COSTS AND BENEFITS OF PHARMACEUTICAL RESEARCH

Papers from a seminar organised jointly by the Department of Health and Social Security and the Office of Health Economics in March 1987, to mark the Silver Jubilee of OHE.

Edited by George Teeling Smith

Foreword by Sir John Butterfield

Office of Health Economics
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Office of Health Economics

The Office of Health Economics was founded in 1962 by the Association of the British Pharmaceutical Industry. Its terms of reference are:

To undertake research on the economic aspects of medical care.

To investigate other health and social problems.

To collect data from other countries.

To publish results, data and conclusions relevant to the above.

The Office of Health Economics welcomes financial support and discussions on research problems with any persons or bodies interested in its work.

Printed in England by White Crescent Press Ltd, Luton

Foreword

These papers are a selection from those prepared for a seminar held jointly by the Department of Health and Social Security and the Office of Health Economics at the end of March 1987. The theme of that seminar was the cost and the benefit of pharmaceutical research. It was held as part of a year of celebration to mark the Silver Jubilee of OHE.

The whole subject of medical innovation has been central to the development of the National Health Service not only over the past 25 years, but since its inception in 1948. At that time, it will be remembered, Beveridge and Bevan believed that the future cost of health care would be reduced because, once the backlog of untreated sickness had been tackled, Britons would become healthier and would therefore require less medical care. This was subsequently described by Enoch Powell as a 'miscalculation of sublime proportions'.

In reality, although we are certainly much healthier than in 1948, health care costs have escalated in a dramatic fashion, as a result of medical innovation. It has become possible to tackle health problems for which treatment was inconceivable in the 1940s – transplants, open heart surgery, elaborate brain surgery, and a whole host of new pharmacological treatments have all been developed.

The central question tackled in these papers is whether such progress has been justified in economic terms. Have we become richer or poorer as a result of our better health? In other words, does medical research pay off or is it just a costly burden on society. And predominantly medical research in this context means pharmaceutical research. Almost all the medical progress since 1948 has been made possible by advances in pharmacology – antibiotics, anaesthetics, muscle relaxants, and immuno-suppressant compounds have all made the new surgery possible, while treatments for such diseases as diabetes, hypertension, bronchitis and asthma, mental illness and arthritis come directly from pharmaceutical research. The Research Councils and the University departments have all played essential roles and made enormous contributions, especially in the fields of pure science, but most of the practical advances for our patients – both pure and applied, have come from industry.

In national economic terms, pharmaceutical research has certainly paid off for Britain. In 1986 the positive balance of trade in pharmaceuticals was £853 million. The highly skilled employment in the industry itself brings national wealth.

But in the context of the National Health Service, the economic benefits of pharmaceutical research are less self-evident. There are conceptual difficulties in relating the savings which occur as a result of better medication to the costs of current pharmaceutical research. Will today's pharmaceutical investments in R and D bring economic benefits in the future?

In some cases the issue is easy and clearcut. George Teeling Smith's paper shows the way in which development in antibiotics continue to save money by reducing extra time in hospital due to post-operative infection. However, there are few cases where such obvious benefits in terms of 'patient turnover' can be unequivocally demonstrated. For the majority of treatments, the more complex approach hinted at by Michael Drummond becomes necessary.

In a sense, the frontiers of health economics are advancing in parallel with the advances in medicine itself. New ways of looking at the outcome of medical progress are having to be developed in order to quantify the benefits which most of us intuitively feel must exist. That is what the papers are all about.

The most challenging thinking comes in Jeremy Hurst's paper, where he discusses explicitly the new techniques for the measurement of the quality of life. There is still a long way to go before the idea of the QALY (quality adjusted life year) is validated and accepted as a measurement of economic outcome. Perhaps, indeed, some other unit may eventually replace the QALY. However, there seems no doubt that the role of epidemiologists and economists working together must be to produce economic methods which do quantify the benefits arising from the medical progress of the latter part of the 20th century.

In planning the joint DHSS/OHE Symposium it was hoped that solutions might emerge to show whether modern medical research paid off in economic terms. These papers may fall short of that objective, but they take an important step forward in clarifying the issues which need to be addressed in eventually making such an evaluation.

One thing is clear from the papers. Economists now have a central role to play in evaluating the benefits of medical care. It is no longer sufficient to rely on 'clinical impressions' or even the purely medical results of 'clinical trials'. What matters in modern medicine is how much better the patients feel, how much more fully they can live their lives, and how much they can contribute to the wealth of society in a cultural rather than a simply financial sense. That is the real test of whether medical research 'pays off'.

All this heralds a new era in assessing the outcome of future innovation in medicine. It is not the doctor alone who should decide whether his patient is 'getting better'. What matters is the way the patient feels, and how the community judges the social and economic contribution of the patient. This is a radical change of viewpoint, and it will take time for its full implications to be appreciated.

So, these papers make an important contribution to the discussion which must develop as this new approach to medicine takes shape. In the late 1980s, and increasingly into the 21st century, the achievements of medical research are going to be assessed in social and economic as well as clinical measurement terms, and this in itself is what good clinicians have been saying for some time!

John Butterfield

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A critical look at traditional measures of the economic benefits of medicines

Nicholas Wells

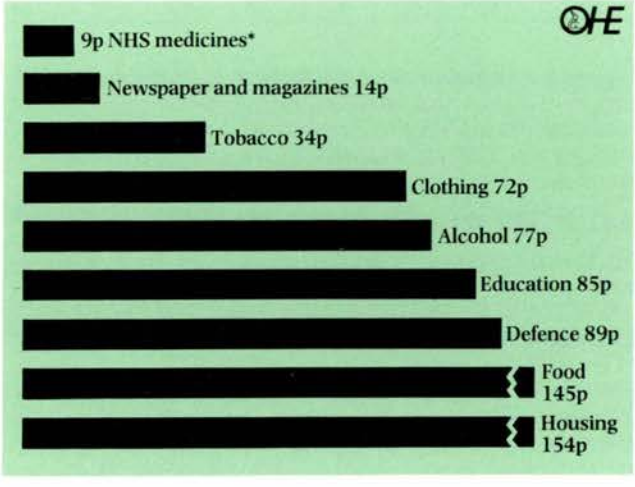
Introduction

In 1985, pharmaceutical manufacturers' sales of medicines to the National Health Service were valued at £1.8 billion. Table 1 shows that this sum – which is equivalent to just under 10 per cent of total NHS expenditure – has grown considerably in recent years. Between 1980 and 1985, for example, NHS purchases of medicines at manufacturers' prices increased by 74 per cent. Even after adjustment is made for the effects of price inflation, real growth amounted to 23 per cent over the period.

There are, however, several important explanations for this trend. The costs of researching and developing significant new medicines have escalated rapidly over time. The Centre for Medicines Research currently estimates that an investment of up to £93 million may be required to finance the discovery of a new chemical entity and its transition from the laboratory bench to the pharmaceutical market place (CMR, 1987). The R and D content of such products coupled with the therapeutic advantages offered over existing alternatives means that they command a price premium which is reflected in the medicines bill as consumption patterns switch in their favour. Concurrently, recent years have witnessed continuing growth in the numbers of elderly people in the population – individuals aged 75 years and over increased by almost half a million between 1980 and 1985 and average pharmaceutical consumption in this age group, at 15 or more prescriptions per capita, is five times that in the population of working age – as well as rising unemployment rates and both of these trends are positively associated with pharmaceutical consumption and expenditure.

The magnitude of current NHS expenditure on medicines may also be seen in a more favourable light when comparisons are drawn with other familiar items of daily expenditure. Figure 1 shows, for example, that expenditure on NHS medicines per person per day was in 1985 a quarter of that on tobacco and about a tenth of spending on alcohol. And from an international perspective, Table 2 indicates that spending on medicines in the United Kingdom is considerably lower than in many other nations of the industrialised world.

Figure 1 **Average daily expenditure per person, UK 1985**



Note: *Total sales at manufacturers' prices excluding dispensing fees and other distribution costs.

Source: CSO and DHSS.

Table 2 **Pharmaceutical consumption per person in 1983.**

	£	£
Japan	94	(75)
USA	81	(55)
West Germany	66	(61)
Switzerland*	64	(58)
France	52	(51)
Belgium	49	(45)
Canada	46	(35)
Italy	37	
Sweden*	35	(34)
Finland	34	(32)
UK	32	(32)
Australia	28	(26)
Denmark*	28	(26)
Norway	27	(26)
New Zealand	25	(30)
Ireland	25	
Netherlands	25	(22)
Spain	24	(24)
Greece	17	
Portugal	12	

*1982 data.

Notes

1 Pharmaceutical consumption is equated with manufacturers' returns and therefore dispensing and other related expenditures are not included.
2 The figures in the first column were calculated using January 1985 exchange rates. Those in parentheses were based on 1983 rates.

Source

Taylor and Griffin, 1985.

Table 1 **Pharmaceutical sales to the NHS at Manufacturers' prices, UK**

					Total NHS sales:	
Year	*Chemists £m*	*Doctors £m*	*Hospital £m*	*Total NHS £m*	*as % GNP**	*as % gross NHS cost*
1970	131	7	33	171	0.38	8.3
1975	280	14	73	367	0.38	6.9
1980	777	43	213	1,033	0.52	8.7
1981	903	52	247	1,202	0.55	8.8
1982	1,054	60	284	1,398	0.59	9.6
1983	1,191	69	317	1,578	0.61	9.6
1984	1,274	79	336	1,689	0.61	9.7
1985	1,344	88	365	1,797	0.60	9.8

Notes

Figures may not add up to total because of rounding.
*At factor cost.

Sources

DHSS and CSO.

Table 3 **Age specific male mortality per 1,000 population, England and Wales 1946–85.**

Quinquennium	*All ages*	*1–4*	*5–9*	*10–14*	*15–19*	*20–24*	*25–34*	*35–44*	*45–54*	*55–64*	*65–74*	*75–84*	*85+*
1946–50	12.8	1.90	0.88	0.69	1.33	1.75	1.92	3.23	8.55	22.4	51.6	119.0	241.6
1951–55	12.5	1.23	0.55	0.48	0.86	1.23	1.39	2.71	7.93	22.5	54.6	126.7	265.9
1956–60	12.3	0.99	0.49	0.40	0.88	1.12	1.17	2.45	7.35	21.9	53.7	122.7	239.2
1961–65	12.4	0.94	0.47	0.41	0.95	1.11	1.11	2.46	7.38	21.7	54.0	121.3	253.2
1966–70	12.4	0.87	0.43	0.39	0.96	0.97	1.02	2.38	7.18	21.0	55.3	115.9	254.2
1971–75	12.4	0.75	0.39	0.35	0.88	0.99	0.97	2.22	7.22	20.2	51.4	116.3	240.9
1976–80	12.3	0.59	0.32	0.29	0.87	0.93	0.94	2.01	6.73	18.9	48.8	112.5	237.1
1985	12.0	0.50	0.22	0.29	0.68	0.82	0.84	1.71	5.40	17.1	44.3	104.1	223.1
Percentage reduction 1946–85	6	74	75	58	49	53	56	47	37	24	14	13	8

Source:
OPCS.

Table 4 **Age specific female mortality per 1,000 population, England and Wales 1946–85.**

Quinquennium	*All ages*	*1–4*	*5–9*	*10–14*	*15–19*	*20–24*	*25–34*	*35–44*	*45–54*	*55–64*	*65–74*	*75–84*	*85+*
1946–50	10.9	1.62	0.64	0.54	1.05	1.54	1.76	2.56	5.51	12.8	34.4	93.2	208.9
1951–55	10.9	1.04	0.39	0.34	0.50	0.70	1.09	2.11	4.89	11.8	33.1	92.4	222.0
1956–60	10.9	0.82	0.33	0.27	0.38	0.52	0.81	1.83	4.46	10.9	30.7	86.4	212.5
1961–65	11.2	0.78	0.32	0.25	0.38	0.47	0.73	1.78	4.43	10.6	29.8	83.6	206.7
1966–70	11.2	0.70	0.28	0.25	0.39	0.44	0.65	1.68	4.34	10.3	28.0	77.5	203.0
1971–75	11.4	0.61	0.27	0.21	0.39	0.43	0.57	1.56	4.37	10.2	26.5	75.4	193.5
1976–80	11.6	0.48	0.22	0.21	0.34	0.40	0.56	1.40	4.11	9.9	25.3	70.9	192.9
1985	11.7	0.41	0.18	0.19	0.28	0.31	0.46	1.14	3.33	9.7	24.1	64.1	178.0
Percentage reduction 1946–85	(+7)	75	72	65	73	80	74	55	40	24	30	31	15

Yet given the competition between the different sectors of the NHS for scarce resources, justification for the substantial amount of public expenditure on pharmaceuticals has to be sought, in the final analysis, in the benefits generated by medicines usage. From the individual patient's point of view these gains – experienced, for example, as reduced pain, increased mobility or enhanced social functioning – may generally be self-evident. From an overall perspective, however, an accurate portrayal of these benefits is less straightforward. As this paper will show, evidence available from traditional sources is subject to qualification and in conjunction with the changing nature of the impact of chemotherapy this highlights the need for more refined methodological approaches to measuring the benefits of medicines.

Reductions in mortality

Since the second half of the 1940s when anti-infective medicines first started to enter widespread use, there has been relatively little change in all ages mortality rates for both males and females in England and Wales (Tables 3 and 4). Substantial reductions have, however, been experienced in all age groups up to 44 years and in large part these improvements reflect the decline in mortality from infectious diseases. In 1948, deaths from these causes accounted for 31.4 per cent of mortality between the ages of 1 and 44 years and for this age group the death rate from infectious diseases was 542 per million population. The corresponding figures in 1984 were 1.5 per cent and 10 per million respectively.

Within the infectious diseases grouping there have been major reductions in mortality from respiratory tuberculosis. In 1948, deaths from this cause totalled 18,798. By 1984, the number had fallen to 376. Application of the 1948 age specific mortality rates to population data for 1984 suggests that in the absence of improvement almost 22,000 respiratory tuberculosis fatalities might have been expected in the latter year. Furthermore, 35 per cent of this total would have involved people aged between 25 and 44 years and 90 per cent of cases would have been people of working age. These reductions coincided with the introduction and increasing use of anti-tubercular medicines.

Yet considerable care has to be exercised in interpreting this apparent 'saving' of life. The calculation ignores the fact that tuberculosis mortality was already on a declining trend prior to the introduction of medicines from the late 1940s. The death rate in 1984 would therefore in any event have been markedly less than the level recorded in 1948. As a result, any saving of life attributable to chemotherapy will also be less than might have been inferred from the calculations above. Furthermore, other factors besides chemotherapy – such as vaccination – also contributed to the improving mortality pattern. Nevertheless, McKeown (1976), a principal critic of medical science as a major contributor to man's improving health, has estimated that the introduction of streptomycin in 1948 prevented almost 140,000 deaths over the period 1948–71.

Despite such estimates uncertainty surrounds the precise extent of chemotherapy's contribution to falling mortality from infectious diseases over the last 35–40 years. The role of medicines in reducing mortality today is even more unclear. Certainly, the major impact of contemporary pharmaceuticals is on the quality rather than the quantity of life. It would nevertheless be misleading to imply that benefits gained in this respect are insignificant. Deaths from coronary heart disease and stroke, for example, are undoubtedly being avoided, or postponed, in people at the high extremes of the population distributions for blood pressure and serum cholesterol by the use of medicines for hypertension and hypercholesterolaemia. And there is evidence that the use of beta blockers following acute myocardial infarction reduces subsequent mortality by about 20 per cent (Peto, 1985). Yet in these other areas of therapy, comprehensive data do not exist to show either

the number of years of life being saved by medicines (let alone their quality) or at what expense these gains are being achieved.

