Case Report Form

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Definition

- CRF = Case Report Form

- Goal : to collect data that can be verified and used for analysis according to Good Clinical Practice (GCP)

Designing the CRF

- Should reflect the protocol
- Must be developed and tested in advance
- Must follow a logical order
- Must be easy to enter in a database
- Can be computerized (eCRF)
- Collect only needed variables depending of the objective of the study
  - Neither too few nor too much

Questions 1

- Should be easily understood
  - Clarity, simplicity, neutrality

- Closed-ended questions should be preferred
  - Offer an 'other category' and space to specify

Questions 2

- Unambiguous response
  - For a list of items
    - do not ask to mark all that apply
    - but rather ask for each question if it applies
  - For a Yes/No question
    - Offer a don't know and/or a NA (not applicable) option
  - For a relative question (change, improvement, deterioration)
    - Specify the reference period
      - Since last visit

Example

LOCATION	NORMAL		SPECIFY DIAGNOSIS
	YES	NO	
General Appearance	❑	❑	………………………………………………………………
Eyes	❑	❑	………………………………………………………………
Ears/ Nose/ Throat	❑	❑	………………………………………………………………
Cardiovascular System	❑	❑	………………………………………………………………
Respiratory System	❑	❑	………………………………………………………………
Gastrointestinal System	❑	❑	………………………………………………………………
Neurological System	❑	❑	………………………………………………………………
Musculoskeletal System	❑	❑	………………………………………………………………
Skin	❑	❑	………………………………………………………………
Other	❑	❑	………………………………………………………………

Physical Examination

Questions 3

- Collect raw data
  - Date of birth rather than age
  - Weight and height rather than BMI

- To collect Patient Related Outcomes
  - Such as Quality of Life, Fatigue, …
  - Use existing instruments that have been validated in your country

Form

- Use an easy to read font
- Precise the unit
  - biological variables, weight, height, …
- Leave enough space for the answer

  - Height (cm): |__|__|__|
  - Weight (kg): |__|__|__|,|__|

- Group the items by domain
- Align the answers
- Use a graph if needed to explain where the measures should be taken (anthropometric measurements, lesion of Kaposi sarcoma, …)

Example

Patient characteristics

Date of birth: |__|__|/|__|__|__|/|__|__|__|__| (dd/mmm/yyyy)

Gender: M   a   le ☐   Female ☐

Ethnicity:

Caucasian ☐   African ☐   Asian ☐   Other ☐ Precise: ………………………………

HIV transmission group:

Homo Bisexual ☐   Heterosexual ☐   IV Drug addiction ☐

Unknown ☐   Blood transfusion ☐   Mother to foetus ☐

Other ☐   Precise: ……………………………………………………………………..

Lifestyle

Tobacco:

Non smoker ☐

Former smoker ☐   *If former smoker*, Packets number/year * |__|__|__|

Smoking cessation date |__|__|/|__|__|__|/|__|__|__|__|

day   month   yea r

Actual smoker ☐   *If actual smoker*, Packets number/year * |__|__|__|

Packet number/year = (nb of smoked cigarettes/day x nb of smoking year)/20

Alcohol consumption:

Never ☐

Occasional ☐

Regular ☐   *If regular*, precise the number of glasses per day |__|__ |

Content 1

- On the front page provide
  - Title of the study
  - Registration number (Eudract, …)
  - Name or code of the centre
- On the second page provide a contact list
  - Sponsor, investigator, …

- Patient identifier
  - on each page

ORVACS 010   **SCREENING VISIT**   **W-4**

Patient ID code	|_|__|__|_|	|_|__|__|_|	|_ _|__|__|__|
	Site No	Patient No	Letter code

