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Review of Bioequivalence Studies submitted to the Health Research Ethics Committee (HREC) in Indonesia.

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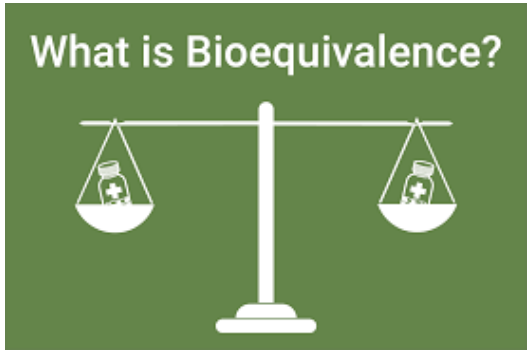
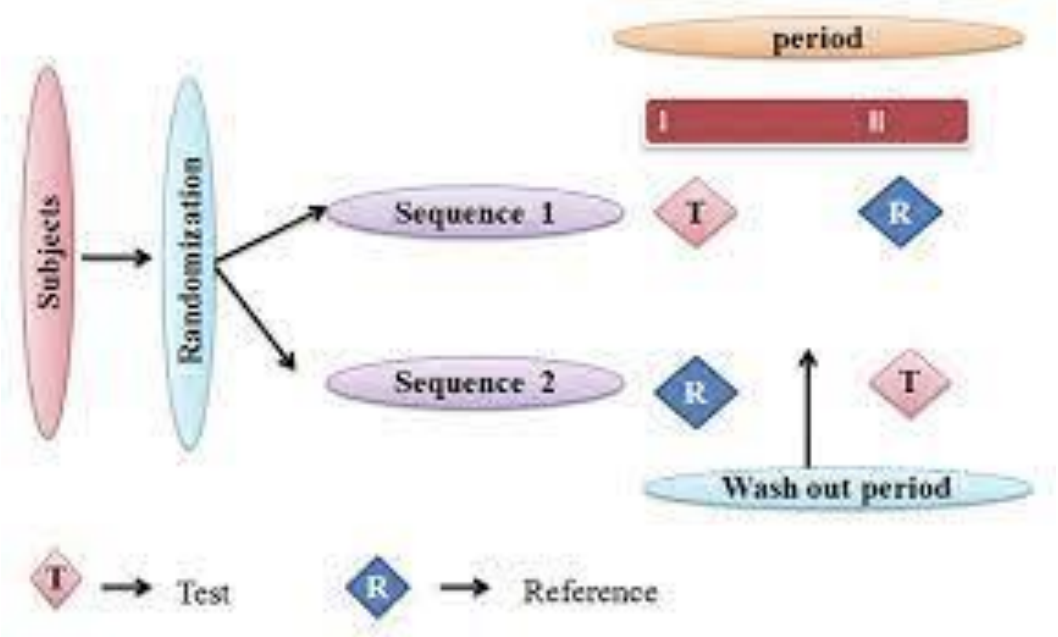
Background

Bioequivalence (BE) Study

- Finding **generic** equivalents of **brand name** drugs has always been the strategy for reducing the cost of medicines.
- BA/BE study aimed to obtain approval of generic equivalents of the branded name drugs is recommended
- Increasing number of BA/BE studies
- Human subjects for BA/BE studies recruited by the clinical research organizations (CROs) and might be potentially vulnerable.
- Several ethical concerns need to be considered.

Bioequivalence (BE) Study





- Two medicinal products containing the same active substance are considered bioequivalent if they are pharmaceutically equivalent) or pharmaceutical alternatives and their bioavailabilities (rate and extent) after administration in the same molar dose lie within acceptable predefined limits.
- Two formulations are compared in randomized, two-period, **two-sequence single dose crossover design**
- Sufficient wash out period between the two-sequences

Selection of human subjects in BE Study

- **Healthy volunteers subjects required**– to reduce variability not related to formulation differences between products
- Inclusion/exclusion criteria:
  - 18-55 years of age, preferably BMI 18 and 30 kg/m^2 .
  - Screened by clinical laboratory tests, medical history, physical examination.
  - No gender distinction; risk to women of childbearing potential should be considered.
  - Preferably nonsmokers, no history of alcohol or drug abuse.
- Repeated blood sampling (16-18x/sequence, 2 sequences)
- Under fasting condition: 24 jam

Bompart F, et al. The VolREthics initiative to protect the well-being of healthy volunteers in biomedical research. Nature Medicine, October 2023 | 2393–2394 https://doi.org/10.1038/s41591-023-02490-6.