Sickness absence from work

The use of medicines might also be expected to generate economic benefits by reducing sickness absence from work – either by cutting the number of spells of absence or by reducing their duration. The data contained in Table 5 suggest that this may indeed have been the case in respiratory tuberculosis and in certain other diagnostic categories, for example, asthma. In total, however, certified incapacity rates have clearly increased over time.

This overall picture is composed of a large number of trends for specific diagnoses, each one of which will be influenced to varying degrees by changing incidence patterns, diagnostic fashions and many other factors. Indeed, Table 6 lists 31 factors that have been shown to influence sickness absence from work. It is noteworthy that only two of the factors are strictly concerned with ill-health. Against this background, it inevitably follows that the impact of new medicines on sickness absence is almost impossible to isolate and quantify from generally available data.

Even if it proved possible to derive reasonably accurate estimates for medicines-related reductions in sickness absence, the problem of how to measure the economic value of such change would still have to be overcome. The economic significance of absence is conventionally represented by the value of potential output that is foregone and may be calculated by applying earnings data to the number of days of certified incapacity estimated by the Department of Health. Yet any figure arrived at in this way – for example, the 33.3 million days of incapacity due to back pain in 1982/83 deprived the nation of an estimated £1 billion worth of output (Wells, 1985) – would be likely to misrepresent the true costs involved. Understatement, for example, would be inevitable since losses attributable to absences of very short duration are not included. Furthermore, workers who remain outside the sickness benefit system (from which days of certified incapacity are derived) are not taken into account. Alternatively, the calculated cost may be an overstatement because work teams may be able successfully to re-organise to accommodate the temporary absence of one of their members through sickness. Arguably of yet greater contemporary significance, estimates of production loss may be perceived as more notional than real in economic circumstances in which high levels of unemployment prevail.

Table 5 **Certified days of male incapacity per 100 at risk aged 20–64 years by diagnostic group, 1954/55 and 1978/79, Britain.**

	Days per 100 men at risk	
Diagnosis	*1954/55*	*1978/79*
Sprains and Strains	9.4	51.4
Nervousness, debility, headache	9.5	59.7
Ill-defined symptoms	36.7	73.8
Psychoneuroses and psychoses	107.6	160.3 (a)
Displacement of intervertebral disc	10.3	32.3
Eczema and dermatitis	12.5	9.1
Cellulitis	10.7	4.7
Arteriosclerotic and degenerative heart disease	64.4	150.7 (b)
Other forms of heart disease	24.7	34.0
Hypertensive disease	26.4	59.0
Varicose veins	7.0	6.8
Neoplasms	9.1	11.6
Acute tonsilitis	10.6	4.7
Pneumonia	11.3	3.1
Bronchitis	144.3	171.1
Stomach and duodenal ulcer	42.7	22.0 (c)
Gastritis and duodenitis	22.1	15.1
Hernia of abdominal cavity	17.6	22.1
Diarrhoea and enteritis	9.5	23.3
Appendicitis	8.5	3.4
TB of respiratory system	104.8	9.0
Asthma	20.0	11.8
Arthritis	43.9	125.8 (d)
Rheumatism	51.6	30.3 (e)
All causes	1,330	1,908

(a) Mental disorders in 1978/79.
(b) Acute myocardial infarct, chronic and other ischaemic heart disease in 1978/79.
(c) Stomach, duodenal and peptic ulcer in 1978/79.
(d) Osteo, allied conditions, other arthritis and spondylitis in 1978/79.
(e) Rheumatism and lumbago in 1978/79.

Source:
DHSS.

Table 6 **Some factors known to influence sickness absence.**

Geographical	*Organisational*	*Personal*
Climate	Nature	Age
Region	Size	Sex
Ethnic	Industrial Relations	Occupation
Social Insurance	Personnel Policy	Job Satisfaction
Health Services	Sick Pay	Personality
Epidemics	Supervisory Quality	Life Crises
Unemployment	Working Conditions	Medical Conditions
Social Attitudes	Environmental Hazards	Alcohol
Pension Age	Occupational Health Service	Family Responsibility
	Labour Turnover	Journey to Work
		Social Activities

Source
Taylor 1979.

Hospital savings

Focusing specifically on the hospital sector of the NHS, the development of new medicines generates economic benefits by reducing both the number of admissions and the duration of in-patient stay. An attempt at quantifying some of these benefits was published in 1985 (Teeling Smith and Wells, 1985) and these findings have been updated for the present discussion.

Table 7 shows six diseases in which the development of effective medicines has contributed to a reduction in the

Table 7 **Total hospital bed days required for treatment of six diseases in 1957 and 1984.**

Disease	*1957*	*1984*
Asthma	394,331	357,917
Epilepsy	500,053	211,426
Glaucoma	148,969	95,075
Hypertensive disease	1,204,277	178,020
Bronchitis	1,262,028	417,377
Skin diseases	1,122,385	1,063,521
Total	4,632,043	2,323,336

volume of hospital in-patient treatment. In total, hospital bed days for the six specified conditions fell by 50 per cent between 1957 and 1984 in England and Wales. The reductions have been achieved by varying combinations of fewer hospital admissions and shorter mean durations of in-patient stay. Table 8 shows the estimated savings in 1984 hospital costs generated by the reduction in hospital bed days for the six diseases combined with the corresponding gains in three other diagnostic groupings – respiratory tuberculosis, other infectious diseases and mental illness. In total it is estimated that the reduction in occupied beds for these nine disease groups between the second half of the 1950s and 1984 created a 'saving' of £1,900 million for NHS hospitals in England and Wales in the latter year. The original paper (Teeling Smith and Wells, 1985) proceeded to compare this sum with the cost of NHS purchases of pharmaceuticals at manufacturers' prices. In 1984 this amounted to £1,473 million for England and Wales, thereby appearing to imply net savings to the NHS of £446 million.

These estimates are designed only to indicate in broad order of magnitude terms the benefits arising from certain pharmaceutical innovations and as such may require refinement from a number of both 'technical' and economic points of view. Focusing on the former, it should be pointed out, for example, that disease classification procedures have been modified three times over the period 1957–84 and coupled with changes in diagnostic fashion and accuracy this may give rise to some inconsistencies in seemingly corresponding data for the two years. This consideration may be particularly relevant in the context of hypertensive disease.

In addition, the data source from which the in-patient days are calculated – the Hospital In-patient Enquiry – related to England and Wales in 1957 but was confined to England alone in 1984. An adjustment on the basis of population size has been made to the latter year's figures, but it is not clear how accurately this method compensates for the recent gap in the data. Furthermore, allowance has not been made for changes in the age structure of the population. If any of the diseases analysed is more common in certain age groups than others, alterations in the population structure over the 27-year period would have an impact on overall hospitalisation rates irrespective of other potential influences.

Of more fundamental significance, the exercise should take account of shifts in disease incidence. Focusing on respiratory tuberculosis, which accounts for 30 per cent of the saving shown in Table 8, it has already been pointed out that incidence was falling prior to the availability of chemotherapy and appeared set to continue this decline. Consequently a smaller number of bed days would have been anticipated in 1984 even in the absence of therapeutic advance. The magnitude of the savings attributed to the reduced number of hospital bed days for respiratory tuberculosis therefore needs to be adjusted downwards, but to what extent is unclear.

A related observation also applies in the case of the savings generated by the falling in-patient population of mental illness hospitals in England and Wales. Available data indicate that following the introduction of chlorpromazine in 1954, the previously rising trend in the number of occupied mental illness beds was reversed. However, attitudes towards the treatment of mental illness were already beginning to change at this time and the introduction of new medicines acted as a catalyst towards new patterns of community based care rather than simply as a cause of the reduction in the number of in-patients. This might be taken to imply that not all of the savings from the depopulation of mental illness hospitals should be attributed to therapeutic advance.

Turning to economic considerations, it might first be pointed out that the savings calculations are sensitive to seemingly small shifts in the data base. For example, the recalculated savings shown in this paper are 13 per cent greater than those reported in the original *Pharmaceutical Journal* paper even though there is only a two-year time gap and despite the inclusion of Wales in the 1984 analysis which would of course serve to diminish the magnitude of the savings relative to 1982 (when data for England alone were employed). In addition, the choice of hospital costs – which themselves have to be used carefully because they are averages – can also markedly influence the outcome of the savings calculations. The latter could, for example, have been based on the daily in-patient costs in acute teaching hospitals located outside London which are 24 per cent higher than those actually employed in the analysis. Alternatively, a 10 per cent lower daily in-patient cost could have been used on the assumption that treatment for the diseases shown in Tables 7 and 8 is provided in non-teaching hospitals classified as mainly acute.

Second, the 'savings' are compared with the revenues received by pharmaceutical manufacturers from their sales of medicines to the NHS. The principal argument underlying the analysis is that the use of medicines in the community generates savings in the hospital sector by avoiding or reducing hospitalisation. Consequently, it might be argued that other costs involved in medicines usage in the community ought to be taken into account. It would therefore seem appropriate at least to take account of the pre-

Table 8 **Financial savings from the reduction in hospital bed days 1957–1984.**

Disease	*Bed days 1957*	*Bed days 1984*	*Savings in bed days 1957–84*	*Saving in hospital costs £ million**
Six diseases	4,632,043	2,323,336	2,308,707	193
Respiratory tuberculosis	6,886,552	79,118	6,807,434	568
Other infectious diseases	2,766,190	512,340	2,253,850	188
Mental illness	52,487,000†	25,916,873	26,570,127	970
Total saving				1,919

Note:
*Calculated on the basis of a daily in-patient cost of £83.50 in acute non-teaching hospitals in England in 1984/85. Average daily in-patient cost in mental illness hospitals in England in 1984/85 was £36.50.
†1959 data.

scribing and dispensing costs for medicines. In this event, adding the cost of general medical services in England and Wales in 1984 (£1,077 million) to the cost of the drug bill revised to include dispensing and other related expenditures (£1,922 million) would yield a new 'cost' figure of £2,999 million to be compared with the estimated hospital sector 'benefit'. There is, however, a further area of uncertainty: it might, for example, be argued that the costs arising from the demands on general practitioners' time would still be generated – and possibly to a yet greater extent – even in the absence of medicines innovation.

Third, it has to be recognised that new pharmaceuticals can also be cost increasing for the hospital sector. At one extreme, the development of immunosuppressant agents has facilitated an expansion of expensive high technology surgical procedures. In addition, medicines have promoted the survival of some individuals who eventually come to need hospital care. In this general regard, it would be instructive to analyse hospital in-patient data with a view to identifying those diagnostic categories in which total bed days have risen over time, perhaps linked to pharmaceutical innovation. However, it is likely that an exercise of this type, in common with the present investigation of reductions in hospital bed days, would be equally subject to the difficulties posed by confounding variables.

On a negative note, the availability of new medicines has also been associated with an increase in hospital treatment for adverse drug reactions. Although recent years have witnessed a steady decline in the proportion of hospital bed days attributable to 'poisoning and toxic effects of medicinal agents' – from 0.45 per cent in 1977 to 0.30 per cent in 1984 – these episodes may still be estimated to have generated a hospital cost of £14 million in 1984. However, an unknown but probably substantial number of these cases involve deliberate self-harm so that unintentional adverse effects of medicines may account for only a relatively small proportion of the total cost calculated in this way.

Yet at the same time, it is also true that patients admitted to hospital for other reasons may experience an adverse effect from a medicine employed during their in-patient spell. It is not possible to estimate from the Hospital Inpatient Enquiry the numbers involved in such episodes nor the extent of additional hospital stay thereby required. However, a recent study suggests that 1 per cent of hospital cases may be attributed to serious adverse reactions to medicines (Pedroni, 1984). Applying this proportion to the total number of bed days in England and Wales in 1984 yields a cost for serious adverse reactions of £46 million. This sum has therefore to be offset against the savings figure show in Table 8.

Finally, important considerations relate to the time frame of the savings analysis, especially with regard to respiratory tuberculosis. It might be argued that a substantial part of the savings shown in Table 8 derives from improvements gained in the earlier segment of the 1957–84 period and that from the perspective of a cost : benefit analysis it is not strictly accurate to compare them with contemporary expenditures on medicines. Available incidence data show a fall in notifications per 1,000 population from 0.83 in 1954 to 0.22 in 1967 and from 0.19 in 1970 to 0.11 in 1983. Consequently, it might be deemed more appropriate to compare contemporary expenditures and benefits rather than present costs and past benefits.

Conclusion

There is no doubt that pharmaceutical innovation has generated economic benefits for the National Health Service. In particular, new medicines have produced savings in the hospital sector by reducing the need for and duration of in-patient stays. At a global level it is not however possible to put an accurate figure on the overall saving – there are too many confounding variables to allow disentanglement of the specific impact of medicines. Furthermore, in order to reach an overall assessment, attention would need to be given to the potential effects throughout the entire diagnostic spectrum – not confined to a few selected disease categories – and this would involve a formidable programme of work.

Instead, arguably more is to be gained by concentrating efforts on the new approaches to measuring the benefits of innovation discussed at this meeting. Underpinning the observation is the changing nature of the impact of chemotherapy. Gains in the form of fewer premature deaths, diminished sickness absence from work and reduced hospital costs have largely been superseded by benefits which are principally apparent in an improved quality of life. This does not of course mean that traditional economic benefits have lost all relevance. For example, a recent Swedish study has shown that use of the beta blocker metoprolol after myocardial infarction can significantly reduce hospital re-admission costs (Olsson *et al*, 1987). Furthermore, it might be speculated that the traditional types of economic benefit associated with the use of pharmaceuticals in treating infectious diseases may be destined to reappear in connection with the AIDS virus. But for the moment, it is the measures showing the quality of life gains generated by contemporary medicines and the potential benefits of therapeutic progress in diseases where treatments are either inadequate or lacking altogether that constitute the appropriate indicators of the need for sustained pharmaceutical innovation.

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The cost-benefit of antibiotic prophylaxis in surgery

George Teeling Smith

One of the principal problems in assessing the cost-benefit effectiveness of medicines is what can be described as the 'stony ground syndrome'. From biblical days onwards it has been recognised that not all seeds which are sown will germinate and flourish. The yield from those which fell on fertile ground has to be set not only against the cost of those particular seeds, but also all the other seeds which failed to germinate because they fell on stony ground.

The first Lord Leverhulme expounded the same principle in relation to his advertising. He said he knew much was wasted, but who could tell him which particular advertisements sold his soap, as against all those which were thrown un-read into the dustbin?

Whether in agriculture, or in advertising or in therapeutics the objective must be to achieve the maximum yield from the minimum outlay, but it is hopelessly Utopian to suppose that every investment of scarce resources will be totally productive.

On the other hand it is the worst form of specious special pleading to try to justify total costs of any type on the basis of the cost-effectiveness of the marginally most effective unit. Hence in looking at the cost-effectiveness of pharmaceuticals it is important to take account of the costs of 'unnecessary' treatment as well as the cost of the successful treatments in producing the final balance.

Nowhere is this general principle more true than in preventive medicine. The great majority of people who receive prophylaxis would not have suffered from any disease even without their protective cover. Vaccination against poliomyelitis is one of the earliest examples which the Office of Health Economics examined in this context.[1] It was shown that, because polio was normally a very rare disease, vaccination was actually more expensive for the health service than the alternative cost of treating the relatively few cases which would otherwise have developed.

