Received: 12 February 2021 | Revised: 9 July 2021 | Accepted: 6 August 2021

DOI: 10.1111/pai.13654

ORIGINAL ARTICLE

WILEY

The dilemma of open or double-blind food challenges in diagnosing food allergy in children: Design of the ALDORADO trial

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Funding information
The Pediatric Department of Martini Hospital, Groningen, is supported by an unrestricted research grant from Nutricia, the Netherlands. The funding sources had no role in the study design; in the collection, analysis or interpretation of data; and in the writing of the report or the decision to submit the article for publication.

Editor: Hugh Sampson

Abstract

Background: It is of major importance to diagnose food allergy accurately. Current guidelines support the use of oral food challenges to do so. The double-blind placebo-controlled food challenge (DBPCFC) has been regarded as the 'gold standard' for decades. However, DBPCFCs are costly, and time- and resource-intensive procedures. Structural implementation of less demanding open food challenges will only find support if research demonstrates that their outcome is comparable to DBPCFC, yet this has been proven difficult to investigate.

Methods: We performed a literature review to investigate the diagnostic accuracy of oral food challenges and interviewed 19 parents of children with proven or suspected food allergy about the design of a trial to study this.

Results: An overview of the dilemma of diagnosing food allergy using oral food challenges, and the methodological issues and parents' opinions to study this. No comparative studies have been performed using the latest guidelines on oral food challenges.

Conclusions: There is an urgent need to investigate the diagnostic accuracy of different oral food challenge protocols. We present the rationale and design of the ALDORADO trial (ALlergy Diagnosed by Open oR DOuble-blind food challenge) that has been set up to investigate whether the outcome of the open food challenge is comparable to DBPCFC.

KEYWORDS
adverse effects, allergens, allergy and immunology, diagnosis, double-blind method, food, food hypersensitivity, placebos

1 | INTRODUCTION

'What is food to one, to another is rank poison', Roman philosopher Titus Lucretius Carus quoted in one of his poems, thereby indicating one of the first references to food allergy.[1] From that moment, reports on food-allergic reactions can be found in the literature for centuries. Prausnitz discovered in 1921 that a transferable factor in serum was associated with allergen sensitivity, today known as immunoglobulin E (IgE) antibodies.[2] In the decades that followed, food allergy had raised attention and, with it, the need for reliable

diagnostic tools.[3] Dr. Mary Loveless, a paediatrician, provided the promising basis for the double-blind oral food challenge to diagnose food allergy, and since 1976, the double-blind placebo-controlled food challenge (DBPCFC) had been increasingly accepted as 'gold standard' to diagnose food allergies.[4–6]

Over the past decades, an increasing number of people suffer from self-reported food allergy.[7] Globally, research has shown differences in food allergy prevalence between continents and indicated a growing prevalence of clinically confirmed food allergies.[8,9] As suspected food allergy is associated with a poorer quality of life, it is of great importance to confirm or exclude the diagnosis and act accordingly.[10] Moreover, if childhood food allergy is suspected, parents will be hesitant to introduce a variety of foods into their child's diet leaving it unclear whether the food can be eaten safely. Given the necessity of early introduction of potential food allergens to prevent the development of an allergy, it is of utmost importance to determine whether someone is food-allergic or not.[11–14] In addition, confirmation of food allergy by oral food challenges (OFCs) may lead to successful elimination of the specific food from the diet, avoiding potential life-threatening food reactions.

Key Message

Current guidelines support the use of oral food challenges to diagnose food allergy accurately. This paper discusses the challenges of diagnosing food allergy using either open or double-blind food challenges, and the methodological issues to study this. A very important topic for practitioners and further research is discussed: how to diagnose food allergy in children?

