



FKUI



Central General Hospital

Health Research Ethics Committee FKUI-RSCM

INFORMATION SHEET TO PROSPECTIVE SUBJECTS

The *Informed Assent* form cannot replace the *consent* form signed by the parent or guardian. *Assent* is complementary to *consent* and signifies the child's willingness participate in a study.

[*Informed Assent* Form for _____]

(This informed assent form is intended for children aged 12 - 17 years old who are students of Junior High School / equivalent or Senior High School / equivalent in Jakarta, Surabaya, Yogyakarta and who we invite to participate in the study **Dietary Modulation of Gut Microbiota on Nutritional Status and COVID-19 Infection in Adolescents: Gut-Lung-Axis (DIVINE) (Modulasi Diet Mikrobiota Usus terhadap Status Gizi dan Infeksi COVID-19 pada Remaja: Gut-Lung-Axis)**.

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[Dietary Modulation of Gut Microbiota on Nutritional Status and COVID-19 Infection in
Adolescents: Gut-Lung-Axis (DIVINE) (Dietary Modulation of Gut Microbiota on
Nutritional Status and COVID-19 Infection in Adolescents: Gut-Lung-Axis, Version
02/VI/2022)]

This *Informed Assent* form consists of two parts:

- Information Sheet (which will provide information about the study)
- Certificate of Assent (on this sheet you will sign as assent to participate in this study)

You will be given one copy of this *Informed Assent* Form.

Part I: Information Sheet**Introduction**

My name is _____ and I am a researcher looking at the health benefits of probiotics in adolescents. We want to find out if probiotics **and health education** can help with weight loss in overweight adolescents. In addition, we want to find out if probiotics and **education** can improve immunity to COVID-19, gut **bacteria**, diet quality and intelligence. We also want to know what are the factors that determine adolescent health. We think that this study can provide the answers.

I will provide you with information and will invite you to participate in this study. You can choose whether or not to participate in this study. We have discussed with your parents/guardians about the study and they know that we will also ask for your assent. If you are willing to participate in this study, your parents must also agree to it. However, if you are not willing to participate in this study, you do not need to take part in this study even if your parents agree.

You can discuss everything in this form with your parents, friends, or anyone you feel comfortable with. You can decide whether you want to participate in this study after you have discussed it. You do not have to make a decision immediately.

There will probably be some words you don't understand or things you want me to explain further because you are interested or concerned. Please ask me to stop and I will explain it for you.

Objective

We want to know how probiotic supplementation combined with counselling on healthy eating, physical activity and psychosocial stimulation affects the health of overweight and obese adolescents, especially during the COVID-19 pandemic. This research will relate to changes in the quality of your diet and the composition of bacteria in your gut, which will affect your nutritional and immune status. In addition, we also want to find out what factors determine adolescent health and the cost-effectiveness of probiotics in boosting immunity against COVID-19. We hope that by knowing these things, we can develop disease prevention efforts to keep adolescents healthy.

Selection of research subjects/participants

We conducted this study on children around your age - between 12 and 17 years old - living in Jakarta, Surabaya and Yogyakarta. We are only conducting this study in healthy children who have received the full COVID-19 vaccine (2 vaccines). You must also have an active BPJS (national health insurance) or other health insurance to take part in this study. In addition, you can only participate if you have received permission from your father/mother to participate in the study

Participation is voluntary

You don't have to take part in this study if you don't want to. It is entirely up to you. If you decide not to take part in the study, it's okay and nothing will change. You can still go to school, and everything will be the same as before. If you say "yes" now, you can change your mind later and it's okay.

If things change and we want you to stay in study even if you want to stop, we will talk to you first.

- ***Example questions to test understanding:*** *If you decide not to participate in this study, do you know what your options are? Do you know that you are not obliged to take part in the study if you do not want to? Is there anything you would like to ask?*

I have confirmed with the child and the child understands that participation in this study is voluntary. _____ (initials)

Information about the Tested Drug [Name of Drug: Probiotic with *Bifidobacterium* and/or *Lactobacillus* 10⁹ CFU/day]

The probiotic supplement we will be trialling in this study will contain *Bifidobacterium* and/or *Lactobacillus* 10⁹ CFU/day. These supplements have previously been widely used as general health

support, for example to support digestive system health.

We currently want to test the effect of this probiotic supplement on the health of overweight or obese adolescents and the study is about to enter into phase 3 clinical trials. This trial means that the effect of the supplement on health will be tested on a large number of individuals, including you.

Probiotic supplements have been widely used for various health benefits such as maintaining gastrointestinal function, boosting immunity, and weight loss. The use of probiotic supplements has not been reported to have any adverse effects in healthy children and adolescents (Van den Nieuwboer et al., 2015), making them generally safe for consumption.

