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# Evaluation of randomized controlled trials of foods with functional claims request: The learning outcomes from studies in Japan

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ABSTRACT

A new system for foods with functional claims (FFC) was implemented in April 2015. The efficacy of FFC must now be proven by systematic review or randomized clinical trials (RCTs). The aim of this study was to establish the scientific reporting quality of RCTs on the efficacy of FFC and to identify areas that require improvement. The reporting quality of 33 RCT papers on 31 FFC that were received between April 1, 2015 and December 31, 2016 were analyzed by two experts with regard to consistency with the 29 Consolidated Standards of Reporting Trials (CONSORT) items. RCTs on FFC reported 13.8 (47.6%) of the CONSORT items, which is similar to those on FOSHU. There were 7 least reported items, including study design. Determining the reporting quality of FFC studies is an important way of identifying items that require improvement in future papers.

## 1. Introduction

Since first developing the concept in the late 1980s, Japan has been a leader in the field of functional foods with health claims (FHC). In Japan, three categories of FHC can qualify for labeling with the third function of foods (adjustment of physical condition to improve human health), namely (1) food for specified health uses (FOSHU), (2) foods with nutrient function claims (FNFC), and (3) foods with function claims (FFC). A new evaluation system for FFC, including a small number of agricultural products, was introduced and implemented according to the United States dietary supplement regulation on April 1, 2016 (Consumer Affairs Agency., 2016b). Some companies have recently taken advantage of the fact that FFC under the new evaluation system does not require FFC to be reviewed and approved by the Consumer Affairs Agency in Japan, and the number of FFC has accordingly increased to 1155 products (as of November 11, 2017).

Furthermore, the Ministry of Agriculture, Forestry and Fisheries of Japan aims to export valuable functional foods like FHC overseas as a national strategy. This strategy will require consideration of the differences in thinking about scientific evidence, and thereby help improve the global harmonization of regulatory systems. This will in turn produce a broad global understanding of the methods used in Japan to regulate functional foods (Tanemura, Hamadate, & Urushihara, 2017). However, differences in the regulation of FHC among countries often act as trade barriers (Fig. 1). For example, bowel regulation by Morinaga's Bifidobacterium longum BB536, which was "notified" as an FFC in Japan, was evaluated under the scientific opinions of the European Food Safety Authority (EFSA) (European Food Safety Authority., 2012). Nine out of 13 studies were conducted in Japan, and 3 of these 9 papers were rejected by the EFSA primarily because of the absence of a sufficient description of randomization (Ogata, 1997; Yaeshima, 1997, 2001). This indicates that the results of randomized controlled trials (RCTs) conducted in Japan may be reviewed by the regulatory authorities of other countries such as the EFSA, and must therefore be of sound quality. This experience of potential scrutiny by the agencies indicated that it is important to have adequate and precise reporting the methods, results and discussion on RCTs that clearly reflect the quality of FHC, in order to ensure unbiased judgement or validity of study results.

According to the new evaluation system on FFC, food business operators, which include food importers, manufacturers, retailers and producers, can evaluate the efficacy of their FFC either by a systematic review of the finished product or its functional substance(s), or by a RCT of the finished product. It is important to obtain reliable evidence regardless of the evaluation methods used. A review of evidence based on systematic reviews was conducted by the Consumer Affairs Agency in 2016 (Consumer Affairs Agency., 2016a) clarified the systematic review process and reporting points and recommended best practices, and has proved useful for food business operators. The Consumer Affairs Agency pointed out that the quality of papers reporting RCTs of

*Abbreviations:* FOSHU, food for specified health uses; FFC, foods with functional claims; CONSORT, consolidated standards of reporting trials

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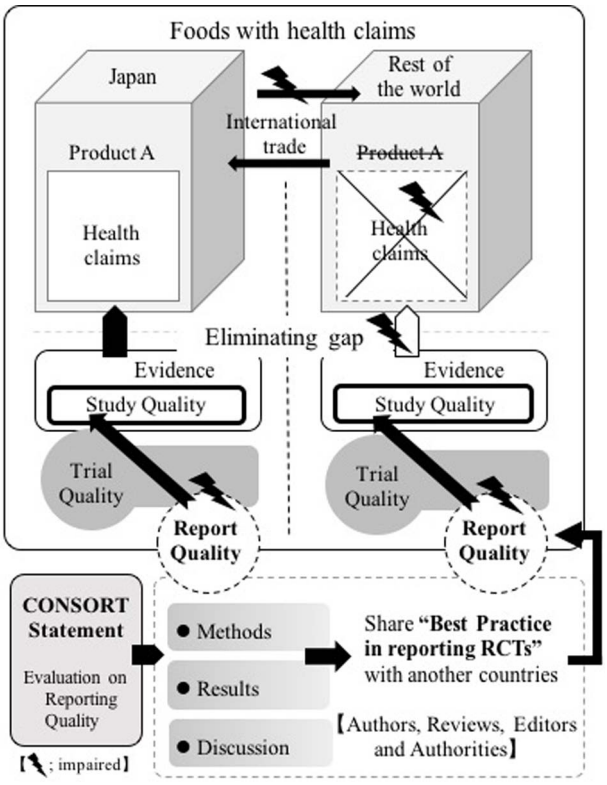


**Fig. 1.** The eliminating gap under international trade between Japan and rest of the world considering health claims of the global regulatory environment.

