Clinical Research on Probiotics: The Interface between Science and Regulation

Carmen Tamayo
Flora Inc. USA, Bethesda, Maryland

Although there exists some evidence of the safety and efficacy of probiotics for treatment of disease, many of the clinical trials have lacked methodological quality, particularly with regard to protocol design, selection of population, and product characterization. Depending on the regulatory route, data need to be collected carefully to satisfy regulatory requirements in the United States and elsewhere. This article discusses how the regulations for probiotics affect clinical research. It also describes clinical trial design and issues that affect the design of trials for probiotics conducted to improve the scientific evidence for these products.

Placebo-controlled randomized clinical trials (RCTs) have demonstrated the clinical efficacy of probiotics for functional gastrointestinal problems [1–5], and preliminary studies show some benefits of probiotics for atopic diseases, food allergies, and inflammatory bowel disease [6–13]. However, probiotic trials suffer from shortcomings similar to those of trials for dietary supplements: small sample size; lack of appropriate randomization, allocation concealment, or blinding; different periods of treatment and different doses; lack of product characterization; ill-defined patient populations; lack of data on etiology and severity of disease; and potential confounding factors. Although some recent trials have corrected these failings, there are still inadequate data to draw valid conclusions about many conditions. Also, major meta-analyses and systematic reviews have yielded conflicting results [14–17].

The lack of a uniform definition of "probiotics," as well as the lack of characterization of specific strains, designation of appropriate doses, and conformity to required product characteristics [18–20]—all of which have been described at great length in previous articles in this supplement—are major issues that need to be addressed for the design of good trials. A viable probiotic agent should display nonpathogenic properties, the same features as the strain itself, the ability to survive transit through the gastrointestinal tract, adherence to intestinal epithelium, colonization in the intestinal tract, production of antimicrobial substances, and a good shelf life (stability) in food or powdered form [18]. Unfortunately, not all probiotics tested in clinical trials meet these requirements.

Because probiotics may confer potential health benefits by preventing or treating specific pathological conditions [8, 9, 21–23], they are often used as "drugs." Currently, few (if any) probiotics are able to meet the manufacturing requirements for drugs [24, 25].

Both US and European markets for probiotics are set for emphatic growth in the coming years, despite widespread consumer ignorance about probiotics and their benefits to the human body [26]. Major concerns exist about the widespread use and quality of probiotics. Up to half of the "friendly bacteria" products sold are ineffective, and some may even be harmful [27]. No international consensus exists regarding the methodology used to assess the efficacy and safety of these products, and only specific brands have proven effects [2]. Considerable differences exist in bioavailability, biological activities, doses, and composition among probiotic preparations.

The document from the Food and Agriculture Organization of the United Nations and the World Health Organization refers to probiotics only as food, thus precluding them to be used as biotherapeutic agents

Reprints or correspondence: Dr. Carmen Tamayo, Research and Development Director, Flora Inc. USA, 8003 Thornley Ct., Bethesda, MD 20817 (ctamayo2@comcast.net).

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or drugs [2]. The report, however, underscores the need for taxonomy, definition, and measurement of health benefits, including the minimum daily amount required to confer an effect, and the need for sample sizes large enough or powered to determine an effect. With respect to evaluation of probiotics for use in food, the strain must be identified and functionally characterized on the basis of in vitro and animal studies. Safety should be assessed for new strains on the basis of in vitro and/or animal studies and phase 1 and 2 clinical trials.

With the emergence of the hygiene hypothesis, the role of bacteria in host health is being reconsidered. Probiotics are being used to treat disease. However, this poses a major challenge because of their regulation as foods and dietary supplements. The current market refers to them as "microorganisms which when consumed in adequate amounts, confer a health effect on the host, *preventing, cure, mitigating or treating a disease*" which, for the United States, is akin to the claims for drugs [25]. Health claims for probiotics range from general claims, such as "regulation of bowel activity or increased well-being," to more specific claims, such as "exerting antagonistic effect on the gastroenteric pathogens or for the treatment of IBS [irritable bowel syndrome]" [28, 29]. Differences in health-related claims applicable to probiotics, related concepts, and marketing implications are discussed in this supplement [25, 29–31] and are reviewed elsewhere [32, 33–38].

