GETTING BIOMEDICAL RESEARCH INTO PRACTICE – THE CITATIONS FROM UK CLINICAL GUIDELINES

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Synopsis
Clinical guidelines are used in the UK National Health Service to provide advice on diagnosis and treatment, or the cost-effectiveness of new drugs. Separate guidelines are published in England and Wales, and in Scotland. The research papers they cite as evidence (n = 2254 + 4045) have been matched to the Science Citation Index and analysed. They are relatively recent, overwhelmingly clinical rather than basic, and published in high-impact journals. Research from the UK and some other northern European countries is preferentially cited; that from Japan and developing countries is largely ignored. Almost one third of UK research papers are industrially-funded. By contrast, very few UK papers acknowledge the Wellcome Trust in relation to its overall support for biomedical research.

Introduction

Although there are many routes by which biomedical research can influence human health, both by improving clinical practice and by the prevention of illness (Lewison, 2003), they are not well mapped in the bibliometric literature. Standard evaluation indicators such as numbers of paper-to-paper citations, as recorded in the Science Citation Index (SCI), fail to describe the way research is put to practical use. There is, however, an extensive literature (Buxton and Hanney, 1996; Hanney *et al*., 1999; Bero, Garner, Glanville, Haines, Haynes, Sheldon, Straus, 1998) on "getting research into practice", which is primarily concerned with the development of effective methods for doing this.

Recently, the Royal Netherlands Academy of Arts and Sciences published an essay (RNAAS, 2002; van Weel, 2002) on how social and economic considerations could be brought to bear on the research evaluation process for biomedical research. One of the main routes is through the preparation, publication and dissemination of clinical guidelines. These normally depend on a body of research evidence, which is cited on the guideline, or on its underpinning technical appraisal.

In recent years, there has been a rapidly growing interest in the development of clinical guidelines, and Figure 1 shows the numbers of papers in the Science Citation Index with "evidence" and "guideline or guidelines" in their titles in the last 10 years. However attention seems to have been concentrated largely in the Anglophone countries, as the leading countries represented on the 177 papers with addresses are the USA (46%), the UK (32%), Canada (11%), Australia (7%) and New Zealand (2%).

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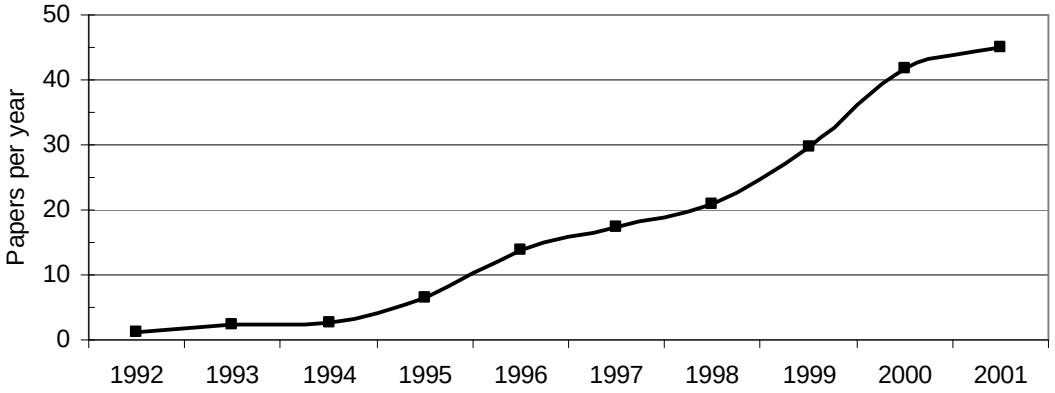

Figure 1. Numbers of papers in the SCI with "evidence" and "guideline*" in their titles, three-year moving averages.

Grant's surveys (Grant, 1999; Grant *et al*., 2000) of samples of first 3, and then 15, clinical guidelines appraised by St George's Hospital for the UK National Health Service were helpful in drawing attention to the importance of clinical work, as opposed to basic research, in providing the evidence base for these guidelines. He also showed that a relatively high proportion of the work was supported by industry – not altogether surprising as many of the guidelines concerned the use of drugs – and that UK work was over-cited by about 2.5 times compared with its presence in world biomedical literature. But he also found that the references were quite old, with a median age of 7.5 years.

