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This Week's Citation Classic

Armitage P. Restricted sequential procedures. *Biometrika* **44**:9-26, 1957. [Statistical Res. Unit, Medical Res. Council, London Sch. Hygiene and Tropical Medicine, England]

A family of closed sequential plans is described, providing control over error probabilities for a two-sided hypothesis test. The results are based on diffusion theory, but provide useful approximations for various distributional forms. Applications to clinical trials are proposed. [The *Science Citation Index®* (*SCI®*) and the *Social Sciences Citation Index®* (*SSCI®*) indicate that this paper has been cited over 115 times since 1961.]

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"In 1947, I joined the Medical Research Council's Statistical Research Unit under A. (now Sir Austin) Bradford Hill, whose advocacy of the randomized controlled trial for the comparison of rival therapeutic measures was strong and influential. Within a few years I started to explore the possible use of sequential methods for the design and analysis of clinical trials. The motivation seemed clear: if the results of a trial were analysed as they became available, one could stop the trial early if treatment differences were clearly emerging. I had done some fragmentary work on sequential analysis during the war, in connection with sampling inspection. The theory was dominated by the important work of Abraham Wald, published later in his book,[1] and I was at first inclined to think that Wald's methods could be applied fairly directly to clinical trials However, it later seemed more realistic to incorporate 'closure' (an upper limit on the number of observations) as an integral feature of the plans. Some ad hoc plans of this type were published by Bross[2] at about this time.

"The 1957 paper represented one of the first attempts to provide a general theory. The name 'restricted' was chosen as I needed something more specific than 'closed,' and 'truncated' had been used by Wald for a rather different approach. The plans that emerged seemed to have the right sorts of characteristics for clinical trials. There would typically be a cumulative sum plotted against the number of observations, with two divergent boundaries, the crossing of which indicated an advantage for one treatment over another. If no boundary had been crossed before a certain sample size N, the trial was closed. The theory was based on a diffusion approximation to the distributions of sums of Gaussian variables, but this could be regarded as a 'normal approximation' to other situations. For the common case of binary observations, the approximation could be checked by exact calculations.

"The paper formed the basis of the first edition of my book,[3] and the methods were used a good deal, particularly in the 1960s. In the second edition[4] I advocated use of curved boundaries corresponding to the repeated use of standard significance tests, but the plans were really very little altered. I suppose that the general interest in sequential trials since 1960 is the reason for the citation of my (now rather outdated) paper. Practical interest has now moved away from the idea of sequential analysis after every observation towards that of interim analyses after each of a small number of stages.[5] This shift of emphasis is probably related to the wider implementation of very large multi-center chronic disease trials, where interim analyses are conveniently done for the periodic meetings of investigators. The techniques involved[5] spring directly from the earlier work on sequential analysis, thus (I suppose) providing a continuing trickle of citations. Theoretical work by others on the original restricted procedures has taken the theory well beyond that in my paper."

1. **Wald A.** *Sequential analysis.* New York: Wiley, 1947, 212 p.
2. **Bross I.** Sequential medical plans. *Biometrics* **8**:188-205, 1952.
3. **Armitage P.** *Sequential medical trials.* Oxford: Blackwell, 1961. 105 p.
4. ..... *Sequential medical trials.* Oxford: Blackwell, 1975. 194 p.
5. **Pocock S J.** Group sequential methods in the design and analysis of clinical trials. *Biometrika* **64**:191-9, 1977.