INA RESPOND

INDONESIA RESEARCH PARTNERSHIP ON INFECTIOUS DISEASE

Clinical trial databases are a crucial investment in clinical research

Part 2 - Design and Development of Case Report Forms (CRFs)

PIT PETRI 2018

B-IDeaS

1st Annual Scientific Meeting of the
Indonesian Society of Tropical and Infectious Disease
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The 7th Annual Bandung Infectious Disease Symposium
Harnessing innovative strategies tocontrol and manage infectious diseases
October 12th-14th 2018 | El Royale Hotel, Bandung

Speakers: M.Duvenhage
K. Laras
S. Erari
12 Oct 2018

Case Report Forms (CRFs)

- Study protocol is arguably the most important document used during a clinical study, CRFs are of vital importance
- CRFs are the most frequently used tools for data collection
- A well-structured CRF simplifies database design
- Study data quality relies on the quality of the tools (CRFs) used to collect the data

Poorly managed CRF development

Common risk and consequences
Increase the time of CRF creation
Delayed on clinical database creation and go-live
Collection of redundant data
Miss collection of relevant data (i.e. question on CRF not precise enough, may lead into wrong direction)
Increase number of queries (increase data cleaning timelines)
Create strain on internal resources due to iterative review circles
Increase of the likelihood of database changes and unlock
Increase downstream impact on programming such as remapping of variables

Minimum Standards

- Design CRFs to collect the data specified by the protocol
- Document the process for CRF design, development, approval, and version control
- Document training of team on the protocol, CRF completion instructions and data submittal process
- CRFs based on rating instruments must be properly licensed
- Ensure CRFs are available at the clinical site prior to enrollment of subjects

Best Practices

- Establish and maintain a library of standard forms to include:
  - CRFs
  - CRF completion instructions
  - Subject diary cards
- Multidisciplinary team to provide input into the CRF design & review (data management, biostatisticians, and clinical operations)
- Design CRFs with study safety and efficacy endpoints in mind
- Keep the CRF's questions, prompts, and instructions clear, concise
- Comply with CDISC CDASH standards
- Design the CRF to follow the data flow of person completing the CRF
- Avoid referential and redundant data points
- Use carbonless copy paper (NCR) paper to ensure exact replicas of CRFs

Design and Development Process (continue)

- First step into translating the protocol into data
- Multidisciplinary approach to designing and developing CRFs
- Input from entire study team
- Design CRFs to collect the data specified by the protocol
    - If you collect it, you need to enter it, clean it, analyze and report it
- CRF design should be taken into consideration before the protocol is finalized
- If Protocol and CRFs are designed concurrently, the quality of both the protocol and the CRFs can be improved through continuous collaboration between these teams

Design and Development Process (continue)

- CRFs should not collect data that ultimately will not be used for analysis
- Extraneous data can adversely affect overall data quality by drawing the attention of site personnel away from key variables
- All data must be attributable to a subject
- All CRFs should also contain a provision for investigator signature

Design and Development Process (continue)

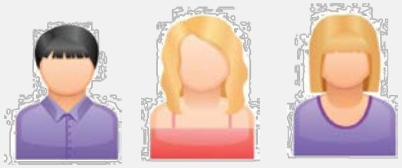
- Data collected on CRFs will be consolidated for statistical analysis, therefore use standard data structures
- Ensure biostatistician review of CRF's primary and secondary endpoints
- Consider developing standardized protocol templates, CRFs, database structures, validation procedures, and reporting tables.
- Consider CRF approval, CRF change management and version control
- Training on CRF completion and CRF submission to data coordination center
- Distribution of CRFs to sites – prior to first subject enrolled

CRF Development Process

Draft CRF from Protocol

CRF Designer

Diverse review team
CRF Review meeting
Provide comments to CRF designer

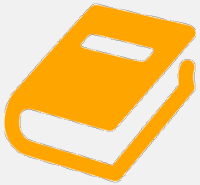


CRF Review Team

Implement all comments
Apply version control even on draft version
Might require additional review cycles

CRF Designer

Provide sufficient printing specifications to CRF print vendor



CRF Book

Ensure CRF is approved and version control is applied.
Distribute to sites

Site(s)

CRF development – Clarity and ease of use

A number of factors contribute to ensuring a CRF is easily understood and used:

- CRF layout,
- Section and concise question wording,
- Coding,
- Use of minimal text field responses,
- Avoid redundant data collection

CRF should be designed with the entire study team in mind; All CRF data should be attributable to a subject

CRF development – General considerations

Consistency of CRF

- Formats, text font, size, question alignment, docum
  neatness

CRF whitespace

- Is there enough OR too much?

Page layout

- Portrait or Landscape

Page number

- Use consistently. Either use or don't use at all.
- CRF book – ensure that numbers make sense when repeating pages into different visits

CRF development – General considerations

Section headers

- Differentiate data modules on CRF
- Separate data into groups that are logically related e.g. Demographics, Vital Signs, Medical History, Physical Examination, Adverse Events, etc.

