Ethical Protocol in Health-related Research Involving Human Subjects

Please fill out this following form with short answers and tick (X/V) in the box or circle one of the answers which would best describe this research.

P: Protocol Serial Number CIOMS 2016 – Appendix 1;

S: Standard Ethics (WHO-2011 and KEPPKN Guidelines 2017);

C: Check List

G: CIOMS Guidelines 2016

IC: CIOMS 2016 – Appendix 2

Contents:

1. Title of study (p-protocol number 1)\*
2. Summary of the research proposal (p-protocol number 2)
3. Potential ethical issues
4. Summary of references
5. Field condition
6. Research design
7. Sampling
8. Intervention
9. Results monitoring
10. Termination of study and the justifications
11. Adverse events and complications (sentinel events)
12. Management of complications
13. Benefits
14. Guarantee on the continuity of benefits
15. Informed consent
16. Guardians
17. Incentives
18. Confidentiality
19. Analysis
20. Security monitoring
21. Conflict of interest
22. Social benefits
23. Rights to data
24. Publication
25. Funding
26. Ethical commitment
27. References
28. Appendix
29. Curriculum Vitae of Main Researcher
30. Sample form of case report

Ethical Protocol in Health-related Research Involving Human Subjects

Please fill out this following form with short answers and tick (X/V) in the box or circle one of the answers which would best describe this research.

P: Protocol Serial Number CIOMS 2016 – Appendix 1;

S: Standard Ethics (WHO-2011 and KEPPKN Guidelines 2017);

C: Check List

G: CIOMS Guidelines 2016

IC: CIOMS 2016 – Appendix 2

1. Title of Study (p-protocol number 1)\*

The Effect of High Calorie Formula on Weight, Height Increment, IGF-1 and TLC in Growth Faltering Children

1. Place of research:

Pediatric clinic in Husada Utama Hospital

1. Time of research:

September 2021 – September 2022

|  |  |  |
| --- | --- | --- |
|  | Yes | No |
| 3. Is this a multi-center research? |  | √ |
| 4. If yes, is an ethics approval from other centers/institutions involved already obtained? (attach them if yes) |  |  |

Identification (p10)

1. Researchers

(Please attach the main researcher’s CV)

Main researcher : Dr. dr. Nur Aisiyah Widjaja, Sp.A(K)

Institution : KSM Ilmu Kesehan Anak – FK Unair

1. Fellow researcher : Dr. dr. Roedi Irawan, M.Kes., Sp.A(K)

Institution : Department of Pediatrics – Faculty of Medicine, Universitas Airlangga

Fellow researcher : Dr. Meta Herdiana Hanindita, dr., Sp.A(K)

Institution : Department of Pediatrics – Faculty of Medicine, Universitas Airlangga

Fellow researcher : dr. Azariana Satjadibrata

Institution : Department of Pediatrics – Faculty of Medicine, Universitas Airlangga Fellow researcher : dr. Putri Permatasari

Institution : Department of Pediatrics – Faculty of Medicine, Universitas Airlangga Fellow researcher : dr. Hamidah

Institution : Department of Pediatrics – Faculty of Medicine, Universitas Airlangga Fellow researcher : dr. Marina

Institution : Department of Child Health (Pediatrics) – Faculty of Medicine, Universitas Airlangga

3. Sponsors (p9)

Name : Sarihusada Generasi Mahardika

Address : Jalan Kusumanegara No.173, Yogyakarta, lndonesia

Summary of research proposal (p-protocol number 2)

1. Summary of the research in 200-300 words (in lay/non-medical language)

Failure to thrive or stunting is still prevalent in Indonesia. Stunting children are susceptible to infections, as well as decreasing intellectual abilities due to chronic malnutrition. Children with failure to thrive who also has infection are suspected to experience an imbalance in their immune system, in which the level of IL-6 as the pro-inflammatory cytokines are high, while the level of IL-10 as the anti-inflammatory cytokines are low, lactoferrin is proven to be effective in treating infections and is safe to consume even for babies. The administration of lactoferrin is expected to improve the inflammation response and growth profile in failure to thrive children with infection.

