Pharmacovigilance study to define the long-term safety profile of etravirine in HIV-infected children and adolescents in Europe: Study protocol

European Pregnancy and Paediatric HIV Cohort Collaboration (EPPICC)

Final protocol, version 11 October 2013

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1. Introduction

Paediatric HIV infection is mainly acquired vertically, through mother-to-child transmission (MTCT). There were an estimated 3.3 million children aged less than 15 years living with HIV worldwide at the end of 2011, with 330,000 new infections in 2011 alone[1]. The number of HIV-infected children <15 years of age living in Western and Central Europe, was estimated by the WHO to be 1600 (range 1300-2000) for 2011, with data not reported for most countries, and is likely to be an underestimate (see Discussion) [2]. In the European Union, the rate of newly diagnosed HIV infections was estimated at 5.75 per 100,000 in 2010 [3]. MTCT rates in Western Europe are at an all time low (<1-2%) due to a combination of interventions, particularly the widespread use of combination antiretroviral therapy (cART) both for treatment of maternal HIV disease and as prophylaxis for prevention of MTCT[4-6]. However, immigration of HIV-infected children born abroad also contributes to the population of infected children living in Europe.

The aim of antiretroviral therapy in children is to achieve undetectable HIV RNA levels, to maintain viral suppression and thus to allow normal immune function, whilst minimising drug toxicities. Current guidelines recommend the use of cART with at least three drugs, including a dual nucleoside analogue reverse transcriptase inhibitor (NRTI) backbone with either a boosted protease inhibitor (PI) or a non-nucleoside reverse transcriptase inhibitor (NNRTI). Vertically infected children with access to cART have substantially improved health and life expectancy[7-11] and can expect to survive into adult life. Paediatric HIV infection is thus now recognised as a chronic disease, requiring life-long therapy.

Etravirine (ETR, Intelence®), a non-nucleoside reverse transcriptase inhibitor, is indicated in Europe for use in antiretroviral treatment experienced patients aged ≥6 years[11]. The paediatric dose is based on body weight as follows:

- ≥16-<20kg 100mg twice daily
- ≥20-<25kg 125mg twice daily
- ≥25-<30kg 150mg twice daily
- ≥30kg 200mg twice daily (adult dose).

In clinical trials in adults patients the most common (≥ 10%) adverse drug reactions (ADRs) in the ETR group were rash, diarrhoea, nausea, and headache, with rash occurring more

frequently in females. The frequency, type and severity of adverse drug reactions in clinical trial paediatric patients were comparable to those observed in the adult trials.

The Risk Management Plan (RMP) for ETR mentions the following risks for adult and paediatric patients: severe cutaneous reactions, severe hypersensitivity including DRESS, hepatotoxicity, pancreatitis, hyperlipidaemia, coronary artery disorders, and development of drug resistance. Overdose due to medication errors is identified as a potential risk. The RMP identified a lack of information on long-term safety in children aged 6 to <18 years of age. Indeed, little is known about the "real life" use and safety of ETR in the European population of HIV-infected children and adolescents. The Committee for Medicinal Products for Human Use (CHMP) has highlighted the need for a post-marketing surveillance study of ETR use in the paediatric population. Janssen-Cilag International NV has approached the PENTA Foundation/ European Pregnancy and Paediatric HIV Cohort Collaboration (EPPICC) about establishing such a study in HIV-infected children and adolescents living in Europe.

2. Aim and objectives

The aim of this study is to collect long-term safety data on ETR use in children and adolescents with HIV infection in a "real world" setting in Europe.

The objectives are:

1) to describe the clinical characteristics of patients at start of ETR-based therapy
2) to describe the incidence of grade 3 and 4 adverse events for key laboratory markers by duration of ETR use
3) to provide the incidence and describe clinical serious adverse events which are considered to be causally related to ETR by duration of ETR use
4) to report clinical non-serious adverse events which are considered to be causally related to ETR, where available
5) to characterise reasons for discontinuation of ETR
6) to provide information on any off-label use of ETR in children (excluding in utero exposure), including in treatment naive children and those <6 years.

3. Study design

This is an observational study involving the pooled analysis of individual patient data from prospective cohort studies participating in the EPPICC pharmacovigilance programme. EPPICC conducts epidemiological research on the prognosis and outcome of HIV-infected pregnant women, children and children exposed to HIV in utero and currently consists of the following paediatric studies:

Belgium: Hospital St Pierre Cohort, Brussels
Contact: Dr Tessa Goetghebuer

Europe-wide: European Collaborative Study
Contact: Dr Claire Thorne

Germany: Competence Network on HIV infected children
Contact: Dr Chris Koenigs

Italy: Italian Register for HIV infection in children

Contact: Dr Maurizio de Martino, Dr Luisa Galli

Romania: "Victor Babes" Hospital Cohort, Bucharest

Contact: Dr Dan Duiculescu, Dr Luminita Ene

Spain: Madrid Paediatric HIV Cohort Study

Contact: Dr Jose Thomas Ramos Amador

Spain: CoRISPE-cat study, Catalonia

Contact: Dr Ton Noguera

Spain: CoRISPE-1 study, rest of Spain

Contact: Dr Pablo Rojo Conejo

Sweden: Swedish Cohort Study
Contact: Lars Naver

Ukraine: Ukraine Paediatric Cohort Study

Contact: Ruslan Malutya

UK/Ireland: Collaborative HIV Paediatric Study (CHIPS) and National Study of HIV in Pregnancy and Childhood (NSHPC)

Contact: Dr Ali Judd (CHIPS)/ Dr Pat Tookey (NSHPC)

Inclusion criteria:

All HIV-infected children and adolescents with current or previous use of ETR treatment (excluding in utero exposure), regardless of clinical stage, and who were aged < 18 years at commencement of ETR treatment will be included in the study.

Study size:

At the time of the first data merger for the study in early 2014, it is expected that approximately 80 patients will be eligible for inclusion in the study. In the second year of the

study, follow-up data on these 80 ETR-exposed children will be collected as well as new data on any children newly reported to have started an ETR-containing regimen over the previous 12 months. This process will be repeated in subsequent years, and it is envisaged that this study will run for five years, with the number of exposed subjects expected to increase to approximately 100 and the total cumulative duration of exposure similarly increasing over time.

Each year the data merger itself will take place in January. Data checking, query resolution and data analyses will take place over the next 5 months, with a draft study report available to Janssen-Cilag International NV in July, and a final study report at the end of September. The same timetable will be followed in subsequent years of the study.

Coverage:

It is not possible to reliably estimate the coverage of the EPPICC paediatric cohorts, in terms of the number of children included in these cohorts compared with the number infected as a whole in the countries represented. This is due to a wide variation in the quality of the surveillance systems used in these countries, making national estimates, and comparison of estimates between countries, unreliable. However, several participating cohorts do have complete or near complete national coverage: for example, the UK and Ireland cohort (CHIPS) which has in recent years included all children receiving HIV-related care in these countries[6] and the Italian Register, which covers 80-90% of HIV-infected children in Italy[9]. As the EPPICC cohorts tend to include the largest clinical sites caring for and treating HIV-infected children it is unlikely that many ETR-treated children will be missed in this study. Thus, the relatively small number of children and adolescents expected to be included in the first year is largely a reflection of the currently relatively low levels of ETR use in the European paediatric population.

4. Methods

Data collection:

Data captured by cohorts through their routine study data collection include information on demographics, growth, use of antiretroviral drugs (including start and stop dates), HIV clinical status, HIV RNA levels, CD4 counts and percentages and medical history. Although the EPPICC

cohorts have similar protocols, there are some differences with regard to specific data items that are routinely collected, including dosing, non-ART medications, adverse events (AEs) and biochemistry/haematology. For example, although CHIPS and CoRISPE-cat routinely collect information on AEs through study data collection forms, for the other participating cohorts this is not the case, and additional data will be requested from reporting clinics as necessary.

A detailed standard operating procedure (SOP) for data collection processes for the study will be developed and reviewed by all participating cohorts. The SOP will include the data specification (see Appendix), together with instructions on the data extraction and transfer procedures. An electronic data collection form will be provided for circulation by participating cohorts to the relevant treatment physicians to aid data extraction from patient records on variables not included in the cohort database (where applicable). Data formats based on the HIV Cohorts Data Exchange Protocol (HICDEP) will be used for this study (Appendix 1).

The HICDEP format is based on a relational structure, and the data for this study will be collected in a series of tables, which are described in the Appendix, together with the lookup tables for the codes to be used. All available data on laboratory test results (in particular, absolute neutrophil count, total, HDL and LDL cholesterol, triglycerides, alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, total bilirubin, blood glucose, pancreatic amylase and lipase) are to be collected for the 12 months prior to starting ETR up to the most recent follow-up visit, with normal as well as abnormal results to be reported. Fasting values will be requested but it is likely that most values reported will be non-fasting. Baseline data will include ART history, classified as ART-naïve prior to initiation on ETR-containing regimen, ART-experienced (one to three previous ART drugs) and highly pretreated (four or more previous ART drugs). For children stopping ETR use, data collection will continue for all follow-up visits up to 12 months after ETR cessation. Data collected on serious adverse events will include type of AE, date of event, date of resolution, severity, seriousness category and causality assessment by the original reporter (see Variable definitions and Appendix). Where possible, data will also be collected on non-serious adverse events related to ETR. Complete CD4, viral load, weight and height data from first visit will also be collected.