The healthy subjects receive compensation for their participation in the study

- What amounts?
- Not too much -could be an inducement; not too little because - will compromising the subject' welfare
- Common formula:
  - the number of visits/admissions/time: estimated time lost
  - travelling cost
  - inconvenience caused to the volunteers: number of blood sampling
- State whether the participants will be eligible for compensation when they withdrawal before the study completion

Lured by Money

Pulla P. Lured by bloodMoney
https://www.thehindu.com/opinion/op-ed/lured-by-blood-money-clinical-trials/article61841026.ece

- Mr X, 33 y, resident of [redacted]
- Participated in over 25 Clinical Trial between 2005-2009 – eligibility?
- One year after he stopped, began experiencing severe seizures and other mental symptoms
- A government doctor told him his health complaint could be due to the **repeated participation** in clinical trials.

Mr X displays his CT scan film. Next to him is his mother, who earns a living by selling home-made papad.

Challenges in BE Study

- Risks of exploitation of volunteers: “Bioequivalence studies can pay up to ₹25,000 for a week-long commitment, during which a daily wage earner would have otherwise earned a tenth of the amount”.

- **How to protect healthy volunteers from any potential risks of harm or exploitation?**

Our STUDY, HREC FKUI –Cipto Mangunkusumo National Hospital, Jakarta

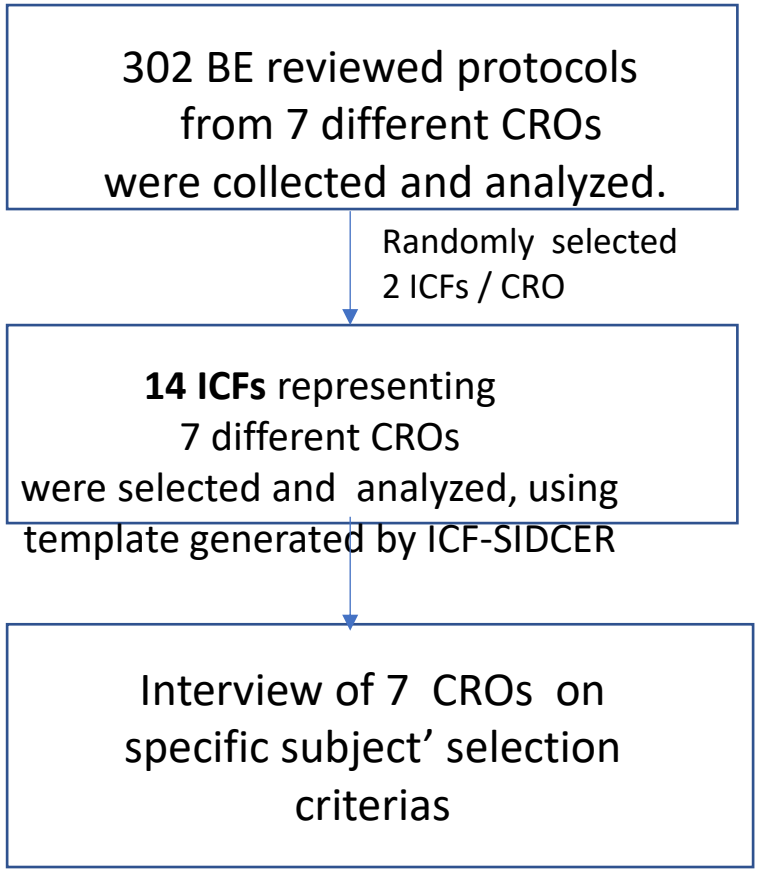
Objectives

- To evaluate current practice and regulations concerning information that has been -given to research subjects when obtaining consent in BE study
  - To analise elements in the ICF developed by CROs

Materials and Methods:

- All BE study proposals initially reviewed by the HREC FMUI-RSCM during year 2023 were collected and analyzed retrospectively.
- Two informed-consent-forms (ICF) developed by each of the respective local CROs were randomly selected
- -- Analyze the following items on the ICFs based on template developed by Enhanced ICF formula by SIDCER :
  - the scientific soundness of the study,
  - rights of the subjects,
  - volunteers' recruitments and eligibility,
  - confidentiality,
  - monetary compensation/ remuneration
- Interview CROs on specific subject's elegibity criteria

Results:



Results 1

Results	N = 302	%
Approved	202	66.9
Rejected	1	0.3
Major revision	10	3.3
Minor revision	89	29.5

Tabel 1. Results of review of BE studies submitted to HREC FMUI-RSCM in 2023
(n=302 protocols; 7 CROs)

Results 2

Reasons for revision	n	%
Informed consent (ICF)	68	68.4
Methodology	44	43.9
General ethical issues	10	10.2

Table 2. Reasons for Recommending Protocol Revision of BE studies submitted to HREC FMUI-RSCM in 2023 (n=99; 7 CROs)

Notes:
Some protocols have combined reasons for revision.
One protocol was rejected due to requesting too many blood samples taken (21x) from the subjects
ICF: - financial compensation : do not meet the standard developed by HREC FKUI RSCM

Results-3

Analyzing the elements of ICF

- 14 ICFs representing 7 CROs randomly selected and analyzed.
- Different ICF template of each CRO, but all have included elements of
  - General Items,
  - Rights of the Subject,
  - Scientific Aspects and
  - Ethical Aspects

Table 1
Elements required in an informed consent form classified into four categories*

General items	*Rights of the participant*
- Recognition that this is research	- Right to refuse
- Participants' responsibility	- Right to withdraw
- Confidentiality of records	- Consequences of withdrawal
- Who can access the data	- Right to receive new relevant information
- Research contact person(s)	
Scientific aspects	*Ethical aspects*
- Eligibility of the subject	- Alternative procedure(s) or course(s) of treatment
- Number of subjects required	- Foreseeable risks
- Purpose of the study	- Expected direct and/or indirect benefits
- Trial treatment	- Post-trial benefits
- Trial procedures	- Criteria for the termination of participation
- Identification of any experimental procedures	- Prorated payment for participation
- Duration of the subject's participation	- Anticipated expenses
- Data collection, storage and/or the reuse of human material	- Compensation for injury

The Enhanced ICF and the Conventional ICF

	Enhanced ICF	Conventional ICF
Number of pages	4	7
Number of required elements provided	21	15
General items		
Recognition that this is research	✓	✓
Subject's responsibility	✓	✓
Confidentiality of records	✓	✓
Who can access the data	✓	Not stated
Research contact person(s)	✓	✓
Rights of the subject		
Right to refuse	✓	✓
Right to withdraw	✓	✓
Consequences of withdrawal	✓	Not stated
Right to receive new relevant information	✓	Not stated
Scientific aspects		
Subject eligibility	✓	✓
Number of subjects required	✓	✓
Purpose of the study	✓	✓
Trial treatment	✓	✓
Trial procedures	✓	✓
Duration of the subject's participation	✓	Not stated
Ethical aspects		
Foreseeable risks	✓	✓
Expected direct and/or indirect benefits	✓	Not clear[a]
Participant termination criteria	✓	Not stated
Prorated payment for participation	✓	✓
Anticipated expenses	✓	✓
Compensation for injury	✓	✓

[a] "No direct benefit from study participation" was not stated

ICF: **"subjects must not take part in the similar study during the previous 3 (three) months from the start of the study"**

Nut Koonrungsesomboon, Supanimit Teekachunhatean , et al. Improved participants' understanding in a healthy volunteer study using the SIDCER informed consent form: a randomized-controlled study..Eur J Clin Pharmacol (2016) 72:413–421