2. Justification for the research (p3). Write down the reason this research is necessary to conduct, also the benefits for the people in the region of this research (Country, region, local) – Standard 2/A (Fair)

This research is necessary to decrease the mortality caused by infections especially in subjects with chronic malnutrition, as well as to treat children with failure to thrive.

1. Potential Ethical Issues

1. Researcher’s opinion on the potential ethical issues of this research, and how to manage them (p4) – according to the 7 principles of ethical standards (S) and G

A potential ethical issue in this research is stunting children with infection (UTI and TB) who are included in the vulnerable population. Because this research would be needing blood sample, the risk of the procedure includes some pain or hematoma.

1. Summary of References

1. Summary of previous studies according the research topic, including unpublished studies known by the researches and sponsor, and information on published studies, including studies on animals, if any. Maximum of 1 page (p5) – G 4

The use of high-calorie formula milk in Indonesia is regulated by The Decree of Health Ministry Number 29 Year 2019 on the use of high-calorie milk in children with malnutrition caused by a disease. The administration of high-calorie milk is prioritized for children in need of special means for survival and affects the incident of stunting, which include children with the risk of failure to thrive in under 2 years old, stunted or severely stunted, low birth weight baby, and severely premature baby.1

The use of high-calorie milk is necessary in order to catch up with the late growth due to insufficient calorie intake to maintain optimal growth. In failure to thrive children with infection, high-calorie milk is necessary for 2 things: combating infection, as well as maintaining optimal growth, but with lower volume.2 High-calorie formula milk is preferred; not only because the contents of micronutrient, vitamin, and macronutrient it provides, but also because it tastes better. In improving severely stunted children (normal albumin level), they can consume 4200 kcal/kg/day.3 In a case report of patient with failure to thrive, the administration of high-calorie milk (100 kcal, 2.6 g of protein per 100 mL) 50-100 kcal/kg/day, is effective in increasing the nutrients and energy intake in children with failure to thrive in PICU, with no side effects.4 Meanwhile, the administration of nutrition using the WHO formula (F100) as a nutrition intervention has several problems, such as:

1. Needs to be made once every two days by a dietician, which might be a limited resource in some places (made once every two days with an expiry date because the milk powder has already been mixed with oil and sugar, increasing its risk of contamination).
2. Sometimes parents who make their own F100 would refuse to follow the appropriate guideline and omit the oil because they assume the oil in F100 would make their kid cough. This affects the acceptability and results.
3. Mineral mix is often unavailable in primary care facilities, causing the micronutrient (vitamin and mineral) is not fulfilled.
4. Field Condition
5. Briefly describe the location of research (p8) see G-2

*This research is conducted in the pediatric clinic in Husada Utama Hospital. In order to find the subjects, researchers will coordinate with paramedics (nurses, lab technicians) in the hospital. The measurements of weight, height, and head circumference would be done in the clinic. Blood sample would be taken in the laboratory. A simple presentation and person-to-person approach from the researcher would be done in the clinic.*

1. Information on the availability of the appropriate facilities for security and precision of the research

*Researchers would bring their own scales to measure weight, infantometer, head circumference meter, and food models (recall diet). Blood sampling would be done by lab techinicians in a closed room in order to not scare the other subjects.*

1. Information on the relevant demography/epidemiology regarding the region of the research

*Provide data on demography of the management of failure to thrive children with infection.*

1. Research Design
2. Research objective, hypothesis, research question, assumptions and research variable (p11).

* *To determine the total lymphocyte count and IGF-1 level in failure to thrive children with infection, before and after receiving intervention of lactoferrin in high-calorie formula milk.*
* *To determine the effect of administering lactoferrin in high-calorie formula milk in the increase of length/height in failure to thrive children in infection in the first month (day 30), second month (day 60), and third month (day 90).*

1. Detailed description about the research (p12).

*This research is a quasi-experimental (pre- and post- design) which studies the effect of lactoferrin in high-calorie formula milk using the parameter of total lymphocyte count and IGF-1. Before the administration of high-calorie milk, subjects would be measured for their weight, length/height, head circumference, and blood sampling to measure total lymphocyte count and level of IGF-1. During the research, subjects would be given SGM Ananda Optigrow® (Sari Husada, Danone) for 3 months. The amount of milk given is 400 mL in subjects aged 1-5. Anthropometric measurements and determining the parents’ adherence would be done each month. After 3 months (90 days) of administering high-calorie milk, another anthropometric measurements and blood sampling would be done to determine the total lymphocyte count and IGF-1 post-intervention.*

1. If the research is a clinical trial, the description should include whether the treatment group is determined at random (including the randomization method), and whether it is blinded or opened. (If not a clinical trial, write down: irrelevant) (p12)
2. Sampling
3. The number of subjects needed in accordance to the research objectives and the determining method using statistics (p13).

