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Conducting Clinical Trials in the Nutrition Industry: We're Not in Academics Anymore!

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Introduction

Like research in academic institutions, industry directed prospective clinical trials start with an idea or hypothesis. Differences between academic and industry-directed clinical trials are numerous and include funding sources, study objectives, source of idea and clinical trial process. In the nutrition industry funding frequently comes from a research and development budget. In contrast, non-industry research funding is oftentimes funded by small institutional grants, foundations, government agencies, and professional associations like the American Dietetic Association. Regardless of differences between industry and non-industry, it is paramount that all researchers strive to improve the quality of clinical trials by understanding the fundamental concepts. Clinical trials in industry and other research areas should abide by common principles of high standards and quality.

Nutrition-industry prospective clinical trials (NICTs) are often developed to show either safety/tolerance or efficacy, or both in many cases for a new nutrition product. NICTs may also be initiated to support a marketing claim based on either a novel ingredient (e.g. docosahexaenoic acid-DHA) or new application (e.g. liquid versus powder).

By definition clinical trials are prospective studies comparing the effect of an intervention on a specific outcome. Clinical trials are not retrospective studies, only prospective.[1] In industry, it is rare to undertake a retrospective study; however, these studies may be cited to support the safety of specific nutrient or identify the clinical need for a new nutrition product or ingredient.

Types of NICTs include drugs (investigational new drug - IND), infant formula, medical food, biologics and medical devices. We will limit discussion on clinical trials to medical foods (orphan nutrition products) indicated for nutrition therapy of either acute or chronic medical conditions. In simple terms, "medical foods" are nutrition products intended to be used as either sole source of nutrition or part of a restricted diet plan in individuals diagnosed with specific medical conditions. The term medical food, as defined in section 5(b) of the Orphan Drug Act (21 U.S.C. 360ee (b)(3), is "a food which is formulated to be consumed or administered enterally under the supervision of a physician and which is intended for the specific dietary management of a disease or condition for which distinctive nutritional requirements, based on recognized scientific principles, are established by medical evaluation."

One reason medical foods are to be used under strict medical supervision is that improper use and clinical monitoring may result in a severe adverse event. For

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example, if a medical food for an infant with diagnosed phenylketonuria (PKU) was given to an infant without PKU, and used as a sole source of nutrition, it would result in severe protein malnutrition and amino acid deficiency. In this case, the PKU medical food has phenylalanine, an indispensible amino acid, removed. Dietary phenylalanine is then carefully prescribed by the metabolic dietitian to meet the needs of the infant while not causing excessive accumulation in blood and organs.

Medical foods, like drugs and foods are regulated by the FDA. Clinical trials with medical foods require the strictest adherence to good clinical practice guidelines (GCP)[2] and quality to assure correct interpretation of data. More importantly, conducting high quality clinical trials is a requisite for any product requiring FDA review and approval- technically the FDA does not "approve" a product, but rather does not "disapprove" product commercialization. The FDA assures that any marketing claims, like "improves immunity" are supported by unbiased clinical evidence. Like pharmaceutical clinical trials, failure to rigorously follow GCP in medical food research could result in unwarranted adverse event and serious adverse events (SAE) (Table 1).

Nutrition Industry Research Development (Ideation to Clinical Trial Completion)

Research and development in the nutrition industry yields new product innovations that contribute to improved patient care and clinical outcomes. Major objectives for industry are to develop products that are safe, of high quality, and effective. Another major objective is to identify gaps in nutrition therapy where a new product might be indicated or where a modification to an existing product is beneficial. Some new product ideas may include minor changes in micronutrients or adding a functional nutrient, like fiber to a tube feeding product. "Tranformational" ideas,

Table 1. Adverse Events and Serious Adverse Events

Adverse Event	is any untoward or unfavorable medical occurrence in a human subject, including any abnormal sign (for example, abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with the subject's participation in the research, whether or not considered related to the subject's participation
Serious Adverse Event	is any undesirable experience associated with the use of a medical product in a patient. The event is serious and should be reported when the patient outcome is (FDA MedWatch Safety Program): **Death** Report if the patient's death is suspected as being a direct outcome of the adverse event. **Life-Threatening** Report if the patient was at substantial risk of dying at the time of the adverse event or it is suspected that the use or continued use of the product would result in the patient's death. **Hospitalization (initial or prolonged)** Report if admission to the hospital or prolongation of a hospital stay results because of the adverse event. **Disability** Report if the adverse event resulted in a significant, persistent, or permanent change, impairment, damage or disruption in the patient's body function/structure, physical activities or quality of life. **Congenital Anomaly** Report if there are suspicions that exposure to a medical product prior to conception or during pregnancy resulted in an adverse outcome in the child. **Requires Intervention to Prevent Permanent Impairment or Damage** Report if you suspect that the use of a medical product may result in a condition which required medical or surgical intervention to preclude permanent impairment or damage to a patient.

