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| protocol THE FLAKE STUDY |
| The Flake Study: Investigating the Rate of Flake Co-allergy in Fish Allergic Children |
| Protocol Version 2.7, date: 10/01/19/12/18**Revision Chronology:**

| **Date of change** | **Summary of changes** |
| --- | --- |
| **10/01/19** | **Protocol amended as per initial RCH HREC review** |
| **24/08/18** | **Recruitment, methodology and adverse events sections substantively rewritten as per initial ethics review.**  |
| 12/09/18 | **Peer review suggestions regarding long term follow up suggestions and ensuring IgE-fish allergy at recruitment incorporated** |
| **10/10/18** | **Revisions as per Drug and Device Trial Subcommittee** |

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# PROTOCOL SYNOPSIS

|  |  |
| --- | --- |
| ***Title*** | **The Flake Study: Investigating the Rate of Flake Allergy in Fish Allergic Individuals** |
| ***Objectives*** | 1. To ascertain the rate of tolerance to gummy shark in fish allergic children. Tolerance is defined as the ability to successfully ingest gummy shark at medically supervised oral food challenge (OFC)..2. To assess the predictive value of allergy skin prick testing (SPT) using homogenized gummy shark extract to assess for gummy shark allergy versus clinical tolerance.3. To assess the predictive value of using gummy shark immunoblot in the serum of fish allergic children to assess for gummy shark allergy versus clinical tolerance.4. To identify other possible fish species to which fish allergic children may be clinically tolerant by serum immunoblot to novel Australian fish allergens. |
| ***Design*** | This is a prospective interventional study, where the outcome of interest in tolerance or allergy to gummy shark in children with fish allergy. The design includes a medically supervised food challenge to gummy shark, skin prick testing to gummy shark and various bony fish species, and a single blood test. |
| ***Outcomes*** | Primary outcome:The proportion of fish allergic children who are tolerant to gummy shark at a medical supervised OFC.Secondary outcomes:Determining the accuracy of the SPT and immunoblot to homogenized gummy shark extract in predicting a positive/negative challenge outcomes |
| ***Study Duration*** | 24 months |
| ***Number of participants*** | 35 participants |
| ***Population*** | Fish allergic children |
| ***Number of sites*** | Epworth Richmond  |

#

# GLOSSARY OF ABBREVIATIONS

|  |  |
| --- | --- |
| ***ABBREVIATION*** | ***TERM*** |
| *AE* | *Adverse Event* |
| *CRF* | *Case Report Form* |
| *HREC* | *Human Research Ethics Committee* |
| *ASCIA* | *Australasian Society of Allergy and Clinical Immunology* |
| *OFC* | *Oral Food Challenge* |
| *SPT* | *Skin Prick Test* |
|  |  |

# ADMINISTRATIVE INFORMATION

# Sponsor

| **Study Sponsor** | **Epworth Research Institute**  |
| --- | --- |
| **Contact name** | **Professor Nikolajs Zeps** |
| **Address** | **185-187 Hoddle Street, Richmond, 3121** |

# Expected duration of study

The study is expected to last 24 months from the commencement of recruitment to the completion of data analysis.

#

# Contributorship

| **Name** | **Summary of contribution** |
| --- | --- |
| **Dr Sam Mehr****Consultant Allergist/Immunologist** **Epworth/RCH Hospitals****Primary Investigator** | **Initial draft and revisions** |
| **Dr John Ainsworth** **Consultant Paediatrician, Allergy/Immunology Fellow Epworth/RCH Hospitals** | **Initial draft and revisions**  |

#

# INTRODUCTION AND BACKGROUND

# Background and rationale

Food allergy in children is rising. Fish allergy is amongst the 6 most common causes of food

allergy in children[1]. Unlike allergy to foods such as cow’s milk, wheat and egg, fish allergy

tends to be persistent throughout life.

