Randomized Controlled Trial (RCT)

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Outline

- History of RCT
- RCT
  - Randomization or Random allocation
  - Allocation Concealment
  - Blinding
  - Analysis
- Conduction RCT
- Trial Registration

History of RCT

- The first random allocation of patients to experimental and control conditions is attributed to James Lind, a surgeon, in 1747.
- Lind randomly assigned 12 sailors to 6 different candidate treatments for **scurvy**. The two patients who were given lemons and oranges recovered most quickly, suggesting a beneficial effect of citrus.
- The first RCT in medicine is credited to Sir A. Bradford Hill, an epidemiologist for England's Medical Research Council. Published in the British Medical Journal in 1948.

Clinical Trial

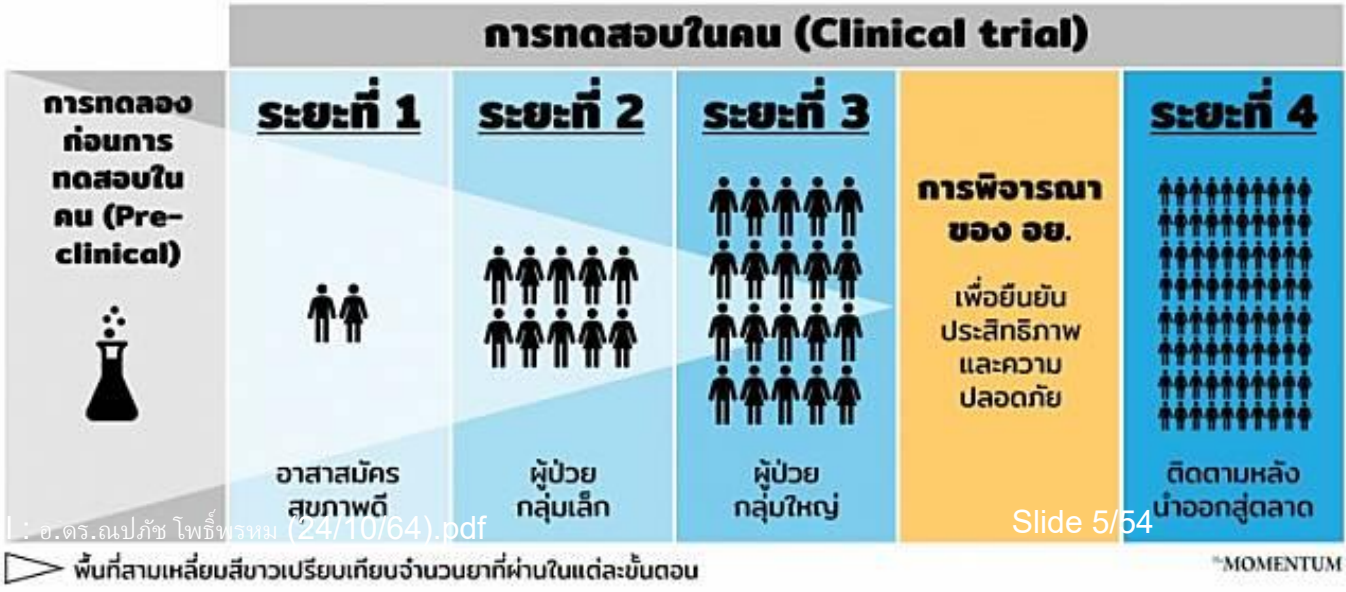
A systematic study on pharmaceutical products in human subjects in order to discover or verify the effects of and/or identify any adverse reaction to investigational products.

Main objectives are efficacy and safety.

Clinical trial phases

Phase I	Phase II	Phase III	Phase IV
20-80 participants	100-300 participants	1,000-3,000 participants	Thousands of participants
Up to several months	Up to (2) years	One (1) - Four (4) years	One (1) year +
Studies the safety of medication/treatment	Studies the efficacy	Studies the safety, efficacy and dosing	Studies the long-term effectiveness; cost effectiveness
70% success rate	33% success rate	25-30% success rate	70-90% success rate

Phases of Clinical Trials(1).jpg

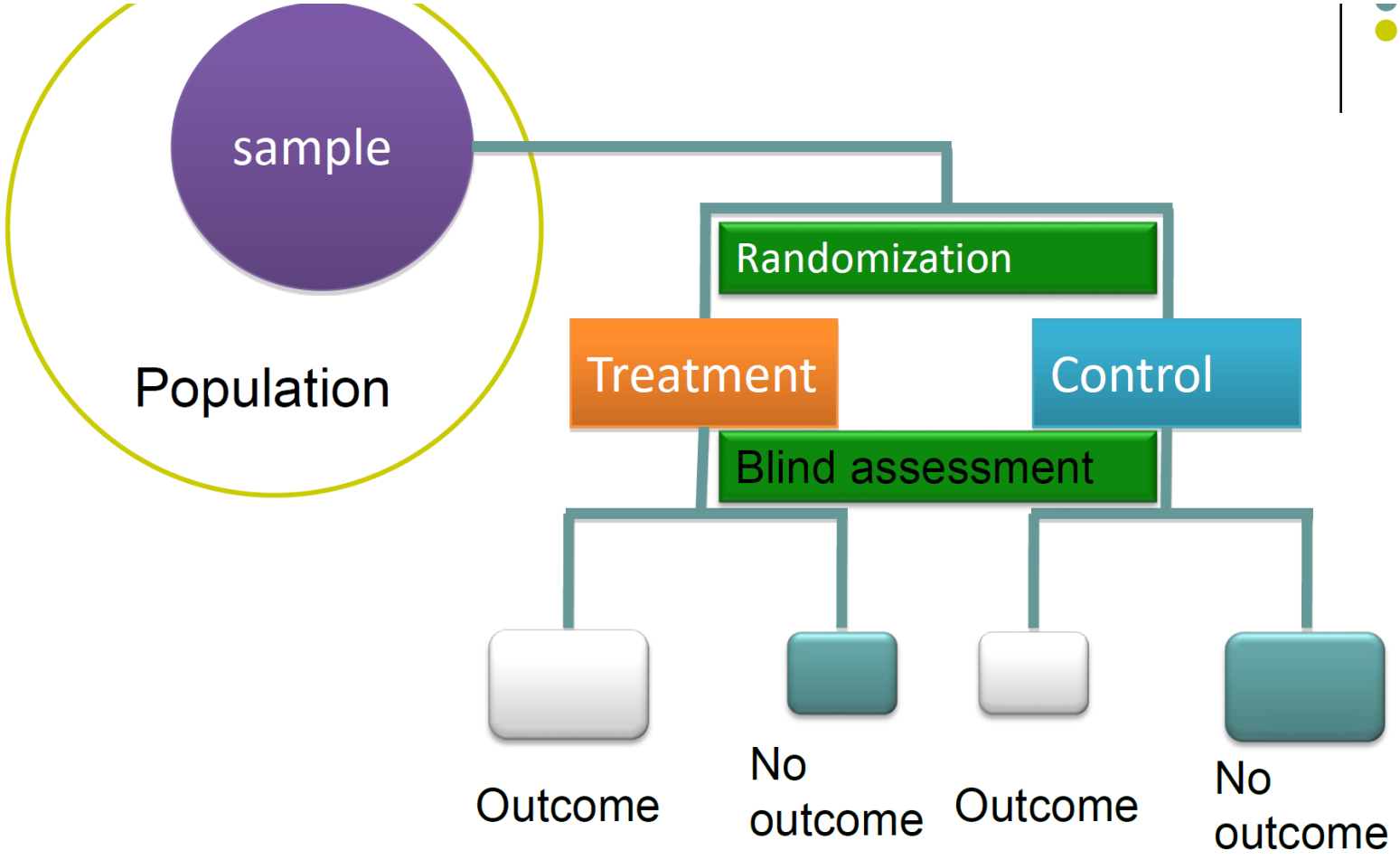


Randomized controlled trial (RCT)

RANDOMIZATION OR RANDOM ALLOCATION

- Allocation of individuals to groups by ***chance.***
- Randomization should make the control and the ***experimental groups similar*** at the start of the investigation and ensure that ***personal judgment*** of the investigator do not influence allocation.
- All subjects in the sample have *same probability* of being assigned to the experimental or control group.
- Underlying factors the may affect the outcome are *equivalent* for each group.

Randomized Control Trial



Why Conduct a Randomization?

- To ensures that known and unknown person and environment characteristics that could affect the outcome of interest are **evenly distributed** across conditions.
- To **equalizes the influence** of nonspecific processes not integral to the intervention whose impact is being tested.

(Nonspecific processes might include effects of participating in a study, being assessed, receiving attention, self-monitoring, positive expectations, etc.)

Why balance is important?

