

ORIGINAL ARTICLE

Quality assurance of ethical issues and regulatory aspects relating to good clinical practices in the HELENA Cross-Sectional Study

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Rationale: Research involving humans is regulated by regulatory authorities through their specific requirements and controls. The Healthy Life Style in Europe by Nutrition in Adolescence Cross-Sectional Study (HELENA-CSS) is a multicenter biomedical research study of adolescents in several representative European cities, which requires satisfying medico-regulatory requirements including Independent Ethics Committee (IEC) approval and agreement by the national or local regulatory authorities. To achieve a high level of quality assurance relating to ethical issues, we followed the good clinical practices (GCP) described at the International Conference on Harmonisation (ICH), which we adapted to the national and local situations of each of the 11 participating cities in 10 European countries.

Objective: The main objective of the HELENA-CSS is to evaluate reliable and comparable data of nutritional habits and lifestyle in a representative sample of European adolescents. The aim of this paper is to present the methods relating to the ethical and regulatory issues of this study and to describe the current state of the medico-regulatory requirements involved in conducting this kind of study in each country.

Materials and Methods: Following the GCP-ICH guidelines, a protocol describing the HELENA-CSS was written and approved by all partners. In the pilot study, a case report form adapted to the study objectives and its manual of operation was constructed and used by all partners. All information letters to adolescents and their parents and consent forms were first written in English, then translated into the local language, and adapted to each local situation. All documents were then checked centrally for any deviation and corrected if required. An operation manual relating to ethical issues and other medico-regulatory requirements was also developed. This paper presents the current status of the medico-regulatory requirements from each HELENA-CSS participant country.

Results: Before the beginning of the study, most centers had satisfied the medico-regulatory requirements of IEC approval and agreement with other national or local regulatory authorities/organizations. For a few centers, some problems were detected and corrective actions were taken to improve missing information to reach a high level of quality assurance of ethical issues.

Conclusion: The GCP-ICH guidelines about nontherapeutic biomedical research are interpreted and applied differently across Europe. This study shows that high-quality nontherapeutic biomedical research can address the ethical issues included in the GCP-ICH regulations and can be harmonized among the HELENA European partners.

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¹⁴See Appendix at the end of the supplement on page S82.

Introduction

Healthy Life Style in Europe by Nutrition in Adolescence Cross-Sectional Study (HELENA-CSS) involves human participants; it

requires satisfying medico-regulatory requirements including Independent Ethics Committee (IEC) approval and agreement by the national or local regulatory authorities/organizations.

The aim of this paper is to describe the application of quality assurance methods relating to ethical issues and regulatory requirements comprising the Guideline for Good Clinical Practices (GCP) from the International Conferences on Harmonisation of Technical requirements for Registration of Pharmaceuticals for Human Use (ICH). During the preparation of this international project, the different research teams have been assigned roles according to their experience in the chosen area. The University of Lille and the Clinical Investigation Center of Lille (CIC-L) were assigned to apply the GCP-ICH in the HELENA-CSS, including traceability of blood samples.

Methods

Protocol for submission to Independent Ethics Committees

To provide rigorous quality assurance with regard to ethical issues, the core group wrote a protocol that conformed to the GCP-ICH based on concepts about ethics in biomedical research that originated from the Nuremberg Code and the Declaration of Helsinki.^{1,2} The most recent published guidelines are the ICH, E6 and 2001/20/CE directives, which were written originally for therapeutic clinical trials (available at <http://www.ich.org>).³ Following these guidelines and those concerning the ethical conduct of medical research involving children,⁴ each center named a principal investigator (PI) (Table 1). The protocol included information relating to the study in as much detail as possible (Table 2). After several reviews by the core group, by each PI, work package leader and the HELENA partners, the protocol was modified and corrected at three plenary meetings (two in Lille and one in Madrid). The English version of the information letter for adolescents and parents and the consent form were accepted, and these were then translated by the PIs into their local languages and adapted to the local rules or habits for presenting these documents. The conformity of the translations to the GCP rules was then controlled centrally by checking each of the local documents for the following items: freedom to withdraw from the protocol, general design and details about the tests. The protocol, along with the information letter and consent form adapted to the local language, was submitted to the local or national IEC of each center. For the adolescents assigned to provide blood samples, the sample volume was calculated to not exceed 3 ml kg⁻¹ in a single blood withdrawal, which was consistent with the Guidelines of the National Institutes of Health (USA) General Clinical Research Centers.