2 | ORAL FOOD CHALLENGES

Since 1976, three types of oral food challenges have been used to expose a suspected food-allergic child to the potential food allergen in increasing dosages and in a controlled and standardized setting, namely the open, single-blind and double-blind placebo-controlled food challenge.[3,15] OFCs are mainly used for three goals: to confirm the diagnosis of food allergy, to identify the threshold dose and to determine possible tolerance in case the food has been excluded from their diet previously.[16,17] The simplest method is the open food challenge, in which case the healthcare professionals, the caregiver(s) and the child are aware of the food being administered. In the single-blind food challenge, the masked food allergen is administered in a way that only healthcare professionals know which food is offered but not the caregiver(s) or child, to avoid the possibility that the outcome is influenced by the (psychological) fact that the food is known or tasted. A third possibility is the double-blind placebo-controlled food challenge, which consists of two test days: at 1 day, the potential food allergen is introduced (verum) in a masked version; and at the other day, a placebo is offered in random order. This provides the opportunity to introduce the food in such way that neither the child, the caregiver(s) nor the healthcare professionals know when the potential food allergen is being eaten, thereby eliminating potential bias.[15,18] The open food challenge and the DBPCFC are diagnostic tools most frequently used to investigate whether someone is food-allergic.[19]

The DBPCFC is regarded as the 'gold standard' for diagnosing food allergy.[6] Current guidelines have provided important steps towards methodological standardization of DBPCFC, which include randomization of test days, masking of the allergen, definition of dosages of allergens and intervals between dosage steps during OFC and scoring of signs and symptoms.[6,20,21] However, there are some drawbacks as DBPCFC is resource-intensive, time-consuming and expensive.[22] Since there is no comparative test to investigate DBPCFC, its accuracy for diagnosing 'real' food allergy is not known and it has been suggested to perform repeated DBPCFCs.[23] The DBPCFC is approximately twice as expensive as the open food challenge due to the need for a randomized and blinding procedure and experienced personnel (e.g., kitchen staff that is capable of preparing the provoking material in the correct manner). It has therefore been proposed that the less intensive open food challenges might be sufficient in specific cases.[7,15] This may be valuable if parents and/or child are not anxious or if the food has never been eaten before (no bias), although this assumption has not been formally investigated.

Furthermore, it has been proven difficult to interpret the occurrence of subjective and objective signs and symptoms in a consistent manner.[24] To address this issue, multiple scoring systems have been developed (e.g., PRACTALL), but still, no universal scoring system is available and different methods exist to score the presence and severity of food reactions during OFCs.[25,26] In DBPCFC, symptoms can occur after administration of placebo, which might also complicate interpretation of OFC outcome.[27] Next to this, previous research showed that uncertain symptoms during open food challenge were followed by successful introduction at home in 80% of the cases.[28]

3 | OTHER DIAGNOSTIC METHODS

Other available diagnostic methods, such as serum specific IgE (sIgE) and skin prick test (SPT), have been used to predict the outcome of the 'gold standard'. Previous studies have shown that these laboratory measurements alone do not provide enough information to conclude whether someone is actually food-allergic and thus cannot replace OFCs.[15,29] However, during the past decade, component-resolved diagnostics (CRD) provided detailed information on sensitization to specific IgE components and might improve prediction of food allergy.[30] Several studies were able to demonstrate high accuracy of Ara h 2 in the diagnosis of peanut allergy in children.[31] Next to this, Cor a 9 and Cor a 14 were found to be important markers for hazelnut allergy.[32] For walnut, Jug 1, 2 and 3 showed to be important

markers.[33,34] Previous research has also shown that Ana o 1, 2 and 3 could be used as predictor of a positive outcome of OFCs with cashew nut, although these markers alone could not discriminate between mild and severe food allergy.[35,36]

The basophil activation test (BAT) is another potential valuable diagnostic, which can be used to identify activation markers on the surface of basophils.[37] Previous research showed that, in cases where SPT and CRD are unequivocal, BAT could be used as second step to conclude whether someone is peanut-allergic, thereby limiting the number of OFCs needed.[38] Moreover, a recent study has shown that BAT could provide information about the eliciting or threshold dose, and the severity of a possible allergic reaction to peanut.[39]

Despite these encouraging prospects, BAT still has some limitations. First, BAT is complex to perform and therefore limited to specific (research) laboratories.[40] Second, international guidelines support further development of BAT as an integral diagnostic tool in food allergy, but conclude that OFCs are still necessary to perform, especially if it is expected that food allergy is uncertain.[41] Therefore, until BAT has been developed in such a way that is suitable for daily practice, the majority of allergy clinics around the world will remain to use OFCs for routine diagnosis of food allergy.