Table I. *Baseline characteristics in the minimal access spine surgery (MASS) and the open surgery groups (OS).*

Characteristics	MASS Group, n=23	OS group, n=26	*p*-Value[2]

Table 1 General characteristics of study groups

Table 1. *Baseline characteristics.*

	"No levetiracetam" ($n = 35$)	Levetiracetam ($n = 41$)	*p* value
Age	55.9 (8.9)	54.6 (12.4)	0.6
Gender (male/female)	9/26	14/27	0.5
Aneurysm size (mm)	5.2 (2.2)	6.7 (3.1)	0.01
Length of procedure (minutes)	335 (105)	354 (125)	0.5
Surgeon's assessment of degree of brain retraction			
Less than average	5	4	0.7
Average	30	34	1
More than average	0	3	0.2
Surgeon's assessment of degree of cortical injury			
Less than average	4	5	1
Average	29	32	0.8
More than average	2	4	0.7
Follow-up duration	20.4	19.1	0.8

Group 3
16
10:6
41.4 ± 0.5 years
43.1 ± 0.2 years
40.5 ± 0.3 years
16*
4:12
16
1.1 ± 0.1 years

Spinal level of the i
decompressed duri
TH 5-8
TH 9-12
L 1-3

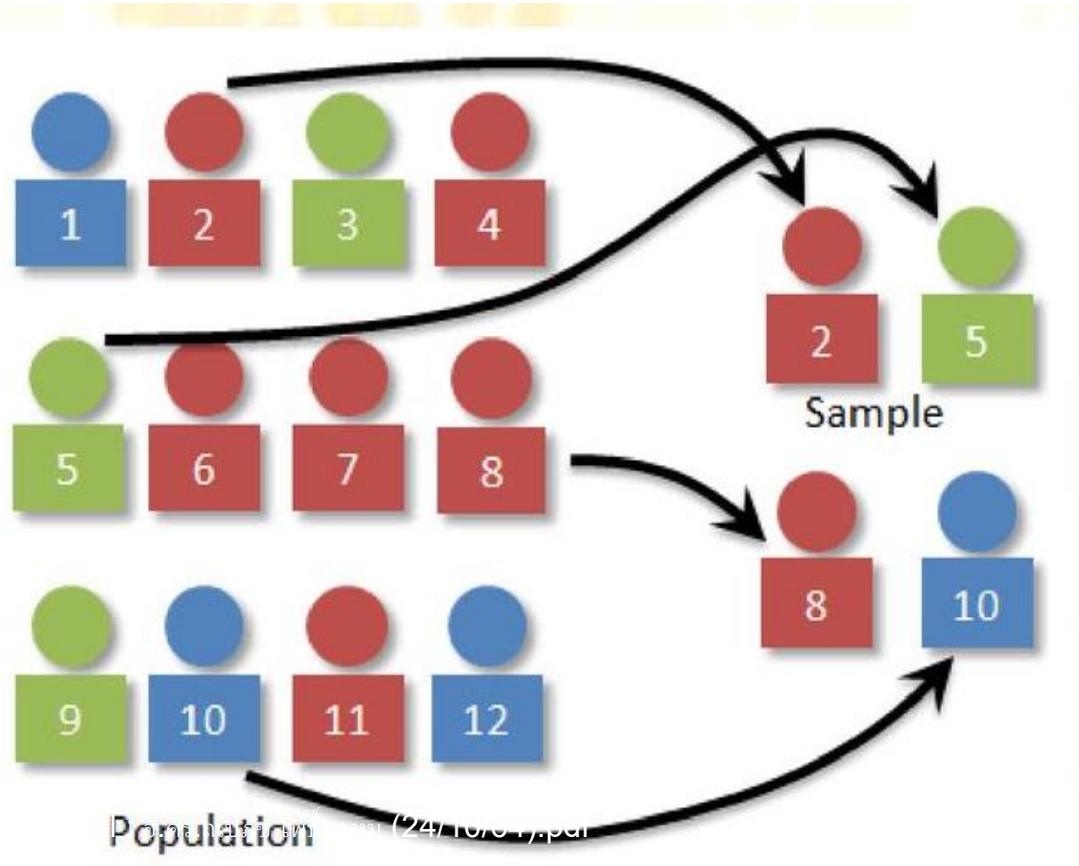
[1]Values are percenta
variables with a ske
with a normal distri
tests for categorical

in years (mean ± SD)			
Duration of peri-implant mucositis in days (mean ± SD)	5 ± 1.2 days	6 ± 0.2 days	6.3 ± 0.1 days
Toothbrushing once daily (n)	15	15	15
Daily flossing	None	None	None
The implants were located in the region of a missing premolar or molar.			

Types of randomization

Simple randomization

- การสุ่มอย่างง่าย(Simple random sampling) เป็นการสุ่มตัวอย่างเมื่อประชากรมีลักษณะใกล้เคียงกัน เช่น การจับสลาก การโยนเหรียญ

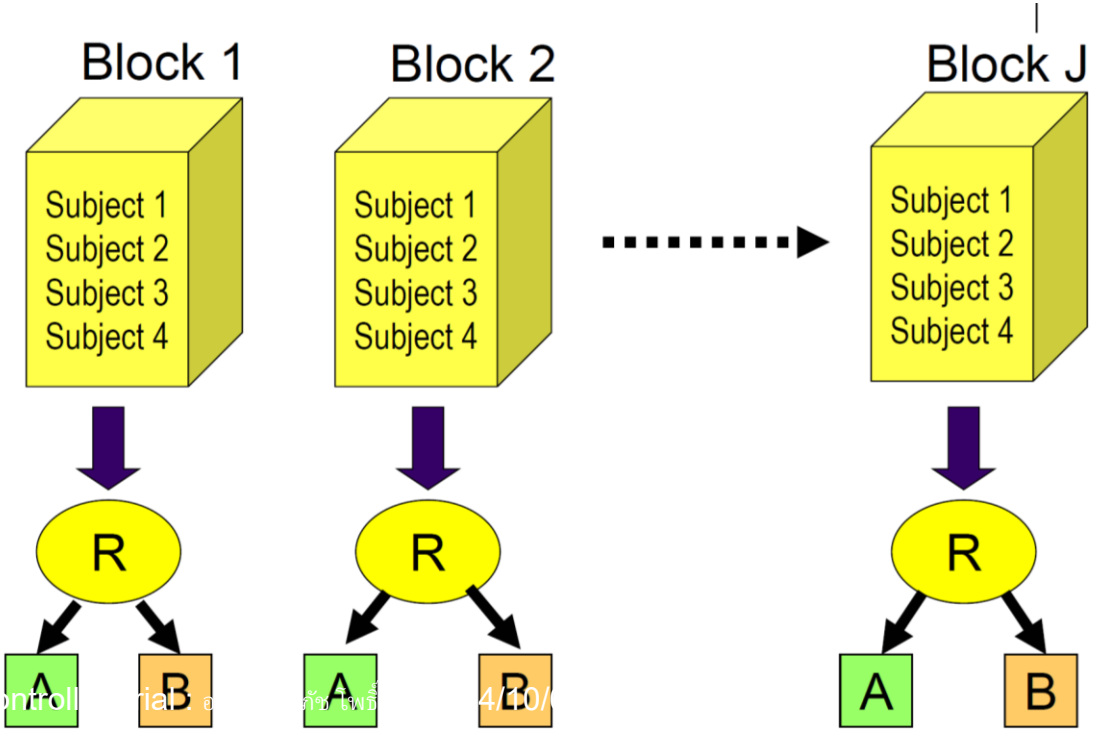


Block Randomization

- Blocked randomization **reduces the risk that different numbers of people** will be assigned to the treatment (T) and control (C) groups.
- Blocked randomization offers the advantage that at any point in the trial, there will be a balance in the number of cases assigned to T versus C.