Operation manual

To provide the guidelines, an operation manual was written that detailed each step needed to comply with the local

Table 1 List of principal investigators per center

Code center number	Participating center (city and country)	Name and qualification of the principal investigator
1	Athens (Greece)	Dr Y Mannios (PhD)
2 ^a	Birmingham (UK)	C Gilbert (statistician)
3	Dortmund (Germany)	Dr M Kersting (PhD)
4	Ghent (Belgium)	Pr S De Henauw (MD, PhD)
5	Heraklion (Greece)	Pr A Kafatos (MD)
6	Lille (France)	Pr F Gottrand (MD, PhD)
7	Pécs (Hungary)	Dr D Molnar (MD, PhD)
8	Rome (Italy)	Dr C Leclercq (PhD)
9	Stockholm (Sweden)	Pr M Sjöström (MD, PhD)
10	Vienna (Austria)	Pr K Wildhalm (MD)
11	Zaragoza (Spain)	Pr L Moreno (MD, PhD)

^aUnited Kingdom was involved only in the use of attitudinal questionnaires. There were no objectives or intentions to conduct any type of biomedical research, and none of the clinical/paraclinical examinations, blood sampling or physical fitness tests were administered, therefore GCP/ICH regulations were not applicable.

Table 2 Content of the protocol

Item	Name of the item
1	Title and name and address of the coordinator
2	List of principal investigators of each center
3	List of laboratories for blood analysis
4	Summary
5	Study rationale
6	Study objectives
7	Study end points
8	Selection of adolescents, inclusion criteria and exclusion criteria
9	Study design
10	Description of laboratory analysis and clinic exams
11	Sample size justification and statistical analysis
12	Sponsor and investigator obligations, regulatory assessments and insurance
13	Subject information and informed consent
14	Study monitoring, sponsor audits and inspection by regulatory authorities
15	Information letter for the adolescent, information letter for the parents and informed consent form

regulations and the GCP (Table 3). This operation manual comprised information about applying to the IEC and the competent authorities, and it emphasized the need to obtain the support of a 'sponsor' as defined in ICH E6 in each country. This type of 'local sponsor' is not related exclusively for financial support, but has other responsibilities. In biomedical research, the need of a sponsor relating to GCP is particularly needed. According to ICH E6 and 2001/20/CE directives, the sponsor takes the responsibility of quality assurance of GCP/ICH rules. It submits the protocol to IEC for approval, pays the insurance policy to cover people involved in the study (adolescents and investigators), assumes quality control audit, checks and manages adverse events and serious adverse events. 'GCP related local sponsor' could be an institutional or private organization or a named person. The operation manual also described the PI's engagement in the project. Specifically, when applying

Table 3 What type of declarations relating to Good Clinical Practices are required to carry out HELENA-CSS?

Code center	Submission of the protocol is a local, regional or a national IEC?	Is the IEC agreement valid: locally or nationally?	Is a submission to a competent authority/ organization required concerning nontherapeutic biomedical research?	Is a local sponsor (relating to GCP) required?	Is an insurance contract required for this study?	Is a declaration to an authority/ organization to personal informatics data required?	Does a national law or decree exist concerning nontherapeutic biomedical research?
1 Athens (Greece)	Local	Nationally	Yes, to MNERA	No	No	Yes, to HDPDA	No
2 Birmingham (UK)	NA ^a	NA ^a	NA ^a	NA ^a	NA ^a	Yes	No
3 Dortmund (Germany)	Local	Locally	No	Yes	Yes	Yes	No
4 Ghent (Belgium)	Local	Nationally	No	Yes	Yes	Yes	Yes, law of 7 May 2004
5 Heraklion (Greece)	Local	Nationally	Yes, to MNERA	No	No	Yes, to HDPDA	No
6 Lille (France)	Local	Nationally	Yes, to Health ministry	Yes	Yes	Yes, to NICI	Yes, law Huriet/Serusclet
7 Pécs (Hungary)	National	Nationally	Yes, to MRCS	No	No	No	Yes, decree 23/2002 V09
8 Rome (Italy)	National	Nationally	Yes, to Health ministry	No	Yes	Yes, PID	Yes, law 196/03
9 Stockholm (Sweden)	Regional	Nationally	No	Yes	No	Yes, to Datainspektionen	Yes
10 Vienna (Austria)	Local	Locally	Yes, to Health ministry	No	No	No	No
11 Zaragoza (Spain)	Regional	Nationally	No	No	No	No	No

