



Omega-3 fatty acids in preventing premature birth



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An overview of the Omega-3 Test-and-Treat Program and the OPAL-3 Trial

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Evidence: Omega-3 and Preterm Birth

Study	Outcome	Reduction (%)
2018 Cochrane Review (1)	Preterm Birth (<37 weeks) Early Preterm Birth (<34 weeks)	11% reduction (preterm birth); 42% reduction (early preterm birth). * <u>No intake</u> of omega-3 supplements was common amongst pregnant women at this time.
2019 ORIP trial (2), Australia (Largest Contemporary Trial led by our group)	Early Preterm Birth <34 weeks	No overall effect on the risk of early preterm birth. * <u>Intake</u> of low dose omega-3 supplements was common at this time.
2020 ORIP trial (3), Australia Secondary analysis	Early Preterm Birth <34 weeks	77% reduction ; The benefit to reduce the risk of early preterm birth is limited to women with low omega-3 status at study entry.

¹Middleton P, Gomersall JC, Gould JF, Shepherd E, Olsen SF, Makrides M. Omega-3 fatty acid addition during pregnancy. Cochrane Database Syst Rev. 2018;11:CD003402

²Makrides M, Best K, Yelland L, McPhee A, Zhou SJ, Quinlivan J et al. A randomized trial of prenatal omega-3 fatty acid supplementation and preterm delivery (ORIP trial). New England Journal of Medicine. 2019;381:1035-45.

³Simmonds LA, Sullivan TR, Skubisz M, Middleton PF, Best KP, Yelland LN, et al. Omega-3 fatty acid supplementation in pregnancy – baseline omega-3 status and early preterm birth: exploratory analysis of a randomised controlled trial (ORIP). BJOG. 2020;27(8):975-981.





NHMRC Pregnancy Care Guidelines



Advise pregnant women that supplementation with omega-3 long-chain polyunsaturated fatty acids (800 mg DHA and 100 mg EPA per day) may reduce their risk of preterm birth, **if they are low in omega-3.**

Approved by NHMRC in Nov 2020; expires Nov 2025



Omega-3 Test & Treat Program

Dissemination, implementation and evaluation of a state-wide screening program to prevent preterm births



MATERNAL SERUM SCREENING TEST
Down syndrome, Neural Tube Defects and other Pregnancy Pathologies

SA PATHOLOGY

Patient Details Ethnic Group: Caucasian Aboriginal Asian African-Caribbean

Family Name: _____ Given Name(s): _____

Date of Birth: _____ UR Number: _____ Medicare Number: _____

Address: _____

Suburb: _____ State: _____ Postcode: _____

Clinical Details – Mandatory

First Trimester Screen Second Trimester Neural Tube Defect only **Omega-3 status (SAHMRI)**

EDD/LMP: ____/____/____ Cycle length (days): ____ Maternal weight (Kgs): ____

GA Clinical weeks + days: ____ on ____/____/____

GA Ultrasound weeks + days: ____ on ____/____/____

Crown-rump length (CRL) mm: ____ on ____/____/____

Pregnancy: Singleton Twins Triplets IVF: Yes No Age at egg retrieval/age of egg donor: ____

Pregnancy complications: Diabetes (IDMM only) Yes No Smoker Yes No Previous T21 T18/13

Name of Imaging Practice: _____

For first trimester screening risk assessment an Ultrasound request form is required for Nuchal Translucency, 11-14w0d.

Patient status at the time of the service or when the specimen was collected:
 a private patient in a private hospital or approved day hospital facility
 a private patient in a recognised hospital
 a public patient in a recognised hospital
 an outpatient public of a recognised hospital
 an outpatient private of a recognised hospital

Medicare Benefits (Section 20A of the Health Insurance Act 1973). I offer to assign my right to the approved pathology practitioner who will render the requested pathology service(s) and any eligible pathologist determinable service(s) established as necessary by the practitioner.
 Do Not send to My Health Record

X: _____ Date: ____/____/____
 Patient signature
 Practitioner's Use Only
 (Reason patient cannot sign)

Privacy Disclosure SAMSAS requires the personal information contained in this request form for the purpose of Risk assessment and Program Audits. SAMSAS may therefore request copies of ultrasound and cytogenetic reports from your doctor in order to complete its testing and audits.

5-10ml CLOTTED BLOOD SAMPLE Gel or plain tube - no anticoagulant
 First trimester blood sample 9-14w0d Second trimester blood sample 14w1d-20w6d

I have verified FULL NAME, DOB and URN on the sample label and request form verbally with the patient and/or checking the patient's ID band.

Collector's Signature: _____ Specimen Collected: ____/____/____ : Hrs

Requesting Doctor SAMSAS risk assessment calculation not required

Name: _____ Copy of report to: _____
 Provider No: _____ Name: _____
 Address: _____ Address: _____
 Tel: _____ Fax: _____
 Email: _____
 Signature: _____
 Request Date: ____/____/____

Deliver to: South Australian Maternal Serum Antenatal Screening (SAMSAS) Program
 SA Pathology, Specimen Reception Area, Level 3, Royal Adelaide Hospital, Port Rd ADELAIDE SA 5000.
 T (08) 8161 7285 F (08) 8161 8085 samsas.program@health.sa.gov.au www.wch.sa.gov.au/samsas.html

Enquiries 8222 3000 www.sapathology.sa.gov.au

PUB-0452 v11 Published 15/1/21 Page 1 of 2

How?