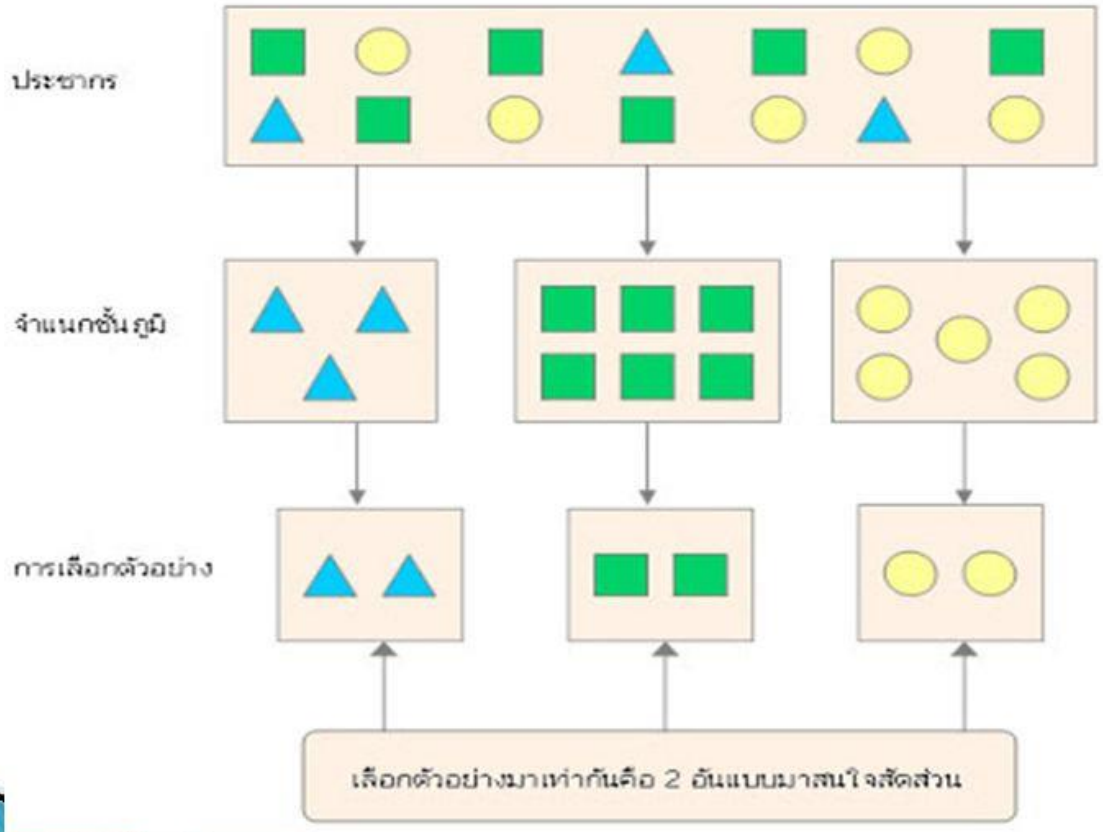
Block Randomization

- Report allocation ratio.
- The random method of selection.
- Block size.

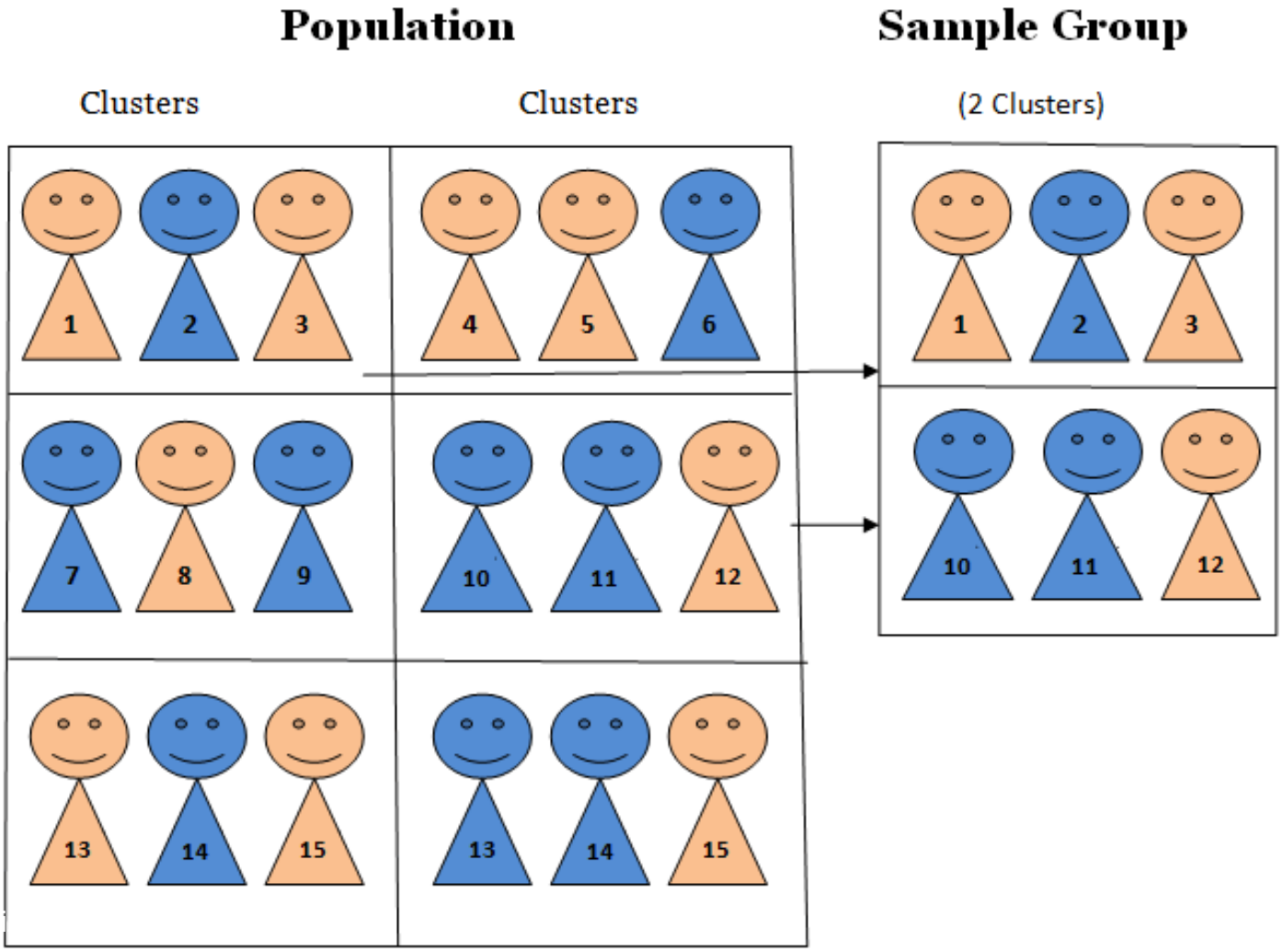


Stratified random sampling

- Ensure that the treatment and control groups are balanced on im
influence the stu
ethnicity, age, s
- Use when it is be
may affect the
- Achieving progr
stratification pric



Cluster random sampling



Example

- Not able to read, write and understand Dutch or English.

*Deep endometriosis extends beneath the peritoneum and uterosacral ligaments, pelvic sidewalls, rectovaginal septum bladder or ureter (Dunselman et al., 2014).

The study schedule is presented in the flowchart (F meeting the inclusion and exclusion criteria will be ver about the study by their physician who will provide the information. Each subject will be informed that parti study is voluntary and that withdrawal of consent her right to the most appropriate treatment or affec doctor relationship. If a patient agrees to participate after the consideration time of 1 week, written info will be obtained after which randomisation will b Women will be randomly allocated in a 1:1 ratio to or treatment with medication, with use of dynamic b randomisation with blocks of 2, 4 or 6. Stratification by performed.

Women who decline randomisation due to a spe preference for one of the treatments will be asked to a prospective cohort according to the study protocol outcome of the randomised trial (successful pain red reduction of pain) measured by the NRS after 6 m presented as the headline result. Addition of the pros enables us to:

Randomisation

Patients will be randomised 1:1 to undergo either intravenous contrast CT or native CT. Randomisation sequence will be generated using a computer software with variable block size (4, 6 and 8) and will be concealed from recruiters, attending physicians, patients, data collectors and data analysts. Randomisation will be done using web-based computer system. Randomisation sequence will be stratified for:

- eGFR 15 to <30 vs 30 to 45 mL/min/1.73 m^2
- Patient age <65 vs 65 years or over
- Centre

As the attending physicians need to be able to analyse the CT images, the study is open-label. After a patient gives written informed consent, the attending physician performs randomisation and orders a CT scan.

Outcomes

The primary outcome is a composite that combines all-cause mortality and RRT within 90 days of CT. The secondary outcomes are: (1) the most severe AKI

ALLOCATION CONCEALMENT

- Generation of an *unpredictable* randomized allocation sequence.
- It represents the first crucial element of randomization in a RCT.
- Allocation concealment refers to the ***technique*** used to implement the ***sequence***, not to generate it.
- Allocation concealment means that the person who generates the random assignment remains blind to what condition the person will enter.

How to conceal?

- Local: Sequentially numbered, opaque envelopes

Sequentially numbered, opaque, sealed envelopes (SNOSE)

- Central: Computer-based

Web-based response system

Example

Randomisation, sequence concealment and blind

All eligible participants will be randomly
either group R or the group I in a ratio of 1:1
software (R Foundation for Statistical Comp
random allocation sequence will be compute
by an independent researcher who has no
any participant and will not be involved in t
research. The participants' respective treat
(group R or group I) will be sealed in an o
lope and will only be opened after the enrol
participants in the study. An investigator wil
sible for enrolling patients, obtaining conse
requesting randomisation.

This study is an open-label study whereby
pants, the personnel who carry out the inter
the outcome assessor cannot be blinded be
nature of the intervention. However, the rese
are responsible for the statistical analysis wil
to the allocation.

The study included pregnant women whose infants were below 60 days of age, according to the following inclusion criteria: having a landline or cell phone and practicing EBF during hospitalization in the rooming-in facility. The exclusion criteria were the following: medium- and high-risk mothers and infants, or pre-term infants who were not able to be breastfed, as well as postpartum women with communication difficulties, e.g., with a hearing disability or who did not speak Portuguese.

