CLINICAL TRIAL PROTOCOL WITH DRUGS

Cost-effectiveness of different antiretroviral treatment regimens in naïve patients. Randomized, open-label clinical trial comparing DRV/r+3TC, AUC+3TC (Kivexa)+RPV, or EVG/COBI/FTC/TDF (Stribild) for 48 weeks

Protocol Code: Cost-Effect-Clinic

Version / Date: 1.0 / October 04, 2014 EudraCT number: 2014-004820-24

SPONSOR: Clinic Foundation for Biomedical Research
Principal Investigator and coordinator of the study:
Dr. Josep Mallolas
Infectious Diseases Service. Hospital Clínic de Barcelona.
Spain.
Phone: +34 932275400 / ext 3312 Email: mallolas@clinic.ub.es

1. SUMMARY

1.0. Type of application:

Prospective, comparative, randomized, open-label, single-center, phase IV clinical trial.

1.1. Identification of the developer:

Clínic Foundation for Biomedical Research
C. Roselló, 143
08036 Barcelona

1.2. Clinical Trial Title:

Cost-effectiveness of different antiretroviral treatment regimens in naïve patients. Randomized, open-label clinical trial comparing DRV/r+3TC, AUC+3TC (Kivexa)+RPV, or EVG/COBI/FTC/TDF (Stribild) for 48 weeks

Version / Date: 1.0 / October 4, 2014.

1.3. Protocol code: Cost-Effect-Clinic.

EudraCT number: 2014-004820-24

1.4. Principal Investigator and Study Coordinator: Dr Josep Mallolas,

Collaborating Investigators: Dr Maria Martínez

1.5. Centres in which the trial is planned to be carried out:

The study will be Unicentric (Hospital Clínic de Barcelona).

1.6. Clinical Research Ethics Committees that have approved the trial:

The trial has been submitted to the CEIC of the Hospital Clínic de Barcelona.

1.7. Name and qualification of the person responsible for monitoring:

Dr. Anna Cruceta.
Clinical Trials Unit.
CTU Clinic. Clinical Pharmacology Service.
(Hospital Clínic de Barcelona).

1.8. Information about study medications:

DRV/r+3TC,
ABC+3TC (Kivexa)+ RPV
ECG / COBI / FTC / TDF (Stribild)

1.9. Clinical Trial Phase: Phase IV

1.10. Objectives:

1.10.1. Main objective:

The main objective of this study is to determine the efficiency (cost-effectiveness) or cost per responder) at 48 weeks after initiation of antiretroviral treatment, taking as a reference the Stribild arm

1.10.2. Secondary objectives:

- Virologic efficacy at 48 weeks (using standard plasma viral load with a limit of detection of 50 copies/mL)
- CD4+ Cell Response
- Change in body composition and bone mineral density (body and lumbar) measured with DEXA
- Renal function markers (creatinine, estimated glomerular filtration rate (eGFR)) and renal tubular function
- Mortality and clinical progression
- Safety study, including: vitamin D levels, plasma lipids at the beginning and end of the study, as well as overall tolerability.

1.11. Design:

Prospective, comparative, three-parallel-group, randomized, open-label, single-center, Phase IV clinical trial.

1.12. Disease under study:

HIV infection

1.13. Assessment variables:

1.13.1. Principal

Cost-effectiveness of antiretroviral therapy at 48 weeks from baseline, based on the Stribild arm.

Economic evaluation of costs and efficiency (cost/effectiveness) through the construction of decision trees. Efficacy was defined as the probability of having a viral load <50 copies/mL at week 48 in intention-to-treat analysis. The cost of starting treatment with a regimen was defined as the costs of ART and all its consequences (adverse effects, changes in antiretroviral regimen, resistance study, days of work missed by the patient and number of days of hospital admission) that occur in the following 48 weeks. The perspective of the National Health System was used, considering only differential direct costs: drugs (at official price), management of adverse effects, resistance studies and determination of HLA B*5701. The scope is the Spanish state, with updated costs. Deterministic sensitivity analyses were performed constructing three scenarios for each guideline: baseline, most favorable and most unfavorable.

The application to calculate the prices of antiretrovirals is located on the GSIDA website and can be accessed completely free of charge.

http://www.gesida-seimc.
org/contenidos/utilidades/aplicacion-tarv-vih-gesida-2014.exe or
https://dl.dropboxusercontent.com/u/35731022/coste-eficacia-2014/aplicacion-tarv-vih-gesida-2014.exe.

1.13.2. Secondary

- Proportion of patients with virologic response at 48 weeks (plasma viral load less than 50 copies/mL)
- Change in CD4+ cell count at 48 weeks
- Change in body composition and bone mineral density (body and lumbar) measured with DEXA at baseline and at 48 weeks
- Change in markers of renal function (creatinine, estimated glomerular filtration rate – eGFR-) and renal tubular function at 48 weeks
- Mortality rate and clinical progression at 48 weeks
- Safety and overall tolerability: description of adverse events (AEs) and serious AEs.

1.14. Study population and total number of patients:

Adult patients with chronic HIV infection who have not received antiretroviral treatment.

A total of 150 patients will be included, 50 per arm, to detect differences in the cost-effectiveness ratio of more than €300 per year.

1.15. Duration of treatment:

The approximate expected duration for the inclusion of patients is 12 months; The duration of treatment will be 48 weeks.

1.16. Schedule and expected completion date:

The study is expected to begin, once permits have been obtained, in March 2015. The recruitment period will be one year. Patients will be followed for 48 weeks from the start of treatment. The study is expected to be completed after the last visit of the last patient included in March 2017.

1. INDEX

Annexes and documents:

3. Overview

3.1 Trial identification

Title:
Cost-effectiveness of different antiretroviral treatment regimens in naïve patients. Randomized, open-label clinical trial comparing DRV/r+3TC, AUC+3TC (Kivexa)+RPV, or EVG/COBI/FTC/TDF (Stribild) for 48 weeks

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3.2 Developer Identification

Clinic Foundation for Biomedical Research.
C/ Rossello 143
8036 elona

3.3 Identification of the promoter's representative

Manager: Ms. Rosa Vilavella Gasull Clinical Foundation for Biomedical Research. C/ Rossello 143
8036 elona

3.4 Identification of researchers of the sponsoring entity

Hospital Clínic
Principal Investigator and Study Coordinator:
Dr. Josep Mallolas Masferrer
Infectious Diseases Service.

Collaborating researchers:
Dr Maria Martínez from the Infectious Diseases Service

3.5 Identification of principal investigators from participating centers

The study is single-center. It will be held at the Hospital Clinic of Barcelona

3.6 Identification of researchers from other services involved.

Biostatistician: Elisa DeLazzari
Pharmacy: Begoña Gómez, GloriaMolas
Laboratory Technician: Pilar Callau

3.7 Information on the laboratories or technical departments involved

Clinical evaluation of patients included in the study, routine blood/urine laboratory determinations and viral (HIV) determinations, will be performed at the Infections Day Hospital. And Retrovirology and Immunopathology Laboratory of the Infection Service:

3.8 Monitoring

CTU (Clinical Trials Unit). Clinical
Pharmacology Service. Hospital
Clínic de Barcelona

Monitoring manager: Dr. Anna
Cruceta. acruceta@clinic.ub.es
tel 932275400 ext 4380 fax 932279877

4. Justification

HIV-infected patients can live longer thanks to effective antiretroviral treatment. In addition, efforts are being made to diagnose people who may be infected with HIV as soon as possible, and the initiation of antiretroviral treatment is increasingly recommended and at earlier stages.

On the other hand, antiretroviral treatment must be administered indefinitely. All these factors have contributed to the incessant increase in the budget for antiretroviral treatment, in such a way that its provision free of cost represents a major challenge for public health systems even in developed countries such as Spain.

Stribild ® has become standard of care in patients not previously treated with antiretrovirals. It is a triple antiretroviral treatment option in a single pill, very effective, well tolerated and whose treatment cost is competitive compared to other options in naïve patients.

Kivexa ® + RPV was tested in the Thrive study and the overall result was similar to Truvada ® + RPV. However, the direct cost may be lower, the more favorable cost-effectiveness, renal tubular toxicity, and the reduction in bone mineral density should be lower.

Finally, the efficacy of a nucleoside analogue-sparing regimen composed of LPV/r +3TC in patients without prior antiretroviral treatment was demonstrated in the Gardel study (even among those patients with a high baseline viral load). Most likely, substituting LPV/r for DRV/r would be associated with an even better outcome, including better tolerance. Considering that 3TC, the combination of ritonavir-boosted PI in treatment-naïve patients may be associated with the most favorable cost-effectiveness.

Hypothesis:
In naive patients, DRV/r + 3TC or Kivexa ® + RPV will have a similar cost-effectiveness (efficiency) compared to Stribild ® at 48 weeks in patients not previously treated with ARV and with a baseline viral load below 100,000 copies of HIV per mL.

4.1 Identifying investigational drugs

Study Guidelines:

1. Darunavir 800 mg (Prezista®) 1 pack of 800 mg + Ritonavir 100 mg (Norvir®) 1 tablet of 100mg + lamivudine (Epivir®) 1 pack of 300 mg. QD. When Darunavir

800 mg plus Cobicistat 150 mg is marketed as a single tablet, DRV/r will be replaced by said single tablet.

1. Abacavir 600 mg + lamivudine 300mg (Kivexa®) 1cp + rilpivirine (Edurant®) 1 coated purchase of 25 mg. QD. With food.
2. EVG / COBI / FTC / TDF (Stribild®) 150 mg de elvitegravir, 150 mg de cobicistat, 200 mg de emtricitabina y 245 mg de tenofovir disoproxil. 1 compr recubierto QD

4.2 Investigational Drug Information

The antiretrovirals used in the study are approved and registered in the European Union for use in patients with HIV infection.