The omega-3 test can be ordered for women with singleton pregnancies anytime <20 weeks' gestation.

Two ways to order:

By checking an additional box on the SAMSAS form.

OR

By writing "omega-3 to SAMSAS" on any standard pathology form.

With private screening (i.e. NIPT):

Collection centres will collect the SAMSAS sample at the same time and forward onto SA Pathology.

****The SAMSAS form can be submitted digitally in Best Practice, ZedMed and Medical Director****

Supplement Advice Based on Omega-3 Status

Omega-3 Status		Guidance
Low	Less than 3.7%	Take omega-3 fatty acid supplements until 37 weeks to reduce the risk of early preterm birth. Suggested dose: 800 mg DHA and 100 mg EPA per day.
Moderate	Between 3.7 and 4.3%	No action required. If already taking omega-3 fatty acids as part of a multivitamin and mineral supplement or a standalone supplement, this may continue.
Sufficient	Above 4.3%	Omega-3 supplements are not required and provide no benefit to risk of early preterm birth. If women are already taking omega-3 fatty acids as part of a multivitamin and mineral supplement and wish to continue, the dose of DHA+EPA should not exceed 250 mg per day.



Recommended Omega-3 Supplements

for women with low omega-3
levels



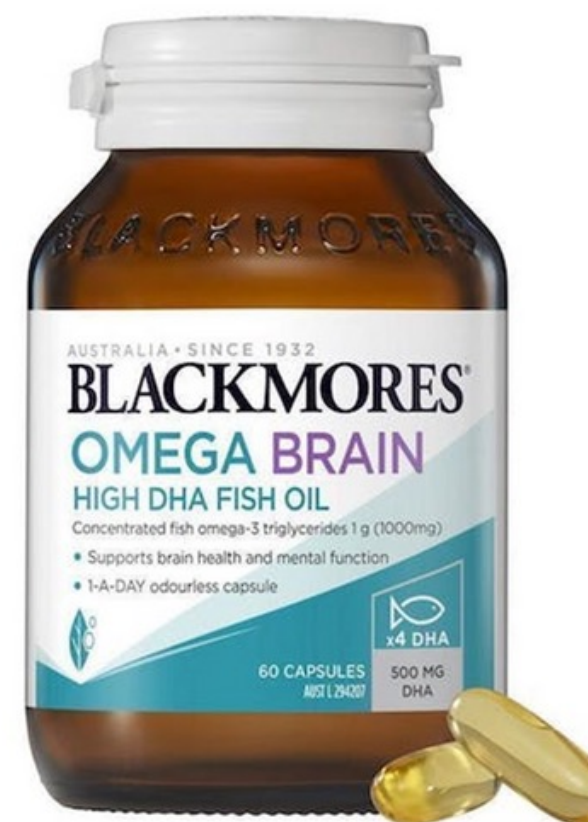
Suggested dose: 800 mg DHA and
100 mg EPA per day



Blackmores

Contains fish oil

www.blackmores.com.au



Current focus of the Test & Treat Program - Enhancing uptake

- ~50% of pregnant women in SA are having their omega-3 tested.
- 1 in 6 women have a low omega-3 status.
- To successfully see reductions of prematurity in the community we estimate **about 80% of pregnant women need to have their omega-3 tested.**

Supplement Advice Based on Omega-3 Status

Omega-3 Status		Guidance
Low	Less than 3.7%	Take omega-3 fatty acid supplements until 37 weeks to reduce the risk of early preterm birth. Suggested dose: 800 mg DHA and 100 mg EPA per day.
Moderate	Between 3.7 and 4.3%	No action required. If already taking omega-3 fatty acids as part of a multivitamin and mineral supplement or a standalone supplement, this may continue.
Sufficient	Above 4.3%	Omega-3 supplements are not required and provide no benefit to risk of early preterm birth. Suggested dose: 1000 mg of DHA+EPA

We lack guidance about the **dosage recommendations** for women with moderately low levels.

 **OPAL-3 STUDY**

Determining the Optimal Dose of Omega-3 Fatty Acids in Pregnancy for Women with Moderate Status



OPAL-3

Determining the Optimal Dose of Omega-3 Fatty Acids in Pregnancy for Women with Moderate Status



Government of South Australia
Women's and Children's
Health Network



Current recommendations

Omega-3 status test for prematurity risk
 SA Maternal Serum Antenatal Screening (SAMSAS) Program

Information for health professionals



Omega-3 status ^{4,5}	Guidance to incorporate into pregnancy care plan
Less than 3.7% (low status)	<p>Take omega-3 fatty acid supplements until 37 weeks, to reduce the risk of early preterm birth.</p> <p>Suggested dose: 800 mg DHA and 100 mg EPA per day.</p> <p>Typical suitable supplements include Infantem (Pharmamark)* and Omega Brain (Blackmores).</p>
Between 3.7 and 4.3% (moderate status)	<p>No action required.</p> <p>If already taking omega-3 fatty acids as part of a multivitamin and mineral supplement or a standalone supplement, this may continue.</p>
Above 4.3% (sufficient status)	<p>Omega-3 supplements are not required and provide no benefit to risk of early preterm birth.</p> <p>If women are already taking omega-3 fatty acids as part of a multivitamin and mineral supplement and wish to continue, the dose of DHA+EPA should not exceed 250 mg per day.</p>

*Vegan algal oil supplement of DHA and EPA.