FFC is important for improving the quality of systematic reviews of FFC (Consumer Affairs Agency, 2016a). Under the new regulation, papers reporting RCTs must be published by a scientific journal with a peer review system to show that evidence from the RCT is reliable, thereby replacing the Consumer Affairs Agency review.

Against this background, assessment of the study quality of RCTs aimed at evaluating evidence on the efficacy and safety of FFC assumes new importance. This knowledge can subsequently be passed on to consumers. Study quality can be assessed according to (1) reporting quality or (2) trial quality, with the former being related to the latter. Insufficient reporting on the results of RCTs, which included the method, results and discussion, has been suggested to be associated with biases and reduced comprehension of the validity of clinical trials results (Consumer Affairs Agency., 2017). Insufficient reporting of randomization and blinding methods may lead to overestimation of the intervention effect (Schulz, Chalmers, Hayes, & Altman, 1995). Insufficient reporting of information in published papers on RCTs hinders the ability to assess the validity of the results, and may lead to bias. It is therefore important to first check a study's reporting quality for all readers and consumers before assessing trial quality; that is, to first check whether a report contains sufficient information to allow the quality of the reported trial to be evaluated.

A previous study showed that the reporting quality of RCT papers on FOSHU in Japan was worse than that of RCTs published in major journals despite the review system for FOSHU by the Consumer Affairs Agency of Japan (Noriuchi & Ohashi, 2006). The reporting quality of RCTs has also been evaluated in other medical research fields, including those conducted in Japan and other countries (Uetani, Nakayama, Ikai, Yonemoto, & Moher, 2009).

Here, we aimed to identify the reporting quality and its associated issues for RCTs of FFC to establish an acceptable standard, which will be helpful for developing future best practices (Fig. 1). We will present the main learning outcomes, which enhance understanding at a global level from the following three perspectives: (1) The precautions that need to be taken in reporting the results of a randomized-controlled trial of FFC in compliance with the CONSORT statement have been revealed from this study; particular focus should be given on how to write about the item of trial design, sample size, allocation and blinding, results of outcomes and estimation and the generalizability of the results by authors, reviewers, editors and authorities. (2) The evidence level of FFC required for international trade, can be shared with the world and (3) the papers with high quality reporting inform quality writing research papers in the area of functional foods.

## 2. Materials and methods

### 2.1. Selection of papers

FFC were selected from the database of FFC on the Government of Japan's Consumer Affairs Agency website. Published papers about these FFC were subsequently selected based on the following criteria: (1) randomized clinical trial design, and (2) documents regarding the FFC were submitted to the Consumer Affairs Agency from April 1, 2014 to December 31, 2016. Exclusion criteria were (1) re-analysis of clinical trials, (2) single arm design, and (3) duplication of evidence from RCTs for the same functional substance.

### 2.2. Research items

The following background information was collected for each study: journal information (country in which the journal was published, whether or not use of the consolidated standards of reporting trials (CONSORT) statement was indicated in the author guidelines, language), study information (affiliation of authors, publication date, number of pages), RCT details (number of arms in trials, number of subjects, trial design).

Twenty-nine items in the CONSORT statement were used in this study (Supplementary Table 1). We excluded eight of the 37 total items because they were considered to be conditional on study details and were therefore not applicable to all studies. The excluded items were "3b) important changes to methods after trial commencement (such as eligibility criteria), with reasons"; "6b) any changes to trial outcomes after the trial commenced, with reasons"; "7b) when applicable, explanation of any interim analyses and stopping guidelines"; "12b) methods for additional analyses, such as subgroup analyses and adjusted analyses"; "14b) why the trial ended or was stopped"; "17b) for binary outcomes, presentation of both absolute and relative effect sizes is recommended"; "18) results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing prespecified from exploratory", and "24) where the full trial protocol can be accessed, if available".

### 2.3. Evaluation procedure

The reporting quality of papers on FFC were checked for any description or indication of the CONSORT statement items (Moher et al., 2010). Since the purpose of this research was not to evaluate trial quality, but reporting quality, we did not evaluate the scientific quality of the RCTs. The study plan, CONSORT statement checklist and an explanation for utilization of the checklist were shared with two reviewers who evaluated the reporting quality of the RCTs. Reporting quality was separately reviewed and the results were collated. Any differences between the evaluations were discussed and re-evaluated until there were no discrepancies.

### 2.4. Analysis

The number and proportion of papers were reported for background information items and were calculated first. The total number of CONSORT items (out of 29) reported in each paper was calculated to