Current diagnostic methods for fish allergy, such as the allergy skin prick (SPT) and serum

specific IgE tests (ssIgE) rely on allergen extracts for determining the presence of IgE allergy antibodies to relevant allergenic protein components in fish. Because of a lack of local

Australian commercial fish extracts for allergy testing, diagnostic testing for fish allergy in

Australia usually relies upon extracts from European fish species, which are usually not

relevant in the diagnosis of fish allergy in Australian patients.

Due to these limitations, current recommendations are to avoid all types of fish in those with a history of IgE-mediated fish allergy. This is based on the observation that 30-50% of fish allergic individuals will cross-react to other species of fish[2]. However, some fish allergic patients can tolerate other species of fish, including tinned fish. There are anecdotal, unpublished reports of children with fish allergy that can tolerate gummy shark, also known as flake (*Mustelus antarcticus*), a commonly eaten species in Victoria. Although this has never been formally examined, it does makes biologic sense, given that most fish descend from the bony fish family, whereas sharks and rays descend from the cartilaginous group.[3] Thus it is likely that they have different proteins, which trigger the formation of allergy antibodies (IgE). No commercial testing tools for allergy to gummy shark currently exists, so predicting which fish allergic individuals may be tolerant to gummy shark (or other more distantly related fish species) is currently only possible by direct food challenge.

# Aim(s)

* Assess the rate of tolerance to gummy shark in fish allergic children as measured by

 by tolerance to gummy shark at medically supervised oral food challenge (OFC).

* To assess the predictive value of allergy skin prick testing (SPT) using homogenized

 gummy shark extract for gummy shark allergy/clinical tolerance.

* To assess the predictive value of using gummy shark immunoblot in the serum of fish allergic children for gummy shark allergy/clinical tolerance.
* To identify other possible fish species to which fish allergic children may be clinically

tolerant by serum immunoblot to novel Australian fish allergens.

# STUDY OBJECTIVES

**3.1 Primary objective:**

* To ascertain the rate of tolerance to gummy shark in fish allergic children. Tolerance is defined as the ability to successfully ingest gummy shark at medically supervised oral food challenge (OFC).

# 3.2 Secondary objectives:

* To assess the predictive value of allergy skin prick testing (SPT) using homogenized gummy shark extract to assess for gummy shark allergy versus clinical tolerance.
* To assess the predictive value of using gummy shark immunoblot in the serum of fish allergic children to assess for gummy shark allergy versus clinical tolerance.
* To identify other possible fish species to which fish allergic children may be clinically tolerant by serum immunoblot to novel Australian fish allergens.

# STUDY DESIGN

# Type of Study

This is a prospective interventional study, where the outcome of interest in tolerance or allergy to gummy shark in a fish allergic population. The design includes a medically supervised food challenge to gummy shark, skin prick testing to various fish species, and a single blood test.

# Study Setting

Children will be assessed at Epworth Hospital Richmond/Geelong, and OFC to

gummy shark will only be performed at Epworth Hospital Richmond.

The study is a collaboration with the Allergy/Immunology Department at Westmead Children’s

Hospital in Sydney (who are currently collecting serum from fish allergic children and sending

samples for immunoblot analysis to James Cook; but not offering challenges to gummy shark)

and James Cook University, Townsville, Queensland (who are processing the serum to

characterise novel fish allergens and provide homogenised extracts for fresh fish allergy skin

testing).

# PARTICIPANTS AND RECRUITMENT

1.

# Number of Participants

We aim to recruit 35 children for this study. Children will be prospectively recruited at the time of referral. Children referred to the Epworth Allergy specialists with a fish allergy, will be

offered the opportunity to participate in the study. Currently we see ~120 children per week

with various food allergies, and expect to be able to recruit 35 children with fish allergy over

the next 24 months.

# Data collection techniques:

# Eligibility Criteria

Participants will be recruited to the study only if they meet all of the inclusion criteria and none of the exclusion criteria.

# Inclusion criteria

Participants must be between the ages of 1 and 18 years have a convincing history of an IgE-mediated reaction to ingestion of an identified fish within the past 24 months and have a positive skin test (>3mm) and/or serum specific IgE to the fish species that triggered the allergic reaction.

