistent diarrhoea with >2 liquid stools/d for >1 month or weakness for >1 month or fever for >1 month, (C) tests for alternate causes of weight loss, such as cancer, TB, MAC, cryptosporidiosis or other specific causes of weight loss, if obtained, should be negative
INFECTIONS		
Aspergillosis, invasive pulmonary	A plus B plus C: (A) CXR abnormality compatible with aspergillosis, (B) invasive mycelia consistent with Aspergillus on lung biopsy, (C) positive culture from lung biopsy or sputum collected by any method	A plus B: (A) CXR abnormality compatible with aspergillosis, (B) invasive mycelia consistent with Aspergillus on lung biopsy or positive culture of lung tissue or positive culture of sputum collected by any method
Aspergillosis, other invasive	A plus B plus C: (A) compatible clinical course, (B) invasive mycelia consistent with Aspergillus on tissue biopsy or clinical evidence of infection, (C) positive culture from the affected tissue	A plus B: (A) clinical evidence of invasive infection, (B) invasive mycelia consistent with Aspergillus on tissue biopsy or positive culture at a normally sterile site (e.g., blood) apart from the involved tissue
Bartonellosis	A plus B: (A) Clinical or histologic evidence of bacillary angiomatosis or bacillary peliosis, (B) a positive culture or PCR for *B. quintana* or *B. henselae*	A plus B: (A) Clinical evidence of bacillary angiomatosis or bacillary peliosis, (B) positive silver stain for bacilli from a skin lesion or an affected organ
Candidiasis of bronchi, trachea or lungs	Macroscopic appearance at bronchoscopy or autopsy plus microscopic evidence of yeasts or pseudo hyphae	None
Candidiasis, esophageal	A plus B: (A) Macroscopic appearance at esophagoscopy or autopsy, (B) microscopic evidence of yeasts or pseudo hyphae	A plus B plus C: (A) Recent onset of retrosternal pain or difficulty on swallowing, (B) a clinical diagnosis of oral candidiasis plus microscopic evidence of yeasts or pseudo hyphae from oropharyngeal mucosa, (C) clinical response to treatment
Chagas disease (American trypanosomiasis) of the CNS	Histologic evidence obtained by brain tissue biopsy or autopsy	A plus B plus C plus D: (A) Focal, typically hemispheral neurological dysfunction with onset over several days or weeks; (B) enhancing focal lesion(s) with mass effect, and surrounding edema and contrast enhancement, typically located in grey matter; (C) serum antibodies to *T. cruzi*, (D) response to standard therapy with documented clinical or radiographic improvement (if radiography was done, it must be improved), or peripheral blood smear or CSF smear positive for *T. cruzi*
Coccidioidomycosis, disseminated or extrapulmonary	From tissue other than lung or hilum, A or B or C: (A) Microscopic demonstration of spherules, (B) positive culture, (C) antigen detection	None

	CONFIRMED	PROBABLE
INFECTIONS (CONTINUED)		
Cryptococcosis, meningitis or extrapulmonary	From tissue other than lung or hilum, A or B or C or D: (A) microscopic demonstration of narrow based budding yeast, (B) for meningitis, if done, a positive CSF India ink test, (C) positive culture, (D) antigen detention	None
Cryptosporidiosis	Diarrhea for >1 month and positive microscopy	None
CMV retinitis	Autopsy demonstration	Typical appearance on fundoscopy of discrete patches of retinal whitening, spreading along blood vessels, associated with vasculitis, hemorrhage and necrosis, confirmed by ophthalmologist
CMV radiculomyelitis	Autopsy demonstration	A plus B plus C plus D plus E plus F: (A) Loss of sensation, leg weakness, or decreased reflexes, (B) presentation over 3 days to 3 weeks, (C) CT, MRI or myelogram must be done and all imaging studies must not show a mass lesion, (D) CSF shows >10 WBC with >50% polymorphs, (E) CSF shows no other pathogen, (F) persistence of symptoms in the absence of CMV treatment, or elevated quantitative CMV in the CSF by PCR
CMV meningoencephalitis	Autopsy or brain biopsy demonstration	A plus B: (A) Rapid <4 weeks syndrome with progressive delirium, cognitive impairment and fever, (B) CT/MRI demonstration of periventricular abnormalities or elevated quantitative CMV DNA in the CSF by PCR
CMV, other disease	A plus B plus C plus D: (A) compatible illness, (B) histologic demonstration of inclusion bodies from affected tissue, (C) if done, detectible CMV antibodies, (D) if done, detectible CMV DNA or CMV antigen in blood	A plus B plus C plus D: (A) Compatible illness, (B) moderate to markedly high CMV antigen or CMV DNA in blood, (C) response to therapy, (D) if done, detectible CMV antibodies
HSV mucocutaneous ulceration	A plus B: (A) Ulceration for >1 month, (B) histology or culture or detection of antigen from affected tissue	A plus B: (A) Typical HSV ulceration for >1 month, (B) response to an antiviral active against HZV unless resistance is demonstrated
HSV, bronchitis, pneumonitis, esophagitis or other visceral disease	A plus B: (A) Compatible symptoms, (B) histology or culture or detection of antigen from affected tissue	None
HZV, disseminated	A plus B: (A) multiple ulcerated lesions affecting at least 2 non-contiguous dermatomes, or with genralised cutaneous dissemination: or HZV involvement of the lung, liver, brain, or other internal organs (B) positive culture, PCR, or antigen asssay from from affected tissue	A plus B: (A) multiple typical ulcerated lesions affecting at least 2 non-contiguous dermatomes, or with generalised cutaneous dissemination (B) response to an antiviral active against HZV unless resistance is demonstrated
Histoplasmosis, disseminated or extrapulmonary	A plus B: (A) Compatible symptoms, (B) histology or culture or elevated blood or urine antigen levels	None

