

SAMPLE CLINICAL GROWTH TRIAL PROTOCOL
FOR HEALTHY TERM INFANTS

Protocol Title

Sponsor Name

Date

This protocol reflects current practice of U. S. Infant Formula Manufacturers.
November, 2002

For Further Information: Contact the International Formula Council, 404-252-3663

I. BACKGROUND AND RATIONALE

This section shall include information on the following items:

- Purpose and rationale of the trial.
- Name and description of investigational product(s).
- References to literature and data that are relevant to the trial, and that provide background for the trial.
- A summary of findings from relevant clinical and non-clinical studies.
- A summary of known and potential risks, if any, to human subjects.
- A description of the population to be studied.

II. STUDY OBJECTIVES

A. Primary Objective

The primary objective of this study is to assess nutritional adequacy as measured by growth (weight gain) of normal term infants fed (specify, e.g., an experimental formula), as compared to infants fed (specify, e.g., a control, commercial formula).

B. Secondary Objectives

The secondary objectives of this study are to assess:

1. Interval weight gains at pre-specified intervals
2. Physical development measures: attained weight and recumbent length
3. Comparison of group to reference data
4. Other outcomes as stated in purpose and rationale

III. STUDY DESIGN

A. Description of Study

This study is a double-blind, randomized, controlled, parallel, single/multi-center, prospective trial.

B. Subjects, Groups, Centers

Forty subjects per group must complete the study protocol, based on the AAP/CON 1988 guidelines, assuming a standard deviation (SD) of 5.3 g/d, one-sided alpha = 0.05, and a power of 0.8. To allow for a 20%-30% drop-out rate in all groups, total recruitment is estimated to be 54 infants per group. If a power of 0.9 is desired, the number of subjects will be 55; and the number after accounting for drop-outs, approximately 70. The study will be a single/multicenter study.

C. Duration of Subject Participation

Subjects will receive study formula exclusively from 14 days until 112 days of age.

D. Study design schematic

Study Design Schematic

| Scheme of Data Collection | | | | | | |
|---------------------------|-------------------------------|-----------------------------|-----------------------------|-----------------------------|-----------------------------|------------------------------|
| | Enrollment Visit ¹ | 14 days of age ² | 28 days of age ² | 56 days of age ² | 84 days of age ² | 112 days of age ² |
| Enrollment/Randomization | X | | | | | |
| Demographic Data | X | | | | | |
| Weight, Length | X | X | X | X | X | X |
| Interval History | | X | X | X | X | X |
| Adverse Events | X | X | X | X | X | X |

¹Date of Birth is Day Zero of life (enrollment 0-14 days of age); enrollment may be on day 14 of age visit.

² Visit window ± 3 days.

IV. STUDY POPULATION

A. Description

Subjects are healthy, full-term newborn infants, 0-14 days of age at enrollment. Both male and female infants will be included in the study.

B. Subject inclusion criteria

All subjects must comply with the following inclusion criteria:

- Healthy newborn
- Singleton, term infant (37-42 weeks gestation)
- Birth weight 2490-4200 g
- Less than or equal to 14 days of age at enrollment
- Signed informed consent obtained

C. Subject Exclusion Criteria

Subjects presenting with any of the following:

- History of underlying disease or condition or congenital malformation which, in the opinion of the Investigator, is likely to interfere with the normal growth and development or the evaluation of the participant
- Non-exclusive formula feeding by initiation of study feeding
- Participation in another clinical study that has not been approved by the Sponsor

V. INVESTIGATIONAL PRODUCT DESCRIPTION

- Composition
- Form
- Quality control (e.g., storage, stability, inventory, product accountability/reconciliation)
- Packaging and labeling
- Blinding technique

VI. MEASURES TO ASSESS STUDY ENDPOINTS

A. Primary Outcome

The primary outcome is mean daily growth over the course of the study, expressed as weight gain in g/day, (14 -112 days).

B. Secondary Outcomes

1. Interval weight gains will be calculated. If a difference in interval gain but not overall study gain is detected, additional assessment may be needed.
2. Body weight: Weight will be measured at 14, 28, 56, 84 and 112 days.
3. Body length: Length will be measured at 14, 28, 56, 84 and 112 days.

VII. STATISTICAL METHODS

A. Sample Size

Based on the AAP/CON 1988 guidelines, the number of subjects necessary to detect a 3 g/day difference in weight gain ($p < 0.05$) with a power of 0.8 in a one-sided test is 40 based on an assumed SD of 5.3 g/day. To allow for a 20%-30% drop-out rate in all groups, total recruitment is estimated to be 54 infants per group. If a power of 0.9 is desired, the number of subjects will be 55; and the number after accounting for drop-outs, approximately 70. Gender should be included in the statistical model. If a gender by formula interaction is identified, additional assessment may be needed.

B. Randomization

Description of randomization procedures (e.g., blocking, if any), software used, etc.

C. Statistical Hypothesis and Analytical Plans

Describe statistical hypothesis and analytical plans.

D. Participant Withdrawal Criteria

For all participants who withdraw from the study prior to the last study visit, the principal investigator should make a reasonable attempt to follow up to determine a reason for drop out. Reasons for withdrawing from the study feeding protocol, and/or study procedures, will be summarized by category and compared for the feeding groups. Categorical analytical techniques will be used as needed.

VIII. ADVERSE EVENTS

A. Definition

The adverse event (AE) is defined as any untoward occurrence in a clinical investigation subject. The AE does not necessarily have a causal relationship with the study feedings.

AEs are illnesses, signs or symptoms occurring or worsening, and/or abnormal laboratory findings during the course of the study. AEs include occasions when the subjects contact the investigator or their private physician and are examined or given medical direction. They may or may not lead to the withdrawal of the subject from the study.

AEs are generally classified as serious or non-serious. An AE is considered serious if it meets one or more of the following criteria:

- results in death
- is life-threatening
- requires inpatient hospitalization or prolongation of existing hospitalization
- results in persistent or significant disability/incapacity, or
- is a congenital anomaly/birth defect

B. Reporting and documentation of AEs

All AEs occurring during the study will be reported and recorded whether or not they are considered to be non-serious, serious or related to the study feeding.

The following information will be recorded as appropriate:

- Subject and date
- Description of event
- Duration
- Frequency
- Intensity
- Seriousness
- Action taken

Investigators will record all serious adverse events (SAEs), including documentation of the outcome and sequelae. The investigator will determine the relationship, if any, of the SAEs to the study feeding. In addition, the investigator will notify the sponsor of SAEs. The investigator is to report SAEs as required by the Institutional Review Board (IRB). The sponsor is responsible for determining any trends relative to the incidence of SAEs.

C. Follow-up of study subjects with SAEs

If further information examinations are required to assess the relationship between an SAE and treatment following the occurrence of the SAE, all pertinent examinations or laboratory findings must be noted with their results in the Case Report Form (CRF) or attached to a follow-up file.

IX. ETHICAL STANDARDS FOR INVESTIGATORS

This study will be conducted in accordance with the ethical principles and rules that have their origin in the Declaration of Helsinki and its subsequent amendments (October 2000) and will be consistent with Good Clinical Practice (GCP) and applicable regulatory requirements.

The study will be conducted in compliance with the protocol. The protocol and any amendments, and the informed consent will receive IRB approval/favorable opinion prior to initiation.

Freely given written permission must be obtained from participant's parent(s) or legally acceptable representative prior to clinical trial participation.