Procedure

We will conduct a trial of probiotic supplements by giving probiotic supplements to some children in the study, while other children will receive blank supplements (no probiotics). All children in the study will also receive counselling on healthy eating, physical activity and psychosocial stimulation modules, whether they receive probiotic supplements or blank supplements. Neither you nor the researchers know what type of supplement each of you received until the end of the study.

By doing this, we can determine whether probiotic supplements are truly beneficial for adolescent health without being influenced by our thoughts or expectations regarding the results of this study.

We will interview you about several things related to nutrition and health. In addition, we will take some measurements to determine your nutritional status. We will also take blood, intelligence tests (for Yogyakarta study participants only), and saliva samples. Finally, we will ask you to provide us with a sample of your faeces for us to study. By doing this, we can collect data on your health and what influences it.

If you decide to take part in this study, you will go through two stages of research. In the first stage of the research, there are 4 (four) things that will happen.

1. You will be interviewed to ask: Name, age, sociodemographic information (parents' education, occupation and income, family size, place of residence and ethnic origin), medical history, drug use history, allergy history, COVID-19 vaccine history, dietary intake history and eating habits, physical activity and exercise habits, puberty stage, behavioural and mental disorders and self-confidence, parental and peer support for nutritional behaviour, psychosocial conditions, sleep quality and quality of life. Interviews on food intake history will be conducted on two different days.
2. You will undergo a physical examination by a medical doctor to check your health status.
3. You will undergo nutritional status measurement by a nutritionist which includes body weight weighing, height measurement, upper arm circumference, waist circumference, and hip circumference.
4. You will have 2 tablespoons of blood drawn by a nurse using a needle from a vein in your forearm. Approximately the night before the blood draw, you will be asked to fast, but allowed to drink water as needed. Then on the day of the blood draw, you will be asked to arrive at 6.45am. The blood draw may feel uncomfortable, but the discomfort will disappear quickly. This blood draw is the initial data for laboratory tests on blood condition, immunity to COVID-19, cognitive function, inflammatory factors, and gastrointestinal function.

In the second stage of the research, there will be 12 (twelve) things happening.

1. After conducting interviews, physical examinations, and nutritional status measurements, we will screen subjects according to the inclusion criteria and exclude subjects with exclusion criteria.
2. Furthermore, if you fulfil the criteria, you will be asked to provide us with a saliva sample as well. Your saliva sample will be collected by the nurses. We will use your saliva sample to determine your immune function against COVID-19.
3. We will also ask you to give us a sample of your faeces that you will have to be collected independently at home. We will give you the tools that you can use. We will use this faeces to determine the condition of your digestion.
4. You will also undergo intelligence test **conducted by a psychologist. This test will be done using paper and pencil. You will be asked to open a questionnaire book and start writing the answers on the answer sheet. The questionnaire will present the participant with various and complex visual patterns with one part omitted. You are then asked to find the missing part to complete the pattern from the given answer alternatives. There are five sections (A, B, C, D, and E) to complete and each section consists of twelve patterns to complete. The average time given to complete the whole test is 1 hour.**
5. The study then moves on to phase 2 where those who are overweight and obese are randomised into two groups where one group will receive probiotic supplementation while the other group will receive a blank supplement. Neither you nor the research team know who gets the probiotic supplement and who gets the blank supplement. Both groups will receive counselling on healthy eating, physical activity, and psychosocial stimulation which will be explained by the research team to support the supplementation
6. We will ask you to take probiotics every day for 20 weeks. The probiotics will be given to you through your teachers at school and our staff will deliver the probiotics regularly to your school. In addition, supplements taken on holidays will be delivered monthly to your home.
7. You will also be asked to access counselling modules on healthy eating, physical activity and psychosocial stimulation and complete a questionnaire on your understanding of these modules.
8. During the probiotic consumption period (20 weeks), you will be visited by our staff every 5 weeks (weeks 5, 10, 15, and 20) for an interview regarding your dietary intake, physical activity, medical history, and compliance with taking probiotic supplements. In addition, nutritional status measurements will also be implemented.
9. At the end of weeks 10 and 20, you will have blood and saliva samples taken again according to the procedures described above to assess changes in blood status, immunity to COVID-19, inflammatory factors, cognitive function, and gastrointestinal function during the study process.
10. At the end of week 20, you will again be asked to provide *faecal* samples as per the procedure described above to assess changes in gut microbiota state, inflammation, GI tract integrity, **SCFA, and untargeted fecal metabolomics** at the end of the study.