Importance of the study

Addresses knowledge gap:

Moderate omega-3 group are halfway towards achieving sufficient status and dosage recommendations may differ to the low omega-3 group.

Aim:

To identify the optimal DHA and EPA dose for pregnant women with moderately low omega-3 status to match the profile of women with the lowest risk of preterm birth.

Wider impact:

Aids in further reducing prematurity rates.



Study Design

Structure:

Dose-response study, randomised controlled trial

Focus:






Women with omega-3 status in the lower half of the moderate range (Low-moderate defined as: ≥ 3.7 to $\leq 4.1\%$ in blood serum)

Basis:

A previous study (ORIP), the low moderate group had indications that they might benefit from supplementation to reduce their risk of early birth

Study timeline

1. During pregnancy

-  Enrolment & consent phone call before 21 weeks gestation
-  Blood sample (enrolment)
-  Commence study supplements*
-  Blood sample at 26-28 weeks & 34-36 weeks
-  37 weeks: stop study supplements*

2. Baby born

3. Post delivery: 4-6 weeks

-  Phone call 6 weeks post delivery
-  Breastmilk sample collected

* Supplement group only





Study Design

Participants with a **Low-moderate Omega-3 Status** will randomly receive **one of four omega-3 doses** from ≤ 21 weeks to 37 weeks' gestation:

- Control/No DHA+EPA
- 200mg DHA, 25mg EPA
- 400mg DHA, 50mg EPA
- 800mg DHA, 100mg EPA

Also: **Low** and **Sufficient** reference groups (not supplemented).

Study requirements for participants:






During pregnancy: **3 x blood spots** and **short online surveys**.

Post-partum: **1 x breastmilk sample**





Study timeline

1. During pregnancy

-  Enrolment & consent phone call before 21 weeks gestation
-  Blood sample (enrolment)
-  Commence study supplements*
-  Blood sample at 26-28 weeks & 34-36 weeks
-  37 weeks: stop study supplements*

2. Baby born

3. Post delivery: 4-6 weeks

-  Phone call 6 weeks post delivery
-  Breastmilk sample collected

* Supplement group only





We need your help to recruit participants into this study.

How?

1. Order the Omega-3 Test for all singleton pregnancies
2. Refer participants to the OPAL-3 Study

The OPAL-3 team will be responsible for maintaining ongoing contact with participants after you have recruited them



Study Eligibility

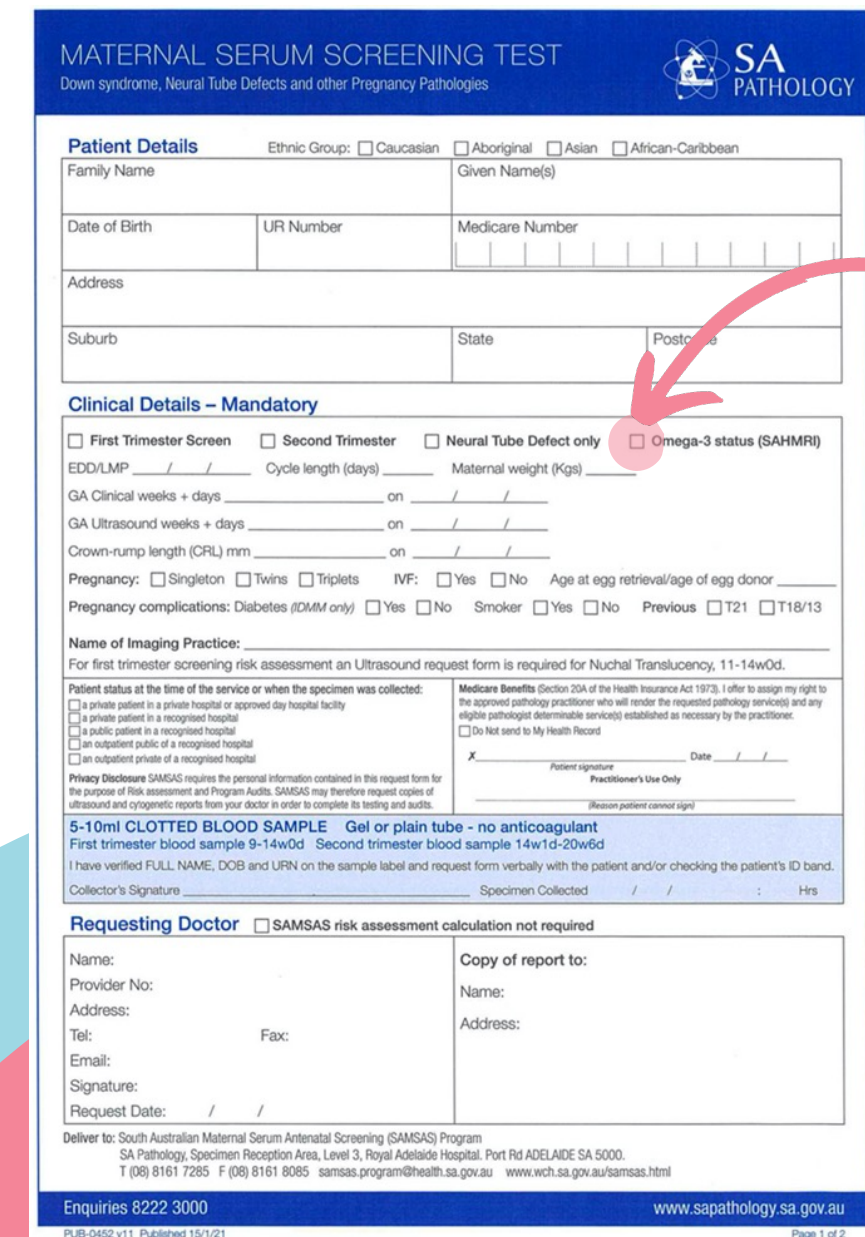
Pregnant women	Less than 21 weeks pregnant
Singleton pregnancy	Known omega-3 results