Abbreviations: HELENA-CSS, Healthy Life Style in Europe by Nutrition in Adolescence Cross-Sectional Study; HDPDA, Hellenic Data Protection Authority; MNERA, Ministry of National Education and Religious Affairs; NICI, National Informatics Commission for personal Informatics data; MRCS, Medical Research Council Scientific; PID, Personal Informatics Data. ^aUnited Kingdom was involved only in the use of attitudinal questionnaires. There were no objectives or intentions to conduct any type of biomedical research, and none of the clinical/paraclinical examinations, blood sampling or physical fitness tests were administered, therefore GCP/ICH regulations were not applicable.

the protocol, the PI should consider the participants' well-being and health, respect for ethics, methodological and statistical considerations, protecting participants' data, qualified staff and the need to use validated and suitable working methods and documents.

Study site initiation meeting

Before the study began, all centers hosted a study site initiation meeting. This launching meeting reviewed the study's scientific background, objectives, evaluation criteria, inclusion and exclusion criteria, duration of the study and practical aspects; discussed procedures for serious adverse events; reviewed the case report form (CRF) and questionnaire thoroughly; showed the devices, materials, blood sample tubes and technical considerations relating to sample transport; noted which classes had been randomized in the study and confirmed responsibilities with regard to protocol adherence, quality assurance and providing information and support to best realize the study. This meeting involved all staff involved locally in the study: PI, subinvestigators, nurses, dieticians or nutritionists, clinical research assistants (CRAs), fellows or trainees, technicians and other assistants.

Coding of participants to ensure confidentiality

To comply with the GCP, data from each participant were recorded anonymously using a specific coding, including the

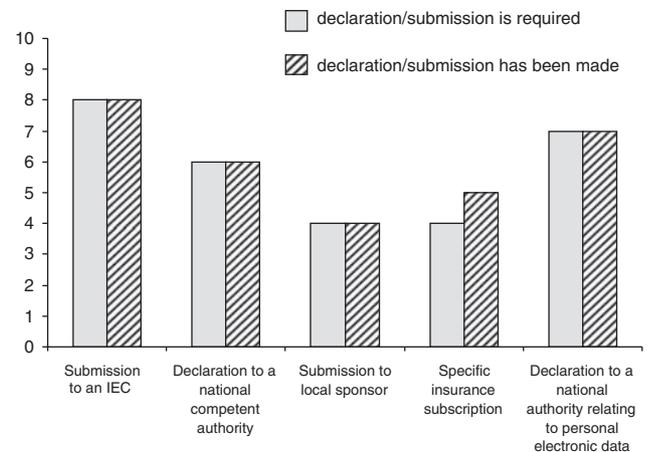


Figure 1 Comparison of the number of countries in which each type of declaration/submission is required versus the number of countries in which it was made. IEC, Independent Ethics Committee.

code numbers of the study, center, school, school class and participant (for example, H2 01 01 01 01).

Results

Figure 1 presents information about the ethical submission and national regulatory requirements in each country

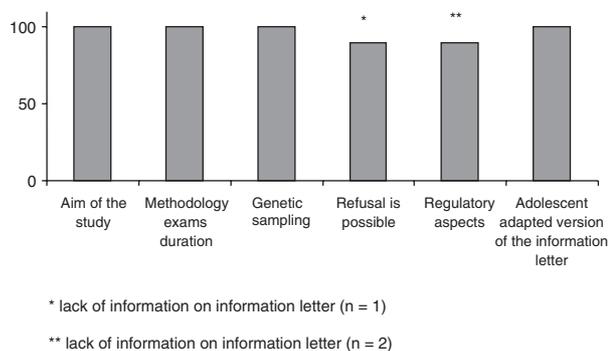


Figure 2 Respect of the content of information letter to the GCP recommendations.

