Guidance Sheet 11:

Supplement Management and Control

Infants enrolled in the DOLFIN study will be randomised to receive either:

(1) Treatment supplement: Micronutrient supplement that can be added to breast milk/infant formula/food (contains LCPUFAs, choline, UMP, and CMP).

or

(2) Matched placebo control supplement, contains fractions of the active components in the investigational product and no UMP or CMP.

This study is classified as a Clinical Trial of a non-Investigational Medicinal Product (non-CTIMP). The treatment supplement is not classifiable as an IMP therefore clinical trials authorisation from the MHRA is not required. Any pharmacy involvement is a site level decision, it is not a trial requirement.

The DOLFIN supplement is manufactured and supplied by Nutricia, Netherlands who are responsible for testing the quality and safety of supplement. The supplements are produced by the factory in 13g sachets and are then boxed. Each box has a unique identifier code (pack ID) supplied by the National Perinatal Epidemiology Unit (NPEU) Clinical Trials Unit (CTU). The product is distributed via a distribution company (IPS Pharma) who are not part of Nutricia.

Supplement management is via the secure web-based randomisation system using a centre-wide login (https://rct.npeu.ox.ac.uk/dolfin) (see **Guidance Sheet 3 – Randomisation**). DOLFIN treatment allocation is blinded. Sites will be supplied with sealed numbered packs containing either the treatment supplement or control supplement. Once randomised, infants will be allocated a pack containing the trial allocation generated by the randomisation process; the trial allocation itself will not be revealed. Parents will not know which supplement their infant has been allocated. All investigators and CTU staff with the exception of the Senior Trials Programmer and Trial Statisticians will be blinded to trial allocation.

Receipt of study supplement

Depending on local setup, shipments of study packs can be received either by the ward/unit directly or by the hospital pharmacy. There is no trial requirement for pharmacy involvement – it is a site level decision.

Upon receipt, the shipment should be checked for any damage or inconsistencies against the accompanying inventory sent by IPS and the email sent by the randomisation program. The DOLFIN packs **must be receipted** at the first opportunity using the DOLFIN website randomisation program.

Sites should report any missing or damaged packs to DOLFIN study team vie email or phone as soon as possible and retain any damaged packs until further notice. Sites may be requested to send photographs or return the box for investigation.

See **Guidance Sheets 4a and 4b – Study Intervention** for further information on supplement use, storage, and disposal

For sites receipting supplement via pharmacy:

Sites should follow local procedures and policy for managing products received via pharmacy.

For sites receiving supplement into local pharmacy departments/units, sites should record receipt of supplement by completing the **DOLFIN Pharmacy Receipt and Destruction Log.** Disposal of unused or expired supplement will also be documented on the **DOLFIN Pharmacy Receipt and Destruction Log.**

The supplement should remain in the pharmacy until an infant is randomised. Packs should not be moved to the neonatal ward or other location until an infant is randomised. If sites wish to split their supplement stock between pharmacy and the neonatal ward this must be agreed with the DOLFIN study team.

When the supplement is transferred from pharmacy to the research team at NNU the site team should complete the paper form **DOLFIN Supplement Management and Control Log** to document receipt of the supplement.

For sites receipting supplement directly to wards/units (not via pharmacy)

For sites receiving supplement directly to wards/units the research team should complete the **DOLFIN Supplement Management and Control Log** to document receipt of the supplement. Disposal of unused or expired supplement will also be documented on the **DOLFIN Supplement Management and Control Log.**

Supply of supplement to sites

During site setup an initial batch of supplement will be provided to sites. A minimum and maximum stock level will be agreed with the site. Stock levels are monitored by the DOLFIN study team at NPEU CTU using the web-based randomisation program and sites will be resupplied with supplement as required.

It is essential that the receipt and movement of DOLFIN supplement packs are carried out in an accurate and timely fashion and recorded using the randomisation program. (DOLFIN randomisation website: https://rct.npeu.ox.ac.uk/dolfin). If packs are not receipted on the randomisation system they will not be available for allocation. If there is insufficient stock available on the randomisation system, sites will not be able to randomise an infant.

Sites can designate specific individuals to receive email communication from the DOLFIN study team informing them when an infant is randomised and supplement notifications (e.g. which supplement packs have been sent, and when packs are assigned and logged into the ward/unit or pharmacy). The DOLFIN study team at NPEU CTU will also receive these emails.

