

THE EPIDEMIOLOGY OF THE GASTROINTESTINAL RANDOMIZED CLINICAL TRIAL

ERIK JUHL, M.D., ERIK CHRISTENSEN, M.D., AND NIELS TYGSTRUP, M.D.

Abstract Has the randomized clinical trial (RCT), generally accepted as the method of choice for evaluation of most treatments, obtained a footing in gastroenterology? Among 35,228 citations on gastroenterologic therapy indexed in MEDLARS 1964-1974 306 (0.9 per cent) were RCT's. During the decade their frequency rose significantly ($P < 0.05$) from 0.3 per cent in 1964 to 1.7 per cent in 1973. The "typical" RCT was a double-blind two-group comparison of a new and an established drug on the symptoms of peptic ulcer; 50

THE randomized clinical trial (RCT) is the only scientifically reliable method for assessment of the efficacy (and risks) of most clinical treatments. The status of the RCT in a medical discipline may be used as an index of the scientific standard of therapy. In 1964 Truelove and Wright¹ reviewed the RCT's of gastroenterology and concluded that they were few in number, and that the need for more trials was great. They predicted that a larger number of RCT's would be performed in the future. We have analyzed the literature to see if the decade 1964 to 1974 brought the expected progress.

CRITERIA

We searched MEDLARS for the period of 1964-1973 for items. Our search profile contained *digestive disease* or *digestive system neoplasms* (criterion 1) as medical subject headings and *drug therapy*, *surgery*, *radiotherapy*, or *therapy* (criterion 2) as subheadings.² Furthermore, the "check tags" *human* (criterion 3) and *comparative study* or *clinical research* (criterion 4) from the annotated version of Medical Subject Headings³ were included. The instructions for the use of the last two "check tags" are as follows:

COMPARATIVE STUDY: To retrieve articles comparing two or more drugs or chemicals, two or more therapeutic or diagnostic procedures, or two or more determinative technics.

CLINICAL RESEARCH: To retrieve articles on controlled clinical research on human beings in contrast to ordinary articles on humans or on human matter examined in vitro. A clue of the use of this "check tag" is mention by the author of "double-blind study," "triple-blind study," or "controlled study." The tag should be used when the research is performed under controlled conditions, with a preconceived research design. For the years 1964 and 1965 no subheadings were available in MEDLARS; therefore a manual search in relevant periodicals was used for these two years.

During the decade studied a total of 1,976,561 citations had been indexed in MEDLARS, among them

From the Division of Hepatology, Medical Department, Hvidovre Hospital, Division of Hepatology, Medical Department A, Rigshospitalet, and Medical Department II, Kommunehospitalet, 2100 Copenhagen, Denmark (address reprint requests to Dr. Tygstrup at the Division of Hepatology, Medical Department A, Rigshospitalet, DK 2100 Copenhagen Ø, Denmark).

Supported by the Municipal Authorities in Copenhagen and the Research Council for Copenhagen, the Faroe Islands and Greenland (grant 74/75, 5).

patients were followed for six weeks, and the number of dropouts was unknown. The new drug was found to be more effective. It is postulated that the RCT's in gastroenterology are quantitatively and qualitatively insufficient and that co-ordinated planning of RCT's and uninhibited publication of statistically proved negative results may help to ensure that the patient with gastrointestinal disease receives the best available treatment. (N Engl J Med 296:20-22, 1977)

144,569, or 7.3 per cent, on gastroenterology (criterion 1). Of these 35,228, or 24 per cent, dealt with therapy (criterion 2). The number of citations in these categories shows no statistically significant change with time during the period examined (linear regression of citations on time shows slope to be not significantly different from zero). Criteria 3 and 4 eliminated almost 96 per cent of the citations on gastroenterologic therapy, so that 1490 citations were left. Except for 25 that were not available (mainly Russian and Chinese), these reports were read and analyzed. In 425 papers gastroenterologic disease was not a major topic (we eliminated papers dealing with the teeth, mouth and throat from our analyses), 13 had been included owing to frank errors in indexing, 89 were reviews with no original data, and seven were duplicate publications.

