Adverse events and the National Health Service: 
an economic perspective

a report to the 
National Patient Safety Agency

by 
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Final report 
November 2003
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Introduction

The publication in the UK of the Department of Health reports “An organization with a memory” (Chief Medical Officer 2000) and Making Amends (Department of Health 2003) and in the US of the Institute of Medicine report To Err is Human,(Kohn, Corrigan, & Donaldson 2000) and the establishment of the National Patient Safety Agency, have helped to increase awareness of the issues surrounding medical errors and adverse events in health care. However, although there is a substantial literature on the frequency of medical errors, much less attention has been paid to identifying and evaluating actions that might reduce them, and even fewer attempts have been made to consider these issues from an economic perspective, and in particular to address the role of cost-effectiveness analysis in this area.

The objective of this report is to begin to set out a cost-effectiveness approach to patient safety. The report begins by setting out some terminology concerning patient safety, then collates information on the main published empirical studies on the incidence of medical errors, in general hospital settings, in specific areas of patient care, in medication prescribing, and in primary care. It then identifies the cost analyses that have been published to date, and proceeds to consider some of the methodological features and limitations of the studies that have been reported to date. The report then sets out the general framework of cost-effectiveness analysis and places medical errors and adverse events within that framework. It concludes by suggesting ways in which the cost-effectiveness approach could be encouraged in the area of patient safety.

Terminology

The IoM locates patient safety within a more general framework of quality of care, consisting of three broad domains; 1) the first domain is safety, defined as “freedom from accidental injury” (p18); 2) the second domain is practice consistent with current medical knowledge and best practice; and 3) the third domain is responsiveness to customer-specific values, expectations and preferences. (Kohn, Corrigan, & Donaldson 2000)

Within this framework, quality problems are likely to arise for three broad reasons: misuse, meaning avoidable complications that prevent patients from receiving the full potential benefit of a service; overuse, meaning a potential for harm arising because the provision of a service exceeds the likely benefit, and underuse, meaning failure to provide a service that would have been likely to produce a favourable outcome for the patient. It follows that misuse is most likely to be within the safety
domain, while underuse and overuse will primarily be within the domain of current medical knowledge and best practice.

Continuing the IoM approach, if safety can be defined as freedom from accidental injury, then an adverse event can be defined as an injury caused by medical management rather than by the underlying disease or medical condition of the patient, and a preventable adverse event can be defined as an adverse event attributable to error. Finally, a negligent adverse event can be defined as a subset of preventable adverse event that satisfies legal criteria used in determining negligence (i.e. whether the care provided failed to meet the standard of care reasonably expected). (IoM page 28) Figure 1 sets these definitions out in the form of a Venn diagram. It can be seen some errors do not result in adverse events (so-called “near misses”), and not all adverse events arise from error. However, all preventable adverse events do involve error, and all negligent adverse events are preventable. One feature if the schema is that it does not make provision for negligence that does not result in an adverse event: in effect is not possible within this schema to be negligent unless and until an adverse event has occurred.

Figure 1: Venn diagram representing Institute of Medicine terminology

```
All episodes of care
  All errors
    All adverse events
      Preventable adverse events
        Negligent adverse events
```
The incidence of medical errors and adverse events

Because the characteristics of errors and adverse events, and the typical methodologies employed, vary in different areas of health care, it is useful to review the literature on errors and adverse events separately for hospital care, medications, and primary care, and also to consider cost estimates as a separate sub-section. This categorisation broadly follows that used by the Institute of Medicine study in 2000, (Kohn, Corrigan, & Donaldson 2000) in which a literature summary of studies examining the frequency of errors and adverse events referred to 11 general studies of errors and adverse events, 32 medication related studies, and 6 cost studies. However, that study did not give details of the methods used to identify relevant literature, and cannot be considered a systematic review; in addition, a significant number of studies have been published since it appeared. The review that follows is based on a structured review of published English language studies reporting estimates of the incidence of medical errors, adverse events and preventable or negligent adverse events, and of the costs associated with these events.

Hospital care- general studies

Some early estimates of the rate at which adverse events occur in hospital were reported as early as 1964 by Shimmel for the USA, (Shimmel EM 1964) and by Ogilvie and Ruedy for Canada in 1967. (Ogilvie & Ruedy 1967) These were followed in 1977 by the California Medical Association report on the medical insurance feasibility study, which conducted detailed analysis of the hospital records of 2 hospitals in California in order to estimate the number of events with the potential to give rise to litigation. (Mills 1977)

Another early study attempting to quantify the incidence of errors or adverse events in health care was performed by Steel and colleagues (Steel et al. 1981), who collated information on 815 consecutive patients admitted to the general medical service of an American university hospital in a 5-month period in 1979. They classified 36% of all patients as having an iatrogenic illness, 9% as having experienced a major incident that threatened life or produced considerable disability, and 2% as having an iatrogenic illness that they believed contributed to the death of the patient.

In 1991 Brennan and colleagues reported the first results of the Harvard Medical Practice Study, in which the methods adopted by Mills et al in California were applied to a much larger sample of hospital records. (Brennan et al. 1991) They reviewed a total of 30,121 randomly selected patient records drawn from 51 randomly selected acute care nonpsychiatric hospitals in New York State in 1984,
and used a two-stage record review process to identify adverse events – defined as an injury caused by medical management rather than the underlying disease that prolonged the hospitalization, produced a disability at discharge, or both. They defined negligent adverse events as adverse events arising from care that fell below the standard expected of physicians in their community. They found a total of 1,133 adverse events during hospitalization in 1984, of which 647 had occurred and were discovered during the index hospitalization, 167 had occurred during outpatient care before the index hospitalization but were discovered during the index hospitalization, and 319 had occurred during earlier hospitalization but were discovered during index hospitalization; the overall crude adverse event rate was therefore 3.76%, and adjusted by age and other characteristics to the New York State population was 3.7% (95% c.i. 3.2, 4.2). Of these 1,133 adverse events, 280 (crude rate 24.7%) were classified as being due to negligence, giving a negligent adverse event rate of 0.92%; again, adjusted to the overall New York State population the results suggested that 27.6% of all adverse events were due to negligence, a weighted rate of 1.0% (95% c.i. 0.8, 1.2). Of the total adverse events identified in the Harvard Medical Practice Study, 56.8% were categorized as causing minimal impairment and recovery in less than one month, and a further 13.7% as moderate impairment with recovery within 1-6 months, but 2.8% were classified as causing longer-term moderate impairment, 3.9% as causing permanent impairment (<50% disability), 2.6% permanent impairment (>50% disability) and 13.6% as leading to death. Amongst negligent adverse events, the corresponding percentages were 45.7%, 12.1%, 3.0%, 3.2%, 3.2% and 25.4%. A small proportion of cases could not be classified according to degree of disability. By specialty, the highest rates of adverse events occurred in vascular surgery (16.1%) and thoracic and cardiac surgery (10.8%).