involved in the HELENA-CSS. There were 10 countries and 11 centers (two centers were in the same country: Greece). The number of countries in which each type of declaration/submission is required was compared with the number of countries in which it was made (Table 3). IEC submission of the protocol was obligatory in 8 of 10 countries. In these countries ($n=8$), IEC approval was obtained. In two countries, IEC submission of the protocol was not applicable or not obligatory. Six centers declared the study to a national competent authority/organization, which for most was the country's ministry of health. Four countries obtained the support from a 'local sponsor' as defined earlier in this paper. Specific insurance to conduct a nontherapeutic biomedical research was mandatory in only four countries but five countries subscribed to a specific insurance policy. Declaration of the study to a national authority/organization responsible for protection of personal electronic data storage was obligatory in seven countries and has been obtained.

Figure 2 presents the major items that should be included in the information letter according to the GCP. Eight of 10 centers presented an information letter that included all these items. Two centers did not explain in the information letter that a specific insurance has been contracted to cover the participants and staff. One center did not explain that it was possible for the parents or adolescents to refuse to take part in the study.

Discussion

Ethical consideration is fundamental to a study such as the HELENA-CSS, which involves a presumably healthy population that will be studied extensively through medical examinations, physical tests and, for one-third of the participants, a blood sample and genetic evaluation. The ICH considers that adolescents are a vulnerable population with regard to therapeutic evaluations (available at <http://www.ich.org>). Before starting this biomedical research study, we chose to comply with the European legislated biomedical research regulations. We decided to do this even though this study is not subject to the harmonized European

legislation as required for therapeutic trials. In Europe, GCP-ICH and 2001/20/CE directives are required for therapeutic trials (available at <http://www.ich.org>)³ and have been effectively taken up progressively throughout Europe since 2004.⁵ In the context of biomedical investigation of adolescents, ethics tends to reconcile two fundamental principles: first, the right and freedom of individuals to participate in research studies and second, the respect and protection of the autonomy of adolescents,⁶ especially in terms of harm prevention. We decided to adhere to the guidelines published for therapeutic biomedical research by naming one PI per center, and by obtaining approval of and agreement with the relevant committees and organization/institutions according to national and local regulatory requirements.

Role of the PI

A PI was named in all centers to comply with the requirements of the GCP. In most centers, the PI is a medical doctor trained in clinical research; some PIs have a medical degree and PhD, and others have only a PhD. The PI is responsible for ensuring that his/her center follows the HELENA-CSS protocol and operating manual with respect to the GCP-ICH guidelines. All PIs agreed to be interviewed remotely by phone, fax or e-mail, and directly by a monitor from the CIC-L, which is in charge of auditing and controlling compliance with the GCP-ICH guidelines. During the consent process and the study, the PI will also be available to explain the procedures to the participants and answer questions during the examinations and tests, and to answer questions from parents.

Submission of the study to an IEC

Independent ethics committees are responsible for determining when and how to obtain consent from adolescents, checking the content of the protocol, whether the study poses risks for adolescents, whether the information letter and consent forms are understandable by parents and adolescents, and the qualifications of the PI and staff. The IECs to which we have submitted our study differed between centers in that some are organized at the local, regional or national level. The time required to obtain approval from the IECs also varied between centers: median 4.5 weeks (minimum–maximum, 3–10 weeks) because IECs have different agendas and requirements for application. In most participating countries, each hospital institution or group of hospital institutions have their own IEC. In two countries, regulatory requirements as IEC approval were not applicable or were not obligatory.

In the first country (UK), the center did not participate in the full HELENA-CSS. The research that took place in the United Kingdom only involved the use of attitudinal questionnaires. There were no objectives or intentions to conduct any type of biomedical research and none of the clinical/paraclinical examinations, blood sampling or physi-

cal fitness tests were administered; therefore, IEC approval was not applicable. The UK study was considered to be a type of 'consumer survey', where the main aim of the data collection was the development, testing and administration of a 'Food Choices and Preferences' questionnaire. After checking comprehensibility and length of the questionnaire, it was modified to be used in fieldwork. Thereafter, it was used in all centers involved in the HELENA-CSS.

For the second country (Sweden), regulations about nontherapeutic biomedical research do not require IEC approval for a pilot study. In that country, however, results from the pilot study and subsequent amendments to the protocol are needed before application for IEC approval of the main study. IEC approval was obtained before the main part of the HELENA-CSS fieldwork begun in Sweden.