	CONFIRMED	PROBABLE
INFECTIONS (CONTINUED)		
Isosporiasis	Diarrhea for >1 month, plus microscopic identification of *Isospora belli*	None
Leishmaniasis, visceral	Compatible symptoms, plus microscopic identification of Leishmania	None
Microsporidiosis	Diarrhea for >1 month plus Microscopic identification of Microsporidia	None
MAC and other mycobacterial disseminated disease	A plus B: (A) Fever, fatigue, anemia or diarrhea, (B) positive culture from blood, body fluids or tissue other than pulmonary, hilar or stool	A plus B plus C: (A) Fever, fatigue, anemia or diarrhea, (B) AFB or positive direct MAC PCR in blood, body fluids or tissue other than pulmonary, hilar or stool (C) no concurrent non-pulmonary TB
M. tuberculosis disease, pulmonary	A plus B: (A) Compatible symptoms of fever, dyspnea, cough, weight loss or fatigue, (B) culture or PCR from sputum or bronchial lavage or lung tissue	A plus B plus C plus D: (A) Symptoms of fever, dyspnea, cough, weight loss or fatigue, (B) abnormal chest X-ray, (C) AFBs seen in sputum or lavage or lung tissue but not grown in culture, (D) responds to treatment
M. tuberculosis disease, extrapulmonary	A plus B: (A) Compatible symptoms, (B) culture or PCR from blood or affected tissue	A plus B plus C: (A) Compatible symptoms, (B) AFBs seen from affected tissue or blood (C) concurrent diagnosis of pulmonary TB or responds to treatment
Nocardiosis	Clinical evidence of invasive infection plus a positive culture from the affected tissue or blood	Clinical evidence of invasive infection plus microscopic evidence of bronchial weakly acid fast organisms from the affected tissue
Penicillium marneffei, disseminated	Culture from a non-pulmonary site	Known presence in a *P. marneffei* endemic area plus characteristic skin lesions plus response to antifungal therapy for penicillosis
PCP	A plus B: (A) compatible clinical syndrome, (B) microscopic or histoloical demonstration of *P. carinii* cysts in a pulmonary specimen	A plus B plus C plus D plus E: (A) dyspnea or cough, or fever progressive over >1 week, (B) diffuse chest x-ray abnormality or, if on inhalational pentamidine, diffuse upper lung field abnormality, (C) evidence of hypoxia, (D) not suggestive of bacterial pneumonia (i.e., not purulent sputum or hemoptysis, no bacterial pathogen identified in blood or bronchial wash), (E) response to PCP treatment
Pneumocystis jirovecii, extrapulmonary	Compatible symptoms, plus microscopy	None

	CONFIRMED	PROBABLE
INFECTIONS (CONTINUED)		
Pneumonia, recurrent bacterial excludes, (a) post-obstructive pneumonias, including in those with intrapulmonary/bronchial lesions, (b) aspiration pneumonia, including in those with decreased consciousness levels, (c) nosocomial ventilator-associated pneumonias	Both pneumonia episodes must occur after enrolment and satisfy criteria (A) plus (B) plus (C). The recurrent pneumonia must also satisfy criteria (D) plus (E): (A) Signs and symptoms suggestive of bacterial pneumonia, (B) focal CXR abnormality compatible with bacterial pneumonia, (C) identification of a bacterial pathogen by positive blood culture, positive bronchoscopic sputum culture, detection of Legionella or pneumococcal antigen in urine or blood or diagnostic serologic findings, (D) the second pneumonia had onset of symptoms <365 days after the first episode, (E) there is strong evidence that the first episode was cured such as an intervening clear CXR or absence of symptoms after >1 month off antibacterials effective against pathogens commonly producing pneumonia	Both pneumonia episodes must occur after enrollment and satisfy criteria (A) plus (B) plus (C). The recurrent pneumonia must also satisfy criteria (D) plus (E): (A) Signs and symptoms suggestive of bacterial pneumonia, (B) focal CXR abnormality compatible with bacterial pneumonia, (C) diagnosed by a doctor, physicians' assistant or nurse practitioner, (D) the second pneumonia had onset of symptoms <365 days after the first episode, (E) there is strong evidence that the first episode was cured such as an intervening clear CXR or absence of symptoms after >1 month off antibacterials effective against pathogens commonly producing pneumonia
PML (progressive multifocal leukoencephalopathy)	A or B: (A) positive histology, (B) compatible clinical and radiologic course and positive CSF PCR for JK virus	A plus B plus C: (A) Consistent symptoms, (B) brain image consistent with PML, (C) no response to toxo treatment or toxoplasma seronegative
Rhodococcus equi disease	Clinical evidence of invasive infection plus microbiologic identification of the organism in the affected tissue or blood	None
Salmonella septicemia, recurrent	Both episodes must occur after enrollment and met criterion (A). The second episode must meet criteria (B) and C: (A) Positive blood or tissue culture, (B) the second septicemia had onset of symptoms <365 days after the first episode, (C) the second septicemia must be due to a different Salmonella serotype or there must be strong evidence that the first episode was cured such as a negative blood culture off effective antibacterials for >1 week or absence of symptoms off antibacterials for >1 month	None
Toxoplasmosis of brain	Microscopy	A plus B plus C: (A) Symptoms of focal intracranial abnormality or decreased consciousness, (B) brain image consistent with lesion(s) enhanced by contrast, (C) positive toxoplasma serology or responds to treatment clinically or by scan

	CONFIRMED	PROBABLE
INFECTIONS (CONTINUED)		
NEOPLASMS		
Cervical carcinoma, invasive	Histology (NOT carcinoma-in-situ)	None
Kaposi sarcoma, (mucocutaneous or visceral)	Histology	Highly typical appearance and persistence for >1 month
Lymphoma, primary, of brain	Histology	Symptoms consistent with lymphoma plus at least one CNS lesion with mass effect plus lack of clinical and radiographic response to at least 2 weeks of treatment for toxoplasmosis
Lymphoma, Hodgkin's	Histology	None
Lymphoma, non-Hodgkin's, all cell types	Histology	None
NEUROLOGICAL		
HIV encephalopathy (including AIDS Dementia Complex)	None	Cognitive or motor dysfunction interfering with usual activity, progressive over weeks or months plus no other condition to explain the findings plus brain image obtained and suggests no other causes plus grade 2 or worse impairment in at least 2 domains by NARS (see below) excluding abnormal domains at trial entry. (For persons with abnormal domains at entry worsening by at least two grades meets criteria.)

