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# NICE GUIDANCE IMPLEMENTATION TRACKING

## DATA SOURCES, METHODOLOGY & RESULTS

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## 1. INTRODUCTION

The National Institute for Clinical Excellence (NICE) began issuing guidance in a range of disease areas to PCTs and Trusts in April 2000. NICE guidance should be incorporated into local health care delivery plans within 3 months of publication and appropriate funding provided.

Therefore if clinicians were adopting NICE recommendations, one would expect to see a change in clinical practice in line with the recommendations. However to date, there has been a limited attempt to measure this change in clinical practice.

In December 2003, NICE commissioned Abacus to develop a methodology to measure the impact of 28 individual pieces of NICE guidance. See Appendix 1 for a complete list of reviewed disease areas.

This report outlines how the impact of NICE guidance in these disease areas was measured and presents the results in the context of an expected impact if guidance were to be fully implemented.

### **1.1 Aims and objectives**

1. Identify sources of data to monitor the impact of NICE guidance on selected health technologies.
2. Consult with NICE to establish the expected change in health technology utilisation following guidance publication.
3. Use the best available data to measure actual change in health technology utilisation.
4. Present the data in tabular and graphical format with commentary.
5. Produce presentation materials in the form of PowerPoint slides and other materials as requested.

## 2. METHODOLOGY

Abacus considered a variety of alternate data sources for the global analysis of 28 different disease areas reviewed by NICE. IMS were selected because they provided a good range of datasets allowing analysis of both primary and secondary care settings. They also provide a unique oncology data set that gives useful information of how cancer products are used and in what stage of disease.

IMS provided data for 20 of the topics under review. Where no IMS data was available, individual manufacturers were contacted to access unit sales data and these were combined to provide a total picture for England and Wales. For obesity surgery, specialist centres were contacted directly.

Results needed to be put into context. Was prescribing within the expectations described in each set of NICE guidance? We therefore reviewed the relevant guidance and quantified the expected numbers of patients to be treated if guidance were to be fully implemented. In most cases this is clearly described in the NHS impact section of the guidance.

A model predicting expected numbers of patients treated for each disease area reviewed was developed using the epidemiological data and risk group definitions described in the NICE guidance.

IMS Mediplus data takes information at read code level from sampled GP Practice Systems and contains data on over 1 million patients. (Projection factor 49.9). We used a defined list of read code definitions to extract prescribing information on patients within the disease areas that we were reviewing that were predominantly primary care based treatments. These included asthma inhalers in 5-15 year olds, pioglitazone in diabetes, sibutramine in obesity, NRT for smoking cessation and COX IIs for arthritis. This type of longitudinal patient database is an excellent source of prescribing information but is unfortunately limited to primary care.

Hospital Pharmacy Audit data (HPA) has been used by the pharmaceutical industry for many years to track global change in prescribing trends for hospital products. The data is limited in that pack sales are presented rather than the patient/read code type information available from the primary care database systems. However, the data is collected from 2,000 NHS centres including 1,600 hospitals giving a near census level picture. The data presented includes inpatient and outpatient prescribing and measures monthly use of product. Although no information on disease indication is available an analysis by department can be carried out. This enabled us to make broad assumptions of product usage. Infliximab in Crohn's disease could be measured by filtering data for gastroenterology, whereas reviewing use in rheumatology and orthopaedics would give a picture of infliximab prescribing in rheumatoid arthritis.

British Pharmaceutical Index (BPI) data provides similar information on product packs sold in primary care. Every quarter a panel of 200 cancer specialists send 5-25 completed questionnaires to IMS. They fill in complete details of cancer patient diseases and treatment histories by referring to patient records.

IMS now have 8,000 cancer case histories and this is expected to grow to 12,000 for 2004. The data presents numbers of patients by cancer type and by therapeutic history. It is useful for reviewing 1<sup>st</sup> line versus 2<sup>nd</sup> line prescribing, particularly as NICE guidance makes specific recommendations for each product. However, caution should be taken when interpreting results because national projections are based upon relatively small numbers of patient notes.

Table 1: Summary of data sources

## Summary of IMS data used

	<b>Mediplus</b>	<b>HPA</b>	<b>BPI</b>	<b>Oncology</b>
<b>Data</b>	<b>Patients/Rx</b>	<b>Units/Sales</b>	<b>Units/Sales</b>	<b>Patients</b>
<b>Source</b>	<b>Torex GP practice system</b>	<b>Hospital pharmacy</b>	<b>Retail sales (Wholesaler)</b>	<b>Questionnaire</b>
<b>Size of dataset</b>	<b>1.1m patients</b>	<b>“Census” 1600 hospitals</b>	<b>“Census” 97% retail</b>	<b>8000 cancer records</b>
<b>PRO</b>	<b>Rich information source</b>	<b>Global hospital trend</b>	<b>Global primary care trend</b>	<b>1<sup>st</sup> line versus 2<sup>nd</sup> line Rx</b>
<b>CON</b>	<b>Primary care only</b>	<b>Pack information only</b>	<b>Pack information only</b>	<b>Patient numbers for projections</b>

### 3. RESULTS

When NICE was first established there was a general feeling that it would form an additional hurdle to the introduction of new therapeutic interventions. In this analysis of 28 of the earlier NICE reviews there were 33 different recommendations. Only 4 sets of guidance could be classified as negative. Approximately one third of these recommendations were for 1<sup>st</sup> line or routine product use and 57% were a recommendation for 2<sup>nd</sup>/3<sup>rd</sup> line use or for a defined patient risk group.

In 28 reviewed topics there were 33 sets of recommendations:

- 1<sup>st</sup> line or routine use: 10/33 (30%)
- 2<sup>nd</sup> or 3<sup>rd</sup> line: 8/33 (24%)
- Defined patient group: 11/33 (33%)
- Neutral or negative: 4/33 (12%)

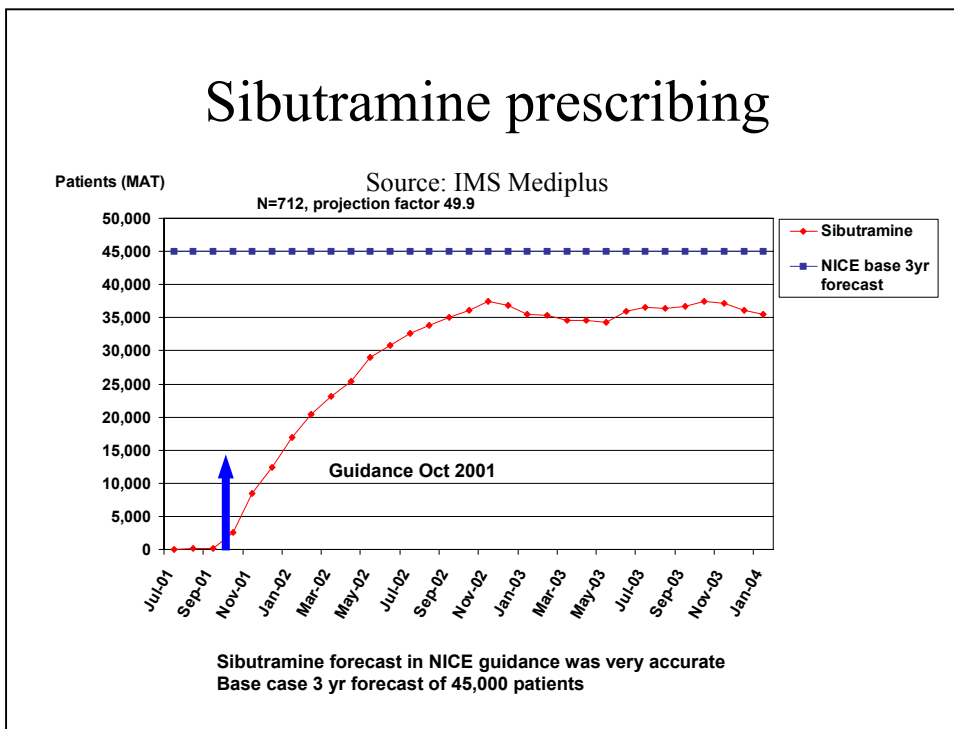
### 3.1 Sibutramine for the treatment of obesity

The prevalence of obesity in the IMS Mediplus dataset was 1.6%, compared to 20% estimated by NICE guidance and epidemiological studies. This suggests that much obesity remains undiagnosed as the Mediplus data only measures what is recorded in patient notes. NICE guidance recommended sibutramine as part of an overall obesity management plan and was published around the time of product launch.

The guidance estimated that 45,000 patients would be treated with sibutramine by year 3 of launch (September '04). Although initial uptake of sibutramine was rapid, total patients treated per year have reached a plateau of around 37,000. (Projections for England and Wales are based upon 712 actual patient records). It appears that sibutramine prescribing is within expectations described in the NICE guidance.

95% prescribing was within the recommended age group of 18-65.

**Figure 1: Patients prescribed sibutramine over a 12-month period**



NB: Data are presented as Moving Annual Totals (MATs). These are the cumulative results for a 12-month period, updated on a monthly basis. For example, a July MAT would present the cumulative data from August of the previous year to July of the current year. The next data point would give the cumulative from September to August. In this way, trend lines are smoothed by ironing out individual monthly fluctuations.

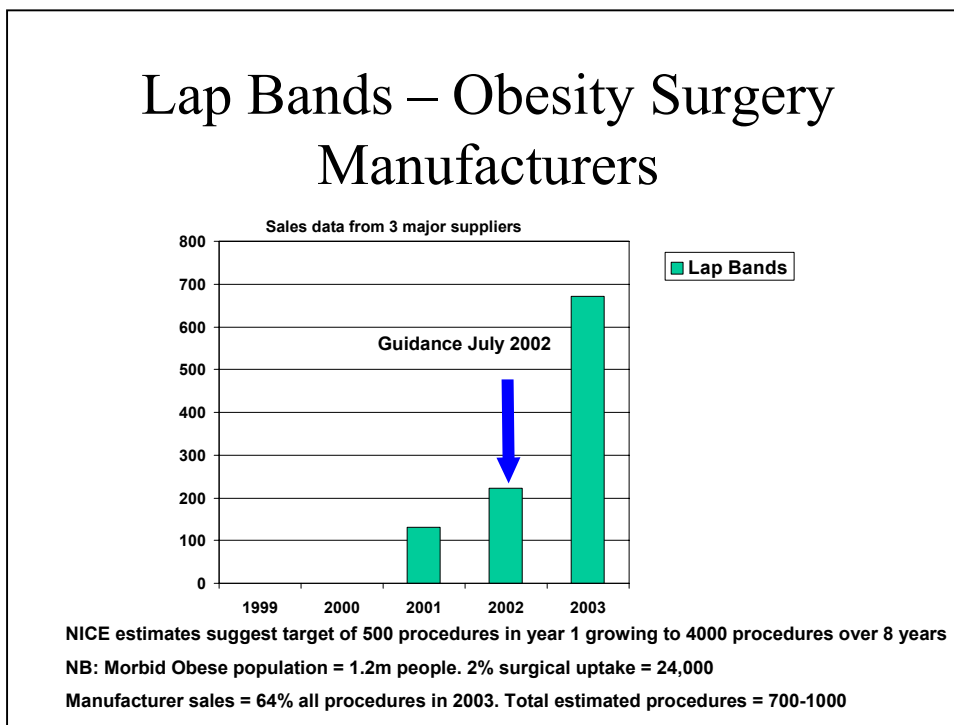
### 3.2 Surgery for morbid obesity

NICE guidance published in July 2002 endorsed the use of gastric bands and surgical treatments for obesity in a defined patient risk group, estimated to be 2-4% of the morbid obese population. In England and Wales there are around 1.2m people with morbid obesity giving an estimate of 24-48,000 people who could benefit from surgery.

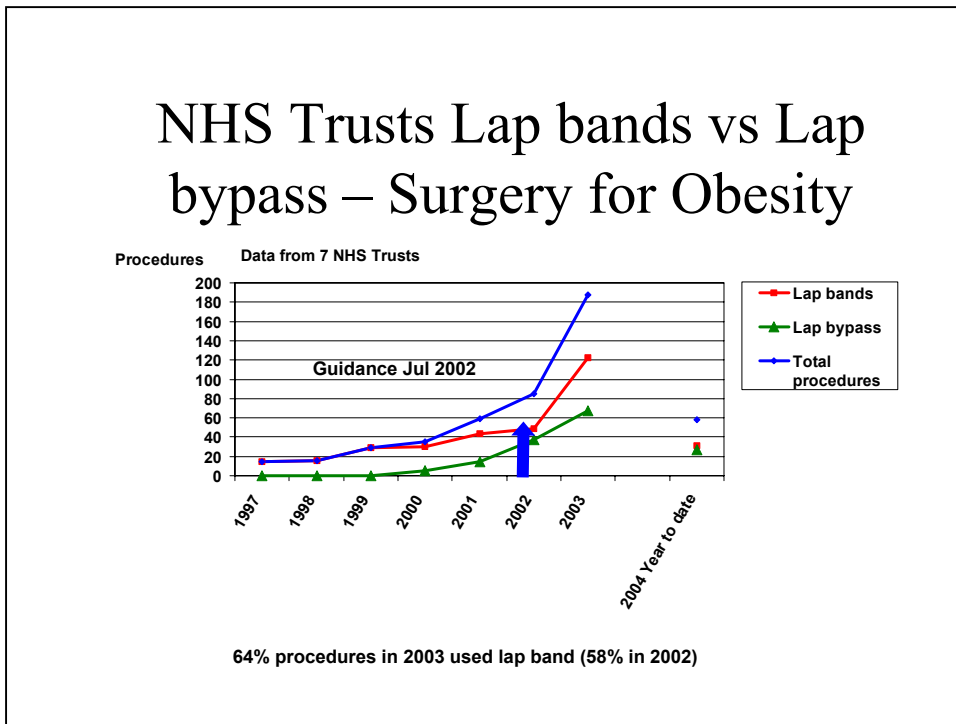
Capacity for surgery prior to guidance was limited to 200-500 procedures and NICE guidance suggested that capacity should be increased by 500 procedures per year, reaching a maximum of 8,000 obesity procedures per year by 2010.

This audit of the major suppliers of gastric bands shows a significant increase in sales of bands in the year following guidance. This does not equate totally to numbers of procedures carried out but is a good indicator that NICE guidance is accelerating uptake of surgery for obesity. From our audit of 7 of the 12 key centres for obesity surgery, gastric bands are used in 64% of all procedures. From these data we have estimated that there were in the region of 700 surgical procedures carried out in 2003, in line with year 1 expectations described in the NICE guidance.

**Figure 2: Unit sales of gastric bands in England and Wales**



**Figure 3: Obesity surgery procedures reported in 7 of 12 Trusts**



A similar picture to the manufacturer sales of gastric bands is shown in the hospital audit; a marked increase in the year following NICE guidance. Data was collected from 7 of the 12 major hospitals carrying out obesity surgery. The % of procedures using a gastric band jumped from 58% in 2002 to 64% in 2003. Sixty procedures had been carried out in the 1<sup>st</sup> month of 2004 suggesting an annual rate of over 700 procedures in these 7 centres. Following guidance expectations we would expect 2003 procedures for surgical obesity to rise to 500-1,000 and in 2004 to 1,000-1,500. This data suggests that the uptake of surgical procedures for obesity is in line with expectations, although it has a long way to go before reaching the target capacity of 8,000 procedures per year.