4 | CURRENT RECOMMENDATIONS FOR CLINICAL PRACTICE

The European Academy of Allergy and Clinical Immunology (EAACI) position paper and national Dutch guidelines recommend to perform a DBPCFC if a positive or inconclusive outcome is expected.[20,21] The authors stated that it is reasonable to expect this outcome if previous consumption led to the development of subjective or unconvincing objective symptoms, if symptoms occurred within 2 h after ingestion, if the patient suffered from eczema and/or if the patient has become anxious. On the contrary, it is recommended to perform an open food challenge if a negative result is expected (e.g., the food has been eaten without symptoms in the past and/or an allergic reaction has occurred in the absence of sensitization).[20] In case the outcome of the open food challenge is not convincing, it is advised to perform a DBPCFC afterwards. This advice might be given if only subjective, mild objective or late symptoms occurred during the open food challenge and/or if the occurred symptoms did not match the expected allergic reaction.[6,21] Furthermore, Dutch guidelines recommend to perform an open food challenge after DBPCFC with negative outcome to find out whether an age-appropriate amount of the food can be eaten safely.[21] See Table 1 for a summary of all published recommendations.

5 | PLACEBO REACTIONS

Administration of placebo is part of a DBPCFC as a control. Interestingly, the occurrence of allergic symptoms has been reported on placebo days (e.g., urticaria, flare-up of eczema, diarrhoea or vomiting), presumably due to stress at the day of the food challenge, expectation bias and fluctuation of (allergic) symptoms that may or may not be related to food responses. Furthermore, children who are suspected to be food-allergic often suffer from other atopic diseases (e.g., eczema, asthma or allergic rhinoconjunctivitis), which can influence the occurrence of possible symptoms that can be (mis-) interpreted as food reactions.

The prevalence of false-positive OFC outcomes was previously defined as 'the number of subjects who responded with a positive reaction to the placebo challenge, divided by the total number of challenges'.[42] In one study, positive placebo events occurred in 17 (12.9%) out of a total of 132 DBPCFCs for cow's milk, egg, peanut, hazelnut and soy, consisting of symptoms from all organ systems except anaphylaxis. This study population consisted of a total of 105 sensitized children (median age 5.3 years; 64.8% male). Sensitization was determined by skin prick testing (median 0.90 histamine equivalent prick) and sIgE (median 3.54 kU/L). Only three children were exposed for the first time during a DBPCFC as part of the study, and 102 of 105 children had previously eaten the specific food. Comorbidities were present as follows: 89% of the children suffered from eczema, 37% had rhinitis, and 55% were known to be asthmatic. About two third of the placebo events consisted of objective symptoms. Local and upper airway symptoms were significantly

TABLE 1 Overview of differences between oral food challenges

	Open	Single-blind	DBPCFC
Awareness of food administration	child parents caregiver	caregiver	third party (e.g., kitchen staff)
Risk of bias	high	high	low
Burden	1 day	2 days	2 days
Administration of placebo	no	possible	yes
Masking of food	no	yes	yes
Risk of psychological interference	likely	possible	limited
Risk of placebo reactions	no	yes	yes

Note: Adapted from Dutch guidelines and EAACI position paper.[20,21]

Abbreviation: DBPCFC, double-blind placebo-controlled food challenge.

more common during immediate events when compared to symptoms during late-onset events (i.e., between 2 and 48 h after the last challenge dose). Thus, a variety of symptoms can occur during the administration of a placebo and require the DBPCFC to be repeated in selected cases.[42]

Another study aimed to retrospectively analyse allergic reactions during 740 placebo challenges, independent of the potential food allergen that was tested (cow's milk, hen's egg, soy and wheat, respectively). On 21 of 740 (2.8%) placebo challenge days, symptoms occurred, mainly in children up to 1.5 years old. Skin symptoms were reported the most, mainly worsening of eczema (atopic dermatitis). All these 21 children had eczema, five asthma and two allergic rhinoconjunctivitis. Within the group of children who did not react during the administration of placebo, 77.6% suffered from eczema, 15.3% suffered from asthma, and 7.6% suffered from allergic rhinoconjunctivitis. Median total IgE levels were 201 and 110.5 kU/L within the group a placebo reaction did and did not occur, respectively. Therefore, the authors strongly advise to perform DBPCFC in young children who suffer from eczema.[43]