Guidelines have become an important part of the National Health Service (NHS) in England and Wales through the National Institute for Clinical Excellence, NICE (Dean, 1999). Its recommendations (based on commissioned Health Technology Assessments, HTAs) on which treatments are deemed cost-effective are meant to standardise medical practice but have sometimes proved controversial both with pharmaceutical companies and patient groups (Dean, 2000; Dobson, 2000). In Scotland, the Scottish Intercollegiate Guidelines Network (SIGN) was set up in 1993 (Petrie *et al*., 1995; Petrie and Harlen, 1997). Its aim is to improve the quality of health care for patients in Scotland by reducing variation in practice and outcome, through the development and dissemination of national clinical guidelines containing recommendations for effective practice based on current evidence. It, too, has not been immune from criticism (Finlayson, 2000). There are now (November 2002) 46 NICE HTAs and 50 SIGN guidelines, each citing a body of research evidence, and all available on the Web. Scotland also has its equivalent to NICE in the form of the Health Technology Board for Scotland (HTBS), set up in 2000 as a Special Health Board, and since January 2003, part of NHS Quality Improvement Scotland. HTBS comments on NICE HTAs and also publishes its own ones, but so far there are only three of them.

In this study, we sought to investigate the evidence cited on the NICE HTAs and the SIGN guidelines on a systematic basis. This would enable those funders of UK biomedical research who participate in the Research Outputs Database project (Dawson *et.al*., 1998) to identify which of their published papers had led to clinical outcomes through the medium of guidelines. It would also provide further evidence on how long it takes for research to be cited on guidelines, and which countries' research is likely to be so cited.

Method

The references in the two sets of documents were matched to articles, notes and reviews in peer-reviewed journals covered in the SCI (since 1980) and the Social Sciences Citation Index (SSCI) since 1988. First, the relevant parts (cover page and references) of the NICE HTAs and SIGN guidelines were downloaded from the Web in pdf format and printed (see Annex for sample, showing the first 9 references to journal papers). For each HTA or guideline, a worksheet was prepared on which were noted the serial numbers of the references in journals against their publication years (shown in **bold** in the sample at Annex). They were then individually sought for on the SCI or SSCI (CD-ROM version) using several title words for matching. The CD-ROMs were searched in chronological order as a few references were found on the disk for a year subsequent to that of publication. Bibliographic data (authors, title, document type, source, addresses) were downloaded, and then all copied, together with the reference number of the NICE HTA or SIGN guideline, to one MS Excel file for analysis. The analysis included the time delay between publication and citation, the research level (from clinical to basic) and potential citation impact category of each journal, and the country or countries represented in the address field. Altogether, there were 2254 papers that were cited by NICE HTAs and 4045 papers cited by SIGN guidelines. The allocation of journals to a research level followed the system developed by CHI Research Inc., based on expert opinion and journal-to-journal citation patterns (Narin *et al.*, 1976). The categories used, and samples of the journals in each category, are as shown in Table 1.

Table 1. Four journal research levels and examples of each

RL	*Description*	*Examples*
1	Clinical observation	*Brit J Rheumatol, Brit Med J*
2	Clinical mix	*Ann Rheum Dis, Clin Exp Immunol, Lancet*
3	Clinical investigation	*J Bone Miner Res, Osteoporosis Int*
4	Basic research	*Biochem J, J Physiol London*

The papers with an address in the UK were matched to the Research Outputs Database (ROD) so as to reveal their acknowledged funding sources, and hence which organisations were having an influence on practice in the NHS through the research they were supporting. Their geographical distributions within the country were analysed through their postcodes, which were corrected or added to the ones in the SCI file as necessary. These distributions were compared with those for all UK biomedical papers in a recent year so as to show which cities were contributing most to the evidence for the guidelines, both absolutely and relative to their biomedical research outputs.