*Samples are counted using the following formula, and this research will use a total of 80 samples (pre- and post-, total 160).*



1. Participant or subject criteria and justifications for include/exclude. (Guideline 3) (p12)

Inclusion criteria: Children aged 1-5 with failure to thrive and infection

Exclusion criteria:

* *Not diagnosed with the following condition: allergy, autoimmune, congenital disorders or chronic illness*
* *Resign from the observation period*
* *Not consuming steroid, antibiotic, or hormone*

1. Sampling vulnerable population: the justification for involving children or adults who are not capable of giving consent after being informed, or vulnerable population, as well as the steps on minimizing risks (Guidelines 15, 16, and 17) (p15)

*No known risk in using high-calorie milk in babies and children*

1. Intervention

(The use of secondary data, qualitative, write down irrelevant and move forward to benefits)

1. Description and explanation on all interventions (treatment administration method, including the route of administration, dosing, dose interval, and treatment duration of products used (investigation and comparator (p17)).

*Before the intervention, blood samples of 1 cc would be collected by the laboratory technicians. The sampling would be repeated after the intervention is finished (day 91). During the period of research, subjects would be given 400 mL/day of SGM Ananda Optigrow® (Sari Husada, Danone) for 3 months. Anthropometric measurements and determining the parents’ adherence would be done each month. After 3 months (90 days) of administering high-calorie milk, another anthropometric measurements and blood sampling would be done to determine the total lymphocyte count and IGF-1 post-intervention.*

*SGM Ananda Optigrow is chosen because*

1. Planning and justification to move forward or terminate the standard treatment during the research (p4 and 5) (p18)
2. Possible or allowed other treatments to be administered, or contraindicated, during the research (p6 (p19)
3. Clinical test or laboratory or other tests (p20)
4. Result Monitoring

*1. Samples of standardized case report forms, methods of recording therapeutic response (description and evaluation of methods and measurements frequency), follow-up procedures, and, where possible, measures proposed to determine the level of compliance of subjects receiving treatment (see appendix) (p17).*

*Data is recorded in the research CRF (case report form). If parental disobedience is found in providing therapy according to the recommended dose, a record is made in the CRF and education is carried out so that parents can comply with the recommended dose/amount of milk to be given.*

1. **Research Discontinuation and Reasons**
2. Rules or criteria for when a subject can be discontinued from research or clinical trials, or, in the case of multi-center studies, when a center/institution can be deactivated, and when research can be discontinued (no longer continued) (p22)

If on administration, there is nausea/vomiting or the subject refuses to give high-calorie milk.

1. **Adverse Events and Complications (Unexpected Events)**

1. Methods of recording and reporting adverse events or reactions, and requirements for handling complications (Guidelines 4 and 23) (p.23).

Side effects (diarrhea, nausea, vomiting) were recorded and reported by parents to the researcher by telephone or text message.

The subject was confirmed to have consumed cow's milk before, so the risk of allergy to cow's milk protein could be avoided.

2. Known risks of adverse events, including risks associated with each planned intervention, and associated with the drug, vaccine, or procedure being tested (Guideline 4) (p24)

There is no risk, the selected subject is confirmed not to have a cow's milk allergy or has consumed formula milk before

1. **Management of Complications (p27)**

*Proposed answers (TBC by dr. Nuril): Any complication is* recorded and reported by parents to the researcher by telephone or text message starting from any mild side effect that happens (as mentioned in part J) and will be manage accordingly

1. **Benefits**

*1. Personal benefits of research for the subject and for others (Guideline 4) (p25)*

*Overcoming stunting and overcoming inflammation due to infection.*

*2. Benefits of research to the population, including new knowledge that research may generate (Guidelines 1 and 4) (p26)*

*This research can be a reference for therapy and management of stunting in children.*