The PENTA Foundation-appointed study team, which includes a database manager with extensive experience of designing and maintaining HIV databases for clinical trials and cohort studies, will obtain data from the participating cohorts through annual electronic data mergers of datasets according to the SOP. The database manager will remove any patient identifiers to ensure patient confidentiality. Data will then be subject to a battery of logical and consistency checks in order to assess accuracy and completeness; any data queries arising will be discussed and resolved with the relevant cohort data manager, before data are pooled into a joint study database.

Variable definitions

Variables to be collected on all children taking ETR will include: basic demographic details (date of birth, sex, mode of infection, ethnicity, hepatitis B co-infection status); patient weights and heights from all clinic visits including prior to start of first ART regimen; ART dosing history, including reasons for stopping a drug; commencing 12 months prior to ETR initiation.

An AE is defined as any untoward medical occurrence in a patient administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not related to the medicinal product (International Conference on Harmonisation).

Severity of the AE will be defined using the Division of AIDS (DAIDS) toxicity tables. A Serious AE is defined as any untoward medical occurrence that at any dose:

- results in death
- is life-threatening (defined as any event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)
- requires inpatient hospitalization or prolongation of existing hospitalization
- results in persistent or significant disability/incapacity
- is a congenital anomaly/birth defect

- is an important medical event (defined as a medical event that may not be immediately life-threatening or result in death or hospitalization but, based on appropriate medical and scientific judgment, may jeopardize the subject or require intervention (eg medical, surgical) to prevent one of the other serious outcomes listed in the definition above)

Causality assessment will be performed by the original reporter for all causes of death and all (S)AEs not classified as HIV-related (CDC B and C) events.

Statistical analysis

Statistical analysis of the pooled dataset will be carried out at the Medical Research Council Clinical Trials Unit, London, using STATA software (StataCorp, College Station, Texas). If relevant, participant follow-up time whilst in a Janssen-Cilag International NV ETR trial will be excluded from analysis as adverse events occurring during this time will have already been reported to the EMA. Children will be characterised by previous ART treatment (naive v previous ART) and viral load (<400 v ≥400c/ml). Standard descriptive statistics will be used to summarise the data. Demographic and baseline disease characteristics (eg sex; ethnic group; mode of infection; ever AIDS diagnosis) as well as antiretroviral therapy exposure (eg age starting any ART; age starting ETR; ART duration before ETR; viral load and CD4 at ETR start; other drug classes prescribed with ETR; and median estimated months and total patient years on ETR) of children taking ETR will be described, by the following groups:

- ART treatment experienced children aged 6-<18 years taking the licensed dose
- ART treatment experienced children aged 6-<18 years taking an unlicensed dose
- ART naive children aged 6-<18 years
- children <6 years of age.

Additionally immunological and virological response at 12 months for ART naïve children, and virological response at 12 months for ART experienced children, will be presented. Also further breakdowns by 6-<12 years and 12-<18 years will be presented if the sample size allows.

Laboratory toxicity data for periods on ETR will be summarised by duration of time on ETR (for example, <12 months, 12-24 months, >24 months). Rates of events for children on the licensed dose will be presented along with 95% confidence intervals, by DAIDS grade. Additional descriptive analyses will be presented on an individual patient basis for all patients with a grade ≥3 test result whilst on ETR.

Medical Dictionary for Regulatory Affairs (MedDRA) will be used for coding all AEs which are reported as free text in the datasets (Appendix). Characteristics of serious adverse events occurring whilst on ETR and which were considered by the reporting physician to be causally related to ETR will be presented, and will include the type of adverse event, severity using the DAIDS toxicity table, the date it was diagnosed and resolved (if relevant) other ART drug and concomitant medications taken at the time of the event, the sex and age of the participant at the time of the event, and the ETR dose taken. Similarly serious adverse events which were not considered to be causally related to ETR and non serious AEs which were considered causally related to ETR will also be presented. If appropriate, additional descriptive analyses will be performed for the identified and potential risks mentioned in the Risk Management Plan (RMP) and for any newly identified potential signals. Relevant cases for the analyses for identified and potential risk will be retrieved using predefined MedDRA queries, as specified in the RMP. Three or more similar SAEs, accumulated in separate individuals, will be considered a potential signal.

The number of children who discontinue ETR-containing treatment will be tabulated and the reasons for drug discontinuation summarised.

It will not be possible to determine whether a potential control group is appropriate and available until after the first year of data collection and the initial characterisation of the group of children and adolescents receiving ETR. The control group would be drawn from the EPPICC studies and thus would be from the same 'real-life' population.

Ongoing data collection in the participating cohorts

All participating studies' protocols require follow-up of enrolled HIV-infected children and adolescents to continue up to age 18 years or up to the time that they transfer into adult care, if this is earlier. In some EPPICC cohorts, follow-up continues into early adulthood. EPPICC is part of a research programme funded by the European Union (EU) FP7 for a 5-year Network of Excellence - the European Coordinating Committee for the Integration of Ongoing Coordination Actions Related to Clinical, Virological and Epidemiological HIV Research (EuroCoord) network. The EuroCoord network formally started on 1st January 2011; funding from EuroCoord

underpins EPPICC activities from 2011 to 2016, and together with individual cohort studies' own country-specific funding ensures that these studies will continue beyond the duration of this study.

Study strengths and limitations

The strength of this study is the large number of prospective paediatric HIV cohorts included in EPPICC which participate in the current post-marketing safety surveillance program. These cohorts routinely collect clinical, laboratory, and treatment data in HIV-infected children across Europe and thus the results derived from this study have good generalisability to most European countries. As the participating cohorts assess the treatment and care of children with HIV served in routine clinical practice, this study provides data on use and safety of ETR in a "real world" setting.

With regard to limitations of the study, the participating cohorts were not specifically designed for pharmacovigilance purposes, and in some cases data may be missing, for example on serious AEs. Cohorts will make every effort to obtain any missing information via treating physicians' review of patient notes. Non-serious clinical related AEs may not have been collected in a systematic manner across the individual cohort studies, and so may be considered a minimum estimate. Also, non-serious not related AEs are not being collected in the context of this study. However laboratory reporting is expected to be much more complete and so rates of grade 1 and 2 laboratory events will be presented. Of note, most participants are likely to be non-fasting at blood sampling.

5. Study conduct

Ethics approval

The individual cohorts will be responsible to adhere to their appropriate local ethics approval procedures for this surveillance program (i.e. to contact their local ethics committee to determine whether additional protocol approval and additional informed consent form is required or an amendment to the existing protocol approval). Data received by the PENTA Foundation appointed team will be anonymised, and patient identifiers will be removed to ensure patient confidentiality.

Roles and responsibilities

A PENTA Foundation appointed team will provide overall study coordination with the individual cohorts, perform the study data management and analysis, draft the annual reports and liaise with Janssen-Cilag International NV. Participating studies will be responsible for extracting available data on eligible children from their study databases, coordinating the extraction of missing values for core variables from medical notes via treating physicians, formatting all available data according to the standard operating procedure, transferring the dataset, liaising with the study data manager with respect to data queries and providing input into the report writing process.

Reports and publication

Results will be written up as a draft report presenting only aggregated data. The draft report will be circulated and reviewed among the participating cohorts as well as with Janssen-Cilag International NV for input and comments prior to finalisation and submission to Janssen-Cilag International NV/ EMA.

Data archiving

Documentation and archiving of the datasets will be implemented at the end of the study period.

6. Expedited reporting of Serious Related Adverse Events

As the design of this study involves analysis of secondary data, identification of any serious adverse events by the PENTA study team would take place a considerable time after the event. In addition, the specific protocols of cohorts and studies participating in EPPICC vary, with some collecting prospective data regularly over the year, whilst others having a system of annual collection of prospectively collected data within participating sites, leading to considerable reporting delay. National systems for reporting of serious related adverse events vary across Europe, with some countries having mandatory reporting systems, while most have voluntary systems in place. For those studies in countries where reporting is voluntary, the responsible cohort coordinator will remind participating clinicians of their obligations towards their local / national Health Authorities regarding expedited reporting of safety data (serious

adverse events); this may be done via a number of means including email, cohort newsletters, web-pages and study meetings.

7. Timelines

The study will start in October 2013 and end in September 2018, and comprises of the following periods:

- Oct – Dec 2013: Finalisation of study SOP for data merger
- Jan – March 2014: First year data merger and data cleaning/ checking
- April – June 2014: First year analysis and report writing
- July 2014: Draft report circulated
- Sept 2014: Final report circulated.

Subsequent years will follow the same January to September timeline, and report delivery dates are shown in the table below. The final report will be prepared by 30 September 2018.

	Report delivery date to EMA
1st year data	September 30 2014
2nd year data	September 30 2015
3rd year data	September 30 2016
4th year data	September 30 2017
5th year data	September 30 2018

8. References

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APPENDIX

European Pregnancy and Paediatric HIV Cohort Collaboration (EPPICC)

Pharmacovigilance studies on the use of ART
in HIV-infected children and young people in Europe

Standard Operating Procedure
Version 0.0
2014 data merger

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Participating cohort studies:

Belgium: Hospital St Pierre Cohort, Brussels
Contact: Dr Tessa Goetghebuer

Europe-wide: European Collaborative Study
Contact: Dr Claire Thorne

Germany: Competence Network on HIV infected children
Contact: Dr Chris Koenigs

Italy: Italian Register for HIV infection in children
Contact: Dr Maurizio de Martino, Dr Luisa Galli

Spain: Madrid Cohort of HIV-infected Children
Contact: Dr Jose Thomas Ramos Amador

Spain: Barcelona Cohort of HIV-infected Children (CoRISPE-cat)
Contact: Dr Ton Noguera

Romania: "Victor Babes" Hospital Cohort, Bucharest
Contact: Dr Dan Duiculescu, Dr Luminita Ene

Sweden: Swedish Cohort Study
Contact: Lars Naver

UK/Ireland: National Study of HIV in Pregnancy and Childhood (NSHPC) and Collaborative HIV Paediatric Study (CHIPS)
Contact: Dr Pat Tookey (NSHPC), Dr Ali Judd (CHIPS)

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1. Introduction

This document provides guidance on the preparation of data files for the EPPICC pharmacovigilance data merger 2013.