4.3 Treatment Dosage Guidelines

1. Guideline 1: (Prezista®): 1 tablet + (Norvir®) 1 tablet (Epivir®) 1 tablet. In total: three tablets orally once daily
2. Guideline 2: (Kivexa®) 1 tablet + (edurant®) 1 coated tablet. In total two tablets orally once a day
3. Regimen 3: (Stribild®) 1 tablet. In total one tablet orally once a day.

Description:

These drugs are all indicated for the treatment of human immunodeficiency virus-1 (HIV-1) infection in adults 18 years of age or older.

The study is an initiative of an independent promoter and does not receive any grant or financial aid from the pharmaceutical industry or any other institution. It is self-financed with funds from the infectious diseases service of the Hospital Clínic

Route of administration: oral

Storage: Keep in the original packaging to protect it from moisture. Keep the bottle tightly closed. The treatments used in the study do not require special conditions for their conservation.

Study period and treatment:

Randomization to three treatment groups:

GROUP 1 (control): (prezista®): 1 tablet + (norvir®) 1 tablet (epivir®) 1 tablet. In total: three tablets orally once daily for a period of 48 weeks.

GROUP 2 (control): (Kivexa®) 1 tablet + (edurant®) 1 coated tablet. In total, two tablets orally once a day for a period of 48 weeks.

GROUP 3: (experimental)(Stribild®) 1 tablet. In total, one tablet orally once a day for a period of 48 weeks.

4.4 Compliance Statement

General considerations:

The study will be carried out in accordance with the principles emanating from the Declaration of Helsinki (see annex), and in accordance with current legal regulations (Royal Decree 223/2004), and will not begin until the approval of the CEIC and the authorisation of the AEMPS have been obtained.

4.5 Study population

Adults with HIV-1 infection who have not received antiretroviral treatment and who attend the Infectious Diseases Service of the Hospital Clinic of Barcelona.

4.6 Relevant Bibliography

1. Blasco AJ, et al. Costs and cost-efficacy analysis of the 2014 GESIDA/Spanish National AIDS Plan recommended guidelines for initial antiretroviral therapy in HIV-infected adults. Enferm Infecc Microbiol Clin. 2014.
2. A randomized, double-blind comparison of single-tablet regimen elvitegravir/cobicistat/emtricitabine/tenofovir DF vs ritonavir-boosted atazanavir plus emtricitabine/tenofovir DF for initial treatment of HIV-1 infection: analysis of week 144 results. Clumeck N, Molina JM, Henry K, Gathe J, Rockstroh JK, DeJesus E, Wei X, White K, Fordyce MW, Rhee MS, Szwarcberg J; GS-236-0103 Study Team. J Acquir Immune Defic Syndr. 2014 Mar 1; 65(3):e121-4.
3. A randomized, double-blind comparison of single-tablet regimen elvitegravir/cobicistat/emtricitabine/tenofovir DF versus single-tablet regimen efavirenz/emtricitabine/tenofovir DF for initial treatment of HIV-1 infection: analysis of week 144 results. Wohl DA1, Cohen C, Gallant JE, Mills A, Sax PE, Dejesus E, Zolopa A, Liu HC, Plummer A, White KL, Cheng AK, Rhee MS,Szwarcberg J; GS-US-236-0102 Study Team. J Acquir Immune Defic Syndr. 2014 Mar 1; 65(3):e118-20.
4. Cohen CJ, Andrade-Villanueva J,Clotet B, et al.on behalf of the THRIVE study group. Rilpivirine versus efavirenz with two background nucleoside or nucleotide reverse transcriptase inhibitors in treatment-naive adults infected with HIV-1 (THRIVE): a phase 3, randomised, non-inferiority trial. The Lancet, Volume 378, Issue 9787, Pages 229 - 237, 16 July 2011
5. Cahn P et al. Dual therapy with lopinavir/ritonavir (LPV/r) and lamivudine (3TC) is non- inferior to standard triple drug therapy in naive HIV-1 infected subjects: 48-week results of the GARDEL study.14th European AIDS Conference, Brussels, abstract LBPS7/6, 2013.

5. Objective and Purpose of the Trial

Principal:

The main objective of this study is to know the efficiency (cost-effectiveness) at 48 weeks after initiation of antiretroviral treatment of three treatment strategies

Side:

1. Proportion of patients with virologic response at 48 weeks (plasma viral load less than 50 copies/mL)

- Change in CD4+ cell count at 48 weeks
- Change in body composition and bone mineral density (body and lumbar) measured with DEXA at 48 weeks
- Change in markers of renal function (creatinine, estimated glomerular filtration rate – eGFR-) and renal tubular function at 48 weeks
- Mortality rate and clinical progression at 48 weeks
- Safety and overall tolerability: description of adverse events (AEs) and serious AEs.

6.0 Trial Design

Prospective, open-label, Phase IV, pilot, single-center prospective study.

6.1 Primary and secondary Endpoints

Primary Endpoint:

The main objective of this study is to know the efficiency (cost-effectiveness) at 48 weeks after initiation of antiretroviral treatment. of three treatment strategies

Methodology: The economic evaluation of costs and efficiency (cost/effectiveness) is carried out through the construction of decision trees. Efficacy was defined as the probability of having a viral load
<37 copies/mL at week 48 in intention-to-treat analysis. The cost of starting treatment with a regimen was defined as the costs of ART and all its consequences (adverse effects, changes in antiretroviral regimen, resistance study if necessary, days of sick leave by the patient and days of hospital admission) that occur in the following 48 weeks. The perspective of the National Health System will be used, considering only differential direct costs: drugs (at official price), management of adverse effects, resistance studies and determination of HLA B*5701. The scope is Spain, with updated costs. Deterministic sensitivity analyses will be performed by constructing three scenarios for each guideline: baseline, most favorable and most unfavorable.

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http://www.gesida-seimc.
org/contenidos/utilidades/aplicacion-tarv-vih-gesida-2014.exe or
https://dl.dropboxusercontent.com/u/35731022/coste-eficacia-2014/aplicacion-tarv-vih-gesida-2014.exe.

Secondary endpoints:

- Proportion of patients with virologic response at 48 weeks (plasma viral load less than 50 copies/mL)
- Change in CD4+ cell count at 48 weeks
- Change in body composition and bone mineral density (body and lumbar) measured with DEXA at 48 weeks
- Change in markers of renal function (creatinine, estimated glomerular filtration rate – eGFR-) and renal tubular function at 48 weeks
- Mortality rate and clinical progression at 48 weeks

6.2 Design

Although the hypothesis of the study has been based on various congruent information that allow us to face with sufficient guarantee the feasibility of the study and the eventual demonstration of the main hypothesis, we are not absolutely certain that an unacceptably high virological failure rate (standard viral load ≥37 copies/mL on two consecutive occasions) may occur in the experimental arm. We will consider a priori that the failure of at least 20% (n=6) of the patients in the experimental arm will represent an unacceptably high virological failure rate. In this case, its conclusion will be considered premature. In this extreme case, the data of the patients already included up to the time of the premature conclusion of the study would be analyzed.

The present study is proposed as a proof of concept to be able to formulate another study with a sufficiently large sample size to adequately demonstrate the non-inferiority of the strategy. The results of the present study can help to design the non-inferiority study and to estimate its sample size.

STUDY PROCEDURES

Vital signs	X
Weight Determination	X
Height determination	X
Demographics	X
Medical history	X
Physical examination	X
Concomitant Medications	X
Confirmation of the use of contraceptive methods by the patient and his or her partner	X

Clinical Evaluations	*Basal Day 0*	*S 4 (#)*	*S 12 (#)*	*S 24 (#)*	*S 36 (#)*	*S 48 (#)*
Meet inclusion and exclusion criteria	X					
Signed informed consent	X					
Vital signs	X					
Weight	X					X
Physical examination	X	X	X	X	X	X
Adverse events		X	X	X	X	X
Concomitant Medications	X	X	X	X	X	X
Simplified Compliance Questionnaire		X	X	X	X	X
Haematology	X			X		X
Blood biochemistry with GFR and renal function	X			X		X
Standard plasma viral load	X	X	X	X	X	X
Immunology (CD4/CD8)	X		X			X
DEXA	X					X
Pregnancy test (only in women susceptible to pregnancy (&)	X	X	X	X	X	X
Urinalysis (basic) (*)	X			X		X
Questionnaire on loss of working days/days of income		X	X	X	X	X

All laboratory specimens should be obtained prior to administration of the first dose of study medication.

& At baseline visit it is advised to perform a blood pregnancy test

* Basic sediment, proteinuria, hematuria, protein/creatinine ratio.
Blood biochemistry: lipids (TG, total cholesterol and HDL), creatinine and estimated glomerular filtration rate (CPK-EPI),
Hematology: basic blood count

6.3 Guidelines for Modifying Patient Treatment Doses

Grade 1 and 2 AEs require close follow-up but no change in treatment.

All grade 3 toxicities will be treated by the investigator of the center according to medical criteria.

Any grade 4 toxicity that, in the opinion of the investigator of the center, is directly related to the treatment of the study, will be treated with the permanent suspension of the study.

In all cases, the recommendations contained in each of the technical data sheets of the drugs used in this study will be followed (see Fact Sheets)

6.4 Trial Treatments

DRUG SUPPLY AND LABELLING

This study uses drugs that have already been marketed and authorized for use in HIV-infected patients; The study drug will be distributed by the Pharmacy service of the Hospital Clínic. For clinical trials carried out in Spain, labelling in Spanish is mandatory in accordance with the regulations currently in force.

6.5 Trial duration

The approximate expected duration for the inclusion of patients is 12 months, and the duration of treatment and follow-up of the included patients will be extended by a maximum of 48 weeks.