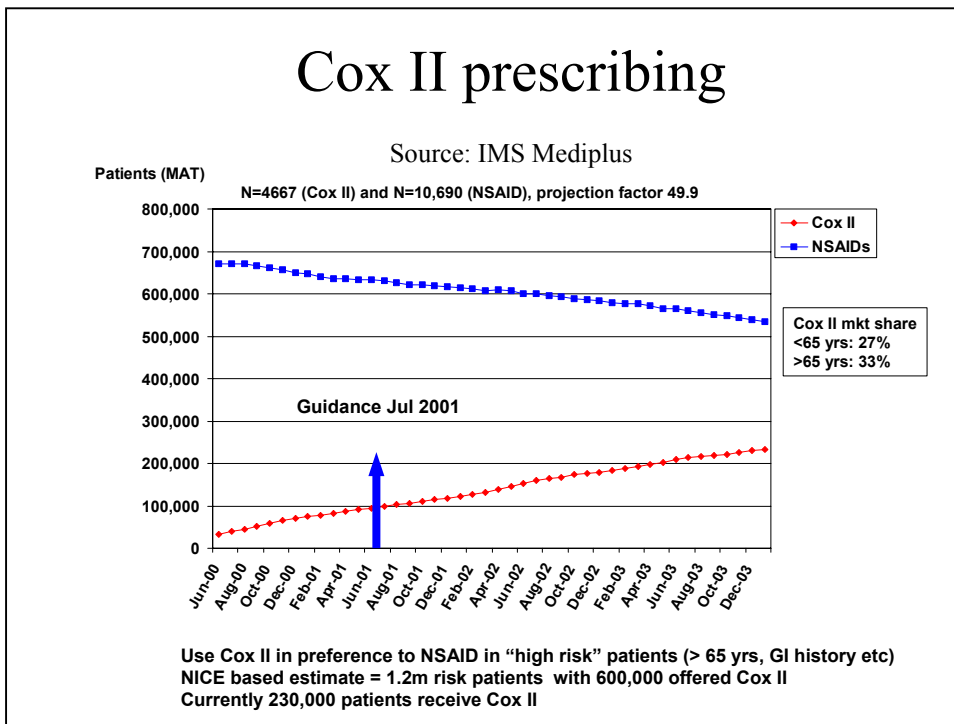
Funding, availability of trained specialists and NHS surgical beds limit growth in numbers of obesity surgery procedures. These larger issues of infrastructure need to be addressed if all patients who need surgery for morbid obesity are to be treated.

### 3.3 Cox II prescribing for arthritis

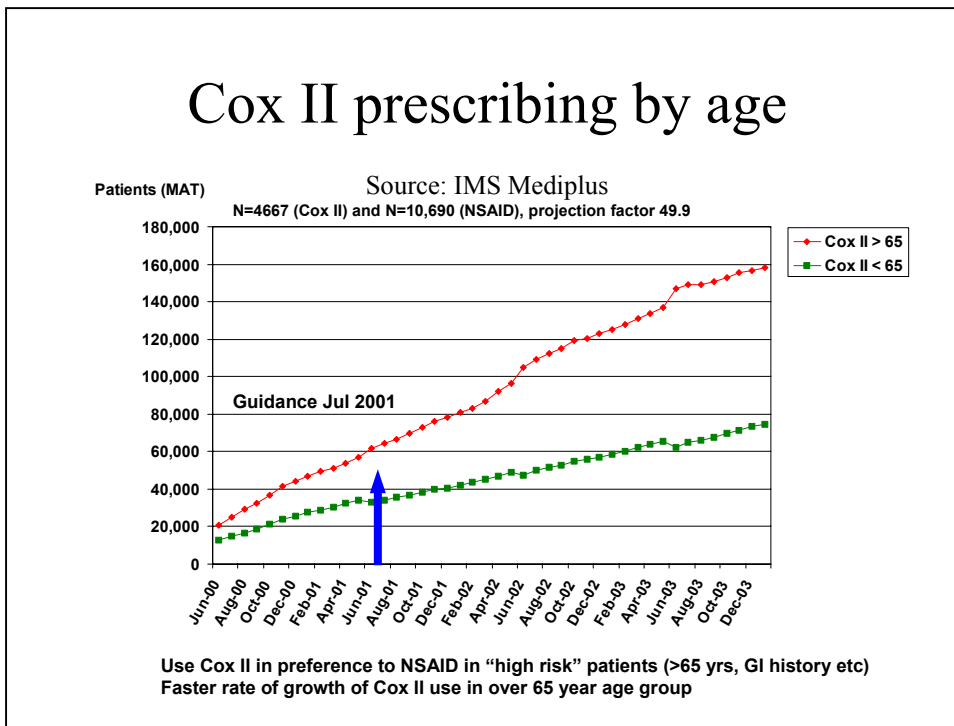
Cox II agents were recommended in preference to NSAIDs for “at risk” arthritis patients. The definition of “at risk” is quite broad covering patients over 65, with gastrointestinal symptoms or a history of GI disease, etc. There has been no significant change in the gradual trend from NSAIDs to Cox II agents, suggesting that guidance was endorsing standard practice.

It is estimated that of the 1.2 million risk patients, 600,000 will be offered a Cox II. So far, IMS data suggests that 230,000 patients receive a Cox II. This data does not split prescribing into risk groups and therefore does not tell us how many of the current Cox II prescriptions are within the “at risk” definition described in the NICE guidance. However by using age as a marker of risk, it appears that the over 65’s are more likely to receive a Cox II than an NSAID. Currently, 27% of the under 65-year group receive a Cox II compared to 33% in the over 65 year group.

Figure 4: Cox II versus NSAID prescribing



**Figure 5: Cox II prescribing by age**



As would be expected, the growth in use of Cox II agents is greater in the over 65-year group than in younger arthritis patients. Cox II prescribing appears to be within NICE guidance expectations.

### 3.4 Riluzole for motor neurone disease

Riluzole was recommended for the treatment of motor neurone disease (MND) in NICE guidance published in January 2001. There are an estimated 2,000 patients with MND in England and Wales. If each of these were to receive the full course of riluzole then each patient would consume 13\*28 day packs of riluzole per year. The maximum number of riluzole 28-day packs to treat 2,000 patients is therefore around 26,000

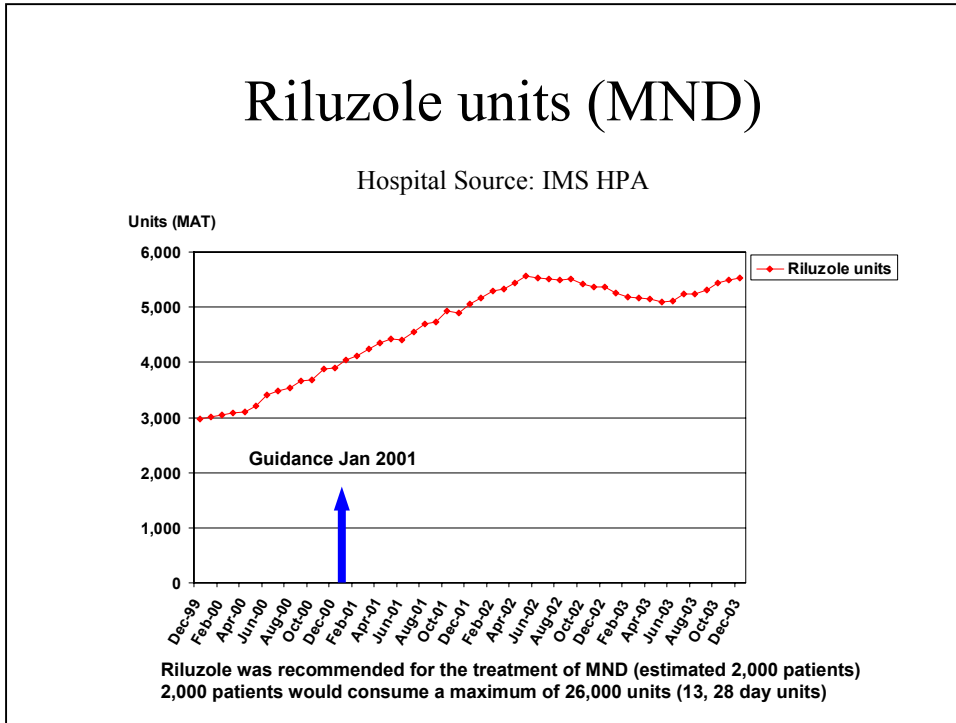
The limitation of IMS hospital pharmacy audit (HPA) data is that it counts units used in hospital rather than patients recorded in the primary care data set (Mediplus). However, as it collects data from the majority of hospitals (>95% coverage) it gives a good idea of national trend.

In secondary care, the increase in use of riluzole did not change following publication of NICE guidance, suggesting that guidance was endorsing current secondary care practice. Subsequently, secondary care usage of riluzole has reached a plateau of between 5,000 and 6,000 units.

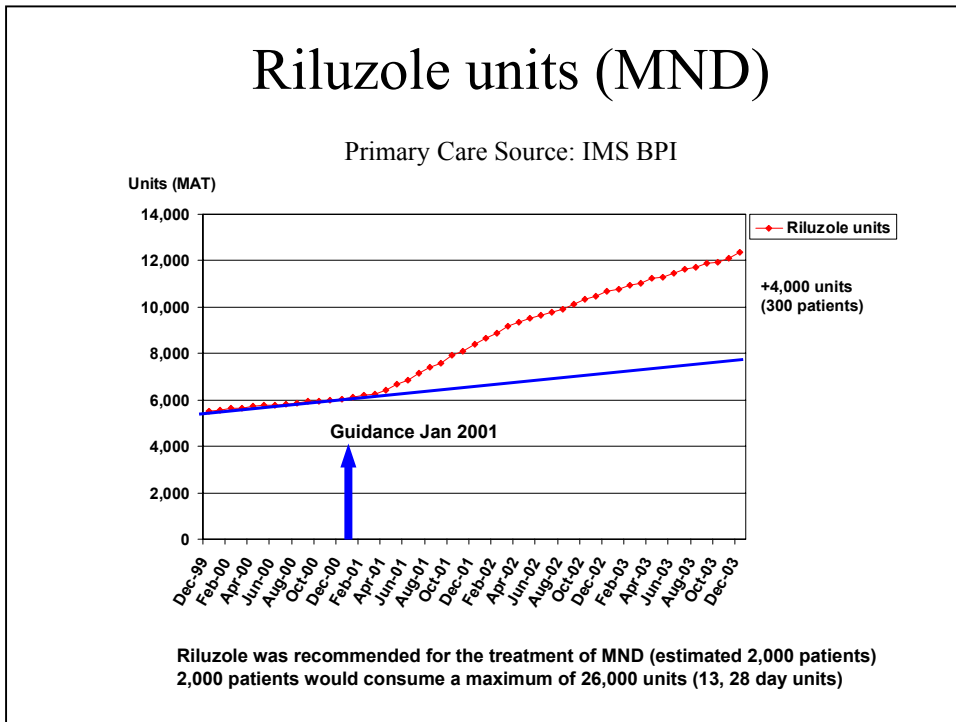
In primary care, the effect of NICE guidance was to accelerate the use of riluzole, adding about 4,000 units per year. The IMS British Pharmaceutical Index (BPI) dataset similar to the HPA

data for secondary care presents units of product sold within primary care. Again it gives near census level coverage to give a global trend. Units counted are 28-day packs of tablets.

**Figure 6: Units of riluzole dispensed in hospital pharmacy**

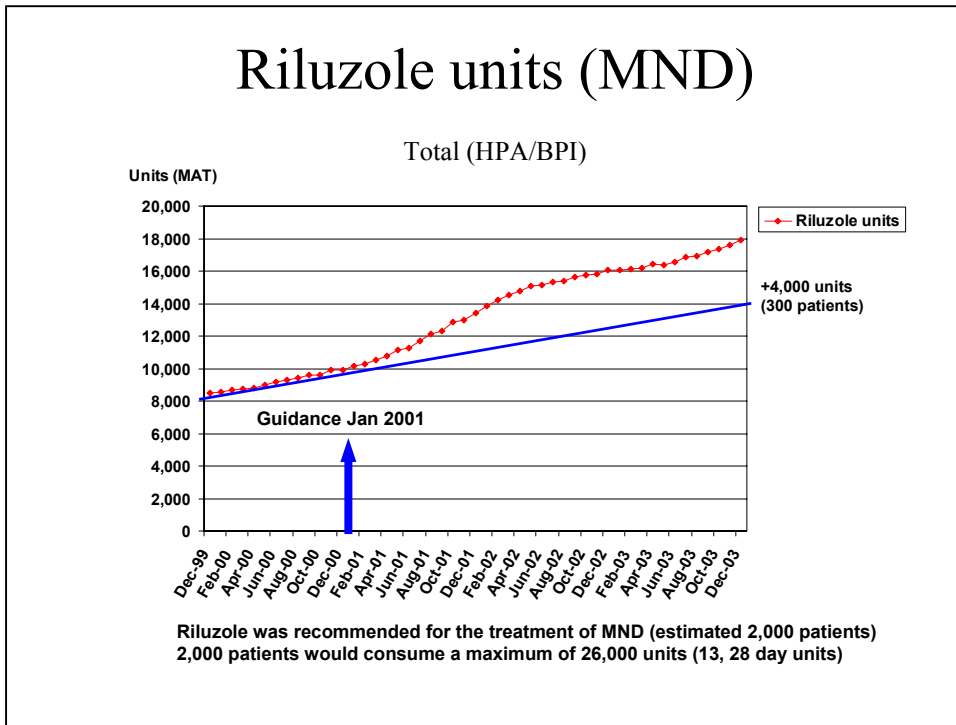


**Figure 7: Units of riluzole dispensed in retail pharmacy**



Adding primary and secondary care unit sales data together shows that riluzole usage has grown to 18,000 units per year in England and Wales. If each patient received 13 units (a full years therapy), then at least 1,400 patients have been treated with riluzole. This will be an underestimate because not all patients will receive 13 packs therapy per year. Usage should plateau somewhere between 20,000 and 26,000 units of riluzole if 2,000 patients are to be treated per year. It can be concluded that this NICE guidance has been fully implemented in secondary care and well implemented in primary care.

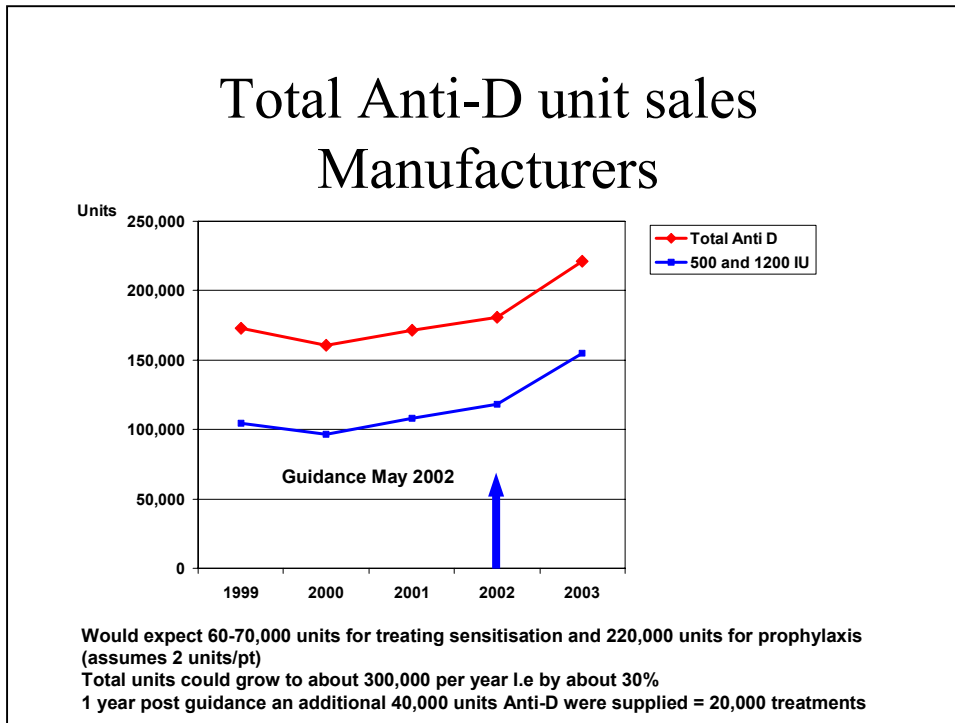
**Figure 8: Total units of riluzole dispensed in England and Wales**



### 3.5 Anti-D for prophylaxis of rhesus disease

Anti-D was recommended for routine use at weeks 28 and 34 of pregnancy for the prophylaxis of rhesus sensitisation. For the 110,000 annual risk births this would increase units of Anti-D by 210,000. About 60-70,000 units are also used for treating sensitisation during pregnancy. We have estimated that units of Anti-D would be expected to grow to about 300,000 per year i.e. by 30%.

**Figure 9: Total Units of Anti-D sold in England and Wales**



### 3.6 Oxaliplatin, irinotecan and raltitrexed for advanced colorectal cancer

The guidance reviewing Oxaliplatin, irinotecan and raltitrexed for use in advanced colorectal cancer gave three separate recommendations.

Oxaliplatin was recommended as a 1<sup>st</sup> line option for patients with advanced colorectal cancer who have metastases confined to the liver and that are deemed to be resectable. The IMS oncology data is collected from patient records and shows an increase in prescribing of oxaliplatin as a 1<sup>st</sup> choice therapy, i.e. within NICE guideline recommendations. Oxaliplatin now equals 24% of all 1<sup>st</sup> line therapy compared to 14% prior to NICE guidance.