Please refer to section 3 for details on the specific drugs under pharmacovigilance this year.

2. Timing

For this data merger, it is expected that each cohort will be responsible for gathering, computerizing and submitting its own data. Subsequently it will be electronically merged by the EPPICC Data Manager.

The deadline for data submission for this merger is 31st January 2014. Data received after this date will not be guaranteed inclusion. Cohorts are welcome to send data in advance of this date.

During the 2 months after the submission of data, from 1st February to 30th March 2014, we will be working closely with studies to clean the data. This will involve:

- sending out data consistency checks in the form of a discrepancy report
- processing responses and sending further checks where necessary.

The cleaning of the data should be completed by Friday 30th March 2014.

3. Information specific to this year's merger

For the 2014 data merger, the drug under pharmacovigilance is:

- Etravirine (ETR) (section 3.1)

The lab measurements that we are particularly interested in this year are described in section 6.8.

3.1 Etravirine (ETR)

The eligibility criteria for patients on ETR in this data merger are as follows:

- Ever (current or previous) use of ETR
- Age <18 years when started ETR

4. General data considerations

Formats based on the HIV Cohorts Data Exchange Protocol (HICDEP) will be used for all data submissions for this study. The HICDEP format is based on a relational structure, and the data for this study will be collected in a series of tables, which are described in the next section, together with the lookup tables for the codes to be used.

The data requested will generally refer to the entire period of follow-up for each patient - ie before, during, and after (if applicable) drugs under pharmacovigilance - unless otherwise indicated. Please provide as complete information as possible. Particularly important are the following variables during the time the patient was on each of the drugs under pharmacovigilance:

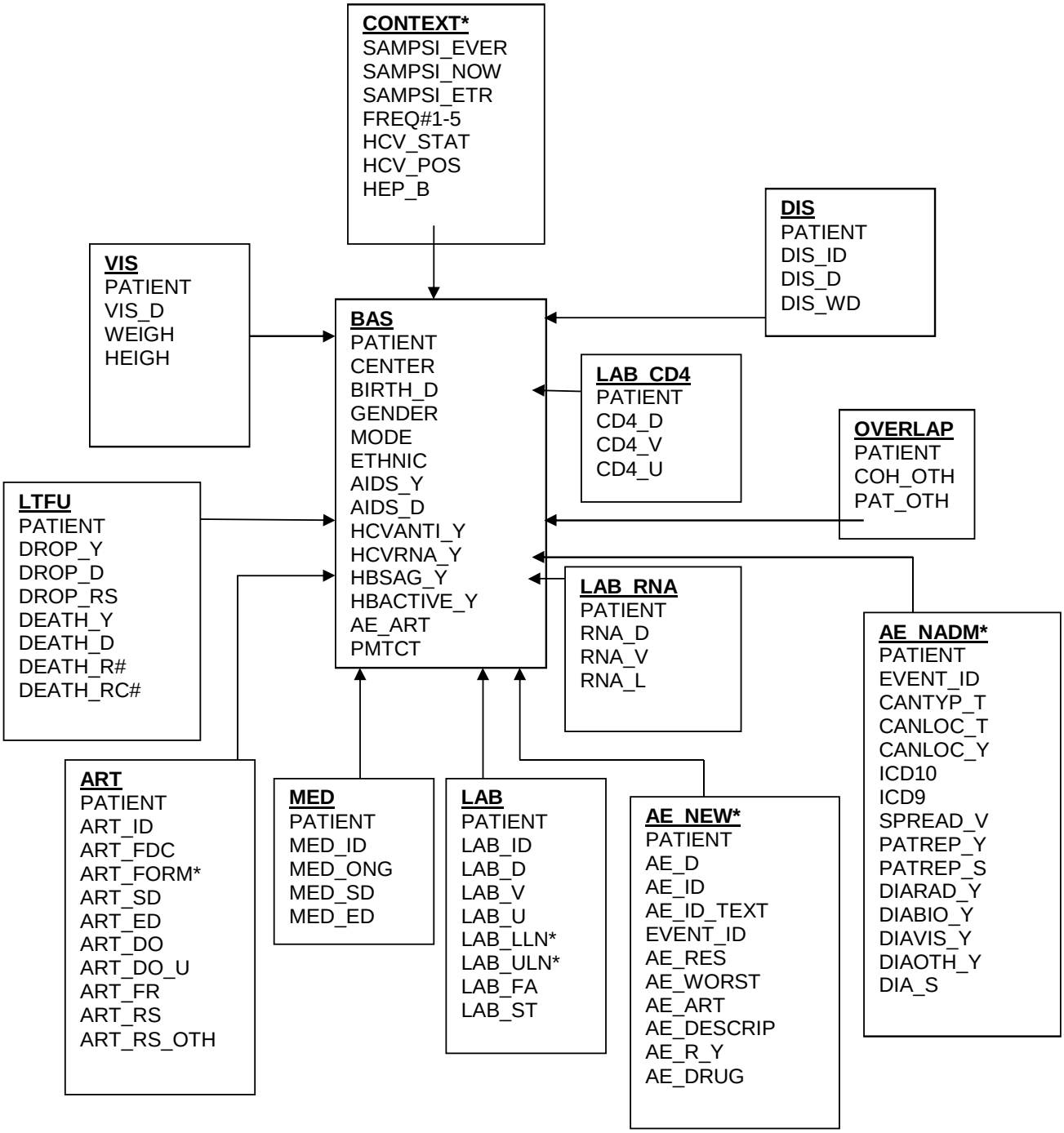
- ART doses
- Weights
- reason for stopping ART if applicable
- laboratory toxicity data for periods immediately before and while on the drugs

- any adverse events possibly related to the drugs or any serious adverse events

Please provide us with your raw data for numeric values, such as weight and height – please do not round these values up or down. If data are missing, please ensure that the field contains a NULL (or "."), unless otherwise indicated; note also that missing data coded as a zero could be misinterpreted as valid coded data.

Please refer to the HICDEP specification (http://www.hicdep.org/wiki/Hicdep_1.50) for further clarification of variable definitions and formats, or contact the EPPICC Data Manager.

The following diagram shows the relationships between the HICDEP tables used in this merger.



* These tables and/or variables are not in HICDEP and have been created specifically for this pharmacovigilance merger.

5. Data transfer procedure

5.1 Extraction

Files may be sent in Access or Excel. If cohorts would like to send in another format, please pre-arrange with the EPPICC Data Manager.

5.2 Transfer process

Files should all be sent together. Please do not send incomplete files or different files on different dates. Files may be sent via email or ftp.

Email:
The initial data files should be zipped and password-protected (preferably using WinZIP AES encryption) and emailed to the EPPICC Data Manager.

In a separate email, the password for the zip file (and the name of the zip software used) should be sent to the EPPICC Data Manager.

ftp:
If a cohort would prefer to ftp their data files, they must pre-arrange this with the EPPICC Data Manager so that a dedicated username and password for that cohort can be set up. The Data Manager will send these details to the cohort along with the ftp address.

The data files should be zipped and password-protected (preferably using WinZIP AES encryption) before sending via ftp.

An email should be sent to the EPPICC Data Manager when data have been transferred by ftp, which includes the password for the zip file and name of zip software used.

For both email and ftp submissions, the EPPICC Data Manager will email the cohort to confirm that the data have been successfully received and opened.

6. Details of variables needed

6.0 CONTEXT table – aggregated data on key contextual characteristics (1 row per cohort)

This table contains some key contextual characteristics of each cohort overall, for all children regardless of age, and also for children aged 6-17 years who are in follow-up since (year) when ETR was licensed in children in Europe. The purpose of this table is to assist in the interpretation of the data on the use of each drug and related adverse events. For example, the sample size in each cohort ever and in current follow-up will be used to describe the population of HIV-infected children included in EPPICC cohorts contributing to this pharmacovigilance study. Also, the number of children aged 6-17 years in follow-up since ETR was licensed will be used to assess the frequency of use of the drug in the licensed population.

