Guidance Sheet 4a:

Study Intervention (supplement)

Treatment Supplement & Control Supplement

- The treatment supplement is a nutritional supplement which contains long chain polyunsaturated fatty acids (LCPUFAs), choline, Uridine-5'Monophosphate (UMP), and Cytidine-5'Monophosphate (CMP).
- The matched control supplement contains many of the same ingredients as the treatment supplement but in much smaller quantities and concentrations and no UMP or CMP.
- The treatment and the control products are isocaloric and have similar levels of fat and comparable energy content. The specific polyunsaturated fatty acids in the supplement are naturally present in human milk and can also be found in infant formula. These nutrients are known to be important for multiple processes important to infant brain development.
- The supplement long-chain polyunsaturated fatty acids are from a fish source. The supplements contain small amounts of cow's milk protein. The supplements do not contain pork or other meat products but they are not certified kosher and halal compliant. Some families may wish to discuss this further with their religious leader.

A small UK study using the same supplement showed it was safe. All nutrients are within recommended daily amounts.

ALLERGENS
Both the treatment and matched control supplement contain fish, egg and milk products

DOLFIN supplement is for **gastric enteral use only (oral, nasogastric or gastrostomy feeds) and must not be given via a jejunal tube.** If an infant starts jejunal feeds supplement should be paused and restarted when infant is no longer on jejunal feeds.

Packaging

The DOLFIN supplement comes in boxes containing one hundred 13g sachets. The box includes a small number of 1g scoops to measure the supplement and clips to close the sachets (these are reusable and should not be discarded) . Each box carries the treatment pack ID of that box. The treatment pack ID should be entered on the infant's **DOLFIN Dosing Log**.

The treatment pack ID is on each box not on individual sachets. Sites must take steps to ensure sachets are not mixed up between boxes and only sachets allocated to a specific infant are used for that infant. This includes:

- Only 1 box out at a time.
- Store in secure location close to infant
- Ensure wider teams who may be involved in supplement administration are aware of study requirements.

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The packaging may vary across batches and during the trial. There is no correlation between the type of packaging and the treatment supplement or control supplement.

Pack Allocation

Each infant will be allocated a treatment pack ID number during randomisation (see **Guidance Sheet 3 – Randomisation**). Enter this treatment pack ID on the first **DOLFIN Dosing Log**. When an infant is allocated a new pack, the new pack ID, should be added to the new DOLFIN Dosing Log. A new **DOLFIN Daily Dosing Log** should be used for each new treatment pack. See **Guidance Sheet 11 – Supplement Management and Control** for further information on managing supplement supply and allocating packs.

Starting supplementation in hospital

The study supplement and study procedures must only be started once informed consent and randomisation have been completed. Infants should commence supplement as soon as they have reached full milk feeds (approx. 120–150ml/kg/day). The exact definition of full feeds will vary by site and infant according to local feeding practices but this represents a typical threshold. **You do not have to be wait until an infant has reached full milk feeds to consent and randomise an infant.**

Infants may start supplementation following transfer to a Continuing Care Site or post-discharge if required. Supplementation is administered by parents at home until 12 months post EDD. Parents must be trained in supplementation before they administer any supplement to their infant (see **Guidance Sheet 5 – Parent Training**).

Supplementation supply at discharge

At discharge, parents should be provided with a sufficient supply of supplement to take home. If transferring to a continuing care site please ensure sufficient supplement supply is sent with the infant. If supplement is not sent with the infant at the time of transfer or discharge, supplement can be sent directly from the distributor to the family home. After discharge home further supplement will be delivered directly to the family home by the distributor. See **Guidance sheet 11 - Supplement management and control**. Parents will receive a notification when the supplementation period has ended (at 12 months of age (EDD)). Parents are advised to discard any remaining sachets.

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Supplement Storage

In hospital the supplement should be stored in a suitably secure location. It should be stored at ambient room temperature in a naturally cool area with a range of 2-25 degrees Celsius. The supplement is stable up to 30 degrees Celsius if it does not reach 25-30 degrees Celsius for more than 30 consecutive days. At home parents are advised to store the supplement at room temperature in a naturally cool place, away from direct sunlight.

The supplement does not require temperature monitoring at sites or in parent's homes. If the temperature in the room is expected to consistently exceed 25°C, an alternative location should be found.

Supplement Disposal

In hospital, unused and expired sachets should be disposed of by placing in a domestic bin or in accordance with local site policy. Discarded packs should be entered onto the current **DOLFIN Supplement Management and Control Log** (for supplement on the ward/unit) or **DOLFIN Pharmacy Receipt and Destruction Log** (for supplement in pharmacy. See **Guidance Sheet 11 – Supplement Management and Control**).

When at home unused or expired sachets should be disposed of in a domestic bin.

Concomitant medication, fortifiers and dietary supplementation

There are no contraindicated medication or dietary supplements. Infants will be able to have all medicines, vitamins and fortifiers they would normally have, throughout the trial.

There is no specific reason why the DOLFIN supplement cannot be given alongside other products such as milk fortifiers or milk thickeners but combining the supplement with another product may make the feed thicker. Clinical teams or parents may consider splitting the supplement dose across more than one feed, or omitting the fortifier/thickener from the feed containing the DOLFIN supplement to help manage this.

Some NNUs may choose to omit fortifier from the feed containing the DOLFIN supplement. Most NNUs try to avoid giving enteral supplements in the same feed in order to avoid increases in osmolality but this is not always possible. The greatest contributors to enteral feed osmolality are from multivitamins and sodium. Some parents may choose to give their infant additional dietary LCPUFA to their infant post-discharge. This is not recommended however as commercially available LCPUFA supplements contain low amounts of LCPUFA this will not significantly alter the overall LCPUFA intake of participants.

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