Log forms (e.g. Adverse Events, Medical History, Concomitant medication)

- Add page numbers positions – important to identify missing pages
- Consider how to identify the last page

CRF development – General considerations

Avoid splitting data modules across pages

- Exceptions may include questionnaires that are too long to fit on the same page.

Questions should be clear / specific

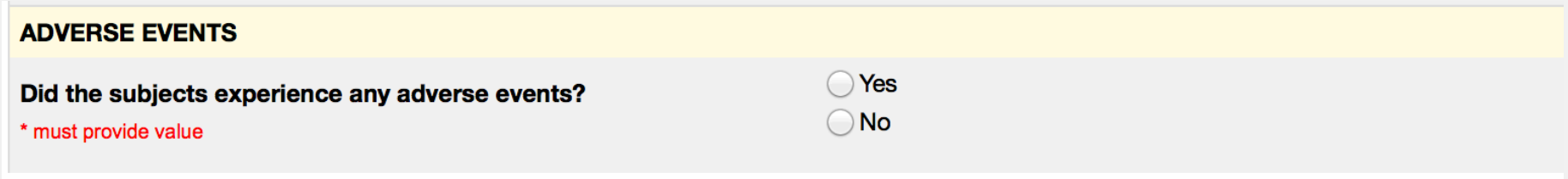
- There should be no doubt what is expected
- Avoid “negative” phrased questions.
- Indicate if one response is expected vs. multiple responses
- If questions are to be skipped due to a specific answer, indicate the skipping pattern clearly on CRF

CRF development – General considerations

Avoid graphics on CRF

- How will this data be captured / analyzed

Use of indicator questions – Yes/No



Repeat CRF modules consistently across different visits

- Vital Signs, Physical examination
- Ensures sections are the same to avoid confusion (e.g. item order)

CRF development – General considerations

Don’t collect fields that can be derived

- Age, BMI, Adverse event durations
- Rather collect date of birth, height & weight, Adverse event start and stop date that is used to calculate the derived values.

Avoid collecting redundant data

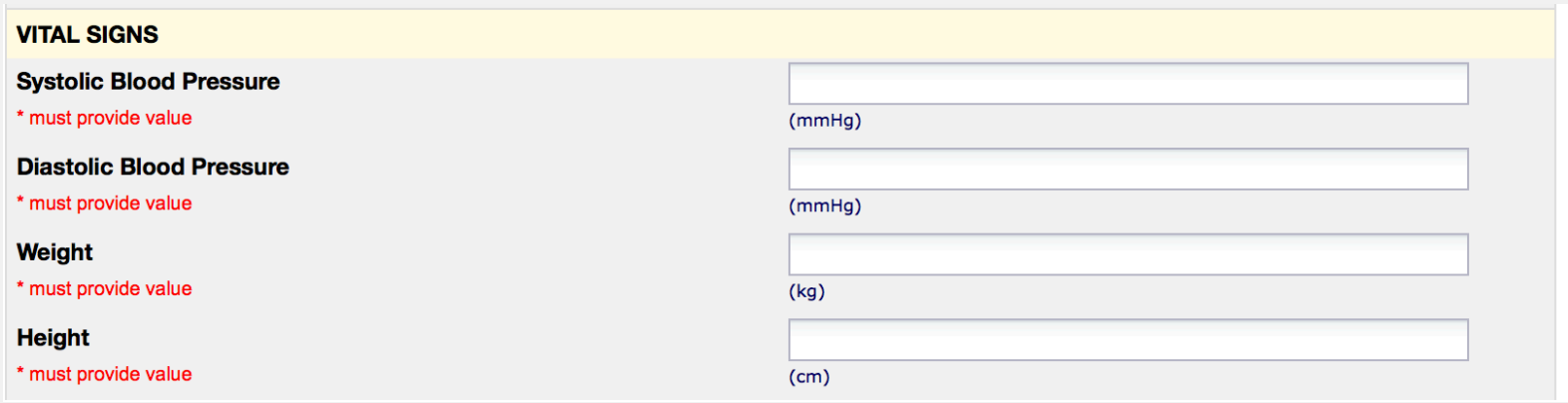
- Increase data entry, validation effort
- Inconsistency between data items – result in queries

Consistent date fields across entire CRF

- dd/MMM/yyyy vs. mm/dd/yyyy vs. dd/mm/yyyy
- Human readable – dd/MMM/yyyy (e.g. 08/NOV/2017) – CDASH format

CRF development – General considerations

Appropriate use of units on CRF



VITAL SIGNS	
Systolic Blood Pressure * must provide value	(mmHg)
Diastolic Blood Pressure * must provide value	(mmHg)
Weight * must provide value	(kg)
Height * must provide value	(cm)

Standard CRF header

- Include protocol title, subject number, standard visit number / names, visit date, repeating log page numbers
- Subject initials – does this add value