Similarly, the economic benefits of many other successful treatments are diluted because it is necessary to take into account the cases which are unsuccessfully or unnecessarily treated, as well as those for which there are dramatic savings.

Furthermore, if too short-term a view is taken of 'cost-effectiveness' longer-term savings may be lost. For example, a 'cheap drugs' policy may inhibit long-term research which would produce benefits over the next ten years instead of the next ten months. The cost-benefit of funding long-term pharmaceutical research is an immensely complex subject, which other contributions to this seminar will undoubtedly discuss.

However, for the present analysis of the cost-benefit of antibiotics as a prophylactic before surgery these longer-term considerations need not arise. It is one of the cases where the benefits in the short-term are clear-cut, even taking into account the 'unnecessary' cover given to cases where no infection would have occurred and even making a comparison between short-term costs and benefits of more expensive modern treatment as against cheaper and less effective 'generic' therapy.

A recent estimate suggests that 5 per cent of all hospital cases are infected during their stay, giving a total cost for hospital infections in England and Wales of £76 million.[2] Turning to the United States, and taking post-operative infections alone, it was estimated in 1982 that the annual cost was between 200 and 800 million dollars.[3] Further evidence of very substantial costs of post-operative infection comes from a controlled clinical trial of antibiotic prophylaxis in high risk biliary operations in Southampton.[4] The surgeons in this study found that 16 per cent of a small series of cases were infected if antibiotics were not used prophylactically. In their text they suggested that in general between 5 and 10 per cent of surgical wounds might end up being infected – with a range from 0.2 per cent in 'clean' operations carried out with a high degree of surgical expertise to 100 per cent in 'contaminated' cases carried out with 'poor' surgical expertise (Table 1).

Based on the figure of 2.3 million operations carried out annually under the NHS and a recent estimate of an average of four extra days spent in hospital if an infection occurs,[2] a 5–10 per cent infection rate gives a cost for post-operative infections of between £40 million and £80 million a year.

The same surgeons in Southampton expressed the opinion – based on the results of their controlled trial – that antibiotic prophylaxis 'virtually eliminated' post-operative infection. However perhaps a more realistic estimate comes from a French study which indicated that 80 per cent of infections were avoided by prophylaxis.[5] On this basis the prophylactic use of antibiotics would save the NHS between £32 million and £64 million in reduced length of hospital stay. Incidentally, it is probably quite fair to use average total hospital costs to calculate this figure, as infected patients will require careful nursing and a full range of pathological and therapeutic services during their period of infection. They certainly do not incur 'hotel' costs alone.

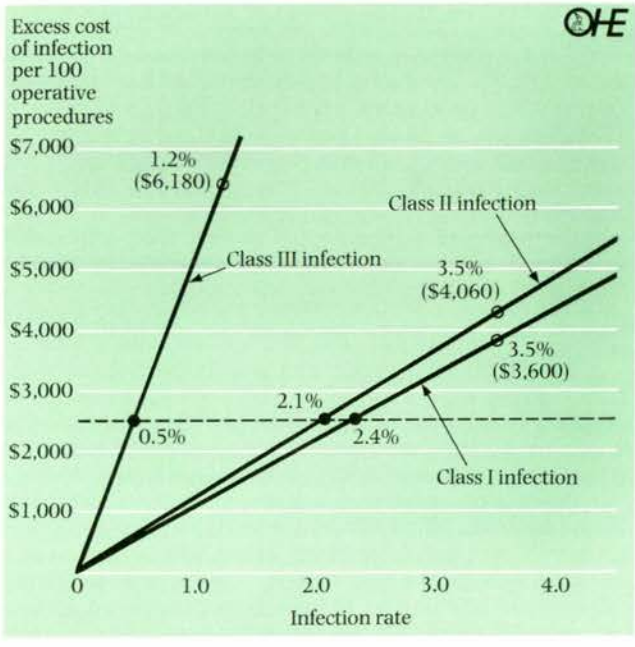
However the statement of these very substantial figures does not automatically answer the question of whether or not antibiotic prophylaxis is cost effective. It has already been pointed out that antibiotic cover has to be provided for the 90–95 per cent of cases who would *not* be infected, as well as those who would. It would thus be possible that the cost of antibiotics themselves would outweigh the savings they achieved. Fortunately, from an economic point of view, this is a question which has been carefully studied in a number of different situations, and in each case the result shows an overall net saving. The following paragraphs give some specific examples, mainly from the United States. However, the conclusions are applicable internationally. The relationship between pharmaceutical costs and hospital costs are similar in all countries.

Table 1 **Approximate risk of septic complications, eg wound sepsis, that may be expected in different areas of surgical practice, without the use of antibiotics, according to the technical expertise of the surgeon.**

	Sepsis rate according to degree of surgical expertise, %		
Type of surgery	*High*	*Average*	*Poor*
Clean			
Hernias, varicose veins, breast surgery, orthodpaedics, vascular surgery	0.2	2	5
Potentially contaminated			
Low risk, Biliary, gastric surgery	3	10	20
High risk, Colorectal surgery (elective)	15	45	70
Contaminated			
Peritonitis, drainage of abcesses	75	85	100

Source:
Karran *et al* (1985).

Figure 1 **The Cost Effectiveness of Antimicrobial Prophylaxis in Clean Vascular Surgery.**



Legend: The effect of the severity of infection and the infection rate on the excess cost of infection in vascular surgery involving the abdominal aorta. Wound infections were graded as Class I if only skin was involved, Class II if sc tissues were involved and Class III, or most severe, if the implanted graft was involved. The open circles denote the observed infection rate and the excess cost of infection per 100 operative procedures. The solid black lines define the relationship between the infection rate and the excess costs of infection. The dotted line represents the cost of cefazolin propylaxis per 100 operations.

Source: Kaiser *et al* (1983).

The first example relates to abdominal hysterectomy.[6] Cefazolin was used for prophylaxis in the treatment group in a controlled trial covering 429 patients. In this trial, patients in the treatment group each cost on average $102 less than those in the control group, after taking account of the cost of the antibiotic. The same paper, published in 1983, also reported on a smaller trial covering vaginal hysterectomy. In this case 44 patients received cefazolin prophylaxis and 42 received a placebo. The net saving was $492 per patient.

The second study, also published in 1983, covered acute non-perforating appendicitis.[7] This was a prospective randomised double-blind trial in which 52 patients received the placebo and 51 received cefoxitin sodium. Post-operative wound infections occurred in 9.6 per cent of the placebo group, but in none of the treated group. It was calculated that prophylaxis in this case resulted in a net saving of $84 per patient.

Another brief communication in 1983 discussed the cost-effectiveness of antibiotic prophylaxis in clean vascular surgery.[8] In this case the cost of five one-gram doses of perioperative cefazolin was $2,500 per 100 patients. Figure 1 shows that the excess costs associated with post-operative infections in untreated patients exceeded the costs of prophylaxis if 0.5 per cent of cases developed the most severe infections; if 2.1 per cent developed infection of the subcutaneous tissue, and if 2.4 per cent developed skin infections only. In the trial, the observed infection rate exceeded the 'breakeven' infection rate for each of the classes of infection, and the authors therefore concluded that antibiotic prophylaxis was always justified for economic as well as for clinical reasons.

In 1984, a further study examined the economic consequences of prophylactic antibiotics in head and neck surgery.[9] The double-blind randomised trial covered 101 patients, who were assigned to one of three treatment groups or to a placebo group. 78 per cent of untreated patients developed an infection; but only 33 per cent of those on cefazolin and 10 per cent of those on cefoperazone or cefotaxime were infected. Table 2 shows the extra costs resulting from less than optimum prophylaxis. It is explained by the authors as follows:

> 'Extrapolation for a theoretical group of 100 patients is even more revealing. The third-generation cephalosporins serve as the standard of comparison. Theoretically, even with the best results and despite perioperative prophylaxis, nine patients (9 per cent) will develop wound infection. The Table compares the number of extra infections and costs with cefazolin. For example, in a group of 100 patients receiving cefazolin prophylactically, 33 will develop postoperative wound infection. The theoretical model would predict nine infections with the use of third-generation cephalosporin. Therefore 24 infections could perhaps have been prevented.
>
> Each of the 24 additional infections results in 14.7 excesss hospital days. This represents 352.8 days collectively. On the basis of our per diem costs of $697.62, these extra infections cost $246,120.33. The cost of cefazolin is $5,000 for 100 patients. Therefore the net increased hospital costs for the patients receiving cefazolin is $251,120.33. Obviously, the extra $6,800 spent on the third-generation cephalosporins is insignificant compared to the added expense of hospitalisation for infected patients.'

Finally the French study published in 1985, which has already been mentioned, examined the use of prophylactic cefoxitine in major surgery for cancer of the upper 'aero-

Table 2 **Theoretical costs associated with development of wound infection of 100 patients according to prophylaxis given.**

Regimen	*Predicted infections*	*Infections in excess of ideal*	*Extra hospital days (14.7/patient)*	*Cost of extra hospitalisation*	*Cost of antibiotics (100 patients)*	*Net extra costs on 100 patients*
No drug	78	69	1,014.3	$707,606.10	—	$707,606.10
Cefazolin	33	24	352.8	$246,120.33	$5,000.00	$251,120.33
Third-generation cephalosporin	9	—	—	—	$11,800.00	$11,800.00

Source:
Mandell-Brown *et al* (1984).

digestive' tract.[5] 80 per cent of controls developed post-operative infection, against 15 per cent of the treated group. This resulted in a net treatment cost of 1,002 French francs for the control group against 470 French francs for those treated prophylactically.

Although the individual experiences and results differ considerably, clearly all of these studies point in the same direction. Antibiotic prophylaxis is cost effective, in addition to reducing suffering and inconvenience for the patient. There appear to be no published studies which contradict this conclusion. This situation is confirmed by a recent article in the *New England Journal of Medicine* which concluded that 'ample evidence suggests that in a broad range of surgical procedures – eg, caesarean section, colon resection and vascular surgery – it is more cost effective to administer prophylactic antimicrobials then to treat the infections which occur in patients who have not received these agents'.[10] Even in the few cases where infections occurred extremely rarely, the author concluded that prophylaxis was justified by the benefit to the patient irrespective of relative costs.

Returning to the British scene, the small trial at Southampton[4] gives another indication of the potential savings for the National Health Service to supplement the estimates quoted earlier in this paper. The authors suggested that prophylaxis could 'virtually eliminate' the 5 to 10 per cent of post-operative infections which would occur. They concluded that the reduction in hospital stay would be between two and three days (a slightly lower estimate than that of other authors). On this basis they concluded that the potential savings would be between £1,000 and £3,000 per 100 surgical patients. That would represent between £23 million and £69 million a year for all surgical cases in the NHS.

On the other side of the equation, the same authors estimated the cost of prophylactic cephazolin (2 grams) to be £600 per 100 patients, or £14 million for every NHS surgical patient in a year. Taking the middle point of the estimates in savings as £45 million this gives a net reduction in National Health Service costs of £31 million a year at 1986 prices from the use of prophylactic antibiotics. Taking the upper estimate of costs, the savings would be £55 million a year.

These figures must be taken as tentative estimates; other experiences quoted from the USA suggest quite different bases for making such estimates. However, once again it is clear that prophylactic antibiotics for surgical cases do produce an economic saving for the National Health Service, even if its precise magnitude may be uncertain. There is also an indication from at least one paper that third generation cephalosporins yield a greater economic benefit than earlier antibiotics.[9] These economic benefits must be added to the even less easily quantifiable benefits in terms of patient well-being. From all of this, there seems to be a clearcut case for the general use of antibiotic prophylaxis in surgical cases both on clinical and on economic grounds.

Finally, a study from Sweden compares the cost of antibiotic prophylaxis in hip replacement against the cost of other types of preventive measures. These other measures were the use of gentamycin-impregnated bone cement and the reduction of airborne infection. This latter approach involved the use of a sterile 'surgical box' and/or the wearing of a ventilated 'body exhaust suit' by the surgical team. Table 3 shows the cost of each approach, depending on the number of operations carried out each year. Obviously the costs for methods requiring a capital investment (such as the 'surgical box') fall per operation as the numbers performed increase. However, even for 200 operations per year, systemic antibiotics still represent the lowest cost per operation. When comparing the costs of prophylaxis with the cost of repeated surgery required by an infection, the authors concluded that antibiotics and gentamycin cement alone represented the most cost-effective approach in small operating units. In larger units, the additional reduction of infection by the other approaches could also be justified in terms of cost. Figure 2 shows the economic effect of various approaches for a unit carrying out 100 operations per year. The lowest 'total cost' comes from the use of gentamycin cement and systemic antibiotics alone.[11]

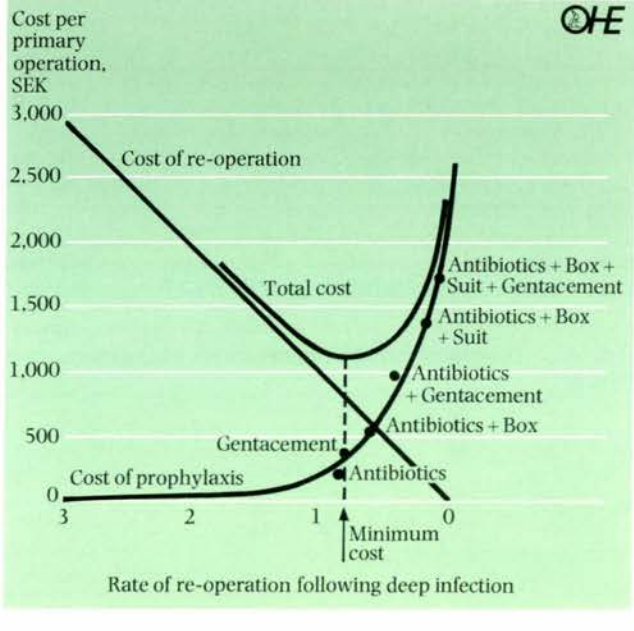
This illustrates the general principle that all approaches to the reduction of surgical infection can be justified by the benefits to the patient, and are certainly to be encouraged on this basis. However, in many situations, in terms of cost effectiveness alone, the use of prophylactic antibiotics is the best approach. Moreover there is an indication from the

Table 3 **Additional costs (Swedish Crowns) per operation of infection prophylaxis following total hip joint arthroplasty in relation to number of operations per annum.**

	Number of operations per annum				
Prophylaxis	50	100	150	200	200
Systemic antibiotics	209	209	209	209	209
Genta cement (Palacos^{R})	350	350	350	350	350
Surgical box	1,531	766	510	383	306
Operational suit	514	384	340	318	305

Note:
The additional costs of each particular combination of prophylactic measures may be estimated by adding the cost of the specific measures employed.

Figure 2 **Medical costs of deep infections at various rates of infections – costs per primary operation. Costs of surgical box and suit based on 100 primary operations per annum.**



Source: Lakartidningen nur. 34, 1986, pp 2725–28.

examples quoted that the latest antibiotics will bring the biggest economic savings, even although they are more costly in themselves than cheaper and older alternatives.

There may of course be, other wider considerations which apply to the use of antibiotics in any situation. One is the risk of antibiotic resistance, which can cause a major problem in a hospital. However, there is no evidence that the appropriate use of antibiotics (such as prophylaxis to prevent surgical infection) greatly increases this risk. Indeed, by preventing the spread of infections in the hospital it may be positively beneficial. Certainly, it could reduce the work-load in the pathology laboratory, as the number of antibiotic sensitivity tests will be reduced by avoiding or reducing post-operative infections. This could lead to additional savings.