How you can help us recruit participants

Step 1: Request Omega-3 Testing

When interacting with your pregnant patients, request omega-3 testing on the SAMSAS form by ticking 'omega-3 test' before 21 weeks' gestation.



MATERNAL SERUM SCREENING TEST
Down syndrome, Neural Tube Defects and other Pregnancy Pathologies

Patient Details Ethnic Group: Caucasian Aboriginal Asian African-Caribbean

Family Name: _____ Given Name(s): _____
Date of Birth: _____ UR Number: _____ Medicare Number: _____
Address: _____
Suburb: _____ State: _____ Postcode: _____

Clinical Details – Mandatory

First Trimester Screen Second Trimester Neural Tube Defect only **Omega-3 status (SAHMRI)**

EDD/LMP: ____/____/____ Cycle length (days): ____ Maternal weight (Kgs): ____
GA Clinical weeks + days: ____ on ____/____/____
GA Ultrasound weeks + days: ____ on ____/____/____
Crown-rump length (CRL) mm: ____ on ____/____/____
Pregnancy: Singleton Twins Triplets IVF: Yes No Age at egg retrieval/age of egg donor: ____
Pregnancy complications: Diabetes (IDMM only) Yes No Smoker Yes No Previous T21 T18/13

Name of Imaging Practice: _____
For first trimester screening risk assessment an Ultrasound request form is required for Nuchal Translucency, 11-14w0d.

Patient status at the time of the service or when the specimen was collected:
 a private patient in a private hospital or approved day hospital facility
 a private patient in a recognised hospital
 a public patient in a recognised hospital
 an outpatient public of a recognised hospital
 an outpatient private of a recognised hospital

Medicare Benefits (Section 20A of the Health Insurance Act 1973). I offer to assign my right to the approved pathology practitioner who will render the requested pathology services and any eligible pathology determinable services established as necessary by the practitioner.
 Do Not send to My Health Record

Privacy Disclosure SAMSAS requires the personal information contained in this request form for the purpose of risk assessment and program audits. SAMSAS may therefore request copies of ultrasound and cytogenetic reports from your doctor in order to complete its testing and audits.

5-10ml CLOTTED BLOOD SAMPLE Gel or plain tube - no anticoagulant
First trimester blood sample 9-14w0d Second trimester blood sample 14w1d-20w6d
I have verified FULL NAME, DOB and URN on the sample label and request form verbally with the patient and/or checking the patient's ID band.

Collector's Signature: _____ Specimen Collected: ____/____/____ : ____ Hrs

Requesting Doctor SAMSAS risk assessment calculation not required

Name: _____ Provider No: _____ Address: _____ Tel: _____ Fax: _____ Email: _____ Signature: _____ Request Date: ____/____/____

Copy of report to:
Name: _____ Address: _____

Deliver to: South Australian Maternal Serum Antenatal Screening (SAMSAS) Program
SA Pathology, Specimen Reception Area, Level 3, Royal Adelaide Hospital, Port Rd ADELAIDE SA 5000.
T (08) 8161 7285 F (08) 8161 8085 samsas.program@health.sa.gov.au www.wch.sa.gov.au/samsas.html

Enquiries 8222 3000 www.sapathology.sa.gov.au

Two ways to order:

By checking an additional box on the SAMSAS form.

OR

By writing "omega-3 to SAMSAS" on any standard pathology form.

How you can help us recruit participants

Step 2: Discuss Omega-3 Results and Study

During your discussion about the omega-3 test results, also explain the opportunity for your patients to be contacted about the OPAL-3 study and provide them with a study brochure.

"I'd like to let you know about a study that's investigating the optimal dosage of omega-3 supplementation for pregnant women, with a particular focus on those with moderate omega-3 levels.