Paper CRF

- CRF is poorly designed, organized, or printed, there is a greater potential for missing, or incorrect data
- CRF pages should be printed single sided
- Appropriate font and size
- Each CRF page should be clearly linked to the correct site, subject, visit and follow-up interval
- Correct usage of CRF page numbers
- Use proper date format (e.g., mm/dd/yyyy, dd/MMM/yy) should be clearly stated. Preferance for CDASH DISC format ddMMMyyyy
- Time should be collected using 24hour clock (HH:MM)

eCRF

- Provide functionality that helps to avoid potential problems that can occur with paper CRFs (e.g. dates use a pop-up calendar)
- Grouping of sites/subjects together thus avoid assigning incorrect site/subject numbers.
- Edit checks programmed within the eCRF application validate the data at the point of entry
- Capability to tab through fields in a prescribed sequence, avoiding the potential for missed data

Patient Reported Outcomes (PRO)

- Data directly reported by subjects is known as patient reported outcomes (PRO).
- Used to quantify subjects' subjective experiences (e.g. pain intensity, quality of life)
- Completed by subjects themselves (instead of trained study personnel)
- Wording of questions and instructions on a CRF collecting PRO data should be clear and understandable
- Translate into local language
- PRO data can also be collected with a variety of electronic tools commonly referred to as ePRO

Paper Diary Cards (PRO) Challenges

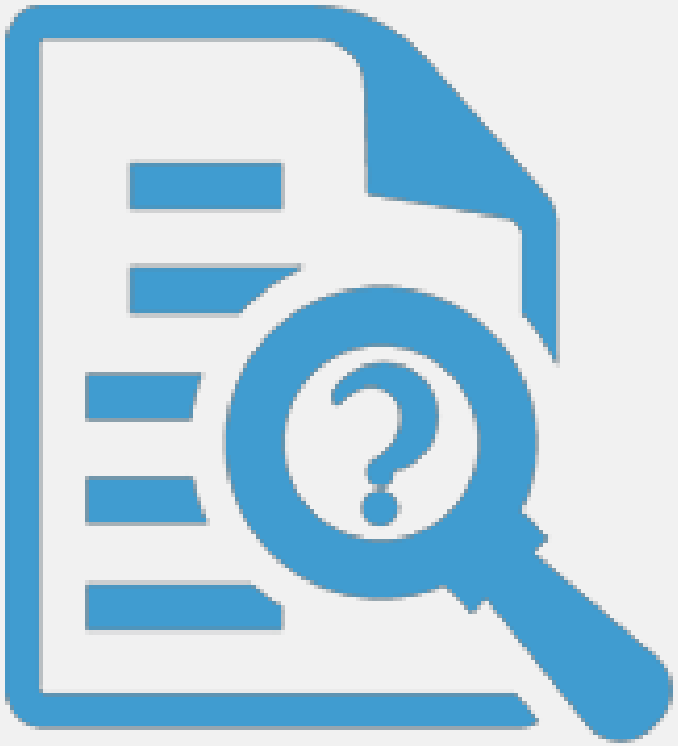
- Have high error rate (up to 80%)
  - Illegible diary cards > Data entry errors
- Participants back-fill diary cards (recollection bias)
- Inability to query data
- Data not instantaneous / Not directly link medication event
- Dataflow not automated
- Inability to effectively (timely) intervene in poor adherence

Up to 80% of paper diary cards contain significant errors (Quinn et al., 2000)