6.6 Termination and/or discontinuation criteria

The treatment will be **compulsorily** terminated during the study for any of the following reasons:

1. Virologic failure, defined by two consecutive standard viral load determinations >37 copies/mL separated by at least one week from each other.
2. I express the patient's wish.
3. Medical decision.
4. Death.

7. Pregnancy detection during the study.

Treatment **may** be terminated during the study for any of the following reasons:

8. The medical investigator determines that a SAE is possibly or likely related to the study drug.
9. Failure to administer, evaluate, or other study requirements.

If the confirmatory result is ≥37 copies/mL, a genotypic resistance detection study would be scheduled and the most appropriate attitude towards modifying their antiretroviral treatment would be discussed with the patient. In this case, unless he or she is against it, the patient would continue in the study.

The resistance study should be carried out only in case of virilological failure.

Do not confuse virological failure with viral load "blip". In case of detection of a single viral load determination > to 37 colpias/mL followed by an undetectable viral load determination, it shall be defined as blip.

To be considered virological failure, there must be **two consecutive determinations** of standard viral load >37 copies/mL separated by at least one week between them and a maximum of 4 weeks.

6.7 End of rehearsal

The end of the trial will be considered the time of the last visit of the last subject recruited.

7. Subject Selection

7.1 Inclusion criteria for subjects

A patient must meet ALL of the criteria listed below in order to participate:

1. Adults (≥18 years)
2. Negative pregnancy test in women of childbearing potential, and commitment to use acceptable contraceptive methods from at least 2 weeks before day 1 and until at least 6 months after the last dose of study drug.
3. Clinically stable HIV-1 infection and who have not received prior antiretroviral treatment
4. Have HIV viral load < 100,000 copies/mL
5. Have CD4 levels >100 mm3
6. Glomerular filtration rate of > 70ml/min
7. Have HLA B5701 negative
8. Patients must have given written informed consent
9. In the opinion of the researcher, to be able to follow the design of the protocol visits.

7.2 Exclusion Criteria

Patients who meet ANY of the following criteria will be excluded from the study:

1. Patients who have had previous virologic failure with any antiretroviral regimen
2. Evidence of prior mutations against some of the study drugs
3. Use of any other chronic antiretroviral therapy has been introduced within 6 months prior to the patient's entry into the study
4. Any contraindications to study drugs
5. Any condition that does not allow the patient to ensure correct adherence to the study at the discretion of the physician
6. Uncontrolled pre-existing psychiatric illness
7. Any current signs of alcoholism or active drug addiction

7.3 Withdrawal criteria

The initial antiretroviral treatment regimen may be changed in any of the following situations:

- Patient with virologic failure or clinical progression
- Serious adverse events possibly or probably related to the study drug.
- Pregnancy during the study.
- Express wish of the patient
- Medical criteria
- Patient non-adherence or non-compliance with study tests, evaluations, or other procedures.

All patients who, after starting the assigned treatment, abandon the treatment under study or are withdrawn for any reason, will be included in an analysis "by intention to treat".

Patients who do not continue to attend the visit (follow-up losses) will be considered for analysis until such time as the loss occurs.

8. Treatment of Subjects

8.1 Treatment Branches

A total of 150 patients will be included.

Randomization to three treatment groups in an equivalent ratio between arms (1:1:1). Random assignment will be centralized.

There will be no stratification by subgroups.

The list of random numbers will be generated by a computer program. The investigator will not know the size of the randomization blocks and will not be aware of the assignment of each patient until the time of inclusion.

The CRD data collection notebook will be electronic.

GROUP 1 (control): (prezista®): 1 tablet + (norvir®) 1 tablet (epivir®) 1 tablet. In total: three tablets orally once daily for a period of 48 weeks

GROUP 2 (control): (Kivexa®) 1 tablet + (edurant®) 1 coated tablet. In total, two tablets orally once daily for a period of 48 weeks

GROUP 3: (experimental)(Stribild®) 1 tablet. In total, one tablet orally once a day for a period of 48 weeks.

8.2 Concomitant and rescue medication

Any concomitant medication must be reflected in the CRF in an appropriate way (detailing the product, dosage, route, days of administration, reason for treatment, etc.).

Treatments not allowed:

Those specified in the technical sheets. (see technical sheets)

8.3 Compliance monitoring

Adherence: to ensure the control and registration of medication, an adherence questionnaire will be added to the data collection notebook. At each visit, the investigator will ask the patient about treatment adherence.

Tablet count: The patient will be asked to bring any leftover medication or empty bottles with them to check whether or not they have taken all the capsules or tablets of the medication since the previous visit.

9. Effectiveness Assessment

9.1 Efficiency parameters

Virological tests

a) Determination of viral load

Standard determination of viral load (limit of detection 37 copies/mL) The virologic response shall be defined as plasma viral load <37 copies/mL. Once undetectability has been achieved, if a plasma viral load ≥37 copies/mL. is subsequently determined, the plasma viral load determination shall be repeated during the following week for confirmation.

b) Methods of Analysis and Sensitivity

The standard HIV-1 viral load in the plasma sample will be previously performed using the commercial VERSANT HIV-1 RNA 1.0 Assay (kPCR) (SIEMENS HEALTHCARE DIAGNOSTICS) technique with a sensitivity of up to 37 copies/mL. The manufacturer's recommendations will be followed.

Other Tests

The estimated glomerular filtration rate will be calculated using the usual formula, available in http://www.nephron.com/MDRD_GFR.cgi .

Cost/effectiveness assessment.
The software available in the GSIDA application will be used:
http://www.gesida-seimc.org/contenidos/utilidades/aplicacion-tarv-vih-gesida-2014.exe or
https://dl.dropboxusercontent.com/u/35731022/coste-eficacia-2014/aplicacion-tarv-vih-gesida-2014.exe.

10. Safety Rating

10.1 Detection and recording of Adverse Events

It is the investigator's responsibility to detect and document any event that meets the criteria and definitions of adverse event (AE) or serious adverse event (SAE) as set forth in this protocol. During the study, the existence of adverse events, whether serious or not, will be checked in accordance with the definition given in this section of the protocol.

a) Minimum information to be specified:

Description/definition:

Adverse event (AE) is any adverse health event in a patient or clinical trial subject treated with a medicine, even if it is not necessarily causally related to that treatment. Therefore, it can be any unfavorable and unintended signs (including an abnormal laboratory finding), symptom, or illness temporarily associated with the use of an investigational drug, whether or not related to the investigational drug.

Laboratory abnormalities of clinical importance that meet one or more of the following criteria are also considered AEs:

- It requires additional intervention or treatment.
- Requires a modification of the dose.
- It is accompanied by a clinical manifestation.

Any analytical anomaly that the investigating physician considers to be of clinical importance must be recorded as such in the printed copy of the laboratory report, indicating the physician's initials and the date of revision. An AA is also considered to be any event associated or observed in conjunction with an accidental or intentional overdose of the product, or with abuse or withdrawal of the product.

All AEs will be recorded in the subject's medical record and in the eCRDe. The start and end dates of each AA, the intensity and the relationship with the study drug will be recorded.

Criteria for subject treatment, dose discontinuation, dosage adjustment, withdrawal, or treatment changes will only apply to toxicities attributable to study drugs.

The classification system for drug toxicity is set out in the DAIDS Table for Grading the Intensity of Adverse Events in Adults and Children, which can be found on the DAIDS RSC website: http://rsc.tech-res.com/safetyandpharmacovigilance/.

In addition, for each AA, the measures taken or the outcome (e.g. hospitalization, discontinuation of treatment) will be recorded.

Adverse reaction (AR) is any harmful, unintended reaction to an investigational drug, regardless of the dose administered. In this case, there is a suspicion of a causal relationship between the investigational drug and the adverse event.

Serious adverse event (SAE) is any adverse event that, at any dose, results in death, threatens the life of the subject, makes hospitalization necessary or prolonged hospitalization, results in permanent or significant disability or disability, or results in a congenital anomaly or malformation. For the purposes of notification, suspected adverse events that are considered medically significant, even if they do not meet the above criteria, will also be treated as serious, including major medical events that require intervention to prevent one of the consequences described above from occurring. Likewise, all suspected transmission of an infectious agent through a drug will be reported as serious. Examples of these events include allergic bronchospasm requiring intensive treatment in an emergency department or at the individual's home, blood dyscrasia or seizures that do not require hospitalization, or the development of drug dependence or abuse.

Medical and scientific judgement should be used to decide whether other situations that have not resulted in the outcomes listed in the above definitions should be reported as SAGs.

A life-threatening term is defined as a situation where, in the opinion of the physician, the patient at the time of the adverse event or adverse reaction is at real risk of death.

Hospitalization or prolongation of a hospitalization is a criterion for considering an AA to be serious. Only admission in which the patient spends the night in the hospital should be considered as hospitalization. The following situations will not meet the AAG criteria:

- if hospitalization or prolongation of hospitalization is necessary to perform a procedure required by the protocol (for example, if day or night visits will be made for biopsies or surgeries required by the protocol).
- if hospitalization or prolongation of hospitalization is part of the facility's routine procedure (e.g., removal of a stent after surgery)
- in case of scheduled hospitalization for a pre-existing process that has not worsened (e.g. scheduled hospitalization for the implantation of a knee prosthesis for a previous osteoarthritis process)

Grade IV laboratory alterations will be considered AAG.

DO NOT confuse the concept of "serious" with "severe" which refers to the intensity of the adverse event or adverse reaction.

Unexpected serious adverse reaction (RAGI) is a serious adverse reaction whose nature or severity does not correspond to the information regarding the product (for example, the investigator's manual in the case of an investigational medicinal product not authorised for marketing or the product label in the case of an authorised medicinal product).

b) Imputability criteria.