There is also the fact that much of the evidence in this paper comes from clinical trial experience. It is important – as Professor Drummond points out in his paper – that behaviour in actual clinical practice should be as carefully controlled as in the clinical trial. More profligate use of antibiotics in un-necessarily large quantities in routine practice can reduce or eliminate the economic savings.

However, the last word must go once again to words quoted in the same article in the *New England Journal*. 'In discussing the impact of antimicrobial technology on society, McDermott and Rogers noted that the greatest effect of modern antibiotic therapy may be its influence on the evolution of modern surgery'.[12]

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Assessing the costs and benefits of medicines: some current measurement issues

Michael F. Drummond

Introduction

There is now a growing literature on the costs and benefits of medicines.[1] This paper examines some of the key measurement issues that have emerged, illustrated where possible by recent examples. Four issues in particular will be explored: these are the estimation of savings in health care resources owing to drug therapy, the measurement of improvements in the quality of life, the estimation of health benefits in money terms and the incorporation of economic measurements in clinical trials.

Estimating savings in health care resources

One of the economic benefits of medicines is that they can bring about reductions in the use of other health care resources. A common case is that of drug prophylaxis in surgery, where, by preventing postoperative infection, days of hospitalisation may be averted.[2] The approaches used to estimate savings in reduced hospitalisation vary in complexity. Some studies merely take the average hospital cost per day, others try to obtain a daily cost for the particular category of patients concerned, by splitting hospital costs into those 'treatment' elements which can be attributed to given patients and those 'hotel' elements that are the same for all patients.[3]

However, a common concern of health service managers and policy makers is that costs may not actually be saved by reduced hospitalisation, as the beds will merely be allocated to other patients. This point was acknowledged a number of years ago by Russell *et al*[4] in their economic evaluation of day case surgery. They suggested that the real economic gain from reduced hospitalisation was that resources would be freed for other uses. The managers of the hospital would therefore have the options of reducing bed capacity, revising downwards their estimates of expansion in capacity, or allocating the beds to other categories of patients.

The same approach has recently been used by Drummond and Ward[5] in an economic appraisal of a drug which had been shown in a controlled clinical trial to reduce the hospitalisation of stroke patients post-stroke. They first estimated the cost savings from use of the drug in the conventional manner, using the routinely available hospital costs for patients on general medical wards (see Table 1). However, they went on to estimate that if 100 patients received drug therapy, the freed bed days (2,500) would result in an extra 216 admissions, given the current average length of stay and turnover interval for the specialty of general medicine. Or, put another way, the hospital would be able to cope with eight fewer beds for stroke patients. They further argued that in the longer term financial savings could be realised if bed capacity were reduced to compensate for technological innovations such as new drug therapies, but that this was a separate managerial decision that would depend on the health care priorities in a given locality.

Another difficulty in estimating the net savings in health service resources from the use of drugs is that the drug may not be prescribed in the right dose, or that the range of indications for which it is used may be wider than that suggested by clinical trial data.

With regard to dosage levels, Shapiro *et al*[2] noted that while the amount prescribed in accordance with their study protocol proved more cost-effective than no prophylaxis, the amounts typically prescribed in US hospitals were much larger. One way forward would be to provide clinicians with information on dosage levels based on the most reliable trials data.

Table 1 **Costs of care in the first year for 100 patients with and without drug therapy (illustrative figures only).**

	Drug therapy	*Conventional care*
Diagnostic workup (150 CT scans @ £120 each)	18,000	—
Drug therapy	24,000	—
Acute hospital costs	358,823	463,223
Other hospital/Local Authority care	21,000	19,000
Domiciliary care (DN visits, GP visits)	15,500	10,500
Total	437,323	492,723

With regard to the range of indications for use of a drug, it is normal for this to increase as more experimentation takes place and, providing it takes place in a controlled way, it should be encouraged. However, this suggests that the assessment of the costs and benefits of medicines needs to be seen as an iterative process. Banta[6] has argued that all too often health technologies are assessed at one point in time, rather than at different stages in their diffusion and use.

Measuring improvements in the quality of life

There has been a growing interest in the measurement of quality of life as part of medicial research, mainly because most modern medicine is concerned not with extending life but increasing its quality through the removal of pain and restriction of activity. Within the field of drug therapy this interest has manifested itself in two ways, through the inclusion of quality of life measurements in clinical trials and through the calculation of 'utility' values for health states.

A recent example of a clinical trial including quality of life measurements is that by Croog *et al*.[7] They compared the effects of three major antihypertensive agents – captopril, methyldopa and propanolol – on the quality of life and control of blood pressure in men with mild to moderate essential hypertension. Quality of life was assessed by five measures: (i) the sense of well-being and satisfaction with life; (ii) the physical state; (iii) the emotional state; (iv) intellective functioning, and (v) ability to perform in social roles and the degree of satisfaction derived from those roles. The authors argued that their findings showed that antihypertensive agents had different effects on the quality of life and that these could be meaningfully assessed with available psychosocial measures.

If quality of life measurement is to be a more regular feature of clinical trials of medicines, two principles should be established. First, researchers should be encouraged to use at least one of the well-known general health status measures, such as the Sickness Impact Profile,[8] the Nottingham Health Profile[9] or the Index of Wellbeing.[10] This is because such measures have already been validated on a number of populations and their further use in clinical trials may enable comparisions to be made across a range of health care interventions. Researchers may in addition wish to use another, condition-specific, measure in case the general health status measure fails to detect small, but clinically important, differences.

Secondly, researchers should attempt to explore the relationship between changes in quality of life (as measured by the various instruments) and changes in the 'standard' clinical indicators for the condition concerned. As more

evidence on convergent validity, or lack of it, is assembled, this would form a better basis for judging both the quality of life measures themselves and the signs and symptoms typically used in clinical practice.

The quality of life measure of particular interest to economists is the health 'utility'. The utility values for health states, on a scale from 1.0 (healthy) to 0.0 (dead), can be combined with survival data to calculate the *quality-adjusted life-years (QALYs)* gained from a health care intervention. The form of economic evaluation which measures benefits in terms of QALYs, called *cost-utility analysis*, has been gaining popularity in recent years.[11] A recent development has been the construction of 'league tables' of health care interventions in terms of their cost per quality-adjusted life-year gained.[12 13] The object is to inform the debate about health care priorities.

So far no cost-utility analyses of drug therapy have been published. However, a utility measure was used in a recent multicentre trial comparing auranofin with a placebo for rheumatoid arthritis patients.[14] The utility measurement instrument was administered in the fifth month of the trial and a change score derived from the patient's comparisons of baseline and current states. The patients in the treatment group showed a significantly higher change score ($p = 0.002$). The next step would obviously be to use these data to calculate the cost per quality-adjusted life-year gained from therapy.

As more utility measurements are made on different populations and by different methods; a number of key issues are beginning to emerge. For example, Torrance[15] has examined the validity, reliability, precision and ease of administration of the most frequently used measurement methods (rating scale, time trade-off and standard gamble). A major finding is that while individual assessments of utility vary from person to person, group means, which are required for most applications, are fairly stable with acceptable standard errors.

The issue of whether different populations would produce different rankings of health states has recently been investigated by Balaban *et al.*[16] They compared the weights (values) that were derived for the Bush quality of well-being scale from a general population sample with those of a disease-specific population composed of patients with moderate and moderately severe rheumatoid arthritis. A close agreement was found between the two groups ($R = 0.937$).

Another issue, which has not yet been resolved, is that different measurement methods can yield different utility values. In a recent study Buxton *et al*[17] compared the index developed by Rosser in the UK[18] with the time trade-off technique which is popular in North America. Taking, as an example, health states relating to breast cancer, the Rosser approach consistently gave utility values significantly higher than those from the time trade-off approach.

The existence of these differences does not necessarily raise a question mark against utility measurement *per se*. Indeed, in such a difficult area of measurement it would be surprising if there were close agreement between instruments. Rather, it is important to be aware of these differences when making comparisons across studies with different methodology. Indeed, in constructing league tables of health care interventions in terms of their cost per quality-adjusted life-year it should be remembered that there are potential methodological differences in the calculation of costs which may have a more profound impact on study results than the choice of utility measurement technique.[19] These include methodological decisions on the range of costs to be included, the apportionment of joint costs, and the inclusion, in the cost-benefit model, of production gains and losses or medical care costs in added years of life. For a detailed treatment of these and other methodological issues see Drummond *et al.*[11]

Estimating health benefits in money terms

Before the gain in popularity of cost-utility analysis, economists had the choice either of undertaking a *cost-effectiveness analysis*, where the benefits of the health care intervention were expressed in the most convenient natural units (eg, years of life gained or cases successfully treated), or of undertaking a *cost-benefit analysis*, where attempts were made to express the benefits in money terms.

Cost-benefit analysis is therefore the broader form of analysis, with the potential to assess whether the total sum of benefits from an intervention is greater than its cost. However, the approach has fallen into disrepute over the years because of the difficulties of expressing the intangible benefits of improved health in money terms. This has meant that the benefits considered in most cost-benefit studies have been limited to savings in health care resources and savings in lost production. There is no evidence that these are closely related to the benefits to individuals from improved health *per se*.

This issue has recently been returned to in a study by Thompson.[20] He used specially trained interviewers to ask 247 subjects with rheumatoid arthritis how much of their income they would pay and how large a mortal risk they would accept to achieve a hypothetical cure. Ninety-eight per cent of the subjects estimated their maximum acceptable risk at an average 27 per cent chance of immediate death. Eighty-four per cent gave plausible responses to the willingness-to-pay (WTP) questions, with a mean of 22 per cent of household income.

Such studies do have the advantage of giving direct financial estimates which could be used in decision-making about the reimbursement levels of new drugs, devices and procedures in health care. However, in order to assess their reliability there would probably need to be studies in a number of fields and some investigation of whether respondents perceive the potential uses of the estimates, thereby influencing the values they give. Given some of the problems with asking individuals to value states of health in money terms, rather than relative to one another (the utility approach), calculations of cost per QALY probably have more credibility at the present time.

Deciding whether to incorporate economic measurements in clinical trials

A few years ago Drummond and Stoddart[21] argued for the more frequent incorporation of economic measurements in clinical trials. They laid down criteria for deciding which trials would be candidates for incorporating economic analysis and suggested a 'phasing policy' for the analysis to minimise unnecessary work. (eg, It would not make sense to perform economic analysis of therapies that were unlikely to be adopted because they were ineffective.)

These suggestions were borne out of the frustration of those economists that have been asked to undertake an economic evaluation after the clinical trial has been completed. For example, Culyer and Maynard[22] found that although a large number of trials of cimetidine had been carried out, none provided a suitable foundation for their study. The existing trials either evaluated inappropriate alternatives (such as a placebo which was unlikely to be

administered in actual medical practice), were not well controlled, were too small, or included an inadequate range of measurements of the 'success' of therapy and resource consequences. Now that there is more experience of undertaking economic analysis alongside clinical trials, including some of drug therapy,[23] it is time to re-examine this issue.

With regard to the measurement of the 'success' of therapy, it is clear from the discussion above that a broader range of measurements is now being considered, including quality of life scales and utility measurement. These changes will themselves assist economists wishing to perform subsequent analyses.

However, there seems to be less work on estimating the resource changes associated with new therapy. There are probably a number of reasons for this. Those undertaking trials may have neither the inclination nor skill to make the measurements, estimation of economic costs and benefits is not a formal requirement in the pricing and registration of new drugs in most countries, and costs observed during the trial stage may be atypical of those observed later.

Against this needs to be balanced the fact that, despite the lack of *formal* requirement to demonstrate economic benefit from new medicines, economic considerations are increasingly important to those managers and clinicians deciding on the allocation of health care resources. Also, although costs observed during the trial may be atypical of those observed later, frequently the economist researcher trying to perform a retrospective analysis has *no* data to go on.

Therefore, it seems that a sensible middle course can be steered, by collecting basic data on resource consumption during the trial, or series of trials, which would form the basis for a subsequent economic analysis. It would be particularly important to collect data that would be costly or difficult to obtain later, such as length of hospital stay by category of ward, details of expensive investigations performed, place of hospital discharge and, if discharged home, details of ambulatory care given. At the end of the trial or series of trials, if it were clear that the clinical performance of a new therapy were satisfactory, it would then be possible to harvest the economic data. In doing so the economic analyst would obviously have to be conscious of any differences between the trial situation and the application of the therapy in practice. In addition, as was mentioned earlier, one might want to reappraise the situation after a time when the indications for use of the therapy have changed and when it is being used by clinical practitioners of different levels of skill.

It is likely that economic evaluations will be more often performed alongside clinical trials of medicines in the future. As more evaluations are performed a number of practical issues will be resolved. These include selecting the most appropriate trial or trials alongside which to undertake economic evaluation, minimising the inconvenience for clinical researchers without compromising the quality of the economic data, interpreting cross-national differences in costs in multicentre trials and finding the best way of reporting the economic results alongside the clinical trial results.

Concluding remarks

This paper has highlighted a number of current measurement issues in assessing the costs and benefits of medicines. It is noticeable how, over the years, many of the methodological problems in economic evaluation in health care have been resolved. Therefore it is likely that those issues raised here will be tackled and resolved by closer collaboration between clinical and economics researchers in the future.

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New attitudes in assessing benefits

Jeremy Hurst

The main differences between medical care in Britain in the late twentieth and late nineteenth centuries spring from the growth of knowledge. The doctors and nurses are much the same kind of people. The patients are much the same kind of people, too, although the pattern of disease has changed and the expectation of life has improved. A good many of the hospital buildings which the Victorians used are still in use today. What has changed out of all recognition is medical technology. The development of powerful and effective medicines is one of the most important examples of this.

There is something else which has not changed much. It is scarcity of resources. True, we have a higher standard of living than the Victorians had. We employ more people in the medical care sector than they did. Nevertheless, as industrialised nations go in the late twentieth century, we enjoy only moderate prosperity – behind the US, Canada, Japan and no less than eight of our West European neighbours in terms of real per capita GDP.[1]

Given the sizeable benefits (and costs) of modern drugs, the market for pharmaceuticals is an important one. Most of the production and marketing of medicines rests in the hands of private companies (often multi-nationals) as does most of the research and development (R and D) expenditure devoted to discovering new drugs. Most prescription medicines in Britain are purchased through the tax-funded NHS and a substantial contribution towards the costs of R and D is included in the pharmaceutical bill. This means that public policy in the drugs field has to wrestle with at least three conflicting objectives:

i) the desire to improve the health of the current population (which entails concern for the safety and efficacy of drugs);

ii) the desire to develop better medicines through R and D; and

iii) the desire to limit the burden on those who pay for current medicines and research – ultimately, the consumer and the tax-payer.

Of course, we have evolved institutions over many years which aim to meet these objectives. Patents are granted for new medicines. If these are to be marketed they have to be licensed and the licensing procedure concentrates on their safety and efficacy.[2] Doctors have considerable clinical freedom to prescribe medicines for their patients under the NHS according to a fairly open-ended budget if they are general practitioners but with cash limits in the background (or foreground) if they are hospital doctors. Individual, new patented medicines may command a considerable premium on their price in the UK if they are successful because companies have much commercial freedom to charge the price that the market will bear. However, the Pharmaceutical Price Regulation Scheme (PPRS) constrains the overall level of profit that a company can make on its NHS sales to a level which the Government considers to be reasonable.