Table 2. Typical Nutrition Industry New Formula Development and Testing

Industry Nutrition (infant formula) and medical food trials	Pre-clinical	Premarketing Clinical Trials	Post-marketing surveillance
	Animal efficacy, toxicity & dose-response studies	First in time human trials Safety trials Randomized controlled trials **(RCTs)** for safety, efficacy in healthy subjects/diseased patients Multi-center RCTs in pts compares new formula to **"gold standard existing formula"** (Like pharma phase 1, 2a, 2b, 3, & 3b combined)	Collect adverse event data (for safety) and show different efficacy or indication Case studies (Like pharma phase 4)

Commonly takes 10 to 15 years of research → **Product Launch & Regulatory Approval**

like developing a nutrition medical food to treat medical conditions where nutrition did not previously play a role in morbidity require extensive pre-clinical and clinical trials, not unlike drug trials (Table 2). For novel product developments, pre-clinical work would require animal studies, tissue (in vitro) studies, and toxicity and dose-response studies. Once the pre-clinical and early phase clinical trials are established more rigorous clinical trial process is initiated to support the basic safety, growth, tolerance and efficacy trials.

The first step of the developing a robust product and research pipeline is determining what new products or modifications in products should be developed (Figure 1). Several types of innovation are considered when filling the pipeline which will determine what type of clinical trial, if any, is required. The several types of innovation include: technical (new ingredient or novel compound; e.g. DHA, prebiotics); new disease application for existing product (e.g. ketogenic formula for mitochondrial diseases); new forms of ingredients (e.g. microencapsulated vitamin D); packaging and flavor; and new form (liquid product of current powdered formula).

Product ideation comes from various sources, including literature review, patent searches, key opinion leaders, (e.g. dietitians), focus groups, and corporate advisory boards (Figure 1). Ideas are collected and a strict process is undertaken to ascertain which ideas move through the pipeline. In industry, multiple teams are involved in the decision making process to identify which new ideas reach fruition and which require clinical trials.

Part of the decision making process in determining which ideas are developed and funded includes:

1. clinical need/insight – is there a current gap in products available for a specific patient population?
2. benefit to patient and company – how will the patient benefit. Will the company benefit from having a new product?
3. reason why – simply, why should this innovation be funded?
4. competitive advantage – will this innovation provide any advantage. Can any new marketing claims be made with this

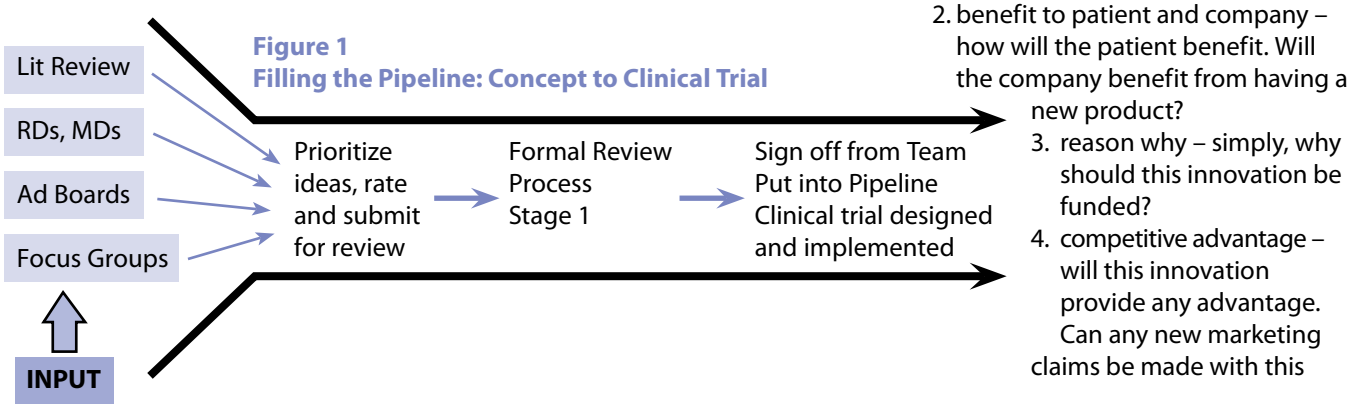

Figure 1
Filling the Pipeline: Concept to Clinical Trial

innovation?
5. opportunity – what opportunity exists in the current marketplace. Could this innovation be a global opportunity? Is it beneficial to a new age group?