Would you be happy for me to pass on your contact details to the Study Team at SAHMRI?"



How you can help us recruit participants

Step 3: Provide Participant 'Expression of Interest' Form

If your patient is interested in obtaining more information, provide them with an 'Expression of Interest' form and complete it during their visit with you.

The form is titled "OPAL-3 Study Patient Expression of Interest" and includes logos for GPEX, GPPartners, and OPAL-3. It contains the following sections:

- Introduction:** Explains the study's purpose and invites patients to provide contact details.
- Agreement:** A list of three bullet points where the patient agrees to be contacted, share results, and understand the form is not consent.
- PATIENT CONTACT DETAILS (OR AFFIX PATIENT STICKER):** Fields for Family Name, Given Name(s), Mobile, Postcode, and Email.
- COMPLETION BY GP:** Fields for Patient Clinical Details (Date of Birth, Estimated Due Date, Or Current Gestation) and OMEGA-3 STATUS.
- GP PRACTICE:** A checkbox for "Verbal consent obtained from patient" and a statement where the GP explains the form's purpose to the patient.
- SIGNATURE OF GP:** Fields for the GP's signature and date.

At the bottom, it says: "Once completed, please send to opa3@sahmri.com. Please call 0436 926 360 if you have any questions." The footer includes "OPAL-3 Patient EOI C2C_v1.3_20231025_CLEAN" and "Page 1 of 1".

****The 'EOI' form can also be found on Best Practice software****

How you can help us recruit participants

Step 4: Email the 'Patient Expression of Interest Form'

After your patient completes the 'Expression of Interest' form, please email it to opal3@sahmri.com

Your involvement is complete.

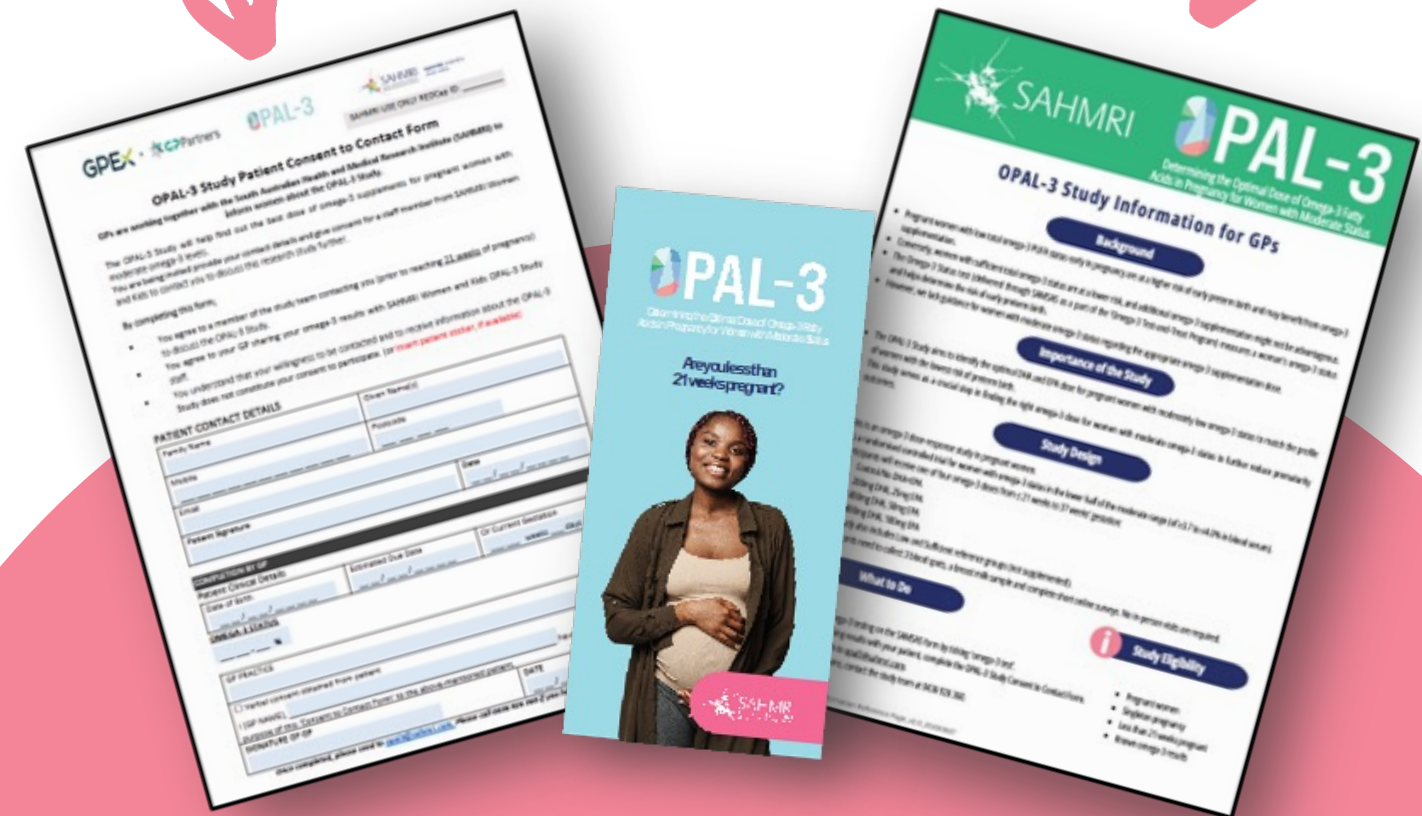
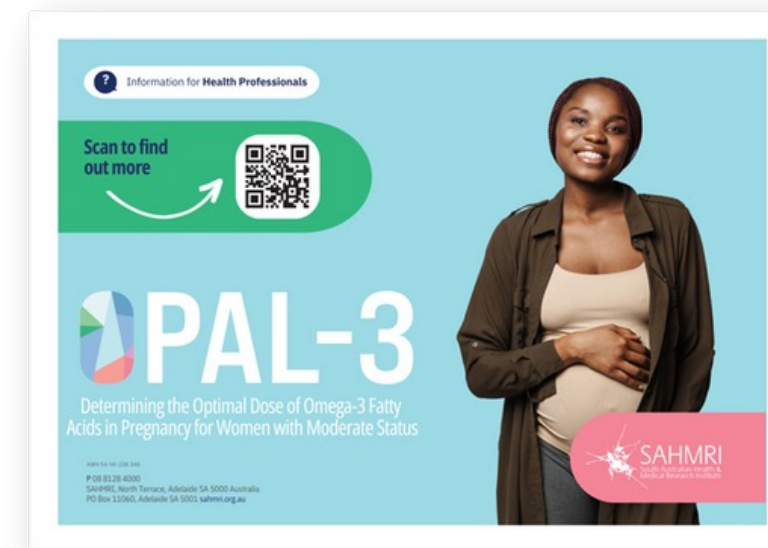
****A referral payment will be automatically arranged for you once you have provided your reimbursement claim form.****