Based on these results, the Harvard group extrapolated to the New York State level, and estimated that there were likely to be 98,609 adverse events and 27,179 negligent adverse events each year among the 2.672 million hospital discharges across the state.

In a further analysis of data from the Harvard Medical Practice Study, Localio et al (1991) matched the medical records of the study sample with statewide data on medical-malpractice claims. They identified 51 malpractice claims, an overall rate of 0.13 claims per 100 hospital episodes discharges. Of the 280 patients previously identified by the study as having experienced an adverse event caused by medical negligence, 8 had filed a malpractice claim, with the remaining 43 malpractice claims not meeting the study’s definition of an adverse event due to negligence. Extrapolating the study results to the level of New York state, they estimated that the overall ratio of adverse events caused by negligence (27,179) to malpractice claims (3570) was 7.6 to 1, but that most
of the events for which claims were made did not meet the definition of an adverse event attributable to negligent care, suggesting that litigation infrequently compensated patients injured by medical negligence or identified providers of substandard care.

The two-stage medical review methodology employed by the Harvard Medical Practice Study was also employed in Australia as part of the Quality in Australian Health Care Study. (Wilson et al. 1995) A total of 14,655 medical admission records from 28 hospitals in New South Wales and South Australia were reviewed, and an estimated 16.6% of these admissions were categorized as adverse events, of which 51% were considered preventable. Using the same classification of severity as the Harvard Medical Practice Study, 77.1% of adverse events were judged to be minor disabilities likely to resolve within 12 months, with 13.7% resulting in permanent disability 4.9% contributing to patient death.

In 2000, Thomas et al published the results of another study utilizing the Harvard Medical Practice Study methodology. (Thomas et al. 2000a) They estimated the incidence and types of adverse events and negligent adverse events in Utah and Colorado, using a random sample of 15,000 nonpsychiatric discharges in 1992 from a representative sample of hospitals, screening records in a two-stage process. They found that adverse events occurred in 2.9% of hospitalizations, with 54% of adverse events deemed preventable and 32.6% attributable to negligence in Utah, and 56% of adverse events deemed preventable and 27.4% attributable to negligence in Colorado. Death occurred in 6.6% of adverse events, 6.9% of preventable adverse events and 8.8% of negligent adverse events. The main cause of adverse events was an operative procedure, which constituted 45% of all adverse events.

As in the Harvard Study, it proved possible to subsequently link data from the Utah/Colorado study to medical malpractice claims data, and this analysis showed that 18 patients who had been examined in the study had also filed malpractice claims: 14 of these were made in the absence of discernible negligence and 10 were made in the absence of any adverse event, while of the patients who were considered to have suffered negligent injury in the study sample, 97% did not sue. (Studdert et al. 2000)

The adverse event rates reported in the Utah/Colorado study and in the earlier Harvard Medical Practice Study formed the basis of the widely reported estimates of the US Institute of Medicine report “To Err is Human: Building a safer health care system”, published in 2000, that between 44,000 and 98,000 Americans die in hospital each year as a result of preventable adverse events, making error the 8th-leading cause of death even using the lower figure. (Kohn, Corrigan, & Donaldson 2000) These figures were apparently obtained by taking the annual total of 33.6 million US hospital admissions in 1997, and then multiplying through by (overall adverse event rate x proportion attributable to error x proportion of events
attributable to error resulting in death). For the Harvard Study this gives a 3.7% overall adverse event rate \times 58\% attributable to management error (Leape et al. 1991) \times 13.6\% of adverse events resulting in death (in fact 13.6\% was the rate for all adverse events rather than adverse events due to error (Brennan, Leape, Laird, Hebert, Localio, Lawthers, Newhouse, Weiler, & Hiatt 1991)), giving a total of 98,000 deaths per annum. For the Utah/Colorado Study this gives a 2.9\% overall adverse event rate \times 53.3\% preventable \times 6.9\% of preventable adverse events resulting in death, giving a total of 35,835 deaths per annum, which does not reconcile with the lower figure of 44,000 quoted in the Institute of Medicine report and elsewhere. It appears in fact that the report accidentally transposed the overall adverse event rates of the 2 studies, giving Harvard a 2.9\% rate and Utah/Colorado a 3.7\% rate, (see page 26 of study) and then used the 3.7\% figure in both calculations (Utah/Colorado would then be 33.6 million \times 0.037 \times 0.533 \times 0.066 (that is, they also used the 6.6\% death rate for all adverse events rather than 6.9\% for preventable adverse events) giving them a total of 43,733 or 44,000.

A similar approach has been used in other studies: for example, Jarman (2000) argued that the 3.7\% adverse event rate found in the Harvard Medical Practice Study combined with the fact that over half were preventable and about 14\% fatal, when applied to the 11 million hospital admissions in England in 1996, implies about 28,000 deaths from medical accidents every year in England or 33,000 in the UK. (Jarman 2000)

The discrepancies between the results of the Utah/Colorado studies and the Australian study – with the latter reporting an adverse event rate 5 times higher than the former – were sufficiently large to prompt direct comparisons between these studies in order to explain the differences. (Thomas et al. 2000b) (Runciman et al. 2000) The Australian data were reanalyzed as they would have been had the study been conducted in the USA, and demographic and other differences were dealt with by standardization. This resulted in the number of cases considered to be adverse events in the Australian study falling from 16.6\% to 10.6\%, primarily due to different thresholds for defining medical causation, different definitions of qualifying time periods, and other methodological differences, while the Utah/Colorado rate rose slightly from 2.9\% to 3.2\%. (Thomas, Studdert, Runciman, Webb, Sexton, Wilson, Gibberd, Harrison, & Brennan 2000b) Further qualitative analysis indicated that the major disability rate arising from adverse events was 1.7\% of admissions in both studies, and the death rate arising from adverse events was 0.3\% of admissions in both studies, illustrating that the main differences concerned adverse events involving relatively minor disabilities. (Runciman, Webb, Helps, Thomas, Sexton, Studdert, & Brennan 2000) Nevertheless, even after adjustment, a 3-fold difference in overall adverse event rates remained between these studies.
In a separate Australian study, O’Hara et al (1997) obtained routine inpatient data from all acute-care hospitals in Victoria, Australia to estimate the adverse event rate by hospital type and specialty, and to examine death rates and other variables associated with adverse events. (O’Hara & Carson 1997) They found that 5% of discharges had Australian Diagnosis Related Group codes suggesting an adverse event had occurred, the most frequent being infections, haemorrhage and pneumonia. 81% of these adverse events involved complications after surgery or other procedures, with most of the remainder attributable to adverse drug effects. The most frequently reported complications were infections, haemorrhage and pneumonia. The in-hospital death rate amongst patients with adverse events was 2.9%, compared with 1.3% in those without an adverse event.