1. **Continuity of Benefits Guarantee (p28)**

*Proposed answer: children involved in this study can later be given the same treatment, i.e. given the FSMP milk by the city health office. (TBC by Dr. Nuri)*

1. **Informed Consent**

*1. Proposed means of obtaining informed consent and planned procedures for communicating subject information, including name and position of guardian for those who cannot provide it. (Guideline 9) (p30 research to candidates)*

*Direct explanation to parents of prospective subjects at the outpatient clinic of Husada Utama Hospital when bringing their child to a doctor's visit.*

*2. Especially for pregnant women: there is a plan to monitor maternal health and child health in the short and long term (Guideline 19) (p29)*

*Irrelevant*

1. **Guardian**

*1. There is a legal guardian if the prospective subject cannot give informed consent (Guidelines 16 and 17).*

*Parents/Guardians act as parties who provide informed consent*

*2. There is a parent or guardian who has the right if the child understands about informed consent but is not old enough (Guidelines 16 and 17)*

*Irrelevant*

1. **Persuasion**

*1. Description of the Persuasion or incentive to the prospective subject to participate, such as money, gifts, free services, or others (p32)*

*Subjects will receive the FSMP milk to be consumed during the study (3 months or 90 days). The amount of FSMP milk given in the first 14 days was 4 cans, given as much as 400 ml/day. On the second 14th day, another 4 cans were given. After the 29th day, 8 cans of FSMP milk were given for consumption for 1 month.*

*2. Plans and procedures, and the person responsible for informing the participants of the harm or benefit, or about other research on the same topic, which may affect the subject's continued involvement in the research (Guideline 9) (p33)*

*Researchers exchanged contacts with parents. So that when side effects occur (nausea, vomiting, diarrhea) researchers can quickly approach the subject.*

*3. Planning to inform research results to subjects or participants (p34)*

*After the laboratory results come out, the researcher will provide laboratory results and anthropometric results (as growth indicators) to the subject's parents.*

1. **Confidentiality**
2. *The recruitment process (eg through advertising), as well as steps to maintain privacy and confidentiality during recruitment (Guideline 3) (p16)*

*Presentation on this research and its benefits.*

*Recording is done using the CRF that has been provided, which is then stored in a special drawer that is locked specifically for research in the Division of Nutrition and Metabolic Diseases (NMD) in Child Health Department up to 5 years. Access to data can only be done by researchers. The drawer keys are held by the secretary of the Division of Nutrition and Metabolic Disease.*

1. *Steps to protect the confidentiality of personal data, and respect for people's privacy, including precautions to prevent the secret of genetic test results from being leaked to families except with the permission of the person concerned (Guidelines 4, 11, 12 and 24) (p 35)*

*Data is collected in CRF, stored in a special research bantex folder. Furthermore, it is stored in a locked drawer in the division of NMD in Child Health Department. Access to data can only be done by researchers. The drawer keys are held by the Division secretary.*

1. *Information about how to code; if any, subject identification is made, where it is stored and when, how and by whom it can be opened in the event of an emergency (Guidelines 11 and 12) (p36).*

*When a record is made at the CRF, the name, address and contact number are still written down. However, in the input to statistical software, the initials of the patient's name (code number 1-80) are used for confidentiality. The data is displayed in the form of mean + SD in the provided table.*

1. **Possibility of further use of personal data or biological material (p37)**

*Irrelevant*

1. **Analytical Plan**

*1. A description of the statistical analysis plan, including the interim analysis plan if necessary, and the criteria if or under what conditions premature termination of the entire study will occur (Guideline 4) (B,S2)*

*1. Homogeneity and normality tests were performed on the variables of age, body weight (pre- and post-), body ​​height (pre- and post-), ​​head circumference (pre- and post-), ​​total lymphocyte count (pre- and post- ) and IGF-1 (pre- and post-). Data is presented in the form of mean + SD. The results of plotting body weight over age, Body height of age and body weight over body height, gender, complaints, evaluation of compliance, and side effects of consumption are presented in descriptive form.*

*2. Independent T-test for body weight (pre- and post-), body ​​height (pre- and post-), ​​head circumference (pre- and post-), ​​total lymphocyte count (pre- and post-) and IGF -1 (pre- and post-) if data is normally distributed or otherwise, Mann-Whitney U-Test.*