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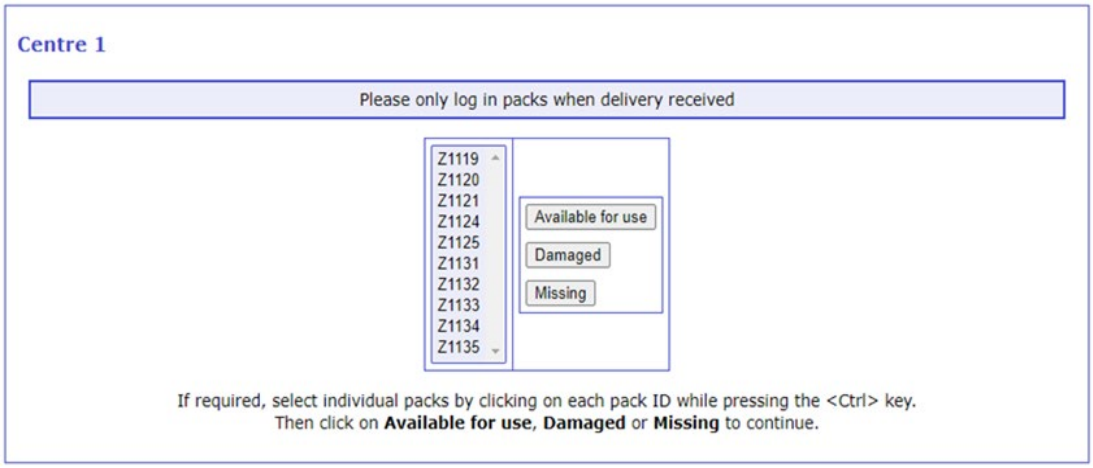
Receipting packs on the randomisation system

If there are packs in transit to the site the following menu item will be enabled (indicating how many packs have been sent). Clicking on this menu item will bring up the following screen listing the packs to be logged in:



If all packs have arrived and are available for use, click on **Available for use**:

Confirm by clicking on **Yes** and the pack status summary will show the packs are now available in the NICU (Note: all packs available for randomisation will be shown in the NICU column including for sites receipting packs in pharmacy):

Pack status summary

Centre	Status	To be sent	In transit	Available	Pharmacy	Pharmacy→NICU	NICU
Centre 1	ACTIVE	0	0	26	0	0	26
Total 1							

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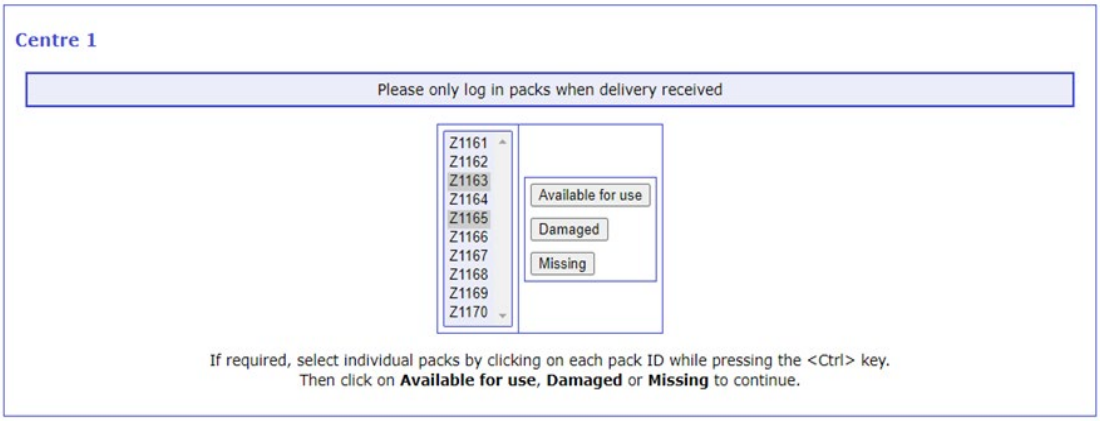
The main menu item for logging in packs will no longer be available.

Damaged packs

If some packs are damaged or missing, they can be selected individually. For example, if a further 10 packs are sent but packs Z1163 and Z1165 arrive damaged, click on the main menu item:

Select those two packs by clicking on their IDs while pressing the <Ctrl> key:



Click on **Damaged**:

Click on **Yes** to confirm:

Pack status summary

Centre	Status	To be sent	In transit	Available	Pharmacy	Pharmacy→NICU	NICU
Centre 1	ACTIVE	0	8	26	0	0	26
Total 1							

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The main menu item will then show that eight packs remain to be logged in:

Allocating a new pack for an infant

Sites should allocate another pack to infants when they have 30 or fewer sachets remaining, or when packs are damaged or lost. The randomisation system estimates the number of remaining sachets based on when supplement was started and assuming one sachet is used per day, but parents may have fewer or more sachets remaining than the estimate. Site may want to discuss with parents ahead of allocating another box. Multiples, for example, twins, triplets, should each be allocated a pack.