# Exclusion criteria

Any child who has had an IgE-mediated allergic reaction to flake in the past will be excluded.

# Recruitment and identification of potential participants

Children aged between 1 and 18 years of age, who present prospectively for assessment to

Epworth Richmond or Geelong with an IgE-mediated fish allergy, are eligible to participate. Patients with objective cutaneous symptoms such as urticaria or angioedema will be recruited to ensure that they are likely fish allergic at the time of recruitment. Patients who meet the above inclusion criteria will be provided information about the study at the time of consultation and asked to contact the researchers via email should they wish to participate. Children with an anaphylactic reaction to other bony fish will not be excluded, but any child who has had an allergic reaction to gummy shark in the past will be excluded. If the patient subsequently contacts the researcher after the initial expression of interest, the patient will be sent written consent forms to complete. In addition, the study co-ordinator will not directly recruit anyone they see in their capacity as treating clinician. Prospective recruits will be identified by other clinicians with the onus on the potential participant to email the study co-ordinator, thereby removing any conflict of interest to the therapeutic relationship.

In addition, the oral food challenge database at Epworth Allergy Specialists will be searched to identify patients who have undergone a challenge to fish in the previous 24 months. Review of the medical record will be required to identify potential candidates (i.e. positive challenge to fish and positive ssIgE/SPT to the triggering fish). Patients who fit the inclusion criteria will be sent the same information sheet provided to prospective candidates about the study inviting them to participate. Should they wish to participate or require further information they can contact the researchers via email.

# Consent

Written consent will be obtained from the patient’s parent after the patient information sheet has been read and the consent form signed. Mature minors (age 14-16) and older participants will be able to consent via a separate written form.

# STUDY VISITS AND PROCEDURES

The study visit and follow up will consist of the following components:

1. ***Direct interview of patient:***  this will be performed by the Allergy/Immunology Fellow at Epworth in order to complete the case report form.

2. ***Skin Prick Testing:*** a panel of 12 commercial and fresh skin testing will be done which will include homogenized gummy shark (all fresh fish extract will be provided by James Cook

University and frozen prior to use; commercial allergen extracts of fish for skin

testing will be purchased and will be the same as used at the Children’s Hospital at

Westmead). Both novel homogenised SPT extracts sourced frozen from James Cook University and commercial extracts will be stored in a refrigerator at Epworth Hospital. Oral food challenges will proceed regardless of the size of the skin test wheal to flake. Although rare, a systemic reaction to SPT is possible, particularly where fresh extracts are utilised. To cover this possibility, there will be at least a 30 minute delay between the administration of the SPT and commencement of the OFC.

3.***Intravenous line and blood collection:*** this will be performed by the Epworth Allergy/Immunology Fellow and serum sent to Melbourne Pathology, for processing and storage at -20oC degrees. A topical local anaesthetic cream will be applied to the skin prior to venepuncture upon participant request. The intravenous line will remain in situ for the duration of the challenge and can be utilised in the unlikely event of severe anaphylaxis requiring either intravenous adrenaline infusion or provision of resuscitation fluids such as 0.9% normal saline. The serum will be batched and sent to James Cook University for performance of the Australian fish blot immunoassay. The serum samples will be de-identified prior to sending to James Cook University, but will be re-identifiable if required. James Cook University will perform immunoblots in kind, using novel Australian allergens isolated in-house to identify the specific proteins that IgE antibodies have been generated

against in fish allergic children. The samples will only be utilised for the purposes outlined

in this study and no ongoing consent will be sought for future studies. A positive result on the immunoblot to other fish will not result in a OFC to that fish; thus the test will not benefit the study participant directly.