The causal relationship between the investigational product and the occurrence of AA/AAG shall be established on the basis of clinical judgment. To this end, other causes will be considered and studied, such as the natural history of the underlying diseases, concomitant treatment, other risk factors and the temporal relationship of the event with the investigational product. In addition, the technical data sheet of the products will be consulted.

In order to analyse the possible cause-effect relationship, the temporal relationship between the administration of the drug and the AA, possible alternative causes, the evolution (complete remission, partial recovery, death, sequelae, persistence), persistence or not after the suspension of administration, reappearance with the readministration of the product or the prior knowledge of said event coinciding with the known or expected response pattern of the drug under study will be considered.

The causal relationship of an AA with the medication under study will be established according to the following definitions:

Unlikely relationship: The adverse event does not occur after a plausible chronological sequence related to the administration of the product under study and/or is reasonably explainable by other factors, such as the patient's clinical status or other concomitant therapeutic, toxic, or environmental interventions. In addition, it does not match the known or expected response pattern of the drug.

Possible relationship: the adverse event occurs after a plausible chronological sequence related to the administration of the product under study, but can also be explained by the patient's clinical status or other concomitant therapeutic, toxic, or environmental interventions. It also matches the known or expected response pattern of the drug.

Probable relationship: the event Adverse drug occurs after a plausible chronological sequence related to the administration of the product under study, cannot be reasonably explained by the patient's clinical status or other concomitant therapeutic, toxic, or environmental interventions, and after withdrawal or reduction of the dose of the suspect drug the event follows a logical clinical sequence. It also matches the known or expected response pattern of the drug.

Very likely relationship: the adverse event occurs after a plausible chronological sequence related to the administration of the product under study, cannot be reasonably explained by the clinical status of the patient or other concomitant therapeutic, toxic or environmental interventions, after withdrawal or reduction of the dose of the suspect drug the event follows a logical clinical sequence and it is necessary that after the readministration of the suspicious drug the adverse event reappears. It also matches the known or expected response pattern of the drug.

Unrelated: Adverse event clearly due to causes unrelated to the medication under study and the criteria for another causal relationship are not met.

Non-assessable relationship: any notification that suggests an adverse effect, which cannot be judged because the information is insufficient or contradictory and which cannot be supplemented or verified.

10.2. Notification

The investigator or designee **must notify all AAGs, regardless of whether or not they are considered drug-related or planned,** to the head of the CTU. Dr. Anna Cruceta (acruceta@clinic.ub.es) tel 2275400 ext 4380 and fax 932279877 in order to notify local and national health authorities **within one working day of becoming aware of the event**., so that the contact of the designated promoter can prepare the corresponding written report. AAGs occurring will be reported at any time from the subject's inclusion in the study and up to 30 days after the study has been completed or discontinued. In the specific case of selection failure, the AAGs will be recorded from the moment the consent is signed until the subject is considered a selection failure.

Regardless of the classification of adverse effects, the Investigator must collect all the AEs in the corresponding section of the study data collection notebook (CRD) and fill in all the information pertaining to them.

The sponsor must notify in an EXPEDITIOUS manner all relevant SAFETY INFORMATION, i.e. that could modify the risk/benefit ratio of the investigational medicine, or determine changes in its administration schedule or in the conduct of the trial, for example:

- a qualitative change or an increase in the percentage of occurrence of expected RAGs, which is considered clinically important.
- RAGIs that occur after the completion of a clinical trial and that are notified by the investigator to the sponsor.
- New developments related to the conduct of the trial or development of the investigational medicinal product that are likely to affect the safety of subjects, such as:
    - Serious adverse events that may be associated with the trial procedures and may modify the conduct of the trial
    - A significant risk to subjects such as the lack of efficacy of an investigational drug used for the treatment of a life-threatening disease.
    - Important new safety findings from new animal studies (such as cardiogenicity).
    - Any premature termination or temporary halt of a clinical trial with the same investigational medicinal product for safety reasons, carried out in another country and by the same sponsor.
    - GRAs related only to an MNI that are considered relevant as they are not subject to RAGI's general rules of expedited reporting of individual cases.
- Any recommendations from the data monitoring committee, which are relevant to the safety of the subjects.

This information must be notified as soon as possible and no later than 15 days after the promoter has become aware of it. In addition, if additional information that is relevant is obtained, it must be notified as quickly as possible.

10.3 Evaluation of toxicity parameters

The classification system for drug toxicity is set out in the DAIDS Table for the Gradation of Intensity of Adverse Events in Adults and Children, which can be found in the annexes section of this protocol and also on the DAIDS CSR website:
http://rsc.tech-res.com/safetyandpharmacovigilance/.

Treatment of adverse effects

In some cases, doses may be reduced. It is important to always follow the express indications for each drug and each specific case.

(see Technical Data Sheets)

10.4 COMMUNICATION TO RESEARCHERS

The sponsor shall communicate to investigators any information that may affect the safety of the trial subjects as soon as possible.

It is advisable when deemed appropriate that information on serious and unexpected adverse reactions (RAGI) be presented in a list together with a brief analysis of the data provided.

Researchers must also be informed of the safety aspects that impact the conduct of the clinical trial or the development of the product. Including disruption of the development program or security-related protocol modifications.

Follow-up of subjects after adverse events will be performed by clinical and complementary examinations necessary for the duration of treatment and then on a monthly basis during follow-up and up to 30 days after the end of treatment. In the event of a possible pregnancy, the health status of both the mother and the newborn will be monitored during the trial, whether the person who has become pregnant is the one who is taking the investigational drug or if it has been taken by her partner.

No interim analyses are planned for the present study.

11. Statistics

The coefficient

11.1 Sample size

A difference in cost-effectiveness ratio> = 300 euros for 48-week therapy will be detected, if any, with a sample size of 45 patients per arm using a two-tailed test, a power of 90% and a p-value of 0.05. Assuming a proportion of 10% of patients lost to follow-up, we would consider including 50 patients per treatment group.11.3 Analysis

The comparison of proportions will be performed using Fisher's exact test and the 95% confidence interval will be calculated for the difference in proportions.

Quantitative data at baseline and at 48 weeks, as well as absolute and relative changes at 48 weeks, will be compared using the Wilcoxon rank sum test. The point estimate and 95% confidence interval of the difference in medians will be estimated using the Hodges-Lehman methodology using the Moses free distribution.

Correlations between continuous variables will be evaluated using Spearman's rank correlation coefficient.
The study of baseline predictors of response will be carried out by means of a multivariate analysis of multiple logistic regression.

Limitations of the study:

Although the hypothesis of the study has been based on various congruent information that allow us to face with sufficient guarantee the feasibility of the study and the eventual demonstration of the virological and immunological efficacy of the treatment strategy, we are not absolutely certain that a virological failure rate (standard viral load ≥37 copies/mL on two consecutive occasions at least one week apart) can be produced in the experimental branch. We will consider a priori that the failure of at least 20% (n=6) of the patients in the experimental arm will represent an unacceptably high virological failure rate. In this case, its conclusion will be considered premature. In this extreme case, the data of the patients already included would be analyzed.

This study, even with the most favorable virologic and immunological results, would not constitute definitive proof of the safety and efficacy of ATRIPLA'® s dose reduction strategy. The present study is only a proof of concept and another study with a sufficiently large sample size would be needed to adequately demonstrate the non-inferiority of the strategy. The results of the present study can help to design the non-inferiority study and to estimate its sample size.

11.2 Completion Criteria

The study will be considered to have been completed on the date of the last visit of the last subject recruited into the study.

11.3 Processing of lost data

Missing data imputation techniques will not be used. Only the available data will be analyzed.

11.4 Deviations from the statistical plan

Any deviation from the planned statistical analyses will be justified and detailed in the reports derived from the processing of the data.

11.5 Populations under analysis

The safety population will consist of all patients included in the study who have received at least one dose of the treatment.

The intention-to-treat population will consist of all randomized patients

The protocol population will consist of all patients included in the study as detailed in the protocol and without major deviations from the protocol.

12. Direct Access to Source Data/Documents

The sponsor shall ensure that it is specified in the protocol or other written agreement that the investigator or institution shall allow direct access to the source data or documents for monitoring, auditing and review by the IRB as well as inspection of the trial by the competent health authorities.

13. Ethics

General considerations: The test will be carried out in accordance with the principles emanating from the Declaration of Helsinki *(See Annex VIII)* and according to the legal regulations in force (Royal Decree 223/2004) and will not be started until the approval of the reference IRB has been obtained, the

approval of the Management of all participating centres, and authorisation from the Spanish Agency for Medicines and Health Products.

Information to the subjects: Patients will be informed orally and in writing and all relevant information adapted to their level of understanding will be communicated to the participants.
(See Attachment III: Patient Information Sheet/Written Consent Sheet)

14. Data Management and Records Archiving

The patient will be informed that their participation in the trial will be treated with the same confidentiality as their clinical documentation.

In the data collection notebook, the patient will be identified only by their inclusion code in the study.

The patient's name will not appear in any publication or communication of the results of the study.

The patient's participation in the trial will be reflected in their medical history.

The investigator will complete a list that will include the names of the patients participating in the trial, their inclusion number in the trial and their medical history.

Only researchers and data quality assurance and data analysis personnel will have access to the participant's clinical documentation. Eventually, persons duly authorised by the Sponsor and the Health Authorities and the Clinical Research Ethics Committee may audit or inspect the trial. Personal information will not be available to the public, in compliance with the provisions of Organic Law 15/1999, of 13 December, on the Protection of Personal Data.

The data will be collected through an online electronic CRD.

15. *Financing & Insurance*

The promoter has taken out civil liability insurance in accordance with current regulations.

16. Publication Policy

The Promoter undertakes to publish the results, both positive and negative, of this study as stated in art. 39 of RD 223/2004.