There are several key sets of decisions that have to be taken regularly within this framework. The Government has to decide on overall spending limits for the NHS. Individual doctors have to make prescribing decisions. Drug and therapeutic committees have to discuss prescribing policies and may decide on formularies. At the same time, pharmaceutical companies will make marketing and pricing decisions for existing products. And the same companies (or some of them) will develop R and D strategies. For resources not to be squandered, it is highly desirable that these crucial decisions are informed by a good understanding of the costs and benefits (or potential benefits) of the various choices on hand.

The main purpose of this paper is to argue that there is some room for improving the quality of the cost effectiveness information that is brought to bear on these decisions, particularly decisions about prescribing policies in the NHS. There is a case for better health technology assessment and economic evaluation in the drugs field. More specifically, there is a case for better ways of measuring the benefits of newer (and older) medicines, in terms of the improvements that they bring in the health of the population.

Part of the reason for arguing this case is that there have been important new developments in the methodology and measuring techniques of health technology assessment recently. These developments have been documented admirably by the Office of Health Economics.[3] [4] [5] The randomised, clinical, controlled trial has been at the heart of clinical evaluation for some years. Increasingly, cost effectiveness studies have been carried out which have enhanced the message of certain trials by including the NHS (and sometimes private) costs of therapies. But perhaps the most important development has been on the benefit side. It is the use of general indicators of health status to compare the health outcome of alternative therapies according to a common unit of account. These developments give us, at least in principle, a measuring rod of therapeutic value for money: health per £.

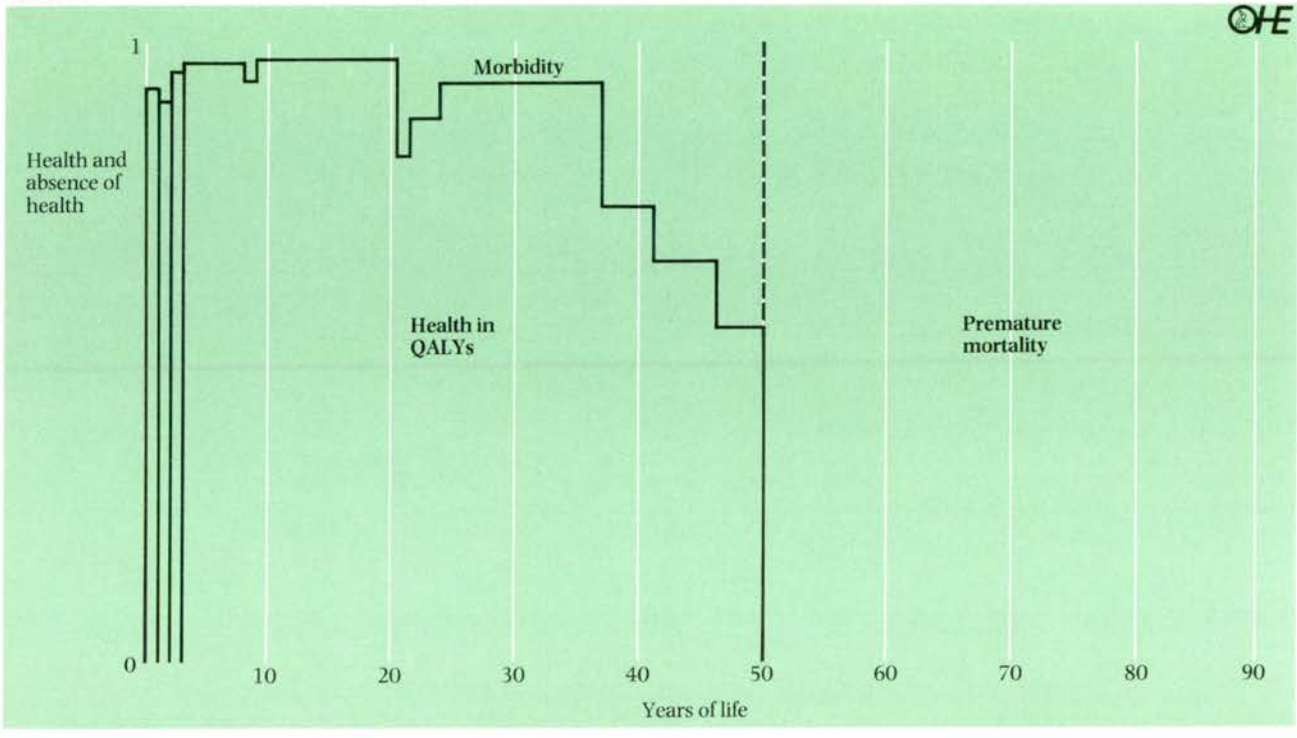
But how do we measure health? There are two leading approaches: health profiles and global indicators. The health profiles – of which the Nottingham Health Profile is the leading British example – rely on patients rating their state of health at any moment along 6 dimensions (energy, pain, emotional reactions, sleep, social isolation and physical mobility). This permits a six-fold assessment of changes in 'qualify of life'. An excellent example of the use of this indicator in a clinical evaluation is the study of heart transplants by Buxton *et al.*[6] The health profiles represent an important step forward in quantifying health. However, they do not solve the problem of weighting or valuing the different dimensions of health and mortality to provide a single index. This bold step is taken in the construction of the more ambitious global indicators of which the best known version is the 'Quality Adjusted Life Year' or QALY.

The idea of the QALY is simple. A year in perfect health is assigned a value of 1. Death is assigned a value of 0. A year impaired by some disabling or distressing condition is assigned an appropriate value, usually between 0 and 1, depending on severity, but it seems that there are a few states worse than death, such as irreversible coma. The course of an individual's health through his or her lifetime may be calibrated in QALYs (Figure 1). Such a diagram provides an unambiguous numerical measurement of health, morbidity and premature death. The aim of health services, of course, is to minimise the areas representing morbidity and premature mortality.

The first British QALY estimates have been made with the aid of a global indicator developed by Rosser and Kind.[7] It should be pointed out perhaps, that this indicator rests on a health profile with 3 dimensions – disability, distress and death. The additional step has been taken to weight these dimensions by seeking relative valuations for *combinations* of 8 disability states, 4 distress states and death.

 The author is grateful to several colleagues for comments on an earlier draft.

Figure 1



Where do the essentially subjective valuations come from which enable us to calibrate QALYs? The answer is that they can be obtained by soliciting the judgements of ordinary people, nurses or doctors about the relative value of health states. Rosser and Kind's values were obtained by careful questioning of 70 respondents about the relative desirability they attached to combinations of disability and distress (and death) followed by scaling and averaging of the results. Figure 2 shows the matrix of values which was obtained.

Provided that an individual's health can be assigned at intervals to one of these 29 disability/distress states or death, then we have an unambiguous way of comparing the health effects of alternative therapies. Of course, it requires clinical trials, or some adequate substitutes, to establish the effect of the alternative therapies on disability and distress for the patient through time. This is illustrated in a stylised fashion in Figure 3 where it is assumed that the line NN shows the natural history of some disease which has afflicted the individual at age 37. It is assumed that if the individual is treated with therapy A then he/she will pass through various disability distress states and his/her health will follow, typically, the path AA. If he/she is treated with therapy B then his/her health will follow, typically, the path BB. Clearly, therapy B is preferable to therapy A in terms both of length and average quality of life but note that the *initial* quality of life under B is less favourable than under the natural history of the disease or under A. Trade-offs between the beneficial and harmful consequences of therapies abound in medicine and QALYs provide a way of weighting them. Of course, there is usually uncertainty about health outcomes before the event so it is usually necessary to consider various paths for any one treatment and to attach probabilities to each.

If we want to value health outcome for more than one individual, we have to make additional value judgements about aggregating QALYs. The convention usually adopted, so far, is that one QALY is of equal value to all individuals irrespective of age, sex or social status. This convention embodies a strong value judgement, broadly consistent with the egalitarian aims of the NHS. Some recent research, however, suggests that many ordinary people put a premium on the value of health for parents with dependent children.[8]

Figure 2 **Rosser/Kind valuations of states of health.**

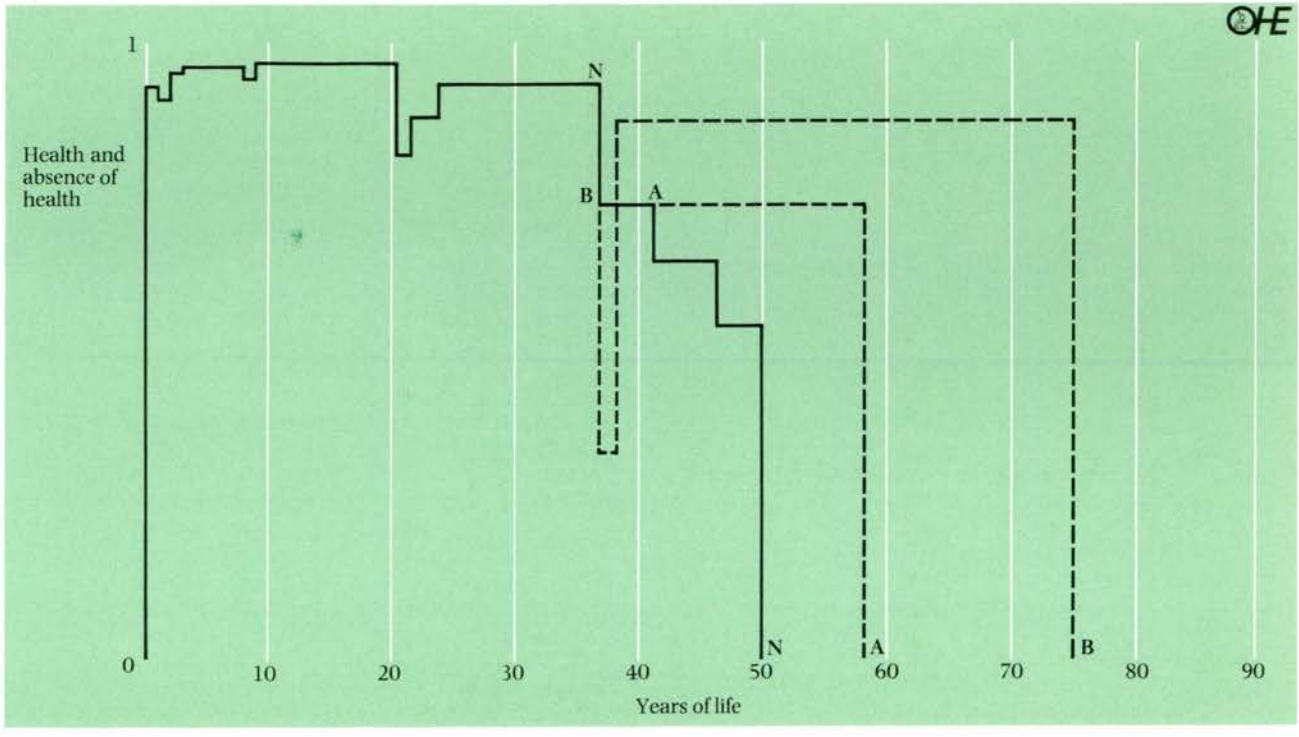
	Distress rating			
Disability rating	*1 None*	*2 Mild*	*3 Moderate*	*4 Severe*
1. None	1.000	0.995	0.990	0.967
2. Slight Social	0.990	0.986	0.973	0.932
3. Severe Social, Slight Work	0.980	0.972	0.956	0.912
4. Severe Work	0.964	0.956	0.942	0.870
5. Unable to Work	0.946	0.935	0.900	0.700
6. Chair Bound	0.875	0.845	0.680	0.000
7. Bed Bound	0.677	0.546	0.000	−1.486
8. Unconscious	−1.028	—	—	—
Dead	0.000	—	—	—

Source:
Kind[7]

It is necessary, of course, for us to measure the costs of treatment 'A' and treatment 'B' to enable us to measure 'health per £' or 'therapeutic value for money'. It is also desirable to discount future benefits (in QALYs) and future costs because people prefer to enjoy benefits and to avoid costs sooner rather than later.

So far, tentative QALY per £ estimates have been produced for only about 20 therapies in Britain using the Rosser/Kind matrix. They should be regarded as experimental estimates because of the experimental nature of the

Figure 3



health index on which they rest. In most cases, they rely on partial evidence from clinical trials, combined with medical judgement. Costings are usually rather rough, because the NHS does not produce patient costs routinely, and are confined to expenditure incurred by the NHS.

Figures 4 and 5 show estimates of QALYs gained, discounted total costs of therapies and cost per QALY prepared by Williams[9] for a Consensus Conference on Coronary Artery Bypass Surgery (CABG) and by Gudex[10] for the North Western Regional Health Authority (NWRHA), respectively. The estimates are intended to measure the *differences* in benefits and costs between the therapies concerned and the best alternative therapies. The calculations by Gudex are particularly interesting because they were commissioned by the NWRHA to assist in choices between competing bids for funds for regional medical specialty developments.

Despite certain inconsistencies in the estimates for similar therapies, both tables suggest that there are major differences in 'value for money' between therapies. This suggests, that if the therapies offering higher value for money were expanded, and those offering lower value for money were held back, more health would be generated for a given budget. This does not mean that inexpensive therapies should be expanded indefinitely. It is highly likely that the law of diminishing returns operates for medical therapies, just as it operates (demonstrably) for other productive activities. If so, the value for money of therapies which are expanded will diminish at an accelerating rate and the value for money of therapies which are contracted will increase at a decelerating rate.

Some evidence that this might be so for CABG was collected by Alan Williams. It seems that the gain in health from giving coronary artery patients surgery instead of drugs will decline as surgery is made available to patients with diminishing angina and diminishing anatomical severity of coronary artery disease.[9] Indeed, it is suggested

Figure 4 **QALYs gained, costs and cost per QALY for various therapies**

	QALYs gained per patient (discounted)	*Discounted total costs (£,000)*	*Cost per QALY (£,000)*
Haemodialysis in hospital	5	70	14
Haemodialysis at home	6	66	11
Heart transplantation	4.5	23	5
Kidney transplant (cadaver)	5	15	3
Valve replacement for aortic stenosis	5	4.5	0.9
CABG for severe angina (with left main vessel disease)	3.5	2.85	0.8
Hip replacement	4	3	0.75
Pacemaker implantation for atrio ventricular heart block	5	3.5	0.7

Source:
Williams[9]

that there will be no gain on average for patients with mild angina and occlusion of one peripheral vessel.

