In 1951, Sir Richard Doll and Sir Austin Bradford Hill sent a questionnaire on smoking habits and general health to all 59,600 physicians in England and received over 41,000 completed questionnaires. They then followed the cohort of physicians until 2001, periodically sending them follow up questionnaires. The primary outcome of interest was cause of death, which the investigators ascertained from a variety of sources, including the Office of Population Census and Surveys, death notices and medical journals, and information obtained from next of kin.

Ultimately, the study determined that at least 24 different causes of death were significantly associated with smoking. They also showed that the risks of smoking were dose related, and that those who quit had a lower risk than those who continue to smoke. This is perhaps the first large prospective cohort study, and it had an enormous impact by both vastly increasing knowledge about the risks of smoking and by shaping opinions of policymakers and the general public.

A crude variation of the cohort study was perhaps introduced as early as 1747. James Linde was a Scottish physician who served in the Royal Navy and developed an interest in scurvy. His theory was that chronic exposure to damp sea air caused scurvy by clogging skin pores and preventing the body from ridding itself of toxic wastes. We now know that sailors got scurvy due to lack of fresh fruit and vegetables, resulting in a severe lack of vitamin c. This in turn weakened blood capillaries and caused them to rupture with even minor traumas. Just chewing food caused bleeding gums in some people.

Linde also believed that acidic foods could open skin pores and cure scurvy. During an expedition in 1747, 12 sailors developed scurvy after two months at sea, and Lynde conducted a crude experiment which was possibly the first clinical trial. The 12 men were divided into six pairs. All 12 got their usual diet, but the pairs received supplements of either a quart of cider each day, a dose of elixir of vitriol, which was a solution of sulfuric acid, a pint of seawater each day, three doses of vinegar per day, or a paste of garlic mustard seed horseradish and some other goodies three times a day.

None of these men improved. The last pair of seamen ate two oranges and a lemon each day. And after six days, one of these men was completely recovered, and the other was nearly fit for duty. Linde published his observations and recommended a ration of citrus fruit for sailors, but his recommendations were ignored for about 50 years. Nevertheless, this primitive experiment was a forerunner of today's randomized clinical trial.

Clinical trials are very much like prospective cohort studies except that the investigators allocate the exposures, that is the treatments, to the subjects randomly rather than simply observing the effects of exposures, which the subjects had self-selected as the British physicians had. In this module will explore the design features and methodology of these studies and also consider their strengths and their weaknesses.