Published in final edited form as:

Am J Gastroenterol. 2012 April ; 107(4): 496–500. doi:10.1038/ajg.2011.450.

Increasing Complexity of Clinical Research in Gastroenterology: Implications for Training Clinician-Scientists

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Abstract

Background—Significant advances have been made in clinical and epidemiologic research methods over the past 30 years. We sought to demonstrate the impact of these advances on published research in gastroenterology from 1980 to 2010.

Methods—Three journals (*Gastroenterology*, *Gut*, and *American Journal of Gastroenterology*) were selected for evaluation given their continuous publication during the study period. Twenty original clinical articles were randomly selected from each journal from 1980, 1990, 2000, and 2010. Each article was assessed for topic studied, whether the outcome was clinical or physiologic, study design, sample size, number of authors and centers collaborating, and reporting of statistical methods such as sample size calculations, p-values, confidence intervals, and advanced techniques such as bioinformatics or multivariate modeling. Research support with external funding was also recorded.

Results—A total of 240 articles were included in the study. From 1980 to 2010, there was a significant increase in analytic studies ($p<0.001$), clinical outcomes ($p=0.003$), median number of authors per article ($p<0.001$), multicenter collaboration ($p<0.001$), sample size ($p<0.001$), and

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Potential competing interests: None.

Conflicts of Interest/Study Support:

Guarantor of the article: Frank I. Scott, MD

external funding ($p<0.001$). There was significantly increased reporting of p-values ($p=0.01$), confidence intervals ($p<0.001$), and power calculations ($p<0.001$). There was also increased utilization of large multicenter databases ($p=0.001$), multivariate analyses ($p<0.001$), and bioinformatics techniques ($p=0.001$).

Conclusions—There has been a dramatic increase in complexity in clinical research related to gastroenterology and hepatology over the last three decades. This increase highlights the need for advanced training of clinical investigators to conduct future research.

Background

The methods of clinical research have dramatically evolved over the last several decades. Novel methods have been developed to test basic science hypotheses and clinical anecdotes in rigorous clinical experiments. These methods are complex, and usually require specialized training. As such, collaborative research teams are increasingly viewed as essential for cutting edge research.

To fully capitalize on advances in technology, the field of gastroenterology needs investigators with the ability to identify new therapeutic targets, to translate these advances to practical therapies, and to then translate these clinical observations from the bedside into the community. Clinicians trained in epidemiology, outcomes research and health services research can provide a link between clinical medicine, basic science research, and clinical observations. Yet, there are currently a limited number of programs that specifically train gastroenterologists in these skills. Although not all advanced training is provided by NIH-funded positions, there are approximately 46 NIH-funded training positions in advanced research methods available among approximately 455 gastroenterology fellowship positions each year. Of these positions, an even smaller percentage is reserved specifically for the methodologies described above.

Recognizing the advances that have been made in the methods of clinical research and the apparent shortage of well-trained clinical investigators, we sought to describe the evolution of clinical research in gastroenterology over the last 3 decades. We describe here a dramatic increase in the complexity of the research and the proportion of studies supported by external funding and involving investigators from multiple institutions. These observations highlight the importance of advanced research methodology training for the next generation of clinical investigators.

Methods

Journal and article selection

We sampled published articles from three leading journals in the field of gastroenterology and hepatology (*Gastroenterology*, *Gut*, and the *American Journal of Gastroenterology*). Each journal was in continuous publication during the study period and includes both hepatobiliary and luminal gastrointestinal clinical research. For each journal, a full list of all published articles from 1980, 1990, 2000, and 2010 was identified from Medline. A random number generator was used to randomly select from the published articles. The first 20

articles from each time point in each journal meeting inclusion and exclusion criteria were selected for full review and abstraction.

Inclusion and exclusion criteria

Original peer reviewed articles were eligible for inclusion. All articles had to be clinical in nature with a focus on human subjects. Studies evaluating human tissues or cells that were directly linked to clinical patient characteristics, such as an individual patient's symptoms or disease course, were also considered eligible. Published abstracts without full articles, review articles, meta-analyses, and letters were excluded.