Field name	Format	Description
SAMPSI_EVER	Numeric	Sample size in cohort ever (including lost to follow-up, deaths, transfers to adult care etc)
SAMPSI_NOW	Numeric	Sample size in cohort in current follow-up

SAMPSI_ETR	Numeric	Number of children aged 6-< 18 in follow-up since (year), when ETR was licensed in children in Europe
FREQ_1	Numeric	No. of patients aged 6-<18 currently on NNRTI + at least 2 NRTIs regimen not containing a boosted PI
FREQ_2	Numeric	No. of patients aged 6-<18 currently on NNRTI + boosted PI + at least 1 NRTI
FREQ_3	Numeric	No. of patients aged 6-<18 currently on another ART regimen containing a boosted PI
FREQ_4	Numeric	No. of patients aged 6-<18 currently on another ART regimen not containing a boosted PI
FREQ_5	Numeric	No. of patients aged 6-<18 currently not taking ART
HCV_STAT	Numeric	Number of patients aged 6-<18 in current follow-up for whom HCV infection status is known
HCV_POS	Numeric	Number of patients aged 6-<18 in current follow-up known to be anti-HCV positive
HBV_STAT	Numeric	Number of patients aged 6-<18 in current follow-up for whom HBV infection status is known
HBV_POS	Numeric	Number of patients aged 6-<18 in current follow-up known to be HBV surface antigen positive

6.1 BAS table - basic clinical and demographic data (1 row per patient)

Field name	**Format**	**Description**
PATIENT	Character or numeric	Cohort patient ID (unique and anonymous)
CENTER	Character	Clinic/centre/hospital where patient is seen
BIRTH_D	yyyy-mm-dd	Birth date
GENDER	Numeric with codes 1=Male 2=Female 9=Unknown	Sex
MODE	Numeric with codes 1= homo/bisexual 2=injecting drug use 3=(1+2) 4=haemophiliac 5= transfusion, non haemophilia related 6=heterosexual contact 7=(6+2) 8 = mother-to-child transmission 11 = parenteral other 90=other 99=unknown	Mode of acquisition of HIV infection

ETHNIC	Numeric with codes 10=White 20=Black 21=Black African 22=Black Caribbean 30=Hispanic 40=Asian 50=American 60=Indigenous 1020=White/black 1040=White/Asian 2030 = Black + hispanic 3040 = Asian + hispanic 97=Other 98=Prohibited 99=Unknown	Ethnic group
AIDS_Y	Numeric with codes 0=No 1=Yes 9=Unknown	Has patient been given an AIDS diagnosis?
AIDS_D	yyyy-mm-dd	If yes, date of AIDS diagnosis
HCVANTI_Y	Numeric with codes 0=No 1=Yes 9=Unknown	Is patient anti-HCV seropositive (excluding tests before age 18 months)
HCVRNA_Y	Numeric with codes 0=No 1=Yes 9=Unknown	Does the patient have positive or detectable HCV RNA?
HBSAG_Y	Numeric with codes 0=No 1=Yes 9=Unknown	Is the patient HBV surface antigen positive?
HBACTIVE_Y	Numeric with codes 0=No 1=Yes 9=Unknown	Does the patient have active hepatitis B (i.e. detectable HBV DNA and/or HBeAg positive?)
AE_ART	Numeric with codes 0=No 1=Yes 9=Unknown	Has the patient had any adverse events whilst taking ART? Note that if the answer to this is YES, then they should be reported in table AE_NEW
AE_nonser	Numeric with codes 0=No 1=Yes 9=Unknown	Does your cohort collect non-serious AEs related to ETR? Note that if the answer to this is YES, then they should be reported in table AE_NEW.
PMTCT	Numeric with codes 0=No 1=Yes 9=Unknown	Did the patient receive ART for PMTCT?

6.2 LTFU table - death and drop-out data (1 row per patient)

Field name	**Format**	**Description**
PATIENT	Character or numeric	Cohort patient ID
DROP_Y	Numeric	Has the patient dropped out?

	0=No 1=Yes	
DROP_D	yyyy-mm-dd	If YES, date of last visit
DROP_RS	Numeric with codes: *See below for coding*	If YES, reason for DROP
DEATH_Y	Numeric 0=No 1=Yes	Has the patient died? Please note that all deaths must also be reported in AE_NEW
DEATH_D	yyyy-mm-dd	If YES, date of death
DEATH_R1	Numeric *See below for coding*	Cause of death
DEATH_RC1	Character with codes: I=immediate cause U=underlying cause/condition C=contributing cause N=not available	Coding of causal relation of the code given in DEATH_R1 to the death
DEATH_R2	Numeric *See below for coding*	Cause of death
DEATH_RC2	Character with codes: I=immediate cause U=underlying cause/condition C=contributing cause N=not available	Coding of causal relation of the code given in DEATH_R2 to the death
DEATH_R3	Numeric *See below for coding*	Cause of death
DEATH_RC3	Character with codes: I=immediate cause U=underlying cause/condition C=contributing cause N=not available	Coding of causal relation of the code given in DEATH_R3 to the death

DEATH_R# and DEATH_RC# should be continued for as many reasons as are recorded. For more information on DEATH_RC# fields, please visit http://www.cphiv.dk/CoDe/tabid/55/Default.aspx

Lookup table for reason for drop out

Code (DROP_RS)	**Reason for Drop Out**
0	Patient was not infected (mainly for children)
1	Patient lost to follow-up / not known to be dead
2	Patient has not had visit within required amount of time
2.1	Patient did not respond to several invitations
3	Patient moved away
3.1	Patient moved to another country
4	Patient moved and is followed by another centre
5	Patient's decision
5.1	Patient's caretaker wanted to discontinue (for children)
6	Consent withdrawn*
7	Incarceration/jail
8	Institutionalisation (drug treatment, psychological …etc.)
9	Other

Codes for cause of death

Code (DEATH_R#)	**Cause of death**
1	Myocardial Infarction
2	Stroke

3	Other cardiovascular diseases
4	Symptoms caused by mitochondrial toxicity
4.1	Lactic acidosis
5	Complications due to diabetes mellitus
6	Pancreatitis
7	Complications due to hepatitis
7.1	Hepatitis-related
7.2	Liver failure not related to hepatitis/ mitochondrial toxicity
8	HIV-related
8.1	AIDS defining event
8.2	Invasive bacterial infection
9	Renal failure
10	Bleeding (haemophilia)
20	Non AIDS-defining cancer
50	Sudden infant death
51	Neonatal death (including prematurity/other complications)
55	Child abuse
90	Other
91	Suicide
92	Drug overdose
93	Accident
99	Unknown, fatal case with no information

6.3 OVERLAP table – patients overlapping with other cohorts (1 row per overlap)

Field name	Format	Description
PATIENT	Character or numeric	Cohort patient ID (unique and anonymous)
COH_OTH	Character	Other cohort who this patient is part of
PAT_OTH	Character	Unique patient ID in the other cohort

6.4 VIS table - basic follow-up/ visit related data (1 row per measurement)

Please report every weight and height measurement you have, preferably from first presentation. For the patient to be included in the analysis for this study, we will need at least one weight within 3 months of starting each drug under pharmacovigilance. Please also include the corresponding height, if available.

Field name	Format	Description
PATIENT	Character or numeric	Cohort patient ID
VIS_D	yyyy-mm-dd	Date of patient visit
WEIGH	Numeric 999=unknown	Weight at patient visit (kg)
HEIGH	Numeric 999=unknown	Height at patient visit (cm)

6.5 ART table - antiretroviral treatment data (1 row per measurement)

Please report **doses, including all dose changes, for ETR**.

If a child was still receiving a drug at last follow-up, please code reason for stopping as “0”. If a child had stopped taking a drug but the stop date is unknown, please enter the stop date as “1911-11-11”.

Where a child stops taking a study drug, if the main reason for stopping is because of toxicity related to the study drug, please ensure this toxicity is also documented in the AE_NEW table.

This year we have removed the field ART_RIT_LOW as it was causing confusion. We would also like to clarify that ART_DO should be the total daily dose, NOT dose per administration event.

Also, there have been a lot of questions about how to report fixed dose combinations, so we have included an example:

Imagine we have a patient taking a total daily dose of 600/300 Kivexa

You may record this in one of two different ways:

EITHER:
One record for Kivexa :

ART_ID	ART_FDC	ART_DO
J05AR02	6	900

OR:
Two records – one for 3TC and one for ABC.

ART_ID	ART_FDC	ART_DO
J05AF06	6	600
J05AF05	6	300

Field name	Format	Description
PATIENT	Character or numeric	Cohort patient ID
ART_ID	Character with codes (see below for link to codes)	Code representing the antiretroviral treatment
ART_FDC	Numeric 0=No 1=Combivir (3TC+AZT) 2=Trizivir (3TC+ABC+AZT) 3=Kivexa (3TC+ABC) 4=Truvada (FTC+TDF) 5=Atripla (EFV+FTC+TDF) 6=Kaletra (LPV + RTV)	Is the drug part of a fixed dose combination?
ART_FORM	Numeric: 1 = tablet/capsule/gelcap 2 = liquid/syrup/suspension 3 = combination of 1 and 2 4 = powder 5 = subcutaneous 6 = intravenous 9 = unknown	ART drug formulation
ART_SD	yyyy-mm-dd	Start date
ART_ED	yyyy-mm-dd	Stop date
ART_DO	Numeric	Total **daily** dose
ART_DO_U	Numeric with codes: 1=mg 2=ml 9=unknown	Dose unit
ART_FR	Numeric with codes: 0 = total daily dose 1=1 daily dose / qd 2=2 daily doses/bid 3=3 daily doses/tid Etc 9=unknown	Frequency of dosing
ART_RS	Numeric with codes: 0 = Still on drug	Main reason for stopping