11. At the end of week 20, you will also undergo another intelligence test to assess changes at the end of the study

12. At the end of week 20, you will also be interviewed again about your dietary intake history and eating habits, physical activity and exercise habits, disease history, behavioural and mental disorders as well as self-confidence, psychosocial conditions, sleep quality and quality of life to assess changes at the end of the study.

Overall, research process will last for 6 months with a supplementation period of 5 months or 20 weeks and there will be several interviews that you will be involved in. The interview process will take about 1 to 2 hours. Meanwhile, the physical examination, nutritional status measurement, intelligence level measurement, and sample collection (blood, saliva and faeces) will take approximately 3 hours.

You can ask me to stop and re-explain at any time and I will explain the process again. **In order for you to better understand the research process, we present the research procedure and schedule in a table in the appendix of this information sheet.**

- **Example questions to test understanding:** *Can you say how many days you will be involved in the research process? Can you name the stages of the study that you will be involved in? How much blood will be drawn from your vein, with a needle and in which part of your body? Do you have any other questions? Would you like me to explain the procedure again?*

I have asked the child and the child understands the procedure _____ (initials)

Risk

Interview, physical examination, nutritional status measurement, intelligence measurement, saliva sampling, faeces sampling and blood collection are all safe procedures. You may feel uncomfortable after the blood draw. However, your nurse will draw blood according to standard procedures with care to minimise the discomfort. There is no cause for concern. Also, the probiotic supplement you will be taking is safe and has no significant side effects. However, if anything unusual happens to you we need to know about it, and you should contact us anytime with your concerns/questions.

Inconvenience

There are a few things I want you to know.

The process of drawing blood may cause some pain when the needle hits your hand. The skin around the injection site may become bluish green for a while, but this should go away within a few days. If the pain persists after a few days, or if your skin remains bluish green or becomes swollen, tell your parents or me. Also let us know if you feel bad or uncomfortable.

Maybe you don't want to come in for blood tests or to have your physical and nutritional status checked. It is important that you still make the effort to come. This will not take long. You will miss about one to two hours of school on each screening day during the study - and we will notify your teacher so that your teacher knows about it too).

- ***Sample questions to test understanding:*** *Do you understand that there are possible side effects of drawing blood? Do you understand what to do if these side effects occur? Do you understand that you will lose some class time during this study? Do you have any other questions?*

I have asked the child and the child understands the risks and inconveniences that may occur _____(initials)

Benefits

This study can help us find out if probiotic supplements are beneficial for adolescent health during the COVID-19 pandemic so that we can develop measures to keep adolescents healthy. There are several good things you will receive if you participate in this study. You will get a physical examination from a doctor, intelligence measurements, nutritional status measurements and improvements, and blood work results so that if you are sick, you will know about it quickly, which is important. In addition, you will also learn more about healthy eating, healthy physical activity patterns and psychosocial stimulation which will be useful for you.

I have asked the child and the child understands the benefits _____(initials)

Reimbursement

Since you have taken the time to participate in this study and lost some class time, we will give your parents IDR 50,000 **per visit to the data collection site** (at the beginning, middle, and end of the study) to make up for the lost time.

- ***Example questions to test understanding:*** *Can you tell me if you have correctly understood the benefits of taking part in this study? Did you know that this study will reimburse you for lost time, and how will be reimbursed? Do you have any other questions?*

Confidentiality

We will not tell anyone else that you are taking part in this study and we will not share information about you with anyone who is not involved in the study. After the study is finished, you and your parents will be told the results of the tests we have carried out.

The information we receive about you during this study will be stored and no one else will be able to see it except the research team. All information about you will be coded with a number and will not have your name on it. Only the research team will know your number and we will lock the information with a padlock and key. It will not be shared with anyone except representatives of the sponsor and the Ethics Committee

- ***Example questions to test understanding:*** *Do you understand the procedures we will use to keep all the information the research team collects about you confidential? Do you have any other questions?*

Compensation

If you become ill while taking part in this study, we will look after you. We have given your parents additional information on what to do if you become ill during this study. **If there are any side effects from the probiotic supplement, you will be treated. We will advise you to go to the nearest health centre/clinic that works with your BPJS/other health insurance.**

Sharing of research results

When we are done with this research, I will give you a paper with the results of this research. You and your parents can ask questions about the results. After that we will tell more people, such as other researchers, about what we have found. We will do this by writing and sharing reports about the research and by attending meetings with people who are interested in our work.

Right to refuse or withdraw

You don't have to take part in this research. No one will scold you or be disappointed with you if you decide not to. This is entirely your choice. You can think about it first and let us know later. You can say "yes" now and it will be okay if you change your mind later.

