PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Effects of infant feeding with goat milk formula or cow milk formula on atopic dermatitis: Protocol of the randomized controlled Goat Infant Formula Feeding and Eczema (GIraFFE) trial
AUTHORS	Ferry, Jill; Galera-Martínez, Rafael; Campoy, C; Sáenz de Pipaón, Miguel; Jarocka-Cyrta, Elzbieta; Walkowiak, Jarosław; Romańczuk, Bartosz; Escribano, Joaquin; Gispert, Mariona; Grattarola, Paula; Gruszfeld, Dariusz; Iglesia, Iris; Grote, Veit; Demmelmair, Hans; Handel, Uschi; Gallier, Sophie; Koletzko, Berthold

VERSION 1 – REVIEW

REVIEWER	Bahbah, Wael Menoufia University Faculty of Medicine, Pediatric Departement
REVIEW RETURNED	21-Dec-2022

GENERAL COMMENTS	Thanks, Excellent Work. Accepted.

REVIEWER	Palmer, Debra Telethon Kids Institute
REVIEW RETURNED	12-Jan-2023

GENERAL COMMENTS	This is an important large randomized controlled trial that adds to our evidence base on the composition of infant formula which may reduce the incidence of the common condition of atopic dermatitis in infancy. I do however have some major revision requests regarding the manuscript introduction: The first paragraph on page 7 could be removed as this trial is not primarily about food allergy outcomes. Instead the introduction needs to include more details and references regarding the time course of AD development during infancy (for example the common age of commencement) and known risk factors for increased risk of AD development (eg Filaggrin mutations, parental history). Additionally, a paragraph describing the well-known allergenicity cross-reactivity between cow's milk and goat's milk proteins in human with a cow's milk allergy should be included. Also more details about goat milk lipid profiles should be included. Also given the sentence on page 8 lines 6-8 "We hypothesize that goat and cow milk-based infant formulas could differently affect blood based biomarkers, the gut microbiome…" evidence to explain how this hypothesis regarding possible effects on the gut microbiome also needs to be added to the introduction section. In addition, my minor suggestions for enhancement of this manuscript are as follows:

	1) Title: Please include reference to the type of study design (randomized controlled trial) in the title 2) Abstract Line 38: Add in “to be” as per: AD incidence difference was not found to be significant. 3) Abstract Line 46: Add in the allocation ratio for example, two-arm (1:1 allocation), parallel, randomized…. 4) Abstract Line 49: For English language improvement I would suggest rephrasing this sentence “Ten study centres in Spain and Poland take part” to ‘Ten study centres in Spain and Poland will be participating’. 5) Abstract Line 51: I would suggest rephrasing this sentence “either based on whole goat milk or on cow milk until the age of 12 months” to ‘either based on goat or cow milk until the age of 12 months’. 6) Keywords: please also include: cow’s milk 7) Introduction Page 6 Lines 52-60: This paragraph should be moved to the methods section. 8) Introduction Page 7 Line 19: Please include 1-2 references for the statement “Taking the considerable loss of quality of life”. 9) Introduction Page 7 Lines 44-60: Please include more details about the participant numbers in each formula type group, exact AD incidence and between group statistical analysis results that were found in the Australian study described. 10) In the methods section: Please add in details of whether this trial is designed to be a superiority, equivalence or noninferiority trial. 11) Methods Page 13 in the randomized allocation of study formulas section: Please add in details of allocation ratio, and methods relating to generating the allocation sequence (eg, computer-generated random numbers), and who has generated the allocation sequence. 12) Methods Page 17 Lines 8-14: Please provide more details of the collection procedures and planned microbiome analyses methodologies. 13) Methods Page 16 Lines 14-18: Please provide more details as per the SPIRIT guidelines on the composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests. Also please include a description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial.

REVIEWER	Yamamoto-Hanada, Kiwako National Center for Child Health and Development
REVIEW RETURNED	16-Jan-2023

GENERAL COMMENTS	This protocol paper described the study protocol of the effects of infant feeding with goat milk formula or cow milk formula on atopic dermatitis. This paper was well-written. one concern is that the sponsor should be independent of study implementation, including statistical analysis. The outcome assessment needs to be cited by the validation papers such as POEM, SCORAD, FFQ, IGIS, and ITQOL.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

Prof. Wael Bahbah, Menoufia University Faculty of Medicine Comments to the Author:
Thanks, Excellent Work.
Accepted.
Thank you very much for the kind feedback!

Reviewer: 2

Dr. Debra Palmer, Telethon Kids Institute Comments to the Author:
This is an important large randomized controlled trial that adds to our evidence base on the composition of infant formula which may reduce the incidence of the common condition of atopic dermatitis in infancy.
Thank you very much for the kind feedback!