Appendix 4: Diagnostic Criteria for Serious Non-AIDS Events

ACUTE MYOCARDIAL INFARCTION

A. Rise and/or fall of cardiac biomarkers (preferably troponin), with at least one value above 99th percentile of upper reference limit (URL)

B. Occurrence of a compatible clinical syndrome, including symptoms (such as chest pain) consistent with myocardial ischemia

C. ECG changes indicative of new ischemia (new ST-changes or new left bundle branch block [LBBB]), or development of pathological Q waves on the ECG

D. Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality

E. Sudden unexpected cardiac death involving cardiac arrest before biomarkers are obtained or before a time when biomarkers appear, along with (1) new ST-changes or new LBB, or (2) evidence of fresh thrombus on coronary angiography or at autopsy

F. In participants with percutaneous coronary interventions and normal baseline troponin, increases in troponin of three times the 99th percentile of URL

G. In participants with coronary artery bypass grafting and normal baseline troponin, increases in troponin of five times the 99th percentile of URL PLUS at least one of the following: (1) new pathological Q-waves or new LBBB, (2) angiographically documented new graft or native artery occlusion, or (3) imaging evidence of new loss of viable myocardium

H. Pathologic findings of acute myocardial infarction (including acute MI demonstrated as the cause of death on autopsy)

I. Development of 1) evolving new Q waves, or 2) evolving ST elevation, preferably based on at least 2 ECGs taken during the same hospital admission

J. In participants with coronary artery bypass grafting and normal baseline troponin, increases in troponin of five times the 99th percentile of URL

Confirmed: One of the following 5 criteria (adapted from 2007 Universal Definition of Myocardial Infarction):

1. A + (B or C or D)
2. E
3. F
4. G
5. H

Probable: B+I or J

CONGESTIVE HEART FAILURE

A. Clinical signs and symptoms compatible with left or right sided heart failure (e.g., paroxysmal nocturnal dyspnea, rales or S3 on auscultation, jugular venous distention) without an alternative explanation

B. Hemodynamic measurements, radionucleotide ventriculography, echocardiogram, cardiac catheterization, or multiple gated acquisition scan showing a decreased ejection fraction of < 45%

C. Echocardiogram, cardiac catheterization or other studies showing evidence of increased left atrial pressure or right heart failure

D. Elevated levels of Brain Natriuretic Peptide (BNP) or pro-BNP

E. Chest x-ray or other imaging study showing evidence of congestive heart failure, including cardiac enlargement

F. Documentation of treatment for congestive heart failure

Confirmed: (A+B) or (A+C) or (A+D)

Probable: A+E+F

CORONARY ARTERY DISEASE REQUIRING REQUIRING DRUG TREATMENT

Confirmed: A written report in the medical record documenting: (A) myocardial ischemia and/or coronary artery disease, AND (B) use of medications given to treat or prevent angina (e.g., nitrates, beta blockers, calcium channel blockers)

Probable: Not applicable

CORONARY REVASCULARISATION

Confirmed: A written report in the medical record or hospital discharge summary from the hospitalization during which the procedure was performed for treatment of coronary artery disease, including: coronary artery bypass graft, coronary artery stent implant, coronary artherectomy, and percutaneous transluminal angioplasty

Probable: Not applicable

DECOMPENSATED LIVER DISEASE

A. Histologic, radiographic, or ultrasound evidence of cirrhosis, as documented by one of the following:

1. Histologic evidence of cirrhosis obtained by liver biopsy or autopsy
2. MRI or CT consistent with cirrhosis
3. A positive result on transient elastography (FibroScan) or other ultrasound imaging consistent with cirrhosis

B. Clinical evidence of decompensation, as documented by one of the following, and without an alternative explanation:

1. Ascites
2. Hepatic encephalopathy
3. Bleeding from gastric or esophageal varices
4. Spontaneous bacterial peritonitis

Confirmed: A+B

Probable: B

DEEP VEIN THROMBOSIS

A. Diagnosis of deep vein thrombosis (DVT) by contrast venography, helical computed tomography, MRI, or ultrasonography other comparable imaging techniques

B. An elevated D-dimer test OR abnormal plethysmography

C. A score on the Wells Clinical Prediction Rule for DVT of >=3 points

D. Absence of alternative diagnosis as likely or greater than that of deep venous thrombosis

Wells Clinical Prediction Rule for DVT

One point for each of the following:

- Active cancer (treatment ongoing or within previous 6 months, or palliative)
- Paralysis, paresis, or plaster immobilization of lower extremities
- Recently bedridden for more than 3 days, or major surgery, within 4 weeks
- Localized tenderness along distribution of the deep venous system
- Entire leg swollen
- Calf swelling by more than 3 cm when compared with the asymptomatic leg (measured 10 cm below tibial tuberosity)
- Pitting edema (greater in the symptomatic leg)
- Collateral superficial veins (non-varicose)

(Adapted from: Wells PS et al. Lancet 1997;350:1796)

Confirmed: A

Probable: B+C+D

DIABETES MELLITUS

A. Symptoms of diabetes plus casual plasma glucose concentration >= 200 mg/dL (11.1 mmol/L). (Casual is defined as anytime of day without regard to time since last meal. The classic symptoms of diabetes include polyuria and polydipsia).

B. Fasting plasma glucose >= 126 mg/dL (7.0 mmol/L). (Fasting is defined as no caloric intake for at least 8 hours).

C. 2-hour post-load glucose >= 200 mg/dL (11.1 mmol/L) during an oral glucose tolerance test. (The test should be performed as described by WHO, using glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water).