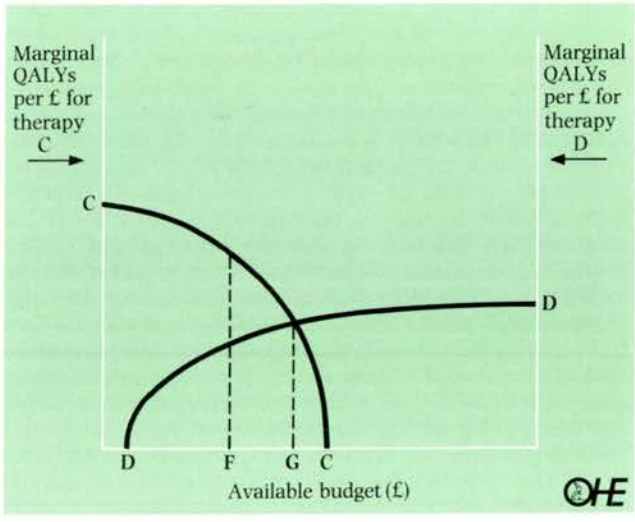
If there are diminishing returns to therapies, we should try to equate their marginal health returns per £. This is illustrated in a simplified way in Figure 6, where it is postulated that a fixed budget, shown on the horizontal axis of the diagram, is to be shared between just two therapies: C and D, whose marginal QALYs per £ are shown by the curves CC and DD respectively. CC should be read from the left-hand vertical axis and DD from the right-hand vertical axis. It is assumed that the unit costs of the two therapies remain constant as they are expanded or contracted. Suppose that we start with the division of the budget shown at F. Therapy C yields considerably more marginal QALYs

Figure 5 **QALYs gained, costs and cost per QALY for various therapies**

	QALYs gained per patient (discounted)	*Discounted total costs (£,000)*	*Cost per QALY (£,000)*
Peritoneal dialysis (4 years)	3.4	45.7	13.4
Haemodialysis (8 years)	6.1	55.4	9.1
Treatment of cystic fibrosis with ceftazidime (over 22 years)	0.4	3.3	8.2
Kidney transplant (lasting 10 years)	7.4	10.5	1.4
Shoulder joint replacement (lasting 10 years)	0.9	0.5	0.6
Scoliosis Surgery			
– idiopathic adolescent	1.2	3.1	2.6
– neuro muscular illness	16.2	3.1	0.2

Source:
Gudex[10]

Figure 6



per £ than therapy D at this point. If we transfer, say, £1,000 from therapy D to therapy C, the gain in health from C will exceed the loss in health from D. It will pay to expand therapy C and to contract therapy D until their marginal returns are equalised, at point G on the horizontal axis. In this way, more health can be generated for a given budget. There will be gainers and losers among patients but the gains will outweigh the losses according to the values embodied in the QALY index and the egalitarian ethic set out above.

Notice that costs play just as important a role as do benefits in this analysis. All the 8 therapies listed in Figure 4 generate similar benefits per patient but their value for money differs by a factor of 20 because their costs differ so sharply. When there is a fixed budget – or more generally, scarcity of resources – spending more on one therapy means spending less on another. Costs are foregone benefits. To be efficient, it is not enough just to show that a therapy is beneficial. It should be *at least* as beneficial as the alternative therapies which could be provided with the resources. Costs matter hugely in such comparison. Yet, as we shall see below, they are still frequently neglected in clinical literature.

It would require a vast amount of epidemiological and evaluative knowledge to measure the curves sketched in Figure 6 for just two therapies; let alone for thousands of therapies. Fortunately, there is no need to fill in the whole picture before we can start to use estimates of £ per QALY. Information of the kind found in Figures 4 and 5 is sufficient to tell us whether we have reached an optimum allocation of resources, or not, and if the laws of diminishing returns apply, the direction in which the optimum lies will be clear. It will be a matter of trial and error to adjust the marginal allocation of resources towards the optimum.

This framework allows us to explore, at least in principle, the effect on the recommended allocation of resources of a number of external changes such as: technical advances, changes in the incidence of disease, changes in the cost of providing therapies and changes in budgets. All of these will tend to shift the curves, or the relationship between them and suggest a new optimum allocation of resources.

Of particular interest, in the context of this paper, is technical advance. A genuine therapeutic advance substituting, say, for therapy C, will shift CC upwards, suggesting a new equilibrium to the right of G. Obviously, we should spend more of a fixed budget in a particular clinical area if a major technical advance comes along. But important technical advances may also cause us to want to relax the overall budget constraint because demand will be affected. The pharmaceutical budget in the Family Practitioner Services is fairly open-ended and is often described as 'demand-led'. Much of the annual rise in this budget can be traced back to the introduction of new drugs for which therapeutic advances are claimed and for which premium prices tend to be charged. In the hospital service it is a little different because of cash limits. But even here an extra ½ per cent per annum is usually set aside nationally for new medical advances. Clearly, economic evaluation in general, and QALYs in particular, could play a role in gauging the benefits and costs of new therapies and assist in budgetary decisions, here.

At this point, it seems important to emphasise that QALY per £ estimates would be likely to act, at best, as only one influence on decisions about resource allocation in the NHS. Clinical, administrative and political judgements will continue to play a part. The question posed in this paper is whether such decisions should not be informed by better evidence on the cost effectiveness of therapies. In a recent paper Alan Williams has made a number of interesting suggestions about just how QALYs might be used to inform NHS decision making.[11]

Although the 'QALY per £' methodology seems to represent a useful advance in techniques of evaluation, it has been stressed above that it should be regarded as experimental. Clearly, there is room for improvement in the clinical trial evidence upon which it rests and the quality and scope of cost estimates. But the most important area for development is certainly the QALY itself because this is the newest and most controversial part of the method.

There are perhaps three elements of the QALY methodology which require further research and development: the description of health states; the valuation of these states; and aggregation of QALYs across individuals. Arguably, the last of these is a matter mainly for politicians, health authority members, clinicians and others who will eventually decide on the allocation of resources and it can, in a sense, be left till later. The most urgent priority would seem to be for further work on the first two elements. We need to know more about how ordinary people describe and classify health states and about how these descriptions

relate to the classifications used by clinicians. Also, we need more work on the elicitation of relative values for these health states from ordinary people and professionals. There are several different measuring instruments, here. They have been reviewed admirably by Torrance, recently.[12] Already, there is British work suggesting that the choice of instrument may affect the values derived.[13] Once we have decided which instrument (or instruments) we prefer we should presumably try to elicit the valuations of a large and representative sample of the population of ordinary citizens, patients and professionals (the values offered by these different groups may not agree). Clearly we need to base valuations on the views of more than 70 respondents.

How might all this relate to medicines? Medicines seem to be a particularly suitable subject for economic evaluation of the kind outlined above. There have been many major pharmaceutical advances in the past and, despite some signs of a slackening in the rate of advance, there is still a high rate of innovation. As mortality rates have come down, the emphasis has switched from finding new medicines to prolong life, to finding new medicines to improve the quality of life for sufferers of chronic diseases. There is a well developed infrastructure of clinical trials – concentrating, admittedly, mainly on safety and efficacy questions. Lastly, the Government remains concerned about costs and about finding the resources to finance improved standards of medical care.

Yet there seem to be few examples of good *economic* evaluations of medical therapies and still fewer which have used a QALY methodology. The oft-quoted, 1982 study[14] by A J Culyer and A K Maynard of 'the cost effectiveness of duodenal ulcer tratement' is characterised by a strong economic approach but it does not make use of a general index of health status. A recent publication on a B blocker[15] possesses somewhat similar merits and limitations. Recently, there seems to have been an upsurge of interest in using quality of life measures in pharmaceutical trials. Although this is a valuable development, most of the attention seems to have focused on health profiles, which do not allow us to weigh, say, an improvement in quality of life against, say, a deterioration in mortality. Also, costs are rarely mentioned in these trials. For example, a recent study of 3 anti-hypertensive agents was reported in the *New England Journal of Medicine*.[16] Pioneering use was made of a number of indicators of quality of life. The conclusions about quality of life were unambiguous, in this instance, because the highest scoring drug of the three dominated the next highest scoring drug on all measures of quality. However, there was no mention of costs. According to MIMS, neither the highest scoring nor the next highest scoring drug is hugely expensive in Britain. Nevertheless, at current price levels the highest scoring drug costs up to 40 times as much per day as the next highest scoring. Moreover, since the trial suggested that the highest scoring drug does not control blood presure as well as the next highest scoring, it would be necessary to supplement the use of the former with diuretics more often than that of the latter. All of this leaves crucial questions about *marginal* benefits and *marginal* costs unanswered.

The most impressive use of health status measures in a drug trial is found in the recent study which compared Auranofin with placebo.[17] A whole battery of health status measures was applied in this large multi-centre trial, including a QALY measure, based on the American 'Quality of Well Being Questionnaire'. Auranofin was shown to be significantly better than placebo over a 6 month period according to most of the measures of quality of life employed in the trial. In particular, whereas the QALY index was unchanged in the placebo group there was a statistically significant improvement from 0.599 to 0.622 in the Auranofin group. This could be expressed as a gain of 2.4 QALYs per 100 patients. Although this trial must surely represent the current, 'gold' standard, for the application of health status measures in a pharmaceutical trial, it is not (yet) a serious contender as an outstanding *economic* appraisal because the published report makes no mention of costs. Also, it is not clear, at least to the layman, that placebo would be the next best therapy.

In addition to looking at some recent pharmaceutical trials which have made pioneering use of health status measures, we decided to make a quick survey of the clinical literature concerned with a particular therapeutic field to try to gauge how far short, if at all, some more routine evaluations of medicines fell from the 'QALY per £' ideal. We chose the area of non-steroidal anti-inflammatory drugs (NSAIDs) because these are aimed mainly at arthritis, a chronic, non-fatal disease, and they account for over 10 per cent of the GP pharmaceutical bill.

A computerised literature search targeted on one of the major NSAIDs, Ibuprofen, yielded 120 articles. At least one of these contained detailed information on comparative changes in disability and distress, which would have permitted use of the Rosser/Kind index, given access to the original trial data. This was mildly encouraging. What was less encouraging was that not a single one of these articles made any mention of the costs of therapies.

Pursuing this theme, we looked at a recent issue of the *Prescribers Journal*[18] which dealt, in a 3-part feature, with the treatment of arthritis. This contained what appeared, to the layman, to be a lucid account of the role of various NSAIDs in the management of arthritis but apart from a remark that there is no 'best buy' among NSAIDs it made no mention of costs. Rather it stressed the variability of individual patient responses to different drugs.

The *Drug and Therapeutics Bulletin*, however, is well known for its comparisons of the benefits and costs of drugs. The last time that it dealt with NSAIDs[19] was in 1981. It also stressed the variability of patient response to different drugs, and it pointed to conflicting evidence from clinical trials about the average efficacy of these drugs. However, it ended up by highlighting the wide differences in costs between NSAIDs which, at that time, ranged from £1.00 to £15.80 for a course of treatment lasting 30 days. It concluded that, 'Despite their similarities in trials, patients' responses to different drugs vary widely and it is often worth finding the best for each patient by a process of trial and error, starting with a cheap drug'.

We looked at some of the *Newsletters* of the Regional Drug Information Services. Judging by those we saw, these contain reviews of the literature on the relative efficacy of pharmaceuticals, information on the cost of each drug for a specified period, and tentative recommendations about 'best buys', very like the *Drug and Therapeutics Bulletin*.

We noted, however, criticisms of the quality of many clinical trials of drugs in a report[20] of a recent pharmaceutical conference. J M Smith listed 8 common weaknesses in trials and he selected for particular mention the inadequate sample size and/or duration of many drug trials.

We are inclined to conclude, on the basis of this admittedly hasty and selective dip into the clinical and pharmaceutical literature on drug evaluations, that there is a considerable gap between the type of evaluations available to doctors and pharmacists currently and the methodology sketched out in this paper. The main differences might be

summarised as follows:

i) There are copious numbers of clinical trials but their quality is not always good.

ii) The great bulk of clinical trial reports make no mention of costs. This is understandable pre-marketing, but questionable post-marketing.

iii) There are hardly any signs yet that global health indicators have been taken up in evaluations in the pharmaceutical field. This is not surprising in view of the recent development of such indicators and their ambitious and experimental nature.

iv) However, there are encouraging signs that health profiles are being taken up by some pioneers and these may form a stepping-stone on the way to QALYs.

v) Most drug evaluations consist of comparisons within a given therapeutic area. There are few studies across therapeutic areas and few comparisons of drug therapies with non-drug therapies.

vi) Although there are some excellent attempts to provide impartial surveys of the clinical literature for doctors these are inevitably handicapped if the quality of trials is lacking.

vii) Although some impartial surveys contain information on costs, this seems to be confined to ingredient costs. The average costs of dispensing are not covered, let alone other NHS (and private) costs that might be associated with, or averted by, particular courses of patient management.

So far, we have stressed the search by the NHS for drugs which provide therapeutic value for money. This means that we have concentrated mainly on the first and last objectives of public policy, set out at the beginning of this paper: the desire to improve the health of the current population; and the desire to limit the drugs bill. But what about the second objective: the desire to develop better drugs through R and D? Would adoption of the '£ per QALY' methodology help or hinder the attainment of this objective?

The patent system is designed to give innovators temporary monopolies of new products which, if successful, will yield exceptional profits which, in turn, will provide an incentive for further innovation and will help to pay for R and D. The price of successful new drugs typically starts at a considerable premium over production costs. This premium is then eroded as proprietary imitators enter the market with close substitutes, before the expiry of the patent, and proprietary and generic imitators enter the market with perfect (or near perfect) substitutes after the expiry of the patent.[21] Under the Pharmaceutical Price Regulation Scheme (PPRS) companies have freedom to set commercial prices for individual drugs. However, the PPRS sets a ceiling on the profits that a drug company can make on the whole range of its drug sales to the NHS. It also sets limits for allowable R and D expenditure under the scheme or, rather, provides for it to be negotiable. The ratio of allowable R and D expenditure to NHS sales would not normally be allowed to fall below the ratio of a company's worldwide R and D expenditure to worldwide sales. It is, in practice, often set some way above that level.

There seems no reason why the '£ per QALY' methodology should hamper the incentive for pharmaceutical companies in general to conduct research, or their ability to pay for R and D under the PPRS. The initial aim in applying the methodology would be to sharpen the perception of prescribers about the benefits and costs of drugs. To the extent that this was successful, it would tend to boost the sales of drugs productive of QALYs, and/or productive of cost savings, and hinder the sales of drugs less successful in these respects. This, in turn, might affect the marketing and pricing strategies of companies. The rewards of innovation would tend to be directed towards those companies producing significant therapeutic advances, *according to the values ordinary people put on health states*, and/or those companies producing cost-saving drugs. In this way, signals would be sent to companies which should help them in devising more useful and, hence, more profitable research strategies in future.

If the '£ per QALY' methodology were to be adopted as the language of health technology assessment it would be in the interests of pharmaceutical companies themselves to commission trials and evaluations in the language. It might be seen as an appropriate aspect of pharmaceutical R and D to assess (after licensing) the incremental health and economic consequences of new drugs. Of course, economic evaluations would not be costless and there would be a continuing need for economy in drug trials. The challenge might be seen as using the *existing* resources devoted to pharmaceutical evaluation to better effect. The '£ per QALY' methodology seems to offer a way forward, here.

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Assessing the cost and benefits of pharmaceutical research

A J Culyer

Most of those who have ever undertaken it would agree that the appraisal of medicines using a cost-benefit framework is no easy task. Appraising *research* leaves all those difficulties intact and adds a new set: evidently a part of the benefits of research are the net benefits of the medicines that may result from it, but to those are added the need to appraise other spin-off benefits from research and the need also to take account of research costs and the relatively distant and highly uncertain nature of the net benefits that may – or may not – be seen to warrant research entrepreneurship.

The main difficulties in evaluating medicines

Cost measurement It has become a commonplace (but is nonetheless true and nonetheless frequently forgotten for that) that the definition and measurement of cost depends on one's perspective (a cost from one may be a transfer from another; a low financial expenditure from one may be a high cost from another). Moreover, what is a *relevant* average or marginal (sometimes all-too-easy to miss) cost depends crucially on the question that is being asked and the implicit decision context (for example, what is being taken as given and what variable). Getting from expenditures *on* medicines or *on* research to the costs *of* medicines or *of* research is thus a dangerous journey, full of subtle pitfalls, and many fall at an early stage.