- Provide the study schedule
- Provide instructions for coding

Schedule of assessments

Procedures	Screening	Intensification Phase		Intensification Plus Immunomodulation Phase							Long Term Follow Up				
		D0	W4	W8	W12	W16	W20	W24	W28	W32	W36	W40	W48	W56	End of Study
Raltegravir dosing		X	X	X	X	X	X	X	X	X	X	X	X	X	D/C[1]
Maraviroc dosing		X	X	X	X	X	X	X	X	X	X	X	X	X	D/C[1]
r-hIL-7 (CYT107) injections cycles (arm B)*				X					X						
Informed Consent	X														
Review Inclusion / Exclusion Criteria	X	X													
Randomization				X[#]											
24-hours Hospitalization[5]				X[°]											
Demographic Information[2]	X														
Relevant Medical History	X														
Record Previous and Current cART	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Record Procedures, Concomitant Medications[3]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Events		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Treatment Compliance			X	X	X	X	X	X	X	X	X	X	X	X	X
Physical Examination[4] (Targeted)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Electrocardiogram[5]				X[6]					X[6]						
Spleen Echography[5]				X[+]					X[+]						
Vital Signs[7]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
HIV-associated Conditions	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Weight	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Proctologic Exam*		X												X	
Pregnancy Test[8] (if applicable)	X	X[9]	X[9]	X[9]	X[9]	X[9]	X[9]	X[9]	X[9]	X[9]	X[9]	X[9]	X[9]	X[9]	X[9]
Fasting Serum Chemistry	X		X	X	X	X		X		X		X	X	X	X
Haematology	X		X	X	X	X		X		X		X	X	X	X
Urine Analysis: – Urea – Creatinine Clearance – Phosphocalcic Balance	X			X						X				X	X
HBV and HCV Serology	X														
HCV-RNA Viral Load by Quantitative PCR	X														
Transaminases (ASAT, ALAT) and γ-GT	X			X[15]					X[15]	X				X	X
Lactic Dehydrogenase (LDH)	X			X					X	X				X	X
Alkaline Phosphatase (ALP)	X			X[15]					X[15]	X				X	X

Content 2

- Inform Consent

- Inclusion / non inclusion criteria
  - As a check list
    - If "NO" is checked for any of the inclusion criteria, patient is not eligible for the study
    - If "YES" is checked for any of the non inclusion criteria below, patient is not eligible for the study

Example

CHECK-LIST OF INCLUSION / NON INCLUSION CRITERIA

FAX to Keyrus Biopharma, +33 1 41 34 28 29

If "NO" is checked for any of the inclusion criteria below, patient is not eligible for the study

INCLUSION CRITERIA (1/2)	YES	NO
1. HIV-1 infection documented by any licensed ELISA test kit and confirmed by Western Blot at any time prior to study entry. HIV-1 culture, HIV-1 antigen, plasma HIV-1 RNA, or a second antibody test by a method other than ELISA is acceptable as an alternative confirmatory test	❑	❑
2. $18 \leq$ Age ≤ 60 years.	❑	❑
3. A t least 3 years of ART (defined as at least 3 ART medications) without any interruption for more than one month (cumulative)	❑	❑
4. A RT treatment unchanged in the 3 months prior to screening	❑	❑
PLEASE SEND AN ANONYMIZED COPY OF THE HIV PLASMA VIRAL LOAD (RNA) RESULTS DOCUMENTED WITHIN <u>3 YEARS</u> PRIOR TO ENTRY, WITH THE TRIAL NAME AND PATIENT'S STUDY SUBJECT IDENTIFIER		
5. O ne HIV plasma viral load (RNA) documented at least 3 years prior to entry, and at least 2 HIV plasma viral loads (RNA) documented per year thereafter	❑	❑
6. HIV plasma viral load (RNA) ≤ 500 copies/ml at least 3 years prior to entry and HIV plasma viral load ≤ 500 copies/ml for 90 % of the measures thereafte r	❑	❑

Content 3

- Depend of the study protocol
- Follow the study schedule
  - Socio-demographic characteristics
  - Clinical and biological data
    - Use anonymized copy of the biological results
  - Treatment
  - Adverse event, safety data
    - Severe adverse event
- Self explanatory

- Appendix
  - Classification used, such as CDC classification system for HIV infection, classification of adverse event severity
  - SOP for inclusion, randomisation, biological sampling,
  - List of Prohibited Concomitant Medications
  - …

Example

Laboratory Test Checklist

Date Specimen(s) Obtained: |__|__|/|__|__|__|/|__|__|__|__| (dd/mmm/yyyy)

ALL EXAMS TO BE PERFORMED AT DAY 0 BEFORE INVESTIGATIONAL DRUG INTAKE AT DAY 3

Please send a anonymized copy of the results with trial name and patient's study subject identifier to Keyrus Biopharma

