**Informed Consent**

**Getting Approval After Explanation:**

**Essential information for potential research participants**

**(WHO-CIOMS 2016)**

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| --- | --- | --- |
| Research Title | : | The Effect of Lactoferrin in High Calorie Formula on IL-6 and IL10 in Children With Failure to Thrive and Infection ( Interleukin ) |
| Type of Research | : | Intervention |
| Researcher’s Name | : | Nur Aisiyah Widjaja |
| Researcher’s Address | : | Villa Kalijudan Indah N-33 Surabaya |
| Research Location | : | Poli Nutrisi Anak RS Husada Utama Surabaya |

Before seeking an individual's consent to participate in the study, the researcher must provide the following information, in language or other forms of communication that the individual can understand (See Guideline 9):

1. Research objectives, methods, procedures to be performed by researchers and participants, and an explanation of how the study differs from routine medical care (Guideline 9);

*Failure to grow is a type of malnutrition disorder in children whose incidence rate is still high in Indonesia. Children who experience growth faltering will be at risk of stunting1. Indonesia is one of the countries with the highest incidence of stunting and wasting in the world, fourth for stunting prevalence, which is 30.8% (Riskesdas, 2018). This number is still far from the WHO standard, which is below 20%. Stunting and wasting illustrate how health services in a country (Unicef, 2020). Growth faltering can trigger a decline in the child's development which will affect cognitive function, especially his/her IQ. In addition, growth faltering will have further health impacts, such as children easily getting sick due to infections, obesity and even death.*

*This study aimed to determine the benefits of high-calorie formula intervention on IL-6 and IL-10 as the pro- and anti-inflammatory markers in children with failure to thrive and infection as well as on their growth profile.*

*This study will be conducted for approximately 12 weeks (3 months / 90 days), the researcher monitors the growth of the subjects twice in the first month, that is on the 15th and 30th day of the intervention. Furthermore, monitoring is carried out monthly (on the 60th and 90th day) including measurement of weight, height, head circumference, evaluation of administration and compliance, and tolerance of subjects in receiving interventions. Monitoring of administration is carried out when the patient comes in control and by telephone by the researcher. On the 0th day (before the intervention) researchers performed a blood draw for a complete blood test, IL-6 and IL-10 levels. The second blood draw is carried out after the intervention (90st day).*

1. That individuals are invited to participate in this research, reasons for considering appropriate individuals for the research, and that participation is voluntary (Guideline 9);

*Your son/daughter is asked to participate as a subject because they experience growth faltering with infection.*

*If you agree to participate in this research, you are required to sign and write the date on the informed consent sheet to participate as a respondent in this study.*

1. That the individual is free to refuse to participate and free to withdraw from the study at any time without penalty or loss of the reward to which he/she is entitled (Guideline 9);

*If you decide not to participate then this will not affect your son/daughter's medical care. Your participation in this research is voluntary. You have the full right to resign or declare void to participate at any time.*

1. The expected length of time of individual participation (including the number and length of visits to the research center and the amount of time required) and the possibility of termination of the research or individual participation in it;

*The research is scheduled to be carried out on October 4, 2021, when the ethical clearance letter has been received, until June 2022.*

*The nutrition intervention will be carried out for approximately 3 months (12 weeks / 90 days), where every month the researcher will come to you to give high-calorie milk to be consumed for the next 1 month based on the needs of your son / daughter. Before the study start, please allow us to do a complete blood test and initial IL6 and IL-10 levels by taking venous blood conducted by laboratory officers of Husada Utama Hospital. Furthermore, in the 3rd month or 91st day, your son/daughter will be subjected to a complete blood test IL6 and IL-10 levels for evaluation of growth markers and immune response markers after the nutritional intervention. The examination does not cause side effects.*

1. Whether money or other forms of material goods will be given in exchange for individual participation. If so, the type and amount, and that the time spent on research and other inconveniences resulting from learning participation will be appropriately compensated, monetary or non-monetary (Guideline 13);

*By participating in this study, you can play an important role in proving the benefits of lactoferrin addition in high-calorie formula milk to children with growth faltering, to achieve growth like other healthy children. Thus, indirectly you participate in reducing stunting rates in Indonesia and creating a healthy and smart young generation.*

*For this participation, your son/daughter will be given a high-calorie formula to be consumed during the first 14 days of 4 cans. Milk is given as much as 400 ml in a day, according to the feeding schedule (feeding rule) that we have written. It is expected that on the 15th day of control to get milk for the next 14 days. Henceforth, your child will receive 8 cans of milk for 30 days consumption. If there are complaints (child nausea, vomiting, abdominal pain, do not want to drink milk), you can contact dr. Hamida (08187851384154), dr. Marisa (08121420042), dr. Azarina (081259406205) and dr. Putri (085236042046). The amount will be calculated according to the needs of your son/daughter.*

1. That, upon completion of the study, participants will be informed of the results of the study in general, if they desire it;

*The results of the complete blood test and IGF-1 levels before and after treatment, as well as reports of weight gain, height, and head circumference during the study will be given to you at the end of the study.*