In New Zealand, Davis et al (2002) used two-stage retrospective review of 6579 medical records in 13 New Zealand public hospitals in 1998. (Davis et al. 2002) They found that 12.9% of hospital admissions were associated with an adverse event (patient incidence rate, 11.2%), approximately 20% of which had occurred outside the hospital in doctors’ rooms, patient homes, rest homes, or private hospitals. 85% had minor patient impact, with less than 15% associated with permanent disability or death. Adverse events added an average of over nine days (median 4 days) to the expected hospital stay.

In the UK, Vincent et al (2001) reported a pilot study in which 1,014 medical and nursing records from 2 acute hospitals in Greater London were retrospectively reviewed, again using a similar methodology to the Harvard Medical Practice Study. (Vincent, Neale, & Woloshynowycz 2001) They classified 110 (10.8%) of patients and 11.7% of all episodes as involving an adverse event, and assessed 48% of these events as preventable with ordinary standards of care. 66% of all patients experiencing an adverse event were assessed as having minimal impairment and recovery in less than one month (compared with 56.8% in the Harvard Medical Practice Study) 19% were classified as experiencing moderate impairment (Harvard 17%), 6% were classified as experiencing permanent impairment (Harvard 4%), and 8% were assessed as contributing to death (Harvard 14%). The overall adverse event rate in this study was therefore comparable to the revised rate from the Australian study. (Thomas, Studdert, Runciman, Webb, Sexton, Wilson, Gibberd, Harrison, & Brennan 2000b)

Fenn et al (2002) asked a random population sample of 8206 individuals if they believed that over the last three years they had suffered some illness, injury or impairment that in their opinion was caused by their medical treatment or care, and further detailed questions of those who gave a positive response to this filter question. (Fenn et al. 2002) 395 (4.8%) indicated that they had suffered some form of illness, injury or impairment, equivalent to 1.6% of the general population per annum. Of these 395, 25% rated their injury as insignificant or emotional only, 44%
as temporary, 16.5% as a permanent minor disability and 13.2% as a permanent major disability. This study design did not permit estimation of deaths caused by medical treatment or care.
Table 1: Summary of results from empirical studies of overall error and adverse event rates in hospitals

<table>
<thead>
<tr>
<th>Study</th>
<th>Sample size</th>
<th>Error/Adverse event rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Steel et al 1981(Steel, Gertman, Crescenzi, &amp; Anderson 1981)</td>
<td>815 general surgery patients</td>
<td>36% iatrogenic illness 9% major incident 2% contributing to death of patient</td>
</tr>
<tr>
<td>California Medical Association 1977(Mills 1977)</td>
<td>Convenience sample of 20,864 records from 2 hospitals</td>
<td>4.6% (870) potentially compensable events 0.8% negligent adverse events</td>
</tr>
<tr>
<td>Harvard Medical Practice Study(Brennan, Leape, Laird, Hebert, Localio, Lawthers, Newby, Weiler, &amp; Hiatt 1991)</td>
<td>30,121 acute care nonpsychiatric hospital cases in New York State in 1984</td>
<td>3.7% overall adverse event rate 1.0% negligent adverse events (27.6% of all adverse events) 13.6% of adverse events leading to death</td>
</tr>
<tr>
<td>Quality in Australian Health Care Study (Wilson, Runciman, Gibberd, Harrison, Newby, &amp; Hamilton 1995)</td>
<td>14,655 medical admission records from 28 hospitals in New South Wales and South Australia</td>
<td>16.6% overall adverse event rate 8.5% preventable adverse event rate 4.9% of adverse events contributing to patient death</td>
</tr>
<tr>
<td>Utah &amp; Colorado study (Thomas, Studdert, Burstin, Orav, Zeena, Williams, Howard, Weiler, &amp; Brennan 2000a)</td>
<td>15,000 nonpsychiatric hospital discharges in Utah and Colorado</td>
<td>2.9% overall adverse event rate 0.9% negligent adverse event rate 6.6% of adverse events led to death</td>
</tr>
<tr>
<td>Revised Quality in Australian Health Care Study(Thomas, Studdert, Runciman, Webb, Sexton, Wilson, Gibberd, Harrison, &amp; Brennan 2000b)</td>
<td>14,655 medical admission records from 28 hospitals in New South Wales and South Australia, classified according to Utah/Colorado methods</td>
<td>10.6% overall adverse event rate</td>
</tr>
<tr>
<td>(McGuire et al. 1992)</td>
<td>44,603 consecutive surgical procedures in one US hospital over the period 1977-1990</td>
<td>3.1% overall error rate (1370/44603) 4.1% of errors (n=56) resulting in death</td>
</tr>
<tr>
<td>(O’Hara &amp; Carson 1997)</td>
<td>All discharges from 247 acute care hospitals in Victoria, Australia in 1994-95</td>
<td>5% overall adverse event rate 1.6% of adverse events contributing to death</td>
</tr>
<tr>
<td>(Davis, Lay-Yee, Briant, Ali, Scott, &amp; Schug 2002)</td>
<td>6,579 discharges from 13 public hospitals in New Zealand in 1998</td>
<td>12.9% overall adverse event rate</td>
</tr>
<tr>
<td>Pilot study in 2 English hospitals (Vincent, Neale, &amp; Woloshynowycz 2001)</td>
<td>1,014</td>
<td>11.7% overall adverse event rate 5.2% preventable adverse event rate 8% of adverse events contributed to death</td>
</tr>
<tr>
<td>Fenn et al (2002)(Fenn, Gray, Rickman, Diacon, Carrier, &amp; Young 2002)</td>
<td>Random sample of 8,206 members of public</td>
<td>1.6% per annum adverse event rate</td>
</tr>
</tbody>
</table>
Hospital care – specialty studies

The empirical studies discussed above all attempted to measure error rates and/or adverse rates for general hospital populations. Many other empirical studies of error rates in health care have been performed, typically focusing on particular areas of care or types of procedure. Table 1 summarises 20 of these, and brief descriptive information is as follows (in chronological order):

Cooper et al (1978) conducted 47 interviews with staff and resident anesthesiologists at one US hospital, obtaining descriptions of 359 preventable incidents and their characteristics, but no overall rate was reported. (Cooper et al. 1978)

Couch et al (1981) conducted a one-year prospective survey of 5,612 surgical admissions to one US hospital to identify adverse outcomes due to error during care, and identified 36 cases, 23 of which had occurred in another hospital before transfer. (Couch et al. 1981) 20 patients died in hospital, and in 11 cases death was directly attributable to the error. Five of the 16 survivors left the hospital with serious physical impairment.

Dubois and Brook (1988) conducted a small study in which 182 deaths across 12 hospitals from cerebrovascular accident, pneumonia, or myocardial infarction were reviewed independently by three physicians to assess whether the death could have been prevented. (Dubois & Brook 1988) Using a unanimity criterion (all three physicians independently agreeing), they found that 14% of the deaths were probably preventable.

de la Sierra et al (1989) reported the incidence and causes of iatrogenic illness in a prospective study of 1,176 patients admitted during 1986 to the department of internal medicine of one US hospital. (de la Sierra et al. 1989) 295 patients (25.1%) were classified as developing 367 episodes of iatrogenic illness, 19 life-threatening events and 2 deaths attributable to the event.