Once all above criteria have been satisfied and the project approved a research and development team (R&D) is created and funding provided for product development and a clinical trial. If a clinical trial is required then the Medical and Scientific Affairs group will coordinate efforts with R&D. The Medical group will assist in protocol development and provide clinical expertise, as well as identify potential principal investigators for collaboration. Before any clinical trial is approved, several criteria must be determined:
1. is the clinical trial directly aligned to business needs?
2. does it add value to a specific brand?
3. is it of high scientific and medical quality?
4. is it in compliance with best clinical practice?

Once a plan is approved, R&D and Medical collaborate with marketing to develop product efficacy claims which would result from a positive outcome study. Along with their marketing colleagues, nutritionists in the nutrition industry review possible outcome parameters in the study and if the results are positive, determine what kind of product claims can be made. For example, "XXX" ingredient "improved eye development." A clinical trial would need a positive outcome on an eye test in the study such as Teller acuity cards or visual evoked potential (VEP). This activity occurs concurrently to protocol development.

Protocol Development

Nutritionists in nutrition industry are responsible for writing the clinical study protocol. Unlike drugs, the clinical protocol and nutrition formulation is the first time testing moves from animals to humans. Therefore, attention to safety is pivotal. Most companies have a protocol template to include GCP protocol components (Table 3)[3] GCP is a standard for the design, conduct, performance, monitoring, auditing, recording, analyses, and reporting of clinical trials that provides assurance that the data and reported results are credible and accurate, and that the rights, integrity, and confidentiality of trial subjects are protected.

Table 3.
Components of Nutrition Industry Protocol[3]

6.1	General Information
6.2	Background Information
6.3	Trial Objectives and Purpose
6.4	Trial Design
6.5	Selection and Withdrawal of Subjects
6.6	Treatment of Subjects
6.7	Assessment of Efficacy
6.8	Assessment of Safety
6.9	Statistics
6.10	Direct Access to Source Data/Documents
6.11	Quality Control and Quality Assurance
6.12	Ethics
6.13	Data Handling and Recordkeeping
6.14	Financing and Insurance
6.15	Publication Policy
6.16	Supplements

The section on general information includes the protocol title, any protocol amendments, name and address of the sponsor, names and titles of those authorized to sign the protocol, as well as the name, title, address, and telephone number of the sponsor's medical expert, and the name and title of the investigator(s) responsible for conducting the trial.

Next in the protocol, is the background information. This section contains the name and description of the investigational product, a summary of nonclinical studies' findings and other clinical trial finding that have relevance to this study, a summary of known and potential risks and benefits to human subjects, and a description and justification for the route of administration, dosage, dosage regimen, and treatment period. In this portion of the protocol, a statement is added that the trial will be conducted in compliance with the protocol, GCP, and regulatory requirements. Finally, a description of the population to be studied and references to literature and data that support the trial completes this section.

Section 6.3, trial objectives and purpose is a detailed description of the objectives and the purpose of the trial. The trial design section 6.4 includes a specific statement of the primary endpoints and secondary endpoints. A description of the trial type (double-blind, parallel, etc.) and measures to minimize bias (randomization, blinding) are included in this section. Additionally, a description

of the trial formula and the dosage and the dosage regimen is provided along with formula form, packaging and labeling. This section describes the expected duration of subject participation and the sequence and duration of all trial periods including follow-up. Subject trial discontinuation criteria and accountability procedures for the treatment formula and comparator formula need to be explained. Finally, the last part of the section includes maintenance of trial treatment randomization codes and procedures for breaking the codes. Identification of any data to be recorded directly on the case report form (CRF) and considered to be source data is explained.