Randomization was performed with numbered, opaque, and sealed envelopes indicating the group to which each woman would be allocated, which were opened by the women themselves or by a companion.

The sample size was estimated by a pilot test (52 subjects in each group), totaling 104 participants. The data were described as absolute frequencies and percentages for the qualitative variables, and as position and dispersion measures for the quantitative variables. The details of the investigation process (Figure 1) followed the Consolidated Standards of Reporting Trials (CONSORT) recommendations.

BLINDING

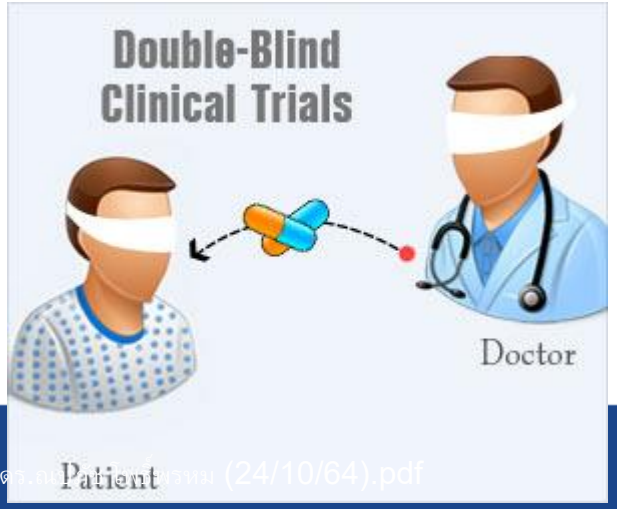
Potential benefits of blinding

Individuals	Potential benefits
Patients	**-Less likely to have biased psychological or physical responses to intervention** **-More likely to comply with trial regimens** **-Less likely to seek additional adjunct interventions**
Clinicians	**-Less likely to differentially administer co-interventions** **-Less likely to differentially adjust dose** **-Less likely to differentially withdraw participants** **-Less likely to differentially encourage or discourage participants to continue trial**
Assessors	**-Less likely to have biases affect their outcome assessments, especially with subjective outcomes of interest**

What to look for in descriptions of blinding?

- *Single-blind*
- *Double-blind*
- *Triple-blind*

*****State explicitly who was blinded, and how.*****

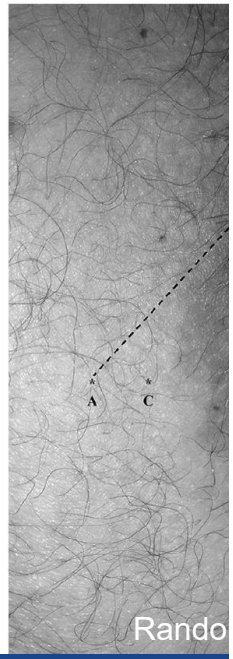


Example

standardized. The patients were discharged based on the clinical discharge criteria [33]. The participating surgeons and the anesthesiologists had completed the learning curves of the respective interventions.

Outcomes

The primary endpoi
the experimental gr
remission rate. Seco
tion; additional ana
ery (mobilization, f



Rando

stays.[11] Therefore, we designed the randomized controlled research to look for the optimal intravenous dexamethasone dose for the treatment of early postoperative pain after the THA. We assumed that the patients who received 3 doses of dexamethasone intravenously possessed the best postoperative results compared to those who received 1 or 2 doses of the dexamethasone.

2. Materials and methods

2.1. Participants

The Declaration of Helsinki principles was followed and the Consolidated Standards of Reporting Trials guidelines for randomized controlled trials was adhered in this study. The trial was registered prior to patient enrollment via the Research Registry (researchregistry5864). The First Medical Center in People's Liberation Army General Hospital approved the study (2020-089). After written informed consent was obtained, patients aged between 18 and 80 years with Physical Status I to III of American Society of Anesthesiologists, scheduled for primary unilateral THA, were included in this present work.

The exclusion criteria involved revision surgery; prior ipsilateral hip surgery; exhibited sensitivity or allergy to dexamethasone, opioids, or any other drugs used in the study; ankylosing spondylitis; systemic lupus erythematosus; daily intake of strong opioids or dexamethasone; have a history of alcohol abuse or intravenous drug use.

2.2. Randomization and blinding

Randomization is the use of a computer-formed list via a secretary (Research randomizer, www.randomizer.org), at a ratio of 1:1:1, each block has 50 numbers. Each participant received a serial research number from 1 to 150 and they also received treatment assigned in accordance with a randomized list. The list was kept and available to only 2 nurses preparing study medications. They do not interact with patients. All other outcome evaluators, participants, and clinicians were blind to this intervention. When all the selected patients completed this study, the randomization key was broken for the first time (Fig. 1).

2.3. Intervention measures

Patients in the group A were given 1 dose of dexamethasone (10 mg) intravenously before the anesthesia induction, and then 2 doses of the normal saline (2 ml) was added after 24 hours and 48 x0200A;hours. Patients in the group B were given 1 dose of dexamethasone (10 mg) intravenously before the anesthesia induction, and 1 dose of dexamethasone (10 mg) after 24 hours, and afterward, these patients received another 1 dose of the normal saline after 48 hours. And patients in the group C were given 1 dose of dexamethasone (10 mg) intravenously before the anesthesia induction, and then 2 doses of the dexamethasone (10 mg) were added after 24 hours and 48 hours. The clinical staff who administered the medication were unaware of the composition of individual test preparation. All the researchers also conducted blind study on these 3 groups.

2.4. Intraoperative management

In the operating room, the patients inhaled oxygen through the mask to maintain blood oxygen saturation above 94%. General

Randomization and blinding

Randomization (1:1) was performed by a dedicated electronic

What should you do when blinding is impossible?

- *Strict to treatment protocol: to prevent unequal co-intervention*
- *Equally intense follow-up of experimental and control patients.*
- *External outcome adjudicators: to reduce biased outcome measurement.*

Analysis

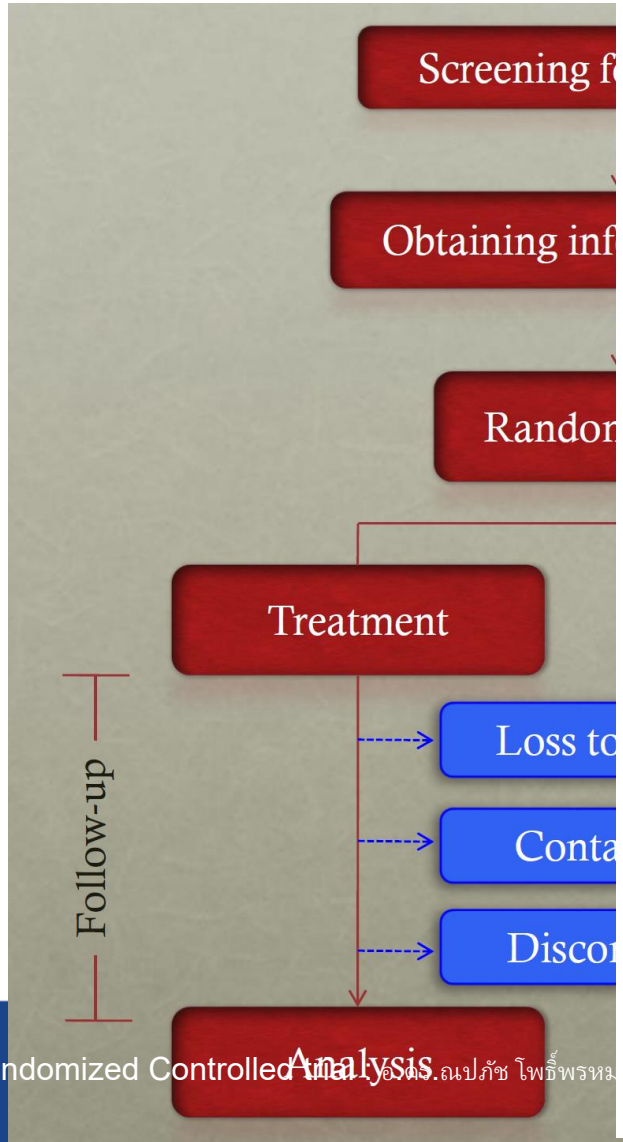
Intention to treat(ITT)