17. Table of Examinations and treatment during follow-up

Selection Evaluations	
Clinical Evaluations	Selection
Informed consent	X
Inclusion and exclusion criteria	X
Assignment of the selection code	X
Vital signs	X
Weight Determination	X
Height determination	X
Demographics	X
Medical history	X
Physical examination	X
Concomitant Medications	X
Confirmation of the use of contraceptive methods by the patient and his or her partner	X

Clinical Evaluations	Basal Day 0	S 4 (#)	S 12 (#)	S 24 (#)	S 36 (#)	S 48 (#)
Meet Inclusion and Exclusion Criteria	X					
Signed Informed Consent	X					
Vital signs	X					
Weight	X					X
Physical examination	X	X	X	X	X	X
Adverse events		X	X	X	X	X
Concomitant Medications	X	X	X	X	X	X
Simplified Compliance Questionnaire		X	X	X	X	X
Haematology	X			X		X
Blood Biochemistry with GFR and Renal Function	X			X		X
Standard plasma viral load	X	X	X	X	X	X
Immunology (CD4/CD8)	X		X			X
DEXA	X					X
Pregnancy test (women only) Y(&)	X	X	X	X	X	X

All laboratory specimens should be obtained prior to administration of the first dose of study medication.

(#) These visits will be made only to patients who are in the experimental treatment arm (3-day-per-week treatment)

& At baseline visit it is advised to perform a blood pregnancy test

Blood biochemistry: lipids (TG, total cholesterol and HDL), creatinine and estimated glomerular filtration rate (CPK-EPI), levels of 25OH vitamin D.

Hematology: Blood count

ANEXO I. DOCUMENTO DEL IP DE ACEPTACIÓN DEL PROTOCOLO

Anexo B. Documento de firma del protocolo por el investigador principal

Don Josep Mallolas
Servicio: Enfermedades Infecciosas
Centro: Hospital Clínic

Hace constar:

Que ha evaluado el protocolo del ensayo clínico titulado *"Coste-efectividad de distintas pautas de tratamiento antirretrovira/ en pacientes naive. Ensayo clínico aleatorizado, no enmascarado, comparando DRV/r+3TC, ABC+3TC (kivexa)+RPV, o EVG/COBI/FTC/TDF {Stribild} durante 48 semanas".*

Código del promotor: COST-EFFECT-CLINIC EudraCT:2014-004820-24
Versión: 1.0 Fecha: 4 de octubre de 2014
Cuyo promotor es Fundacló Clínic pera la Recerca Biomedica.

Que el ensayo clínico respeta las normas éticas aplicables a este tipo de estudios.

Que acepta participar como investigador principal en este ensayo clínico.

Que cuenta con los recursos materiales y humanos necesarios para llevar a cabo el ensayo clínico, sin que ello interfiera en la realización de otro tipo de estudios ni en otras tareas que tienen habitualmente encomendadas.

Que se compromete a que cada sujeto sea tratado y controlado siguiendo lo establecido en el protocolo con dictamen favorable por el Comité Ético de Investigación Clínica y autorizado por la Agencia Española de Medicamentos y Productos Sanitarios.

Que respetará las normas éticas y legales aplicables a este tipo de estudios y seguirá las normas de buena práctica clínica en su realización.

Que los colaboradores que necesita para realizar el ensayo clínico propuesto son idóneos.

En Barcelona, a Z?Je)../(Hc,(µ'etA.,◆ /4 zo14◆

Firmado:

Dr. Josep Mallolas
Investigador principal

ANEXO II. TABLA GRADACIÓN DE TOXICIDAD (OMS)

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

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

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

I. Instructions and Clarifications

Grading Adult and Pediatric AEs

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

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

Addenda 1-3 Grading Tables for Microbicide Studies

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

- Addendum 1 - Female Genital Grading Table for Use in Microbicide Studies - PDF
- Addendum 2 - Male Genital Grading Table for Use in Microbicide Studies - PDF
- Addendum 3 - Rectal Grading Table for Use in Microbicide Studies - PDF

Grade 5

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

Estimating Severity Grade for Parameters Not Identified in the Table

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

Determining Severity Grade for Parameters "Between Grades"

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

Values Below Grade 1

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

Determining Severity Grade when Local Laboratory Normal Values Overlap with Grade 1 Ranges

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

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

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II. Definitions of terms used in the Table:

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Osteonecrosis	NA	Asymptomatic with radiographic findings AND No operative intervention indicated	Symptomatic bone pain with radiographic findings OR Operative intervention indicated	Disabling bone pain with radiographic findings causing inability to perform basic self-care functions
GENITOURINARY				
Cervicitis (symptoms) (For use in studies evaluating topical study agents) For other cervicitis see Infection: Infection (any other than HIV infection)	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	Symptoms causing inability to perform basic self-care functions
Cervicitis (clinical exam) (For use in studies evaluating topical study agents) For other cervicitis see Infection: Infection (any other than HIV infection)	Minimal cervical abnormalities on examination (erythema, mucopurulent discharge, or friability) OR Epithelial disruption < 25% of total surface	Moderate cervical abnormalities on examination (erythema, mucopurulent discharge, or friability) OR Epithelial disruption of 25 – 49% total surface	Severe cervical abnormalities on examination (erythema, mucopurulent discharge, or friability) OR Epithelial disruption 50 – 75% total surface	Epithelial disruption > 75% total surface
Inter-menstrual bleeding (IMB)	Spotting observed by participant OR Minimal blood observed during clinical or colposcopic examination	Inter-menstrual bleeding not greater in duration or amount than usual menstrual cycle	Inter-menstrual bleeding greater in duration or amount than usual menstrual cycle	Hemorrhage with life-threatening hypotension OR Operative intervention indicated
Urinary tract obstruction (e.g., stone)	NA	Signs or symptoms of urinary tract obstruction without hydronephrosis or renal dysfunction	Signs or symptoms of urinary tract obstruction with hydronephrosis or renal dysfunction	Obstruction causing life-threatening consequences

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

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

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

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

DIVISION OF AIDS TABLE FOR GRADING THE SEVERITY OF ADULT AND PEDIATRIC ADVERSE EVENTS
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PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Vulvovaginitis (symptoms) (Use in studies evaluating topical study agents) For other vulvovaginitis see Infection: Infection (any other than HIV infection)	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	Symptoms causing inability to perform basic self-care functions
Vulvovaginitis (clinical exam) (Use in studies evaluating topical study agents) For other vulvovaginitis see Infection: Infection (any other than HIV infection)	Minimal vaginal abnormalities on examination OR Epithelial disruption < 25% of total surface	Moderate vaginal abnormalities on examination OR Epithelial disruption of 25 - 49% total surface	Severe vaginal abnormalities on examination OR Epithelial disruption 50 - 75% total surface	Vaginal perforation OR Epithelial disruption > 75% total surface
OCULAR/VISUAL				
Uveitis	Asymptomatic but detectable on exam	Symptomatic anterior uveitis OR Medical intervention indicated	Posterior or pan-uveitis OR Operative intervention indicated	Disabling visual loss in affected eye(s)
Visual changes (from baseline)	Visual changes causing no or minimal interference with usual social & functional activities	Visual changes causing greater than minimal interference with usual social & functional activities	Visual changes causing inability to perform usual social & functional activities	Disabling visual loss in affected eye(s)
ENDOCRINE/METABOLIC				
Abnormal fat accumulation (e.g., back of neck, breasts, abdomen)	Detectable by study participant (or by caregiver for young children and disabled adults)	Detectable on physical exam by health care provider	Disfiguring OR Obvious changes on casual visual inspection	NA
Diabetes mellitus	NA	New onset without need to initiate medication OR Modification of current medications to regain glucose control	New onset with initiation of medication indicated OR Diabetes uncontrolled despite treatment modification	Life-threatening consequences (e.g., ketoacidosis, hyperosmolar non-ketotic coma)

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

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

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

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

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Gynecomastia	Detectable by study participant or caregiver (for young children and disabled adults)	Detectable on physical exam by health care provider	Disfiguring OR Obvious on casual visual inspection	NA
Hyperthyroidism	Asymptomatic	Symptomatic causing greater than minimal interference with usual social & functional activities OR Thyroid suppression therapy indicated	Symptoms causing inability to perform usual social & functional activities OR Uncontrolled despite treatment modification	Life-threatening consequences (e.g., thyroid storm)
Hypothyroidism	Asymptomatic	Symptomatic causing greater than minimal interference with usual social & functional activities OR Thyroid replacement therapy indicated	Symptoms causing inability to perform usual social & functional activities OR Uncontrolled despite treatment modification	Life-threatening consequences (e.g., myxedema coma)
Lipoatrophy (e.g., fat loss from the face, extremities, buttocks)	Detectable by study participant (or by caregiver for young children and disabled adults)	Detectable on physical exam by health care provider	Disfiguring OR Obvious on casual visual inspection	NA