Section 6.5 addresses the selection and withdrawal of subjects comprises subject inclusion criteria, subject exclusion criteria, and subject withdrawal criteria. Much time is spent on identifying the correct inclusion and exclusion criteria to assure you have a homogeneous subject group. This is not always easy when you consider the clinical spectrum of all medical conditions. For example, in a clinical trial looking at infants with cow milk allergy you need to consider whether to include only IgE-mediated, non-IgE-mediated infants, or maybe both. Other criteria may include whether to restrict specific drugs, like steroids, limit to specific age groups. More specifically, in this population you need to control how diagnosis was determined: patch test, double-blind placebo-controlled formula test etc. Failure to control these criteria results in a non-homogeneous group and can significantly alter interpretation of results.

Subject withdrawal criteria must specify when and how to withdraw subjects from the trial, type and timing of data to be collected for withdrawn subjects, follow-up for withdrawn subjects. Subject withdrawals always occur in nutrition clinical trials, but need to be controlled. Excessive withdrawals need to be identified immediately and careful review between the industry monitor and principal investigator conducted to determine if withdrawal is due to product intolerance or a non-product related incident. All withdrawals are identified and identified in the final trial report which will be submitted for review by the FDA, if required.

Section 6.6 covers the treatment of subjects and includes the nutrition treatment to be administered, dose, dosing schedule, route of administration, and the treatment period including the follow-up period. It also includes a listing of what medications, treatments, dietary supplements are permitted and not permitted during the trial. Finally, the procedures for monitoring subject compliance are described.

Careful review of medications is essential to reducing any confounding reasons in subject outcomes. For most nutrition intervention studies where specific nutrient biomarkers are assessed, dietary supplements are oftentimes not allowed. They may only be allowed if the subject is already on the dietary supplement and if it medically indicated, e.g. iron deficiency anemia.

Assessment of efficacy is section 6.7 where efficacy parameters are specified to include methods and timing for assessment, recording, and analysis. Specification of safety parameters comprises section 6.8 on assessment of safety. Besides methods and timing for assessment, recording, and analysis, procedures for recording, reporting, and follow-up of adverse events are explained. Any reports of serious adverse events are immediately reported to the industry monitor within 24 hours and immediate steps are undertaken to determine the cause. In many cases, a third party medical doctor may be contracted to assist in interpreting the serious adverse event to help determine the best course of action.

Statistics in section 6.9 is where a description of statistical methods is outlined. Reasons for sample size selection and power calculation are provided along with level of significance to be used, criteria for trial termination, and procedures for accounting for missing data are given. The importance of a strong statistical plan cannot be overstated. Regardless of industry or academia, there is no way to accurately predict subject clinical outcomes; both are limited to their statistical design. It is important to note that many studies get rejected for publication based on poor statistical design and interpretation of the strength of the data.

A thorough statistical plan is paramount in assuring either acceptance or rejection of the null hypothesis. In all clinical trials statistics are based on an estimated amount of protocol failures and “drop outs”. For this reason, a minimum number of subjects are identified when running power calculations.

Section 6.10 is direct access to source documents and includes permission and planning to monitor and audit source data and documents. The last

five sections are 6.11 quality control and quality assurance, 6.12 ethics, 6.13 data handling and record keeping, 6.14 financing and insurance, and 6.15 publication policy. Unlike academia, a publication plan is carefully determined. This is especially important in multicenter trials where several or more principal investigators have collaborated.

Typically, thought leaders and nutrition experts are consulted prior to the design and writing of the protocol. Once the protocol is written, there is an internal protocol review and sign off by marketing, regulatory, medical affairs, and clinical research. Following internal review, there is an external protocol meeting where thought leaders, experts and potential investigators formally review the protocol for feasibility and scientific rigor. Getting input and approval from external clinical and research experts is vital to assure that proper assessment markers and study design are fundamentally sound.

Clinical Trial Process

In nutrition industry, the nutrition scientist is usually a member of one of many research teams (probiotics, low protein, low birth weight to name a few). Other members include regulatory, preclinical scientist, project management, product development, manufacturing, marketing, and quality assurance. This team first evaluates the literature, infant formula laws, designs the product, then reviews preclinical results, and sets success criteria to move to a clinical trial. The nutrition scientist takes the lead on the clinical trial. It has been reported that there are over 400 steps to a clinical trial. While the protocol and informed consent are being written in the pre-study phase several parallel activities need to occur. First, study product (active formula and control formula) needs to be calculated per patient and ordered from manufacturing. Production of clinical trial material frequently requires a halt to commercial production so timing is established. Additional study product orders depend upon the shelf life of the study product. Sample size from the protocol is needed for the labeling and randomization is needed for subject assignment to active formula or control formula. Next, a randomization schema needs to be set up and consideration if the study is to be stratified for gender. Warehousing the study material and distribution follows. Computerized randomization can be linked to the distribution center for dispensing study product to the sites.