THE RCT'S

Among the remaining 931 reports we only accepted those as randomized clinical trials that fulfilled two further criteria: patients were allocated to a treatment or a control group at random; and the therapeutic effects were evaluated on the basis of clinical variables (e.g., survival, severity or duration of symptoms), or of variables of indisputable clinical relevance (e.g., disappearance of ulcer crater), but not on the basis of pure laboratory data (e.g., maximum acidity output or the level of aminotransferases). These criteria eliminated two thirds of the reports, leaving 306, or 0.9 per cent, of the citations on gastroenterologic therapy for further analysis. During the whole period 3.3 per cent of the reports on drug therapy were RCT's according to the definition used here, and 0.2 per cent of studies on other treatments, including surgical procedures.

The figures may underestimate the true number of RCT's by an unknown factor, owing to errors in indexing. In a more detailed search for RCT's on duodenal ulcer (unpublished data), 25 per cent of the reports were not included among the citations provided by the MEDLARS search. Indexing errors resulting in "false-positive" inclusions are, as mentioned above, <1 per cent.

During the decade in question, the number of

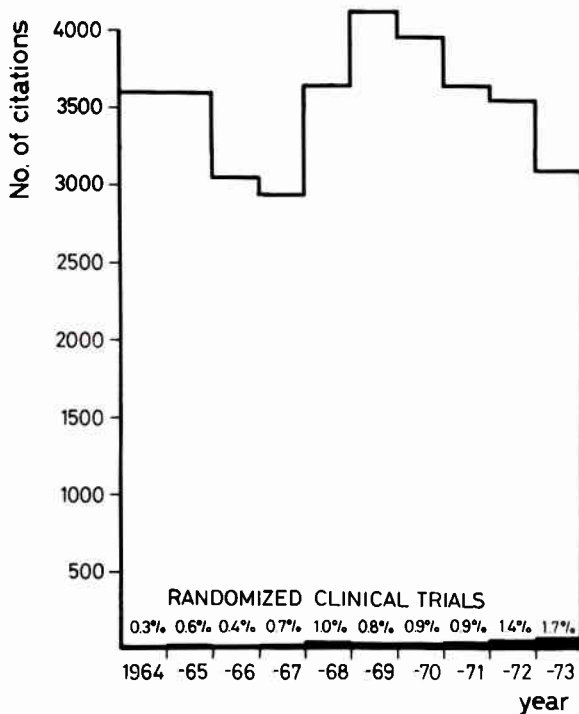


Figure 1. Number of Citations in MEDLARS on Therapy in Gastroenterology during the Decade 1964-1974. The frequency of RCT's among these citations is recorded for each year.

RCT's showed a statistically significant rise with time (slope of regression line different from zero, $P < 0.05$) from 0.3 per cent of indexed citations on gastroenterologic therapy in 1964 to 1.7 per cent in 1973 (Fig. 1). Thus the prediction of Truelove and Wright was confirmed. If the RCT continues to increase its share of therapeutic studies in gastroenterology it will have taken over completely by the year 2010 provided the increase is exponential, and in about 700 years if it is linear.

THE TOPICS

RCT's may be performed for a number of motives: the frequency and social importance of the disease; the severity of the disease; the availability of new promising treatments; or the expectation that the trial will be interesting and simple to perform. As stated by Truelove and Wright, few treatments are so well explored that it would be superfluous to study them in a trial; the number of potential topics, therefore, is practically unlimited. Figure 2 shows the distribution according to organ and disease of the 306 RCT's. It is remarkable that more than one fourth deal with the treatment of peptic ulcer, and 20 per cent with functional disorders of the intestines.

The question of the effect of these 306 trials on morbidity and mortality from gastroenterologic diseases is open to speculation. The more detailed study of RCT's on duodenal ulcer (unpublished) indicates a limited effect of RCT's on clinical practice. The idea that co-ordinated planning of RCT's might increase their impact is near at hand.