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

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

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

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

DIVISION OF AIDS TABLE FOR GRADING THE SEVERITY OF ADULT AND PEDIATRIC ADVERSE EVENTS
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LABORATORY				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
HEMATOLOGY	***Standard International Units are listed in italics***			
Absolute CD4+ count **– Adult and Pediatric > 13 years** (HIV NEGATIVE ONLY)	300 – 400/mm^3 *300 – 400/µL*	200 – 299/mm^3 *200 – 299/µL*	100 – 199/mm^3 *100 – 199/µL*	< 100/mm^3 *< 100/µL*
Absolute lymphocyte count **– Adult and Pediatric > 13 years** (HIV NEGATIVE ONLY)	600 – 650/mm^3 *0.600 x 10^9 – 0.650 x 10^9/L*	500 – 599/mm^3 *0.500 x 10^9 – 0.599 x 10^9/L*	350 – 499/mm^3 *0.350 x 10^9 – 0.499 x 10^9/L*	< 350/mm^3 *< 0.350 x 10^9/L*
Comment: Values in children ≤ 13 years are not given for the two parameters above because the absolute counts are variable.				
Absolute neutrophil count (ANC)				
Adult and Pediatric, > 7 days	1,000 – 1,300/mm^3 *1.000 x 10^9 – 1.300 x 10^9/L*	750 – 999/mm^3 *0.750 x 10^9 – 0.999 x 10^9/L*	500 – 749/mm^3 *0.500 x 10^9 – 0.749 x 10^9/L*	< 500/mm^3 *< 0.500 x 10^9/L*
Infant*†, 2 – ≤ 7 days	1,250 – 1,500/mm^3 *1.250 x 10^9 – 1.500 x 10^9/L*	1,000 – 1,249/mm^3 *1.000 x 10^9 – 1.249 x 10^9/L*	750 – 999/mm^3 *0.750 x 10^9 – 0.999 x 10^9/L*	< 750/mm^3 *< 0.750 x 10^9/L*
Infant*†, ≤1 day	4,000 – 5,000/mm^3 *4.000 x 10^9 – 5.000 x 10^9/L*	3,000 – 3,999/mm^3 *3.000 x 10^9 – 3.999 x10^9/L*	1,500 – 2,999/mm^3 *1.500 x 10^9 – 2.999 x 10^9/L*	< 1,500/mm^3 *< 1.500 x 10^9/L*
Comment: Parameter changed from "Infant, < 1 day" to "Infant, ≤1 day"				
Fibrinogen, decreased	100 – 200 mg/dL *1.00 – 2.00 g/L* OR 0.75 – 0.99 x LLN	75 – 99 mg/dL *0.75 – 0.99 g/L* OR 0.50 – 0.74 x LLN	50 – 74 mg/dL *0.50 – 0.74 g/L* OR 0.25 – 0.49 x LLN	< 50 mg/dL *< 0.50 g/L* OR < 0.25 x LLN OR Associated with gross bleeding

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

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

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

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

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

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LABORATORY				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
CHEMISTRIES	***Standard International Units are listed in italics***			
Acidosis	NA	pH < normal, but ≥ 7.3	pH < 7.3 without life-threatening consequences	pH < 7.3 with life-threatening consequences
Albumin, serum, low	3.0 g/dL – < LLN *30 g/L – < LLN*	2.0 – 2.9 g/dL *20 – 29 g/L*	< 2.0 g/dL *< 20 g/L*	NA
Alkaline Phosphatase	1.25 – 2.5 x ULN†	2.6 – 5.0 x ULN†	5.1 – 10.0 x ULN†	> 10.0 x ULN†
Alkalosis	NA	pH > normal, but ≤ 7.5	pH > 7.5 without life-threatening consequences	pH > 7.5 with life-threatening consequences
ALT (SGPT)	1.25 – 2.5 x ULN	2.6 – 5.0 x ULN	5.1 – 10.0 x ULN	> 10.0 x ULN
AST (SGOT)	1.25 – 2.5 x ULN	2.6 – 5.0 x ULN	5.1 – 10.0 x ULN	> 10.0 x ULN
Bicarbonate, serum, low	16.0 mEq/L – < LLN *16.0 mmol/L – < LLN*	11.0 – 15.9 mEq/L *11.0 – 15.9 mmol/L*	8.0 – 10.9 mEq/L *8.0 – 10.9 mmol/L*	< 8.0 mEq/L *< 8.0 mmol/L*
Comment: Some laboratories will report this value as Bicarbonate (HCO_3) and others as Total Carbon Dioxide (CO_2). These are the same tests; values should be graded according to the ranges for Bicarbonate as listed above.				
Bilirubin (Total)				
Adult and Pediatric > 14 days	1.1 – 1.5 x ULN	1.6 – 2.5 x ULN	2.6 – 5.0 x ULN	> 5.0 x ULN
Infant*†, ≤ 14 days (non-hemolytic)	NA	20.0 – 25.0 mg/dL *342 – 428 µmol/L*	25.1 – 30.0 mg/dL *429 – 513 µmol/L*	> 30.0 mg/dL *> 513.0 µmol/L*
Infant*†, ≤ 14 days (hemolytic)	NA	NA	20.0 – 25.0 mg/dL *342 – 428 µmol/L*	> 25.0 mg/dL *> 428 µmol/L*
Calcium, serum, high				
Adult and Pediatric ≥ 7 days	10.6 – 11.5 mg/dL *2.65 – 2.88 mmol/L*	11.6 – 12.5 mg/dL *2.89 – 3.13 mmol/L*	12.6 – 13.5 mg/dL *3.14 – 3.38 mmol/L*	> 13.5 mg/dL *> 3.38 mmol/L*
Infant*†, < 7 days	11.5 – 12.4 mg/dL *2.88 – 3.10 mmol/L*	12.5 – 12.9 mg/dL *3.11 – 3.23 mmol/L*	13.0 – 13.5 mg/dL *3.245 – 3.38 mmol/L*	> 13.5 mg/dL *> 3.38 mmol/L*
Calcium, serum, low				
Adult and Pediatric ≥ 7 days	7.8 – 8.4 mg/dL *1.95 – 2.10 mmol/L*	7.0 – 7.7 mg/dL *1.75 – 1.94 mmol/L*	6.1 – 6.9 mg/dL *1.53 – 1.74 mmol/L*	< 6.1 mg/dL *< 1.53 mmol/L*
Infant*†, < 7 days	6.5 – 7.5 mg/dL *1.63 – 1.88 mmol/L*	6.0 – 6.4 mg/dL *1.50 – 1.62 mmol/L*	5.50 – 5.90 mg/dL *1.38 – 1.51 mmol/L*	< 5.50 mg/dL *< 1.38 mmol/L*
Comment: Do not adjust Calcium, serum, low or Calcium, serum, high for albumin				

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

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

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

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

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

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

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

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

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

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

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

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

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

ANNEX III. SERIOUS ADVERSE EVENT REPORTING FORM

Clinical Trials Unit	**NOTIFICACIÓN DE ACONTECIMIENTOS ADVERSOS GRAVES – I**	Código Protocolo: Estudio **COST-EFFECT-CLINIC** Nº EudraCT: **2014-004820-24**

1. Tipo informe ☐ Inicial ☐ Seguimiento	2. País: España	3. Código paciente: |___|___|___|___|

I. DATOS PERSONALES DEL PACIENTE

4. Fecha nacimiento: |____|___|___| DD MM AA	5.Sexo ☐ Hombre ☐ Mujer	6. Iniciales: |__|__| N A
7. Peso: |___|___|___| . |___| Kg.	8. Talla: |___|___|___| cm.	9. Edad: |___|___| Años

II. ACONTECIMIENTO ADVERSO GRAVE

10. Descripción del acontecimiento:	11. Fecha de inicio: |____|___|___| 12. Gravedad del acontecimiento: ☐ resultado de muerte ☐ amenaza de vida ☐ hospitalización ☐ prolongación de la hospitalización ☐ invalidez / incapacidad ☐ anomalía / malformación congénita ☐ médicamente relevante

13. Acción tomada	14. Resultado / Desenlace
☐ ninguna ☐ interrupción temporal ☐ discontinuación permanente ☐ tratamiento concomitante de los síntomas ☐ hospitalización ☐ prolongación de la hospitalización ☐ Otros: (especificar) _____ _____	☐ desconocido ☐ recuperación total → Fecha: |____|___|___| ☐ recuperación parcial → Fecha: |____|___|___| ☐ persiste ☐ empeoramiento ☐ muerte → Fecha: |____|___|___| Causa de muerte: _____ _____

III. MEDICACIÓN EN ESTUDIO (registrar cada uno de los medicamentos en estudio)

15. Medicamentos	16. Dosis diaria	17. Vía	18. Fecha inicio	19. Fecha final	20. Relación causal (indicar nº según 20a)
				☐ continúa	
				☐ continúa	

20a. Relación causal: 1 clara 2 probable 3 posible 4 improbable 5 no relacionado 6 no valorable

21. ¿Remitió la reacción al suspender la medicación? ☐ Sí ☐ No ☐ No procede

22. ¿Remitió la reacción al reducir la dosis? ☐ Sí ☐ No ☐ No procede

23. ¿Reapareció la reacción al administrar de nuevo la medicación? ☐ Sí ☐ No ☐ No procede

IV. MEDICACIÓN CONCOMITANTE ☐ No hay

24. Medicamentos	25. Dosis diaria	26. Fecha inicio	27. Fecha final	28. Relación causal (según 20a)	29. Indicación
			☐ continúa		
			☐ continúa		
			☐ continúa		
			☐ continúa		
			☐ continúa		

Clinical Trials Unit	**NOTIFICACIÓN DE ACONTECIMIENTOS ADVERSOS GRAVES – II**	Código Protocolo: Estudio: **COST-EFFECT-CLINIC** Nº EudraCT: **2014-004820-24**

V. DATOS RELEVANTES DE LABORATORIO ☐ No hay

30. Variable de laboratorio	31. Resultado (indicar unidades)	32. Rango de normalidad	33. Fecha extracción

VI. DATOS RELEVANTES DE LA HISTORIA CLÍNICA ☐ No hay

34. Enfermedad / Intervención	35. Fecha inicio	36. Fecha final	37. Sigue
			☐ Sí ☐ No
			☐ Sí ☐ No
			☐ Sí ☐ No
			☐ Sí ☐ No

38. Información complementaria: ☐ No hay

39. ¿Se adjunta informe complementario?: ☐ Sí ☐ No (nº páginas: ___)

VII. DATOS DEL INVESTIGADOR

40. Nombre del investigador que informa:	41. Dirección del investigador:
42. Fecha notificación: |____|____|____|	43. Firma investigador:

VIII. DATOS A RELLENAR POR EL PROMOTOR

44. Nombre del receptor de la notificación:	45. Fecha recepción: |____|____|____|	46. Firma del receptor:

47. Clasificación del acontecimiento descrito:
- ☐ Acontecimiento Adverso Grave
- ☐ Reacción Adversa Grave
- ☐ Reacción Adversa Grave e Inesperada→ **NOTIFICACIÓN A AUTORIDADES SANITARIAS OBLIGATORIA**

48.Notificación expeditiva realizada:	49. Comunicado a Eudravigilance:
☐ Sí → Fecha |____|____|____| ☐ No ☐ No procede	☐ Sí → Fecha |____|____|____| ☐ No Procede

FAX TO THE STUDY COORDINATING CENTRE FAX NUMBER:

93 227 98 77

ANNEX IV. SERIOUS AND UNEXPECTED ADVERSE

REACTION REPORTING FORM

Anexo D Formulario de notificación de reacción adversa grave e inesperada ocurrida en España

NOTIFICACION DE SOSPECHA DE REACCION ADVERSA PARA MEDICAMENTOS EN INVESTIGACIÓN Notificación realizada a Eudravigilance ☐ SI ☐ NO	CODIGO DE PROTOCOLO (promotor)……. Nº EUDRACT/ Nº Protocolo AEMPS……..	Nº NOTIFICACION (Promotor)
	PACIENTE Nº	Nº NOTIFICACION

INFORMACION SOBRE LA REACCIÓN ADVERSA

1a. PAÍS	2. FECHA DE NACIMIENTO			2a. EDAD	3. SEXO	3a. PESO	3b. TALLA	4-6. FECHA DE INICIO DE LA REACCIÓN		
	DÍA	MES	AÑO		☐ HOMBRE ☐ MUJER			DÍA	MES	AÑO
7. DESCRIPCIÓN DE LA REACCIÓN ADVERSA (Incluyendo resultados relevantes de exploración o de laboratorio, y la fecha de finalización, si procede).								8-13b. CRITERIOS DE GRAVEDAD/ DESENLACE ☐ FALLECIMIENTO ☐ LA VIDA DEL PACIENTE HA ESTADO EN PELIGRO ☐ HOSPITALIZACIÓN ☐ PROLONGACIÓN HOSPITALIZACIÓN ☐ INCAPACIDAD PERMANENTE O SIGNIFICATIVA ☐ RA CLINICAMENTE RELEVANTE Desenlace ☐ PERSISTENCIA DE LA RA ☐ RECUPERACIÓN SIN SECUELAS ☐ RECUPERACIÓN CON SECUELAS ☐ DESCONOCIDO		

II. INFORMACION DEL MEDICAMENTO EN INVESTIGACIÓN

14. MEDICAMENTO SOSPECHOSO	15. DOSIS DIARIA	16. VÍA	17. ENFERMEDAD EN ESTUDIO	18. FECHAS DE INICIO	FINAL	19. DURACIÓN DEL TRATAMIENTO
20. ¿REMITIÓ LA REACCIÓN AL SUSPENDER LA MEDICACIÓN? ☐ SI ☐ NO ☐ NO PROCEDE		20a. ¿REMITIÓ LA REACCIÓN AL REDUCIR LA DOSIS? ☐ SI ☐ NO ☐ NO PROCEDE		21. ¿REAPARECIÓ LA REACCIÓN AL ADMINISTRAR DE NUEVO LA MEDICACIÓN? ☐ SI ☐ NO ☐ NO PROCEDE		

III. MEDICAMENTOS CONCOMITANTES E HISTORIA CLÍNICA

22. MEDICAMENTOS CONCOMITANTES (Márquese con un asterisco el o los medicamentos sospechosos)	22a. DOSIS DIARIA	22b. VÍA	22c. FECHAS DE INICIO	FINAL	22d. MOTIVO DE LA PRESCRIPCIÓN
23. DATOS IMPORTANTES DE LA HISTORIA CLÍNICA (ej. diagnósticos, alergias, embarazos, etc.)					

IV. INFORMACION SOBRE PROMOTOR E INVESTIGADOR

24a. NOMBRE Y DIRECCION DEL PROMOTOR		24b. NOMBRE Y DIRECCION DEL INVESTIGADOR
24c. CODIGO DE LABORATORIO (Nº AEMPS)	25a. TIPO DE INFORME □ INICIAL □ SEGUIMIENTO	24c. TECNICO DEL PROMOTOR QUE INFORMA NOMBRE: TELEFONO: FIRMA:
24e. FECHA DEL INFORME	24f. FECHA DE ENTRADA AEM	25b. SE ADJUNTA INFORME COMPLEMENTARIO

GENERAL INSTRUCTIONS

1. This form will be used only to report suspected serious and unexpected adverse reactions (ARs) that occur with investigational medicines.

2. Suspicions of fatal or life-threatening AR (those that would have resulted in the death of the patient if there had not been an immediate therapeutic intervention) will be reported within a maximum period of 7 calendar days; If not all information is available, it can be completed within an additional 8 days. Other suspected serious and unexpected AR will be reported within a maximum period of 15 days.

3. When the available space is insufficient, an additional information sheet will be added, correctly identified with the name of the promoter and the number assigned to the notification. This information may include the assessment of causality carried out by the reporting technician.

SPECIFIC INSTRUCTIONS

1. The protocol code is the one assigned by the sponsor to identify the trial. The promoter's notification number is the one used by the promoter for its filing. In the case of tracking information, the same number shall be used or, if amended, the number of the initial notification shall be indicated. The "Notification number" space that appears in the shade will be left unfilled.

2. The age will be set in years, months, weeks or days as appropriate, but always indicating it. If the age is not precisely known, at least the age group to which the child belongs (e.g., infant, child, adolescent, adult, elderly) should be referred.

7. The RA shall be described in full, indicating the date of completion of the RA and including the results of the complementary examinations or laboratory tests that are considered of interest. This notification may be accompanied by as many reports as deemed appropriate for the proper interpretation of the clinical picture suspected of being an adverse reaction.

8-13. Categories are not mutually exclusive. Assistance in an Emergency Department of a Hospital of less than 24 hours will not be considered hospitalisation.

14. Investigational medicinal products shall be identified if possible by their generic name (DOE or INN), indicating where the trade name is available, or failing that, by the proposed name or laboratory code for the product.

15. In the event that the administration is not daily, an attempt will be made to describe it with one of the following possibilities: cyclical, weekly, monthly, annual or number of times it has been used (in this case putting the dose of each dose, not the total).

17. The pathological process of the patient for whom the investigational product is intended shall be recorded, or "healthy volunteer" in the case of such.

19. The duration of treatment until the onset of the adverse reaction shall be recorded.

22. It shall be explicitly indicated whether no concomitant drugs have been taken. If one or more of the concomitant drugs are considered suspicious, they should be marked with an asterisk (e.g., * AMOXICILLIN). Medicinal products used to treat the adverse reaction shall be excluded.

ANEXO V. DECLARACIÓN DE HELSINKI

Special Communication

World Medical Association Declaration of Helsinki Ethical Principles for Medical Research Involving Human Subjects

World Medical Association

Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964, and amended by the:
29th WMA General Assembly, Tokyo, Japan, October 1975
35th WMA General Assembly, Venice, Italy, October 1983
41st WMA General Assembly, Hong Kong, September 1989
48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996
52nd WMA General Assembly, Edinburgh, Scotland, October 2000
53rd WMA General Assembly, Washington, DC, USA, October 2002 (Note of Clarification added)
55th WMA General Assembly, Tokyo, Japan, October 2004 (Note of Clarification added)
59th WMA General Assembly, Seoul, Republic of Korea, October 2008
64th WMA General Assembly, Fortaleza, Brazil, October 2013

Preamble

1. The World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving human subjects, including research on identifiable human material and data.

   The Declaration is intended to be read as a whole and each of its constituent paragraphs should be applied with consideration of all other relevant paragraphs.

2. Consistent with the mandate of the WMA, the Declaration is addressed primarily to physicians. The WMA encourages others who are involved in medical research involving human subjects to adopt these principles.

General Principles

3. The Declaration of Geneva of the WMA binds the physician with the words, "The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act in the patient's best interest when providing medical care."

4. It is the duty of the physician to promote and safeguard the health, well-being and rights of patients, including those who are involved in medical research. Thephysician's knowledge and conscience are dedicated to the fulfilment of this duty.

5. Medical progress is based on research that ultimately must include studies involving human subjects.

6. The primary purpose of medical research involving human subjects is to understand the causes, development and effects of diseases and improve preventive, diagnostic and therapeutic interventions (methods, procedures and treatments). Even the best proven interventions must beevaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality.

7. Medical research is subject toethical standards that promote and ensure respect for all human subjects and protect their health and rights.

8. While the primary purpose of medical research is to generate new knowledge, this goal can never take precedence over the rights and interests of individual research subjects.

9. It is the duty of physicians who are involved in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects. The responsibility for the protection of research subjects must always rest with the physician or other health care professionals and never with the research subjects, even though they have given consent.

10. Physicians must consider the ethical, legal and regulatory norms and standards for research involving human subjects in their own countries as well as applicable international norms and standards. No national or international ethical, legal or regulatory requirement should reduce or eliminate any of the protections for research subjects set forth in this Declaration.

11. Medical research should be conducted in a manner that minimises possible harm to the environment.

12. Medical research involving human subjects must be conducted only by individuals with the appropriate ethics and scientific education, training and qualifications. Research on patients or healthy volunteers requires the supervision of a competent and appropriately qualified physician or other health care professional.

13. Groups that are underrepresented in medical research should be provided appropriate access to participation in research.