1. That each participant during or after the study or collection of their biological and health-related data will be subjected to life-saving information and data and other important clinical data on relevant important health issues (see also Guideline 11);

*All data or information from blood draws related to the complete blood test and IGF-1 levels before and after treatment, as well as physical examination (weight/height/head circumference) will be given to you as an evaluation of your son/daughter's growth.*

1. Unsolicited/unexpected findings will be disclosed if they occur (Guideline 11);

*Additional examination results obtained from routine examinations will be submitted to you as the parent / guardian of the research subject.*

1. That participants have the right to access their relevant clinical data obtained during the study regarding the request (unless the research ethics committee has approved it temporarily or permanently, the data should not be disclosed. In which case the participant should be told, and given, the reasons);

*You as the subject's parent/guardian have the right to access your data.*

1. Pain and discomfort resulting from experimental interventions, known risks and dangers, to individuals (or others) associated with participation in the study. Includes risks to the health or well-being of direct relatives of participants (Guideline 4);

*As a subject in this study, your son/daughter will be given an injection for a blood draw. This procedure will cause pain in the injection and blood draw area. In some cases this process can also cause slight bruising or swelling. So far, there have never been any serious side effects in oral administration of lactoferrin in infants and children. At the end of the session, you will be asked to fill out a questionnaire. The process of filling out this questionnaire will take approximately 15 minutes.*

1. Potential clinical benefits, if any, for participating in the study (Guidelines 4 and 9);

*By participating in this study, you participate in improving the nutrition of your son/daughter as well as reducing the incidence of stunting, and preventing deaths due to infection and stunting. Thus, you indirectly lower the risk of obesity, diabetes type 2 and cardiovascular disease of your own child.*

1. The expected benefits of research to people or society, or contributions to scientific knowledge (Guideline 1);

*This research is expected to be able to contribute reducing the incidence of stunting in the community and providing input on appropriate interventions for policy making in the field of child health.*

1. How the transition to health care after the study is structured and to what extent they will be able to receive beneficial post-trial study interventions and whether they will be expected to pay for them (Guidelines 6 and 9);

*This research is quasi-experimental (pre- and post-designed). Blood sampling was carried out by laboratory officers of Husada Utama Hospital. Furthermore, blood from the Husada Utama laboratory was transferred to ITD using a cooling box by a designated officer. The payment is borned by the researcher.*

1. Risk of receiving unregistered interventions if they receive continued access to study interventions prior to regulatory approval (Guideline 6);

*There is no such intervention.*

1. Interventions or alternative treatments currently available;

*Provision of ready to use therapeutic food (RUTF) in high-calorie biscuit (according to guidelines for preventing malnutrition management in toddlers in 2019).*

*Provision of the WHO F100 formula.*

1. New information that may be revealed, either from the research itself or other sources (Guideline 9);

*Research on this topic is still limited, especially in Indonesia. The results of this study have a novelty in the field of medicine. At the same time, it can be a reference for policy making related to the handling and prevention of stunting in children in Indonesia.*

1. Provisions to be made ensuring to respect for participant privacy, and for the confidentiality of records that may identify participants (Guidelines 11 and 22);

*All information is confidential. The subject is in anonymous form (code number 1-80).*

1. Limitations, legal or otherwise, to a researcher's ability to maintain secure confidentiality, and the possible consequences of a breach of confidentiality (Guidelines 12 and 22);

*All data will be kept confidential.*

1. Research sponsors, institutional affiliations of researchers, the nature and sources of funding for research, and, if any, conflicts of interest of researchers, research institutes and research ethics committees and how these conflicts will occur are managed (Guidelines 9 and 25);

*There is no conflict of interest. Research sponsor, PT. Sarihusada Generasi Mahardhika as a provider of high-calorie formula milk or PKMK.*

1. Whether the researcher is only a researcher, or other than the researcher, is also a participating doctor (Guideline 9);

*Only as researcher.*

1. Clarity of the researchers' responsiblity level to provide care for participants' health needs during and after the study (Guideline 6);

*This procedure will cause pain in the injection / blood draw area. In some cases, this process can also cause slight bruising or swelling. So far, there have never been any serious side effects on giving high-calorie milk to babies and children. If there is a hematoma at the blood collection site, the researcher and the hospital where the study is located will carry out management in accordance with the applicable Clinical Practice Guidelines.*

1. That treatment and rehabilitation will be provided free of charge for a particular type of research-related injury or for complications related to the study, the nature and duration of such treatment, the name of the medical service or the organization that will provide the treatment. In addition, whether there is uncertainty regarding the funding of such care (Guideline 14);

*There is no intervention in this study.*

1. In what way, and by what organization, the participant or the participant's family or dependent persons will be compensated for disability or death as a result of the injury (or it should be clear that there is no plan to provide such compensation) (Guideline 14) ;

*As there is no intervention, there is no compensation.*

1. Is there any, in the country where potential participants are invited to participate in the study, the right of compensation is legally guaranteed;

*There is.*

1. That the research ethics committee has approved the research protocol (Guideline 23);

*Yes, subjects can contact the Health Research Ethics Committee of Faculty of Medicine of Airlangga University.*

1. That they will be informed in case of violation of protocol and how their safety and well-being will be protected in such cases (Guideline 23).