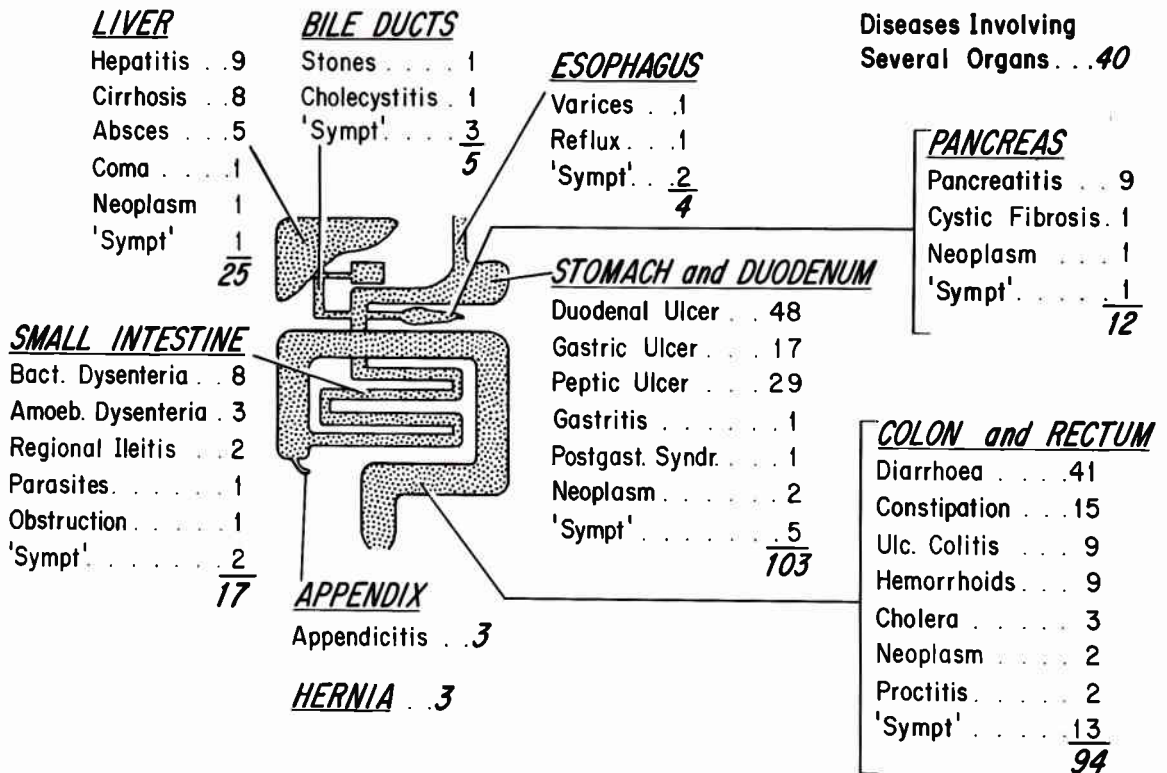


Figure 2. Distribution of RCT's in Gastroenterology, 1964-1974, on Organ and Disease. ('Sympt' Signifies Trials on Therapy of Symptoms Compatible with Several Diagnoses.)

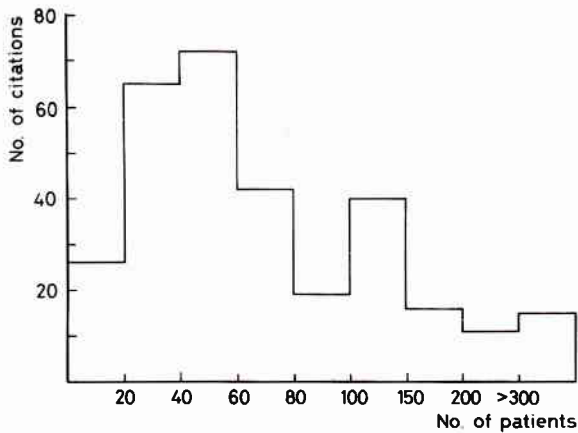


Figure 3. Distribution of Sample Size in 306 RCT's in Gastroenterologic Therapy, 1964-1974.

The last column includes trials with more than 300 patients.