Competent authority/organization to conduct nontherapeutic biomedical research

We found some differences between countries regarding the need for a declaration to a competent authority mainly because the aim of this study is not therapeutic. Six countries declared this biomedical research to their respective competent authorities/organization, mainly the ministry of health in their country. Five participating countries also subscribed to a specific insurance policy specialized in biomedical research, which was subscribed for most of these centers by the local sponsor. In some centers ($n=4$) with no 'local sponsor', the PI provided an insurance contract document, usually through their own professional insurance. Indeed, local regulations concerning GCP did not require specific insurance to conduct nontherapeutic biomedical research. In these countries, the university provided insurance coverage for all academic biomedical research projects.

Sponsor role

Although this study is supported by the European Commission, the Commission cannot be the 'local sponsor', because this type of sponsor must assume the legal responsibilities relating to the biomedical research. It was therefore necessary to define a 'local sponsor' relating to GCP, at the national or local level to assume all responsibilities involved in the regulatory obligations (as mentioned in the material and method section). This included providing insurance to cover the various people involved in the study, especially the adolescent participants, and submitting the protocol to the IEC. According to the GCP, only one sponsor could have been declared for the HELENA-CSS. However, in practice, it was not possible to have one common 'sponsor', for the whole study and a local sponsor was appointed for only four participating centers. Other countries did not require a 'local sponsor' to start nontherapeutic biomedical research. However, before the beginning of the study, we asked all countries to name a 'local sponsor' because it was of help to assume medico-regulatory requirements of nontherapeutic

biomedical research. According to ICH, E6 and 2001/20/CE directives, 'GCP relating sponsor' is in charge of taking the responsibility of quality assurance of GCP/ICH rules. It submits the protocol to IEC for approval, pays the insurance policy to cover people involved in the study, assumes quality control audit, checks and manages adverse events and serious adverse events. In most centers, submission of protocol to the IEC was made directly by the PI instead of the sponsor. When available, the 'local sponsor' was a university ($n=3$) or a public hospital ($n=1$). These sponsors only took part in the study in providing insurance to cover people involved in the study, but they were not involved in the GCP process, because of their lack of experience in managing in this field. Moreover, European legislation concerning nontherapeutic biomedical research is not well established and harmonized.⁷ This problem explains several discrepancies existing between the participating countries. Laws and decrees concerning nontherapeutic research are lacking in several countries (see Table 3). Fortunately, a new project concerning state of the art of GCP/ICH regulations at the European level is ongoing (ECRIN project: European Clinical Research Infrastructure Network, available at <http://www.ecrin.org>).^{8,9} The aim of this project is to develop harmonization and compatibility of procedures, tools and practice, to improve quality in clinical research and to act as a support to sponsors (academic or industry) in the conduct of multinational studies in Europe. This project could contribute to developing harmonized laws and decrees in biomedical research.

For this study, responsibilities concerning quality assurance and GCP were assumed by one center (CIC-L, Lille, France). Ethical issues and data collection were audited by CIC-L: ethical approval documents, regulatory requirement, consent form and data collection process were checked. Audits were made directly on site by a well-experienced (in terms of GCP/ICH and HELENA Study) CRA. With the help of the local PI, and before starting the fieldwork, the CRA from CIC-L checked regulatory documents in all centers. The CRA checked important and obligatory regulatory requirements:

- IEC approval document;
- translation in local language of information letter and consent form;
- curriculum vitae of the PI and medical doctors involved in clinical exam;
- the list of all the staff involved in the local team;
- if applicable, name and address of 'local sponsor' and the name of insurance company for conducting the study;
- informed consent process of each participant and both parents and
- absence of protocol violations.

When a problem was detected, the PI was immediately informed and corrective action was taken. For example, one center did not explain that it was possible for the parents or adolescents to refuse to take part in the study. The PI was

required to add this information in the information letter and made the change before the fieldwork.

During the fieldwork, the CRA was also in charge of quality control checking of the data collection of 20% (chosen by randomization) of CRF/questionnaires and ensure that nonserious and serious adverse events, if existing, had been properly documented, reported and declared.