RESULTS
Subject Eligibility

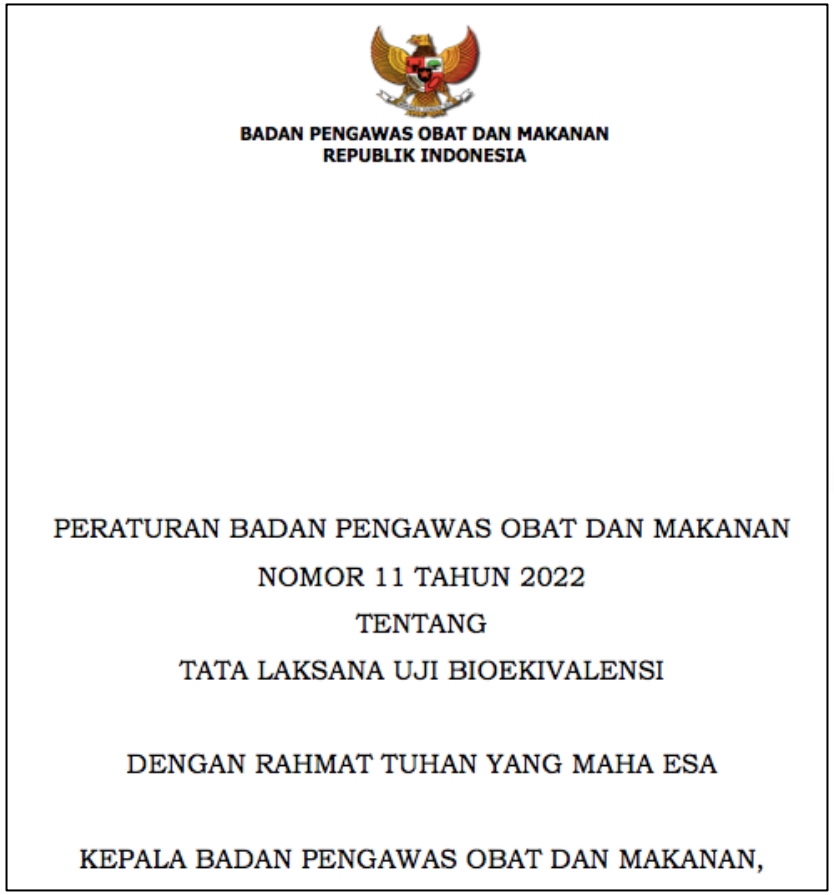
- ICF: **“subjects must not take part in the similar study during the previous 3 (three) months from the start of the study”**
- --- Our Study: 14/14 (100%) ICFs CROs contain this statement

- Q: Can the ICF’ statement alone be relied on, to anticipate Over-volunteering, multiple repeated participation of the subjects?
- A: NO. ICF should not be based only on check-list ICF’ data alone,.. is a process
  - Why? Financial pressure makes subjects dishonest in eligibility criteria –
  - How? Verified Centralized Database System, Healthy Volunteers Registries (Malaysia), Online Volunteer Information System
  - Feed back from the participants: are they understand, aware of the potential risks and/or harm

Results-4: Interview CRO representatives regarding the eligibility of the prospective subjects

- . …. “Not participated in a previous similar trial in 3 months from the start of the study”
- All of the CROs (n=7) have Centralized Subject Database System between BE centers
  - The filter on subject's National ID Card (NIK) number would be enabled to track the subjects’ latest study participation.
  - Every CRO would be given a password to maintain the confidentiality of the data.

- BPOM Regulation Number 11, 2022 concerning BE Study Procedures:
  - **“**Each BE study center must have a centralized subject database between BE Centers which is managed **by an independent party while maintaining subject confidentiality.”**