Results

The references on the NICE HTAs were found to be much more recent than the ones cited on the St George's guidelines, with a median age of only 3.5 years compared with 7.5 years. This was an even faster rate of citation than that observed for the papers cited by UK biomedical papers in the SCI, for which the median age was 5.2 years. The SIGN guidelines also cited relatively recent work, with a median age of 5.1 years. Figure 2 shows the distribution of the time delays from publication to citation for the four groups of papers.

There was a similar concentration on clinical work with 89% of the NICE HTA references and 92% of the SIGN ones being in journals classed (on the CHI system) as "clinical observation" or "clinical mix" compared with only 39% of world biomedical papers in the

SCI. The difference in research level distributions between the NICE and SIGN references is shown in Table 2: it is statistically significant at $p < 0.01\%$, so the Scottish guidelines are using research that is even more clinical than the English ones.

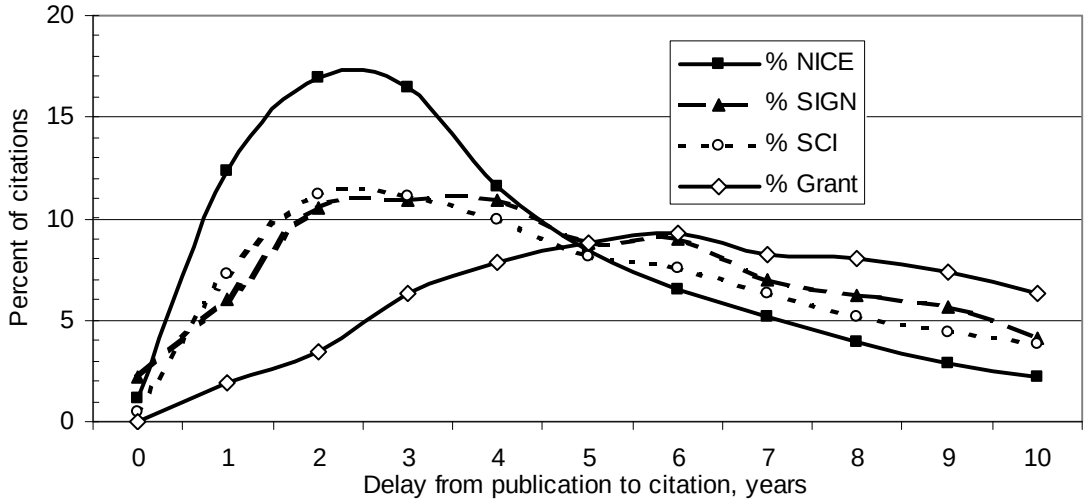

Figure 2. Distribution of time intervals between publication and citation of biomedical papers by NICE HTAs (NICE) and SIGN guidelines (SIGN), UK biomedical papers in the SCI (SCI), and St George's guidelines (Grant): first 10 years only

Table 2. Numbers and percentages of papers cited by NICE HTAs and SIGN guidelines that are in SCI/SSCI journals classed at each of four research levels (RL) on the CHI system.

Set	*RL1*	*% RL1*	*RL2*	*% RL2*	*RL3*	*% RL3*	*RL4*	*% RL4*
NICE	797	*25.4*	1180	*52.4*	220	*9.8*	12	*0.53*
SIGN	1890	*46.7*	1833	*45.3*	302	*7.5*	18	*0.45*

Note: 45 of the NICE HTA citations are in journals not classified by RL

The cited papers were in relatively high impact journals, and Table 3 shows the 10 leading journals cited by the two groups of guidelines. Three journals: the *BMJ*, *The Lancet* and the *New England Journal of Medicine*, dominate the publications list and account for 22% of all the SIGN citations but only 12% of the NICE ones. Of course, the specialist journals reflect the choice of subjects selected for the guidelines and it can be expected that these will change in future as the guidelines cover additional subjects. Altogether, the HTAs and guidelines cited papers in 681 different journals.

Table 3. Leading journals in which papers cited by NICE HTAs and SIGN guidelines are published. Mean = mean of two percentages.