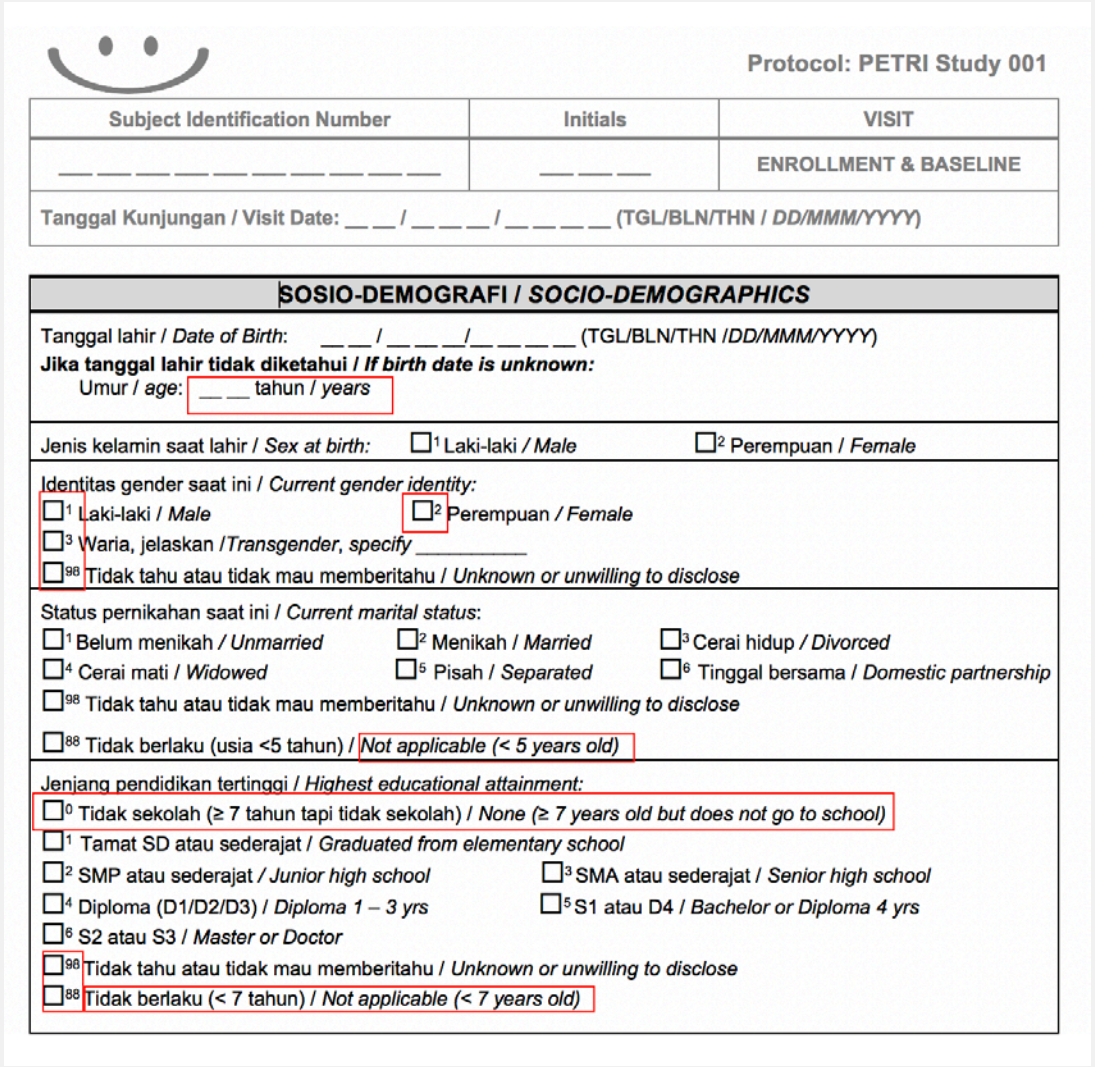
CRF Review and Quality Process

- Review against the protocol to ensure all protocol-specified data are captured
- Various team members may be involved in CRF design (statistical, clinical, safety monitoring, regulatory)
- Certain types of CRFs (e.g., translations) may require specialized input
- CRFs translated into multiple languages should be carefully reviewed (e.g. back-translations)
- Reviewed prior to printing by preparing a prototype using the same paper size
- eCRF should undergo User Acceptance Testing (UAT) by team members / sites responsible for data entry.

CRF Review Group Exercise



CRF Review Group Exercise (Answers)



Protocol: PETRI Study 001

Subject Identification Number	Initials	VISIT
__ __ __ __ __ __ __ __ __ __	__ __ __	ENROLLMENT & BASELINE

Tanggal Kunjungan / Visit Date: __ __ / __ __ __ / __ __ __ __ (TGL/BLN/THN / *DD/MMM/YYYY*)

SOSIO-DEMOGRAFI / *SOCIO-DEMOGRAPHICS*

Tanggal lahir / *Date of Birth*: __ __ / __ __ __/__ __ __ __ (TGL/BLN/THN /*DD/MMM/YYYY*)

Jika tanggal lahir tidak diketahui / *If birth date is unknown:*

Umur / *age*: __ __ tahun / *years*

Jenis kelamin saat lahir / *Sex at birth:* ☐1 Laki-laki / *Male* ☐2 Perempuan / *Female*

Identitas gender saat ini / *Current gender identity:*

☐1 Laki-laki / *Male* ☐2 Perempuan / *Female*

☐3 Waria, jelaskan /*Transgender, specify* _____

☐98 Tidak tahu atau tidak mau memberitahu / *Unknown or unwilling to disclose*

Status pernikahan saat ini / *Current marital status*:

☐1 Belum menikah / *Unmarried* ☐2 Menikah / *Married* ☐3 Cerai hidup / *Divorced*

☐4 Cerai mati / *Widowed* ☐5 Pisah / *Separated* ☐6 Tinggal bersama / *Domestic partnership*

☐98 Tidak tahu atau tidak mau memberitahu / *Unknown or unwilling to disclose*

☐88 Tidak berlaku (usia <5 tahun) / *Not applicable (< 5 years old)*

Jenjang pendidikan tertinggi / *Highest educational attainment:*

☐0 Tidak sekolah (≥ 7 tahun tapi tidak sekolah) / *None (≥ 7 years old but does not go to school)*

☐1 Tamat SD atau sederajat / *Graduated from elementary school*

☐2 SMP atau sederajat / *Junior high school* ☐3 SMA atau sederajat / *Senior high school*