An estimation of the number of study sites will determine the number of investigators needed and is based upon the sample size and expected enrollment rate. After that, selection and qualification of study sites occurs. Selection and qualification entails physical visits to inspect each facility, review the study protocol, record keeping, experience of physician with clinical trials, and availability of a study coordinator to manage study site activities. Next the physician is asked to compile a study budget (Table 3) to estimate expected site costs to execute the study. Once the budget has been approved, the investigator is required to complete and return such regulatory documents as the 1572, curriculum vitae, laboratory certifications, etc. All of the returned documents are then organized in an investigator binder for each site. The binder also includes a site screening and enrollment log, study formula accountability log, adverse event forms, and various communication documents (Table 4). During this time a detailed data analysis plan is written. Concurrently, the investigator submits the protocol, informed consent, any advertising to their local Institutional Review Board (IRB) or the central IRB for approval. No aspect of the study may start until IRB approval is received. At the same time, case report forms (CRF) are developed. These forms are used to capture study data and may be paper or computerized.

Just prior to the start of the study an investigator meeting is held for all study investigators and study coordinators. This meeting is where the protocol, inclusion and exclusion criteria, schedule of procedures and visits are reviewed, training on any and all study-related procedures, adverse event reporting, randomization, CRFs, adverse event reporting, study product details, shipping and dispensing are provided. Following the investigator meeting, study sites that have IRB approval receive a study initiation visit. Alongside and just prior to the visit the investigator binder, CRFs, and initial supply of study formula and any other clinical trial supplies (such as containers for blood and/or stool collection) are shipped to the site. Typically, the study monitor conducts the site initiation visit and checks in the study formula as instruction for study product accountability. The study monitor will describe future monitoring visits and review all training with the study staff. The last step to the site initiation is to turn on randomization for the site which enables the site to

Checklist for Clinical Trials **Clinical trial Number: _____ Principal Investigator:_____**
Protocol completed and sign off
Identify clinical sites
Establish timeline for study
Non-Disclosure Agreement (NDA) to each site
Develop budget and approval
Laboratory costs
Shipping costs
IRB costs
Researcher costs
Indirect costs to institution
Clinic visit costs
Travel stipend to families
Develop summary sheets for each site
Collect Curriculum Vitaes
Identify number system for sites and subjects
Identify monitoring strategy
Contract agreements signed
Get research product made
Develop Clinical Research Forms and Professional Research Forms along with binders
Develop forms (enrollment, inventory log, product accountability form, product ordering log, close out form)
Print forms
Investigator Binders:
Contact information
Protocol (signed and completed)
Site Visit Monitoring Log
Subject Enrollment Log
Delegation of Responsibility and Site Personnel Log
Formula Accountability
General Correspondence
IRB Correspondence
Laboratory information
Serious Adverse Event Reporting
Case Report Forms
Product Information
IRB signed and approved
Initiation Visit (pre-study activities accomplished checklist)
Consent form developed and IRB approved
File regulatory forms signed by Investigators
FDA 1572
CV's for the PI and any sub-investigators
Copies of medical licenses for all CV's submitted
Financial Disclosure agreement
Signed protocol (by PI)
IRB approval letter
IRB approved consent
Lab license
Lab normal ranges
Lab Certification (e.g. CLIA)
W-9
Establish Fed Ex Airbills for shipment as needed (logistically)
Blood samples: if shipments are to a central laboratory
Send few airbills for ongoing logs/documents being returned from research sites
Checklist is Complete

Table 4. Checklist for Clinical Trials

begin subject enrollment.