*Yes, the report will be submitted to the Health Research Ethics Committee of Faculty of Medicine of Airlangga University.*

In certain cases, before seeking the individual's consent to participate in the study, the researcher must provide the following information, in language or other forms of communication that the individual can understand:

1. For controlled experiments, an explanation of the features of the study design (e.g. randomization, or double blind), that participants will not be notified of the assigned treatment until the study is complete and the blind has been opened;
2. Whether all important information is disclosed and, if not, that they are required to agree to receive incomplete information and the complete information will be provided before the results of the study are analyzed and participants are given the possibility to withdraw their data collected under this study (Guideline 10);
3. Policy regarding to the use of genetic test results and family genetic information, and precautions to prevent disclosure of participants' genetic test results to immediate family or to others (e.g. insurance companies or employers) without participant consent (Guideline 11);
4. The possibility of research using, directly or secondary, medical records of participants and biological specimens taken in clinical care;
5. For the collection, storage and use of biological materials and health-related data, extensive informed consent will be obtained, which must determine: the purpose of the biobank, the conditions and duration of storage; rules of access to the biobank; how donors can contact the custodian of the biobank and can stay informed about future uses; the use of foreseeable material, regardless of studies already completely defined or extended to a whole or partially undefined number; the purpose for which such use is intended, whether for research, basis or application, or also for commercial purposes, and whether the participant will receive monetary or other benefits from the development of commercial products developed from his biological specimens; possible unsolicited findings and how they are handled; safeguards to be taken to protect their confidentiality as well as limitations, whether it is planned that biological specimens collected in the study will be destroyed at their conclusions, and if not, details about their storage (where, how, for how long , and the initial disposition) and the possibility of future use, that the participant has the right to decide on such future use, refuse storage, and destroy the stored material (Guidelines 11 and 12);
6. When women in childbearing age participate in health-related research, information about possible risks, if they become pregnant during the study, for themselves (including future fertility), their pregnancy, their fetuses, and their future offspring; and guaranteed access to pregnancy tests, effective and safe contraceptive methods, legal abortions before exposure to potential teratogenic or mutagenic interventions. When effective contraception and/or safe abortion is not available and alternative study sites are not feasible, women should be informed about:
   * Risk of unwanted pregnancy;
   * Legal basis for performing an abortion;
   * Reducing harm from unsafe abortions and subsequent complications;
   * If the pregnancy is continued/not terminated, there is a follow-up guarantee for their own and the baby and child's health, and information about the difficulty of determining the cause if there is a case of fetal or infant abnormalities (Guidelines 18 and 19);
7. When it comes to pregnant and lactating women, the risks of participation in health-related research for themselves, their pregnancies, their fetuses, and their future offspring, what has been done to maximize individual profit potential and minimize risk, evidence regarding risks can be unknown or controversial, and it is often difficult to determine the cause of cases of fetal or infant abnormalities (Guidelines 4 and 19);
8. When it comes to disaster victims who are mostly under pressure, the difference between research and humanitarian assistance (Guideline 20); and
9. When research is conducted in an online environment and uses online or digital tools that may involve vulnerable groups, there is information about privacy and security controls to be used to protect their data; limitations of the measures used and the risks that may exist despite security (Guideline 22).

INFORMED CONSENT

RESEARCH APPROVAL SHEET

I, who sign this following sheet:

Name : .................................................................................

Age : .................................................................................

Parent / guardian of : .................................................................................

Child’s age : ……………………………………………………

Address : .................................................................................

Phone / Email : .................................................................................

states that :

1. I have been briefed on the Research entitled " The Effect of Lactoferrin in High Calorie Formula on IL-6 and IL10 in Children With Failure to Thrive and Infection (Interleukin)" (the "**Research Team**") and have been given the opportunity to raise questions related to this Research.
2. I understand that breast milk is the best and this study is not intended to influence and hinder my decision to breastfeed.
3. I understand that my child has a medical condition that fits the criteria of the subject of this study.
4. I understand my obligation to follow and carry out the Research protocols that have been explained to me, including the anthropometric measurements and blood draws (for complete blood measurements, IL-6 and IL-10 levels) before the start of FSMP (*Food for Special Medical Purposes*) milk feeding and the 90th day after FSMP milk administration. In the event of a violation of the protocol that I committed and/or the consequences related to the violation, I will release the Researcher and/or the manufacturer whose product is used in the research from any claim and/or request for compensation or costs of any kind either now or in the future.
5. I understand that my participation in this Research is voluntary and I may withdraw my participation from this Research at any time.
6. I give **CONSENT** to take part in the Research as a research subject.

Thus, I made this Letter of Consent with full awareness and without coercion from any party.

Statement maker Witness,

(.............................................) (……………………………)