	1 = Treatment failure (i.e. virological, immunological, and/or clinical failure) 1.1 = Virological failure 1.2 = Partial virological failure 1.3 = Immunological failure – CD4 drop 1.4 = Clinical progression 2 = Abnormal fat redistribution 3 = Concern of cardiovascular disease 3.1 = Dyslipidaemia 3.2 = Cardiovascular disease 4 = Hypersensitivity reaction 5 = Toxicity, predominantly from abdomen/G-I tract 5.1 = Toxicity – GI tract 5.2 = Toxicity – Liver 5.3 = Toxicity – Pancreas 6 = Toxicity, predominantly from nervous system 7 = Toxicity, predominantly from kidneys 8 = Toxicity, predominantly from endocrine system 8.1 = Diabetes 9 = Haematological toxicity (anaemia…) 10 = Hyperlactataemie/lactic acidosis 70 = Pregnancy – toxicity concerns 75 = Pregnancy –switch to more appropriate regimen for PMTCT 76 = post-partum prophylaxis 77 = Dose change for height/ weight 88 = Death 90 = Side effects – any of the above but unspecified 90.1 = Co morbidity 91 = Toxicity, not mentioned above 92 = Availability of more effective treatment (not specifically failure or side effect) 92.1 = Simplified treatment available 92.2 = Treatment to complex 92.3 = Drug interaction 93 = Structured Treatment Interruption (STI) 93.1 = Structured Treatment Interruption (STI) – at high CD4 94 = Patient's wish/decision 94.1 = Non-compliance 95 = Physician's decision 97 = Study treatment 98 = Other causes 99 = Unknown	Where "Toxicity" is recorded as the reason for stopping (codes 5-10, 90, 91, 92.3), please also report this toxicity in the AE_NEW table, so that a causality assessment is also documented.
ART_RS_OTH1	Character (free text)	Other reason for stopping (if ART_RS = 98 ("Other causes")
ART_RS1	Codes same as for ART_RS or text if unable to code	If multiple reasons for stopping are given, and not just a main reason, please enter here and continue with extra fields ART_RS# for as many reasons as are recorded

Please continue ART_RS# for as many reasons as are recorded, but only where "main reason" is not available.

For an up-to-date list of codes for ART_ID, please follow this link:
http://www.hicdep.org/wiki/Hicdep_1.50/TableArt/FieldArtId#CodingTable

6.6 MED table - other non-ART medication (1 row per measurement)

If a child had stopped taking a drug but the stop date is unknown, please enter the stop date as "1911-11-11".

Field name	Format	Description
PATIENT	Character or numeric	Cohort patient ID
MED_ID	Character with codes (see below for link to codes)	Code representing other medication
MED_ONG	Numeric 0=No, stopped drug 1=Yes, patient still on drug 9=Unknown	Is the patient still on the drug?
MED_SD	yyyy-mm-dd	Date of initiation
MED_ED	yyyy-mm-dd	Date of stopping

For an up-to-date list of codes for MED_ID, please follow this link:
http://www.hicdep.org/wiki/Hicdep_1.50/TableMed/FieldMedId#CodingTable

6.7 DIS table - CDC B and AIDS-defining events (1 row per event diagnosed)

Please note that we are collecting CDC clinical category B and C events for this project.

Field name	Format	Description
PATIENT	Character or numeric	Cohort patient ID
DIS_ID	Character with codes See table below	Code to identify event
DIS_D	yyyy-mm-dd	Date of event
DIS_WD	1=definitive 2=presumptive 3=diagnosis from autopsy 4=diagnosis from registry 9=unknown	Means of diagnosis

Codes for category B events - paediatric

Code (DIS_ID)	CDC disease description
ANAE	Anaemia (<8 gm/dL), neutropenia (<1,000/mm3), or thrombocytopenia (<100,000/mm3) persisting >=30 days
BACT	Bacterial meningitis, pneumonia, or sepsis (single episode)
CAND	Candidiasis, oropharyngeal (thrush), persisting (>2 months) in children >6 months of age
CARD	Cardiomyopathy
CYTO	Cytomegalovirus infection, with onset before 1 month of age
DIAR	Diarrhoea, recurrent or chronic
HEPA	Hepatitis
HSVS	Herpes simplex virus (HSV) stomatitis, recurrent (more than two episodes within 1 year)
HSVB	HSV bronchitis, pneumonitis, or esophagitis with onset before 1 month of age
SHIN	Herpes zoster (shingles) involving at least two distinct episodes or more than one dermatome
LEIO	Leiomyosarcoma
LYMP	Lymphoid interstitial pneumonia (LIP) or pulmonary lymphoid hyperplasia complex
NEPH	Nephropathy
NOCA	Nocardiosis
PFEV	Persistent fever (lasting >1 month)
TOXO	Toxoplasmosis, onset before 1 month of age
VARI	Varicella, disseminated (complicated chickenpox)

Codes for AIDS defining events - paediatric

Code (DIS_ID)	CDC disease description
SRBI	Serious recurrent/ multiple bacterial infections
CANO	Candidiasis, oesophageal, bronchi, trachea, or lungs
COCC	Coccidioidomycosis, disseminated or extrapulmonary
CRCO	Cryptococcosis, extrapulm.
CRSP	Cryptosporidiosis (duration > 1 month)
CMVP	Cytomegalovirus (CMV) disseminated with onset >1 month, paediatrics
ENC	Encephalopathy
HERP	Herpes simplex virus ulcers (duration > 1 month) or pneumonitis/ esophagitis/ bronchitis
HIST	Histoplasmosis, extrapulm. or disseminated
KS	Kaposi Sarcoma
NHGP	Non-Hodgkin Lymphoma - Primary Brain Lymphoma
NHGB	Non-Hodgkin Lymphoma - Burkitt (Classical or Atypical)
NHGI	Non-Hodgkin Lymphoma - Diffuse large B-cell lymphoma
MCX	Mycobact. tuberculosis extrapulm.
MCO	Mycobact., other
MC	Mycobact. avium complex (MAC) or Kanasii, extrapulm.
PCP	Pneumocystis carinii pneumonia (PCP)
LEU	Progressive multifocal leucoencephalopathy
SAM	Salmonella bacteriaemia (non-tyhpoid) (recurrent)
TOX	Toxoplasmosis, brain
WAST	HIV Wasting Syndrome

Codes for AIDS defining events - adult

Code	Severe Opportunistic Infections
DEM	AIDS dementia complex
BCNE	Bacterial pneumonia, recurrent (>2 episodes within 1 year)
CANO	Candidiasis, oesophageal, bronchi, trachea, or lungs
COCC	Coccidioidomycosis, disseminated or extrapulmonary
CRCO	Cryptococcosis, extrapulm.
CRSP	Cryptosporidiosis (duration > 1 month)
CMVR	Cytomegalovirus (CMV) chorioretinitis
CMVO	CMV – other location
HERP	Herpes simplex virus ulcers (duration > 1 month) or pneumonitis/esophagitis
HIST	Histoplasmosis, extrapulm.
WAST	HIV Wasting Syndrome
ISDI	Isosporiasis diarrhoea (duration > 1 month)
LEIS	Leishmaniasis, visceral
MCDI	Microsporidosis diarrhoes (dur. > 1 month)
MC	Mycobact. avium complex (MAC) or Kanasii, extrapulm.
MCP	Mycobact. tuberculosis pulm.
MCX	Mycobact. tuberculosis, extrapulm or disseminated
MCPO	Mycobact. pulm., other
MCXO	Mycobact. extrapulm., other
PCP	Pneumocystis carinii pneumonia (PCP)
LEU	Progressive multifocal leucoencephalopathy
SAM	Salmonella bacteriaemia (non-tyhpoid) (recurrent)
TOX	Toxoplasmosis, brain
FBLS	Focal Brain lesion
Code	**Malignancies**
KS	Kaposi Sarcoma

Code	Severe Opportunistic Infections
HG	Hodgkins Lymphoma
NHG	Non-Hodgkin Lymphoma -not specified
NHGB	Non-Hodgkin Lymphoma – Burkitt (Classical or Atypical)
NHGI	Non-Hodgkin Lymphoma – Diffuse large B-cell lymphoma (Immunoblastic or Centroblastic)
NHGU	Non-Hodgkin Lymphoma - Unknown/other histology
NHGP	Non-Hodgkin Lymphoma - Primary Brain Lymphoma
CRVC	Cervical Cancer

6.8 LAB table - laboratory data (1 row per measurement)

Please provide **all available data** on laboratory test results (eg liver enzymes, haematology, biochemistry etc), and normal as well as abnormal results, for the 12 months prior to starting the drug under pharmacovigilance up to the present.

Please report ALL results for the following markers which we are particularly interested in this year, and use SI units as specified:

Marker	Abbreviation	Preferred units
Absolute neutrophil count	**ANC**	10^9/L
Total cholesterol	**CHOL**	mmol/L
Low-density lipoprotein cholesterol	**LDL-C**	mmol/L
High-density lipoprotein cholesterol	**HDL-C**	mmol/L
Triglycerides	**TRIG**	mmol/L
Alanine aminotransferase	**ALT**	u/L
Aspartate aminotransferase	**AST**	u/L
Total bilirubin	**BIL**	µmol/L
Blood glucose fasting	**FPG**	mmol/L
Blood glucose non-fasting	**Non-FPG**	mmol/L
Pancreatic amylase	**P-AMY**	u/L
Lipase	**LIP**	u/L

Please do not report CD4 and HIV-1 RNA values here – see separate tables below.