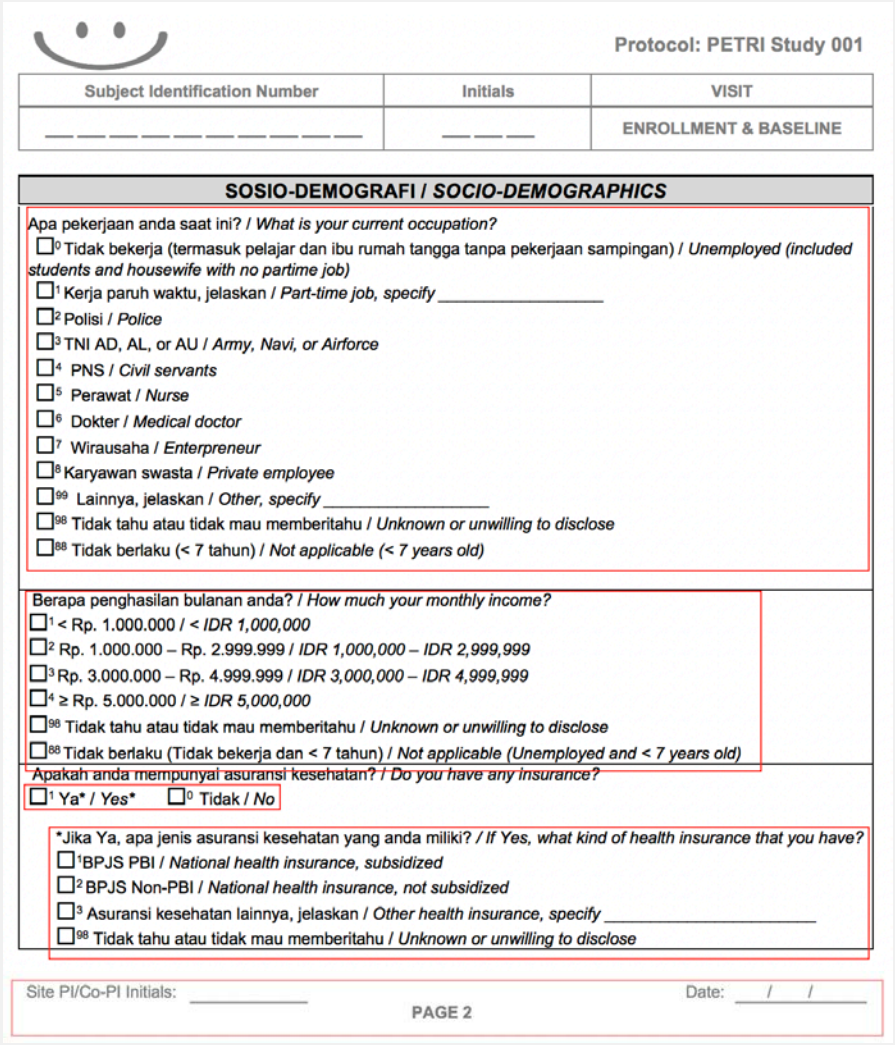
☐4 Diploma (D1/D2/D3) / *Diploma 1 – 3 yrs* ☐5 S1 atau D4 / *Bachelor or Diploma 4 yrs*

☐6 S2 atau S3 / *Master or Doctor*

☐98 Tidak tahu atau tidak mau memberitahu / *Unknown or unwilling to disclose*

☐88 Tidak berlaku (< 7 tahun) / *Not applicable (< 7 years old)*

CRF Review Group Exercise (Answers)



Protocol: PETRI Study 001

Subject Identification Number	Initials	VISIT
_ _ _ _ _ _ _ _ _ _	_ _ _	ENROLLMENT & BASELINE

SOSIO-DEMOGRAFI / *SOCIO-DEMOGRAPHICS*

Apa pekerjaan anda saat ini? / *What is your current occupation?*

- ☐ 0 Tidak bekerja (termasuk pelajar dan ibu rumah tangga tanpa pekerjaan sampingan) / *Unemployed (included students and housewife with no partime job)*
- ☐ 1 Kerja paruh waktu, jelaskan / *Part-time job, specify* _____
- ☐ 2 Polisi / *Police*
- ☐ 3 TNI AD, AL, or AU / *Army, Navi, or Airforce*
- ☐ 4 PNS / *Civil servants*
- ☐ 5 Perawat / *Nurse*
- ☐ 6 Dokter / *Medical doctor*
- ☐ 7 Wirausaha / *Enterpreneur*
- ☐ 8 Karyawan swasta / *Private employee*
- ☐ 99 Lainnya, jelaskan / *Other, specify* _____
- ☐ 98 Tidak tahu atau tidak mau memberitahu / *Unknown or unwilling to disclose*
- ☐ 88 Tidak berlaku (< 7 tahun) / *Not applicable (< 7 years old)*

Berapa penghasilan bulanan anda? / *How much your monthly income?*

- ☐ 1 < Rp. 1.000.000 / *< IDR 1,000,000*
- ☐ 2 Rp. 1.000.000 – Rp. 2.999.999 / *IDR 1,000,000 – IDR 2,999,999*
- ☐ 3 Rp. 3.000.000 – Rp. 4.999.999 / *IDR 3,000,000 – IDR 4,999,999*
- ☐ 4 ≥ Rp. 5.000.000 / *≥ IDR 5,000,000*
- ☐ 98 Tidak tahu atau tidak mau memberitahu / *Unknown or unwilling to disclose*
- ☐ 88 Tidak berlaku (Tidak bekerja dan < 7 tahun) / *Not applicable (Unemployed and < 7 years old)*