*3.****Oral food challenge (OFC) to flake (gummy shark):*** Challenge will be conducted according to the ASCIA standard food challenge protocol, using incremental dosing of cooked gummy shark up to a total dose of 100 grams of gummy shark (a standard serve size; equivalent to 21 grams of protein). The gummy shark will be sourced and cooked by the patients themselves (as per standard clinical practice for food challenges) weighed prepared by the study nurses on the day of challenge. The increments (in grams of total gummy shark), which will be given every 20 min, and include: touch to the lip, 0.5g, 1.4g. 4.8g.14.3g.28.5g and rest of the fish (approximately 52g) equating to 21g of actual fish protein in total. The food challenge to gummy shark will proceed regardless of the size of the skin test to gummy shark. Cumulative and eliciting threshold doses will be recorded in grams of gummy shark ingested. A challenge will be deemed positive and stopped according to the PRACTALL criteria[4]. PRACTALL is a European/North American co-operative of allergist and immunologists that provide consensus statements regarding best practice, including the OFC procedure, within the discipline.

Our Immunology Fellow and an Allergy nurse will be performing the oral food challenges. A Consultant Allergist/Immunologist (Dr Mehr or Dr Smart) will always be present at the time of the challenge. The estimated total time commitment for the visit is between 4-6hrs. Patients who successfully passed the challenge will be asked to eat two serves of flake per week for the following two weeks. It is well established that failure to re-incorporate a food post successful OFC can potentially lead to recurrence of the allergy. However, it remains unclear just how frequent the food needs to be consumed in order to maintain tolerance. Serving suggestions of 1-2 times a week are consistent with standard clinical practice in the absence of clear, empirical evidence.

5.***Follow up procedure:*** all patients will be contacted via phone 2 weeks following the challenge to ensure patient welfare. If any post challenge reactions occur in that period or at any period following completion of the study, they will be seen at Epworth Allergy Specialists free of charge. After the initial post-challenge follow up period, participants who successfully pass the challenge will be advised to incorporate flake that they source directly, rather than purchased at a restaurant, in order to minimise the risk of inadvertent exposure particularly if allergic to another species of white fish. Participants who react to the gummy shark during the challenge will be advised to strictly avoid gummy shark.

# Study timeline



# OUTCOMES

# Primary outcome

* The proportion of fish allergic children who are tolerant to gummy shark at supervised OFC.

# Secondary outcome(s)

* The predictive value of the SPT to homogenized gummy shark extract in fish allergic children undergoing gummy shark OFC.
* The predictive value of gummy shark immunoblot in this fish allergic cohort undergoing gummy shark OFC.
* Proportion of fish allergic children who are identified as having sensitisation/no sensitisation to other bony fish species on the serum immunoblot.

# ADVERSE EVENTS AND POTENTIAL RISKS (where relevant)

#

Skin Prick Test

Skin prick testing carries a relatively low risk. Most patients experience localised itch with a minority of patients occasionally developing urticaria. Systemic reactions or anaphylaxis has been described but is exceedingly rare, particularly when a limited number (i.e less than 20) of allergens are utilised. The procedure will be performed by a qualified practitioner (nurse/doctor) in accordance with the ASCIA protocol for Skin Prick Testing.

Blood Draw

Having a blood sample taken may cause some discomfort, bruising, minor infection or bleeding at the site of IV insertion. The procedure will be performed by a qualified (nurse/doctor) in line standard clinical practice to reduce the risk of harm. The intravenous line will remain in situ until the OFC is complete to avoid further discomfort should intravenous adrenaline infusion or provision of resuscitation fluids in the event of anaphylaxis.

Oral Food Challenge

The major risk inherent in our study is oral food challenge-related morbidity. Oral food challenges are can induce allergic reaction, including anaphylaxis. Anaphylaxis is defined as a generalised allergic reaction involving compromise of the respiratory and/or cardiovascular system. All challenges will be performed in the controlled setting of the Epworth Allergy Specialists centre at Epworth, monitored by experienced nursing staff and supervised by a senior allergist/immunologist. . We currently perform OFC at Epworth as part of standard clinical care and have all the necessary equipment, and staff to safely perform OFCs. We currently perform over 400 OFCs per year at Epworth Challenges will be performed according to the ASCIA oral food challenge protocol and governed by the PRACTALL consensus guideline on oral food challenges. The patient will be observed for a period of 1 hour following completion of the challenge. Anaphylaxis will be managed with intramuscular adrenaline and mild to moderate reactions managed by anti-histamine and other medications at the treating clinician’s discretion. Should admission of the patient be required following a positive challenge, this will occur at Epworth Hospital, Richmond with no expense to the patient. Patient parking costs will also be covered by Epworth for all patients irrespective of challenge outcome.