opal3@sahmri.com

What now?

Your referrals are **crucial** in advancing our understanding of omega-3 supplementation during pregnancy.

You will find all the items you need to begin making referrals in our 'Study Pack' envelope

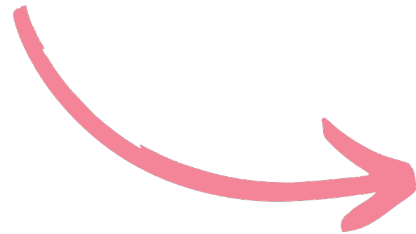
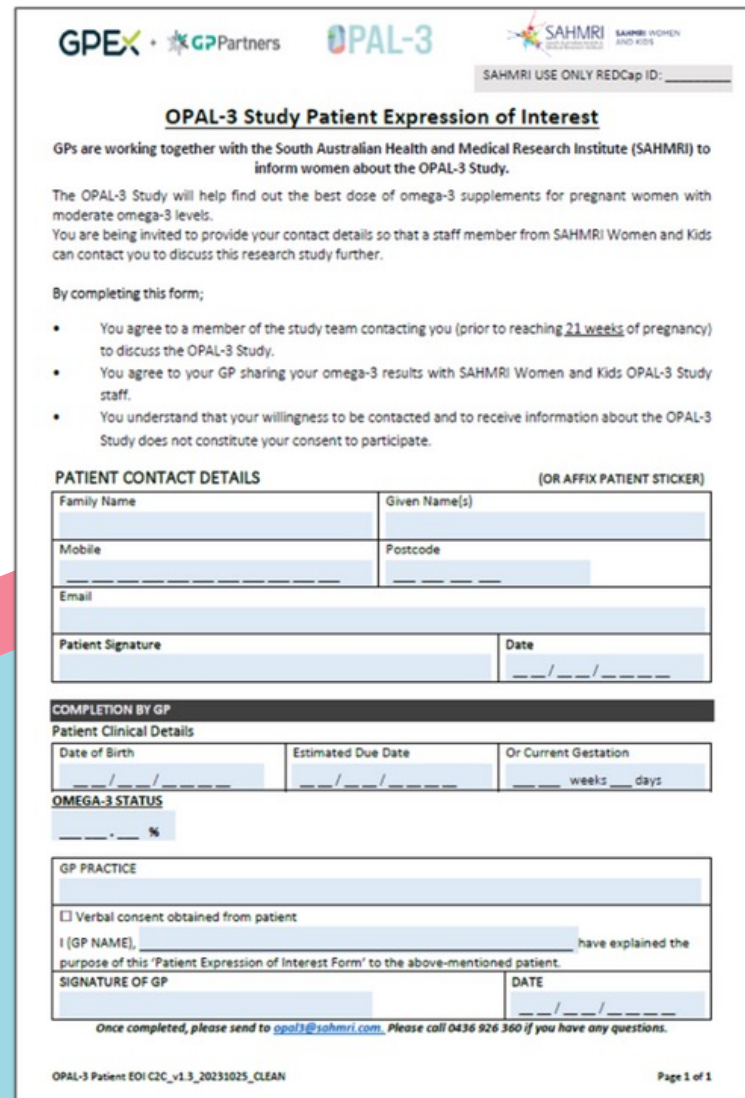




What now?