Bedell et al (1991) looked at 203 cardiac arrests in which resuscitation was attempted among patients hospitalized in 1981 in a US university teaching hospital. (Bedell et al. 1991) They classified 28 (14%) of these as events following an iatrogenic complication, 17 of which (61%) died, and found the most common cause of potentially preventable arrest to be medication errors and toxic effects (44%), and suboptimal responses by physicians to clinical signs and symptoms (28%) such as dyspnea and tachypnea.

McGuire et al (1992) conducted a much larger study of 44,603 consecutive surgical procedures in one US hospital over the period 1977-1990, and reported a complication rate of 6.3%, with 49% (n=1370) of these attributable to error and 4.1% of errors (n=56) resulting in death. (McGuire, Horsley, Salter, & Sobel 1992)
Giraud et al (1993) examined 382 patients aged 15 or over in 400 consecutive admissions to 2 intensive care units in France, and identified 316 iatrogenic complications in 124 (31%) of the 400 admissions. (Giraud et al. 1993) Of these iatrogenic complications, 107 (in 53 [13%] of the 400 admissions) complications were major, three leading to death.

Andrews et al (1997) used an ethnographic research method during which trained researchers attended ward-rounds, nursing shift changes, case conferences and other meetings in one large US hospital over a 9-month period from 1989 to 1990, recording all adverse events discussed. (Andrews et al. 1997) During the study, of 1047 patients discussed, 185 (17.7%) were recorded as having had at least one serious adverse event.

Burton et al (1998) focused on the discordance between autopsy diagnoses and clinical diagnoses of malignant neoplasm, using a 10-year retrospective study (1986-1995) design of all autopsies performed in one US hospital. (Burton, Troxclair, & Newman 1998) 1105 cases were examined, with 250 malignant neoplasms identified in autopsy. 111 of these (in 100 patients) were either undiagnosed or misdiagnosed, and in 57 patients of these patients the malignant neoplasm was the immediate cause of death. The overall discordance between clinical and autopsy diagnoses of malignant neoplasms was 44%.

Sonderegger-Iseli et al (2000) retrospectively compared diagnosis and necropsy results in 300 randomly selected patients who died at a tertiary-care teaching hospital in Switzerland (100 in each of 1972, 1982, and 1992). (Sonderegger-Iseli et al. 2000) They found that the frequency of major discrepancies declined from 30% in 1972 to 14% in 1992, while the rate of minor diagnostic errors increased significantly from 23% in 1972 to 46% in 1992. Improvements occurred in cardiovascular diseases and infectious diseases, but no improvement was observed in neoplastic diseases.

Wanzel et al (2000) adopted a study design in which a single observer prospectively monitored complications for all patients admitted to a general surgery service in one US hospital over a 2-month period in 1996. (Wanzel, Jamieson, & Bohnen 2000) 192 patients were admitted, of whom 75 (39%) suffered a total of 144 complications. 2 complications (1%) were fatal, 10 (7%) were life threatening, 90 (63%) were of moderate severity and 42 (29%) were trivial. Of these 144 complications, 26 (18%) were deemed potentially attributable to error.

Pope et al (2000) reported missed diagnoses of acute cardiac ischemia, using data from a multicentre, prospective clinical trial of all patients with chest pain or other symptoms suggesting acute cardiac ischemia who presented to the emergency departments of 10 U.S. hospitals. (Pope et al. 2000) 17% of 10,689 patients ultimately met the criteria for acute cardiac ischemia. 19 (2.1%) of the 889 patients with acute myocardial infarction were mistakenly discharged from the emergency department,
and 22 (2.3%) of the 966 patients with unstable angina were mistakenly discharged (95 percent confidence interval, 1.3 to 3.2 percent). The risk-adjusted mortality ratio for patients with acute infarction who were not hospitalized compared with those who were was 1.9, and for patients with unstable angina was 1.7.

Graff (2000) used a retrospective two-arm observational cohort study at 12 acute care hospitals in the US to assess false-positive rates in patients having appendectomy for appendicitis and false-negative rates in patients presenting at an emergency department with abdominal pain. (Graff et al. 2000) In the appendectomy arm of the study, 110 (10.5%) of the 1,026 patients operated on were false-positive decisions. In the abdominal pain arm, 170 (18.6%) of the 916 patients with appendicitis initially received false-negative decisions, with correspondingly elevated risk of perforation and abscess formation. Similar results were obtained by Flum et al (2001), who reported the incidence of misdiagnosis of appendicitis in the USA in 1997, and estimated that 39,901 (15.3%) of the 261,134 appendectomies performed in that year nationally were negative for appendicitis. (Flum et al. 2001)

Christakis and Lamont (2000) compared the survival estimates made by 343 doctors for 468 terminally ill patients at the time of hospice referral with their actual survival duration of survival. (Christakis & Lamont 2000) They found that only 20% (92/468) of predictions were within 33% of actual survival time, with 63% (295/468) significantly overoptimistic and 17% (81/468) significantly overpessimistic. Overall, doctors overestimated survival by a factor of 5.3.

Hayward et al (2001) also examined potential optimism in assessments of survival prospects. (Hayward & Hofer 2001) The medical records of 111 hospital deaths at 7 US Department of Veterans Affairs medical centers from 1995-1996 were reviewed by trained internists on a 5-point scale of whether deaths could have been prevented by optimal care. While a total of 22.7% of deaths were rated as at least possibly preventable by optimal care, the same reviewers considered that only 6.0% of these patients were likely to have left the hospital alive had optimal care been provided.

MacPherson et al (2001) reported a survey in which 1,848 professional acupuncturists were asked to record prospectively on standardised self-report forms details of adverse events following treatments they provided over a four-week period. (MacPherson et al. 2001) These practitioners reported on adverse events and transient reactions associated with 34,407 treatments. No serious adverse events were reported (defined as requiring hospital admission, prolonging hospital stays, permanently disabling, or resulting in death); 43 significant minor adverse events were reported, a rate of 1.3 per 1,000 treatments, of which three were considered avoidable: two patients had needles left in by mistake, and one patient had moxa burns to the skin, also caused by practitioner error. 10,920 mild transient reactions occurred in 5136 treatments, a rate of 15% of the 34,407 total, but not all were
adverse: they included feeling relaxed (11.9\% of all mild transient reactions) and feeling energised (6.6\%).

A very similar study was undertaken by White et al (2001) on 31,822 consultations involving 78 acupuncturists in the UK over a 21-month period from 1998-2000. (White et al. 2001a;White et al. 2001b) A total of 2178 minor adverse events were reported (684 per 10,000 consultations), the most common being bleeding, needling pain, and aggravation of symptoms. 43 significant minor adverse events were reported, a rate of 14 per 10,000, of which 13 (30\%) interfered with daily activities.