Variables of interest and data extraction

Data were extracted by two members of the research team using pre-constructed data collection forms (SUPPLEMENTAL INFORMATION 1). Articles were assessed for number of authors, the topic of investigation, whether the outcome was physiologic or clinical, endoscopic or surgical methods, evidence of multicenter collaboration, and study design. Study designs were grouped into three broad categories: descriptive studies (case reports, case series, and cross-sectional studies), observational analytic studies (case-control and cohort studies), and clinical trials. Sample size for each study was assessed. Statistical methodologies were evaluated, including the presence of confidence intervals, p-values, sample size and power calculations, and the use of advanced statistical methods (e.g., multilevel modeling, bioinformatics, and adjustment for confounding). Intention-to-treat analysis was also assessed. If any variables were unclear, they were discussed among the investigators for adjudication.

Statistical analyses

Abstracted data was entered into a Microsoft Access database and exported to Stata version 11.2 for further analysis. For each study year, sums and percentages were calculated for all categorical variables. Medians and interquartile ranges (IQRs) were calculated for all continuous variables. For variables unique to analytic studies, such as confidence intervals and p-values (which would not be present in observational studies), calculations excluded non-analytic studies. Categorical variables were assessed using Chi-square tests. Spearman's correlation coefficients were calculated to assess trends in author number and sample size. Twenty of the papers were randomly selected for review by a second reviewer to determine the degree of inter-rater reliability and kappa statistics for four key variables: multicenter collaboration, prospective or retrospective data collection, the utilization of advanced statistical methodologies, and documentation of external funding.

Results

A total of 240 articles were included in the study. Inter-rater agreement between the two reviewers demonstrated a high level of agreement, with 3 of the 4 variables assessed demonstrating 95% inter-rater agreement ($\kappa=0.83$) and the fourth demonstrating 100% agreement. There was a significant increase in analytic studies over the study period. 30 of 60 publications (50%) from 1980 were either observational analytic or clinical trials compared to 53 of 60 (88%) in 2010 ($p<0.001$) (FIGURE 1). This was largely due to

increasing prevalence of case-control and cohort studies and a decrease in descriptive studies, with clinical trials remaining relatively stable. There was not a significant trend in the proportion of studies involving endoscopic or surgical techniques during the study period. There was a significant increase in both viral ($p=0.002$) and non-viral hepatology related publications ($p=0.005$), but no trend in other topics. The proportion of studies assessing clinical outcomes increased from 38/60 (63%) to 55/60 (92%) ($p=0.003$) (TABLE 1). The median number of authors per study increased from 4 to 9 ($p<0.001$), as did the degree of multicenter collaboration (3% to 28%, $p<0.001$). Sample sizes increased as well, from a median of 12 to 340.5 ($p<0.001$). There was a significant increase in studies reporting external funding, from 35% to 77% ($p<0.001$).

Statistical complexity increased significantly during the study period, with increased reporting of p-values ($p=0.01$), confidence intervals ($p<0.001$), and power calculations ($p<0.001$). There was also increased utilization of large multicenter databases ($p=0.001$), multivariate analyses ($p<0.001$), and bioinformatics ($p=0.001$).

Discussion

These data document a dramatic evolution in clinical research related to gastroenterology and hepatology over the last three decades. The most apparent change was the evolution from descriptive studies to hypothesis testing analytic designs. This was accompanied by a shift from physiologic measures to clinical outcomes, with more than 90% of the publications in 2010 focusing on clinical outcomes. Reflecting the challenges of testing hypotheses related to clinical outcomes, the size and complexity of these studies evolved as well, with larger sample sizes, increased utilization of large electronic databases, increased prospective data collection and increased use of more advanced statistical methods, such as multivariable analysis and bioinformatics.

Other trends reflect the increased organizational complexity of modern clinical research. We observed a dramatic increase in multi-institutional research, with more than a quarter of studies entailing multicenter collaborations in 2010, and in the number of authors per paper. Furthermore, grant funding increased from approximately 30% in 1980 and 1990 to more than 75% of studies in the year 2010.

These trends reflect several important features of modern research. It is difficult for a single investigator to possess all of the skills necessary to bring a study to completion. Thus, collaborative research will almost certainly continue to be prominent in the coming decades. The need for increased sample sizes to provide adequate statistical power is another reason for multi-investigator and multi-institutional collaborations. However, such collaborations are expensive, as reflected by the increased proportion of studies supported by grant funding.