Start referring patients to the OPAL_3 Study.

OPAL-3 Study Patient Expression of Interest

GPs are working together with the South Australian Health and Medical Research Institute (SAHMRI) to inform women about the OPAL-3 Study.

The OPAL-3 Study will help find out the best dose of omega-3 supplements for pregnant women with moderate omega-3 levels. You are being invited to provide your contact details so that a staff member from SAHMRI Women and Kids can contact you to discuss this research study further.

By completing this form:

- You agree to a member of the study team contacting you (prior to reaching 21 weeks of pregnancy) to discuss the OPAL-3 Study.
- You agree to your GP sharing your omega-3 results with SAHMRI Women and Kids OPAL-3 Study staff.
- You understand that your willingness to be contacted and to receive information about the OPAL-3 Study does not constitute your consent to participate.

PATIENT CONTACT DETAILS (OR AFFIX PATIENT STICKER)

Family Name	Given Name(s)
Mobile	Postcode
Email	
Patient Signature	Date

COMPLETION BY GP

Patient Clinical Details

Date of Birth	Estimated Due Date	Or Current Gestation
_____ / _____ / _____	_____ / _____ / _____	_____ weeks _____ days

OMEGA-3 STATUS

_____ %

GP PRACTICE

Verbal consent obtained from patient

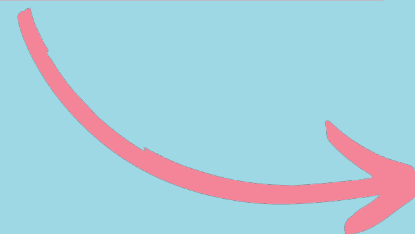
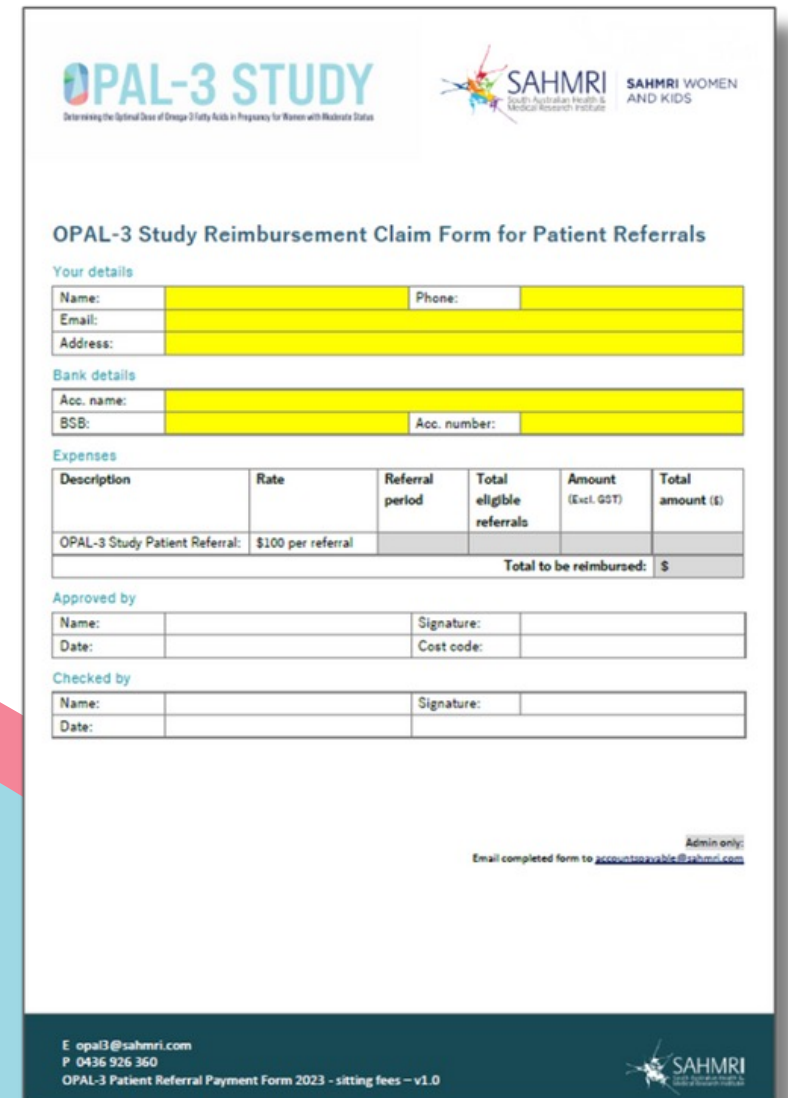
I (GP NAME) _____ have explained the purpose of this 'Patient Expression of Interest Form' to the above-mentioned patient.

SIGNATURE OF GP _____ DATE _____ / _____ / _____

Once completed, please send to opal3@sahmri.com. Please call 0436 926 360 if you have any questions.

OPAL-3 Patient EDI C2C_v1.3_20231025_CLEAN Page 1 of 1

Return the enclosed Reimbursement Claim Form
so we can process your referral payment promptly.