Journal	*NICE*	*%*	*SIGN*	*%*	*Mean*
BMJ (British Medical Journal)	88	*3.9*	354	*8.8*	*6.3*
Lancet	99	*4.4*	308	*7.6*	*6.0*
New England Journal of Medicine	86	*3.8*	250	*6.2*	*5.0*
JAMA Journal of the American Medical Association	55	*2.4*	123	*3.0*	*2.7*
Journal of Clinical Oncology	63	*2.8*	60	*1.5*	*2.1*
Circulation	48	*2.1*	82	*2.0*	*2.1*
Journal of Clinical Psychiatry	64	*2.8*	16	*0.4*	*1.6*
Chest	18	*0.8*	72	*1.8*	*1.3*
Journal of Rheumatology	38	*1.7*	33	*0.8*	*1.3*
Arthritis and Rheumatism	41	*1.8*	24	*0.6*	*1.2*

As found previously by Grant, UK publications were over-cited on the British guidelines in comparison with their overall presence in world biomedical literature in recent years (about 10.2%). They accounted for 23% of NICE citations and 34% of SIGN ones. The SIGN guidelines also favoured Scottish research, and almost 10% of the 3973 papers with addresses were from Scotland, compared with just 1.5% in the biomedical literature. However the papers from some other northern European countries were also over-cited, as Figure 3 shows. Thus papers from Belgium, Denmark, Finland, the Netherlands and Sweden, as well as those from Canada, are all preferentially cited on both sets of guidelines. The main "losers" are papers from Japan, Russia, India and Brazil, which although fairly prominent in the biomedical literature (at 10% for Japan and 1% for the other three) are seldom cited on British HTAs and clinical guidelines.

A geographical analysis of the UK papers (see Table 4) showed that the leading city whose work was cited on the guidelines was Oxford. This was followed by London WC (the location of University College London and the Institute of Child Health) and London SE (where Kings', Guys' and St Thomas' hospitals are all located). The relatively large contributions of Southampton and Aberdeen are also noteworthy. By contrast, Cambridge is rather low on the list of cities, probably because it does relatively little clinical work compared with its large output in basic research.

The UK papers published between 1988 and 2000 were matched to the Research Outputs Database in order to obtain funding information for them. Data were obtained for 448 NICE citations and 1145 SIGN ones. Table 5 shows the numbers of papers financially supported by each of the main sectors, and the leading funders within each sector.

Overall, the UK government, UK private-non-profit and industrial sectors each supported about 30% of the cited papers, and a further 30% had no financial acknowledgement. [Some papers, of course, acknowledge several funding sources – one credited as many as 37 different funders.] The notable difference from the papers in the ROD is the large amount of support from industry, particularly on the papers cited by the NICE HTAs, many of which were concerned with the cost-effectiveness of new pharmaceutical drugs. The relatively small amount of support for these papers from the Wellcome Trust is also noteworthy: it was acknowledged on 10% of ROD papers in 1993-2000, but only on 2.4% of papers cited by these sets of guidelines.

Table 4. Leading UK post-code areas represented on NICE HTA and SIGN guideline citations, compared with their presence on UK biomedical papers for 1996 (UK BM).

Code	*Post-town*	*NICE*	*NICE %*	*SIGN*	*SIGN %*	*Mean %*	*UK BM*	*BM %*
OX	Oxford	65	*12.6*	129	*9.5*	*11.1*	2037	*7.4*
WC	London (WC)	46	*8.9*	111	*8.2*	*8.6*	2682	*9.7*
SE	London (SE)	45	*8.7*	112	*8.3*	*8.5*	1579	*5.7*
G	Glasgow	24	*4.6*	164	*12.1*	*8.4*	1282	*4.6*
M	Manchester	45	*8.7*	104	*7.7*	*8.2*	1304	*4.7*
EH	Edinburgh	24	*4.6*	126	*9.3*	*7.0*	1365	*4.9*
SW	London (SW)	28	*5.4*	102	*7.5*	*6.5*	1435	*5.2*
NG	Nottingham	39	*7.6*	66	*4.9*	*6.2*	747	*2.7*
W	London (W)	33	*6.4*	78	*5.7*	*6.1*	1900	*6.9*
B	Birmingham	32	*6.2*	55	*4.1*	*5.1*	961	*3.5*
SO	Southampton	25	*4.8*	64	*4.7*	*4.8*	575	*2.1*
AB	Aberdeen	22	*4.3*	66	*4.9*	*4.6*	518	*1.9*
CB	Cambridge	22	*4.3*	66	*4.9*	*4.6*	2097	*7.6*
LS	Leeds	27	*5.2*	52	*3.8*	*4.5*	761	*2.8*