Summarily, the occurrence of symptoms after placebo administration during DBPCFC underscores the potential false-positive outcome of open food challenges, which are subject to bias.[44]

6 | METHODS: CHALLENGES WHEN COMPARING THE OPEN FOOD CHALLENGE TO DBPCFC

We performed PubMed searches to retrieve papers discussing the methodology of oral food challenges, as well as manuscripts actually comparing open food challenges to DBPCFC. Moreover, we interviewed 19 parents to get their opinion on such studies, as well as their willingness to participate with their children.

Several attempts have been made to standardize the diagnostics for food allergy.[23] At this time, OFCs remain most reliable in the majority of cases.[45] However, the previously summarized aspects clarify that DBPCFC might possibly be redundant in daily health care for many children with a suspected food allergy. To the best of our knowledge, only few studies have been performed to compare the open and double-blind food challenge.

The design of such study is very challenging. A first concern is the safety of the child.[46] In a comparative study, each child should undergo both a DBPCFC and an open food challenge despite the outcome of the first OFC, which increases the risk of a repeated (severe) allergic reaction. It is therefore essential to define clear stopping criteria to guarantee safety as parents and/or children might be hesitant to participate. Thus, the use of a standardized scoring system with predefined stopping criteria is essential. This could also be helpful to motivate participants to continue the study if symptoms occurred during the first OFC. However, not completing the second OFC if a severe reaction has occurred during the first one may introduce bias as the most severe cases may be excluded during the course of the study.

Second, the minimum age of children who should be invited to join such study is debatable. Children may be asked to decide for themselves if they would want to join a study, but this excludes many preschool children, which might be undesirable given the high prevalence of most food allergies at preschool age. Thus, a cohort design, including children who are referred and selected for OFC by the attending physician, is preferable as this has the lowest risk of introducing bias.[23]

Third, an OFC may hypothetically induce desensitization and thus affect the outcome of the subsequent test. Previously, successful desensitization or even sustained unresponsiveness was achieved after oral immunotherapy (OIT) for specific food allergens.[47,48] However, we expect this risk to be negligible since exposure for a longer period of time is usually necessary to obtain positive results from regular OIT treatment. Also, as tolerance can develop by repeated food allergen ingestions, there should be a predefined minimum time frame of at least 7 days between the two OFCs.

Fourth, methodological issues regarding the OFCs should be critically appraised, such as the use of quality-controlled, sensory-tested recipes, the comparison of DBPCFC and open food challenge with the same masked allergen in the same matrix, and a similar and sufficient amount of allergen that can be given in both OFCs.

Finally, specific questions relate to the design of a comparative study, as the outcome of the first OFC may affect participation and interpretation of the second OFC. If the OFC is performed blinded, healthcare professionals performing the second OFC should not be aware of the outcomes of the first OFC, complicating execution of such a study.

7 | PREVIOUS STUDIES COMPARING THE OPEN FOOD CHALLENGE TO DBPCFC

Only two studies have compared different types of OFCs (see Table 2).[49,50] These studies have addressed the study design challenges mentioned above in different ways.

The first study included 41 British children (1–15 years of age), whom all were sensitized for or had previously reported an allergic reaction to cow's milk, egg, wheat or prawn. These children took part in a population-based study aiming to define the prevalence of food allergy. All participants underwent an open food challenge and, if positive, were invited for DBPCFC.[49] Of the 69 children with positive open food challenges, 41 consented to DBPCFC. The DBPCFC outcome was positive in 28 of 46 challenges (60.9%) in 41 children. Symptoms on placebo days occurred once during DBPCFCs with positive outcome and five times during DBPCFCs with negative outcome. This study has several limitations. First, the protocol used to perform OFCs is different from the ones regularly used nowadays (e.g., dose schedule and challenge period). Second, symptoms were not always objectified by a clinician but only reported by the parents in some cases. Third, symptoms that occurred during clinically performed OFC were not scored following an internationally accepted scoring system. Finally, specificity and sensitivity for OFCs could not

TABLE 2 Comparison of open food challenge and DBPCFC (previous studies)[49,50]