14. Physicians who combine medical research with medical care should involve their patients in research only to the extent that this is justified by its potential preventive, diagnostic or therapeutic value and if the physician has good reason to believe that participation in the research study will not adversely affect the health of the patients who serve as research subjects.

15. Appropriate compensation and treatment for subjects who are harmed as a result of participating in research must be ensured.

Risks, Burdens and Benefits

16. In medical practice and in medical research, most interventions involve risks and burdens.

    Medical research involving human subjects may only be conducted if the importance of the objective outweighs the risks and burdens to the research subjects.

17. All medical research involving human subjects must be preceded by careful assessment of predictable risks and burdens to the individuals and groups involved in the research in comparison with foreseeable benefits to them and to other individuals or groups affected by the condition under investigation.

    Measures to minimise the risks must be implemented. The risks must be continuously monitored, assessed and documented by the researcher.

18. Physicians may not be involved in a research study involving human subjects unless they are confident that the risks have been adequately assessed and can be satisfactorily managed.

    When the risks are found to outweigh the potential benefits or when there is conclusive proof of definitive outcomes, physicians must assess whether to continue, modify or immediately stop the study.

Vulnerable Groups and Individuals

19. Some groups and individuals are particularly vulnerable and may have an increased likelihood of being wronged or of incurring additional harm.

    All vulnerable groups and individuals should receive specifically considered protection.

20. Medical research with a vulnerable group is only justified if the research is responsive to the health needs or priorities of this group and the research cannot be carried out in a non-vulnerable group. In addition, this group should stand to benefit from the knowledge, practices or interventions that result from the research.

Scientific Requirements and Research Protocols

21. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and adequate laboratory and, as appropriate, animal experimentation. The welfare of animals used for research must be respected.

22. The design and performance of each research study involving human subjects must be clearly described and justified in a research protocol.

    The protocol should contain a statement of the ethical considerations involved and should indicate how the principles in this Declaration have been addressed. The protocol should include information regarding funding, sponsors, institutional affiliations, potential conflicts of interest, incentives for subjects and information regarding provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the research study.

    In clinical trials, the protocol must also describe appropriate arrangements for post-trial provisions.

Research Ethics Committees

23. The research protocol must be submitted for consideration, comment, guidance and approval to the concerned research ethics committee before the study begins. This committee must be transparent in its functioning, must be independent of the researcher, the sponsor and any other undue influence and must be duly qualified. It must take into consideration the laws and regulations of the country or countries in which the research is to be performed as well as applicable international norms and standards but these must not be allowed to reduce or eliminate any of the protections for research subjects set forth in this Declaration.

    The committee must have the right to monitor ongoing studies. The researcher must provide monitoring information to the committee, especially information about any serious adverse events. No amendment to the protocol may be made without consideration and approval by the committee. After the end of the study, the researchers must submit a final report to the committee containing a summary of the study's findings and conclusions.

Privacy and Confidentiality

24. Every precaution must be taken to protect the privacy of research subjects and the confidentiality of their personal information.

Informed Consent

25. Participation by individuals capable of giving informed consent as subjects in medical research must be voluntary. Although it

may be appropriate to consult family members or community leaders, no individual capable of giving informed consent may be enrolled in a research study unless he or she freely agrees.

26. In medical research involving human subjects capable of giving informed consent, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, post-study provisions and any other relevant aspects of the study. The potential subject must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal. Special attention should be given to the specific information needs of individual potential subjects as well as to the methods used to deliver the information.

    After ensuring that the potential subject has understood the information, the physician or another appropriately qualified individual must then seek the potential subject's freely-given informed consent, preferably in writing. If the consent cannot be expressed in writing, the non-written consent must be formally documented and witnessed.

    All medical research subjects should be given the option of being informed about the general outcome and results of the study.

27. When seeking informed consent for participation in a research study the physician must be particularly cautious if the potential subject is in a dependent relationship with the physician or may consent under duress. In such situations the informed consent must be sought by an appropriately qualified individual who is completely independent of this relationship.

28. For a potential research subject who is incapable of giving informed consent, the physician must seek informed consent from the legally authorised representative. These individuals must not be included in a research study that has no likelihood of benefit for them unless it is intended to promote the health of the group represented by the potential subject, the research cannot instead be performed with persons capable of providing informed consent, and the research entails only minimal risk and minimal burden.

29. When a potential research subject who is deemed incapable of giving informed consent is able to give assent to decisions about participation in research, the physician must seek that assent in addition to the consent of the legally authorised representative. The potential subject's dissent should be respected.

30. Research involving subjects who are physically or mentally incapable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that prevents giving informed consent is anecessary characteristic of the research group. In such circumstances the physician must seek informed consent from the legally authorised representative. If no such representative is available and if the research cannot be delayed, the study may proceed without informed consent provided that the specific reasons for involving subjects with a condition that renders them unable to give informed consent have been stated in the research protocol and the study has been approved by a research ethics committee. Consent to remain in the research must be obtained as soon as possible from the subject or a legally authorised representative.

31. The physician must fully inform the patient which aspects of their care are related to the research. The refusal of a patient to participate in a study or the patient's decision to withdraw from the study must never adversely affect the patient-physician relationship.

32. For medical research using identifiable human material or data, such as research on material or data contained in biobanks or similar repositories, physicians must seek informed consent for its collection, storage and/or reuse. There may be exceptional situations where consent would be impossible or impracticable to obtain for such research. In such situations the research may be done only after consideration and approval of a research ethics committee.

Use of Placebo

33. The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best proven intervention(s), except in the following circumstances:

    Where no proven intervention exists, the use of placebo, or no intervention, is acceptable; or

    Where for compelling and scientifically sound methodological reasons the use of any intervention less effective than the best proven one, the use of placebo, or no intervention is necessary to determine the efficacy or safety of an intervention

    and the patients who receive any intervention less effective than the best proven one, placebo, or no intervention will not be subject to additional risks of serious or irreversible harm as a result of not receiving the best proven intervention.

    Extreme care must be taken to avoid abuse of this option.

Post-Trial Provisions

34. Inadvance of a clinical trial, sponsors, researchers and host country governments should make provisions for post-trial access for all participants who still need an intervention identified as beneficial in the trial. This information must also be disclosed to participants during the informed consent process.

Research Registration and Publication and Dissemination of Results

35. Every research study involving human subjects must be registered in a publicly accessible database before recruitment of the first subject.

36. Researchers, authors, sponsors, editors and publishers all have ethical obligations with regard to the publication and dissemination of the results of research. Researchers have a duty to make publicly available the results of their research on human subjects and are accountable for the completeness and accuracy of their reports. All parties should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results must be published or otherwise made publicly available. Sources of funding, institutional affiliations and conflicts of interest must be declared in the publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication.

Unproven Interventions in Clinical Practice

37. In the treatment of an individual patient, where proven interventions do not exist or other known interventions have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorised representative, may use an unproven intervention if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. This intervention should subsequently be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information must be recorded and, where appropriate, made publicly available.

ARTICLE INFORMATION

Corresponding Author: World Medical Association, 13, ch. du Levant, CIB - Bâtiment A, 01210 Ferney-Voltaire, France; wma@wma.net.

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Online-Only Content: Audio podcast is available at www.jama.com.

ANEXO VI. SEGURO DE RESPONSABILIDAD CIVIL

Certificado de seguro

ZURICH

Zurich Insurance PLC Sucursal en España.

C E R T I F I C A:

1. Que la **FUNDACIÓ PRIVADA CLÍNIC PER A LA RECECA BIOMÈDICA** domiciliada en c/Rosselló 149, 08036 Barcelona, tiene contratada la póliza de seguros num (riesgo aceptado en proceso de emisión por la Compañía) con el fin de cubrir la Responsabilidad Civil derivada de la realización de Ensayos Clínicos. Esta cobertura es válida para el producto y estudio siguiente:

   Ensayo: *"Coste-efectividad de distintas pautas de tratamiento antirretroviral en pacientes naive. Ensayo clínico aleatorizado, no enmascarado, comparando DRV/r+3TC, ABC+3TC (Kivexa)+RPV, o EVG / COBI / FTC / TDF (Stribild) durante 48 semanas".* Versión / Fecha: 1.0 / 4 de octubre de 2014.
   Código del protocolo: cost-effect-clinic, NºEudraCT: 2014-004820-24

   Tomador: FUNDACIÓ PRIVADA CLÍNIC PER A LA RECECA BIOMÈDICA
   Fecha inicio: 01.01.2015
   Fecha final: 01.01.2017
   Nº Pacientes: 150
   Fase: IV
   Investigador principal: Dr Josep Mallolas
   Promotor del ensayo: FUNDACIÓ PRIVADA CLÍNIC PER A LA RECECA BIOMÈDICA
   Que va a realizarse en el siguiente hospital:
   Hospital Clínic de Barcelona

2. La póliza mencionada cubre, en los límites y condiciones pactados y de acuerdo con el Real Decreto Ley de 6 de Febrero de 2004 nº 223/2004 al promotor, investigador y colaboradores, así como al centro hospitalario donde se realice el ensayo.

3. Que los límites de garantía establecidos son:
   EUROS 600.000,00 (seiscientos mil) por paciente sometido a ensayo, límite de EUROS 6.000.000,00 (seis millones) por ensayo y año.

4. Que el período de validez de este seguro vence el día 01.01.2017 .

5. Coste del seguro: Prima Neta: 5.878,47euros.
   Prima Total: 6.240,00euros.

1. Y para que conste en donde convenga se expide el presente certificado en Barcelona, a 02 de Diciembre de 2014.

ZURICH INSURANCE PLC, SUCURSAL EN ESPAÑA

Zurich Insurance PLC Sucursal en España
Global Corporate

Diagonal, 431 bis
08036 Barcelona

Fax 93 400 44 22

www.zurichspain.com