OPAL-3 Study Reimbursement Claim Form for Patient Referrals

Your details

Name:	Phone:
Email:	
Address:	

Bank details

Acc. name:	
BSB:	Acc. number:

Expenses

Description	Rate	Referral period	Total eligible referrals	Amount (Excl. GST)	Total amount (£)
OPAL-3 Study Patient Referral:	\$100 per referral				
Total to be reimbursed:					\$

Approved by

Name:	Signature:
Date:	Cost code:

Checked by

Name:	Signature:
Date:	

Admin only:
Email completed form to opal3@sahmri.com

E opal3@sahmri.com
P 0436 926 360
OPAL-3 Patient Referral Payment Form 2023 - sitting fees - v1.0



Thank you for your time



Please feel free to reach out to us if you or your patients require further information.

Omega-3 Test-and-Treat Program



Phone

0438 273 155



Email

omega3@sahmri.com



Website

sahmri.org/omega3

OPAL-3 Study



Phone

0436 926 360



Email

opal3@sahmri.com



Website

sahmri.org.au/opal-3

Questions



Is it okay to do the Omega-3 Status Test in a women's first set of pregnancy bloods (i.e. around 6-8 weeks)?

Yes, omega-3 testing can be done at any gestation up until 20 weeks

If we submit a SAMSAS request form for testing Omega-3 Status, in addition to private NIPT screening (i.e Harmony, NEST, Sonic Genetics NIPT), will the collection centres be able to collect the SAMSAS sample at the same time and forward onto SA Pathology?

Yes, the SAMSAS request will be processed as an omega-3 only test sample.

Are women provided with Omega-3 supplements if they enrol in the OPAL-3 Study?

Participants involved in this study will receive **one of four omega-3 doses** from ≤ 21 weeks to 37 weeks' gestation. One of these will be the control group that are not supplemented. The study also includes Low and Sufficient reference groups (not supplemented).

Questions



Is the OPAL-3 Study Patient Expression of Interest Form (EOI) available as an electronic version to make it easier to complete?

Yes, the Expression of Interest Form is available in electronic format, please see Best Practice software.

What are the benefits for HCPs and patients in participating in this study?

For HCPs, participation **supports research** and may potentially enhance antenatal care. HCPs will also receive a **referral payment** for each patient. Participants will contribute to the generation of valuable information that may guide optimal omega-3 fatty acid intakes for pregnant women with moderate omega-3 status. They will also receive a **\$25 grocery voucher** for reimbursement of their time.

How does the study plan to measure and account for potential differences in dietary habits and lifestyles that might affect omega-3 levels?

We recognise that dietary habits and lifestyles can impact omega-3 levels. To address this, **we plan to measure total omega-3 status through dried blood spots**. This method allows us to directly assess individual omega-3 levels and consider factors such as diet, lifestyle, and supplementation. By doing so, **we can account for these variables** in our study analysis, providing a more comprehensive understanding of the impact of omega-3 on pregnancy outcomes.

Questions



Does it matter what patients' omega-3 levels are to refer them for the study?

No, it does not matter. As long as they meet the criteria of being pregnant, having a singleton pregnancy, are less than 21 weeks pregnant, and have known omega-3 results, they are eligible for referral. All moderate omega-3 status participants will be randomly assigned to one of four omega-3 dose groups as part of the study, and participants with low or high omega-3 status will serve as reference groups.

What if women are already taking an omega-3 supplement or a multivitamin that contains omega-3?

These women may have started with very low omega-3 levels or might not be getting as much omega-3 as they think, keeping them in the low end of the moderate range.

We will closely monitor their omega-3 levels, conducting tests as needed throughout the study. This allows us to identify any extremely low or high levels and respond appropriately.

Are there any additional responsibilities for GPs in the study beyond recruitment?

No, once you have provided the OPAL-3 team with the 'Expression of Interest' form, your role as a GP is essentially complete.

Your primary responsibility is **patient recruitment**, which involves informing your patients about the study, offering them the 'Expression of Interest' form, and sending the completed forms to our team.

Questions



If a woman has an omega-3 test early in pregnancy but her next follow up appointment does not occur until around 20 weeks, is it appropriate to wait until then to discuss the result and the action needed?

Yes. Even for women who have low omega-3 status, the data from the clinical trials indicate that **starting supplementation around 20 weeks gestation is more than adequate.** This may also help overcome any issues with supplement taking and morning sickness.

Can an omega-3 status test be added to a stored SAMSAS sample if not ordered at the time of other SAMSAS tests?

Yes, it may be possible to add the omega-3 status test if it was not initially ordered on the SAMSAS request form by calling the **SAMSAS program on (08) 8161 7285** before the woman is 20 weeks of gestation.

Does my patient need to attend a SA Pathology collection site to have a blood sample collected for an omega-3 test?

No, any pathology collection centre can collect the blood sample for the omega-3 test. Any private laboratory collection centre will be reimbursed with a collection fee by SA Pathology as usual process.



Extension to meet the needs of Aboriginal Families



Culturally-appropriate service via AMIC workers, midwives and health professionals

Informational brochures for HCPs and patients

Awareness-promoting workshops

Cost-free Omega-3 supplements

No additional blood sample required, if part of SAMSAS first trimester testing