Calland et al (2002) constructed a dataset of all patients who had died within 30 days of surgery at one US hospital in the first 6 months of 1999, and then assessed the clinical records of those who had died for evidence of adverse events. (Calland et al. 2002) A total of 119 deaths occurred in the 30 days after 7,379 operations performed on 6,296 patients, giving a patient death rate of 1.9\%. 23 deaths (19.3\% of deaths, 0.37\% of all patients, could not be attributed to the patient’s primary disease and thus were suspicious for an adverse event as the cause of the death. Of these, 15 followed an error in care and thus were classified as potentially preventable, affecting 0.24\% of the study population.

Healey et al (2002) examined complication rates in all operative and nonoperative inpatients in 4 different surgical services (general surgery, combined general surgery and trauma, vascular surgery, and cardiothoracic surgery) in one US hospital. (Healey et al. 2002) The numbers of patients were 1363, 978, 914, and 1403 respectively, and numbers of complications were 413, 409, 295, and 378, giving total complication rates of 30.3\%, 42.4\%, 32.3\%, and 26.9\% respectively. The minor complication rate was assessed as 13.3\%, 19.9\%, 13.5\%, and 13.0\% respectively, the major complication rate at 16.2\%, 21.1\%, 18.1\%, and 12.9\%, and the mortality rate at 1.83\%, 3.33\%, 2.28\%, and 3.34\%. They estimated that the percentage of mortality that was avoidable was 28.0\%, 44.1\%, 19.0\%, and 25.0\% respectively. In total, errors in care were adjudged to have contributed to 38 (30\%) of 128 deaths.

Hodgetts et al (2002) looked at 118 primary in-hospital cardiac arrest resuscitations in a district general hospital in Ireland. (Hodgetts et al. 2002) Panel retrospective review unanimously agreed that 61.9\% of these arrests were potentially avoidable, rising to 68\% when emergency department arrests were excluded (66\% and 73\% for majority opinion).

Forster (2003) designed a study to estimate the incidence of medical injuries occurring after discharge amongst 400 consecutive patients discharged home from the general medical service of one US hospital. (Forster et al. 2003) Events were determined by performing a medical record review and a structured telephone interview approximately 3 weeks after each patient’s discharge. They found that 76 (19\%) patients had adverse events after discharge, of which 23 (6\%) were classified
as preventable adverse events. 94% of adverse events involved symptoms alone or symptoms with a nonpermanent disability, with 3% serious laboratory abnormalities and 3% permanent disabilities. Adverse drug events were responsible for 66% of adverse events.

Meinberg et al (2003) reported a survey in which 1,560 hand surgeons were sent by mail a confidential questionnaire requesting information about the frequency of wrong-site surgery over their working career. (Meinberg & Stern 2003) Of the respondents, 173 surgeons (16%) reported having prepared to operate on the wrong site but noting the error prior to the incision, and 217 (21%) reported performing wrong-site surgery at least once. Of an estimated 6,700,000 surgical procedures, 242 were performed at the wrong site, an incidence of one in 27,686 procedures.
<table>
<thead>
<tr>
<th>Study</th>
<th>Sample size</th>
<th>Error/Adverse event rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Cooper, Newbower, Long, &amp; McPeek 1978)</td>
<td>Interviews with 47 staff and resident anesthesiologists at one US hospital</td>
<td>Not given</td>
</tr>
<tr>
<td>(Couch, Tilney, Rayner, &amp; Moore 1981)</td>
<td>5,612 surgical admission in US in 1979-80</td>
<td>0.64% adverse event rate due to error</td>
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<td></td>
<td></td>
<td>30.3% of adverse events due to error resulted in attributable death.</td>
</tr>
<tr>
<td>(Dubois &amp; Brook 1988)</td>
<td>182 deaths across 12 US hospitals in 1986-7</td>
<td>14% of deaths preventable</td>
</tr>
<tr>
<td>(de la Sierra, Cardellach, Cobo, Bove, Rouge, Santos, Ingelmo, &amp; Urbano-Marquez 1989)</td>
<td>1,176 patients in US internal medicine department in 1986</td>
<td>25.1% iatrogenic illness rate</td>
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<td></td>
<td></td>
<td>0.7% of iatrogenic episodes resulted in death</td>
</tr>
<tr>
<td>(Bedell, Deitz, Leeman, &amp; Delbanco 1991)</td>
<td>203 cardiac arrests in US hospital in 1981</td>
<td>14% following iatrogenic complications</td>
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<tr>
<td></td>
<td></td>
<td>61% of iatrogenic events resulted in death</td>
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<td></td>
<td></td>
<td>3.1% preventable adverse events</td>
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<td></td>
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<td>8.4% of preventable adverse events resulted in death</td>
</tr>
<tr>
<td>(Giraud, Dhainaut, Vaxelaire, Joseph, Journois, Bleichner, Sollet, Chevret, &amp; Monsallier 1993)</td>
<td>400 consecutive intensive care unit admissions in France.</td>
<td>31% iatrogenic complication rate</td>
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<td></td>
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<td>2.4% of iatrogenic complications resulted in death</td>
</tr>
<tr>
<td>(Andrews, Stocking, Krizek, Gottlieb, Krizek, Yargish, &amp; Siegler 1997)</td>
<td>1047 patients discussed during ethnographic research in one US hospital in 1989-90</td>
<td>17.7% overall adverse event rate</td>
</tr>
<tr>
<td>(Burton, Troxclair, &amp; Newman 1998)</td>
<td>250 malignant neoplasms identified by autopsy in one US hospital in 1986-95</td>
<td>44% undiagnosed or misdiagnosed.</td>
</tr>
<tr>
<td>(Sonderegger-Iseli, Burger, Muntywler, &amp; Salomon 2000)</td>
<td>300 necroscopy results in one hospital in Switzerland 1972-1992</td>
<td>30% to 14% major discrepancies</td>
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<td>23% to 46% minor diagnostic errors</td>
</tr>
<tr>
<td>(Wanzel, Jamieson, &amp; Bohnen 2000)</td>
<td>192 patients in a general surgery service in one US hospital in 1996</td>
<td>39% overall adverse event rate</td>
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<td>7% preventable adverse event rate</td>
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<tr>
<td>(Pope, Auferheide, Ruthazer, Woolard, Feldman, Beshansky, Griffith, &amp; Selker 2000)</td>
<td>889 patients with acute myocardial infarction in a clinical trial in US in 1993</td>
<td>2.1% diagnostic error rate</td>
</tr>
<tr>
<td>(Graff, Russell, Seashore, Tate, Elwell, Prete, Werdmann, Maag, Krivenko, &amp; Radford 2000)</td>
<td>1026 appendectomy procedures in USA in 1998-9</td>
<td>10.5% diagnostic error rate</td>
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<td></td>
<td></td>
<td>18.6% diagnostic error rate</td>
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<tr>
<td>Study Reference</td>
<td>Procedures/Events</td>
<td>Outcomes</td>
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<tr>
<td>(Flum, Morris, Koepsell, &amp; Dellinger 2001)</td>
<td>261,134 appendectomy procedures in USA in 1997</td>
<td>15.3% diagnostic error rate</td>
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<tr>
<td>(Christakis &amp; Lamont 2000)</td>
<td>468 terminally ill patients in 5 hospices in Chicago in 1996</td>
<td>80% survival prediction error rate</td>
</tr>
<tr>
<td>(White, Hayhoe, Hart, &amp; Ernst 2001b)</td>
<td>31,822 acupuncture procedures in UK in 1998-2000</td>
<td>0.14% adverse event rate</td>
</tr>
<tr>
<td>(MacPherson, Thomas, Walters, &amp; Fitter 2001)</td>
<td>34,407 acupuncture procedures in UK in 1999-2000</td>
<td>0.13% adverse event rate of which 7% preventable</td>
</tr>
<tr>
<td>(Calland, Adams, Benjamin, O’Connor, Chandrasekhar, Guerlain, &amp; Jones 2002)</td>
<td>119 deaths after 7,379 operations in one US hospital in 1999</td>
<td>0.37% adverse event resulting in death 0.24% preventable adverse event resulting in death</td>
</tr>
<tr>
<td>(Hodgetts, Kenward, Vlackonikolis, Payne, Castle, Crouch, Ineson, &amp; Shaikh 2002)</td>
<td>118 in-hospital cardiac arrest resuscitations in one hospital in England in 1999</td>
<td>61.9% preventable</td>
</tr>
<tr>
<td>(Forster, Murff, Peterson, Gandhi, &amp; Bates 2003)</td>
<td>400 discharges from general medical service of one US hospital in 2001</td>
<td>19% adverse event rate 6% preventable adverse event rate</td>
</tr>
<tr>
<td>(Meinberg &amp; Stern 2003)</td>
<td>173 hand surgeons with 6,700,000 lifetime procedures</td>
<td>1 in 27,686 wrong site procedures.</td>
</tr>
</tbody>
</table>
Medications