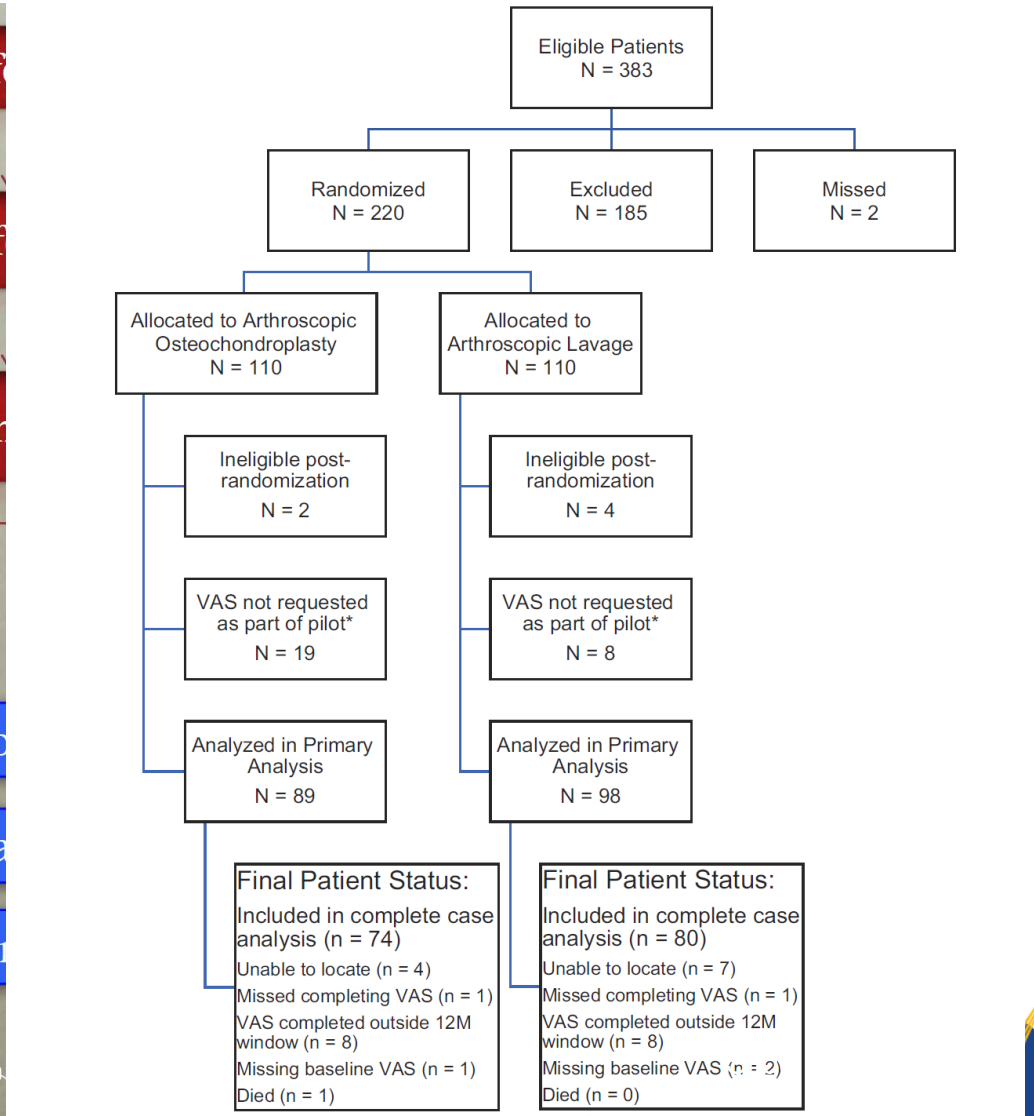
- *Analysis according to the assigned group.*
- *Increasing the chance of a negative study.*

Per protocol

- *Analysis according to the treatment each patient actually received, regardless of the treatment to which they were randomized.*
- *Dissimilarities between groups.*

How to check ITT vs. per protocol analysis





Randomized Controlled Trial : อ.นพ.ณปภัช โพธิ์พรหม

Conduction RCT

Structured of Randomized control trial (PICO)

- Population ????
- Intervention ????
- Comparison ????
- Outcome ????

Populations

- The study population should be defined in advance, stating unambiguous inclusion (eligibility) criteria.
- The selection criteria will have impact on study design and ability to generalize.
- Subject recruitment must be taken into account.

How to set inclusion & exclusion criteria

Include:

- Subjects who have the potential to benefit from the intervention.
- Subjects who have high likelihood to show event of interest
- Subjects who are likely to comply with the study protocol.

Exclude:

- Subjects who have the potential to harm from the intervention.
- Subjects at high risk of developing conditions which preclude the ascertainment of the event of interest.

Intervention

- Is it ethical ?
- Is it feasible?
- Is the intervention well enough developed

to permit evaluation? (especially surgical procedures or psychological therapies).

- Is there preliminary evidence that

The intervention is likely to be beneficial (from observational studies).

Study intervention

"5W 1H"

- What is the intervention?
- Who will administrate the intervention?
- Whom will be administrated the intervention?
- Where the intervention will be administrated?
- When the intervention will be administrated?
- How the intervention will be administrated?

Comparison

Active control

- Superiority
- Non-inferiority (equivalence)

Inactive control

- No treatment control
- Placebo control

Outcome (endpoint)

Clinical outcome

- Clinical events (perceivable by patient) e.g. death, stroke, or myocardial infarction.

Intermediate outcome

- Surrogate outcome e.g. serum creatinine, degree of glucose control, or patency of coronary arteries.
- Quality of life measurement, pain score.
- Economic evaluation e.g. cost-effectiveness.

Composite outcome

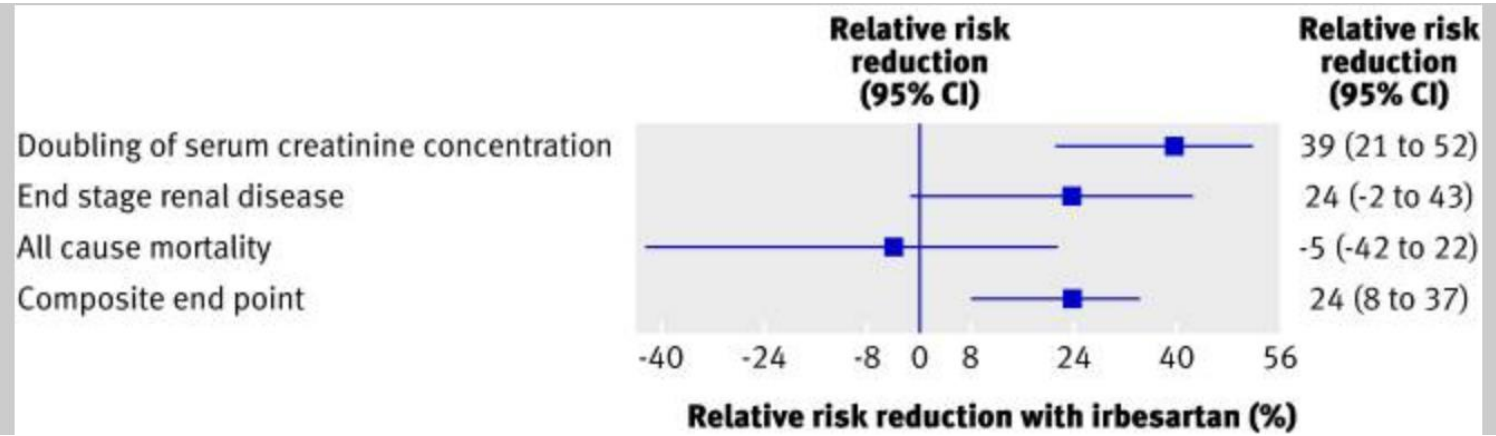
Advantages of composite endpoint?

- To increase statistical precision and efficiency of a trial. (*higher number of events*).
- To avoid a choice between several important outcomes. (*when several outcomes are judged to be of equal value in terms of differentiating between successful and unsuccessful interventions*).

Disadvantages of composite endpoint?

- Discrepancy in size of difference among outcomes make misleading interpretation.
- Difficult for meaningful interpretation.
- Lack of relevance to patients.
- May be misleading.

Example of discrepancy among composite endpoints



Comparison of irbesartan with amlodipine in the diabetic nephropathy study

Ferreira-Gonzálezl. *BMJ 2007*

Guideline of RCT

CONSORT 2010 checklist of information to include when reporting a randomised trial*

Section/Topic	Item No	Checklist item		Reported on page No
Title and abstract				
	1a			
	1b		assessing outcomes) and how	
Introduction			11b If relevant, description of the similarity of interventions	
		Statistical methods	12a Statistical methods used to compare groups for primary and secondary outcomes	
Background and objectives	2a		12b Methods for additional analyses, such as subgroup analyses and adjusted analyses	
	2b	**Results**		
Methods		Participant flow (a diagram is strongly recommended)	13a For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	
Trial design	3a		13b For each group, losses and exclusions after randomisation, together with reasons	
	3b	Recruitment	14a Dates defining the periods of recruitment and follow-up	
Participants	4a		14b Why the trial ended or was stopped	
	4b	Baseline data	15 A table showing baseline demographic and clinical characteristics for each group	
Interventions	5	Numbers analysed	16 For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	
Outcomes	6a	Outcomes and estimation	17a For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	
	6b		17b For binary outcomes, presentation of both absolute and relative effect sizes is recommended	
Sample size	7a	Ancillary analyses	18 Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	
	7b	Harms	19 All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	
Randomisation:		**Discussion**		
Sequence generation	8a	Limitations	20 Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	
	8b	Generalisability	21 Generalisability (external validity, applicability) of the trial findings	
Allocation concealment mechanism	9	Interpretation	22 Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	
Implementation	10	**Other information**		
		Registration	23 Registration number and name of trial registry	
Blinding	11a	Protocol	24 Where the full trial protocol can be accessed, if available	
		Funding	25 Sources of funding and other support (such as supply of drugs), role of funders	

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.