Confirmed: A or B or C

Probable: none

END-STAGE RENAL DISEASE

A. Hemodialysis or peritoneal dialysis for a period of at least one month, documented in a clinical note

B. A kidney transplant, documented in a clinical note.

Confirmed: A or B

Probable: Not applicable

NON-AIDS-DEFINING CANCER

A. Diagnosis of cancer other than lymphoma, Kaposi's sarcoma (KS), or invasive cervical cancer in an autopsy report

B. Diagnosis of cancer other than lymphoma, KS, or invasive cervical cancer in a pathology report that established the diagnosis

C. Diagnosis of cancer other than lymphoma, KS, or invasive cervical cancer in a hospital discharge summary or consultation note from the hospitalization or clinic visit during which the diagnosis was stablished

Confirmed: A or B

Probable: C

PERIPHERAL ARTERIAL DISEASE

A. Compatible clinical signs and symptoms (e.g., intermittent claudication, femoral bruit, decreased peripheral pulses, change in color or temperature of limb suggesting peripheral arterial disease)

B. Positive results on diagnostic imaging studies (e.g., Doppler ultrasound, contrast arteriography, MRI arteriography)

C. Ankle Brachial Pressure Index < 0.90 in non-diabetics

D. A procedure report, hospital discharge summary, or other medical record from the hospitalization during which the procedure was performed documenting an invasive procedure for treatment of peripheral arterial disease (e.g. percutaneous transluminal angioplasty, endovascular procedures, or vascular surgery), or a consultation note documenting the occurrence of the procedure.

Confirmed: (A+B) or (A+C) or D

Probable: A

PULMONARY EMBOLISM

A. Symptoms compatible with pulmonary embolism, such as shortness of breath, chest pain, or hemoptysis

B. Results consistent with a diagnosis of pulmonary embolism on pulmonary angiography, helical CT, ventilation-perfusion scan or other comparable imaging studies

C. A diagnosis of pulmonary embolism on autopsy

D. Results consistent with a diagnosis of deep venous thrombosis on venography, ultrasound, or other comparable imaging studies

E. A chest x-ray which, if performed, does not suggest an alternative etiology for the symptoms described in criteria A

Confirmed: (A+B) or C

Probable: A+D+E

STROKE

A. Acute onset with a clinically compatible course, including unequivocal objective findings of a localizing neurologic deficit

B. CT or MRI compatible with diagnosis of stroke and current neurologic signs and symptoms

C. Stroke diagnosed as cause of death at autopsy

D. Positive lumbar puncture compatible with subarachnoid hemorrhage

E. Death certificate or death note from medical record listing stroke as cause of death

Confirmed: (A+B) or C

Probable: (A+D) or (A+E)

Appendix 5: Participant Information Sheet and Consent Form

[Insert institutional logo]
[name of local institution/s where research is being conducted]

PARTICIPANT INFORMATION AND CONSENT FORM

A double blind randomised comparison of vorapaxar versus placebo for the treatment of HIV associated inflammation and coagulopathy in patients with well controlled HIV replication

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ADVICE Study: Attenuation of D-dimer using Vorapaxar to target Inflammatory and Coagulation Endpoints

Principal Investigator(s): *[insert]*

Site Address: *[insert]*

Invitation

You are invited to participate in the ADVICE research study to investigate the use of a new anti-clotting drug (vorapaxar sulphate) because you are currently being treated for Human Immunodeficiency Virus (HIV) infection with a combination of antiretroviral treatments that does not include HIV Protease Inhibitors and/or Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs) and you have a relatively high level of d-dimer in your blood. This is explained in more detail in section 1 below.

The study is being conducted by **[insert local institution name]**. The study is part of an international collaborative study sponsored by the Kirby Institute at the University of New South Wales in Australia and The National Institute of Allergy and Infectious Diseases (NIAID) in the USA.

Before you decide whether or not to take part in this research study, it is important that you understand why the study is being done, and what it will involve. Please read this information carefully and discuss with others if you wish.

1. What is the purpose of the study?

The main purpose of this study is to compare the safety and efficacy of vorapaxar versus placebo in reducing levels of chemical markers of clotting (d-dimer), immune activation and immune inflammation in people with well controlled HIV infection.

Some people with HIV infection (even very well controlled HIV infection) are at increased risk of death (from any cause), and both fatal and non-fatal episodes of cardiovascular, renal and hepatic disease and cancer. Higher than normal levels of chemicals in the body associated with blood clotting, immune activation and inflammation appear to be closely associated with these unwelcome outcomes. One of the chemicals the body produces after it has broken down a blood clot is called d-dimer. It is normally present in small quantities in the blood. When there are increased levels of d-dimer it suggests increased clotting activity in the body.

While combination antiretroviral therapy (cART) helps to reduce the level of chemicals associated with blood clotting, immune activation and inflammation, people with HIV infection still have higher levels of these chemicals than people without HIV infection. Vorapaxar may help to lower the level of these chemicals in the body.

Vorapaxar is an anti-clotting medication made by Merck & Co, Inc. It is approved by the U.S. Food and Drug Administration (FDA) for use with other medications to reduce the risk of heart attack in some people with existing cardiovascular disease. We want to see if vorapaxar will lower d-dimer levels in people with well-controlled HIV infection who are taking cART. We will also study the safety of vorapaxar treatment in this same group of people.

2. Why have I been invited to participate in this study?

You are being invited to participate in this study because you:

- are aged 40 years or older
- have well controlled HIV infection (plasma HIV RNA less than 50 copies/mL for at least 24 weeks and a CD4 T cell count >50 cells/mm^3)
- are being treated with combination antiretroviral treatments that does not include HIV Protease Inhibitors and/or Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)
- have elevated d-dimer levels in your blood (greater than 200 ng/mL)

3. What if I don't want to take part in this study or if I want to withdraw later?

Participation in this study is voluntary. It is completely up to you whether or not you participate. If you decide not to participate, it will not affect the treatment you receive now or in the future. Whatever your decision, it will not affect your relationship with the staff caring for you.