Field name	Format	Description
PATIENT	Character or numeric	Cohort patient ID
LAB_ID	Character with code See table below for coding	Laboratory test type
LAB_D	yyyy-mm-dd	Date of lab measurement
LAB_V	Numeric	Value of measurement
LAB_U	Numeric with code See table below for coding	Unit of measurement used
LAB_LLN	Numeric	Lower limit normal for lab conducting test
LAB_ULN	Numeric	Upper limit normal for lab conducting test. Note – this MUST be completed for bilirubin, pancreatic amylase and lipase
LAB_FA	Numeric with code: 0=No 1=Yes 9=unknown	Was the blood sample taken whilst fasting?
LAB_ST	Character WB = whole blood P=plasma	Specimen type

	S=serum	

Codes for laboratory tests on next page:

Code (LAB_ID)	Measurement
ALB	Albumin
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AMY	Amylase
ANC	Absolute neutrophil count
AST	Aspartate aminotransferase
BIL	Total Bilirubin
CHOL	Total Cholesterol
CRE	Creatinine
FPG	Blood glucose fasting
Non-FPG	Blood glucose non-fasting
GLUC	Glucose
HAEM	Haemoglobin
HDL-C	Serum HDL
HEMA	Hematocrit
LACT	Lactate
LDL-C	Serum LDL
LEUK	Leukocytes
LIP	Lipase
LYM	Lymphocyte count
LYMP	Lymphocyte percentage
MCV	MCV
Na+	Na+
NEUT	Neutrophil count
P-AMY	Pancreatic amylase
PHA	Ph arterial
PHV	Ph venous
PLT	Platelet count
THR	Thrombocytes
TRIG	Serum triglycerides
URA	Uric acid
WBC	WBC count

Codes for units of measurement

Code (LAB_U)	units
1	mmol/L
5	IU/L (u/L)
6	μmol/L
8	1E+9/L

Please don't use any units not coded here as it causes us great difficulty in analysis.

6.9 LAB_CD4 table - CD4 data (1 row per measurement)

If both CD4 count and CD4 percentage are recorded, please provide both in separate records.

Field name	Format	Description
PATIENT	Character or numeric	Cohort patient ID
CD4_D	yyyy-mm-dd	Date of CD4 measurement
CD4_V	Numeric	Value of CD4 measurement
CD4_U	Numeric with codes 1=cells/mm^3 2=%	CD4 cell count or CD4 %

	3=total lymphocytes/μl	

6.10 LAB_RNA table – HIV-1 RNA data (1 row per measurement)

Field name	Format	Description
PATIENT	Character or numeric	Cohort patient ID
RNA_D	yyyy-mm-dd	Date of HIV-1 RNA measurement
RNA_V	Numeric -1=undetectable / below level of detection 1= above level of detection	HIV-1 RNA measurement value (copies/ml)
RNA_L	Numeric	Lower limit of HIV-1 RNA assay (if available)
RNA_U	Numeric	Upper limit of HIV-1 RNA assay (if RNA_V=1)

6.11 AE_NEW table - adverse events (1 row per measurement)

Please note that this table is different from the HICDEP AE table, and is now more relevant to pharmacovigilance. **It should contain all serious non-HIV-related adverse events and non-AIDS-defining malignancies. It must also include all deaths, which means that deaths should be reported in BOTH the LTFU table and this AE_NEW table. For deaths use code D1 for AE_ID.**

Please also report all non-serious AEs related to ETR use, where available.

Any HIV-related adverse events (i.e. CDC B and C events) should be reported in table 6.7 DIS.

Please use table 6.12 AE_NADM to report any **extra** information on non-AIDS defining malignancies reported here, and ensure that the unique identifier EVENT_ID is completed in both this table and table 6.12 to link the information on each malignancy event.

Please refer to DAIDS toxicity tables when completing AE_WORST:
http://rsc.tech-res.com/Document/safetyandpharmacovigilance/Table_for_Grading_Severity_of_Adult_Pediatric_Adverse_Events.pdf

Field name	Format	Description
PATIENT	Character or numeric	Cohort patient ID
AE_D	yyyy-mm-dd	Date of event
AE_ID		Code for event as in coding list below
AE_ID_TEXT	Character (free text)	Free text to identify event if cannot be coded in AE_ID
EVENT_ID	Numeric	Unique numeric identifier for the event – used to link to table AE_NADM where necessary
AE_RES	yyyy-mm-dd	Date resolved
AE_WORST	Numeric with coding 1 = Mild 2 = Moderate 3 = Severe 4 = Life threatening 9=unknown	Worst grade (please refer to and code from DAIDS toxicity tables)
AE_ART	Numeric with coding 0=no 1=yes	ART stopped or modified

	9=unknown	
AE_DESCRIP	Character (free text)	Full description of the event (this field replaces AE_TEXT)
AE_R_Y	Numeric with coding 0 = not related 1 = definitive 2 = remote/unlikely 3 = possible 4 = probable 9 = unknown	Relation to treatment – note if coded 1,3 or 4 then AE_DRUG must be completed
AE_DRUG	Character with codes	Code representing the causally related antiretroviral treatment (see codes for ART table in table 6.5) MUST be filled in if AE_R_Y, 3 or 4=1

A Serious AE is defined as any untoward medical occurrence that at any dose:

- results in death
- is life-threatening (defined as any event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)
- requires inpatient hospitalization or prolongation of existing hospitalization
- results in persistent or significant disability/incapacity
- is a congenital anomaly/birth defect
- is an important medical event (defined as a medical event that may not be immediately life-threatening or result in death or hospitalization but, based on appropriate medical and scientific judgment, may jeopardize the subject or require intervention (eg medical, surgical) to prevent one of the other serious outcomes listed in the definition above)

Codes for adverse events

Code (AE_ID)	Event
B1	Palpitations
B2	Changes in heart rate/rhythm, arrhythmia
B3	Shock or heart failure, CCF, pulmonary oedema
B19	Myocardial infarction
B4	Ankle/leg swelling
B7	Hypertension, high blood pressure
B9	Angina,Ischaemic heart disease
B10	Cardiomyopathy, unspecified
B13	Cardiomyopathy, symptomatic
B15	Bacterial endocarditis, SBE
B16	Thrombosis, DVT
B18	Varicose veins
B8	Other cardiovascular disease
BX	Cardiovascular - unspecified
C2	Rash, erythema
C3	Itching, pruritus, excoriation, scratching
C5	Alopecia, hair loss, balding
C6	Pigmentation change
C8	Exfoliative dermatitis,StevensJohnson,TEN,
C9	Reaction localised to site of administration
C10	Generalised hypersensitive reaction,urticaria
C15	Acne
C16	Molluscum contagiosum

C17	Tinea(all types),athletes foot,fungal infect.
C18	Candida skin rash, intertrigo
C13	Seborrhoeic dermatitis, seborrhoeic eczema
C19	Dermatitis, eczema, otitis externa
C20	Cutaneous warts, facial warts
C22	Psoriasis
C23	Pityriasis versicolor
C24	Folliculitis,furunculosis,cellulitis,impetigo
C25	Fungal infection of nails, paronychia
C26	Cutaneous herpes simplex
C27	Herpes simplex caused mucocutaneous ulcer >1m
C28	Multidermatomal herpes zoster (ARC)
C12	Herpes zoster, shingles (1 dermatoma/unspec.)
C29	Dry skin, ichthyosis, xeroderma, flaking skin
C11	Other skin changes(flushing,PCT,etc)
E1	CMV Retinitis
E3	Conjunctivitis, blepharitis, keratitis
E8	Retinal detachment
E9	Blindness
E10	Toxoplasmosis of the eye
E6	Other ophthalmalogical disorders
EX	Ophthalmalogical - unspecified
F1	Chills or fever/rigor (pyrexia)
F6	PUO (pyrexia unknown origin), drug fever
F2	Flu syndrome, flu-like illness
F3	Night sweats
F4	Night sweats/fever
F5	Fever >14 consecutive days or 15 days in 30
M1	General malaise
M2	Tiredness,lethargy,fatigue,weakness(not musc)
M3	Fainting
M4	HIV wasting
M5	Other systemic disorder
G1	Nausea
G2	Vomiting
G3	Diarrhoea,loose stool,unspecified or <30 days
G53	Diarrhoea without cause >30 days (ARC)
G4	Constipation
G5	Abdominal pain, epigastric pain
G6	Indigestion, oesophageal reflux, gastritis
G8	Anorexia - loss of appetite
G9	Weight gain
G13	Weight loss and cachexia - unspecified
G46	Weight loss <10%
G47	Weight loss >10% in 6 months
G10	Infectious gastroenteritis (eg campylobacter)
G12	Difficulty swallowing - dysphagia
G14	Oral candida, oral thrush
G42	Recurrent or persistent oral candida
G18	Oesophageal candida
G15	Oral hairy leukoplakia, OHL
G16	Oral herpes, cold sores, herpetic ulcers
G19	Anal/perianal candida

G20	Retrosternal discomfort
G21	Salmonellosis (stool)
G22	Flatulence, eructation, wind, bloating
G23	Gingivitis,painful/bleeding gum,periodontitis
G24	Ulcers mouth/palate/tongue/oesophageal unspec
G26	Tooth abscess, toothache
G27	Angular cheilitis, angular stomatitis
G28	Stomatitis,pharyngitis,glossitis,inflammation
G32	Perianal abscess, excoriation, irritation
G33	Piles, haemorrhoids
G34	Rectal & lower gastrointestinal bleeding
G36	Upper gastrointestinal bleeding, haematemesis
G37	Cholecystitis, cholelithiasis, gall stones
G38	Pancreatitis - certain
G39	Pancreatitis - chronic
G40	Colitis, unspecified
G44	Ascites
G45	Dry mouth
G51	Giardiasis
G52	Parotitis
G54	CMV oesophageal ulcers, CMV oesophagitis
G55	CMV stomach/gastritis/duodenum
G56	Taste change/perversion, metallic taste
G62	Appendicitis
G11	Other changes in mouth
G29	Other gastro-intestinal disease
GX	Gastrointestinal - unspecified
H1	Pancytopenia, bone marrow depression/aplasia
H2	Anaemia
H3	Leucopenia
H4	Thrombocytopenia
H6	Purpura,bruising,petechiae-abnormal platelets
H9	Lymphadenopathy unspecified
H10	Neutropenia
H13	Persistent generalised lymphadenopathy, PGL
H7	Other haematological disorder
H12	Other bleed
J2	Pain in muscles (myalgia)
J3	Pain in joints (arthralgia)
J4	Swelling and tenderness of joints, arthritis
J5	Gout
J6	Back pain
J8	Muscle weakness
J12	Connective tissue disorder, eg. ante. uveitis
J13	Cramp, spasms, tetany
J14	Bacterial bone or joint infection
J15	Bacterial bone/joint infection (AIDS Penta)
J7	Other musculoskeletal disease
JX	Musculoskeletal - unspecified
K1	Cystitis, UTI
K24	Raised creatinine
K3	Pyelonephritis
K4	Renal failure