Information letter and consent form

The GCP principles are based on the ethical principles stated in the Helsinki Declaration, which are in the case of children and adolescents the consent of parents is essential; the research must lead to results that are for the good of society, it is based on a pertinent hypothesis, it avoids any useless mental or physical suffering and is conducted by qualified persons; the degree of risk taken into account may not exceed that determined by the humanitarian importance of the problem to be solved by the research; all precautions must be taken to protect participants, who must be free to withdraw from the investigation; the investigator must be able, in good faith, to withdraw a participant from the investigation if he or she believes that it may harm the participant; the investigator must respect and guarantee protection of all participants' privacy and confidentiality; the participant must be fully informed before he or she takes part in the research and the data collected must be confidential and recorded anonymously.

The content of the information letter is especially important in biomedical research involving minors, and it represents a core element in the conduct of ethically appropriate research involving human participants. For several reasons, it was important to inform the adolescents who were screened for the HELENA-CSS that this research had no direct benefit to their health or well-being, although they would be given data about their health status. The information letter took into account the limited capacity of the adolescents to understand all the scientific objectives and details of the study design,¹⁰⁻¹⁴ and assumed that the parents or guardians would act in the best interest of the adolescents when deciding to participate in the research. For these reasons, the information letter was written in the local language using adapted explanations and vocabulary to avoid misunderstanding and to allow the adolescents and their parents or guardians to understand the difference between research and medical care.¹⁵ Such letters need to take into account the potential low educational level or understanding about terminology relating to biomedical research.¹¹ To facilitate the participants' understanding of the information provided, two forms of the information letter were first written in English: one written for the adolescents and the other for the parents. The two forms were then translated into the national language and adapted to comply with the local regulatory demands. These information letters were written using simple words to be understandable by most people. According to the 2001/20/

CE directive (available at <http://www.ich.org>),³ parents and adolescents could be informed about the global results of HELENA-CSS obtained in all countries. For the consent form, because this research included minors, the approval and signature by one or both parents was required depending on local regulations. None of the participants was paid to take part in the study.

CRF

The CRF included important information derived from the GCP: checking of the inclusion and exclusion criteria, collecting the signature of the medical doctor who examined the adolescent and collecting clinical and paraclinical data. The CRF also contained a specific section to record serious and nonserious adverse events. In purely observational studies, the European Parliament Directive 2001/20/CE states that data about serious and nonserious adverse events must be collected but not declared to a competent authority.

Report letter of results

The benefit of participation in this study for adolescents is as follows: all the adolescents participating in the pilot study received a report letter including several pieces of information: weight, height, body mass index, blood pressure, heart rate at rest, the result of global clinical examination and the white/red blood cell counts for those participating to the blood collection. When clinical or biological abnormality was detected, a specific letter was sent to the parents and family doctor to inform them about the situation.

According to 2001/20/CE directives, the PI could inform all participants about global results of the study. In this project, we decided to disseminate global results on specific information provided by a specialized work package 'dissemination activities'.

Conclusion

HELENA-CSS is a European multicenter biomedical research study of adolescents, and it was necessary to apply harmonized medico-regulatory regulation according the GCP-ICH. Most centers satisfied the medico-regulatory requirements such as IEC approval and agreement with other mandatory national or local regulatory authorities/organizations. In some cases, corrective actions were taken to improve the level of quality assurance of ethical issues and regulatory requirements. Other actions relating to the GCP-ICH are ongoing or planned, including onsite monitoring to check that informed consent is obtained for each participant and one or both parents, to record the occurrence or absence of protocol violations, to ensure the proper use of the CRF and questionnaire and to ensure that any nonserious and serious adverse events are documented, reported and declared.

This survey showed that application of the GCP-ICH guidelines on nontherapeutic biomedical research differs across Europe. This disharmony between countries in the regulatory requirements derived not only from law, but also in points of practice, from specific rules for each institution and differences in definitions and interpretation of local laws/decrees. However, major rules such as IEC submission were applied all the time. Some improvements concerning GCP-ICH application concerning nontherapeutic biomedical research across Europe are expected in the next few years. There was unanimous agreement among countries to harmonize common rules.

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Conflict of interest

Frédéric Gottrand has received consulting fees from Numico Clinical Nutrition, lecture fees from SMS and grant support from Danone Research. The remaining authors state no conflict of interest.

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