If you wish to withdraw from the study once it has started, you can do so at any time without having to give a reason and without affecting your medical care. However, data collected during your time on the study will still be used.

If you wish, any blood samples that can still be identified as yours will be destroyed.

If at any time your study doctor considers that it is in your best interest to be withdrawn from the study, he or she will explain the reasons and arrange for your care to continue.

4. What does this study involve?

If after reading this information and discussing the study with your doctor, you decide to take part you will be asked to sign a form confirming that you agree to participate. An ethics committee has reviewed and approved this study prior to any participant being allowed to enroll in the study.

New information about the treatment being studied may become available during the course of the study. You will be kept informed of any significant new findings that may affect your willingness to continue in the study.

A total of approximately 60 participants will participate from various approved sites in Australia and the USA. The study runs for 18 weeks. You will be required to attend the clinic 7 times over this period.

If you are eligible to enter the study, you will be randomised to receive either vorapaxar (one 2.5mg capsule) or one placebo capsule daily. A placebo is a medication with no active ingredients. It looks like the real thing but is not. You will be required to take the one capsule orally, once a day, with or without food. You will be required to stop taking the study treatment at the week 12 visit (for 6 weeks) and then be seen for a final visit at week 18.

'Randomised trial': Sometimes we don't know the best way of treating patients with a particular condition so comparisons need to be made between different treatments. To do this, study participants are put into groups and given different treatments, and the results are compared to see whether one treatment is better. To ensure the groups are similar to start with, a computer allocates each study participant into a group randomly, like the flip of a coin. You will have a 50% chance of receiving vorapaxar and 50% chance of receiving placebo. Neither the doctor nor the study participant can decide which treatment the participant receives.

This research project has been designed to make sure the researchers interpret the results in a fair and appropriate way and avoids study doctors or participants jumping to conclusions. You will be participating in a double-blind study. Neither you nor the study staff will know which treatment you are receiving. However, in case of emergency, this information can be made available to your study doctor. At the end of the study you will be told in which treatment you received.

By signing this informed consent form, you give permission for the researchers, authorised personnel from the UNSW, the ethics committee and government authorities to access your medical records to obtain information about you that is relevant to the study.

You need to attend the clinic for the specified study visits within the specified time periods and provide complete and accurate information about your health, including any changes to medications, as the study progresses. These requirements are in place to protect your safety and should be adhered to.

It is desirable that your local doctor be advised of your decision to participate in this research project. If you have a local doctor, we strongly recommend that you inform them of your participation in this research project. If you consent to participate in this study, we will also write to your local doctor to let them know you are participating in this study and provide them with information on medications that should not be prescribed during this time.

If you agree to participate in this study, you will then be asked to undergo the following procedures (see Table 1):

Initial Screening Visit (to determine whether you are eligible to enter the study)

- Discussion and completion of informed consent;
- Review of your medical history, full HIV history as well as previous and current medications;
- A physical examination based on any symptoms you are experiencing;
- Blood or urine pregnancy test if you are a women of child-bearing potential;
- Blood tests:
  - Biochemistry tests to measure the level of salts in your blood, kidney and liver function tests,
  - Haematology tests to measure the number of red blood cells, white blood cells and platelets (these help your blood to clot),
  - HIV viral load (the amount of HIV in your blood),
  - Immune monitoring tests to measure the number of CD4 and CD8 T cells,
  - Chemistry tests to measure your d-dimer levels.

The total amount of blood drawn at this visit will be approximately 26 mLs (approximately 1.7 tablespoons where 1 tablespoon equals 15 mLs).

Day 0/Randomisation Visit (commence study drugs)

If you are found to not be eligible you will be informed of this by the site staff. You will not need to return to the clinic for this study. If you are found to be eligible you will be asked to come back to the clinic (up to 14 days after your initial screening visit) to complete baseline assessments and be randomised to a treatment arm.

You will need to be fasted (you can drink plain water but must not have anything else to eat or drink for at least 8 hours) for this visit.

At this visit, the following assessments will take place:

- Medical history, including review of current medications and any side effects;
- Physical examination (height, weight and blood pressure) and examination based on any symptoms you are experiencing;
- Blood or urine pregnancy test if you are a woman of child-bearing potential;
- Blood tests:
  - The same biochemistry, liver and kidney function, haematology and HIV viral load tests as at screening will be repeated,
  - Immune monitoring tests to measure the numbers of CD4 and CD8 T-cells,
  - Metabolic tests to measure your blood fats (different types of cholesterol, triglycerides),
  - Test a protein (PAR-1) that is part of the clotting system,
  - Storage bloods, these are bloods that are taken and stored for measuring chemical markers of clotting and immune function as well as HIV research later on. There is more information provided below on how these samples will be used later on to increase our understanding of the HIV virus, the immune system and the complications of HIV infection.

The total amount of blood drawn at this visit will be approximately 86 mLs (5.7 tablespoons where 1 tablespoon equals 15 mLs).

You will be supplied with a one month supply of study treatment. You should commence taking your randomised study treatment within 1 day of your randomisation visit (that is, the same day or the next day).

Follow up visits at week 1, 4, 8, 12 & 18

You will need to return to the clinic 1, 4, 8, 12 and 18 weeks after you have been randomised. You do not need to be fasting for these follow up visits. The following assessments will take place during these visits:

- Your blood pressure will be measured and a physical examination based on any symptoms you are experiencing (all follow up visits). Your weight will be checked again at week 18
- Review of any medical issues you report and a review of all your medications and any side effects (all follow up visits)
- Blood or urine pregnancy test if you are a woman of child-bearing potential (all follow up visits but not at week 1)
- Blood tests:
  - The same haematology, HIV viral load and CD4 and CD8 T-cell tests (all follow up visits),
  - The same biochemistry, liver and kidney function tests (at weeks 12 and 18 only),
  - The same PAR-1 test (all follow up visits but not at week 8),
  - Storage bloods, these are the bloods that are taken and stored for measurement of clotting and immune function as well as other HIV research later on (all follow up visits).