	Venter et al. (2007)[49]	Wang et al. (2007)[50]
Number of participants	41	20
Age (range)	1–15 years (63% ≤2 years)	25–61 years
Major inclusion criteria	History of food hypersensitivity or with sensitization to a food without known previous consumption	Food-allergic compatible symptoms At least one intradermal food weal
Major exclusion criteria	Severe reactions during OFC and/or history of anaphylaxis	No history of food anaphylaxis
Dose schedule	1 day†: total of 8–10 g of dried food 1 week‡: normal daily portion	Standard portion sizes
Food	Milk, egg, wheat, prawn	Organic foods (including baker's yeast, black pepper, corn, egg, garlic, soy, malt, cow's milk, and wheat)
Method performing DBPCFC	Only if open challenge was positive 1 day or 1 week In hospital (positive SPT), at home (negative SPT) or combination	2 days (interval of 5 to 7 days) 2 identical meals at each day (either verum or placebo)
Method performing open food challenge	1 day or 1 week In hospital (positive SPT), at home (negative SPT) or combination	2 normal servings in 1 day
Number of performed challenges	46 DBPCFC	38 DBPCFC and 28 open
Positive OFC outcome	28 of 46 (60.9%)	DBPCFC: 25 of 38 (65.8%) Open: 25 of 28 (89.3%)
Allergic reaction at placebo day	6	7 of 20 patients
Percentage of false negative	N/A	N/A

Abbreviation: DBPCFC, double-blind placebo-controlled food challenge; OFC, oral food challenge.

†in case of immediate symptoms during previous allergic event.

‡in case of delayed symptoms during previous allergic event.

be analysed as DBPCFC was not performed after open food challenges with a negative outcome.

A second study compared open food challenges to DBPCFC in an adult population of 20 patients (mean age 46 years) with suspected food allergy and at least one intradermal food weal from Singapore.[50] OFCs were performed with several foods in standard portion sizes, starting with open food challenges, and, in selected cases, followed up by DBPCFC. Remarkably, in only 1 out of 20 cases, serum specific IgE was increased for the food used to perform the OFC. Reported symptoms were variable, started late (after approximately 2 h or later) and included mostly nasal and eye symptoms, and headache. Seven out of 20 patients (35%) reported placebo reactions. The authors report that the open food challenge had a sensitivity of 65.8% (25/38) with a positive predictive value of 89% when compared to DBPCFC. However, interpretation of this study is hampered by the atypical, non–IgE-mediated symptoms and the non-validated DBPCFC protocol.

In conclusion, until now there is no clear answer whether open food challenges are comparable to DBPCFCs. No studies have been performed that use current quality standards and validated scoring systems. Therefore, it is recommended to compare these oral food challenges in individual patients following the latest guidelines in future studies.[6,20,21] Since such a study design is challenging, we

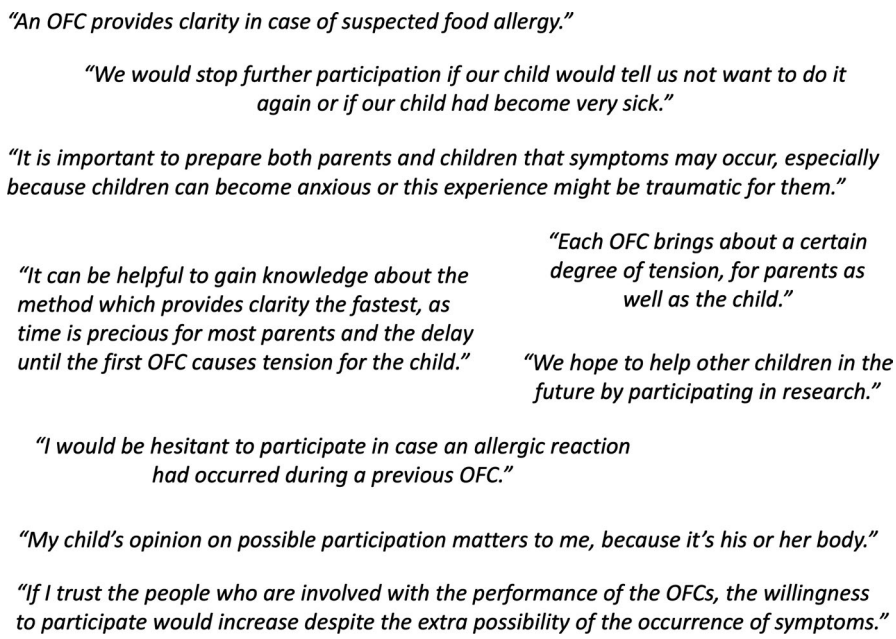

FIGURE 1 Selection of answers provided by parents during the interviews. OFC, oral food challenge