The next study segment is known as the execution phase. As each site enrolls subjects into the study the study monitor returns to the study sites to ensure that the study staff are following the protocol, inspect the study formula accountability, and verify CRF data entries alongside source documents. Discrepancies in data are documented as data queries which must be reconciled by the study staff. The industry clinical nutrition scientist manages all of these activities and all study monitoring reports during the study. In addition, weekly to monthly enrollment rates are calculated and reported in order to monitor the study's progress and to determine if more study sites are needed. Any study sites that are not enrolling subjects may be closed during this time. Typically, a medical monitor handles adverse event and serious adverse event reporting with the study sites. If a site investigator judges that a subject's serious adverse event has been caused by the study product, he/she has the authority to unblind that subject's treatment code for further assessment and clinical care. Tracking study supplies, data transfer, study formula, CRFs, and regulatory documents

is fundamental to the conduct of the trial. Once enrollment is complete, a study site's last subject has completed, and all data queries have been reconciled, the study monitor will go to the site for the close-out visit. This visit is needed to rectify any outstanding data queries, oversee study formula return and destruction, and review the policy for study document retention with the study staff.

The last element of the study is the post-study period. After the last subject has completed the study and all queries have been reconciled at all study sites, the database is locked. Upon locking the database, unblinding subjects to treatment occurs followed by data analysis. Data analysis tables are produced and then used to write the clinical study report (CSR) which is used internally and for regulatory purposes. It contains results on demographics, safety, growth, efficacy endpoints, and concomitant medications and procedures. Depending upon study results, commercialization of study product begins and label claims are crafted. Furthermore, the industry clinical nutrition scientist drafts the manuscript as a co-author for submission to the predetermined peer-reviewed journal. Journal selection is usually based upon impact factor, timing of product launch, and popularity within the targeted medical community. As with all medical and nutrition journals financial disclosure is reported.

Like pharmaceutical research, post-market surveillance and monitoring is undertaken. A formal product monitoring is required to identify complaints and clinical matters relevant to consumption of all nutrition products. All complaints are carefully handled by "nutrition specialists" or medical affairs. The department and personnel who monitor complaints and "medical alerts" differ among companies. Regardless, a rigorous process must be in place to manage any clinical issues. The FDA has an official online "MedWatch" process where any individual can directly contact the FDA and file a purported safety alert. The FDA then contacts the specific company and submits the complaint which receives immediate attention.

Summary

Industry-driven research has resulted in many product innovations that have benefited infants, children and adults. For patients with acute and chronic disease these innovations have significantly and positively impacted clinical outcomes and quality of life. Collaboration with nutrition experts, like dietitians, is integral to the success of outcome-based clinical trials. Continued innovation and industry-academic collaboration will ensure a steady "diet" of novel nutrition products and improved clinical efficacy for patients.

Reference List

1. Friedman L, Furberg C, DeMets D. *Fundamentals of Clinical Trials*. New York: Springer; 1999.
2. Mackintosh DR, Molloy V, Mathieu M, eds. *Good Clinical Practice: A Question & Answer Reference Guide*. Waltham, MA: Barnett International, a subsidiary of Parexel International Corporation; 2004.
3. Center for Biologics Evaluation and Research. Guidance For Industry, E6. *Good Clinical Practice: Consolidated Guidance.* 1996:1-58. http://www.ich.org.
4. Federal Drug Administration. Med Watch Program. 2010; http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/default/htm.

Congratulations to RDPG Member Dr. Bettie Carter Stanislao

Bettie Carter Stanislao, PhD, RD, LN from Bozeman MT is celebrating her 50th year of ADA membership. She has been invited to attend the Food & Nutrition Conference & Expo (FNCE) in Boston for a special ceremony to honor the 50 Year Members. Bettie joined the American Dietetic Association in 1960 and continues as an Active ADA Member as well as an RDPG member. She has specialized in nutritional counseling for endocrine and auto-immune diseases including diabetes and celiac disease, and, although retired, still keeps in touch with some of her patients. She says that the American Dietetic Association has been very important to her throughout her career. We are proud to have her as a member of the RDPG.

The RDPG is honored to have a number of distinguished 50 Plus Members who have passed the 50 year milestone and continue to be affiliated with ADA. These include Esther Winterfeldt (Stllwater, OK), Margaret Bogle (Little Rock, AR), Jean Hankin (Honolulu, HI), Julia Kula (Maunton MA), Eva Orton (San Jose CA), Grace Ostenso (Bethesday MD), Rachel Schemmel (East Lansing MI) and Helen Shaw (Greensboro NC).

We will recognize all of these special RDPG members at the Annual RDPG Member Breakfast in Boston.