Error rates and adverse event rates have been studies most frequently in relation to the use of medications, and a relatively large literature now exists: as noted earlier, the Institute of Medicine report in 2000 documented 32 medication-related studies. However, this was not a fully comprehensive list and is now dated, while some of the studies listed did not report overall error rates or adverse event rates.

One systematic review in this area, by Winterstein et al (2020), looked for studies published in peer-reviewed journals that contained information on the crude prevalence rate of drug therapy requiring hospital admission and included a quantitative preventability assessment. (Winterstein et al. 2002) They found 15 studies meeting the review criteria, and these reported a median prevalence of preventable drug-related hospital admissions of 4.3%, constituting a median of 59% of all drug-related admissions.

Table 3 summarises information on 27 empirical studies published up to 2003 which give overall estimates of medication-related error rates and adverse event rates. The terminology and definitions in use in this area are complex: a framework is set out by Edwards and Aronson (2000). (Edwards & Aronson 2000) For the purposes of this section, a medication error is defined as “a failure in the [drug] treatment process that leads to, or has the potential to lead to, harm to the patient”, (Ferner RE 2003) such as a medication order, prescription or decision which was incorrect in terms of agent, dose or mode of administration with respect to the patient’s medical state. An adverse drug event (ADE) is defined as an injury resulting from medical intervention related to a drug. As with other categories of adverse event, not all adverse drug events can be attributable to error, while the literature generally describes all events attributable to error as preventable.

In an early study, Burnum (1976) looked at 1,000 patient visits to a community medical practice in the US, and estimated that 42 (4.2%) were associated with adverse drug reactions, and that 23 of these were potentially avoidable. (Burnum 1976)

Folli et al (1987) looked at the medication error rate in two US paediatric hospitals over a 6-month period. Of 101,022 medication orders examined, 479 errors were identified, or 4.9 and 4.5 per 1,000 medication orders in the two hospitals, with an overall error rate of 1.35 and 1.77 per 100-patient days, particularly arising from overdosage. (Folli et al. 1987)

Raju et al (1989) also reported results for a paediatric hospital. Over a 4-year prospective study of 2147 neonatal and paediatric intensive-care admissions, they found 315 iatrogenic medication errors, or 1 per 6.8 admissions (14.7%), of which 66
resulted in injury of any sort, 32 of which caused mild patient injuries. (Raju et al. 1989)

Lesar et al (1990) examined 289,411 medication orders written during a 1-year study period in one US hospital, and found 905 prescribing errors, of which 522 (57.7%) were rated as having potential for adverse consequences. (Lesar et al. 1990)

The overall detected error rate was 3.13 errors for each 1000 orders written and a rate of 1.81 significant errors per 1000 orders.

Classen et al (1991) used an automated system coupled to pharmacist review of suspect records to assess 36,653 patients admitted to one US hospital over an 18 month period. The automated system was designed to detect signs of adverse drug reactions, such as use of phytonadione, antidiarrheals, diphenhydramine hydrochloride, and naloxone hydrochloride, high serum drug levels, and leucopenia. They detected 731 verified adverse drug reactions in 648 patients, 701 of which were characterized as moderate or severe. Over the same period traditional detection methods recorded only 9 such events, while physicians, pharmacists, and nurses voluntarily reported 92 of the 731 events detected. The most common symptoms and signs amongst patients were pruritus, nausea and/or vomiting, rash, and confusion-lethargy, and the most common drug classes involved were analgesics, anti-infectives, and cardiovascular agents. (Classen et al. 1991)

Between 1990 and 1992, Hallas and colleagues reported the results of a series of studies of drug related hospitalization rates in Denmark. Of 333 consecutive patients in a medical ward, 36 cases (10.8%) were classified as drug-related hospitalizations (DRH), consisting of 8.1% adverse drug reactions and 2.7% therapeutic failures due to ineffective dosage. In 8 cases (2.4%) the drug event could definitely have been avoided, and a further 13 cases (3.9%) were considered to have been potentially avoidable. (Hallas et al. 1990b) In a similar study of 366 consecutive admissions to a department of cardiology, ‘definite’ or ‘probable’ drug events accounted for 15 admissions (4.1%), of which eleven were adverse drug reactions and four were dose-related therapeutic failures. (Hallas et al. 1990a) Including six ‘possible’ drug events, the rate of drug-related hospitalizations (DRH) was 5.7%. Among the 15 ‘definite’/‘probable’ DRHs, five were considered to be due to an error in prescription, and a further five cases were judged to have been avoidable. In a similar study of 328 consecutive admissions to a department of medical gastroenterology, drug related hospitalisations accounted for 26 admissions (7.9%), or 39 admissions (11.9%) with the additional inclusion of ‘possible’ drug events. (Hallas et al. 1991a) Of the 26 ‘definite’ or ‘probable’ drug related hospitalisations, none were considered definitely avoidable. In a similar study of 294 consecutive admissions to a geriatric department, 39 cases (13.3%) were considered to be definite, probable or possible drug events, of which 11.2% were adverse drug reactions and 2.1% were dose-related therapeutic failures. (Hallas et al.
1991b) Five of these cases (1.7%) were judged to be due to errors in prescription and a further seven (2.4%) were considered have been avoidable. In a similar study of 313 consecutive admissions to a department of respiratory medicine, 11 patients (3.5%) were admitted because of adverse drug reactions and 14 patient (4.5%) were admitted because of dose-related therapeutic failures, half due to noncompliance. (Hallas et al. 1992a) 17% of the drug events were considered avoidable. Finally, in a summary of 1999 consecutive admissions to six medical wards, (general medicine, geriatrics, endocrinology, cardiology, respiratory medicine and gastroenterology) the prevalence of drug related hospital admissions was 11.4% of which 8.4% were caused by adverse drug reactions and 3.0% by dose-related therapeutic failures. (Hallas et al. 1992b)