# Assessment and documentation of adverse events

Adverse events will be recorded on the challenge record, a standardised instrument created by ASCIA. Baseline observations, patient weight, eliciting dose of allergen, symptoms and treatment will be documented for each oral food challenge performed

# 9.4.1 SAEs

Any SAE occurring in a study participant will be reported to the HREC in accordance with the NHMRC *Safety Monitoring and Reporting in Clinical Trials* principles.

#  DATA MANAGEMENT

# 10.1 Data Collection

The investigators are responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported. All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data. The investigators will maintain adequate case histories of study participants, including accurate case report forms (CRFs – see appendices, and source documentation.)

The majority of the data will be obtained by direct interview of the participant documenting the specific nature of their fish allergy, previous reactions and investigation. The Allergy/Immunology Fellow will record the data/outcomes on the above CRF form. Reference to the patients’ medical record, clinical letters and any laboratory investigations will also be required.

# Data Storage

CRF will be completed at the time of the challenge. Information will be transferred to a password

protected excel database by the Allergy/Immunology Fellow at Epworth Hospital, Richmond. Paper copies of the CRF will be

stored in a locked cupboard at the Allergy Specialist Clinic, at Epworth Richmond with access restricted to members of the study team..

# Record Retention and Security

All CRFs, excel spreadsheet will be retaineduntil the youngest participant turns 25(GCP) . Strict confidentiality will be maintained at all times. Access to study materials will be restricted to the PI and AIs by permission of the PI.

# STUDY OVERSIGHT

# Quality Control and Quality Assurance

Quality assurance and control of the study will be the primary responsibility of the PI Dr Sam Mehr in collaboration with the AI Dr John Ainsworth.

# STATISTICAL METHODS

# Statistical Analysis Plan

The primary outcome, i.e the proportion of fish allergic individuals tolerant to flake, will be reported as a discrete percentage.

Diagnostic accuracy of SPT and immunoblot will be assessed via calculating the positive and negative predictive value (PPV, NPV CI: 95%) and diagnostic test

characteristics (sensitivity, specificity CI: 95%) of the SPT/immunoblot to homogenized gummy shark extract in fish allergic children undergoing gummy shark OFC.

# Population to be analysed

We estimate that approximately 90% of white fish allergic children will be avoiding flake given the high rate of cross-reactivity between species of white fish. We have powered the study, such that we wish to show, at least 30% of fish allergic children will be able to tolerate flake, which gives a sample size of 27, at 90% power, at a 0.01 significance level. We anticipate a possible drop out rate of 30% (i.e perform SPT and do not wish to go ahead or unable to finish challenge), and require 35 patients to obtain an adequate sample size of 27.

# ETHICS AND DISSEMINATION

All research must be approved by a Human Research Ethics Committee (HREC) before it can commence. This section details how you will seek HREC approval and how any changes to the study will be communicated to the HREC and others.

# Research Ethics Approval

This protocol and the informed consent document and any subsequent modifications will be reviewed and approved by the human research ethics committee (HREC) at <the Royal Children’s Hospital>. A letter of protocol approval by HREC will be obtained prior to the commencement of the study.

# Modifications to the protocol

This study will be conducted in compliance with the current version of the protocol. Any change to the protocol document or Informed Consent Form that affects the scientific intent, study design, participant safety, or may affect a participants willingness to continue participation in the study is considered an amendment, and therefore will be written and filed as an amendment to this protocol and/or informed consent form. All such amendments will be submitted to the HREC, for approval prior to becoming effective.