Some second line use is recorded but this has remained flat since guidance publication. Please note that IMS oncology data projections are based on relatively small numbers when analysing data at product level, in advanced disease and by line of therapy. In this instance there were 32, 1<sup>st</sup> line patient case histories and 9, 2<sup>nd</sup> line. Projection factors are therefore large and estimates should be viewed as an approximate global trend.

Figure 10: Oxaliplatin use in patients with advanced colorectal cancer

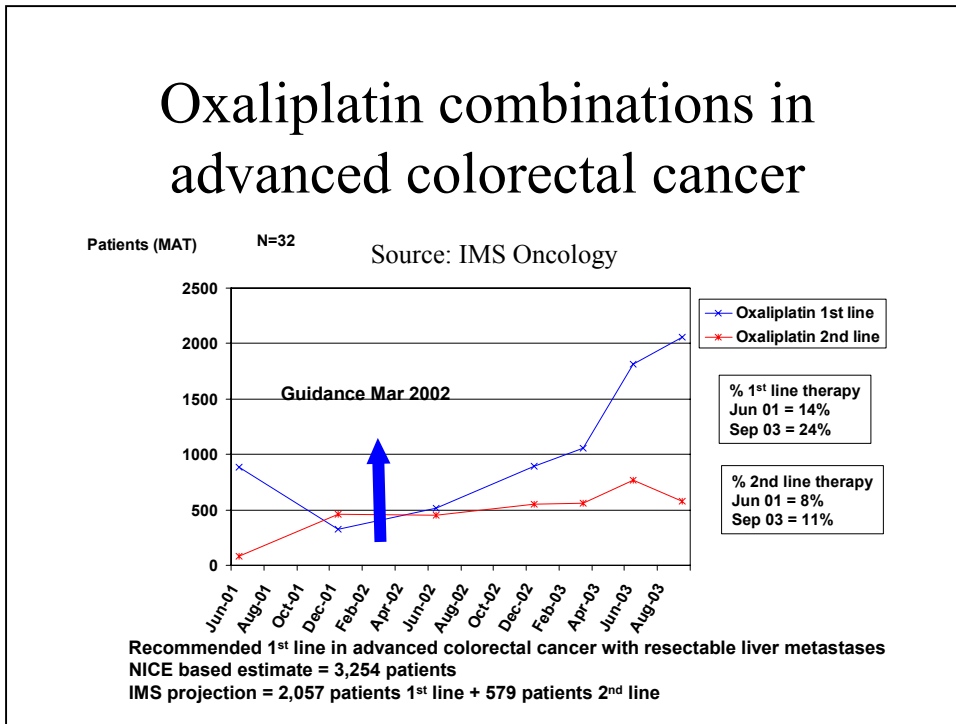
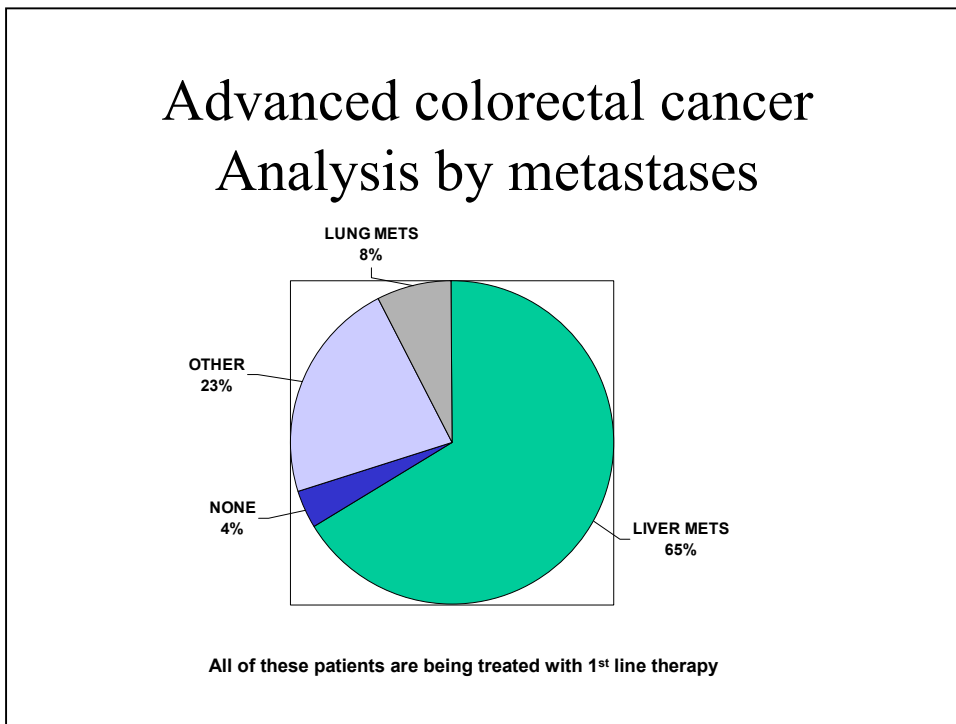
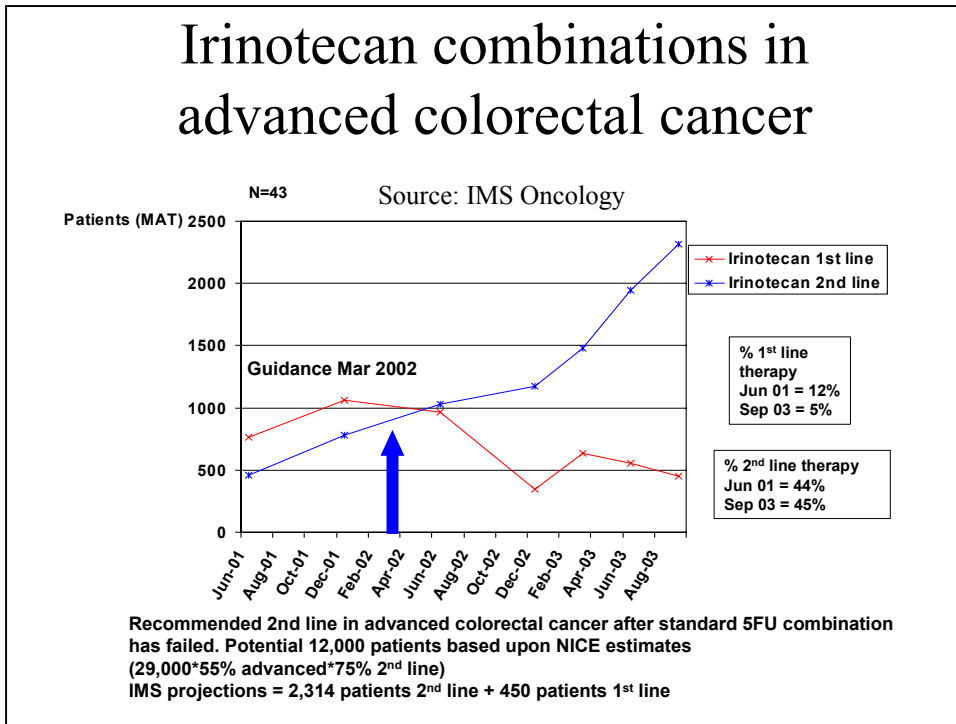


Figure 11: Oxaliplatin use by site of metastases



NICE guidance recommends oxaliplatin is to be used 1<sup>st</sup> line in patients with metastases confined to the liver. Two thirds of the patients with advanced colorectal cancer and who had received oxaliplatin 1<sup>st</sup> line fulfilled this criteria. NICE guidance for oxaliplatin appears to be reasonably well implemented.

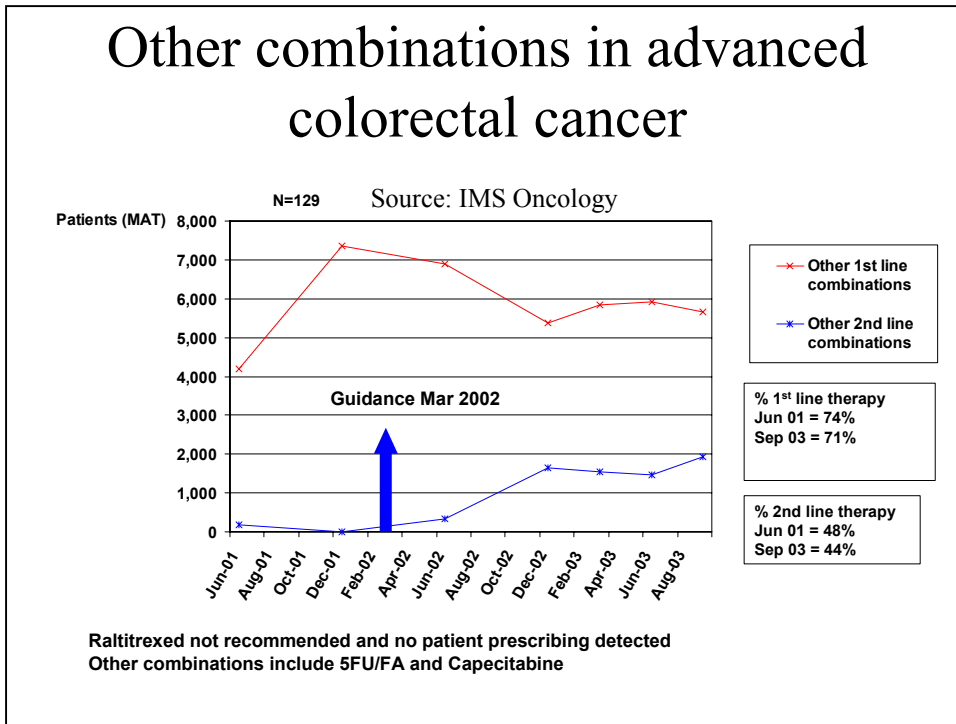
**Figure 12: Irinotecan use in patients with advanced colorectal cancer**



Irinotecan was recommended by NICE as a 2<sup>nd</sup> line combination therapy after standard 5FU combinations have failed. Since NICE guidance was published in March 2002, 1<sup>st</sup> line use has dropped from 12% to 5% of all 1<sup>st</sup> line therapy. At the same time an increase in the rate of growth of irinotecan 2<sup>nd</sup> line use is seen.

NICE guidance appears to have been adhered to although of the 29,000 patients with colorectal cancer approximately 12,000 could be potential candidates for irinotecan. This assumes that 55% of patients have advanced disease and 75% of these require 2<sup>nd</sup> line therapy. So far, approximately 3,000 patients per year receive irinotecan. Again note that IMS projections are based upon relatively small numbers, in this case 43 patient records.

Figure 13: Other agents used in patients with advanced colorectal cancer



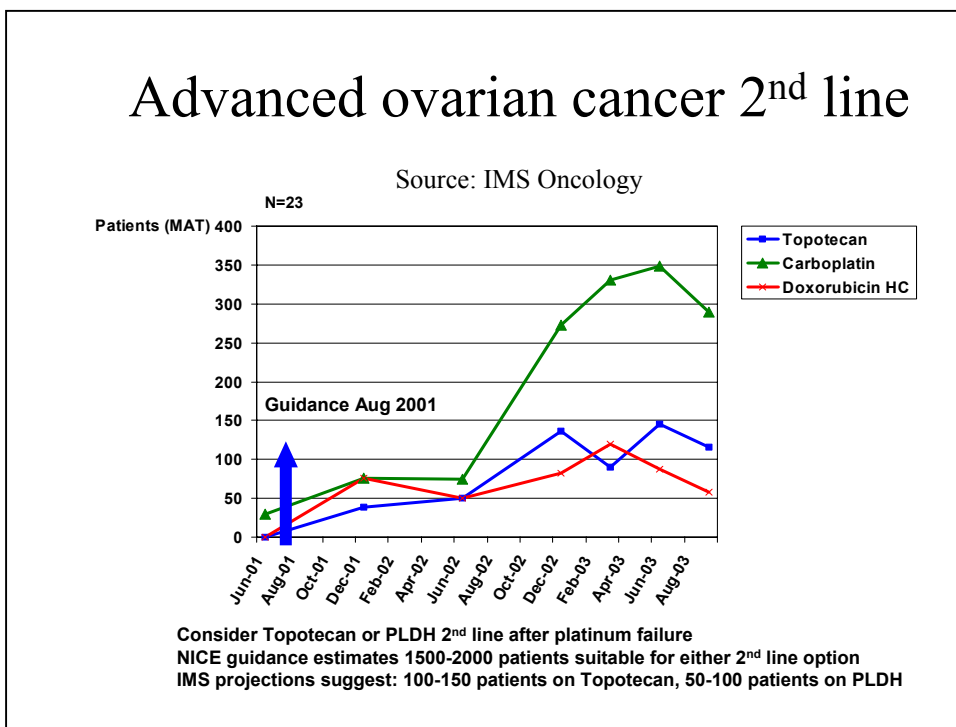
Raltitrexed, the 3<sup>rd</sup> product for advanced colorectal cancer reviewed by NICE in March 2002 was not recommended for use. No raltitrexed use was detected in the IMS oncology dataset. This does not mean that the product is not used; just that usage is too small to be detected using this methodology.

In general, the NICE review of advanced colorectal cancer has been adhered to. The three products were given three different recommendations, with guidance driving 1<sup>st</sup> line use of oxaliplatin, 2<sup>nd</sup> line use of irinotecan and no use of raltitrexed.

This disease area is a very good example of how NICE recommendations can shape prescribing behaviour.

### 3.7 Topotecan and PLDH for advanced ovarian cancer

Figure 14: 2<sup>nd</sup> line treatments in advanced ovarian cancer

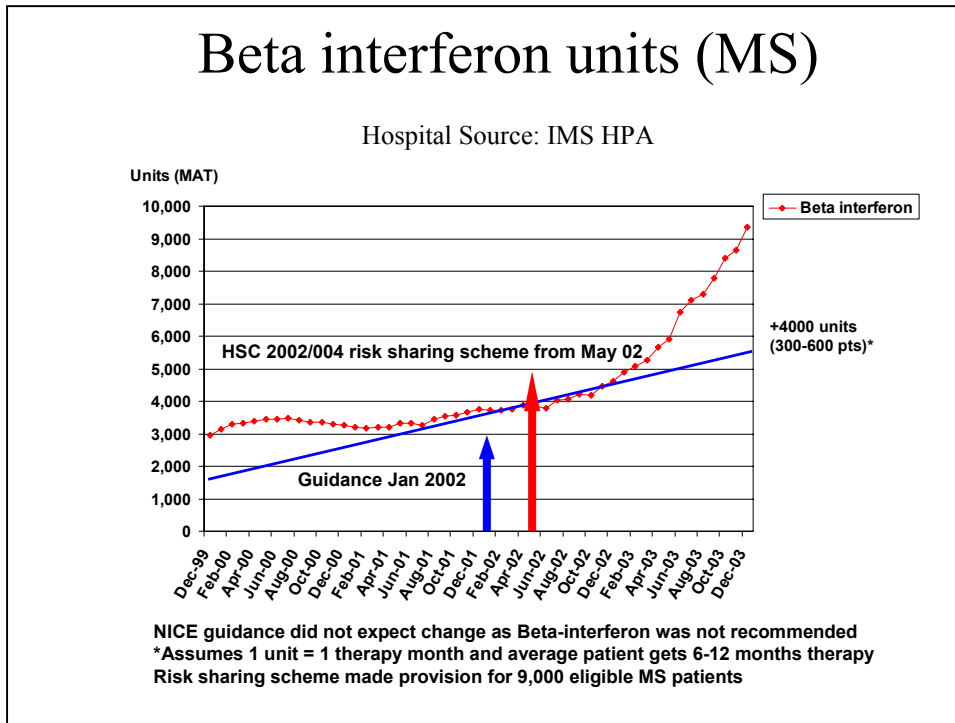


This disease area is covered by 2 sets of NICE guidance published in 2001.

Both topotecan and Pegylated Lyposomal Doxorubicin Hydrochloride (PLDH) were recommended as 2<sup>nd</sup> line treatment options in advanced ovarian cancer after platinum therapy has failed. Between 1,500 and 2,000 patients are estimated to be suitable for either product. IMS oncology data suggests that 100-150 patients received topotecan and 50-100 patients received PLDH in 2003. The numbers here are very small and based upon 23 patient records only therefore caution has to be made when looking at projections. However, it does appear that a 10-fold increase in product use would occur if guidance were to be fully implemented.