considered it essential to ask parents of children with a (suspected) food allergy for their opinion.

8 | ETHICAL CONCERNS AND PARENT INVOLVEMENT

Parents were interviewed to investigate their willingness to participate in a hypothetical study to compare the DBPCFC and open food challenge, as well as their opinion on which important aspects that should be taken into account (MEC 2020–053, Martini Hospital). We included both parents whose child had already underwent at least one OFC (n = 12), as well as parents who were advised to perform their child's first OFC (n = 7). Parents were selected irrespectively of the fact whether it was an open food challenge or DBPCFC. We did not include children, because we aimed to collect information useful for a study design and estimated this would be too difficult for children to understand. In case parents of teenagers were interviewed, they were stimulated to discuss the topic with their child beforehand so their opinion could also be taken into account. As we included a limited number of nineteen parents and did not interview children, there might be a selection bias. However, the results provide insight into aspects that appear to be relevant for these parents.

The main results of these interviews showed that all parents understood the relevance of the study and were well aware of the necessity to perform an OFC to draw firm conclusions about a suspected food allergy. On the contrary, they mentioned that they themselves and their child may be more anxious to perform a second OFC in case severe objective symptoms (e.g., dyspnoea) or discomfort occurs during the first OFC. Therefore, they recommended to define clear stopping criteria. A selection of quotes from parents can be found in Figure 1.

TABLE 3 Criteria to end an oral food challenge

OFC will be ended if one of the following symptoms (or combination) occurs:

1. Skin
   a. generalized marked erythema (>50%)
   b. ≥3 urticaria (if not located around the mouth) or generalized involvement (>10)
   c. significant lip or face oedema
2. Respiratory
   a. nose: long bursts, persistent rhinorrhoea or continuous rubbing
   b. eyes: continuous rubbing, periocular swelling, reddening
   c. expiratory wheezing to auscultation
   d. inspiratory and expiratory wheezing to auscultation
   e. use of accessory muscles or audible wheezing
   f. laryngeal: frequent dry cough or hoarseness
   g. laryngeal: stridor
3. Gastrointestinal
   a. oral cavity: blisters of oral mucosa
   b. >1 episode of emesis
   c. >1 episode of diarrhoea
4. Cardiovascular
   a. >20% drop in blood pressure
   b. cardiovascular collapse
5. Neurologic
   a. significant change in mental status
   b. loss of consciousness

Note: Adapted from Grabenhenrich et al.[26]
Abbreviation: OFC, oral food challenge.

9 | A PROPOSAL FOR A DIAGNOSTIC CLINICAL TRIAL OF OPEN FOOD CHALLENGES VERSUS DBPCFCs

Based on parent's input, as well as methodological considerations described in this paper, the ALDORADO (ALlergy Diagnosed by

Open oR DOuble blind food challenge) trial was designed to test the hypothesis that the open food challenge outcome is comparable to the 'gold standard' DBPCFC. The major aspects of this trial are summarized below. Our study protocol has been approved by the Dutch Central Committee on Research Involving Human Subjects (CCMO), and further information about the study design can be found in the Dutch trial register (URL: https://www.trialregister.nl/trial/9533).

Participants will undergo a DBPCFC and open food challenge for the potential food allergen according to the EAACI guidelines.[6] In short, both DBPCFC (2 days) and open food challenge (1 day) consist of a maximum of seven steps (increasing dose) and 30 min of waiting time between each dose. Based on the EAACI guidelines, the total amount of food protein that should be offered during OFCs is 4443 milligrams with a starting dose of 3 mg.[6] For this study, during the open food challenge the recipe for the verum day of DBPCFC will be used to exclude possible matrix differences. In case the outcome of both food challenges is negative, parents will receive instructions to introduce the specific food into the child's diet.