K5	Syphilis
K9	Genital candidiasis, thrush, balanitis
K10	Gonorrhoea
K11	Non specific urethritis, NSU
K14	Genital and perianal warts
K15	Haematuria - blood in urine
K16	Polyuria, frequent micturition
K17	Pregnancy
K19	CIN, cervical dysplasia
K20	Menorrhagia
K21	Other gynaecological
K27	Proteinuria
K29	Proximal renal tubular dysfunction (PRTD)
K30	Renal colic, renal stones, urolithiasis
K13	Other renal/kidney disease
K6	Other GU disease (eg. epididymitis,prostatis)
KX	Renal/GU - unspecified
L14	Raised bilirubin
L15	Raised AST
L16	Raised ALT
L17	Raised GGT
L2	Symptomatic hepatitis without jaundice
L3	Symptomatic hepatitis with jaundice
L5	Enlarged spleen, splenomegaly
L6	Enlarged liver, hepatomegaly
L7	Hepatosplenomegaly
L8	Hepatitis B
L9	Hepatitis C
L10	Chronic active/persistent hepatitis
L11	Raised alkaline phosphatase (ALP,ALK)
L12	CMV hepatitis
L4	Other hepatic disease (eg. failure,cirrhosis)
LX	Hepatic - unspecified
N1	Headache
N2	Drowsiness
N3	Hemiparesis
N4	Transient numbness/tingling (paraesthesia)
N5	Peripheral neuropathy, unspecified
N6	Insomnia
N7	Convulsions, fits, epilepsy
N12	Memory loss
N13	Toxoplasmosis - cerebral
N18	HSV encephalitis
N19	HIV encephalopathy/dementia/ADC/encephalitis
N21	Cryptococcal meningitis
N22	Viral meningitis
N23	Bacterial meningitis (incl. listeria)
N24	Tuberculous meningitis
N26	Myelopathy, HIV vacuolar myelopathy
N64	CMV encephalitis or meningitis
N29	Dementia - unspecified
N30	Confusion
N31	Speech disturbance,dysarthria,dysphasia

N32	Impotence
N33	Urinary sphincter disturb,retention,incontin.
N34	Anal sphincter disturb., faecal incontinence
N40	Post herpetic neuralgia
N65	Bacterial meningitis (AIDS Penta)
N42	Bells palsy, 7th nerve palsy
N46	Progressive multi-focal leukoencephalopathy
N50	Guillain-Barre syndrome
N51	Partial fits/abscences/focal fits
N52	Cerebral haemorrhage,subdural haematoma
N53	Cerebral atrophy,cortical atrophy
N55	Spastic diplegia
N57	Speech delay
N68	Neurocysticercosis
N67	Cerebrovascular accident, stroke
N11	Other neurological condition
NX	Neurological - unspecified
P3	B cell (non Hodgkin's) lymphoma
P13	T cell (non Hodgkin's) lymphoma
P4	Primary CNS lymphoma
P5	Hodgkins lymphoma
P7	Primary skin neoplasm, eg. Bowens, SCC, BCC
P2	Kaposi's Sarcoma, KS
P9	Kaposi's Sarcoma,KS - oral
P1	Other malignant disease
PX	Neoplasm - unspecified
Q2	Failure to thrive (fallen 1 centile/unspec.)
Q3	Failure to thrive (fallen 2 centiles) severe
Q4	Pneumococcal septicaemia
Q6	Development delay/loss of milestones level 1
Q7	Development delay/loss of milestones level 2
Q8	Nappy rash, candida
Q9	Mumps
Q10	Measles
Q11	Chickenpox
Q15	Premature baby
R1	URTI, sorethroat,earache,cough,cold,sinusitis
R2	Breathlessness, dyspnoea, SOB
R3	Wheezing or rhonchi
R4	Lower respiratory infection, eg. bronchitis
R5	Chest pain/discomfort, pericardial pain
R6	Haemoptysis, coughing up blood
R7	Asthma
R9	Pneumocystis carinii pneumonia (PCP)
R10	Pulmonary tuberculosis
R11	Chronic lymphoid interst. pneumonitis -mild
R14	Chronic lymphoid interst. pneumonitis -severe
R12	Pleural effusion
R13	Pulmonary disease due to MAI or atypical
R15	Pulmonary embolism
R16	Pneumothorax
R17	Lung abscess
R18	CMV pneumonitis

R19	Acute otitis media
R20	Chronic otitis media or conductive deafness
R21	Croup
R22	Bronchiolitis
R24	Lobar pneumonia - pneumococcal
R25	Pneumonia - other bacterial
R26	Pneumonia - viral or other
R28	Pulmonary aspergillosis
R30	Recurrent bacterial pneumonia
R31	Bacterial pneumonia (AIDS Penta)
R8	Other respiratory disease
RX	Respiratory - unspecified
T2	Specific viral illness
T3	Malaria
T4	Infestation - e.g. scabies,pediculosis
T7	Cryptosporidia > 1 mth
T8	Extrapulmonary tuberculosis
T14	Atypical mycobacterial - MAI - disseminated
T35	Atypical mycobacterial infection not MAI
T9	Extrapulmonary pneumocystis
T11	Salmonella septicaemia (1st episode)
T22	Salmonella septicaemia/bacteraemia(recurrent)
T15	Isosporiasis with diarrhoea > 1 mth
T16	Histoplasmosis disseminated
T18	CMV excl neurological,liver,spleen,lymph node
T42	CMV spleen, lymph nodes
T26	CMV colitis, CMV proctitis
T43	CMV other end-organ disease (eg. skin, mouth)
T19	Visceral disease due to herpes simplex
T20	Candidiasis of trachea, bronchi or lungs
T21	Extrapulmonary cryptococcal infection
T25	Septicaemia (not salmonella or pneumococcal)
T27	Shigella colitis
T31	Cryptosporidia, unspecified or < 1 mth
T33	Microsporidiosis>1mth,enterocytozoon bieneusi
T44	Herpes simplex, any episode (non-AIDS)
T37	Bact. abscess of internal organ/body cavity
T1	Other viral infection (eg. parvovirus)
T5	Other fungal infection (not aspergillosis)
T29	Other bacterial infection
T6	Other infection
T45	Septicaemia (AIDS in Penta)
T46	Bacterial abscess internal organ (AIDS Penta)
TX	Infection - unspecified
V1	Dizziness or giddiness
V2	Vertigo
V3	Ataxia gait, failure of muscle coordination
V4	Tinnitus (ringing sound in ears)
V5	Deafness
V7	Nystagmus
X4	Raised amylase,unspecified(+/- raised lipase)
X18	Raised pancreatic amylase (+/- raised lipase)
X5	Hypokalaemia, low potassium

X7	Diabetes, hyperglycaemia, high blood sugar
X16	Congenital abnormality (in offspring)
X20	Overdose (involving trial treatment)
X32	Overdose (not involving trial treatment)
X15	Other endocrine
X10	Other biochemical abnormality
X11	Advanced HIV disease/general deterioration
X13	Multi organ failure
X28	Trauma, sprain, fracture
X29	Surgical operation
X25	Raised CK
X33	Raised triglycerides
X34	Raised cholesterol
X35	Lipodystrophy, unspecified
X39	Lipodystrophy, loss of fat
X40	Lipodystrophy, fat accumulation
X36	Clinical lactic acidosis
X37	Raised lactate with symptoms, not acidosis
X38	Raised lactate, no symptoms
X41	Gynaecomastia
X1	Other condition/event for coding
K8	Reduced libido
N8	Anxiety
N9	Depression
N48	Parasuicide (unsuccessful suicide attempt)
N60	alcohol abuse
N61	IV drug abuse
N10	Other psychiatric disturbance
N14	Other mood changes,dysphoria,aggression,mania
N17	Other psychiatric/psychological disease

6.12 AE_NADM – non-AIDS defining malignancies

Field name	Format	Description
PATIENT	Character or numeric	Cohort patient ID
EVENT_ID	Numeric	Unique numeric identifier for the event – used to link to table AE_NEW where necessary
CANTYP_T	Character	Type of cancer
CANLOC_T	Character	Primary location of cancer (if known)
CANLOC_Y	Numeric 1=Unknown	Primary location of cancer unknown
ICD10	Character	ICD-10 code for cancer disease
ICD9	Character	ICD-9 code for cancer disease
SPREAD_V	Numeric 1=Localized 2=Disseminated 9=Unknown	Stage (spread) at diagnosis
PATREP_Y	Numeric 1=Yes, full report 2=Summary of report 0=No 9=Unknown	Is the pathology report (or summary report) available?