GEOGRAPHY AND PUBLICATION

More than half the RCT's are from Great Britain (83) and the United States (75); 80 per cent of the trials have been made in 10 countries, the others being Italy (16), German Federal Republic (15), Japan (13), Denmark (11), South Africa (10), Australia (nine), France (seven) and Norway (seven). Forty per cent of the trials are published in 10 medical journals, six of them British (28 per cent of all reports), three North American, and one Scandinavian. The geographic distribution of RCT's probably reflects the standard of clinical science rather than the needs for treatment of gastrointestinal disorders. One fourth of the trials are multicentric — in 60 per cent of them more than two units participate. Eight trials are multinational, showing that international co-operation is still limited. Multiauthorship is the rule, the median number of authors being three, and the maximum 12. Sixteen reports are published under the name of the group. Such group authorship means that the individual participant receives relatively little scientific credit from his contribution, and this fact may well discourage participation in a multicenter trial. It should also be noted that most reports are relatively short, the median number of pages being four.

DESIGN AND ASSESSMENT

A two-group comparison was used in two thirds of the RCT's, the crossover and factorial design accounting for the majority of the rest. Five reports did not mention which design had been used. Two thirds of the studies were double blind, the single-blind technique was used in one fifth, and 12 per cent were performed without blinding.

In 80 per cent of the RCT's, a new treatment was evaluated. Thus, only one of five RCT's was used to test established treatments, of which a minority were based on adequate documentation. The control group received some treatment (other than placebo) in 70 per cent of the trials. Survival was the main variable of

evaluation in 10 per cent, and the intensity or duration of clinical symptoms in 70 per cent of the trials.

MATERIALS AND RESULTS

A total of 26,863 patients were involved in RCT's in gastroenterology between 1964 and 1974. If a department of gastroenterology treated 1500 patients per year, two such departments alone could have provided this material. That observation indicates that most gastroenterologic departments have a rather low RCT activity. There are no reliable estimates of the number of patients in the world suffering from gastroenterologic disorders, but it seems fair to conclude that a given patient had an infinitesimal chance to receive the benefits of being included in a RCT.

As shown in Figure 3, few RCT's include more than 150 patients. The peaks around 50 and 100 patients indicate that a "fixed-sample" plan is commonly used. The mean period of observation is two months or less in 70 per cent of the trials; it exceeds one year in 13 per cent.

The number of dropouts is only stated in one third of reports of the RCT's, in which the median dropout rate is 10 per cent. Two trials offer no conclusion; in 191 (62 per cent) a difference between the groups examined was demonstrated, and in five the treatment to be tested was significantly inferior to the control treatment (established treatment or placebo). The remaining 113 RCT's were "negative," but only in seven was the probability of identity between the treatment (the Type II error) tested, in all cases by sequential analysis. In the remaining cases the "negative" result may have been influenced by the small sample size, but the number of patients in "positive" and "negative" trials was not significantly different.

If it is accepted as a condition for a RCT that the patient should have the same a priori chance to benefit from the treatment, independently of the allocation, the number of "positive" and "negative" trials would be expected to be equal. However, it is likely that there will be more falsely "negative" than falsely "positive" trials (the Type II error of a "negative" trial will usually be greater than the Type I error of a "positive" trial). Therefore, the preponderance of "positive" trials indicates a bias (of authors or editors?) toward positive trials. Only when all well motivated trials are properly conducted and published, whether they are "positive" or "negative," can the therapeutic possibilities be assessed on a scientifically sound basis.

We are indebted to the staff of the University Library II, Copenhagen, and to Mrs. O. Monsrud, chief librarian of Rigshospitalet, for technical assistance.

REFERENCES

1. Truelove SC, Wright R: The controlled therapeutic trial in gastroenterology. *Am J Dig Dis* 9:1-30, 1964
2. National Library of Medicine: Medical Subject Headings (DHEW Publication No. [NIH] 76-265). Washington, DC, Government Printing Office, 1976
3. Medical Subject Headings: Annotated version. [Available from National Technical Information Service, US Department of Commerce, 5285 Port Royal Road, Springfield, VA 22161.]