### 3.8 Beta interferon for multiple sclerosis

Figure 15: Beta interferon units dispensed in hospital pharmacy

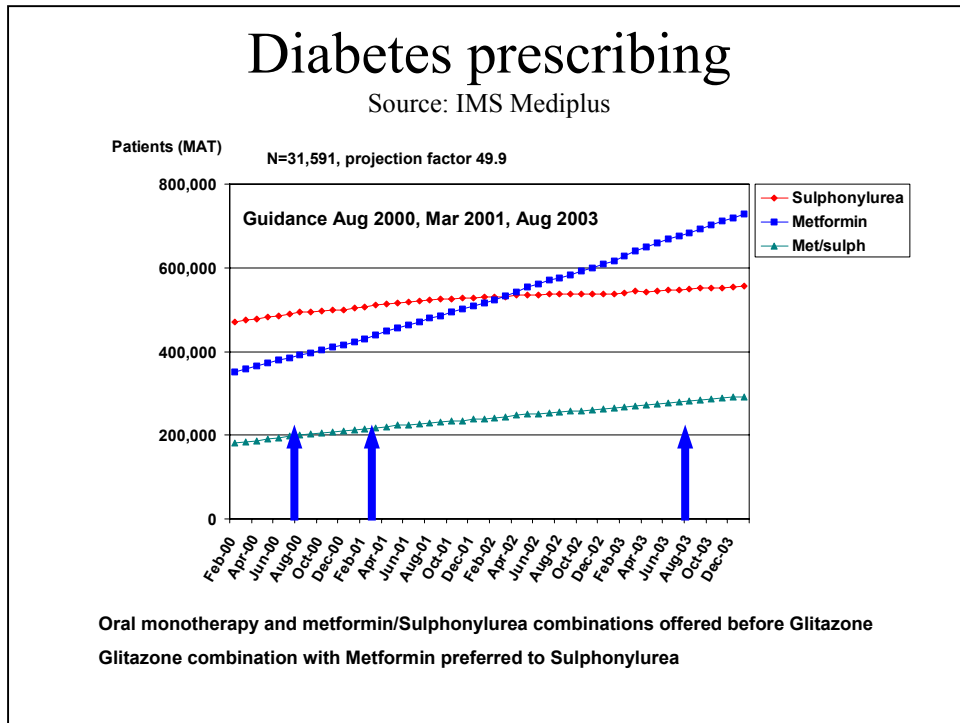


Beta interferon was not recommended for use in multiple sclerosis and therefore a decline in units dispensed in hospital would be expected following the publication of guidance.

As can be seen in figure 15 the opposite has occurred with a sharp growth in the use of Beta interferon since the middle of 2002. It is important to stress that the data presented here simply provides a global indication for trends within England and Wales. There are many factors that drive prescribing change within any given disease area. These include availability of new clinical evidence (both positive and negative); commercial activities such as price changes and sales force promotions and of course clinical guidelines and recommendations developed by bodies such as NICE. In this instance a risk-sharing scheme developed by the companies marketing Beta interferon was announced in a Health Service Circular published soon after the NICE guidance was issued. This scheme gave provision for an additional 9,000 patient treatments and is probably the greatest individual factor driving the increase in use of Beta interferon.

### 3.9 Pioglitazone for type II diabetes

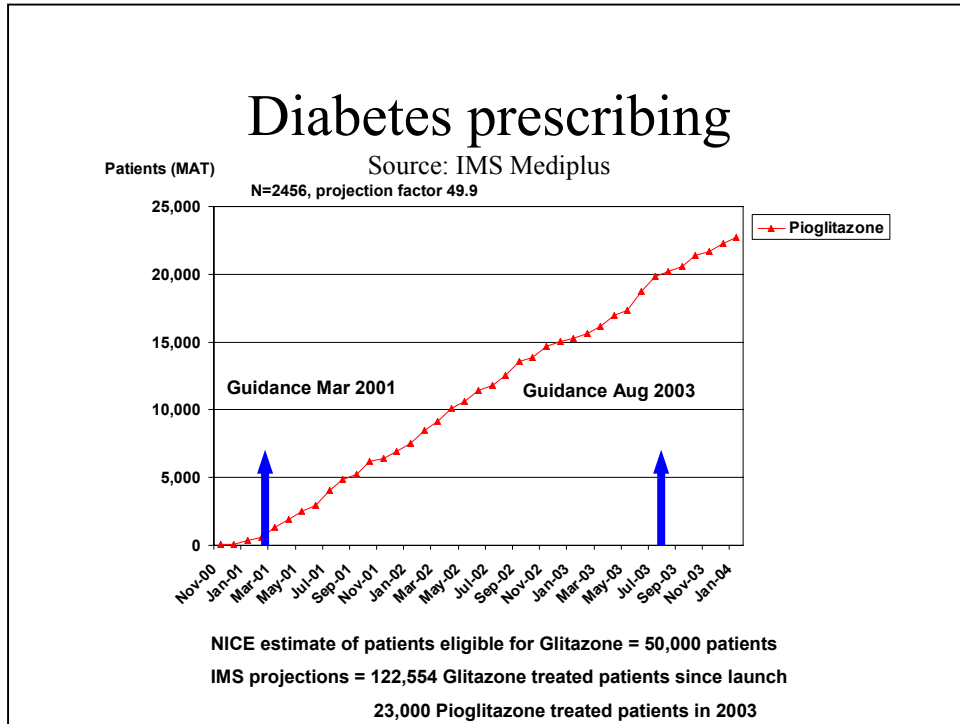
Figure 16: Patients prescribed metformin and sulphonylurea



NICE guidance reviewing glitazone use in type II diabetes suggests that the glitazones should be prescribed after metformin and sulphonylurea monotherapy and in combination have been tried. The guidance is more positive about metformin and the IMS data shows that metformin use continues to grow whereas sulphonylurea use is tailing off at around 550,000 patient treatments in England and Wales per year.

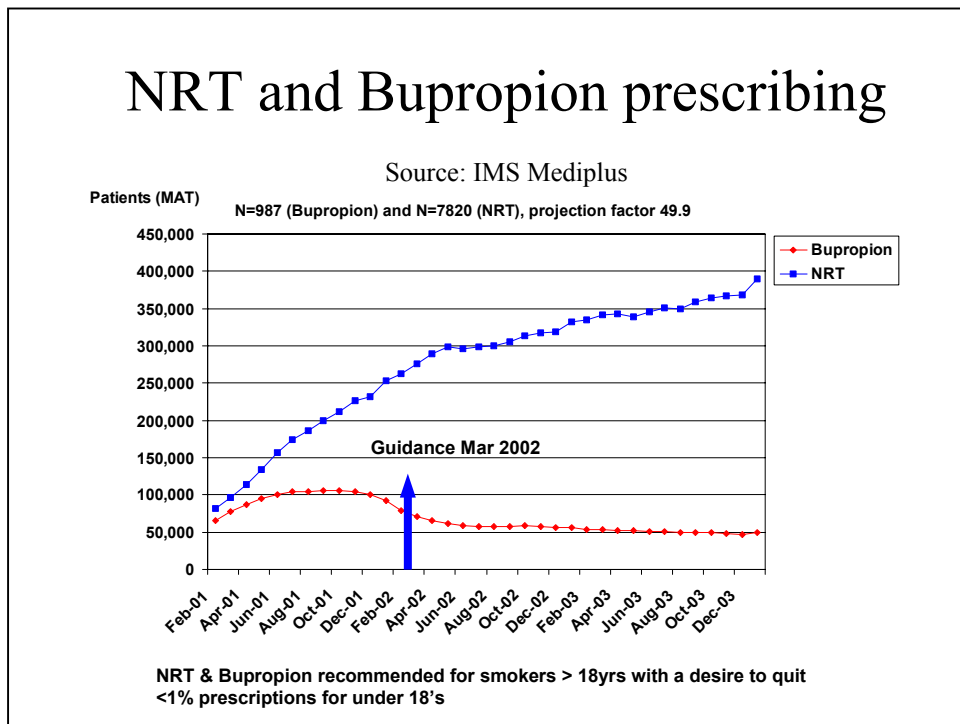
The prevalence of diabetes in the IMS dataset was 2.2%, in line with epidemiological study estimates. Sixty eight percent of these patients had received therapeutic intervention (including insulin) and 4.8% had received a glitazone. Figure 17 shows the uptake of pioglitazone since launch in 2001. It is difficult to interpret the impact of NICE guidance because it was issued at the time of pioglitazone launch. We do not know how much prescribing would have occurred in the absence of NICE guidance. In 2003, 23,000 patients were prescribed pioglitazone. This is nearly half of the total glitazone prescribing estimate presented in the NICE guidance (50,000 patients suitable for a glitazone). Further research is required to measure total glitazone prescribing rather than pioglitazone in isolation.

Figure 17: Patients prescribed pioglitazone since launch



### 3.10 NRT and bupropion for smoking cessation

Figure 18: Patients prescribed bupropion or NRT

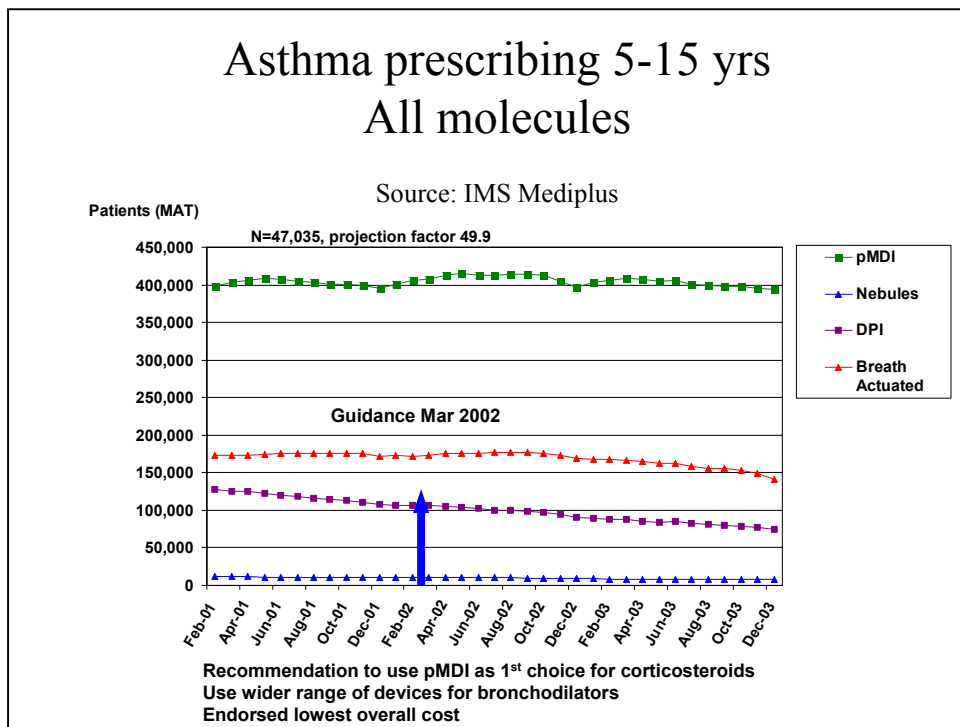


NRT and bupropion were recommended for patients over the age of 18 who are seriously attempting to quit smoking. The IMS data shows that less than 1% prescribing is in the under 18-age group. Since guidance was published in March 2002, prescribing of bupropion has declined whilst the rate of growth of NRT has slowed. Total prescriptions for smoking cessation had reached 1 million by the end of 2003, exactly in the middle of the NICE estimate of 500,000 to 1.5 million prescriptions per year.

Guidance also suggested that a second prescription should only be offered if the quit attempt is continuing. The average number of scripts per patient is 1.5 for bupropion and 2.4 for NRT suggesting that prescribing for smoking cessation is broadly in line with recommendations.

### 3.11 Asthma inhalers for 5-15 year olds

Figure 19: Prescribing by device type for all molecules in 5-15 year olds



In guidance published in March 2002, NICE recommended pMDIs as the 1<sup>st</sup> choice device for corticosteroids and a wider range of devices to be used for bronchodilators. The IMS mediplus data shows that around 400,000 children per year receive a pMDI. Following guidance, there has been a decline in the use of breath-actuated devices and dry powder inhalers (DPIs).

Table 2: Asthma prescribing in 5-15 year olds by device type

Device type	Corticosteroids	Bronchodilators	All
pMDI	69%	72%	68%
BA MDI	23%	23%	21%
DPI	13%	5%	10%
Nebules	0%	1%	1%

% does not always add up to 100% because patients can receive more than one type of device.

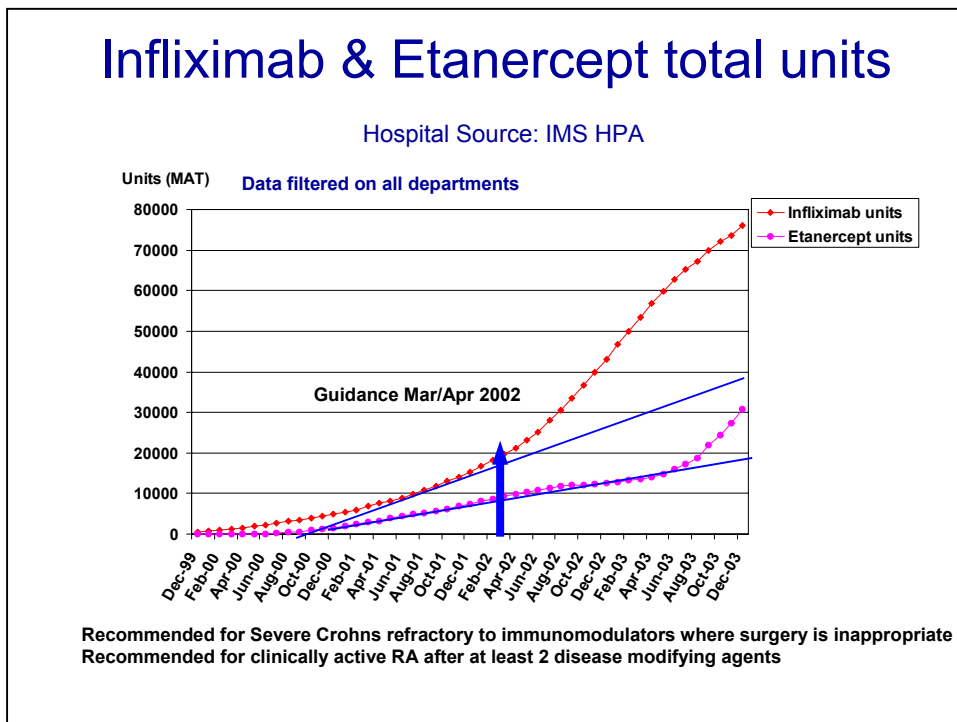
The impact of guidance on asthma devices in 5-15 year olds has been to increase the proportion of prescribing of pMDIs. Although guidance was specifically recommending pMDIs for the delivery of corticosteroid medication, the impact has been the same for bronchodilators. The proportion of pMDI use has risen from 61% in Feb 2001 to 69% in Dec 2003 for steroid inhalers and from 63% to 72% for bronchodilators.

### 3.12 Etanercept and Infliximab

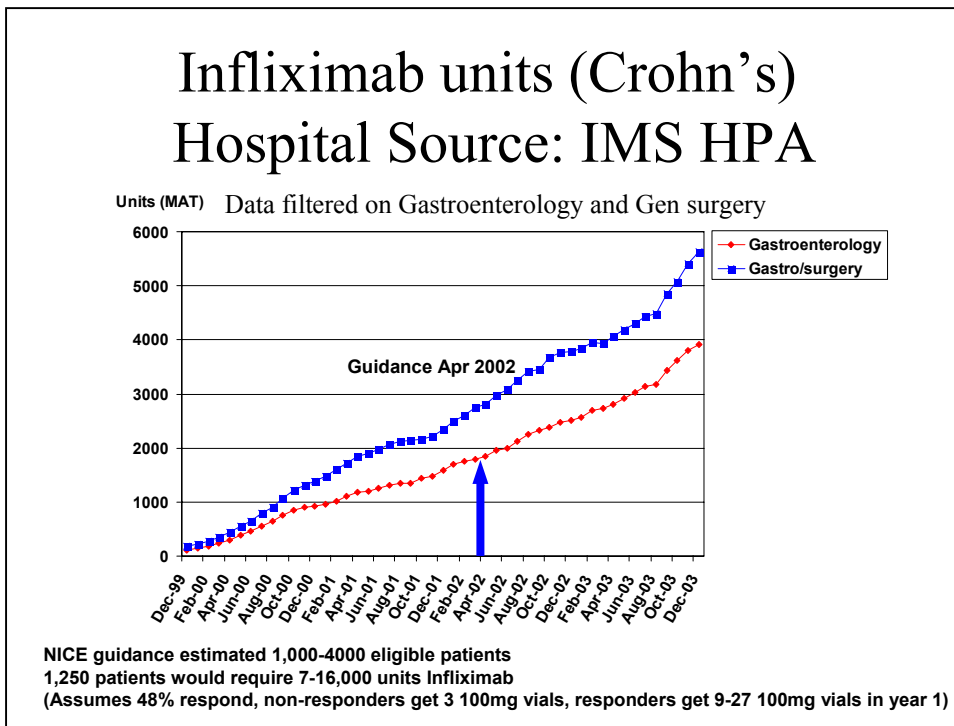
These two products have been reviewed by NICE for different indications. Guidance published in March and April 2002 has recommended both products for clinically active rheumatoid arthritis (RA), after at least 2 disease modifying agents have been tried; recommended infliximab for severe Crohn’s disease refractory to immunomodulators and recommended etanercept for idiopathic juvenile arthritis.