Who to contact

You can ask questions now or later. You can also ask questions to the doctors who examined you, the nutritionist who measured your nutritional status, the nurse who took your blood, and the staff who interviewed you. I have written down the numbers and addresses that you can contact, or if you are in the neighbourhood, you can come and see us. It is not a problem if you want to talk about this to other people such as your teacher, doctor or other family members.

If you decide to participate in this study, I will give you one copy of this paper for you to keep for yourself. You can ask your parents to keep it for you if you want.

- **Sample questions to test understanding:** *Do you know that you are not obliged to take part in this research if you don't want to? Do you know that you can say "No" if you want to?*

Did you know that you can ask me questions later if you want to? Did you know that I have given you information on who you can contact if you want to know more about this research?

Section 2: Certificate of Assent

I understand that this study aims to determine the benefits of probiotic supplements combined with counselling on healthy eating, physical activity and psychosocial stimulation on adolescent health during the COVID-19 pandemic. I understand that I will be interviewed, my health checked, have my nutritional status measured, have my intelligence measured, have my faeces sampled, have my saliva sampled, and have a blood sample taken with a needle through my forearm. I also understand that I will be asked to take probiotic supplements daily for 20 weeks and counselled on healthy eating, physical activity and psychosocial stimulation, and understand what the benefits and risks are for me.

I have read this information (or it has been read to me). I have received answers to my questions, and I understand that I can ask additional questions later.

I agree to take part in this study.

OR

I do not agree to take part in this study and I have not signed the *assent* form below____(child's initials)

Only if the child gives his/her assent:

Child's name: _____

Child's signature: _____

Date_____
 date/month/year

If the child subject is illiterate:

A non-illiterate witness must sign (if possible, this person should be chosen by the research subject/participant, not his/her parents, and should not have any relationship with the research team). Illiterate research subjects/participants must also have their fingerprints stamped.


I have witnessed the accurate reading of the *assent* form to the child, and that the child has been given the opportunity to ask questions. I confirm that the child has given her consent freely.

Name of witness (not parent _____) AND

Fingerprint of research subject

Signature _____

**Date _____
date/month/year**



To be signed by the researcher:

I have carefully read or witnessed the accurate reading of the *assent* form to the potential research subject/participant, and the child has been given the opportunity to ask questions. I confirm that the child has freely given *assent*.

Name of researcher _____

Researcher's signature _____

Date _____
date/month/year

Statement by *researcher/consent* seeker

I have accurately read the information sheet to the potential subject/participant, and ensured to the best of my ability that the child understands that the following will be done:

1. Interview
2. Physical examination
3. Nutritional status measurement
4. Intelligence measurement
5. Blood draw
6. Saliva collection
7. Faeces collection
8. Take probiotics
9. Counselling on healthy diet, physical activity, and psychosocial stimulation

I confirm that the child has been given the opportunity to ask questions about the study, and that all questions have been answered correctly to the best of my ability. I confirm that there was no coercion in the giving of *assent*, and *that assent* was given freely and voluntarily.

One copy of this *assent* form has been given to the subject/participant.

Name of researcher/ assent requestor _____

Signature of researcher/assent requestor _____

Date _____
date/month/year

Copy given to _____ (initialed by researcher/assistant)

Parents/Guardians have signed *informed consent* ____ Yes ____ No
____ (initialed by researcher/assistant)

Appendix 1 Appendix 1 Research Procedures

Table 1 Research procedure

Activities	Stage/Week						
	Screening (0)	Initial (0)	1	5	Centre (10)	15	End (20)
Screening							
Tracking schools and research subjects	x						
Explanation of the study and <i>Informed consent</i>	x						
Stage 1							
Subject interview		x					
Physical examination		x					
Measurement of nutritional status (BW, TB, upper arm circumference, waist circumference, and hip circumference)		x		x	x	x	x
Food consumption interview (1×24 hour <i>food recall</i> and FFQ)		x		x	x	x	x
Physical activity interview		x		x	x	x	x
Blood draw		x			x		x
Stage 2							
Explanation of stage 2 research		x					
Physical examination		x					
Measurement of cognitive ability		x					x
Measurement of nutritional status (BW, TB, upper arm circumference, waist circumference, and hip circumference)		x		x	x	x	x
Interview on food consumption (<i>food recall</i> 1×24 hours)		x		x	x	x	x
Physical activity interview		x		x	x	x	x
Saliva sampling		x			x		x
Collection of faecal samples		x					x
Supplementation			x	x	x	x	x
Access to educational modules (diet, physical activity, and psychosocial stimulation)			x	x	x	x	x