At the week 1, week 4 and week 8 follow up visits the total amount of blood drawn at these visits will be approximately 67 mLs (4.5 tablespoons where 1 tablespoon equals 15mLs). At the week 12 and week 18 visit, the total amount of blood drawn at these visits will be approximately 86mLs (5.7 tablespoons where 1 tablespoon equals 15mLs).

Additional blood draw if you have a bleeding event

If you have a significant bleed during the study, you will have another blood test to check your haemoglobin levels, where approximately 4 mLs of blood will be collected (0.3 tablespoons where 1 tablespoon equals 15mLs). Your doctor will decide if you require this test.

Table 1. Patient visit schedule

Study week number	Screening	Wk 0	Wk 1	Wk 4	Wk 8	Wk 12	No study drug	Wk 18
Clinical assessments								
Informed consent	•							
Doctor/Nurse reviews medical and HIV history	•							
Doctor/Nurse reviews medications and any side-effects	•	•	•	•	•	•		•
Physical examination based on symptoms you may be experiencing	•	•	•	•	•	•		•
Physical examination: blood pressure		•	•	•	•	•		•
Physical examination: weight		•						•
Height		•						
Blood/urine tests								
Fasting blood tests		•						
Biochemistry	•	•				•		•
Liver Function	•	•				•		•
Haematology	•	•	•	•	•	•		•
Viral load	•	•	•	•	•	•		•
Immune monitoring tests		•	•	•	•	•		•
d-dimer levels tested	•	•	•	•	•	•		•
Storage bloods		•	•	•	•	•		•
Urine pregnancy test (if you are a woman of child-bearing age)	•	•		•	•	•		•
Provided with study medication		•		•	•			

Blood storage

Bloods will be stored at each visit from Week 0 to the last study visit at Week 18. The total amount of blood stored over the 18 week period will be approximately 316 mL (about 21 tablespoons).

Approximately 62 mL (4.1 tablespoons) of blood will be stored at weeks 0, 12 and 18. 48 mL (3.2 tablespoons) will be stored at weeks 1, 4 and 8. These blood samples will be stored for tests to be conducted at a later stage for this research project as well as future medical research that relates to the treatment of HIV, blood clotting, the immune system and the complications of HIV. No tests of your genes (human genetic tests) will be performed on these samples.

Some of the results from the tests done on your stored blood can be given to your doctor at the end of the study (tests for blood clotting and aspects of immune function). Other results cannot be given to you as the tests may not be conducted until years after the end of the study. None of the results from the tests undertaken are part of routine care. Therefore your health is not affected as a consequence of not knowing the results.

This is explained further in section 10 below.

5. How is this study being paid for?

Financial support to cover the costs of carrying out this study is being provided by The National Health and Medical Research Council of Australia.

All of the money being paid by the Sponsor to run the trial will be deposited into an account managed by [insert hospital/Area Health Service]. No money is paid directly to individual researchers.

6. Are there risks to me in taking part in this study?

All medical procedures involve some risk of injury. In addition, there may be risks associated with this study that are presently unknown or unforeseeable. In spite of all reasonable precautions, you might develop medical complications from participating in this study. The known risks of this study are:

Risk of bleeding

Vorapaxar, like other anti-clotting drugs increases the risk of bleeding. General risk factors for bleeding include older age, low body weight, reduced kidney or liver function, and a history of bleeding disorders. Taking vorapaxar with certain other medications, such as other anti-clotting drugs (eg. warfarin, enoxaparin or thienopyridine), opiates (cocaine, heroin and morphine) or aspirin, can also increase the risk of bleeding. The study doctor will carefully review the medications you are currently taking before you join this study; you will not be able to participate in this study if you are taking these types of medications.

The most common side-effects experienced by 20,108 people receiving vorapaxar in a previous study are outlined in the tables below. It is important to remember that these people had a history of heart attack or reduced blood flow in their legs and were taking other anti-clotting medications such as aspirin and clopidogrel.

	placebo	**vorapaxar**
Bleeding that needs medical treatment or bleeding that results in a significant drop in haemoglobin levels	9.5% (9.5 people out of every 100 people)	13.4% (13.4 people out of every 100 people)

In a total of 39,239 patients who have taken vorapaxar or placebo, other less common side effects have occurred at these rates:

	placebo	**vorapaxar**
Anemia	4 % (4 people out of every 100 people)	5% (5 people out of every 100 people)
Depression	2.1%	2.4%
Rashes or skin eruptions	2%	2.2%
Double vision /eye problems	0.06%	0.2%

Call your study doctor right away if you have any of these signs or symptoms of bleeding while taking vorapaxar:

- bleeding that is severe or that you cannot control
- pink, red, or brown urine
- vomiting blood or your vomit looks like "coffee grounds"
- red or black stools (looks like tar)
- coughing up blood or blood clots.

While you take vorapaxar and for about 4 weeks after your treatment with vorapaxar is stopped:

- you may bruise and bleed more easily (nose bleeds may be more common)
- it will take longer than usual for any bleeding to stop.

You should talk with your study doctor about any precautions you should take whilst participating in this study to reduce your risk of bleeding. eg. avoid contact sports.

There are no risks associated with taking placebo pills.

Interaction with other medications

There can be a risk of serious and/or life threatening side effects when non-study medications are taken with the study drug. For your safety, you must tell the study doctor or nurse about <u>all</u> medications you are taking <u>before</u> you start the study. You must tell any doctor you see <u>during</u> the study about all of the medications you are taking, especially before starting any new medications. This includes any other prescribed medicines, over-the-counter medicines, herbal medicines or supplements and illicit substances. In addition, you must tell the study doctor or nurse before enrolling in any other clinical trials while participating in this study.

It is recommended that if you experience headaches or any other pain during the trial that you use paracetamol instead of ibuprofen (Neurofen™). It is also important that you do not take any other non-steroidal anti-inflammatory medicines (NSAIDs) for longer than 5 consecutive days. This includes medicines such as celecoxib (celebrex™) and diclofenac (voltaren™). Ask your doctor if you are unsure about using any medications before you commence their use.