Virology			
HIV-RNA plasma viral load	Done ☐	Not done ☐	
Immunology			
CD4/CD8 count	Done ☐	Not done ☐	
Pregnancy test: [blood (for France) or urine test if suspected pregnancy]			
(βHCG)	Done ☐	Not done ☐	N.A. ☐

Example

Screening procedures

1. Check that inclusion and exclusion criteria has been respected

2. Explain the protocol, comment the information form and answer to the patient's questions

3. All pages of patient's information sheet must be initialed by the patient and investigator

4. The physician and the patient who accepts to participate should date and sign the informed consent. (A reflection time, compatible with the study is necessary for the patient). Give a copy of the informed consent to the patient.

When the patient has signed the informed consent:

5. Each individual participating to this trial should be allocated an anonymous identification code (ID code). It will be written in all the documents sent to Keyrus Biopharma (CRF, copies of biological results rendered anonymous). The ID code is composed of :

   S   ite number which will include the patient (3 numbers)

   E   ntry order number of patient in the site (3 numbers), it correspond to the inclusion chronological order number

   A   4 letters code generated by an automatic procedure transmitted by Keyrus Biopharma during the initiation visit of the site

   rite the correspondence between patient's name and his study ID code in the patient's confidential list of the study (provided in the administrative file during initiation visit). This list must be kept in the investigator file.

   P e r form the clinical, physical and biological exams planned for the screening visit

   • P lan and fix an appointment for the day 0 visit.

To complete the form

- Use a blue or black ballpoint pen
- In case of error
  - Cross out the wrong text
  - Write the correct answer besides
  - Sign

Conclusion

- A good CRF
  - get the right and correct data
  - Neither too few nor too much
  - Simple and easy to read
    - to avoid mistake
  - Collect data directly as much as possible
    - such as laboratory data, …

Database

Definitions 1

- A database consists in one or more tables
  - Row = records (participants)
  - Column = fields (measurements)
- Data dictionary
  - Name, data type, description, range of allowed values for each table
- Data entry system
  - Means by which the data tables are populated
  - Transcription of paper forms
    - Double data entry

Definitions 2

- Electronic data capture
  - On-screen forms of web page
  - Eliminate paper forms
  - A source document can be printed after direct data entry

Spreadsheet and database

- Don't use excel spreadsheet
  - Data can be changed by error
  - Date can have different formats in the same column or be defined differently on two computers
  - No easy check of the possible values at data entry
  - Data for the same participant may be entered several times
  - Repeated measurement are not easily handled

Use a database management software

- Definition of data dictionary and relationships between the different data tables
- Centralized data
- Queries
- Will ensure data integrity
- Will allow secure access to data
- Will allow multiple access to data

Which tool ?

- EpiData
  - Free tool from the CDC
  - For small single centre study

- Access (Open office base)
  - More complex study
  - Multiple access to the database

- Easy PHP / Voozanoo
  - Electronic data capture in multicentre studies

Development 1

- A team work (data manager with investigator, research assistant, statistician, …

- Define the needs

- Analyse the problem

- Conceive the database

- Implement it

Development 2

- Start from the CRF
- Define the data dictionary
- Define the tables and the relationship between the tables
- Define the data check
- Define the data entry screens
- Define the automatic reports
- Test the tool
- Write the documentation

Tracking / Audit trail

- Being able to document data changes
  - Who
  - When
  - What
  - Why
  - Old value
  - New value

Queries

- Sort and filter the data
- Calculate values based on the raw data fields
- Queries are used to
  - Monitor data entry
  - Report on study progress
  - Format the results for analysis

Confidentiality/ security

- To protect confidentiality, databases
  - must be stored on secure servers
    - firewall
  - With access restricted and traced
    - Login, passwords
    - Different rights
      - Read
      - Add
      - Change
      - Suppression
      - Change of the structure

  - And audited

Back-up and storage

- Loss of the database must be prevented
  - Regular back-ups
  - Off-site storage
  - Archiving copies for future use

Freezing the database

- To avoid any further change in the data
- When data have been corrected and validated
- In order to perform intermediate or final analysis

Conclusion

- Data management is a critical step for a good quality study