Apakah anda mempunyai asuransi kesehatan? / *Do you have any insurance?*

☐ 1 Ya* / *Yes** ☐ 0 Tidak / *No*

*Jika Ya, apa jenis asuransi kesehatan yang anda miliki? / *If Yes, what kind of health insurance that you have?*

- ☐ 1 BPJS PBI / *National health insurance, subsidized*
- ☐ 2 BPJS Non-PBI / *National health insurance, not subsidized*
- ☐ 3 Asuransi kesehatan lainnya, jelaskan / *Other health insurance, specify* _____
- ☐ 98 Tidak tahu atau tidak mau memberitahu / *Unknown or unwilling to disclose*

Site PI/Co-PI Initials: _____ Date: _ _ / _ _ / _ _ _ _

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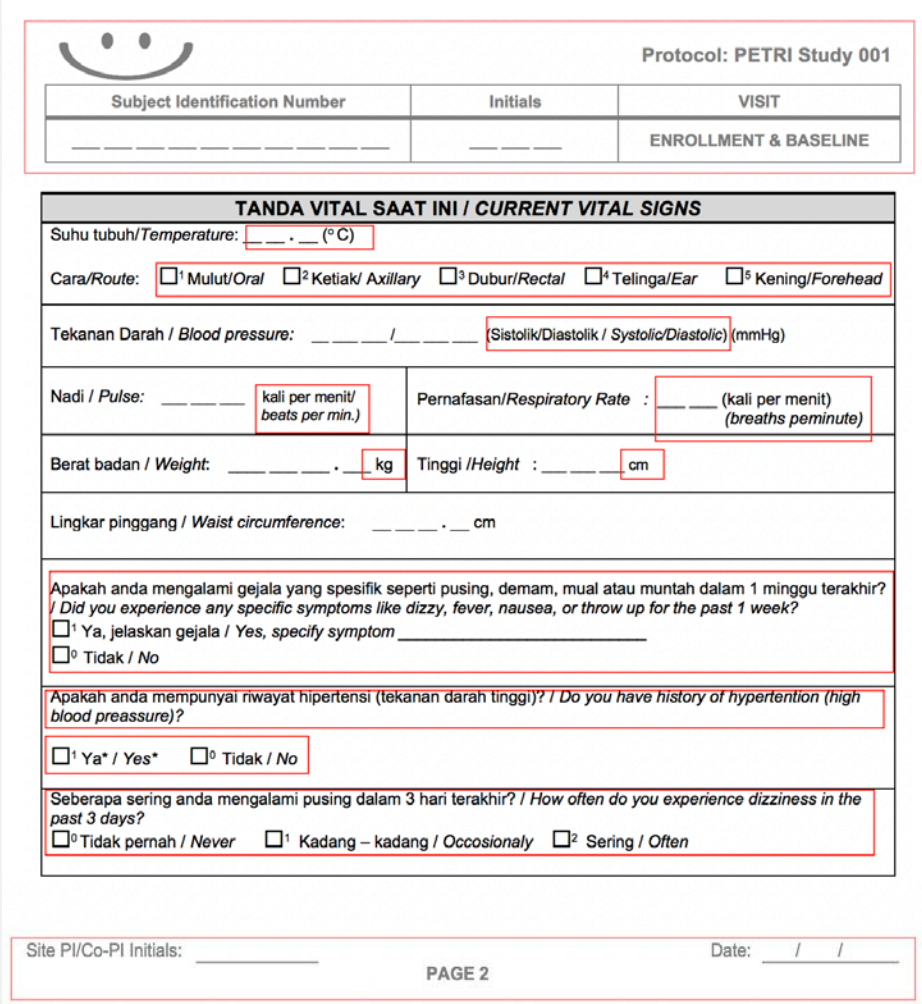
CRF Review Group Exercise (Answers)



Protocol: PETRI Study 001

Subject Identification Number	Initials	VISIT
__ __ __ __ __ __ __ __ __ __	__ __ __	ENROLLMENT & BASELINE

TANDA VITAL SAAT INI / *CURRENT VITAL SIGNS*

Suhu tubuh/*Temperature*: __ __ . __ (° C)

Cara/*Route*: ☐1 Mulut/*Oral* ☐2 Ketiak/ *Axillary* ☐3 Dubur/*Rectal* ☐4 Telinga/*Ear* ☐5 Kening/*Forehead*

Tekanan Darah / *Blood pressure:* __ __ __ /__ __ __ (Sistolik/Diastolik / *Systolic/Diastolic*) (mmHg)

Nadi / *Pulse:* __ __ __ kali per menit/ *beats per min.*)