Effect measurement The measurement of outcome has – as is well demonstrated in Hurst's and Drummond's papers – come on apace. Again a major message is that effect measurement depends on perspective and context. There are some useful methods around but they do not substitute for critical thought. They help problem solving by clarifying problem formulation: what is it relevant to measure? what weights are to be applied? whose value judgements should be applied? and so on. They do not provide off-the-peg answers to all questions.

Given the current state of our knowledge of effect measurement it would be disastrous were we to allow the perfect to become the enemy of the merely good. The variation revealed in Tables 4 and 5 of Hurst's paper are surely robust enough to stand quite substantial variations in the guesstimates and uncertainty about value judgements that are sometimes unavoidably embodied in the QALY measures.[1] And let us also remember that the QALY is but *one* of a set of apparently valid and reliable measures of 'effect'.

This common approach to effect measurement appears at the very least to be a useful sorting device for identifying issues that *already exist* (they are not 'invented' by the method) and must, somehow or other, be resolved (or 'buried'). In that connection it is worth being alert to the risk of confounding the *examples* in the literature with the *method* itself. The chances are that, if you are uneasy about some of the numbers generated, it is *thanks to* (not *because of*) the method, which reveals with brutal clarity what people have done (or not done). Less openness may be more comfortable but that is all that is to be said for it – and there is lots to be said against.

Effect attribution Isolating cause and effect is the task of clinical trials. Their design often continues to leave much to be desired. The difference between efficacy in research and best practice conditions, and effectiveness in routine practice, is often unexplored. Too few trials are designed with the purpose of testing for *relative* efficacy or effectiveness and even fewer have cost-benefit elements built in from the beginning (an addition that nearly always has only minor financial implications for the costs of the trial and need add nothing to the time it takes). The interpretational difficulties that arise are well-discussed in Teeling Smith's paper.

Benefit measurement and valuation Recognition is now general that benefits transcend financial factors and are also more than merely negative costs (cost savings) or productivity gains. Work on the *valuation* of health itself, enabling direct comparison with costs, is, however, at the leading edge of the research programme. This is not, of course, to minimise the value of cost-savings work of the sort exemplified here by Wells' paper. If anything, such estimates are made *more* valuable by the absence of more comprehensive data, for they are all we have. For practical purposes, therefore, to answer the questions, when confronted with (reliable) cost-per-QALY (or similar) data: 'is the "programme" worth expanding, maintaining or contracting?' depends still on rather subjective judgements of value (and judgements about value to whom). That is true of such decisions in the doctor's consulting room on behalf of a specific individual. It is also true of decisions made at Region on behalf of groups.

To all of these problems – whose nature is becoming much clearer thanks to the cost-benefit developments of the past fifteen years – one may add two general observations:

- the problems and the (initially esoteric?) procedures for coping with them are not *inherent* in the cost-benefit approach. The problem of choosing exists independently. The *cost-benefit approach* does not require us to choose. Nature does that. It offers, instead, a *way of choosing* – a way, incidentally, that is *altogether independent* of the values and preconceptions of economists!

- the acceptability or otherwise of the approach rather depends on the way it is presented. Presented with sensitivity to the needs and concerns of decision makers at all levels, and with due modesty, it may be seen as a Godsend. With an insensitive presentation and clumsy design, the method may never get off first base, for it may be seen as no more than an alien and inhumane mercenary calculus. Things could be even worse than that. Uncritical acceptance by those who may see the method as an instrument for advancing their own causes (personal or professional) could lead to a 'bottom line' fixation, with the quantified driving out the important, that is the method's very antithesis, and which could turn a Godsend into an instrument of unmitigated evil, fostering the very inhumanity it is designed to destroy.

Additional difficulties plaguing research assessment

Uncertainty and risk People seem to have immense difficulty in grappling with choices involving small probabilities of major disasters. Suppose you deemed a one-in-a-million chance of a Chernobyl in Britain to be an acceptable risk. What benefit, if any, would induce you to accept a two-in-a-million chance of a Chernobyl? What *is* the risk of a Chernobyl in Britain? Has it been increased or reduced as a result of the *actual* Chernobyl? What – as is more (though not exclusively) relevant in pharmaceuticals research – of very small probabilities of major breakthroughs? What of unknowable probabilities? Can they be 'raised' (or the expectation of a pleasant surprise increased) by particular ways of reducing dependence on pure serendipity in research? How risk-averse is it prudent to be? Should the government be more or less risk-averse than the private sector?

How much more do these considerations weigh in the assessment of R than in D?

Potential payoffs Deaths and morbidity by ICD category, likewise life-years or QALYs lost, are poor indicators of the potential payoff to research. They embody implicit (explicit in the case of QALYs) judgements about the relative importance of deaths and sickness episodes that may not be acceptable. They do not include other payoffs (cost-reductions, balance of payments gains, for example). More importantly, they take no account of either the probability of 'success' in research or the 'success' of treatment. Successful research may alter diagnostic procedures without affecting treatment, or treatment without affecting mortality and morbidity, or mortality and morbidity – but at unacceptably high levels of treatment (etc) cost.

Our thinking about the potential payoff to research is primitive – we have scarcely begun to think about it in any formal sense at all (a charge that is, of course, applicable not only in pharmaceutical research). Unaccountably, the private sector seems to me to be as culpable as the public in this regard, for the private sector has a very direct interest in making the best possible assessment of potential payoff, and is strictly unencumbered by the need to go beyond (future) (possible) direct *willingness-to-pay* for the medicines that R and D creates into (future) (possible) *need-to-have* (though *someone* will of course have to be both able and willing to pay!).

Profits, research and regulation Discussion about the moral status of the profit motive has, in connection with pharmaceuticals, scarcely progressed at all in the past 25 years. It may be helpful, in order to relate the cost-benefit approach to questions of profits, research and regulation, to draw some distinctions between the basic ways in which people seem to approach the question of the morality of the profit motive.

The moral standing of the profit motive There are two quite distinctive approaches to the issue of whether (and to what extent) it is morally right to make profits out of pharmaceutical invention and manufacture. One is the 'entitlements' or 'basic rights' approach. According to this, profits (or losses, come to that) are to be sanctioned because they flow from the same basic rights. You can take two quite opposing views of the legitimacy of profits within this general approach. One is exemplified by the argument: 'the procedures we have followed and the risks we have taken have violated no other basic rights and therefore, in exercising our own legitimate rights, the consequences (whether they be profits or losses) are no less legitimate. We therefore have a right to our profits.' The argument is similar to (though not the same as) a desert-based one: '*we* took the risks so *we* deserve the rewards'.[2] The opposing view is 'no one has the right to profit out of another's misfortune so, since sickness is a misfortune, to make a profit out of sickness is not a legitimate right'. What is distinctive about both these opposing arguments (and therefore about this general type of argument) is that the virtues or otherwise of profits are not *consequential*. They do not depend upon the *results* of a profits system – whether the results be good or bad. They are simply derived from prior moral beliefs. They are, in other words, *intrinsic*. Profits are intrinsically either good or bad. They are also immune to defences or attacks based upon a cost-benefit approach.

The other broad approach is consequentialist, or *instrumental*. In this view profits are justified in terms of what they enable to happen: they promote efficiency (good) or inequality (bad); they enable (good) or distort (bad) research; they serve our (good) or your (bad) interests. Profits are thus good or bad according as the results are good or bad (strictly, better or worse compared to alternative instruments). Those who are committed to the cost-benefit approach to life find this approach to an issue like the moral standing of profits quite natural. I detect among the industry's friends and enemies, however, adherents to *both* these broad approaches: 'basic rights' and 'instrumental'.

Regulation Depending on the side you take in the 'basic rights' camp, you will either oppose or support regulation. The instrumentalist will say, however, 'it all depends'. Price and profit regulation of the British pharmaceutical industry is extraordinarily little researched. Its methods are mysterious; its consequences unevaluated in any systematic way; alternatives have never been systematically appraised.

It seems that there are three potentially interesting ways of justifying PPRS. In summary these are:

- by observing that the market 'imperfections' in health care (many of which seem inherent) and in the industry (which may also be inherent in a research based industry) make it *prima facie* inefficient either to advocate marginal cost pricing of medicines or to rely simply on 'market forces'. A 'second best' solution is required that will involve price regulation *at least*. Given the circumstances, then, it is *absence* of regulation that needs justification rather than its presence. (It is possible for *some* forms of regulation to produce *worse* outcomes than no regulation, bad though 'no regulation' may be thought to be, so this argument is obviously not sufficient.)

- by applying the cost-benefit approach to establish as reliably as is possible (or is necessary – whichever is the less onerous task) the costs and benefits of various types of regulatory scheme, taking account of such things as a shadow price on pharmaceutical exports, effects on the rate of innovation, the distribution of costs and benefits over time and for different generations, etc. At the least, this approach will provide an agenda for systematic discussion of the main issues that may be thought to arise and prompt people to think about issues that may otherwise have escaped their attention.

- by applying industrial organisation theory to demonstrate that regulation enables the most cost-effective enforcement of what is effectively a cartel and is, through the control of chiselling and so on, more productive of long-term profit (maximises current wealth in the sense of the present value of equity) than an unregulated industry would be. An interesting aspect of this view is that, since only *particular* interests are represented in it, it will pay them to let it be thought that PPRS does *not* serve their interests and that the industry and the government are at loggerheads (whereas the contrary would be true in this approach). *Are* the industry's skirmishes with government mere shadow-boxing?

Each of these views has some attractive features. It would be nice to see one (*any* one!) of them taken up in the serious (and public) academic and professional literature.[4]

Types of conflict In broad terms there seem to be three main classes of conflict that arise over pharmaceuticals policy (or probably any other): ignorance, positive sum games and zero sum games.

Ignorance Some of the conflict that arises about the industry, its research record, profits, and research into

pharmaceuticals generally, is based upon ignorance – ignorance about the facts, about how 'the system' works and how a modified system might be expected to work. Although the kind of information required to remove these types of ignorance varies, each type shares with the others a depressingly high prevalence and the main sources of information are not usually self-evidently free from the risk of contamination by self-interest. Luce's Appendix in this book is exemplary: that it should be newsworthy at all speaks volumes for the current state of public knowledge of PPRS, while its studied objectivity is rather exceptional.

Positive sum games (PSGs) PSGs are to do with rival claims about efficiency: maximising B over C, QALYs per £, minimising cost per QALY, and so on. Much of the discussion in this book takes place implicitly in the context of a PSG. Conflict can arise either through disagreement about the expected outcomes of the game (policy, treatment regimen, etc) as already discussed and/or because of disagreement about the acceptability of the distribution of gains and losses. In the case of the latter, however, it is a characteristic of PSGs that *net gains do nonetheless exist*. In principle the losers could be compensated. In that sense, the conflict can be resolved. In economics, the archetypal PSG is market trading: gains from trade are positive and voluntariness ensures that *no one* loses (though not all will gain equally). Pareto-efficiency is the outcome. Most cost-benefit studies are content with *potential* Pareto improvements in which not all may gain, but the gains outweigh the losses, and in which better ways of doing things are identified – not necessarily the best way.

Zero sum games (ZSGs) Zero sum games and, *a fortiori*, negative sum games are quite different. Here what one gains another loses – and the losers may lose more than the gainers gain. A PPRS *may* produce lower prices (hence benefiting current patients and current taxpayers) but harm profits (hence harming current equity owners and, possibly, *future* patients as R and D falls and fewer useful innovations come eventually to the market place). Here the losers may lose more than the gainers gain and the PPRS still be judged a good thing on, say, a 'basic rights' view about the immorality of profits or an 'instrumental' view that the re-distributive effects of benefiting the current relatively poor at the expense of the future relatively rich justify it.

As health economists we can hardly take sides in these (political) issues (though we will doubtless have views as citizens). What we *can* do is to attack the ignorance, estimate as best as may be the relevant gains and losses, and attribute them to relevant gainers and losers.[4] In short, we can adopt the cost-benefit approach!

Advocacy and incentives The cost-benefit approach has been mostly applied *in* pharmaceutical R and D rather than *to* it, so it seems highly unlikely that diminishing marginal returns to its application to research questions have yet set in. But even the use of economic modes of appraisal *in* R and D has been slow getting up a head of steam. Some have been provoked to explain this in terms of the lack of incentives: there is some pressure for *effective* medicines, less for demonstrably *relatively* effective ones, but scarcely any at all for *cost*-effective ones.

I conjecture, however, that there are two other possible explanations that cost-benefit proselytes in particular should entertain:

- one is that the advocates of cost-benefit appraisal methods have done a poor job of explaining the virtues of the method, in all due modesty, as a decision-making aid and so have not switched their customers on.
- the other is that the advocates have done so good a job of explaining the so-called virtues of their methods (explicitness of objective, its multidisciplinary nature, its lack of obscurity, the way it opens controversial assumptions to debate, etc) that they have switched the customers off!

Which is it? A good and valuable method poorly put over to the professions, government and industry, or a good and valuable method sold in a fashion that frightens the life out of them?

Either way it seems that the evaluators sometimes miss an important truth: you will never get anyone to adopt (or impose) a procedure unless they are convinced that it is *in their interest* (not in any necessarily narrow or merely financial sense). Analysis must thus not merely avoid a threatening appearance, nor must it be presented as a *neutral* thing. It must be shown to *serve interests*. In particular, it must be shown to serve *dominant* interests. So I conclude that questions about what is *appropriate* (industry spending on R and D, NHS spending on medicines, profits, regulation, patent protection and so on) is always *as a matter of principle* amenable to the cost-benefit treatment; but whether they are also *usefully* dealt with in that way depends upon how well the analysis is designed to address the concerns perceived by the *decision-makers* rather than the *analysts*; their usefulness also depends on how well the presentation is done, in a spirit of collegiate collaboration and for the exploitation of mutually complementary talents, without asserting intellectual hegemony, without immodesty, and without threat. There is a world of difference between analysts joining with decision-makers in industry or government as partners and analysts cavilling and carping from the side-lines. We could do with a bit more of the former.

Notes

1 It is worth emphasising that these approximations are not avoided (let alone improved upon) by other less formal ways. They (and the fact of their having been made) may be *buried* – but that is an altogether different (and sinister) matter.

2 A difference between these two arguments is that if you are claiming to deserve the profit, then you have to establish (which is usually impossible) that no one else can make a similar claim to the fruits of the research (for example, anyone else without whose cooperation profits would have been smaller).

3 The three are not, in the end, necessarily mutually exclusive and each may contain more than merely a germ of the 'truth'. Unfortunately, the 'truth' is hard to define independently of these, or similar, approaches!

4 'Relevant' is used here to emphasise that the scope of gains and losses is not so much a matter for the analysts to determine as for the (legitimate) decision-makers whom they are there to help. Some entities that an economist may identify correctly as costs or benefits may thus be deemed 'not relevant'. This deeming evidently involves making value judgements – which the (legitimate) decision makers are there to make (provided they are there by a legitimate procedure) but which economists have no special claims to make.

APPENDIX

Thirty years of pharmaceutical price regulation: developments in the National Health Service Price Regulation Scheme since 1957

T R H Luce

Introduction

This paper summarises the main developments since 1957 in the schemes administered by the Ministry of Health (MoH) and subsequently the Department of Health and Social Security (DHSS) for regulating or influencing the prices of pharmaceutical products prescribed for National Health Service (NHS) patients. It concentrates on the evolution of the arrangements as negotiated and published in successive versions of the price regulation schemes – the Voluntary Price Regulation Scheme (VPRS) and the Pharmaceutical Price Regulation Scheme (PPRS).