I do however have some major revision requests regarding the manuscript introduction: The first paragraph on page 7 could be removed as this trial is not primarily about food allergy outcomes.
We agree and have removed the paragraph.

Instead the introduction needs to include more details and references regarding the time course of AD development during infancy (for example the common age of commencement) and known risk factors for increased risk of AD development (eg Filaggrin mutations, parental history).
We have added a sentence describing frequent age of AD onset and describe genetic and other risk factors.

Additionally, a paragraph describing the well-known allergenicity cross-reactivity between cow's milk and goat's milk proteins in human with a cow's milk allergy should be included.
We appreciate this comment and agree that the cow – goat cross reactivity should be mentioned and discussed, and we added why we think the study could nevertheless make sense.

Also more details about goat milk lipid profiles should be included.
As indicated in the manuscript the goat milk formula is made from whole milk and therefore includes milk fat and MGFM. We have included a sentence mentioning a series of lipids, which have been quantified in goat milk and show the complexity of the milk polar lipids. More quantitative details can be found in the added references.

Also given the sentence on page 8 lines 6-8 "We hypothesize that goat and cow milk-based infant formulas could differently affect blood based biomarkers, the gut microbiome…" evidence to explain how this hypothesis regarding possible effects on the gut microbiome also needs to be added to the introduction section.
As a justification for our hypothesis that biomarkers in blood and gut microbiome could be differently affected by the formulas, we have added three corresponding references.
35. Chen Q, Yin Q, Xie Q, et al. Elucidating gut microbiota and metabolite patterns shaped by goat milk-based infant formula feeding in mice colonized by healthy infant feces. Food chem 2023;410:135413. doi: 10.1016/j.foodchem.2023.135413 [published Online First: 2023/01/10]
36. Tannock GW, Lawley B, Munro K, et al. Comparison of the Compositions of the Stool Microbiotas of Infants Fed Goat Milk Formula, Cow Milk-Based Formula, or Breast Milk. Appl Environ Microbiol 2013;79(9):3040-48. doi: 10.1128/aem.03910-12
37. He X, Parenti M, Grip T, et al. Metabolic phenotype of breastfed infants, and infants fed standard formula or bovine MFGM supplemented formula: a randomized controlled trial. Sci Rep 2019;9(1) doi:

10.1038/s41598-018-36292-5

In addition, my minor suggestions for enhancement of this manuscript are as follows:

1)Title: Please include reference to the type of study design (randomized controlled trial) in the title
Thank you for the idea. The study design was included in the title.

2)Abstract Line 38: Add in “to be” as per: AD incidence difference was not found to be significant.
We added “to be” to highlight that the AD incidence was not found to be significant.

3)Abstract Line 46: Add in the allocation ratio for example, two-arm (1:1 allocation), parallel, randomized….
We included the allocation ratio in the abstract.

4)Abstract Line 49: For English language improvement I would suggest rephrasing this sentence “Ten study centres in Spain and Poland take part” to ‘Ten study centres in Spain and Poland will be participating’.
We changed the sentence as you suggested. Thank you for the improvement!

5) Abstract Line 51: I would suggest rephrasing this sentence “either based on whole goat milk or on cow milk until the age of 12 months” to ‘either based on goat or cow milk until the age of 12 months’.
Here we would prefer to state “whole goat milk” to emphasize that in contrast to the cow milk formula, where cow milk fat is not included, the goat formula included protein and fat from goat milk.

6)Keywords: please also include: cow’s milk
Thank you for this suggestion we added the keyword “cow milk”.

7) Introduction Page 6 Lines 52-60: This paragraph should be moved to the methods section.
Thank you for the comment. The whole paragraph describes previous studies comparing goat milk formula with cow milk formula. As GIraFFE is based on this a priori knowledge we think this is better placed in the introduction section. Thus, we would prefer not to move the paragraph.

8) Introduction Page 7 Line 19: Please include 1-2 references for the statement “Taking the considerable loss of quality of life”.
Thank you for your comment the following reference was inserted:
16. Lewis-Jones S. Quality of life and childhood atopic dermatitis: the misery of living with childhood eczema. Int J Clin Pract 2006;60(8):984-92. doi: 10.1111/j.1742-1241.2006.01047.x

9) Introduction Page 7 Lines 44-60: Please include more details about the participant numbers in each formula type group, exact AD incidence and between group statistical analysis results that were found in the Australian study described.
Thank you for this comment. We fully agree, this is an important reason to perform the study and more details should be presented. We have added the information as you suggested.

10) In the methods section: Please add in details of whether this trial is designed to be a superiority, equivalence or noninferiority trial.
The trial is designed to test the superiority of goat milk infant formula on the development of atopic dermatitis. This has been added in the methods section.