Pernafasan/*Respiratory Rate* : __ __ (kali per menit) *(breaths peminute)*

Berat badan / *Weight*: __ __ __ . __ kg

Tinggi /*Height* : __ __ __ cm

Lingkar pinggang / *Waist circumference*: __ __ __ . __ cm

Apakah anda mengalami gejala yang spesifik seperti pusing, demam, mual atau muntah dalam 1 minggu terakhir? / *Did you experience any specific symptoms like dizzy, fever, nausea, or throw up for the past 1 week?*

☐1 Ya, jelaskan gejala / *Yes, specify symptom* _____

☐0 Tidak / *No*

Apakah anda mempunyai riwayat hipertensi (tekanan darah tinggi)? / *Do you have history of hypertention (high blood preassure)?*

☐1 Ya* / *Yes** ☐0 Tidak / *No*

Seberapa sering anda mengalami pusing dalam 3 hari terakhir? / *How often do you experience dizziness in the past 3 days?*

☐0 Tidak pernah / *Never* ☐1 Kadang – kadang / *Occosionaly* ☐2 Sering / *Often*

Site PI/Co-PI Initials: _____ Date: __/__/__

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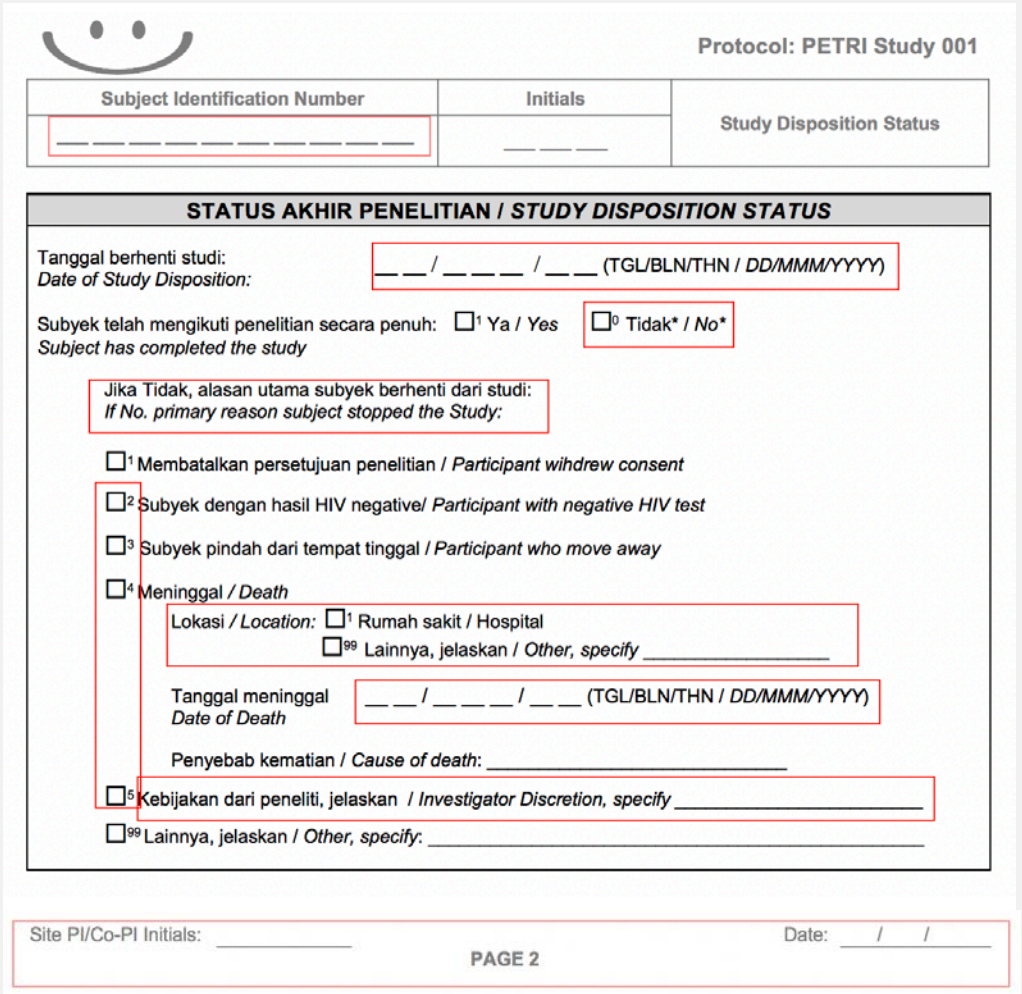
CRF Review Group Exercise (Answers)



Protocol: PETRI Study 001

Subject Identification Number	Initials	Study Disposition Status
__ __ __ __ __ __ __ __ __ __	__ __ __	

STATUS AKHIR PENELITIAN / *STUDY DISPOSITION STATUS*

Tanggal berhenti studi:
Date of Study Disposition: __ __ / __ __ __ / __ __ (TGL/BLN/THN / *DD/MMM/YYYY*)

Subyek telah mengikuti penelitian secara penuh: ☐1 Ya / *Yes* ☐0 Tidak* / *No**
Subject has completed the study