Pros & Cons of RCT

Pros

- Confounding variables can be balance by Randomization.
- Blinding of subjects, medical staff and investigators are achievable.

Cons

- Costly in term of time and money.
- Dropout or loss to follow-up are common events.
- Need time for final results.

Trial Registration

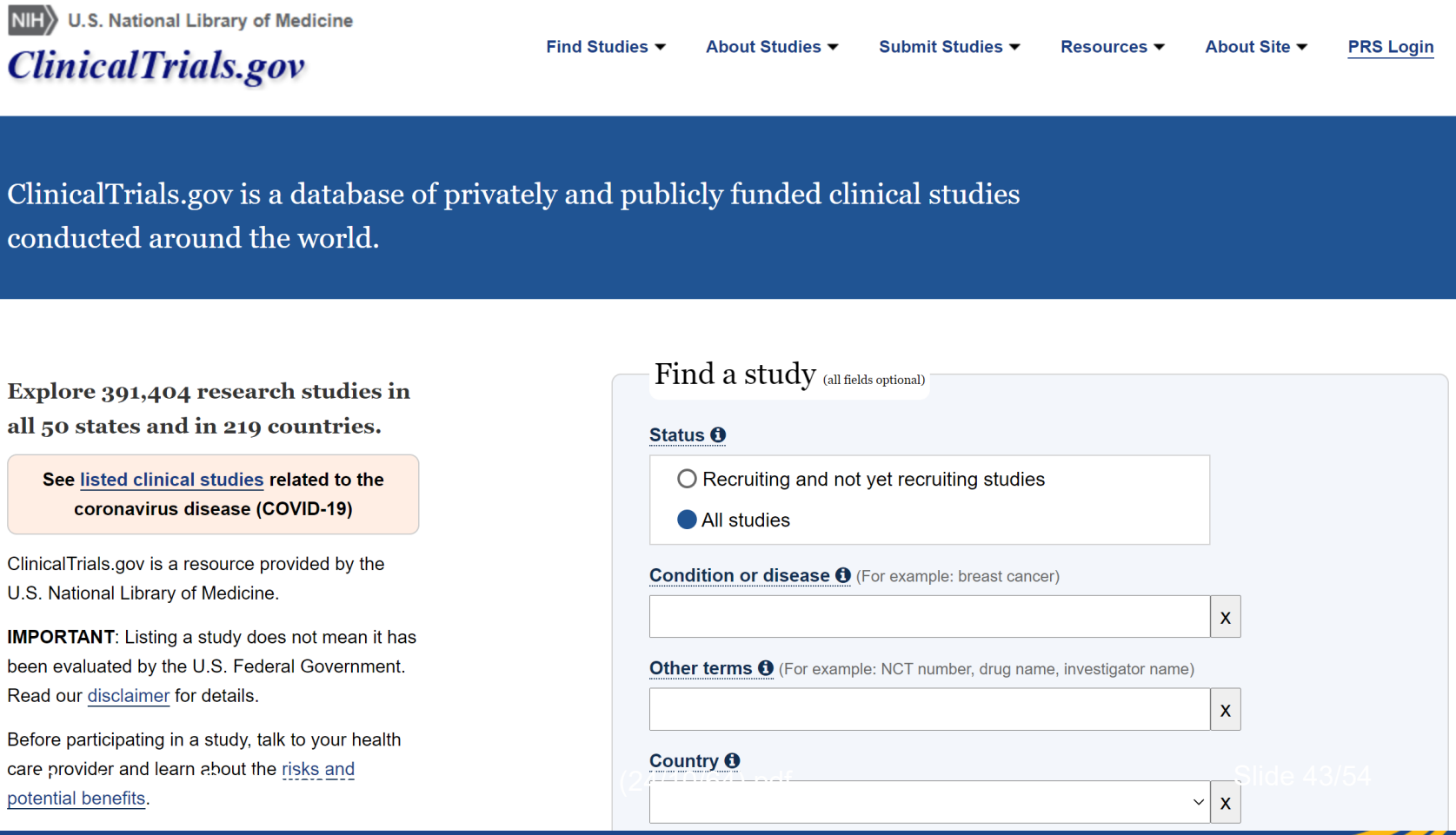
Trial Registration

- The International Committee of Medical Journal Editors(ICMJE) announced that all trials starting enrolment after July 1, 2005 must be registered prior to consideration for publication in one of the 12 member journals of the Committee.

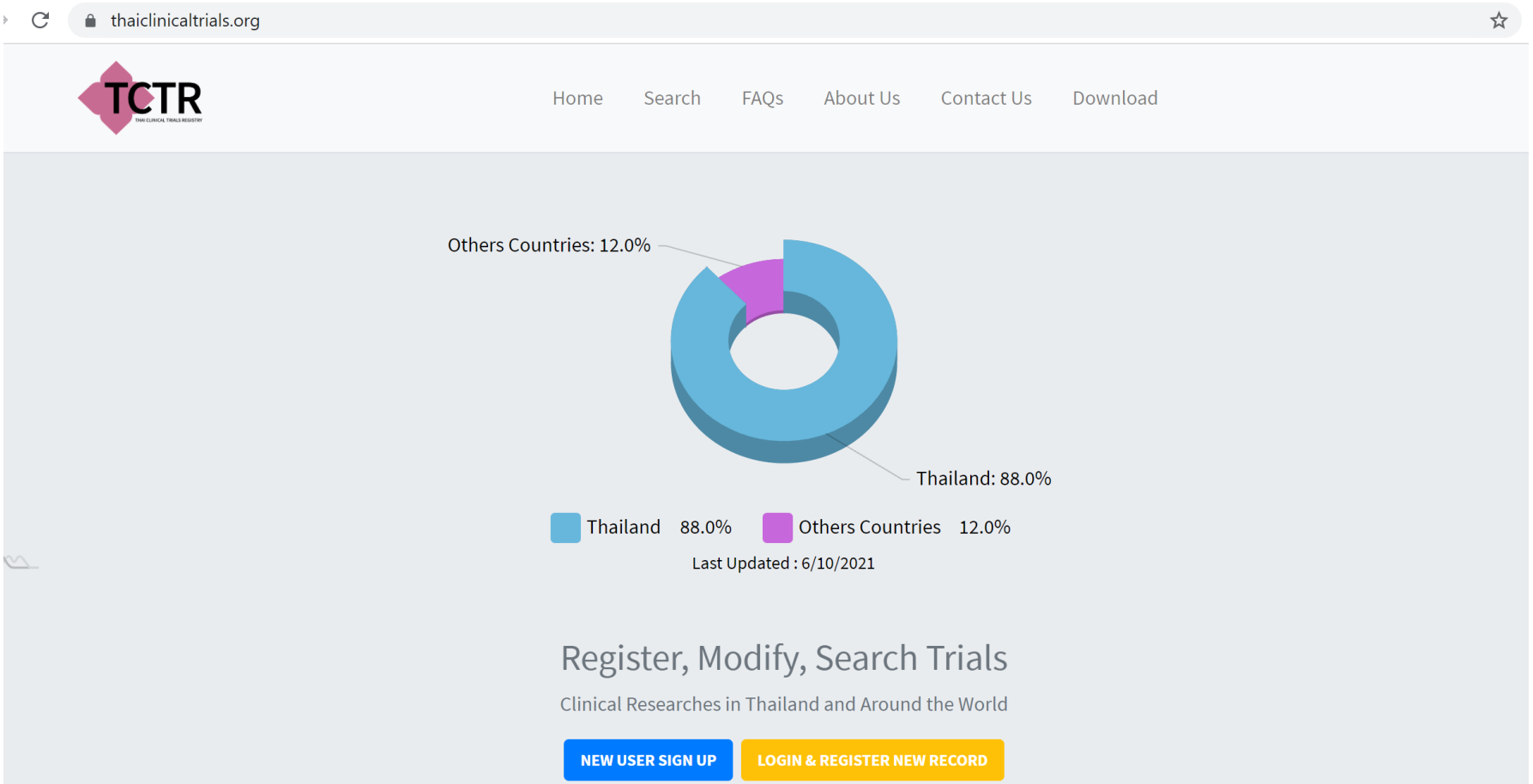
Why is Trial Registration Important?