Bates (1993) prospectively identified adverse drug events in all patients admitted to two medical, two surgical, and two obstetric general care units and a coronary intensive care unit in an urban tertiary care hospital over a 37-day period (2,967 patient-days), using nurse and pharmacist logs, a research nurse to solicit daily incident reports, and research nurse daily chart review. (Bates, Leape, & Petrycki 1993) Overall they identified 73 incidents, of which 27 incidents were judged actual and 34 potential adverse drug events. Of the 27 actual events, five were classified as life-threatening, nine as serious, and 13 as significant, and fifteen (56%) were judged definitely or probably preventable. 67% (18 of 27) of the adverse drug events were identified only by chart review.

Accidental nonadherence to a therapeutic regime plays a contributory role in the total number of adverse drug events. Einarson et al (1993), in a systematic review of studies examining admissions prompted by adverse drug reactions (ADRs) when drugs were used by the patient and admissions resulting from a patient’s noncompliant or unintentionally inappropriate drug use, found ADR rates from 49 hospitals or groups of hospitals in a variety of international settings published in 36 articles between 1966 and 1989. (Einarson 1993) The weighted mean estimate of the proportion of hospital admissions attributable to adverse drug events was 5.1%. Of these, 3.7% died. Data from 11 studies indicated that 22.7% of ADR hospitalizations were induced by noncompliance.

Willcox et al (1994) using explicit criteria previously developed by 13 United States and Canadian geriatrics experts through a modified Delphi consensus technique to assess the extent of inappropriate prescribing of 20 drugs (prescribing that might place patients at risk of adverse drug events) amongst 6171 Americans aged 65 years or older living in the community and participating in the 1987 National Medical Expenditure Survey. They found that 23.5% of people aged 65 years or older living in the community had received at least one of the 20 contraindicated drugs, placing them at risk of adverse drug effects such as cognitive impairment and sedation, but the study design did not permit them to observe or
estimate actual harm. (Willcox, Himmelstein, & Woolhandler 1994) A similar study was undertaken by Zhan et al (2001), with similar findings. (Zhan et al. 2001)

Voluntary reporting has generally been found to identify only a small proportion of all adverse drug events. For example, Cullen et al (1995) found that, of 54 adverse drug events identified amongst all patients admitted to five patient care units (one medical intensive care unit, two surgical intensive care units, and two medical general care units) in one US hospital over 6 months in 1993, only 3 patients (6%) had a corresponding incident report submitted to the hospital’s quality assurance program or called into the pharmacy hotline. 15 (28%) of the adverse drug events were preventable, and 26 were serious or life-threatening, yet only 2 of the 26 led to an incident report. (Cullen et al. 1995)

Bates et al (1995), using self-report by pharmacists, nurse review of all patient charts, and review of all medication sheets, looked at 379 consecutive admissions during a 51-day period (1,704 patient-days) in one US hospital. Over the study period, 10,070 medication orders were written, and 530 medication errors were identified (5.3 errors/100 orders), for a mean of 0.3 medication errors per patient-day, or 1.4 per admission. Of the medication errors, 53% involved at least one missing dose of a medication; 15% involved other dose errors, 8% frequency errors, and 5% route errors. During the same period, 25 actual and 35 potential adverse drug events were found; of the 25, five (20%) were associated with medication errors and all were judged preventable. Thus, five of 530 medication errors (0.9%) resulted in ADEs.

Bates et al (1995) looked at 4031 adult admissions to 11 medical and surgical units in two tertiary care hospitals over a 6-month period, using self-report by nurses and pharmacists and daily review of all charts by nurse investigators to detect drug-related incidents; these were then classified by two independent reviewers as to whether they represented ADEs or potential ADEs and as to severity and preventability. 247 ADEs and 194 potential ADEs were identified, equivalent to 6.5 ADEs and 5.5 potential ADEs per 100 nonobstetrical admissions. Of all ADEs, 1% were fatal (none preventable), 12% life-threatening, 30% serious, and 57% significant. 28% were judged preventable. Of the life-threatening and serious ADEs, 42% were preventable, compared with 18% of significant ADEs. (Bates et al. 1995a)

Schneitman-McIntire et al (1996) examined 62,216 visits to the emergency department of a Californian health maintenance organization (HMO) between August 1992 and August 1993 for evidence of medication “misadventures”, which they defined to include inappropriate prescribing and noncompliance but to exclude intentional overdoses and substance abuse. (Schneitman-McIntire et al. 1996) They found that 1,074 (1.7%) of all visits were due to medication misadventures, which were most often due to allergies or medication underuse among younger patients, and to adverse effects and inappropriate dosage in elderly patients. Of the
1,074 misadventures, 152 (14.1%) resulted in hospital admission, accounting for 1.0% of all hospital admissions.

Cullen et al (1997), using data on 4,031 adult admissions to 11 medical and surgical units in two US hospitals over a 6-month period, estimated the rate of preventable and potential adverse drug events at 19 events per 1000 patient days in intensive care units, compared with 10 events per 1000 patient days in non-intensive care units. (Cullen et al. 1997)

Lesar et al (1997) attempted to look in more detail at identifiable factors associated with medication prescribing errors. In a 12 month period in a 631 bed US hospital, 2103 medication errors thought to have potential clinical importance were detected, or 3.99 errors per 1000 medication orders. The most common specific factors associated with errors were decline in renal or hepatic function requiring alteration of drug therapy (97 errors, 13.9%), patient history of allergy to the same medication class (84 errors, 12.1%), using the wrong drug name, dosage form, or abbreviation (total of 79 errors, 11.4%, for both brand name and generic name orders), incorrect dosage calculations (77 errors, 11.1%), and atypical or unusual and critical dosage frequency considerations (75 errors, 10.8%). (Lesar, Briceland, & Stein 1997)

Lesar et al (1997a) examined all medication-prescribing errors with potential for adverse patient outcome detected and averted by staff pharmacists in one US hospital over the period 1987 to 1995. (Lesar, Lomaestro, & Pohl 1997) 11,186 confirmed medication-prescribing errors with potential for adverse patient consequences were detected and averted during the study period. The annual number of errors detected increased from 522 in the index year 1987 to 2115 in 1995. The rate of errors occurring per order written, per admission, and per patient-day, all increased significantly during the study duration (P < .001). The most common type of errors were dosing errors, prescribing medications to which the patient was allergic, and prescribing inappropriate dosage forms.