PATREP_S	Character	Summary of pathology report
DIARAD_Y	Numeric 1=Yes 0=No	Diagnosis based on radiology
DIABIO_Y	Numeric 1=Yes 0=No	Diagnosis based on biochemistry
DIAVIS_Y	Numeric 1=Yes 0=No	Diagnosis based on visual inspection
DIAOTH_Y	Numeric 1=Yes 0=No	Diagnosis based on other
DIA_S	Character	Specify what the diagnosis is based on

7. Changes made to this document

Date	**Version**	**Sent to cohorts by..**	**Updates**

ANNEX: ENCEPP CHECKLIST FOR STUDY PROTOCOLS

Section 1: Research question	Yes	No	N/A	Page Number(s)
1.1 Does the formulation of the research question clearly explain:				
1.1.1 Why the study is conducted? (e.g. to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	☒	☐	☐	3
1.1.2 The objectives of the study?	☒	☐	☐	4
1.2 Does the formulation of the research question specify:				
1.2.1 The target population? (i.e. population or subgroup to whom the study results are intended to be generalized)	☒	☐	☐	5,9
1.2.2 Which formal hypothesis(-es) is (are) to be tested?	☐	☒	☐	
1.2.3 if applicable, that there is no a priori hypothesis?	☐	☒	☐	

Comments:

Section 2: Source and study populations	Yes	No	N/A	Page Number(s)
2.1 Is the source population described?	☒	☐	☐	5-6, 10-11
2.2 Is the planned study population defined in terms of:				
2.2.1 Study time period?	☒	☐	☐	5-6, 10-11
2.2.2 Age and sex?	☒	☐	☐	5
2.2.3 Country of origin?	☐	☒	☐	
2.2.4 Disease/indication?	☒	☐	☐	5
2.2.5 Co-morbidity?	☒	☐	☐	6-7
2.2.6 Seasonality?	☐	☐	☒	
2.3 Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	5-6

Comments:

Not all cohorts collect data on the patient's country of origin, although ethnicity data is collected (page 8).

Section 3: Study design	Yes	No	N/A	Page Number(s)
3.1 Does the protocol specify the primary and secondary (if applicable) endpoint(s) to be investigated?	☐	☒	☐	
3.2 Is the study design described? (e.g. cohort, case-control, randomized controlled trial, new or alternative design)	☒	☐	☐	4
3.3 Does the protocol describe the measure(s) of effect? (e.g. relative risk, odds ratio, deaths per 1000 person-years, absolute risk, excess risk, incidence rate ratio, hazard ratio, number needed to harm (NNH) per year)	☐	☒	☐	
3.4 Is sample size considered?	☐	☐	☒	
3.5 Is statistical power calculated?	☐	☐	☒	

Comments:

Section 4: Data sources	Yes	No	N/A	Page Number(s)
4.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				
4.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview, etc)	☒	☐	☐	4-7
4.1.2 Endpoints? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics, etc)	☒	☐	☐	4-7
4.1.3 Covariates?	☒	☐	☐	4-7
4.2 Does the protocol describe the information available from the data source(s) on:				
4.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☒	☐	☐	6-9
4.2.2 Endpoints? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	6-9
4.2.3 Covariates? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, life style, etc.)	☒	☐	☐	6-9
4.3 Is the coding system described for:				
4.3.1 Diseases? (e.g. International Classification of Diseases (ICD)-10)	☒	☐	☐	9, 24-25, 28-30
4.3.2 Endpoints? (e.g. Medical Dictionary for Regulatory Activities (MedDRA) for adverse events)	☒	☐	☐	34-40
4.3.3 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC)Classification System)	☒	☐	☐	26-27
4.4 Is the linkage method between data sources described? (e.g. based on a unique identifier or other)	☐	☐	☒	

Comments:

Section 5: Exposure definition and measurement	Yes	No	N/A	Page Number(s)
5.1 Does the protocol describe how exposure is defined and measured? (e.g. operational details for defining and categorising exposure)	☒	☐	☐	5, 9
5.2 Does the protocol discuss the validity of exposure measurement? (e.g. precision, accuracy, prospective ascertainment, exposure information recorded before the outcome occurred, use of validation sub-study)	☐	☐	☒	
5.3 Is exposure classified according to time windows? (e.g. current user, former user, non-use)	☒	☐	☐	5
5.4 Is exposure classified based on biological mechanism of action?	☐	☐	☒	
5.5 Does the protocol specify whether a dose-dependent or duration-dependent response is measured?	☒	☐	☐	9

Comments:

Section 6: Endpoint definition and measurement	Yes	No	N/A	Page Number(s)
6.1 Does the protocol describe how the endpoints are defined and measured?	☒	☐	☐	6-9
6.2 Does the protocol discuss the validity of endpoint measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, prospective or retrospective ascertainment, use of validation sub-study)	☐	☒	☐	

Comments:

Section 7: Biases and Effect modifiers	Yes	No	N/A	Page Number(s)
7.1 Does the protocol address:				
7.1.1 Selection biases?	☒	☐	☐	11
7.1.2 Information biases? (e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods)	☐	☐	☒	
7.2 Does the protocol address known confounders? (e.g. collection of data on known confounders, methods of controlling for known confounders)	☐	☒	☐	
7.3 Does the protocol address known effect modifiers? (e.g. collection of data on known effect modifiers, anticipated direction of effect)	☐	☒	☐	
7.4 Does the protocol address other limitations?	☒	☐	☐	11

Comments:

The pharmacovigilance study presents rates of events and while it collects data on known confounders/effect modifiers, the analyses does not include multivariate analyses and therefore does not address these issues.

Section 8: Analysis plan	Yes	No	N/A	Page Number(s)
8.1 Does the plan include measurement of absolute effects?	☐	☒	☐	
8.2 Is the choice of statistical techniques described?	☒	☐	☐	9
8.3 Are descriptive analyses included?	☒	☐	☐	9
8.4 Are stratified analyses included?	☐	☒	☐	9
8.5 Does the plan describe the methods for identifying:				
8.5.1 Confounders?	☐	☒	☐	
8.5.2 Effect modifiers?	☐	☒	☐	
8.6 Does the plan describe how the analysis will address:				
8.6.1 Confounding?	☐	☒	☐	
8.6.2 Effect modification?	☐	☒	☐	

Comments:

Section 9: Quality assurance, feasibility and reporting	Yes	No	N/A	Page Number(s)
9.1 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	8, 12
9.2 Are methods of quality assurance described?	☒	☐	☐	8
9.3 Does the protocol describe quality issues related to the data source(s)?	☒	☐	☐	8
9.4 Does the protocol discuss study feasibility? (e.g. sample size, anticipated exposure, duration of follow-up in a cohort study, patient recruitment)	☒	☐	☐	5-6
9.5 Does the protocol specify timelines for				
9.5.1 Start of data collection?	☐	☐	☒	
9.5.2 Any progress report?	☒	☐	☐	13
9.5.3 End of data collection?	☒	☐	☐	13
9.5.4 Reporting? (i.e. interim reports, final study report)	☒	☐	☐	13
9.6 Does the protocol include a section to document future amendments and deviations?	☒	☐	☐	41
9.7 Are communication methods to disseminate results described?	☒	☐	☐	12
9.8 Is there a system in place for independent review of study results?	☐	☐	☒	

Comments:

Section 10: Ethical issues	Yes	No	N/A	Page Number(s)
10.1 Have requirements of Ethics Committee/Institutional Review Board approval been described?	☒	☐	☐	11
10.2 Has any outcome of an ethical review procedure been addressed?	☐	☐	☒	
10.3 Have data protection requirements been described?	☒	☐	☐	7,11

Comments:

MARKETING AUTHORIZATION HOLDER(S)

Name of Marketing Authorization Holder:	Janssen-Cilag International, NV
Address:	Turnhoutseweg 30, 2340 Beerse, Belgium
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Qualified Person Pharmacovigilance:

Name:	Dr Logesvaran Yogendran, MB BS MSc MRCP FFPM
Signature:	Electronic signature appended at the end of the protocol
Date:	

RESPONSIBLE PARTIES

Principal Investigator:	Dr Ali Judd
Coordinating Investigators:	Dr Intira Jeannie Collins and Dr Carlo Giaquinto
Contact person for this protocol:	Dr Intira Jeannie Collins
E-mail address or telephone number of contact person:	Jeannie.collins@ucl.ac.uk

INVESTIGATOR AGREEMENT

I have read this protocol and agree that it contains all necessary details for carrying out this study. I will conduct the study as outlined herein and will complete the study within the time designated.

I will provide copies of the protocol and all pertinent information to all individuals responsible to me who assist in the conduct of this study. I will discuss this material with them to ensure that they are fully informed regarding the conduct of the study and the obligations of confidentiality.

Principal Investigator:

Name (typed or printed): Dr Ali Judd

Institution and Address: _____

_____

_____

_____

Telephone Number: _____

Signature: _____ Date: _____

(Day Month Year)

Sponsor's Responsible Medical Officer (Main Author):

Name (typed or printed): Magda Opsomer

Institution: Janssen Research & Development

Signature: Electronic signature appended at the end of the protocol Date: _____

(Day Month Year)

Note: If the address or telephone number of the investigator changes during the course of the study, written notification will be provided by the investigator to the sponsor; a protocol amendment will not be required.

LAST PAGE

SIGNATURES

Signed by	Date	Justification
Magda Opsomer	11Feb2016, 13:37:56 PM, UTC	Document Approval
Logesvaran Yogendran	16Feb2016, 22:36:33 PM, UTC	Document Approval