cisplatin plus 5-fluorouracil (run-in period), followed by diagnosing response to this short period of therapy. Depending on the subject's response, the physician then treated the patient with either (1) chemoradiotherapy (CRT) or (2) surgery followed by radiation. In detail, where a patient achieved a greater than 50% response to the drugs provided in the run-in period, the patient was then treated with chemoradiotherapy. The benefit of this approach was preservation of the patient's tissues. But where a patient achieved a response of 50% or lower, the patient was then treated with surgery followed by radiation (this approach resulted in loss of tissues).

Hutchins et al. (49) also conducted a clinical trial that used a run-in period that contained a decision tree. In a clinical trial on breast cancer, volunteers were screened for inclusion/exclusion criteria, which provided a pool of potential subjects for the trial. Potential subjects found to be at high risk, according to the criteria of tumor size and expression of a hormone receptor, were randomized and allocated to the various study drugs. But potential subjects found to be at uncertain risk, according to the same criteria (tumor size and hormone receptor), were then further screened, where tumor cells were characterized by flow cytometry. Where flow cytometry indicated high risk, these subjects were then randomized and allocated to the various study drugs. But where flow cytometry indicated low risk, the subjects were not randomized and were not treated. Hence, the run-in period served as a supplement to the inclusion/exclusion criteria, where the benefit of the run-in period was to ensure a greater number of subjects enrolled in the trial.

n. To create a self-control group

The run-in period can be used to provide information on baseline adverse events, so that each subject can serve as his own control. In a study of infant formulas, Nakamura et al. (50) used a 7-day run-in period to study the volume of formula intake, the frequency of constipation, the frequency of diarrhea, and the fussiness frequency, of the infants enrolled in the trial. Following the run-in period, all infants were divided into four groups, where each group received a different formula diet. The authors reported, for example, that, "[t]here were no significant differences among the feeding groups in the numbers of infants who experienced constipation or diarrhea during the run-in period or feeding trial." Thus, a purpose of the run-in period was to provide additional controls. In other words, one set of controls was the basal formula during the randomized feeding trial. But another set of controls resulted from comparing each infant's characteristics during the run-in period and during the subsequent randomized trial.

[49] Hutchins LF, Green SJ, Ravdin PM, et al. Randomized, controlled trial of cyclophosphamide, methotrexate, and fluorouracil versus cyclophosphamide, doxorubicin, and fluorouracil with and without tamoxifen for high-risk, node-negative breast cancer: treatment results of Intergroup Protocol INT-0102. *J Clin Oncol*. 2005;23:8313–8321.

[50] Nakamura N, Gaskins HR, Collier CT. Molecular ecological analysis of fecal bacterial populations from term infants fed formula supplemented with selected blends of prebiotics. *Appl Environ Microbiol*. 2009;75:1121–1128.