Table 5. Funding acknowledgements on UK SCI/SSCI papers from 1988-2000 cited on NICE HTAs and SIGN guidelines, grouped by sector.

Funding source	*NICE*	*%*	*SIGN*	*%*	*Mean %*
UK government	120	*26.8*	362	*31.6*	*29.2*
Medical Research Council	54	*12.1*	165	*14.4*	*13.3*
Dep't of Health & NHS regions	70	*15.6*	153	*13.4*	*14.5*
UK private non profit	134	*29.9*	333	*29.1*	*29.5*
British Heart Foundation	19	*4.2*	70	*6.1*	*5.2*
Cancer Research Campaign*	21	*4.7*	49	*4.3*	*4.5*
Imperial Cancer Research Fund*	18	*4.0*	41	*3.6*	*3.8*
Wellcome Trust	9	*2.0*	31	*2.7*	*2.4*
Industry (UK & foreign)	168	*37.5*	259	*22.6*	*30.1*
GlaxoWellcome plc#	31	*6.9*	19	*1.7*	*4.3*
Eli Lilly Inc	24	*5.4*	24	*2.1*	*3.8*
Bayer AG	17	*3.8*	40	*3.5*	*3.7*
AstraZeneca plc	18	*4.0*	35	*3.1*	*3.6*
Bristol Myers Squibb Inc	17	*3.8*	26	*2.3*	*3.1*
SmithKline Beecham plc#	10	*2.2*	12	*1.0*	*1.6*
International	8	*1.8*	36	*3.1*	*2.5*
European Commission	7	*1.6*	24	*2.1*	*1.9*
Other foreign	74	*16.5*	122	*10.7*	*13.6*
US National Institutes of Health	17	*3.8*	39	*3.4*	*3.6*
No funding acknowledged	114	*25.4*	403	*35.2*	*30.3*
TOTAL	448	*100.0*	1145	*100.0*	*100.0*