Certain features of the background to the schemes and their administration have remained broadly constant through the period:

(i) price regulation has been the responsibility of the MoH and the DHSS acting on behalf of all the United Kingdom Health Departments, even though pharmaceutical products are procured and dispensed by NHS pharmacies, hospitals and dispensing doctors and not by the central Health Departments themselves.

(ii) the schemes have been negotiated between the MoH or DHSS and the Association of the British Pharmaceutical Industry (ABPI) representing all sections of the industry trading with the NHS.

(iii) successive Governments have had statutory powers (under NHS legislation) to determine the maximum prices of pharmaceutical and medicinal products supplied to the NHS and, under more general legislation, to refer any suspected abuses of market monopoly for scrutiny by the Monopolies Commission, though the former power has never yet been exercised in any individual case.

The following schemes are reviewed:

Voluntary Price Regulation Scheme – versions of June 1957, January 1961, July 1964, November 1969, September 1972.
Pharmaceutical Price Regulation Scheme – versions of April 1978 and October 1986.

The 1957 scheme and its variants

Concern over pharmaceutical costs started in the very early days of the NHS. In 1953, the 'Joint Committee on Prescribing', chaired by Sir Henry Cohen, recommended that certain drugs of no proved therapeutic value should cease to be provided under the NHS, but new drugs of proved therapeutic value should be prescribable, and that existing drugs 'not therapeutically superior to standard preparations' should be prescribable in the NHS 'subject to satisfactory price arrangements with the manufacturers'.

Negotiations between the MoH and the ABPI started in 1954. In 1956 the Committee of Enquiry into the Cost of the National Health Service (chaired by Mr C W Guillebaud) said, in comments prophetic of all future discussions on these issues:

> '493. The whole problem is obviously one of great complexity and difficulty. On the one side, the Departments must be able to feel satisfied that reasonable, and not excessive, prices are being paid out of the public purse for the pharmaceutical products which are being consumed by the National Health Service. The Service is a very large buyer of these products (in some instances virtually the sole buyer) and it is clearly right that the taxpayer should have a voice, through the Department administering the Service, in the prices which are to be paid. On the other side, account has to be taken of the present position and future development of the pharmaceutical industry of this country. Its representatives, when giving evidence before us, pointed out that the industry must be enabled to carry on with its essential work in supplying the Service with its pharmaceutical requirements; to finance research; to attract the necessary capital for further development; and to maintain and expand its valuable export trade. From the production aspect it must be borne in mind that if the National Health Service were unable to purchase at home the pharmaceutical products it requires, the country would have to import these products from overseas, at higher prices in many cases than those ruling in the home market, and with adverse effects on the balance of payments. So far as research is concerned we understand that by far the larger part of pharmaceutical research now being carried out in this country is promoted and financed by the pharmaceutical industry itself; although here there is the important complicating factor that the great bulk of the research carried out in this way is undertaken by a small minority of the firms – chiefly the larger firms in the industry.
>
> '494. Negotiations between the Departments and representatives of the industry have been under way for some considerable period; and there has been public criticism of the delay in reaching agreement. The issues on both sides are, however, large and of great importance; while the Departments have had to feel their way in a new and, for them, largely unexplored field.
>
> We trust that these negotiations will speedily be brought to a definite and mutually acceptable conclusion.'

The negotiations concluded in an agreement promulgated to the industry in June 1957 by the late Tom Williamson who was then head of the MoH's Pharmaceutical Industry Branch.*

The agreement covered new products, in the sense of providing that their prices should be at their manufacturers' discretion for the first three years after introduction. For the remainder, three specific and alternative pricing routes were to be available:

(i) the *export criterion*, applicable to proprietary products where not less than 20 per cent of the manufacturer's output was exported. In these cases, the NHS price should not exceed the weighted average FOB or net wholesale price in the company's six most important overseas markets.

(ii) the *standard equivalent criterion*, for use where there were generic equivalents of proprietary products, and

*This post has always been amongst the most important and demanding at its level in the MoH and the DHSS. Subsequent holders have been Pat Benner, Geoffrey Hulme, Bill Scott-Moncrieff, Drysdale Marks, John Long and (currently) Bernard Harrison.

requiring the proprietary price to be no greater than that of the generic.

(iii) the *trade price formula criterion*, a form of 'cost-plus' calculation, in which a final price was built up from ingredient costs, a fixed 12½ per cent 'on-cost' allowance, and allowances for processing, packaging and wholesale discounts.

There was also a provision under which any manufacturer could opt to negotiate the price or prices of all or any of his products directly with the MoH without any reference, or with only partial reference, to these pricing formulae. But for manufacturers not exercising that option, products meeting the 20 per cent export quota had to be negotiated under the export criterion; products with less than 20 per cent exports had to be dealt with under the 'standard equivalent criterion' if generic equivalents existed, or under the trade price formula if they did not.

The scheme included 17 pages of explanatory notes and appendices, giving examples of the application of the various formulae. An illustration of part of the example for the 'net wholesale price' version of the export criterion formula is annexed.

The MoH Staff Training Journal for June 1957 said of the newly announced scheme:

> 'It is designed not to reduce prices generally but to curb excesses where they exist. While the overall effect on NHS costs is, therefore, not expected to be large, a number of significant price reductions should result, and it is thought that in total these might produce savings of up to £750,000 a year. The scheme is, however, a novel one and no reliable estimate of savings to the Exchequer will be possible until it is actually running – and even then the constantly changing pattern of pharmaceutical demand may mask its effect'.

The Committee on the Cost of Prescribing (chaired by Sir Henry Hinchcliffe) said of the scheme in its 1959 report:

> 'We are informed that by early 1959 prices had been agreed under the scheme for some 3,200 proprietary preparations representing approximately 88 per cent by value of all preparations falling within the scope of the scheme. Negotiations are still proceeding on the remainder. Three hundred preparations had been reduced in price at an estimated saving to the Exchequer of just over £400,000 per annum'.

The 1961 and 1964 versions

These versions retained the framework and most of the provisions of the 1957 scheme. Most of the changes of detail resulted in tighter and fuller definitions of the circumstances in which the 'freedom period' for new product pricing could be enjoyed, or the export pricing criterion applied. By 1964, the 'freedom period' was to be four years for products 'where it can be shown to the satisfaction of the Ministry that substantial and original research work has been carried out', and two years in other cases; but it was not available to products[6] whose active ingredients' have been official (ie, described in the BP or BPC) for five years or more'. The volume quota triggering the application of the export pricing criterion had risen from 20 per cent to 25 per cent, and the version of that formula depending on FOB weighted average prices remained available only in respect of transactions between independent buyers and sellers. In 1961, the MoH was given the option (available under the original scheme only to companies) of insisting on direct price negotiation instead of pricing by the export formulae, though its freedom to use that option was limited to products with annual NHS sales of £500,000 or more and even in such cases it was obliged to take account of any evidence of effective price competition in external markets for the product concerned.

But two new concepts were introduced. The 1961 version provides that where the MoH exercises its option to insist on direct price negotiation over products which would otherwise have been priced under the export price formula 'the Ministry will take into account, on request, a manufacturer's *overall profitability on medical speciality products or on the whole range of drugs which he supplies to the National Health Service*'. This is the first reference in scheme documentation to an aggregated approach to pharmaceutical price regulation.

The 1964 version added another feature which was to become increasingly significant, and which related to aggregates rather than individual product costs. In the 'Basic Pricing Formula' – itself a combination of the original 'trade price formula' and 'standard equivalent' criteria – a *research and development allowance* was added to the various cost allowances (for ingredients, processing, packaging, and wholesale discounts) from which final product prices were built up:

> 'The percentage addition [for research] to the basic formula price shall be the inverse of the percentage of total research expenditure . . . to total sales of medical specialities by the UK supplier and any overseas parent company, branches or associated establishments over the last year for which figures are available; provided, however, that a research allowance shall be made only where this percentage is not less than 3 per cent, and that the allowance should in no case exceed 10 per cent.'

The 1969 and 1972 versions of the VPRS: and the 1978 PPRS

For the first time, the 1969 version of the VPRS put the concept of an aggregated approach to individual companies' profits and costs at the centre of the price-regulatory arrangements. It introduced for all participant companies the requirement to produce an Annual Financial Return (AFR) showing past NHS sales and their associated costs distinguished from other trading activities; and by implication rather than explicitly made profitability expressed as return on capital employed the main instrument of regulation.

The individual product pricing procedures relating to export price and price comparisons in the domestic market were retained, but only as optional points of reference in negotiations on Annual Financial Returns. However, the negotiators evidently still regarded these procedures as having enough importance to agree changes in two respects:

(i) the export quota (20 per cent of sales) necessary to trigger the export price comparison method was redefined to exclude sales in the United States of America – evidence, perhaps, of the growing trade from the UK in that large and unregulated market and the DHSS's concern over its potential impact on NHS prices;

(ii) the more general procedure concerned with domestic price comparisons was glossed thus:

'. . . It is recognised that there may be good reasons for the differences in the prices of such medicines. The degree to which medicines are comparable, and the grounds on which price differentials may be justified . . . will vary and will be a matter for judgement and negotiation between the

parties and agreement on these matters will not be unreasonably withheld.'

The main provisions of the 1969 scheme set in place the basic administrative apparatus on which the scheme still depends. As well as the provision and negotiation of Annual Financial Returns, the arrangements included:

- details of the form in which AFR information should be provided
- the supplementation of AFRs with more recent material on current sales trends
- replacement of the 'freedom period' for new products with a general requirement to satisfy the DHSS that all price increases were consistent with the companies' AFR position, and to give the DHSS a fortnight's notice of intended price increases
- a provision relating specifically to extra-territorial costs.

The scheme's preamble and statement of objectives assumed a form in many respects still recognisable in the latest (1986) version of the scheme, and for the first time a general provision implying a constraint on Sales Promotion expenditure was introduced.

The 1972 version made little significant change. The 1978 version included a number of alterations apparently designed in the main to clarify questions covered implicitly in the 1969 document. Amongst the more important were:

(i) a requirement to provide forecasts of sales for a year ahead as well as returns for the last accounting period.

(ii) more explicit coverage of the negotiating options available to the DHSS and companies in cases where AFRs show profits considered too high by the DHSS. These included price reductions, deferment of price increases and repayments.

The 1986 version of the PPRS

Negotiations on the 1986 version took place towards the end of a period in which some differences of view had arisen between the DHSS and companies over the interpretation of the 1978 scheme in circumstances as they had developed.

Though retaining the essentials of schemes as established in 1969, and in particular the role of return on capital as the main instrument of regulation, the 1986 scheme document gives greater precision and transparency to certain key features:

(i) the arrangements for determining average profitability of participating companies and the definition of the range for settling the profit targets for individual companies are spelt out; as are the concept of the 'Grey area' under which companies may in some circumstances retain profits above target, and the use of a 'return on sales' arrangement in suitable cases.

(ii) an external yardstick for determining changes in average pharmaceutical industry profitability by reference to changes in the average profitability of British industry generally is introduced.

(iii) the position on the pricing of new products, and of line extensions of existing products, is made more explicit.

In addtion, generic preparations are excluded from the scope of the scheme and there is a greater and considerably more concrete emphasis on the need to restrain the growth in NHS pharmaceutical supply costs. Specific procedures are introduced for the year-on-year analysis and negotiation of individual companies' general and administrative costs, manufacture costs and for the regulation, on a two-year rolling basis, of sales promotion expenditure. A new and explicit framework for the negotiation of Research and Development allowances is introduced. New procedures are also negotiated for dealing with any differences of view over transfer prices.

The preamble and introductory sections of the scheme retain much of the material originating in 1969; but new provisions are added for mutual consultation in the event of the aggregate costs of NHS medicines rising significantly faster than general inflation and some limits are implied to the DHSS's obligations in respect of cost rises in the industry.

The formula pricing procedures for individual products originally introduced in 1957 are finally dropped.

General comment

Viewed over a thirty-year perspective, the arrangements for influencing NHS pharmaceutical prices have altered from regulating the prices of individual products by reference to comparative pricing formulae (export or domestic) or a 'costs plus on-cost' approach, to the flexible regulation of the overall profit made on NHS business by individual companies and the industry as a whole. That major change occured mainly through the 1969 version of the scheme, though the later variants of the original 1957 scheme foreshadowed it.

Since 1969, and particularly in 1986, the trend has been towards a greater precision and transparency in the arrangements for the regulation of profit and the monitoring of costs.

It is beyond the scope of this paper to examine in any depth why particular changes were made when they were, or to investigate the effects on either NHS prices or the pharmaceutical industry of NHS price regulation over the period. The attitudes of successive Governments to NHS expenditure and to questions of industrial policy and procurement were no doubt an influence. But the evolution of pharmaceutical products and of the pharmaceutical market (in both its international and its domestic dimensions) were probably even more important.

In the mid-1950s, when the 1957 arrangements were under negotiation the NHS was using some 4,000 proprietary pharmaceutical products, many of them relatively simple by modern standards (though even then the MoH was anxious about appropriate arrangements for regulating the costs of 'hormones and antibiotics'). It must be doubtful whether maintaining the individual product pricing arrangements introduced in 1957 into, for example, the 1970s and 1980s would have been easy given the very much greater number of products and the greatly enhanced complexity and cost of the research and development and manufacturing processes required to market them.

It may be conjectured, too, that the 'export pricing criterion' would have become more difficult to apply as the pharmaceutical industry became more international in its trading patterns and more multi-national in its ownership structure and as fixed international currency parities were progressively abandoned.

Note

Mr Luce was an Under Secretary in the Family Practitioner Services and Medicines Group of the Department of Health and Social Security between 1984 and 1987. He is at present on secondment to HM Treasury. Any comments or opinions in this article are personal to the author and do not commit either Department.

The author gratefully acknowledges Bernard Harrison's help in suggesting the references quoted in paragraphs 5 and 10.

'Net wholesale prices' which are more than 20 per cent above or below the mean are to be eliminated from the A1 calculation. Where, however, this method would produce anomalies it may be modified in a manner to be agreed between the Ministry and the manufacturer.

Example of calculation of A1 price from 'net wholesale prices'

Notes:

Column (2): If the intermediary's gross margin is less than 10 per cent the lower figure should be used.

Column (6): 'Sales' are either sales to the market (where the finished product is exported from the UK) or, sales in the market (of products processed from active ingredients imported from the UK).

First stage: **Elimination of extremes.**

Market	*(1) Price to wholesaler*	*(2) Less 10%*	*(3) Freight etc*	*(4) Net wholesale price*
A	20/–	18/–	2/–	16/–
B	18/–	16/2	1/2	15/–
C	16/–	14/5	1/5	13/–
D	15/–	13/6	1/6	12/–
E	14/–	12/7	1/1	11/6
F	13/–	11/8	1/2	10/6
			Total	78/–
			∴ Mean	13/–

+20 per cent of mean = 15/7
−20 per cent of mean = 10/5
Hence market A must be eliminated.

Second stage: **Weighted average after elimination of extremes**

Market	*(5) Net wholesale price*	*(6) Sales weighting*	*(5) × (6) shillings*
B	15/–	25	375
C	13/–	20	260
D	12/–	25	300
E	11/6	20	230
F	10/6	10	105
		100	1,270

∴ A1 price = 12.7 shillings = 12/8½.

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