As patients and/or their parents might be reluctant to perform a second test if symptoms occurred during the first one, we decided not to perform the OFCs in random order but to start with the DBPCFC. Furthermore, the DBPCFC outcome will be kept blinded until the last (open) food challenge has been performed. Parents will be instructed not to introduce the food into their child's diet until

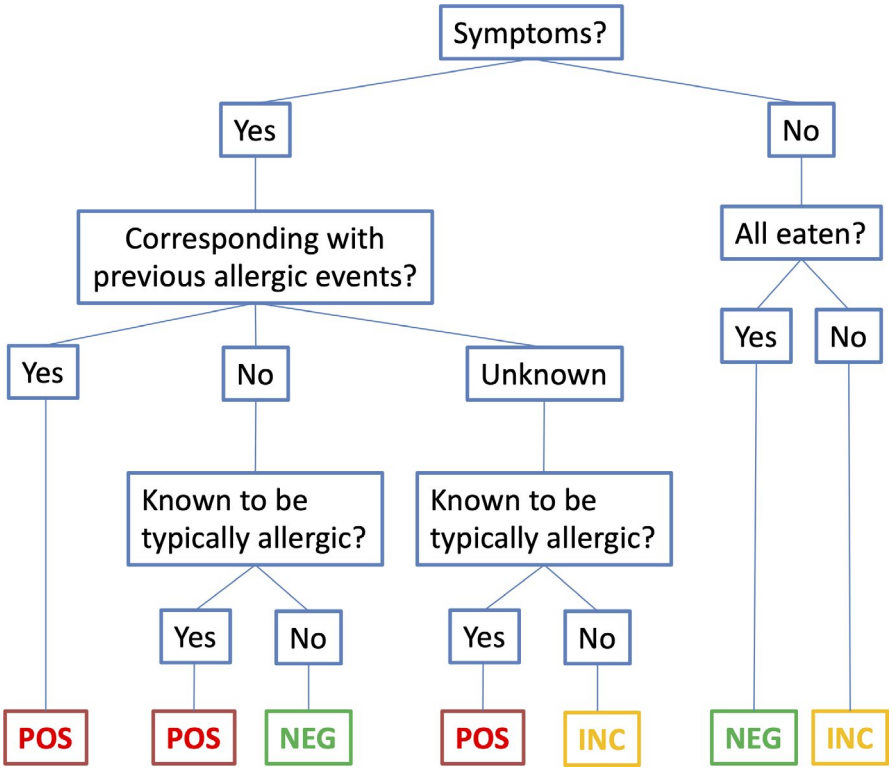

FIGURE 2 Criteria to determine OFC outcome. Symptoms are classified as typically allergic if these are consistent with type 1 immune response. INC, inconclusive; NEG, negative outcome (i.e., tolerant); OFC, oral food challenge; POS, positive outcome (i.e., food-allergic)