The IMS hospital pharmacy audit (HPA) presents packs of product dispensed by hospital pharmacy and used by a named department. Although we do not have details of the indication for which the product was prescribed (as we do for the primary care data), it is possible to assume that specific departments are using products for specific indications. As well as presenting total product usage for etanercept and infliximab, we have used gastroenterology as a marker for Crohn’s disease, rheumatology as marker for RA and paediatrics as a marker for idiopathic juvenile arthritis. For departments such as general medicine, it is not possible to distinguish between Crohn’s disease and RA. Figure 20 shows that both products have accelerated rates of growth in hospital following the positive recommendations of NICE. The blue lines show the underlying growth trend before guidance was published. The increase in etanercept use did not occur until 12 months after guidance was issued. This was primarily due to product supply issues around the time of publication of guidance.

**Figure 20: Infliximab and etanercept use in England & Wales**



**Figure 21: Infliximab use in Crohn's disease**



Filtering the data on gastroenterology only and gastroenterology plus surgery gives an indicator of infliximab use in Crohn's disease. Use of infliximab in these departments has continued to grow at the same rate immediately following the publication of guidance although an increase in the rate of growth can be seen from August 2003 onwards. Approximately 7,000 to 16,000 units of infliximab would be required to treat the eligible patients identified in the NICE guidance (1,000-4,000 patients).

**Figure 22: Infliximab and etanercept use in Rheumatoid Arthritis**

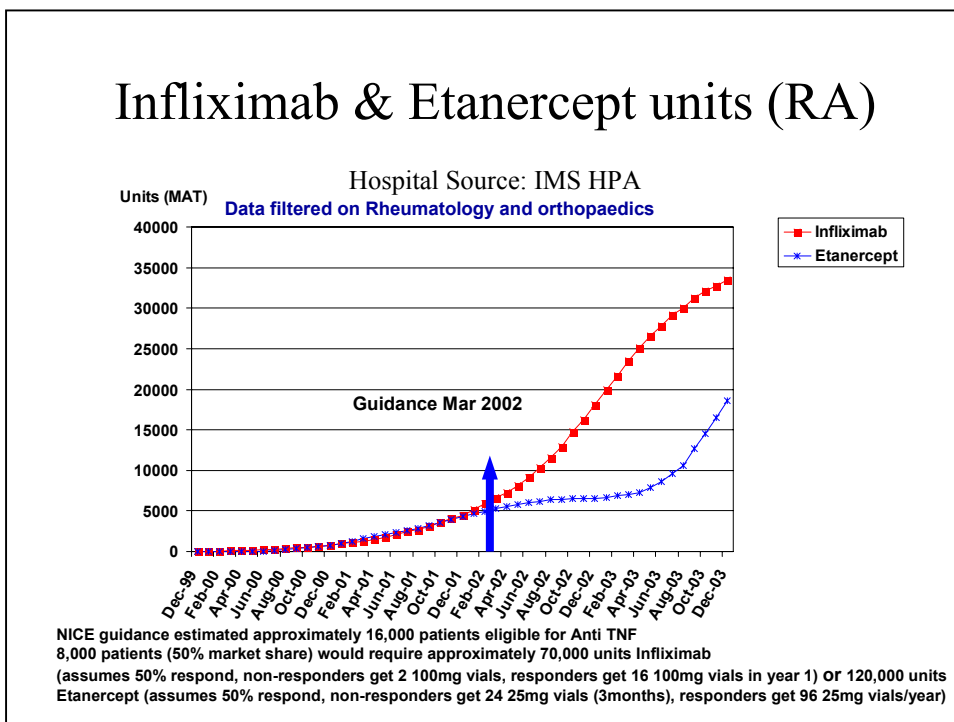
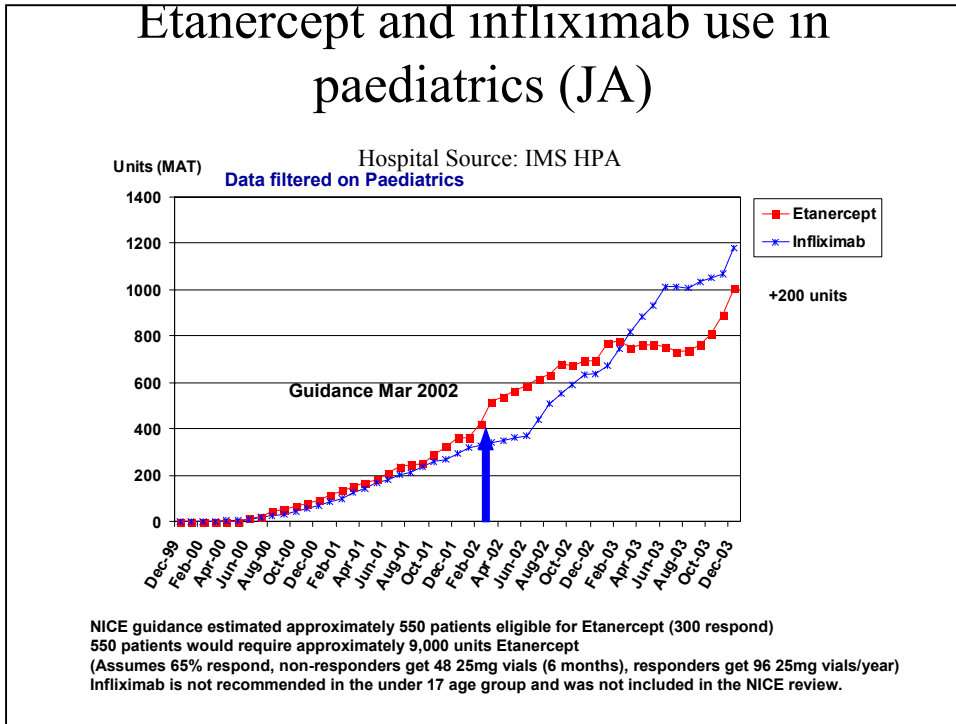


Figure 22 shows that the rate of growth of both infliximab and etanercept use in rheumatology and orthopaedics (markers for RA) have increased since NICE guidance was published. As before, the increase in etanercept use is delayed by 12 months due to supply issues. Approximately 70,000 units of infliximab and 120,000 units of etanercept would be required to treat the 16,000 patients eligible for Anti TNF (assumes 50% prescribing for each product). In 2003, only 20,000 units of etanercept and 35,000 units of infliximab were used in rheumatology and orthopaedics. A substantial proportion of patients will also be cared for in General Medicine.

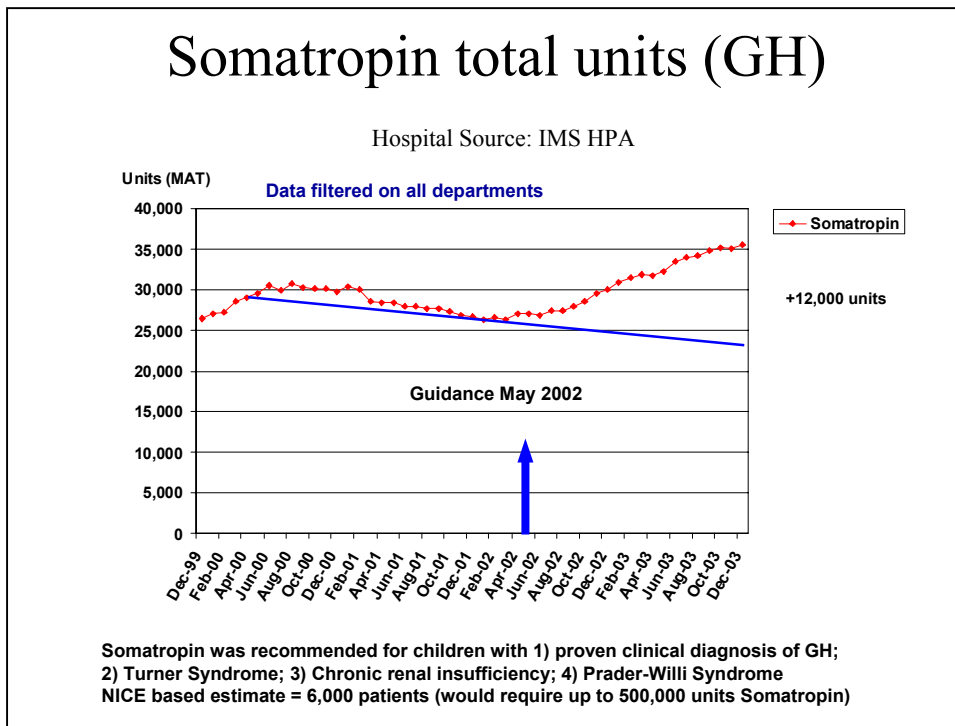
**Figure 23: Infliximab and etanercept use in Paediatrics (Juvenile arthritis)**



Both etanercept and infliximab use in paediatrics has increased at an accelerated rate since guidance was published in March 2002. We are assuming that the majority of prescribing of these two products in paediatrics would be for juvenile arthritis although it is possible that some treatment of Crohn’s disease may be occurring. Use of infliximab in the under 17’s is not recommended and so it is interesting to see this level of prescribing in paediatrics. It is possible that the supply issues with etanercept have artificially increased the use of infliximab here.

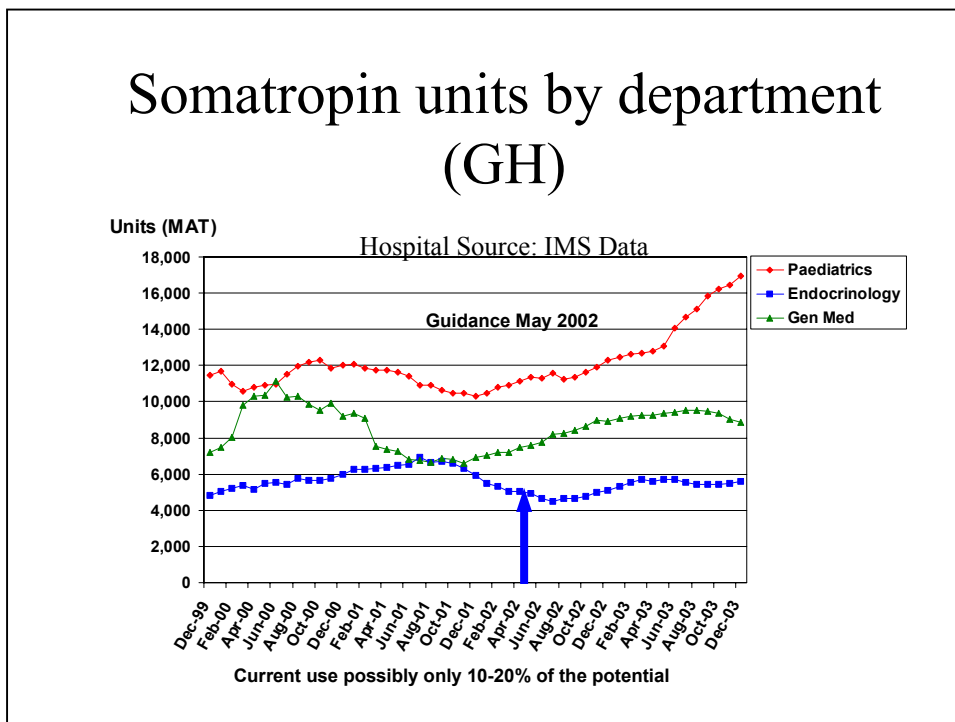
### 3.13 Growth Hormone

Figure 24: Hospital use of growth hormone



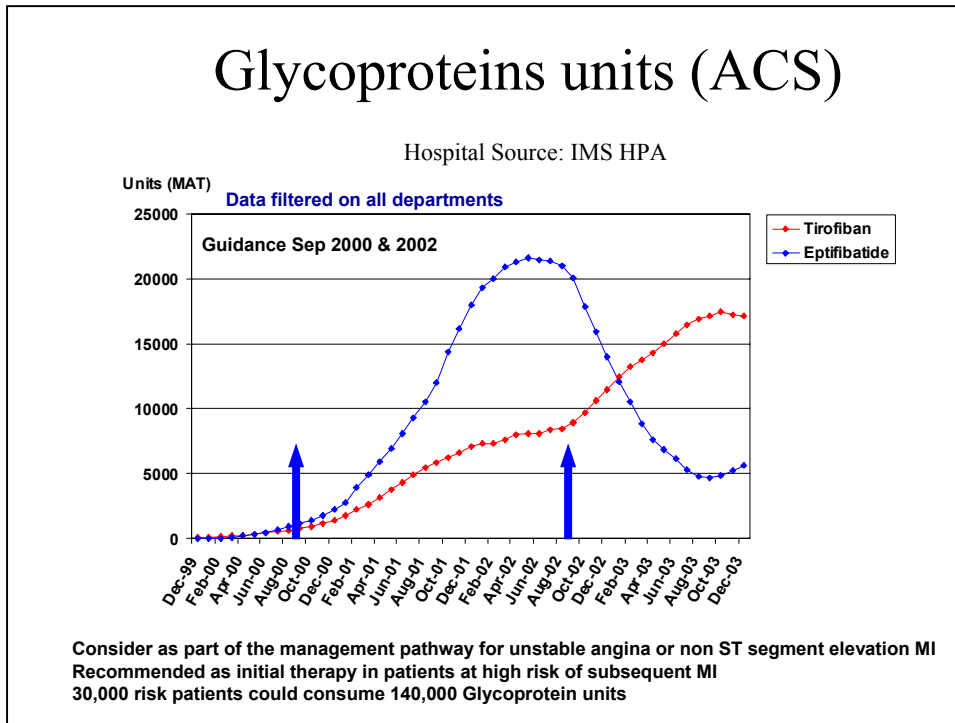
Somatropin was recommended for four different types of growth related diseases. The NICE estimate of eligible patients was in the region of 6,000 patients. If all of these patients were treated then up to 500,000 units of growth hormone would be consumed each year in England and Wales. This very positive guidance has turned a product decline into steep growth.