Jika Tidak, alasan utama subyek berhenti dari studi:
If No. primary reason subject stopped the Study:

☐1 Membatalkan persetujuan penelitian / *Participant wihdrew consent*

☐2 Subyek dengan hasil HIV negative/ *Participant with negative HIV test*

☐3 Subyek pindah dari tempat tinggal / *Participant who move away*

☐4 Meninggal / *Death*

Lokasi / *Location:* ☐1 Rumah sakit / Hospital
☐99 Lainnya, jelaskan / *Other, specify* _____

Tanggal meninggal
Date of Death __ __ / __ __ __ / __ __ (TGL/BLN/THN / *DD/MMM/YYYY*)

Penyebab kematian / *Cause of death*: _____

☐5 Kebijakan dari peneliti, jelaskan / *Investigator Discretion, specify* _____

☐99 Lainnya, jelaskan / *Other, specify*: _____

Site PI/Co-PI Initials: _____ Date: __ / __ / __

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CRF Development Standards

- Clinical Data Interchange Standards Consortium (CDISC)
  - Suite of standards supports medical research of any type from protocol through analysis and reporting of results
  - Dec 2014: FDA published binding guidance regarding the submission of study data in standardized formats, which are available on the FDA Study Data Standards Resources page
  - Requires submissions to be submitted in an electronic format specified by the FDA beginning 24 months (i.e. Dec 2016) from the issuance of guidance (studies with a start date 24 months after the publication)

- Clinical Data Acquisition Standards Harmonization (CDASH)
  - Basic standards for the collection of data in a clinical trial (Case Report Form)
  - CDASH 2.0 released on 25 Sep 2017
  - CDASH User guide contains library of CRF Examples
  - https://www.cdisc.org/standards/foundational/cdash

CDASH Example

VS Domain

Oral temperature *(xx.x)*	Fixed Unit: °C
TEMP_VSORRES	
Temperature unit	TEMP_VSORRESU
Pulse	Fixed Unit: beats/min
PULSE_VSORRES	
Pulse Unit	PULSE_VSORRESU
Location	Left arm ●
VSLOC	Right arm ○
Systolic Blood Pressure	Fixed Unit: mmHg
BP_SYSBP_VSORRES	
Blood Pressure Unit	BP_SYSBP_VSORRESU mmHg
Diastolic Blood Pressure	Fixed Unit: mmHg
BP_DIABP_VSORRES	
Blood Pressure Unit	BP_DIABP_VSORRESU mmHg

Row	SUBJID	RecordPo	TEMP_VSORRES	TEMP_VSORRESU	PULSE_VSORRES	PULSE_VSORRESU	VSLOC	BP_SYSBP_VSORRES	BP_SYSBP_VSORRESU	BP_DIABP_VSORRES	BP_DIABP_VSORRESU
1	100001	1	36.8	C	60	BEATS/MIN	LEFT ARM	138	mmHg	88	mmHg
2	100001	2	36.8	C	60	BEATS/MIN	RIGHT ARM	136	mmHg	84	mmHg
3	100002	1	36.2	C	64	BEATS/MIN	LEFT ARM	120	mmHg	80	mmHg
4	100002	2	36.2	C	64	BEATS/MIN	RIGHT ARM	120	mmHg	80	mmHg

CRF Completion Guidelines

- CRFs should include clearly stated instructions
- May have associated CRF completion guidelines
- Instructions regarding completion and acceptable methods of correcting or changing the CRF
- Paper-based CRFs typically use printed CRF completion guidelines
- EDC systems may use on-line help screens

CRF Change Control and Versioning

- Appropriate authorization should be obtained for CRF changes
- Relevant personnel should be consulted
- CRF changes should be clearly documented
- CRF should contain a clearly identified version number
- Document the reasons for CRF changes
- If updated during an ongoing study, ensure all sites use the latest CRF version

Data Privacy

- CRFs must also avoid collecting data that could lead to direct or indirect identification of the subject
- Subject should be assigned a unique code to be used for identification of that subject within the study
- For example - do not collect: subject names, home or work addresses, telephone number.

CRF Printing – Best Practices

- Select and qualify your CRF printing vendor
- Distribute all study materials such as CRFs, pocket cards, study schedule posters, pre-printed return envelopes, and study contact information simultaneously
- Obtain a prototype of the CRF book from the CRF printing vendor
- Setup a vendor evaluation program throughout the vendor relationship

CRF Printing - Specifications

- Final print-ready electronic CRF files
- Type of binder, binder color, width, number of inside pockets, cover text or art, and spine label.
- Specify the packaging instructions and include a packing list
- List of tabs (different visits)
- Company logo and text for the spine label
- If the printer is shipping to the sites, a list of sites and their mailing addresses
- Specifications for printing the barcode (if applicable)
- Tentative timetable for sending the final-master copy to the printer, final printing run, and deadline for releasing CRFs to sites.
- Vendor should provide a complete prototype of the CRF book for review and approval

Questions