Product labeling should provide consumers with correct and relevant information. At a minimum, the manufacturer must have data to support the identity, potency (i.e., number of viable organisms to which a consumer will be exposed after consumption within the established time frame to expiration), purity, and quality of the product [39].

Although probiotic research has been conducted for the past 28 years, variability in study design, type of probiotic, dose, and duration of treatment have yielded contradictory results [14]. Within the past decade, a large number of scientific studies have addressed mechanisms of action of certain probiotic strains. However, in vitro effects of a probiotic may be opposite of the behavior in vivo, which represents an important objective of current investigations.

Clinical trials seldom report adverse effects and may lack the power or duration to identify them. Thus, population-based samples may be better for assessment of probiotic safety. RCTs are often considered the best methodology for drawing inferences regarding the efficacy of a therapy. Difficulties in interpreting RCTs, particularly lack of generalizability and heterogeneity of the therapeutic effect, may be challenging. Some patients benefit from experimental therapy, whereas others do not benefit and may even be harmed. Nevertheless, RCTs remain the gold standard for evaluation of safety and efficacy of an intervention and should be designed carefully. Previous dose-range studies may be needed to ensure efficacy, and study designs should be selected with care. Well-controlled observational studies and evolving effectiveness studies may also provide valuable evidence.

Clinical trial objectives may vary according to the purpose of the research. For investigator-initiated research, the objectives might be (1) to ascertain safety and efficacy, (2) to identify adverse events related to use, and (3) to discover or verify clinical, pharmacokinetic, or pharmacodynamic effects. Conversely, for research initiated by manufacturers, the purpose may be only to validate or substantiate a health related claim.

To validate a claim, the proposed relationship between the product and the health-related end point should be identified, and appropriate measurements of both should be indicated. The interests of patients and consumer involvement are becoming integral parts of clinical development and should be taken into consideration. Effective funding and collaboration among industry and academic institutions are key for proper development of probiotics.

Probiotic drug development may start at any time in the process and may, in fact, be done "backwards" (compared with the development of conventional drugs), starting with RCTs if a product is well-characterized and if there is sufficient information on previous experience in humans. Phase 3 clinical trials, in this case, should compare the efficacy of the investigational product against that of a placebo, the best available treatment, or both.

Future research should focus on determining the mechanisms of action, evaluating the probiotic interactions, and elucidating how the genetic and bacterial profiles of the patient can influence treatment responsiveness. Gastrointestinal functional assessment, mucosal-integrity laboratory methods, and response-efficacy instruments are paramount to effective research [4]. Combination approaches (e.g., probiotics and prebiotics combined) may offer new therapeutic options [40]. The remaining challenges include identifying the mechanisms of action, to provide the basis for more-refined hypothesis-driven clinical trials, including immunomodulation [41].

For regulatory purposes, health-related claims require sound evidence from all available sources. Positive evidence should not be outweighed by negative evidence, and sufficient evidence based on human experience should be available to support safety and efficacy, including pre- and postmarketing experience, when applicable. The greater the consistency of evidence from different sources, the stronger the evidence will be.

The primary regulatory obligations of manufacturers and marketers should include product safety and accurate descriptions of product identity, composition, and indications in the label and product inserts. Claims for regulatory purposes are dependent on the level of evidence and the design of the clinical trial. In addition, product-specific evidence based on high-quality investigations should be emphasized [42, 43]. In summary,

future large-scale clinical trials that control dosing, viability, and other critical variables will be crucial for providing the necessary scientific evidence required to determine the efficacy of the increasingly used probiotics.

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