- เพื่อให้เกิดความโปร่งใสในการทำงานวิจัย
- เปิดโอกาสให้ผู้ป่วยได้มีส่วนร่วมในงานวิจัยเพิ่มขึ้น
- เพื่อลดความซ้ำซ้อนและสิ้นเปลืองทรัพยากรวิจัยของโลก/ประเทศ
- เพื่อเป็นแหล่งข้อมูลที่สำคัญสำหรับผู้กำหนดนโยบาย นักวิจัย และผู้ป่วย

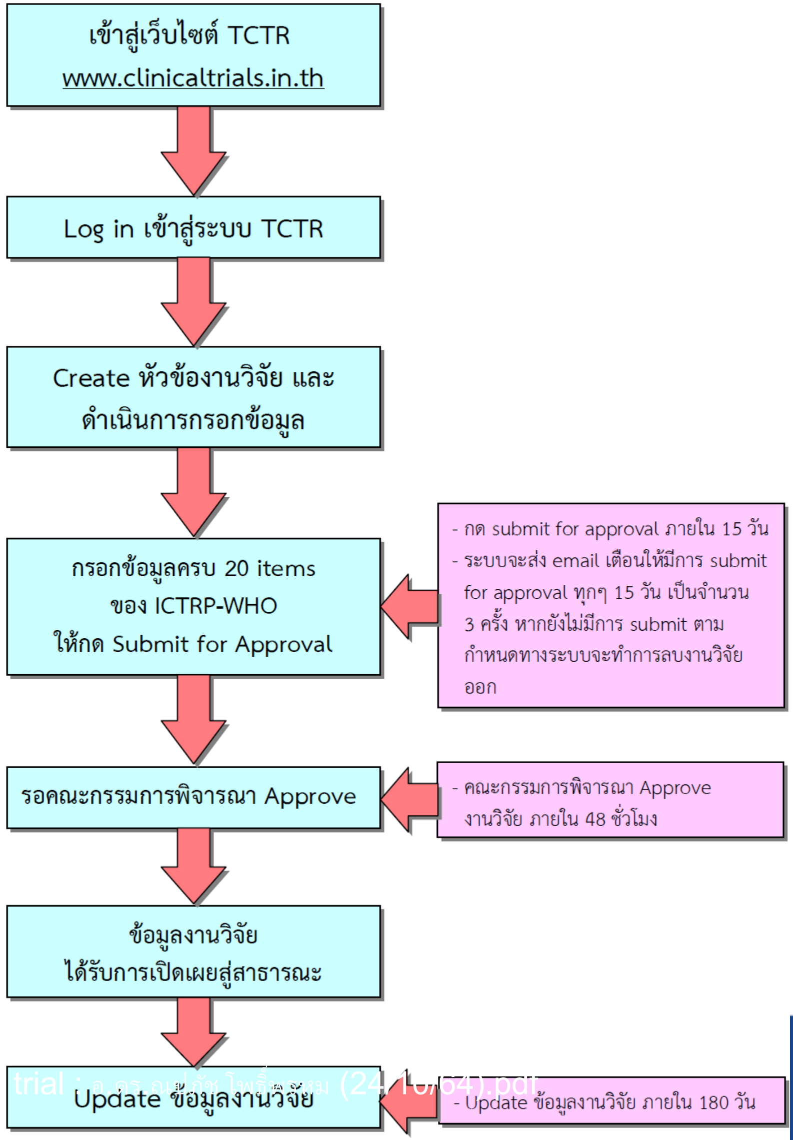
Primary Registries in the WHO Registry Network