If packs are nearing their expiry date, new packs should be allocated sufficiently in advance of the expiry date to allow for any potential issues to be resolved before the supplement reaches expiry. Parents should be advised that expiring or expired stock must be discarded and not used beyond its expiry date.

Sites will receive an automated email notifying them of any infants who may have 30 or fewer sachets remaining or if their supplement is due to expire within 30 days. DOLFIN study team will also receive this notification.

Allocating from hospital stock

At randomisation an infant is allocated a treatment pack ID which corresponds to a pack in the existing hospital stock. If a new pack is required for an infant, the site can allocate a new pack to an infant from hospital stock using the randomisation system.

Allocating from the distributor

If an infant has been transferred to another hospital, discharged home or was recruited remotely or post-discharge, sites should allocate a new pack to be sent by the distributor to the participant's home.

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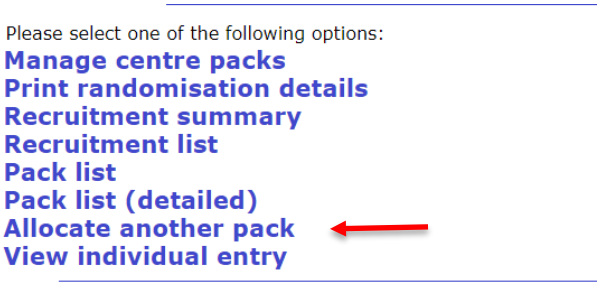
The distributor accesses parent contact details via a secure web-based pack dispatch system; personal identifiable data should not be shared via email with the DOLFIN study team or distributor. If there are any queries about contact details this should be discussed by telephone. Sites should check for any change of address prior to allocating a pack. Any changes to contact details should be updated as soon as possible on the randomisation system (see **Guidance Sheet 3 - Randomisation**).

Parents will receive a text and/or email (if contact details have been provided) to notify them that a supplement delivery is due. Delivery is via Royal Mail and is expected to be within 1–2 days of the request being made. The delivery must be accepted in person at the destination. If the parents are not available to accept the delivery the parents should receive a card with instructions for arranging a redelivery. If a mobile number has been provided parents should also receive a text message with details about the delivery and arranging a redelivery.

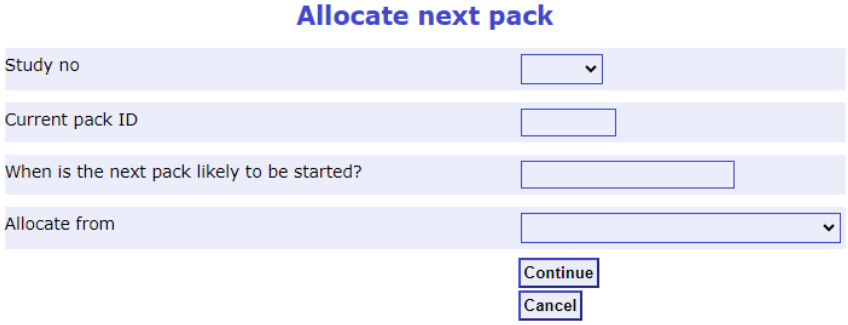
If a delivery arrives damaged or has not been received, parents are asked to notify their local clinical team or the DOLFIN study team. Sites should notify the DOLFIN study team of any missing or damaged boxes. A new box may need to be allocated in this instance.

Process for allocating packs

Login to randomisation system using centre-wide login details.
Select ‘Allocate another pack’



Enter study ID, current pack ID, and when the next pack is likely to be started (this does not affect when supplement is sent; date is used by the system to estimate how many packs are remaining). For ‘Allocate from’ select from drop-down box either ‘Site’ (to allocate from hospital stock) or ‘Distributor to send to participant’s home’ (to send directly to parent’s home). Click ‘Continue’.



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Click ‘Allocate’ on the next screen: a notification email will be sent to designated individuals to confirm new pack allocation.

If you need to contact us urgently with problems with randomisation or supplement supply within office hours phone the trial office on 01865 617919. For urgent out of hours queries please phone 0800 138 5451.

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