*3. Chi square test for the categorical interpretation variables of body weight over age (normal, underweight, severely underweight, overweight, obesity), body length over age or body height over age (normal, stunted, severely stunted), Body weight over body height or body weight over body length (obesity, overweight, normal, wasted, severely wasted), and Head circumference over age (normal, microcephaly, macrocephaly)*

*4. Paired sample t-test was performed on the variables of body weight (pre- and post-), body​​height (pre- and post-), ​​head circumference (pre- and post-), ​​total lymphocyte count (pre- and post-) and IGF-1 levels (pre- and post-) with homogeneous criteria and normal distribution (p>0.05). For variables with non-normal and non-homogeneous distributions, the Wilcoxon test was performed.*

*If there is a stop when treatment is carried out, then the subject is excluded from the analysis.*

1. **Safety Monitoring**

*1. Plans to monitor the continued safety of drugs or other interventions carried out in research or trials, and, where necessary, the establishment of an independent committee for data and safety monitoring (Guideline 4) (B,S3,S7)*

*Irrelevant*

1. **Conflict of Interest**

*1. Arrangements to resolve financial or other conflicts that could influence the decisions of researchers or other personnel; inform the institutional committee about any conflict of interest; the institutional committee then communicates it to the ethics committee and then communicates to the researchers about the next steps to be taken (Guideline 25) (p42)*

*No conflict of interest*

1. **Social Benefit**
2. *For research conducted in a poor resource setting, contributions made by sponsors for capacity building for scientific and ethical review and for health research in the country; and assurance that the purpose of capacity building is to match the values ​​and expectations of the participants and the community of research site (Guideline 8) (p43)*

*After this research, it is hoped that the Indonesia government will cooperate in dealing with stunting. High-calorie formula milk is one type of FSMPs (Food for Special Medical Purposes) provided by the Sarihusada Generasi Mahardika (Danone Group) in the form of dairy products which are handed over to the Husada Utama Hospital (Pharmacy). This type of FSMP is a special milk which is regulated by Permenkes No. 29 of 2019 according to medical indications and prescribed by pediatricians. Funding for the blood tests imposed on the subjects (total lymphocyte count and IGF-1) was privately funded by the researcher. The reason for choosing Surabaya as a study/research site was health services in Surabaya, especially regarding stunting issue and FSMP milk provision by the Surabaya City Health Office, have been running. So that the children involved in this study can later be given the same treatment, i.e. given the FSMP milk by the city health office.*

1. *The research protocol or document sent to the ethics committee should include a description of the community engagement plan, and indicate the resources allocated to these engagement activities. This document describes what has been and will be done, when and by whom, to ensure that the community is clearly mapped to facilitate their involvement during the research, to ensure that the research objectives meet the needs of the community and are accepted by them. If necessary the community should be involved in the preparation of this protocol or document (Guideline 7) (p44)*

* *Proposed answers: Aligned and this is stated in the study protocol (TBC by dr. Nuril)*

1. **Data Rights**

*1. Especially if the sponsor is an industry, a contract that states who owns the rights to publish research results, and the obligation to jointly prepare and give to the PIs a draft research report (Guideline 24) (B and H, S1, S7)*

*If the PKMK product provider requests the results of the research, they are given processed data that includes the increase in body weight, body height and head circumference and is presented in mean + SD, as well as the overall characteristics of the subject [n(%)]*

1. **Publication**
2. *Plans for publication of results in certain fields (such as epidemiology, generics, sociology) that may risk being against the benefit of the community, society, family, ethnic group, and minimize the risk of harm to this group by always maintaining the confidentiality of data during and after the study, and publishing research results in such a way while always considering their dignity and nobility (Guideline 4) (p47)*

*Planned to be published on a Q2 international journal. The data is listed in the form of mean + SD, and does not include the name of the subject. Even when the subject's results are not as expected.*

1. *If the research results are negative, ensure that the results are available through publication or by reporting to the drug registration authority (Guideline 24) (p46)*

*The publication will still be done with additional search for the causes of negative results based on the literature.*