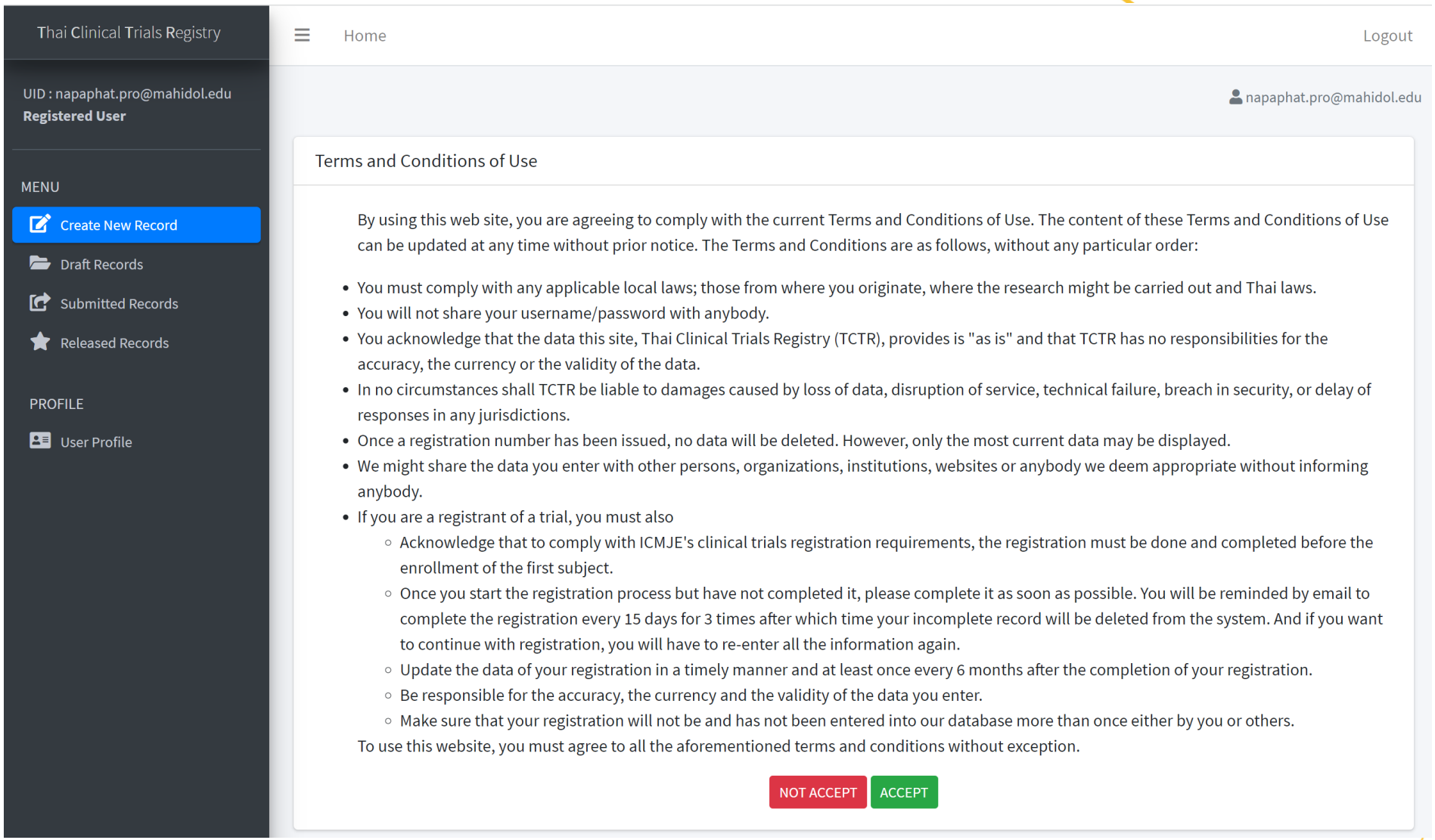


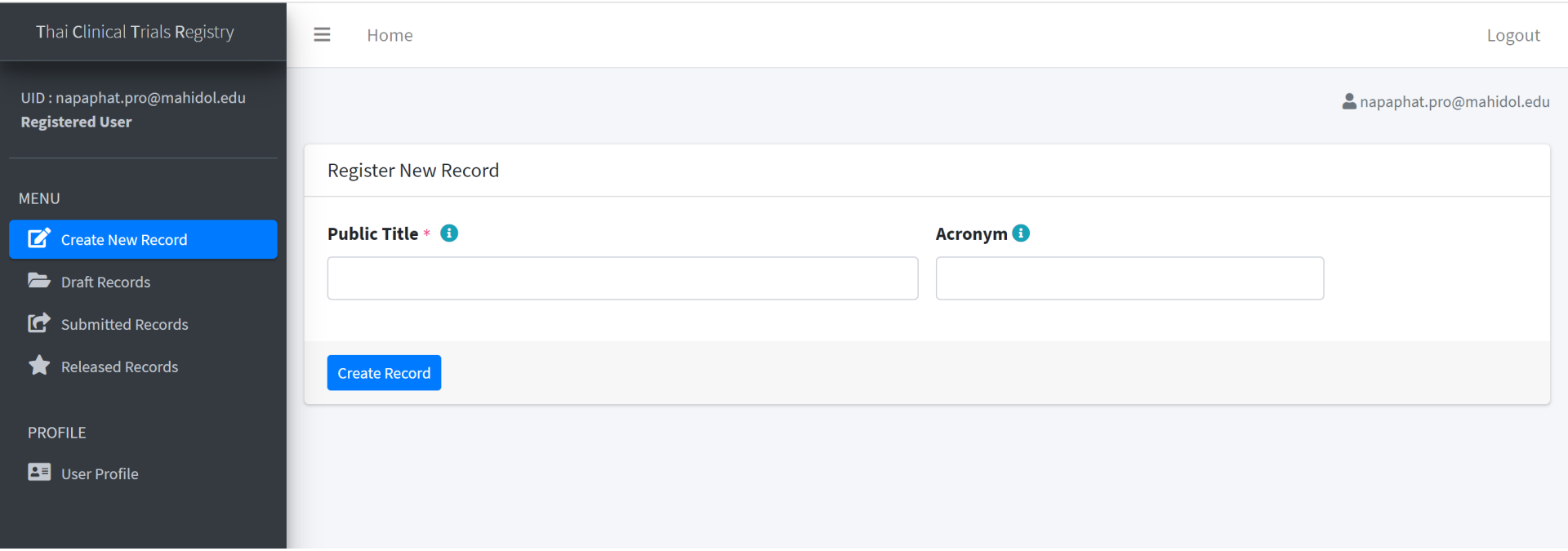
TCTR : Thai Clinical Trials Registry



Step of Clinical Trials Registry




Thai Clinical Trials Registry
UID : napaphat.pro@mahidol.edu
Registered User
MENU
Create New Record
Draft Records
Submitted Records
Released Records
PROFILE
User Profile
Home
Logout
napaphat.pro@mahidol.edu
Terms and Conditions of Use
By using this web site, you are agreeing to comply with the current Terms and Conditions of Use. The content of these Terms and Conditions of Use can be updated at any time without prior notice. The Terms and Conditions are as follows, without any particular order:
You must comply with any applicable local laws; those from where you originate, where the research might be carried out and Thai laws.
You will not share your username/password with anybody.
You acknowledge that the data this site, Thai Clinical Trials Registry (TCTR), provides is "as is" and that TCTR has no responsibilities for the accuracy, the currency or the validity of the data.
In no circumstances shall TCTR be liable to damages caused by loss of data, disruption of service, technical failure, breach in security, or delay of responses in any jurisdictions.
Once a registration number has been issued, no data will be deleted. However, only the most current data may be displayed.
We might share the data you enter with other persons, organizations, institutions, websites or anybody we deem appropriate without informing anybody.
If you are a registrant of a trial, you must also
Acknowledge that to comply with ICMJE's clinical trials registration requirements, the registration must be done and completed before the enrollment of the first subject.
Once you start the registration process but have not completed it, please complete it as soon as possible. You will be reminded by email to complete the registration every 15 days for 3 times after which time your incomplete record will be deleted from the system. And if you want to continue with registration, you will have to re-enter all the information again.
Update the data of your registration in a timely manner and at least once every 6 months after the completion of your registration.
Be responsible for the accuracy, the currency and the validity of the data you enter.
Make sure that your registration will not be and has not been entered into our database more than once either by you or others.
To use this website, you must agree to all the aforementioned terms and conditions without exception.
NOT ACCEPT
ACCEPT


Thai Clinical Trials Registry
Home
Logout
UID : napaphat.pro@mahidol.edu
Registered User
napaphat.pro@mahidol.edu
MENU
Create New Record
Draft Records
Submitted Records
Released Records
PROFILE
User Profile
Register New Record
Public Title *
Acronym
Create Record

MENU

- Create New Record
- Draft Records
- Submitted Records
- Released Records

PROFILE

- User Profile

Register New Record

Create New Record Success

Public Title *

dddddd

Acronym

Save Update

Current Status : In Progress

- Title
- Ethics Review
- Sponsor
- Protocol Synopsis
- Health Conditions
- Eligibility

- Eligibility
- Status
- Design
- Outcome
- Locations
- Summary Results
- Deidentified Individual Participant-level Data (IPD) Sharing
- Publication from this study

Information incomplete, unsubmittable!

SAVE ALL | VERIFY INCOMPLETE INFORMATION

▼ Title

Scientific Title * ⓘ

Sponsor ID/ IRB ID/ EC ID * ⓘ

Study Identification Number * ⓘ

- (•) TCTR is the first registration site.
- ( ) TCTR is NOT the first registration site, please specify below.

Registration Site * ⓘ

-- Select First Registration Site --

Unique ID * ⓘ

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Secondary IDs * ⓘ

ID Type *

- ( ) The Universal Trial Number (UTN), as obtained from WHO website

Health Conditions

Health Condition(s) or Problem(s) Studied *

Enter only condition or focus (no bullets, etc.), one per line.

Keywords * **MeSH Terms**

Enter only Keywords (no numbers, dashes, bullets, etc.), one per line.

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Eligibility

Inclusion Criteria *

Gender *

-- Select Gender --

Outcome

Outcome Name * 

Specify a variable name only

Metric / Method of measurement * 

Not statistical method

Time point * 

Primary Outcome 

Outcome Name	Metric/Method of measurement	Time point	Options
No data available in table			

Showing 0 to 0 of 0 entries

Save Draft

Outcome Name * 

Specify a variable name only

Metric / Method of measurement * 

Not statistical method

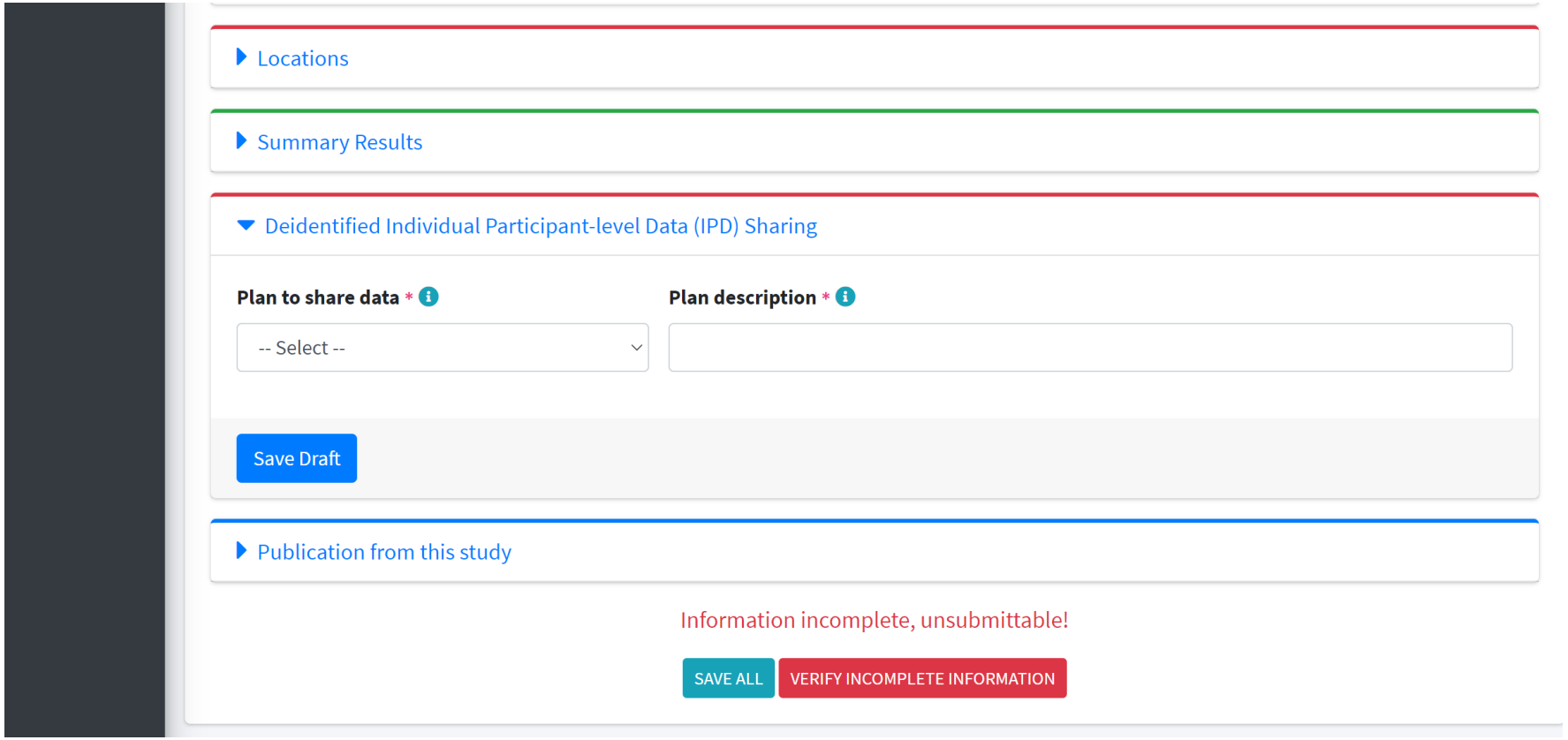
Time point * 

Secondary Outcome 

Outcome Name	Metric/Method of measurement	Time point	Options
No data available in table			

Showing 0 to 0 of 0 entries

Save Draft


Locations
Summary Results
Deidentified Individual Participant-level Data (IPD) Sharing
Plan to share data *
-- Select --
Plan description *
Save Draft
Publication from this study
Information incomplete, unsubmittable!
SAVE ALL
VERIFY INCOMPLETE INFORMATION


Thank You