# Confidentiality

Participant confidentiality is strictly held in trust by the participating investigators, research staff, and the sponsoring institution and their agents. This confidentiality is extended to cover testing of biological samples and genetic tests in addition to the clinical information relating to participating participants. The study protocol, documentation, data and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorised third party, without prior written approval of the sponsoring institution. Authorised representatives of the sponsoring institution may inspect all documents and records required to be maintained by the Investigator, including but not limited to, medical records (office, clinic or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records. All laboratory specimens, evaluation forms, reports and other records that leave the site will be identified only by the Participant Identification Number (PID) to maintain participant confidentiality. Clinical information will not be released without written permission of the participant, except as necessary for monitoring by HREC or regulatory agencies.

# Participant Reimbursement

No reimbursements or financial incentives will be given to study participants.

# Financial Disclosure and Conflicts of Interest

No financial disclosures or conflicts of interest

# Dissemination and translation plan

We plan to publish our findings in a peer reviewed journal to disseminate our findings. A summary of the study’s findings results and ultimate publication will be send to all study participants following the publication. Individual serum specific IgE results will be available to all patients on request

# 14 APPENDICES:

# 14.1-CRF \



**15.2 Informed Consent Materials**

**Consent Form – Parent/Guardian**

|  |  |
| --- | --- |
| **Title** | Investigating the rate of flake co-allergy in fish allergic children |
| **Short Title** | The Flake Study |
| **Principal Investigator** | Dr Sam Mehr |
| **Location** | Epworth HealthCare |
| **Local Reference Number** | EH2019-388 |

**Consent Agreement**

I have read the Participant Information Sheet or someone has read it to me in a language that I understand.

I understand the purposes, procedures and risks of the research described in the project.

I give permission for the child’s doctors, other health professionals, hospitals or laboratories outside this hospital to release information to Epworth HealthCare concerning the child’s allergy and treatment for the purposes of this project. I understand that such information will remain confidential.

I have had an opportunity to ask questions and I am satisfied with the answers I have received.

I freely agree to the child participating in this research project as described and understand that I am free to withdraw them at any time during the research project without affecting their future health care.

I understand that I will be given a signed copy of this document to keep

**Declaration by Parent/Guardian**

|  |  |  |  |
| --- | --- | --- | --- |
|  |  |  |  |
|  | Name of Child (please print) |  |  |
|  |  |  |  |
|  | Signature of Child |  | Date |  |  |
|  |  |  |  |  |  |
|  | Name of Parent/Guardian (please print) |  |  |
|  |  |  |  |
|  | Signature of Parent/Guardian |  | Date |  |  |
|  |  |  |  |  |  |
|  | Witness\* to the informed consent process Name (please print)  |  |  |
|  | Signature of Witness |  | Date |  |  |
| \* Witness is not to be the investigator, a member of the study team or their delegate. In the event that an interpreter is used, the interpreter may not act as a witness to the consent process. Witness must be 18 years or older. |

**Declaration by Study Doctor/Senior Researcher†**

I have given a verbal explanation of the research project, its procedures and risks and I believe that the parent/guardian has understood that explanation.

|  |
| --- |
|  |
|  | Name of Study Doctor/Senior Researcher† (please print) |  |  |
|  |  |
|  | Signature |  |  Date |  |  |
| † A senior member of the research team must provide the explanation of, and information concerning, the research project. |

Note: All parties signing the consent section must date their own signature

# Biological Specimens

The study is a collaboration with the Allergy/Immunology Department at Westmead Children’s Hospital in Sydney (who are currently collecting serum from fish allergic children and sending samples for immunoblot analysis to James Cook; but not offering challenges to gummy shark) and James Cook University, Townsville, Queensland (who are processing the serum to characterise novel fish allergens and provide homogenized extracts for fresh fish allergy skin testing).

James Cook University has received an NHMRC grant to better understand fish allergy in

Australian patients, including the performance of immunoblot analysis in such individuals.

This analysis is being done in kind for samples sent to James Cook from Epworth Richmond.

James Cook University is unable to perform food challenges, and hence the importance of

collaboration between our clinical centre and other research centres. We have established

links with James Cook University, with some authors on this grant have recently co-published a paper on fish allergy (see Ruethers et al above)

**15 REFERENCES**

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