BADAN PENGAWAS OBAT DAN MAKANAN
REPUBLIK INDONESIA

PERATURAN BADAN PENGAWAS OBAT DAN MAKANAN

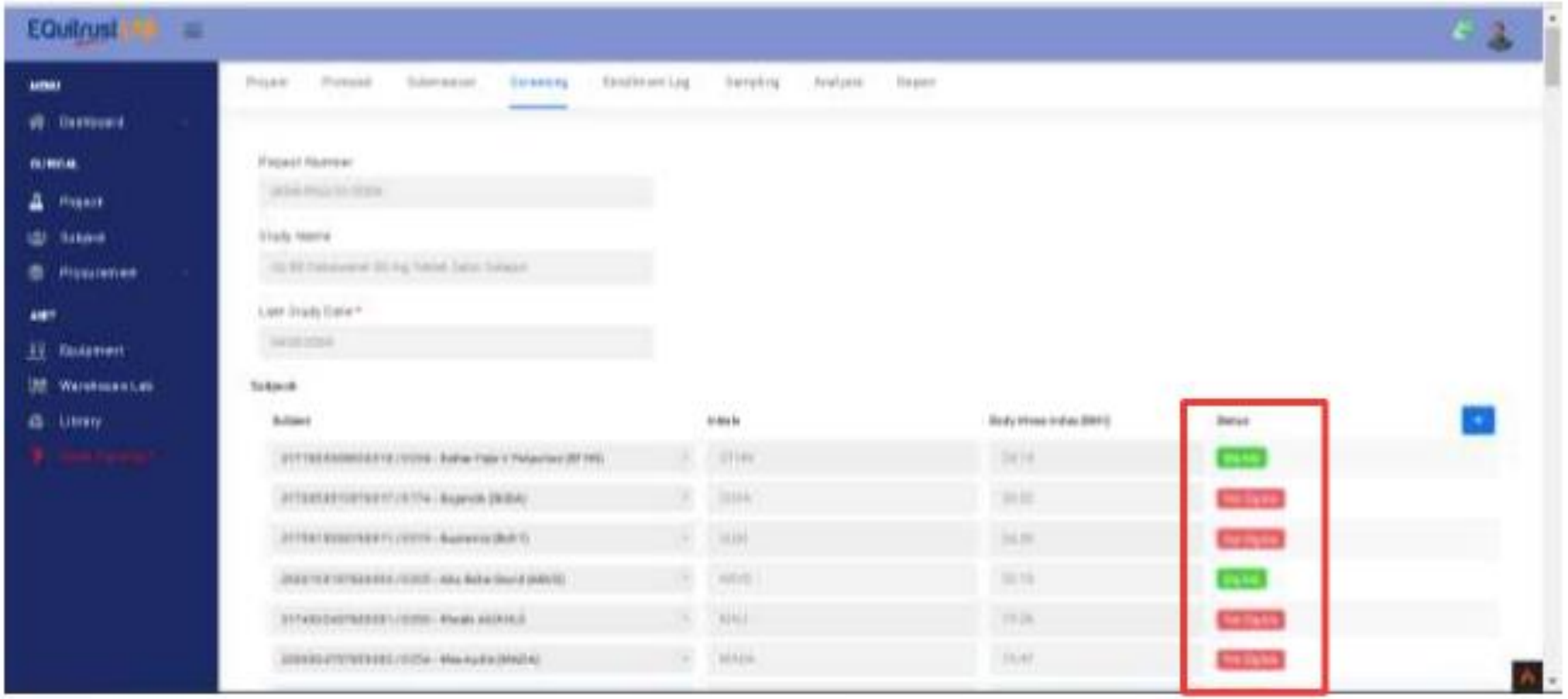
NOMOR 11 TAHUN 2022

TENTANG

TATA LAKSANA UJI BIOEKIVALENSI

DENGAN RAHMAT TUHAN YANG MAHA ESA

KEPALA BADAN PENGAWAS OBAT DAN MAKANAN,

- 

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- The EQuitrust Lab database system is connected to checksubject.com.
- Checks are carried out at the time of registration,
- for prospective subjects who meet the requirements, **Eligible status** will appear. Conversely, for prospective subjects who do not meet the requirements_-- **NOT Eligible**

Take home messages

- Healthy volunteers are vulnerable group in BE study - should be protected to reduce any potential risks of harm or exploitation
- **Health authorities & ethics committee continuous monitoring is critical**
- Challenges: Overworked ethics committees may wrongly assume that “routine” BE studies require less scrutiny than rarer first-in-man studies.
- ICF for BE study needs to contain specific items for subject eligibility *“must not take part in the similar study during the previous 3 months from the start of the BE study”*
- Centralized Data Base system, Centralized/National Health volunteers Registries is important in the recruitment process of the prospective subjects
- Our study showed Completed elements of ICF – still should be ascertained through other means (eg the Online Volunteers Data base System)

Thank you…

- Rita S Sitorus
- Indah S Widyahening

Resources

- PERATURAN BADAN PENGAWAS OBAT DAN MAKANAN NOMOR 11 TAHUN 2022 TENTANG TATA LAKSANA UJI BIOEKIVALENSI
- Bompart F, et al. The VolREthics initiative to protect the well-being of healthy volunteers in biomedical research. Nature Medicine, October 2023 | 2393–2394 https://doi.org/10.1038/s41591-023-02490-6.
- **VolREthics Initiative - Volunteers in Research and Ethics**, Meeting Report: **"Focus on the risks of exploitation of healthy volunteers in biomedical research in Asia" .Asia Workshop, September 23, 2022**
- **Pulla P.** Lured by blood money: serial volunteers set a disturbing trend . The Hindu, 2017. https://www.thehindu.com/opinion/op-ed/lured-by-blood-money-clinical-trials/article61841026.ece
- Nut Koonrungsesomboon, Supanimit Teekachunhatean , Nutthiya Hanprasertpong, Junjira Laothavorn, Kesara Na-Bangchang & Juntra Karbwang. Improved participants' understanding in a healthy volunteer study using the SIDCER informed consent form: a randomized-controlled study..Eur J Clin Pharmacol (2016) 72:413–421