Despite all reasonable precautions there may be some risks that are unforeseeable. Participation in a study may impact on your employment or health insurance. You should be aware of any potential impact before agreeing to participate.

New information about the treatment being studied may become available during the course of the study. You will be kept informed of any significant new findings that may affect your willingness to continue in the study.

Risks of blood drawing

As part of this study, you will have your blood drawn 7 times over 18 weeks. This procedure can be uncomfortable but rarely results in any significant problems. Side effects that have been noted with drawing blood include feeling light-headed or faint, fainting, formation of a blood clot, bruising and/or infection at the site of the needle stick.

Pregnancy and breast feeding

- ***<u>Women</u>***

It is important that women participating in this study are not pregnant and do not become pregnant during the course of the study. If you are a woman of child-bearing potential and there is any possibility that you are pregnant, the researchers will perform a pregnancy (urine) test before you start in the study. With limited data on vorapaxar in pregnancy, women must avoid becoming pregnant during the course of this study.

[Insert for SVH patients only]
You should speak to the study doctor about the need to avoid pregnancy during this study.

[Insert for Non Catholic sites delete for Catholic sites]
If necessary, you should use reliable contraception (such as oral or implanted contraception, an IUD or have had a tubal ligation) during the course of the study.

If you do become pregnant during the study, you should tell your study doctor immediately. It is advised that pregnant women discontinue the use of vorapaxar until the conclusion of the pregnancy. Your study doctor will discuss the options with you at that time and will follow your progress until the baby is born.

If you are found to be pregnant, information on any prenatal tests and the outcome of the pregnancy will be collected. If you agree, this pregnancy data will be submitted to the Antiretroviral Pregnancy Registry, an international register that collects data on antiretroviral treatment and pregnancy outcomes in order to monitor the safety of antiretroviral drugs.

Please make your obstetrician aware of your study participation. Your study doctor will ask that you, or your obstetrician, provide updates on the progress of your pregnancy and its outcome. The study doctor will make this information available to the study sponsor for safety monitoring follow-up.

- ***Men***

If your spouse or partner thinks she is pregnant during the study, tell your study doctor immediately. If your partner becomes pregnant, she will be asked to sign a release of information form to allow your study doctor to contact her obstetrician to collect updates on the progress of the pregnancy and its outcome. The study doctor will make this information available to the study sponsor for safety monitoring follow-up.

You need to attend the clinic for the specified study visits within the specified time periods and provide complete and accurate information about your health, including any changes to medications, as the study progresses. These requirements are in place to protect your safety.

7. What happens if I suffer injury or complications as a result of the study?

[St Vincent's Hospital wording]

If you suffer any injuries or complications as a result of this study, you should contact the study doctor as soon as possible, who will assist you in arranging appropriate medical treatment. If you are eligible for Medicare, you can receive any medical treatment required to treat the injury or complication, free of charge, as a public patient in any Australian public hospital.

You may have a right to take legal action to obtain compensation for any injuries or complications resulting from the study. Compensation may be available if your injury or complication is caused by the drugs or procedures, or by the negligence of any of the parties involved in the study. If you receive compensation that includes an amount for medical expenses, you will be required to pay for your medical treatment from those compensation monies.

If you are not eligible for compensation for your injury or complication under the law, but are eligible for Medicare, then you can receive any medical treatment required for your injury or complication free of charge as a public patient in any Australian public hospital.

The parties to this study agree to follow the Medicines Australia Guidelines for Compensation for Injury Resulting from Participation in an Industry-Sponsored Clinical Trial. These Guidelines allow for some claims for compensation to be settled without the need for legal action to be taken. The fact that the parties have agreed to abide by these guidelines in respect of the clinical trial does not affect your rights to pursue a legal remedy in respect of any injury you may suffer as a result of participation. You can obtain a copy of these Guidelines from the Secretary of the Human Research Ethics Committee.

[MSHC wording]

If you suffer any injuries or complications as a result of this study, you should contact the study doctor as soon as possible, who will assist you in arranging appropriate medical treatment. If you are eligible for

Medicare, you can receive any medical treatment required to treat the injury or complication, free of charge, as a public patient in any Australian public hospital.

You may have a right to take legal action to obtain compensation for any injuries or complications resulting from the study.

8. Will I benefit from the study?

The information we obtain in this study will help us learn more about the use of vorapaxar treatment in people with HIV infection; however it may not directly benefit you.

9. Will taking part in this study cost me anything, and will I be paid?

Participation in this study will not cost you anything. Your reasonable travel expenses up to $50 for each clinic visit will be provided. You will not be paid or reimbursed for participating in this study.

10. What will happen to my blood sample after it has been taken?

You will be asked whether you agree to have some of your blood stored. These specimens will be stored temporarily at your local laboratory and then sent to the central laboratory, St Vincent's Centre for Applied Medical Research (AMR) in Sydney. Some of your stored samples will be then sent to a laboratory at the National Institute for Infection and Disease (NIAID) in Maryland (USA) for testing for this research project. The rest will remain at AMR in Sydney for long-term storage for testing for this research project and future HIV research.

If you agree to your blood samples being stored, they will be used for this study and future medical research that relates to the treatment of HIV. Not all potentially beneficial future research can be known at any one time, as the need for future research is determined by ongoing developments in the field indefinitely for future research. The Human Research Ethics Committee will determine whether, or not, your consent should be obtained at that time for a particular research project.

Your stored sample will not be used by private or for-profit entities, or for research leading to the development of commercial products.