Figure 25: Growth hormone use by department



### 3.14 Glycoproteins for acute coronary syndromes

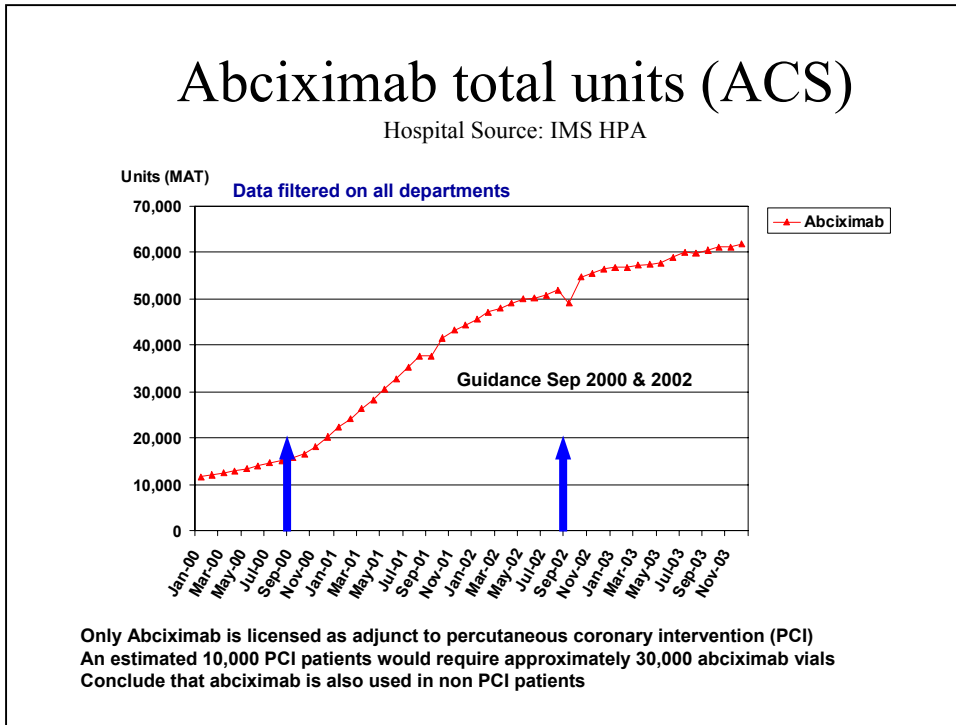
Figure 26: Hospital use of tirofiban and eptifibatide



These two products were recommended as part of a management pathway for unstable angina or non-ST segment elevation MI. They should be considered, as initial therapy in patients at high risk of subsequent MI. Approximately 30,000 risk patients would consume 140,000 glycoprotein units per year. Tirofiban use has accelerated since the publication of guidance. We make no conclusions about the sudden decline in eptifibatide after September 2002. Nothing in the NICE guidance recommendation would have driven this.

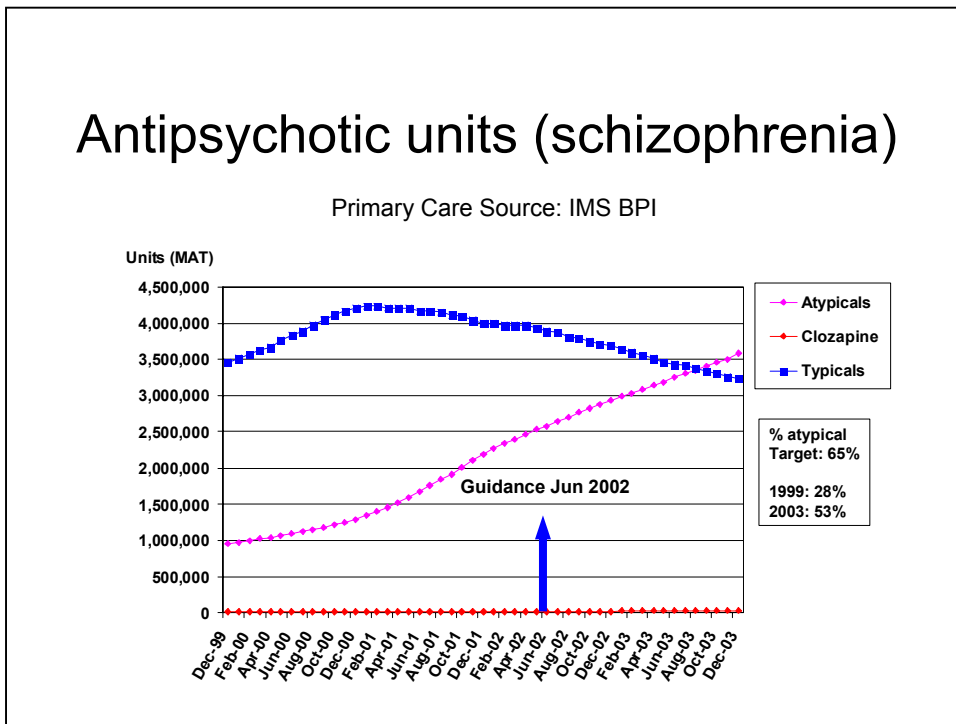
Abciximab is considered separately because it was recommended uniquely as an adjunct to percutaneous coronary intervention (PCI). There are approximately 10,000 PCI procedures carried out in England and Wales each year and these would consume around 30,000 units of abciximab. Following guidance use of abciximab has risen to over 60,000 units per year. We would therefore conclude that this product is also being used in non-PCI procedures.

Figure 27: Hospital use of abciximab



### 3.15 Atypical antipsychotics for schizophrenia

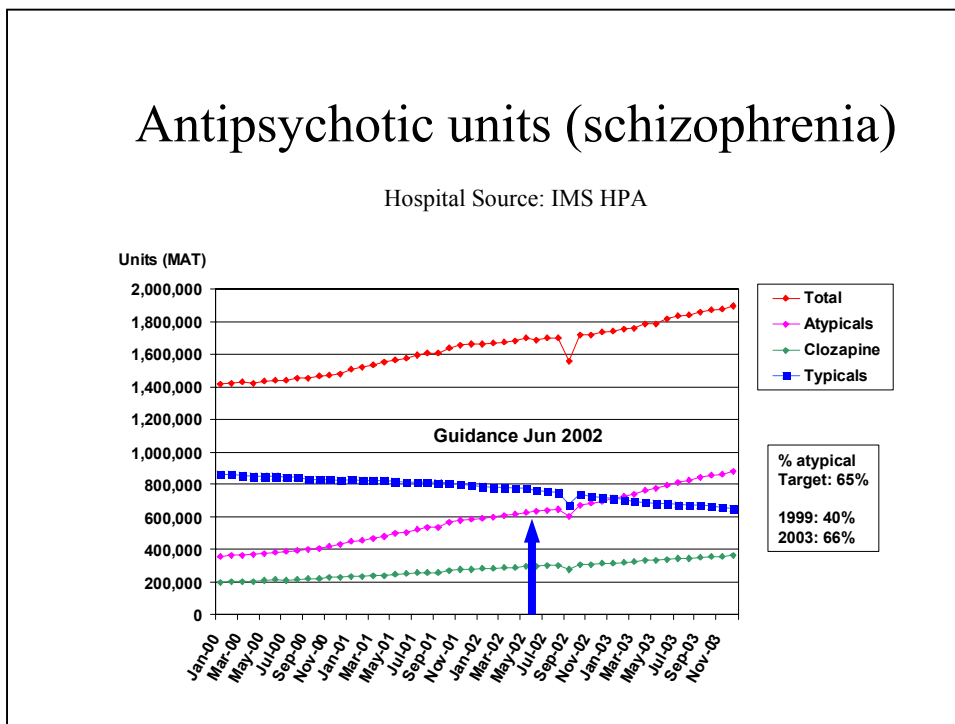
Figure 28: Antipsychotic use in primary care



The atypical antipsychotics were recommended as 1<sup>st</sup> line treatments for newly diagnosed schizophrenia. Therefore one would expect a gradual move from typical to atypical prescribing. clozapine was recommended for treatment resistant schizophrenia. Figure 28 shows that in quarter 4 of 2003, atypical use in primary care overtook typicals for the first time. In 1999 atypicals accounted for 28% of all primary care antipsychotic units prescribed. By December 2003 this had reached 53%. No change in the growth rate of atypicals is demonstrated since NICE guidance was published. This suggests that guidance was simply endorsing current practice, i.e. the gradual move away from typicals and towards atypicals.

A similar picture is seen in secondary care where atypical prescribing has grown from 40% of antipsychotic use in 1999 to 66% in 2003.

**Figure 29: Antipsychotic use in secondary care**



### 3.16 Temozolomide for malignant glioma

Figure 30: Patients receiving temozolomide for malignant glioma

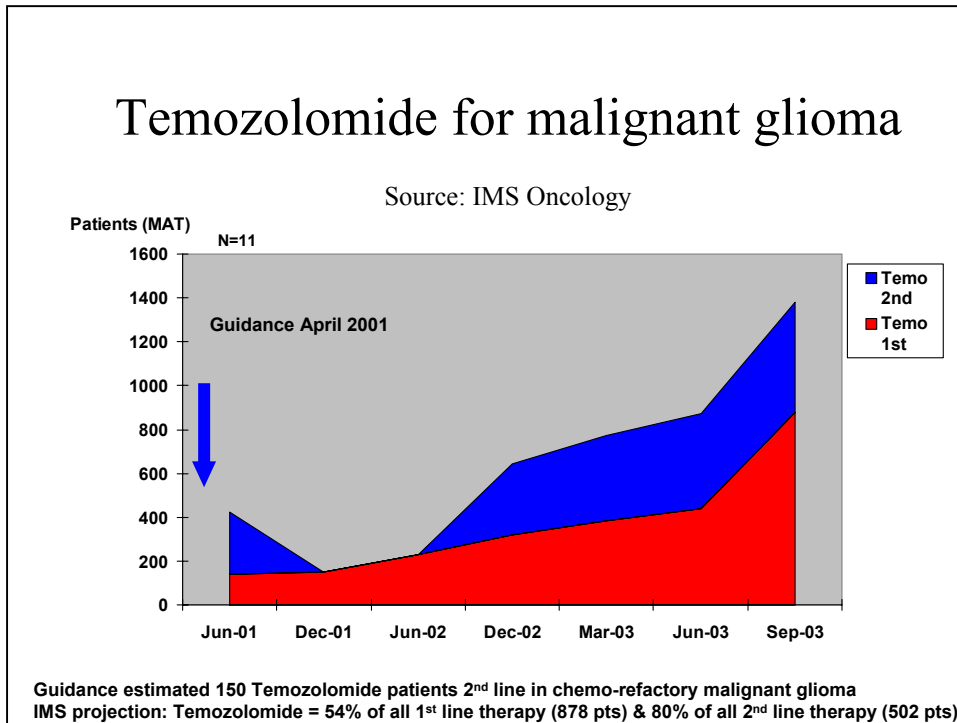


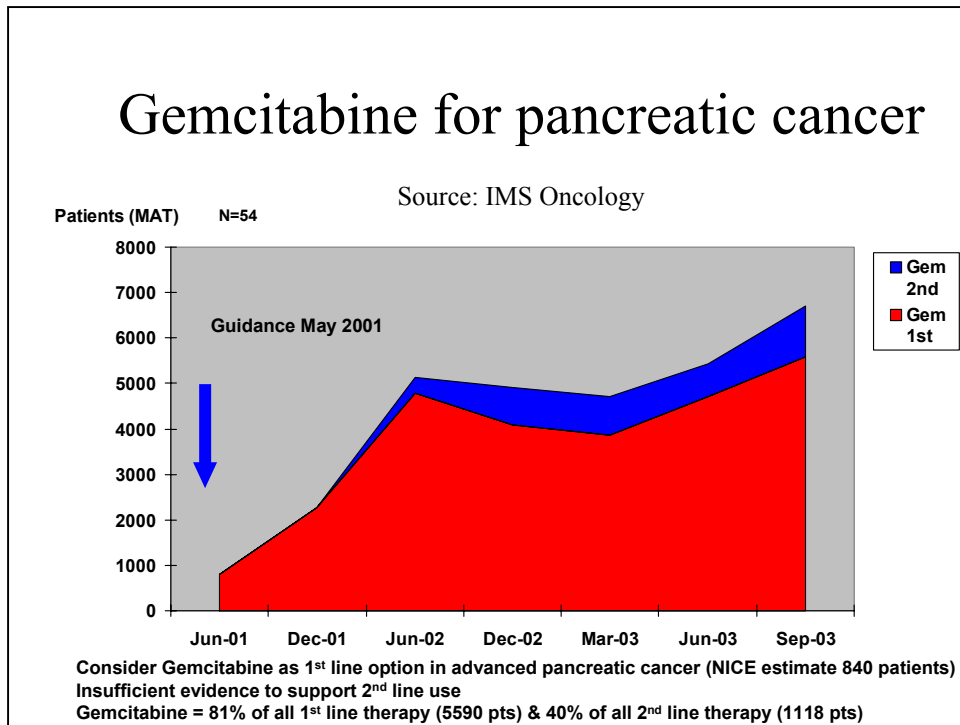
Figure 30 shows the uptake of temozolomide for malignant glioma split by 1<sup>st</sup> and 2<sup>nd</sup> line prescribing. Although the IMS data is projected for England and Wales, it is important to point out the obvious issue. Malignant glioma is a relatively rare disease and in this instance projections are based upon 11 case histories only.

NICE guidance recommended temozolomide as a 2<sup>nd</sup> line agent for malignant glioma and estimated that there were 150 eligible patients in England and Wales. The IMS projected data suggests that around 800 patients were treated with temozolomide 1<sup>st</sup> line and 500 2<sup>nd</sup> line in 2003. In this sample of case notes, temozolomide was used in 54% of all 1<sup>st</sup> line treatments and 80% of all 2<sup>nd</sup> line treatments.

A broad conclusion that can be drawn is that temozolomide is being increasingly used as a 1<sup>st</sup> choice agent in malignant glioma, outside of the recommendations made in April 2001. Any future NICE review may wish to address this issue.

### 3.17 Gemcitabine for pancreatic cancer

Figure 31: Patients receiving gemcitabine for pancreatic cancer



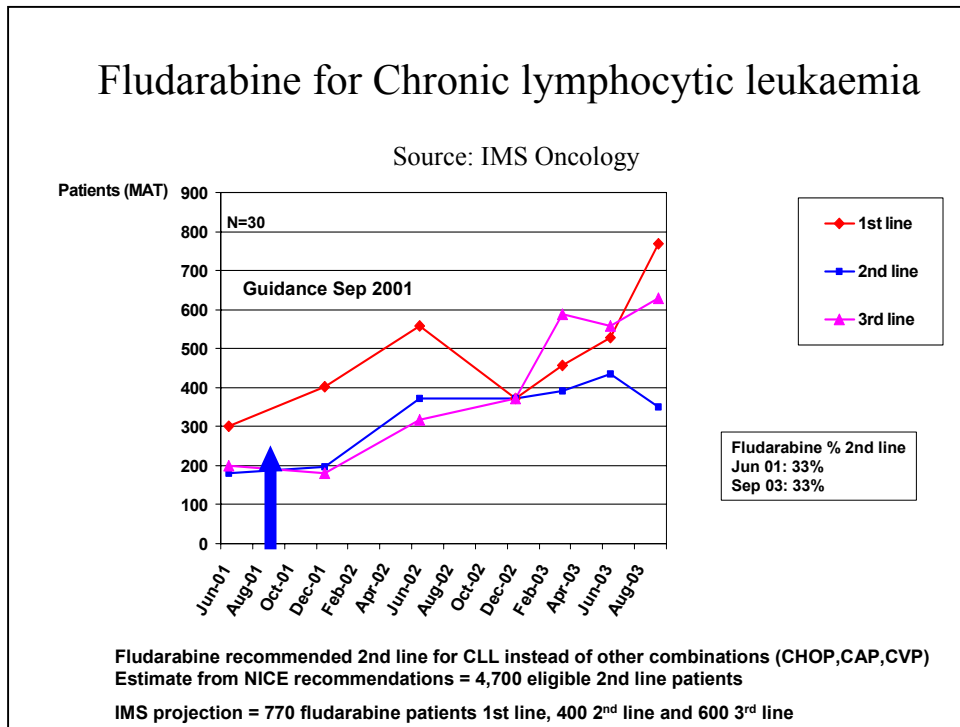
Gemcitabine was recommended as a 1<sup>st</sup> line option in advanced pancreatic cancer in guidance published in May 2001. NICE also suggested that there was insufficient evidence to support 2<sup>nd</sup> line prescribing. By September 2003 gemcitabine formed 81% of all 1<sup>st</sup> line therapy for and 40% of all 2<sup>nd</sup> line therapy for advanced pancreatic cancer.

IMS projected data (based on 54 patient records) suggests that over 6,000 patients received gemcitabine in 2003. This is significantly above the estimate of 840 eligible patients estimated in the guidance.

Again, gemcitabine appears to be being used in a wider sense than the guidance recommended in 2001. Any future review may wish to address this, in particular, the use of gemcitabine as a 2<sup>nd</sup> line option in advanced pancreatic cancer.