The trends observed in this study raise important questions about the training provided to gastroenterologists who wish to pursue clinical investigation as a large part of their career. Clinical research is increasingly team-oriented and requires multidisciplinary expertise. The successful clinical researcher must be familiar with the methods intrinsic to each discipline,

be able to effectively communicate their research vision, and be able to lead a research team. These are the same skills that are needed to successfully compete for research funding. Development of such skills almost invariably requires specialized training in research methodology, comparable to that received by basic scientists.

In 2007, Dr. Vincent Yang described the perilous state of the physician scientist in gastroenterology.^{1, 2} He noted that the proportion of physicians choosing this pathway has been declining and that those who pursue clinical research had lower success rates at obtaining funding than basic scientists. Similar patterns have been reported in other specialties.³ Subsequently, the 2008 report of the American Gastroenterological Association (AGA) Future Trends Committee endorsed “changes in fellowship programs that will facilitate the training of gastroenterology clinical and basic scientists.”⁴ Specifically, the committee recommended that for trainees interested in clinical research, programs should provide “two years devoted to research training integrated with formal coursework in relevant areas.”

Some may argue that fellowship is too late to initiate formal research training. The Association of Professors of Medicine Physician-Scientist Initiative recommended that “The physician-scientist workforce should be strengthened by earlier and more coordinated efforts to identify and prepare successful future investigators with a more enduring commitment to research careers.”⁵ Many medical schools provide brief courses in epidemiology and critical appraisal of the medical literature, geared at preparing young physicians to be able to appreciate the nuance of clinical research. Small blocks of protected time for research are also commonly made available during medical school. However, there are limited data on the quality of those research experiences and how often such experiences lead to careers in clinical research. Internal medicine residency is a particularly difficult time for a trainee to gain practical research experience or formal research training due to the enormous amount of clinical responsibilities and new work hour limitations. Thus, it seems likely that formal research training will continue to be offered primarily to a limited number of fellows who are trained at programs that offer structured curriculum in research methodology.

Several potential solutions are worth considering. Instituting a curriculum in epidemiology and biostatistics as part of the undergraduate requirements for medical school applicants could increase awareness and fluency in the language of clinical research among medical students. The need for increased education in these subjects has been appreciated by some graduating medical students. In the 2011 AAMC graduating medical student questionnaire, 13.6% of students felt their training in epidemiology was inadequate and 18.3% felt their training in biostatistics was inadequate, despite over 60% of graduates anticipating that research will play some role in their future career and 32% envisioning a career participating in full-time clinical research⁶. Several schools offer dual degree programs with master’s or doctoral level training in research methodology in conjunction with an MD to meet these needs, and these programs have demonstrated increasing enrollment over time.⁷

Greater opportunities should be available for physicians to obtain training in research methodology during fellowship. Current training guidelines require a minimum of six months of research or scholarly activity with the flexibility to increase this to 18 months.

The Multi-society Task Force on Training in Gastroenterology recognized that the current design is inadequate to develop well trained investigators.⁸ Furthermore, there is a movement to have the current 36 months of gastroenterology training include more specialized training in areas such as transplant hepatology, inflammatory bowel disease, motility, and advanced endoscopic procedures.^{8, 9} One potential solution is to shorten internal medicine training and increase the duration of gastroenterology fellowship training.^{10, 11} Such programs are currently available to a limited number of trainees each year, typically those with significant prior research experience.

There are a few limitations of this research that deserve comment. We selected only 3 journals from which to review articles. We chose these journals because of their long history and their inclusion of research related to hepatobiliary and luminal gastrointestinal diseases. It is possible that we would have observed different results had we examined other journals in this field. It is also possible that changing criteria for publication among these three journals could have generated the appearance of increasing complexity. However, it is unlikely that the criteria for publication in these three journals evolved differently than the field as a whole. The increasing prominence of endoscopy-centric publications may have impacted our ability to measure changes in the rates of endoscopic research. Similarly, our results may not generalize to other medical specialties. Finally, we selected a limited number of features to study as they were likely to be reported in the published manuscripts. There are many aspects of clinical research that we were unable to assess because they are rarely reported in a final publication. Examples include the size of the research budget, the resources provided by the investigators' institution, ethical considerations in research planning and subject selection, etc.