* Now merged to form Cancer Research UK # Now merged to form GlaxoSmithKline plc

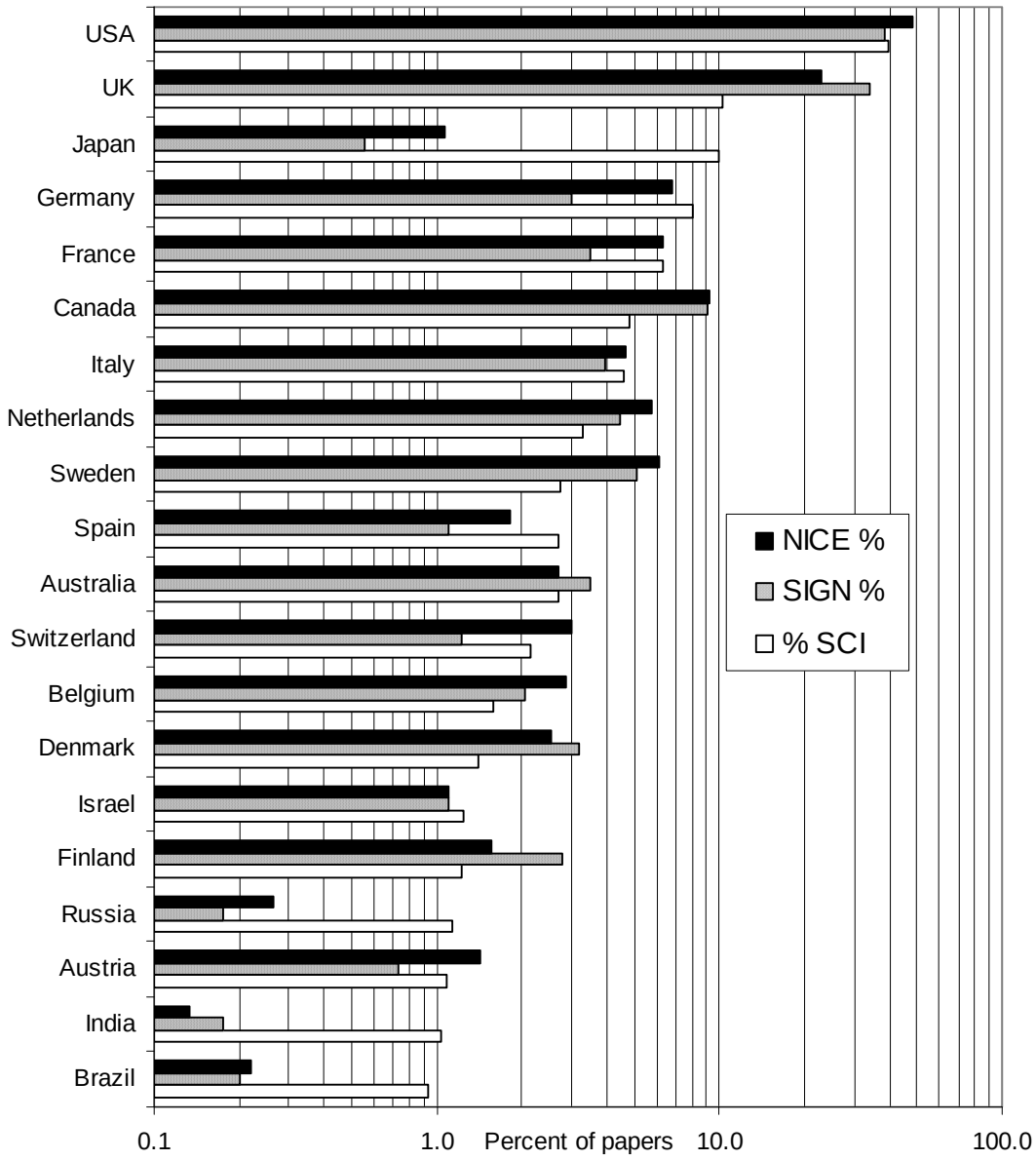

Figure 3. Relative presence of 20 leading countries in the addresses of papers cited by NICE HTAs and SIGN guidelines, and in the world biomedical literature in the SCI, 1995-2000.

Discussion

The work so far is only the beginning of what is intended to be a continuing exercise in which all official UK clinical guidelines will be systematically processed to provide a "Clinical Guideline Citation Index". As discussed above, clinical guidelines are also developed and used in other countries, although they may vary greatly in their authority and in the extent to which they are followed in practice (Belin, 2002; Lynn, 2001; Pearlman, 2002; Raycoquard, 2002; Roche, 2001; Tsuyuki, 2002). However it is clear that doctors everywhere will be under increasing financial pressure to observe local or national, or occasionally international, guidelines if their patients are enrolled in a cash-limited healthcare system. In fact the new emphasis on evidence-based practice is surely beneficial for all patients.

There are some interesting lessons from this study for bibliometricians. First, the study of the citations from clinical guidelines will need to be conducted separately in each country, although exchange of information will be useful for research evaluators, so common methodology should be used. Second, the citations may be time-limited. Some of the early SIGN guidelines have been withdrawn and either replaced with new ones (with an updated evidence base) or are currently under revision. And third, the process of normalisation, which is so important for bibliometric work, is difficult as the guidelines cover different clinical subjects and the overall balance of these is continually shifting. We shall need to develop new standards so that useful indicators of the relevance of given outputs of biomedical research to clinical practice can be produced.

Acknowledgements

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ANNEX Sample excerpt from a SIGN guideline

This has been downloaded from http://www.sign.ac.uk/guidelines/fulltext/29/index.html and shows journal references (others have been omitted)

Breast Cancer in Women

SIGN Publication No. 29

ISBN 1899893 41 5 Published October 1998

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