1. **Source of Funding**

*Source and amount of research funding; funding institutions, and a description of the sponsor's financial commitments to research institutions, to researchers, research subjects, and, if applicable, to the community (Guideline 25) (B, S2); (p41)*

*Personal/private fund of researcher*

1. **Ethical commitment**

*1. Principal investigator's statement on the principles set out in this guide will be followed (p6).*

*2. (Track Record) History of previous ethical protocol review proposals and their results (fill in with the title and date of the study, and the results of the Ethics Committee review (p7)*

*ANALYSIS OF ADIPOQ +45 T>G, ADIPOQ -11377 C>G GENES’ POLYMORPHISM AND ADIPONECTIN LEVELS OF OBESITY ADOLESCENT WITH METABOLIC SYNDROME*

*THE EFFECT OF LACTOFERIN IN HIGH CALORIE MILK FORMULA ON THE IMMUNE RESPONSE OF IL-6 AND IL-10 IN GROWTH FAILUR CHILDREN WITH INFECTION*

*3. A statement that if there is any evidence of data falsification, it will be handled according to the sponsor's policy to take the necessary steps (p48)*

*If in the future evidence of data falsification is found, I will accept the sanctions that have been determined.*

Signature of Principle Investigator

Surabaya, October19th, 2021



## References

1. Wrighting DM, Andrews NC. Interleukin-6 induces hepcidin expression through STAT3. *Blood*. 2006;108(9):3204-3209.

2. Shim JO, Kim S, Choe BH, Seo JH, Yang HR. Effect of nutritional supplement formula on catch-up growth in young children with nonorganic faltering growth: A prospective multicenter study. *Nutr Res Pract*. 2020;14(3):230-241.

3. Pencharz PB. Protein and energy requirements for ‘optimal’ catch-up growth. *Eur J Clin Nutr*. 2010;64:S5-S7.

4. Kareem ZU, Panuganti SK, Bhatia S. Case Report: Energy- and Nutrient-Dense Formula for Growth Faltering: A Report of Two Cases From India. *Front Nutr*. 2021;8(February):1-8.

5. Cooper CA, Nelson KM, Maga EA, Murray JD. Consumption of transgenic cows’ milk containing human lactoferrin results in beneficial changes in the gastrointestinal tract and systemic health of young pigs. *Transgenic Res*. 2013;22(3):571-578.

6. Yang C, Zhu X, Liu N, et al. Lactoferrin up-regulates intestinal gene expression of brain-derived neurotrophic factors BDNF, UCHL1 and alkaline phosphatase activity to alleviate early weaning diarrhea in postnatal piglets. *J Nutr Biochem*. 2014;25(8):834-842.

7. Wu J, Chen J, Wu W, et al. Enteral supplementation of bovine lactoferrin improves gut barrier function in rats after massive bowel resection. *Br J Nutr*. 2014;112(4):486-492.

8. Arciniega-Martínez IM, Campos-Rodríguez R, Drago-Serrano ME, Sánchez-Torres LE, Cruz-Hernández TR, Reséndiz-Albor AA. Modulatory Effects of Oral Bovine Lactoferrin on the IgA Response at Inductor and Effector Sites of Distal Small Intestine from BALB/c Mice. *Arch Immunol Ther Exp (Warsz)*. 2016;64(1):57-63.

9. Mayeur S, Spahis S, Pouliot Y, Levy E. Lactoferrin, a Pleiotropic Protein in Health and Disease. *Antioxidants Redox Signal*. 2016;24(14):813-836. doi:10.1089/ars.2015.6458

10. Saraiva M, O’Garra A. The regulation of IL-10 production by immune cells. *Nat Rev Immunol*. 2010;10(3):170-181.

11. Kell DB, Heyden EL, Pretorius E. The Biology of Lactoferrin, an Iron-Binding Protein That Can Help Defend Against Viruses and Bacteria. *Front Immunol*. 2020;11:0-2.

12. Reznikov EA, Comstock SS, Hoeflinger JL, Wang M, Miller MJ, Donovan SM. Dietary bovine Lactoferrin reduces Staphylococcus aureus in the tissues and modulates the immune response in piglets systemically infected with S. aureus. *Curr Dev Nutr*. 2018;2(4):1-10.

## AB. Appendix

*\* Urutan nomor pada Protokol Asli CIOMS 2016*