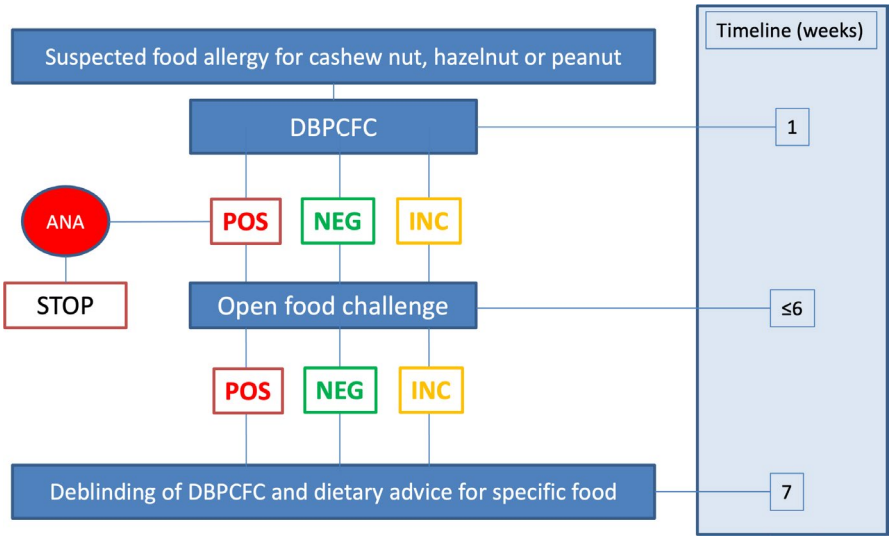

FIGURE 3 Flow chart of ALDORADO trial. OFC outcome is determined according to protocol. Further participation is terminated if anaphylaxis occurs. ANA, anaphylaxis; DBPCFC, double-blind placebo-controlled food challenge; INC, inconclusive; NEG, negative outcome (i.e., tolerant); OFC, oral food challenge; POS, positive outcome (i.e., food-allergic)

this last and final test has been performed. We defined unequivocal criteria to decide whether the OFC can be continued in case of severe symptoms (see Table 3). In case of an anaphylactic reaction, participation in the study will be terminated as it is deemed unethical to expose a child to a potential highly harmful food allergen.[51] We use predefined criteria to decide what the OFC outcome would be at the day the challenge has ended (Figure 2). Furthermore, during a weekly scheduled meeting the performed OFCs will be discussed to decide whether it is safe to perform the second challenge or if participation should be ended. The interval between both challenges will be at least one and no more than 6 weeks.

Symptoms are registered using the scoring system as proposed in a recent publication by Grabenhenrich et al. based on the EAACI guidelines.[6,26] To avoid bias as a healthcare professional may remember a previous food reaction, the second food challenge of each patient will be performed by a different nurse. See Figure 3 for a flow chart of our study.

10 | OUTCOME MEASURES

The primary outcome measure will be the difference in the proportion of positive outcomes of the DBPCFC and the open food challenge.

The following secondary outcome measures will be analysed: OFCs with negative and/or inconclusive outcome, eliciting dose (i.e., first dose that causes allergic symptoms) and stopping dose (i.e., cumulative total dose that has been eaten), occurrence and severity of symptoms on all challenge days and the percentage of false-positive reactions (i.e., the occurrence of allergic symptoms on placebo day in case of DBPCFC).

11 | CONCLUSION

In conclusion, a pressing matter in diagnosing food allergy should be further investigated: Is the outcome of open and double-blind placebo-controlled food challenges comparable in children suspected to be food-allergic? To the best of our knowledge, no studies are performed that have properly compared the open food challenge and DBPCFC. We summarized the major aspects of our ALDORADO trial, which has been designed to address this challenging research question.

ACKNOWLEDGEMENT

Not applicable.

CONFLICT OF INTEREST

AS reports unrestricted grants from Nutricia Netherlands, ALK, Allergy Therapeutics, Thermo Fisher, Meda Pharma, Chiesi, Teva Netherlands, Astra Zeneca, Novartis, GlaxoSmithKline, and Bausch & Lomb NL outside the submitted work. The authors report no proprietary or commercial interest in any product mentioned, concept discussed or personal relationships with other people or organizations that could influence their work and conclusions in this article.

AUTHOR CONTRIBUTIONS

Wouter de Weger: Conceptualization (equal); Investigation (equal); Methodology (equal); Writing-original draft (equal). **Aline Sprikkelman:** Conceptualization (equal); Methodology (equal); Writing-review & editing (equal). **Irene Herpertz:** Conceptualization (equal); Writing-review & editing (equal). **Gerbrich van der Meulen:** Conceptualization (equal); Writing-review & editing (equal). **Judith Vonk:** Conceptualization (equal); Methodology (equal); Writing-review & editing (equal). **Arvid Kamps:** Conceptualization (equal); Methodology (equal); Supervision (equal); Writing-review & editing (equal). **Gerard Koppelman:** Conceptualization (equal); Methodology (equal); Supervision (equal); Writing-review & editing (equal).

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How to cite this article: de Weger WW, Sprikkelman AB, Herpertz CEM, et al. The dilemma of open or double-blind food challenges in diagnosing food allergy in children: Design of the ALDORADO trial. *Pediatr Allergy Immunol*. 2022;33:e13654. https://doi.org/10.1111/pai.13654