### 3.18 Fludarabine for chronic lymphocytic leukaemia (CLL)

Figure 32: Patients receiving fludarabine for CLL

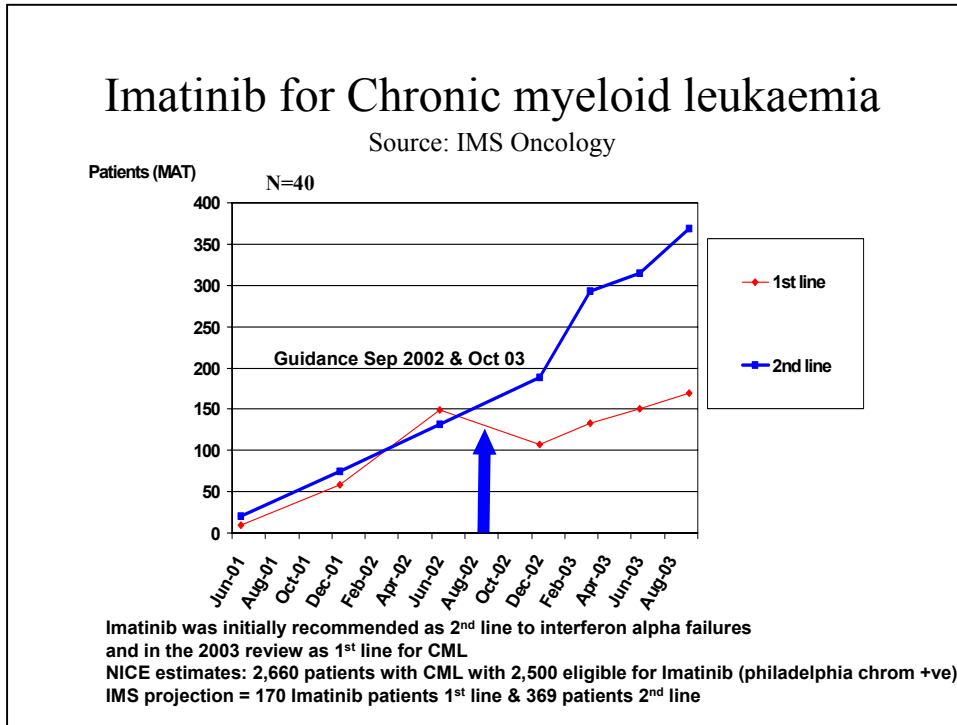


In September 2001, NICE recommended fludarabine as a 2<sup>nd</sup> line option for CLL in preference to other combination therapy such as CHOP, CAP and CVP. An estimated 4,700 patients would be eligible for 2<sup>nd</sup> line fludarabine.

The IMS oncology data (based on 30 case notes) suggests that there were 770 1<sup>st</sup> line patients, 400 2<sup>nd</sup> line patients and 600 3<sup>rd</sup> line patients receiving fludarabine. Interestingly, figure 32 shows that fludarabine use as a 1<sup>st</sup> line and 3<sup>rd</sup> line therapy is increasing whilst 2<sup>nd</sup> line is tailing off. This is the opposite of what would be expected following the NICE guidance recommendations.

### 3.19 Imatinib for chronic myeloid leukaemia (CML)

Figure 32: Patients receiving imatinib for CML

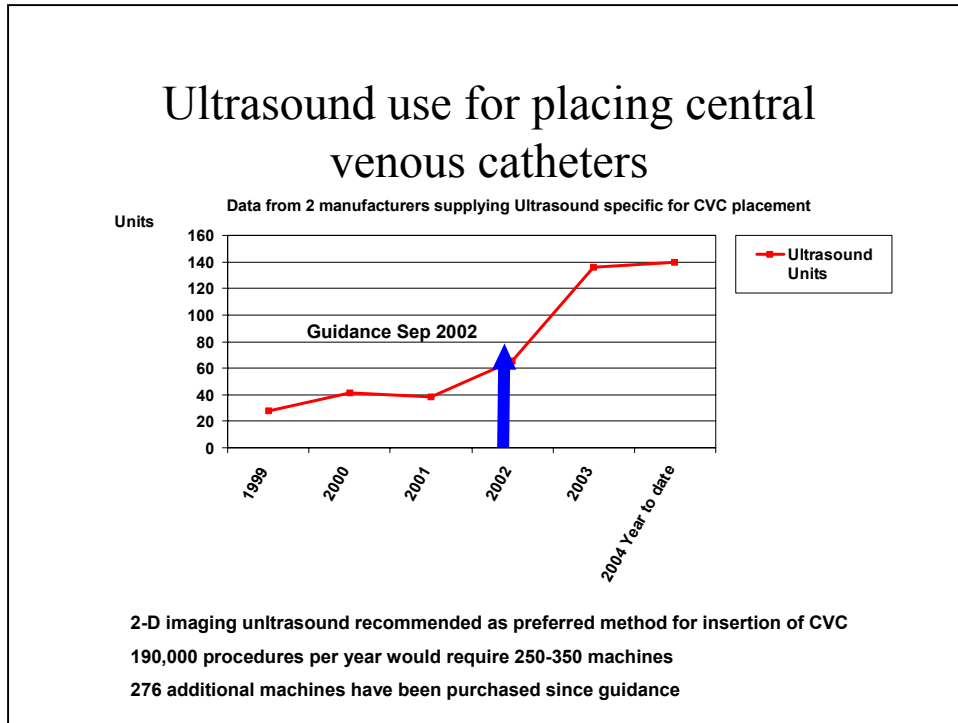


Imatinib was recommended as a 2<sup>nd</sup> line option for alpha interferon failures in guidance published in Sep 2002. In a review published in October 2003 this was upgraded to a 1<sup>st</sup> line recommendation for the treatment of CML. IMS data shows that the effect of guidance was to increase the trend towards 2<sup>nd</sup> line prescribing and it will be interesting to see whether the 2003 review encourages 1<sup>st</sup> line use over the next 12 months or so. Analysing the IMS data by CML stage of disease shows that 63% of imatinib 2<sup>nd</sup> line prescribing was for patients in the chronic stage, 15% were in blast crisis and 7% in the accelerated phase. The remaining 15% were not specified.

There are possibly 2,500 patients eligible for imatinib and around 500 patients currently receiving treatment. One would expect a significant further increase in the use of imatinib if this guidance were to be fully implemented.

### 3.20 Ultrasound use for placing central venous catheters

Figure 33: Manufacturer sales of specific ultrasounds

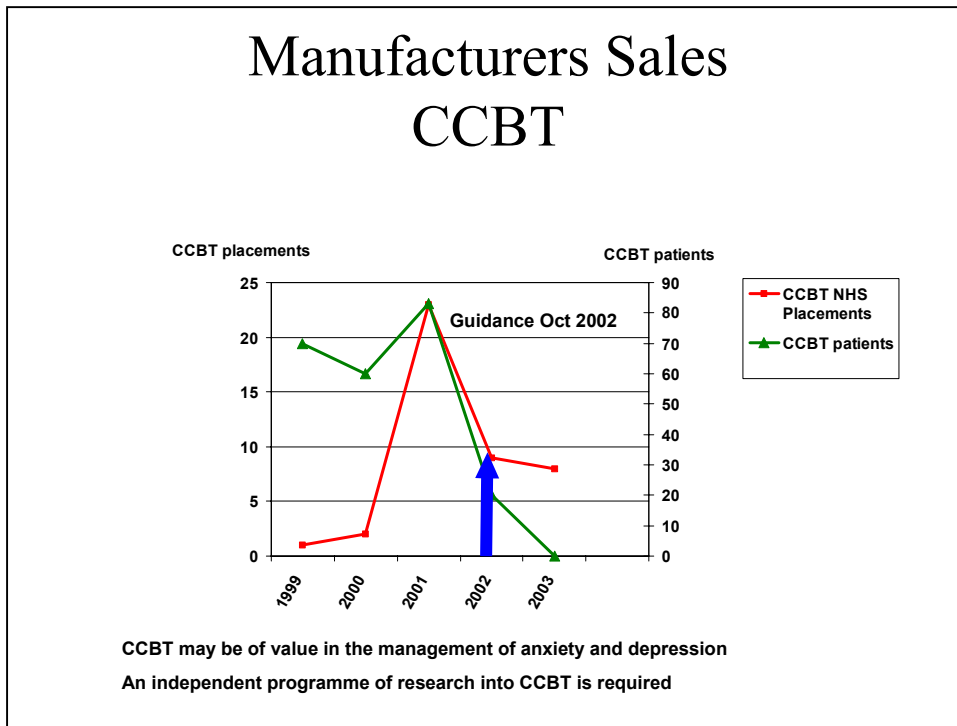


Measuring the impact of guidance in a quantitative way is difficult for this topic. Ultrasound machines are used across a range of disciplines for a range of purposes. However, a marker for impact is the manufacturer sales of two specific ultrasound machines marketed specifically for the purpose of CVC placement. NICE guidance recommended 2-D imaging as the preferred method for CVC insertion. An estimated 190,000 procedures per year would require 250-350 US machines. Figure 33 shows that an additional 276 2-D imaging machines have been purchased since guidance was published in September 2002.

In order to effectively measure whether the specific recommendations made in the guidance are being adopted, Abacus are carrying out an audit of anaesthetists, which will be presented later in 2004.

### 3.21 Computerised cognitive behavioural therapy for depression

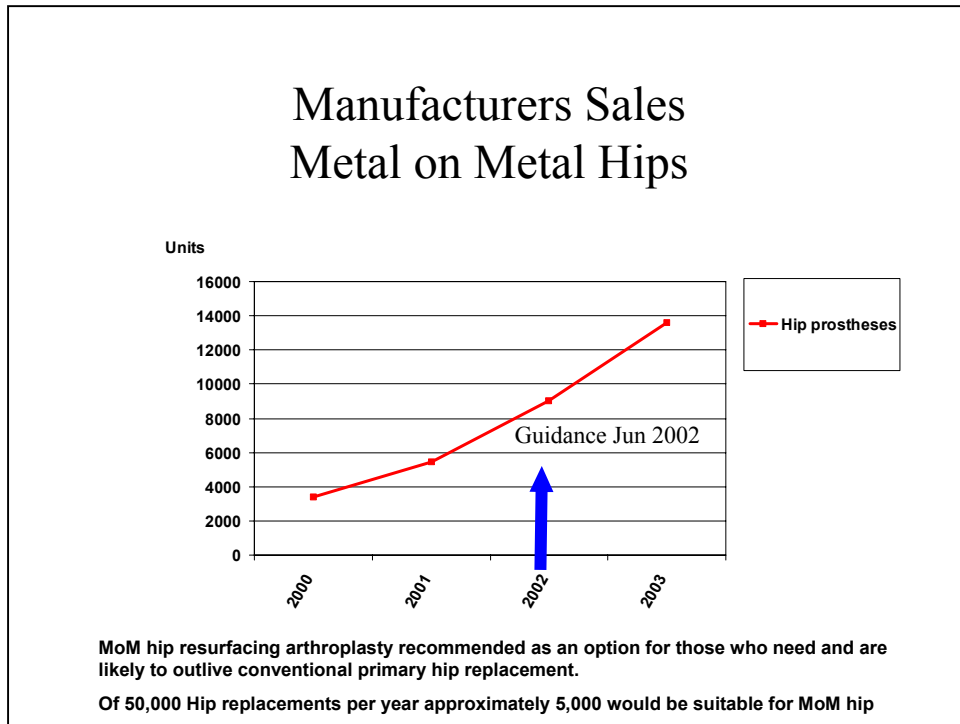
Figure 33: Manufacturer sales of CCBT



NICE guidance concluded that further evidence into the value of CCBT for treating depression was required. In discussion with two major suppliers of CCBT, it was clear that the impact of NICE guidance had been dramatic on enquiries into purchases. There were 44 active enquiries from mental health trusts/PCTs. Following the NICE guidance publication all of these withdrew suggesting that they would wait for further evidence into CCBT or another NICE review.

### 3.22 Metal on metal hips

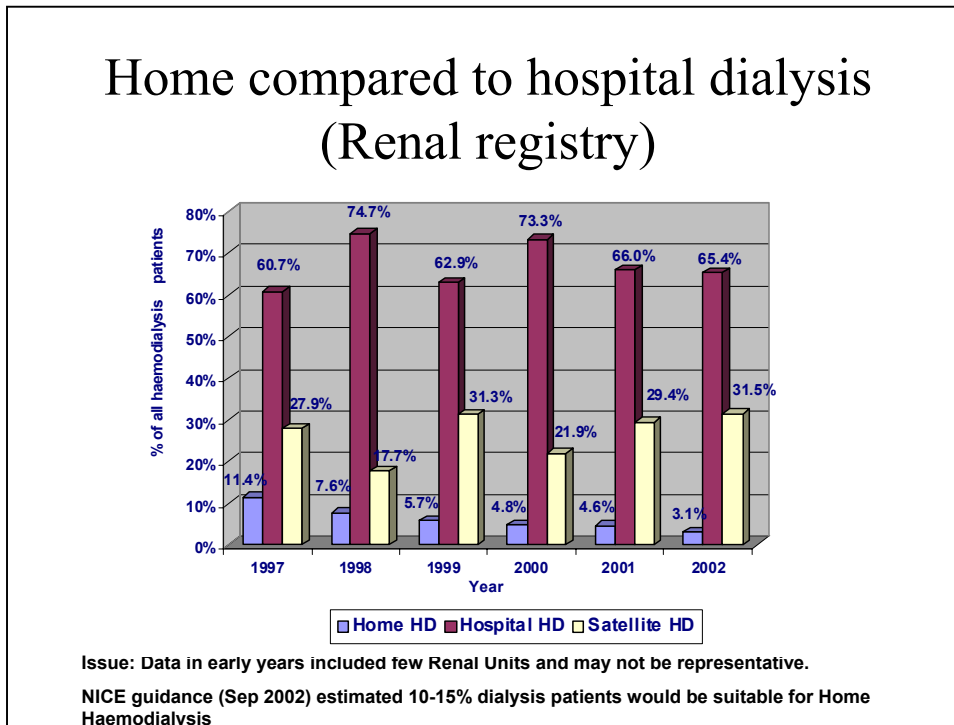
Figure 34: Manufacturer sales of MOM hips



Metal on metal hip arthroplasty was recommended as an option for patients who needed a hip replacement and are likely to outlive the conventional primary hip replacement. Of 50,000 annual procedures in England and Wales, NICE guidance estimated that 10% or 5,000 patients would be suitable for a metal on metal hip. Figure 34 shows the combined sales of MoM hips from 2 major manufacturers. Sales of MoM hips do not exactly equate to numbers of procedures carried out but should be a very good marker as hospitals will not purchase hips to simply hold as stock. In 2003, nearly 14,000 MoM hips were sold to the NHS suggesting that the uptake of this health technology is greater than that estimated in the original guidance.

### 3.23 Home compared to hospital dialysis

Figure 35: Renal Registry data reviewing haemodialysis treatment modalities



This data was simply taken from the renal registry reports with some additional communications with David Ansell at the Renal Registry. NICE guidance in September 2002 estimated that 10-15% patients requiring dialysis would be suitable for home haemodialysis. Figure 35 shows that there has been a gradual decline in the proportion of haemodialysis carried out at home over the last 6 years. Caution should be applied when interpreting the data in earlier years because the Renal Registry was less complete than it is now and therefore may not be fully representative. However, the broad conclusion is that there is scope for significant increases in the number of patients treated at home and it will be useful to monitor the trends on treatment modality over the next few years. It takes some considerable effort to convert a home in order to support haemodialysis. Therefore implementing NICE guidance recommendations would be expected to take some time in this instance.

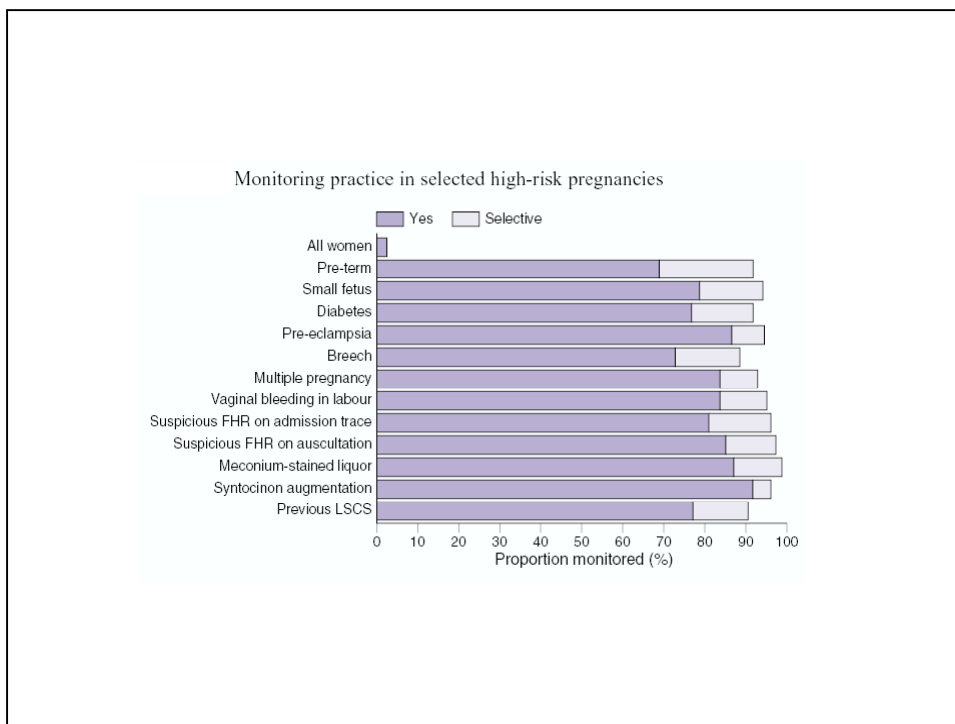
### 3.24 Electronic foetal monitoring

This was the only clinical guideline included in the list of 28 topics for review. The 8<sup>th</sup> annual report by the confidential enquiries into stillborn deaths in infancy (CESDI) included the results of a survey of maternity units carried out by the Royal College of Obstetrics and Gynaecology (RCOG) in 1999/2000. This survey will be repeated and should be published in 2004 giving a before and after NICE picture of EFM use in maternity suites.