11. How will my confidentiality be protected?

Of the people treating you, only the study doctor and study coordinator will know whether you are participating in this study. Any identifiable information that is collected about you in connection with this study will remain confidential and will be disclosed only with your permission, or except as required by law. Your health records and any information obtained during the research project are subject to inspection (for the purpose of verifying the procedures and data) by the relevant authorities and authorised representatives of the Sponsor (University of New South Wales), the institution relevant to this Participant Information Sheet [insert name of MSHC or St Vincent's Hospital] or as required by law. By signing the Consent Form, you authorise release of, or access to, this confidential information to the relevant study personnel and regulatory authorities as noted above. Your study results will be held securely at [insert name of MSHC or St Vincent's Hospital].

Only non-identifiable information will be sent off site. Your name will not appear on any of the information sent to the sponsor; instead your information will be coded using a unique study number and your initials. Your blood samples that are kept in storage will only be labelled with a unique study number.

12. What happens with the results?

If you give us your permission by signing the consent document, we may discuss/publish the results e.g. in peer-reviewed medical and scientific journals, presentations at conferences or other professional forums.

In any publication, information will be provided in such a way that you cannot be identified. The study results will be provided to you, if you wish.

In any publication, information will be provided in such a way that you cannot be identified.

13. What happens to my treatment when the study is finished?

Vorapaxar will not be available after the study finishes. After the end of the study, you will continue to be cared for in the usual way.

14. What should I do if I want to discuss this study further before I decide?
When you have read this information, the researcher [insert name here] will discuss it with you and any queries you may have. If you would like to know more at any stage, please do not hesitate to contact him/her on [insert number here]

15. Who should I contact if I have concerns about the conduct of this study?

This study has been approved by St Vincent's Hospital HREC. Any person with concerns or complaints about the conduct of this study should contact the Research Office who is nominated to receive complaints from research participants. You should contact them on
tel: 02 8382 2075 and quote /14/SVH/413.

The conduct of this study at [insert site name] has been authorised by the St Vincent's Hospital/Alfred Hospital Governance office. Any person with concerns or complaints about the conduct of this study may also contact the Research Governance Officer on tel: 02 8382 2075 and quote reference number: /14/SVH/413.

Thank you for taking the time to consider this study.
If you wish to take part in it, please sign the attached consent form.
This information is for you to keep or dispose of as you see fit.

[Insert institutional logo]
[name of local institution/s where research is being conducted]

CONSENT FORM

To be used in conjunction with Participant Information

ADVICE Study: Attenuation of D-dimer using Vorapaxar to target Inflammatory and Coagulation Endpoints

1. *I agree to participate as a participant in the study described in the Participant Information attached to this form.*

2. *I acknowledge that I have read the Participant Information, which explains why I have been selected, the aims of the study and the nature and the possible risks of the investigation, and the information has been explained to me to my satisfaction.*

3. *Before signing this consent form, I have been given the opportunity to ask any questions relating to any possible harm I might suffer as a result of my participation and I have received satisfactory answers.*

4. *I understand that I can withdraw from the study at any time without prejudice to my relationship with my doctor or to the University of New South Wales [or insert name of local institution].*

5. *I agree that research data gathered from the results of the study may be published, provided that I cannot be identified.*

6. *I understand that if I have any questions relating to my participation in this research, I may contact [insert name] on telephone [insert phone number], who will be happy to answer them.*

7. *I agree to have my blood samples stored for this study as well as future research studies related to HIV infection and immunity.*

8. *I understand that some of the exact studies for which my stored samples shall be processed are not yet known.*

9. *I understand that my local doctor (if applicable) will be informed by the study team in writing of my participation in this research study.*

10. *I acknowledge receipt of a copy of this Consent Form and the Participant Information.*

11. *For women of child bearing potential only: In the event of pregnancy,*
    - *□I agree to have pregnancy data submitted to the Antiretroviral Pregnancy Registry ___(Patient's initial);*
    - *□I do not agree to have pregnancy data submitted to the Antiretroviral Pregnancy Registry ____ (Patient's initial).*

Complaints may be directed to [insert local details]

Signature of participant	**Please PRINT name**	**Date**
Signature of witness*	**Please PRINT name**	**Date**
Signature of investigator	**Please PRINT name**	**Date**

*"By signing the consent form, the witness attests that the information in the consent form and any other written information was accurately explained to, and apparently understood by, the subject or the subject's legally acceptable representative, and that informed consent was freely given by the subject or the subject's legally acceptable representative" (**ref: ICH GCP 4.8.9**)

[Insert institutional logo]
[name of local institution/s where research is being conducted]

ADVICE Study: Attenuation of D-dimer using Vorapaxar to target Inflammatory and Coagulation Endpoints

REVOCATION OF CONSENT

I hereby wish to **WITHDRAW** my consent to participate in the study described above and understand that such withdrawal **WILL NOT** jeopardise any treatment or my relationship with the **Insert Site Name** or my medical attendants.

_____	_____	_____
Signature of participant	**Please PRINT name**	**Date**

The section for Revocation of Consent should be forwarded to *[insert details]*

Appendix 6: Investigator Agreement and Signature Page

between the UNSW/Sponsor (if applicable) and the study investigator(s)

Site Name:

Principal Investigator:

Co-investigators (please list, if applicable):

Study Title: **ADVICE: Attenuation of D-dimer using Vorapaxar to target Inflammatory and Coagulation Endpoints: A double blind randomised comparison of vorapaxar versus placebo for the treatment of HIV associated inflammation and coagulopathy in patients with well controlled HIV replication**

Protocol Version Number: 3

Protocol Version Date: 12 July 2016

I/We agree to follow the procedures outlined in this protocol. I/We accept responsibility for the conduct of the research detailed in the proposal including all protocol-specific assessments, and I/We agree to abide by all decisions made by our Ethics Committee and Regulatory Agency. I/We agree to ensure the informed consent process is conducted with each participant in compliance with ICH GCP guidelines.

PRINCIPAL/RESPONSIBLE INVESTIGATOR
(signature and date)

_____

CO-INVESTIGATOR(S)
(signature/s and date/s)

_____

SPONSOR'S REPRESENTATIVE
(signature and date)

_____

_____

_____

SPONOR'S MONITOR(S)/COORDINATOR(S)
(signature/s and date/s)

_____

_____