In conclusion, there has been a dramatic advancement in the complexity of research published in top tier gastroenterology journals since 1980. These changes include a shift from small descriptive to large analytic studies, a shift from physiologic to clinical outcome measures, and increasing utilization of advanced statistical methods. Increasingly, studies entail multi-institutional collaboration and the vast majority of studies are now supported by research grants. These changes highlight the importance of advanced training in research methodology for physicians who are interested in pursuing careers in clinical investigation.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Financial support: This research was funded via two NIH grants, T32-DK007066-36 and K24-DK DK078228. These funding sources played no role in the design of this study, conduct of this research, or in the drafting of this manuscript.

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Figure 1.

Trends in publication content from 1980 to 2010. There was a significant increase in analytic studies over 4 time points assessed as demonstrated in this graph, with an increase from 50% in 1980 to 88% in 2010 ($p < 0.001$). This was predominantly due to a significant increase in case-control and cohort studies coupled with a decline in descriptive studies, with clinical trials remaining relatively stable.

Table 1

Study characteristics from 1980 to 2010

	1980 n=60	1990 n=60	2000 n=60	2010 n=60	P value
Study Design					
Analytic studies (n, %)	30 (50%)	34 (57%)	43 (72%)	53 (88%)	<0.001
Observational analytic (n, %)	22 (37%)	29 (48%)	35 (58%)	43 (72%)	0.001
Clinical Trials	8 (13%)	5 (8%)	8 (13%)	10 (17%)	0.60
Physiological vs. Clinical	P ^{**} : 22 C ^{**} : 38	P ^{**} : 17 C ^{**} : 43	P ^{**} : 14 C ^{**} : 46	P ^{**} : 5 C ^{**} : 55	0.003
Data Collection (Prospective or ad-hoc vs. Retrospective) (n,%)	P ^{***} : 33 (55%) R ^{***} : 27 (45%)	P ^{***} : 34 (57%) R ^{***} : 26 (43%)	P ^{***} : 36 (60%) R ^{***} : 24 (40%)	P ^{***} : 42 (70%) R ^{***} : 18 (30%)	0.33
Study Topic and Scope					
Number of Authors (Median, IQR)	4 (3-5)	5 (3.5-6)	6.5 (5-8)	9 (6-13)	<0.001
Multicenter Collaboration (n,%)	2 (3%)	5 (8%)	14 (23%)	17 (28%)	<0.001
Sample Size (Median, IQR)	12 (2-34.5)	27 (3-86.5)	48.5 (18.5-226)	340.5 (96.5-1705)	<0.001
Endoscopy (n, %)	3 (5%)	3 (5%)	6 (10%)	2 (3%)	0.44
Surgery (n, %)	1 (2%)	1 (2%)	2 (3%)	0 (0%)	0.57
External Funding (n, %)	21 (35%)	15 (25%)	33 (55%)	46 (77%)	<0.001
Statistical Methods					
Reported P values (n, %) [*]	24 (80%)	27 (79%)	36 (84%)	53 (100%)	0.01
Reported Confidence Intervals (n, %) [*]	0 (0%)	5 (15%)	12 (28%)	34 (64%)	<0.001
Power Calculation	0 (0%)	1 (2%)	5 (8%)	17 (28%)	<0.001
Multivariable Analysis (n, %) [†]	2 (9%)	9 (31%)	10 (29%)	30 (70%)	<0.001
Bioinformatics Methods (n, %)	0 (0%)	0 (0%)	1 (2%)	7 (12%)	0.001
Factor analysis, principle component analysis, principle coordinate analysis, multilevel modeling	0 (0%)	0 (0%)	0 (0%)	1 (2%)	0.39
Use of a large multicenter database (n, %)	0 (0%)	0 (0%)	6 (10%)	8 (13%)	0.001

^{*} Analysis limited to analytic study designs - 1980 n=30; 1990 n=34; 2000 n=43; 2010 n=53

[†] Analysis limited to analytic study designs that were not clinical trials - 1980 n=22, 1990 n=29, 2000 n=35, 2010 n=43

P = Physiologic study, C = Clinical study

*** P = Prospective study, R = Retrospective Study