The CESDI report suggested that basic provision of EFM should require 2-4 monitors per 1,000 deliveries. Guidelines into EFM should also be available in all maternity units. The 2,000 survey of 250 maternity units showed the median number of deliveries per maternity suite was 2,700 and that the median number of machines per suite was 7. This equates to 2.6 machines per 1,000 deliveries, i.e. within the CESDI recommendation. 74% maternity suites had EFM guidelines. The average monitoring in high-risk patients (described in the NICE guideline) was 94% and only 9 of the 248 responding maternity units did not use EFM.

This information will be updates once the 2004 survey data become available.

**Figure 36: Monitoring practice taken from the 8<sup>th</sup> CESDI annual review**



### 3.25 Debriding agents for difficult to heal surgical wounds

A prospective audit is being carried out to measure the impact of this guidance and results will be presented when the data becomes available.

## 4. SUMMARY AND CONCLUSIONS

This research took a global look at the impact that NICE guidance has had on 28 different disease areas, over a third of all NICE appraisals so far. The methodology used does not give as much detailed information as a prospective audit and should be interpreted as such. We present trends rather than specifics. However some broad conclusions can be drawn.

There was a general perception when NICE first began appraising products and disease areas that uptake of new chemical entities would be slowed, i.e. that guidance would have a negative effect on prescribing. Of the 28 disease areas reviewed here, there were 33 recommendations and only four that could be described as negative. The tone of NICE guidance is more often positive, with approximately a third of the recommendations that we reviewed suggesting broad or 1<sup>st</sup> line usage.

Similarly, there is a broad perception that NICE guidance is not implemented fully enough and certainly not within the required 3 months following publication of guidance. This research suggests that different disease areas have been implemented to varying extents.

There are examples of guidance endorsing current practice resulting in continued product growth but at the same rate as before publication of guidance. Cox IIs and atypical antipsychotics are good examples.

There are examples of accelerated product uptake such as riluzole for motor neurone disease and gastric bands for obesity surgery. For these two examples, the majority of patients who fit the criteria for riluzole have now been treated, whereas there is a significant investment in the surgical infrastructure required if the target of 8,000 annual obesity surgery procedures is to be met.

We have also demonstrated the impact of guidance on product positioning within a prescribing pathway. A very good example is the impact of guidance on the treatment of advanced colorectal cancer. Three different recommendations were made for three different products and in each case the corresponding change in use of product has been demonstrated. Oxaliplatin was recommended as a 1<sup>st</sup> line treatment and its usage as a 1<sup>st</sup> choice agent has increased. Irinotecan was recommended as a 2<sup>nd</sup> line agent. First line use has declined as 2<sup>nd</sup> line use has increased. Finally, raltitrexed was not recommended and no prescribing was detected using this methodology.

NICE guidance is driving change but at different rates for different disease areas. Of the 28 topics we reviewed, 12 could be classed as reasonably implemented within the expectations of guidance. Another 12 were classified as under implemented and only 4 driving utilisation of product above the expectations described in NICE guidance. Of these 4, we explained that factors outside of NICE guidance drove the increase in Beta Interferon (risk sharing scheme). Two of the others were for relatively rare cancers and so projections using this methodology are imprecise. Only metal on metal hip usage appears to be used more than the original estimate in the guidance (5,000 MoM hips per year estimated, 14,000 MoM hips sold).

## APPENDIX 1: NICE TOPICS REVIEWED CATEGORISED BY LEVEL OF IMPLEMENTATION

### Guidance Implementation consistent with NICE estimates

<i>Guidance</i>
CCBT
Raltitrexed in colorectal cancer
Infliximab for Crohns
Ultrasound use in CVC placement
Riluzole in MND
Pioglitazone in diabetes
Oxaliplatin (advanced colorectal cancer)
Sibutramine for obesity
Glycoprotein inhibitors *
Routine AADP for RhD negative women
Fludarabine for CLL
Asthma devices in children

12 of 28 sets of guidance reviewed have been implemented as expected

The above topics were deemed to be reasonably well implemented in accordance with expectations described in each NICE guidance.

This includes negative recommendations such as those for raltitrexed and CCBT, which translated into little product use, and positive recommendations such as that for riluzole which drove increased product use, particularly in primary care.

## Guidance Implementation below NICE estimates

<i>Guidance</i>
PLDH for advanced ovarian cancer
Topotecan for advanced ovarian cancer
Etanercept for juvenile idiopathic arthritis
Surgery for Obesity
Irinotecan for advanced colorectal cancer
Cox II's for arthritis
Growth Hormone
Imatinab for CML
Etanercept and Infliximab for RA
Newer atypicals for schizophrenia
Home haemodialysis
NRT for smoking cessation

12 of 28 topics reviewed have not yet been fully implemented

The above topics were deemed to be under implemented according to the expectations derived from each set of NICE guidance. This includes topics such as advanced ovarian cancer where product use appears to be minimal when given a positive recommendation. It also includes disease areas that are showing continued growth but not yet at the expectation described in the NICE guidance. A good example of this is the surgical treatment of obesity where an increase in procedures has been demonstrated but where a significant increase in capacity is required to achieve the target of 8,000 procedures per year. Similarly, Cox IIs, atypicals and NRT for smoking cessation have all shown continued increases in prescribing but not yet at the levels estimated in each guidance.

## Implementation topics above NICE estimates

<i>Guidance</i>
Temozolomide for malignant glioma
B Interferon for MS
Gemcitabine for pancreatic cancer
Metal on metal hips

**NB: Other factors such as the risk share scheme for B Interferon have contributed To this picture.**

**Cancer estimates are based upon small numbers with a high potential margin of error**

Very few of the 28 topics reviewed seem to have resulted in a greater than forecast impact on resource utilisation.

B interferon was not recommended but product usage has increased. This can be explained by the risk-sharing scheme agreed with Industry and published in a health service circular a few months after NICE guidance was published.

Temozolomide and gemcitabine appear to be used in more patients than would be expected from epidemiological forecasts and the recommendations by NICE. Caution should be applied here because the IMS Oncology data uses a sampling methodology and projections are based upon relatively small numbers.

About 10% of the 50,000 hip replacements were expected to be suitable for a metal on metal hip. Instead of 5,000 unit sales of metal hips, our audit of manufacturer sales showed 14,000 units sold in 2003. Again caution should be applied in interpretation because a metal hip sold does not equate to a procedure carried out although this should be a good indicator of overall trend.

## APPENDIX 2: A description of the IMS data sources

IMS specialises in the collection and interpretation of anonymised health information, from hospitals, general practice and pharmacies (primary and secondary care), both within and outside of the UK.

### **Disease Analyser, Mediplus (DAM)**

This is a longitudinal database of the management of primary care patients. Containing a minimum of 10 year's history on each patient it is available for 4 countries in Europe (UK, Germany, France and Austria) with plans to develop databases in other countries.

In the UK, data is collected automatically from the computerised practice systems of a panel of GP practices, using all versions of the Torex Healthcare systems. It records patient information provided by the GP. Data from approximately 3 million patients is collected. However, the final panel used for data analysis is the best quality data from approximately 1.1 million patient records in 135 practices with approximately 720 GPs.

The records are based on a problem orientated recording system (POMR); each consultation is recorded and full information on treatment (and prescribing) is linked directly to a problem/diagnosis (via read codes) and therefore tracks the prescribing habits of GPs for specific indications.

The following type of information is also available through this data set:

Diagnostic tests

Hospital referrals

Demographic details of GP practices and patients

Patient lifestyle information

Cost of prescribed pharmaceuticals

The structure of the database allows searching and linking of data to facilitate even more complicated analyses such as switch, treatment pathways and GP behavioural analyses.

Projection of sample data to approximate national levels is possible in the UK because in the healthcare system any patient may normally be registered with only one practice as an actively registered ('active') patient. This means that a patient may only appear once within DAM as an 'active' patient. The projection methodology that is used is based on this assumption. Projection methodology assumes also that the entire census UK population are registered with a GP. It is therefore theoretically possible for a patient to move between practices on the DAM panel. However, moving between practices means that a patient's registration status becomes inactive in the old practice and active in the new practice. This enables single counting.

The total 'active' patients registered on the panel comprise a fraction of the total UK population (census data). Since both the panel and census figures are known then the multiplication factor can be calculated. For example, if 1 million patients were 'active' within DAM and the total UK population was 60 million, then the projection factor would be 60. On this basis, from the

active total of 1 million patients, if 10,000 had a record of diabetes mellitus, then the total in the UK suffering from this disease at any one time would be around 60,000 (fictitious data).

The projection factor is calculated for each database update (monthly) as the number of patients actively registered within the panel practices vary. The number of practices included within the panel sample can also vary from month to month. If a practice is disqualified from the panel it is replaced with a similar sample practice. For the purposes of this project the projection factor will be adjusted to include the England and Wales population only.

### **Hospital Pharmacy Audit (HPA)**

This data is drawn from the computer systems of hospital pharmacies and covers approximately 94% of all acute beds in the UK. It is usage data rather than sales data showing the true use of products within hospitals, unaffected by bulk purchasing and special deals etc. It includes in-patient and outpatient dispensing and can be split into 64 individual specialities. Data is collected monthly and compiled into two data sets – one for national figures and one by individual hospital. The database allows information on therapy class, molecule and pack to be extracted. There is no information on diagnosis. Data are projected on a regional basis according to the proportion of beds in the region contributing to the sample, compared to the number of beds in the region as a whole.

HPA data can be projected to national level to compensate for any hospitals that are excluded from the panel. To ensure that the data is as accurate as possible, the HPA national data is projected at a 2-digit postcode level, according to acute bed coverage in the panel. By projecting in this way HPA national data takes into account any regional variances and provides an accurate picture for the entire UK. For example, if there were 1,000 beds at postcode level but only 980 beds in the panel, the projection factor would be 1.02. For the purpose of this project data can be projected to account for England and Wales only.

### **Oncology Database**

This database is constructed from cancer patient case histories from a sample of physicians involved in the treatment of cancer. The data is collected quarterly in 5 major European countries including the UK and physicians are asked to report on the last 5 to 25 patients that they have seen. Patient details include:

- General information on patient condition
- Extensive detail on all current drug therapy
- Treatment history from diagnosis including all key drug types
- Patient numbers

The precise structure of the panel varies by country, however broadly speaking the following specialities are covered:

- Key specialities
  - Oncology
  - Radiotherapy
  - Haematology
- Relevant surgical specialities
  - Gynaecology

Urology  
General surgery  
ENT  
Orthopaedics

Medical specialities  
Chest physicians  
Dermatology  
General medicine

The projected figure is an estimate of total patients seen or treated in hospital for cancer. These estimates are made by tumour type. The figure is calculated for the UK as a whole (including Scotland and N Ireland). However, 88% of the data represents England and Wales. Data cannot be provided at any lower geographical detail due to legal requirements of patient anonymity. Information for calculating projection derives from:

Patient number information from physicians

Total patients seen/treated in the last 12 months  
Number of patients newly diagnosed

Published data on cancer incidence

Patient number information is applied to published data on cancer incidence to estimate the total number of patients being treated (Globocan). Globocan collates cancer incidence and mortality worldwide via International Agency for Research on Cancer, World Health Organisation.

For example:

In country A

Total number of patients with cancer X seen/treated in the last 12 months = 220.29

Number of patients newly diagnosed with cancer X in the last 12 months = 143.37

Ratio of new to total patients with cancer X =  $143.3/220.29 = 0.651$

Reported incidence of cancer X (Globocan) 34,815

Estimated total number of patients seen/treated with cancer X  
=  $34,815/0.651 = 53,479$  patients

### **British Pharmaceutical Index - BPI**

The BPI measures the UK retail pharmaceutical market. It provides monthly information on the value and volume of pharmaceutical sales to retail pharmacies and dispensing doctors. The data

comprise a virtual census of information on products purchased by retail pharmacies and dispensing doctors and is then projected to the total national level.

BPI is the most complete source of retail sales data available. All major wholesaler groups, Boots, Lloyds and many smaller pharmacy chains, provide data. Many manufacturers provide full details of their direct sales. Approximately 97%+ of all retail sales are received, with the residue of the market estimated from the purchase data of approximately 700 pharmacies.

Abacus used BPI data in conjunction with HPA data to provide a complete picture of usage of specific molecules. By using the totals from both, an accurate measure of any changes in primary and secondary care can be measured. Again only data from England and Wales was used in this project.

### IMS data sources used for each guidance

NUMBER	DATE ISSUED	GUIDANCE	IMS DATA
20	January 2001	Riluzole (Rilutek) for Motor Neurone Disease	✓ (HPA & BPI)
21	March 2001	Pioglitazone for type 2 diabetes mellitus	✓ (DAM)
23	April 2001	Temozolomide for malignant glioma	✓ (Oncology)
25	May 2001	Gemcitabine for pancreatic cancer	✓ (Oncology)
27	July 2001	Cyclo-oxygenase (Cox) II selective inhibitors for osteoarthritis and rheumatoid arthritis	✓ (DAM)
28	August 2001	Topotecan for advanced ovarian cancer	✓ (Oncology)
29	September 2001	Fludarabine for chronic B cell lymphocytic Leukaemia	✓ (Oncology)
31	October 2001	Sibutramine for obesity in adults	✓ (DAM)
32	January 2002	Beta interferon and glatiramer acetate for multiple sclerosis	✓ (HPA)
39	March 2002	Nicotine Replacement Therapy and bupropion for smoking cessation	✓ (DAM)

<b>NUMBER</b>	<b>DATE ISSUED</b>	<b>GUIDANCE</b>	<b>IMS DATA</b>
36	March 2002	Etanercept and infliximab for rheumatoid arthritis	✓ (HPA)
35	March 2002	Etanercept for juvenile idiopathic arthritis	✓ (HPA)
33	January 2002	Irinotecan, oxaliplatin and raltitrexed for advanced colorectal cancer	✓ (Oncology)
38	April 2002	Inhaler devices for chronic asthma in older children (aged 5 –15)	✓ (DAM)
40	April 2002	Infliximab for Crohn's disease	✓ (HPA)
42	May 2002	Human growth hormone (somatropin) in children with growth failure	✓ (HPA)
41	May 2002	Routine antenatal anti-D prophylaxis for RhD negative women	✓ (HPA)
45	June 2002	Pegylated liposomal doxorubicin hydrochloride for the treatment of advanced ovarian cancer	✓ (Oncology)
43	June 2002	Newer (atypical) antipsychotic drugs for schizophrenia	✓ (DAM)
50	September 2002	Imatinab for chronic myeloid leukaemia	✓ (Oncology)
47	September 2002	Glycoprotein Iib/IIIa inhibitors in the treatment of acute coronary syndromes	✓ (HPA)

### Non-prescription based guidance

<b>NUMBER</b>	<b>DATE ISSUED</b>	<b>GUIDANCE</b>
24	April 2001	Debriding agents and specialist wound care clinics for difficult to heal surgical wounds
Clincial Guideline (c)	May 2001	The use of electronic fetal monitoring
44	June 2002	Metal on metal hip resurfacing arthroplasty
46	July 2002	Surgery to aid weight reduction for people with morbid obesity
48	September 2002	Home compared with hospital haemodialysis for patients with end stage renal failure
49	September 2002	Ultrasound locating devices for placing central venous catheters
51	October 2002	Computerised cognitive behavioural therapy for anxiety and depression