11) Methods Page 13 in the randomized allocation of study formulas section: Please add in details of allocation ratio, and methods relating to generating the allocation sequence (eg, computer-generated

random numbers), and who has generated the allocation sequence.
Allocation ratio and who produces the randomization list have been added to the paragraph.

12)Methods Page 17 Lines 8-14: Please provide more details of the collection procedures and planned microbiome analyses methodologies.
Thank you for the remark. More details on the stool collection procedure and analyses methodologies were included. Currently the microbiome analysis is not fully defined yet.

13) Methods Page 16 Lines 14-18: Please provide more details as per the SPIRIT guidelines on the composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests. Also please include a description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial.
Thank you for the remark. We included details on the composition and role of the data and safety monitoring board (DSMB). The DSMB has no direct involvement in the conduct of the study, financial, professional, or other interests that may affect independent decision-making. We also included information on the stopping guidelines and the interim results.

Reviewer: 3
Dr. Kiwako Yamamoto-Hanada, National Center for Child Health and Development Comments to the Author:
This protocol paper described the study protocol of the effects of infant feeding with goat milk formula or cow milk formula on atopic dermatitis.
This paper was well-written.
Thank you very much!

One concern is that the sponsor should be independent of study implementation, including statistical analysis.
Thank you very much for raising this point. While it is true that there was/is a continuous mutual exchange between sponsor and the study investigators during trial planning and implementation, it is clearly stated in the study protocol that the final decisions in relation to the study including publications are achieved by majority vote in the Trial steering committee (TSC consisting of the key PI, the site PIs and the sponsor) “The TSC will discuss all issues of the study, protocol amendments and publications of the study. Decisions on interpretation and publication of the findings of the trial will preferably be taken by consensus; if no consensus can be achieved a simple majority vote determines the decision. In case of a stalemate situation, the Key PI will have a casting vote” (GIraFFE study protocol section 13.3.).
In that sense the role of the sponsor does not go beyond, what is described in the last paragraph of the section “Funding, role of the sponsor and investigators”

The outcome assessment needs to be cited by the validation papers such as POEM, SCORAD, FFQ, IGIS, and ITQOL.
Publications describing validation of the applied questionnaires were inserted on page 11.

SCORAD:
13. Kunz B, Oranje AP, Labrèze L, et al. Clinical validation and guidelines for the SCORAD index: consensus report of the European Task Force on Atopic Dermatitis Dermatology 1997;195(1):10-19. doi: 10.1159/000245677
14. Oranje AP, Glazenburg EJ, Wolkerstorfer A, et al. Practical issues on interpretation of scoring atopic dermatitis: the SCORAD index, objective SCORAD and the three-item severity score Br J Dermatol 2007;157(4):645-48. doi: 10.1111/j.1365-2133.2007.08112.x

POEM:
12. Spuls PI, Gerbens LAA, Simpson E, et al. Patient-Oriented Eczema Measure (POEM), a core instrument to measure symptoms in clinical trials: a Harmonising Outcome Measures for Eczema (HOME) statement. Br J Dermatol 2017;176(4):979-84. doi: 10.1111/bjd.15179
15. Charman CR, Venn AJ, Williams HC. The patient-oriented eczema measure - Development and initial validation of a new tool for measuring atopic eczema severity from the patients' perspective. Archives of Dermatology 2004;140(12):1513-19. doi: 10.1001/archderm.140.12.1513
FFQ:
43. Lanfer A, Hebestreit A, Ahrens W, et al. Reproducibility of food consumption frequencies derived from the Children's Eating Habits Questionnaire used in the IDEFICS study. Int J Obes 2011;35 S61-68. doi: 10.1038/ijo.2011.36
BISQ:
44. Sadeh A. A brief screening questionnaire for infant sleep problems: Validation and findings for an Internet sample. Pediatrics 2004;113(6):E570-E77. doi: 10.1542/peds.113.6.e570
IGSQ:
45. Riley AW, Trabulsi J, Yao M, et al. Validation of a Parent Report Questionnaire: The Infant Gastrointestinal Symptom Questionnaire. Clin Pediatr 2015;54(12):1167-74. doi: 10.1177/0009922815574075
ITQOL-SF47:
46. Landgraf JM, Vogel I, Oostenbrink R, et al. Parent-reported health outcomes in infants/toddlers: measurement properties and clinical validity of the ITQOL-SF47 Qual Life Res 2013;22(3):635-46. doi: doi:10.1007/s11136-012-0177-8

VERSION 2 – REVIEW

REVIEWER	Palmer, Debra Telethon Kids Institute
REVIEW RETURNED	11-Mar-2023

GENERAL COMMENTS	My manuscript enhancement suggestions have all been incorporated into this revised manuscript which is now comprehensive and well written.