Phillips et al (1998) adopted a different approach to the quantification of medication error, and focused on deaths in the US from 1983 to 1993 that could be attributed to medication error on the basis of the ICD code for cause of death (that is, E850-E858 Accidental Poisoning with Drugs, which includes accidental overdose of drug, wrong drug given or taken in error, drugs taken inadvertently, and accidents in the use of drugs and biologicals in medical and surgical procedures). (Phillips, Christenfeld, & Glynn 1998a) They estimated that the annual number of deaths so classified increased from 2876 people in 1983 to 7391 by 1993, a 2.6-fold increase. This was substantially greater than the 1.4-fold increase in prescriptions, and the increase was particularly evident in outpatient deaths, which rose 8.5-fold, compared to a 2.4-fold increase in in-patient deaths. It is also worthy of note that deaths attributable to medication errors accounted for 1 in 131 outpatient
deaths by 1993, compared with 1 in 854 inpatient deaths. The study suggested that the reason for this trend was the shift to outpatient treatment in which medications are more likely to be taken with less monitoring or control by physicians. Subsequent correspondence drew attention to the uncertainties in classification in this area, the apparent lack of a similar trend in the UK, and the close association between accidental poisoning and alcohol use. (Ferner & Anton 1998); (Phillips, Christenfeld, & Glynn 1998b; Rooney 1998); (Rooney 1998)

Lazarou et al (1998) reported the results of a literature review in which four electronic databases were searched from 1966 to 1996 for studies reporting the incidence of adverse drug reactions in hospital. They found a total of 153 studies, and selected 39 prospective studies from US hospitals for detailed data extraction by 2 investigators. They excluded errors in drug administration, noncompliance, overdose, drug abuse, therapeutic failures, and possible ADRs, and concentrated exclusively on serious ADRs defined as those that required hospitalization, were permanently disabling, or resulted in death. They found an overall incidence of serious ADRs of 6.7%, and an incidence of fatal ADRs of 0.32% of hospitalized patients, making these reactions between the fourth and sixth leading cause of death. (Lazarou, Pomeranz, & Corey 1998)

Wilson et al (1998), in a 2-year prospective cohort study of 682 patients admitted for 5315 inpatient days to a UK hospital, detected 441 medication errors in the study period, most of which (68%) were detected prior to drug administration. Excluding prevented errors, the actual medication error rate was 1 per 5.8 admissions. (Wilson et al. 1998)

Roughead et al (1998) reported the results of a systematic review which identified 14 Australian studies of drug-related hospital admissions. (Roughead et al. 1998) These studies indicated that between 2.4% and 3.6% of all hospital admissions were drug-related, 6% to 7% of emergency admissions, 12% of all admissions to medical wards and 15% to 22% of all emergency admissions among the elderly. Between 32% and 69% of drug-related admissions were reported as definitely or possibly preventable.

In a separate study, Roughead (1999) examined drug-related hospitalisations in Australia using data from the Australian National Hospital Morbidity Collection, the Quality in Australian Health Care Study and Australian studies assessing drug-related hospital admissions. (Roughead 1999) The incidence figures, drugs and conditions most commonly implicated, and estimates of avoidability of medication-related problems were compared. The three data sources were found to provide consistent results, with all sources implicating cytotoxics, antirheumatics, anticoagulants, corticosteroids, antihypertensives and cardiovascular agents in medication-related hospitalisations. Estimates of the extent of the problem were also consistent, suggesting that at least 80,000 medication-related hospitalisations occur
in Australia each year; between 32% and 69% of these hospitalisations were considered avoidable.

Gandhi et al (2003) used a prospective cohort study design to examine adverse drug events amongst 661 outpatients responding to the survey who received at least one prescription during a four-week period in four adult primary care practices in Boston, USA. (Gandhi et al. 2003) 181 adverse drug events were reported by 162 (25%) of the respondents, of which 24 (13 percent) were classified as serious, 51 (28 percent) as ameliorable, and 20 (11 percent) as preventable. Of the 51 ameliorable events, 32 (63 percent) were attributed to the physician’s failure to respond to medication-related symptoms and 19 (37 percent) to the patient’s failure to inform the physician of the symptoms.

Lapointe and Jollis (2003) looked at 14,983 interventions by clinical pharmacists on the cardiology wards of one US hospital between September 1995 and February 2000. 4768 (32%) of these interventions were related to medication errors, equivalent to 24 medication errors per 100 admissions. The most common errors involved the wrong drug (36.0%) or wrong dose (35.3%), and cardiovascular medications were involved in 41.2% of the errors. (LaPointe & Jollis 2003)

Gurwitz et al (2003) focused on adverse drug events among older persons in an ambulatory setting, using 30,397 person-years of observation on Medicare enrollees over a 12-month period from July 1999 to June 2000. (Gurwitz et al. 2003) They used multiple methods to detect adverse events, including reports from health care providers, reviews of hospital discharge summaries and emergency department notes, computer-generated signals, automated free-text review of electronic clinic notes, and review of administrative incident reports concerning medication errors. They identified 1523 adverse drug events, of which 27.6%(421) were considered preventable. The overall rate of adverse drug events was 50.1 per 1000 person-years, with a rate of 13.8 preventable adverse drug events per 1000 person-years. Of the adverse drug events, 578 (38.0%) were categorized as serious, life-threatening, or fatal; 244 (42.2%) of these more severe events were deemed preventable compared with 177 (18.7%) of the 945 significant adverse drug events. Errors associated with preventable adverse drug events occurred most often at the stages of prescribing (n = 246, 58.4%) and monitoring (n = 256, 60.8%), and errors involving patient adherence (n = 89, 21.1%) also were common.
<table>
<thead>
<tr>
<th>Study</th>
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<th>Error/Adverse event rate</th>
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<tbody>
<tr>
<td>(Burnum 1976)</td>
<td>1,000 patient visits to a US community medical practice in 1975</td>
<td>4.2% related to adverse drug reactions</td>
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<td></td>
<td></td>
<td>2.3% potentially avoidable</td>
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<tr>
<td>Folli 1987 (Folli, Poole, Benitz, &amp; Russo 1987)</td>
<td>two US paediatric hospitals over a 6-month period</td>
<td>4.9 and 4.5 per 1,000 medication orders</td>
</tr>
<tr>
<td>Raju (Raju, Kecskes, Thornton, Perry, &amp; Feldman 1989)</td>
<td>2147 admissions to a paediatric hospital over a 4-year period</td>
<td>315/2147 iatrogenic medication errors, or 1 per 6.8 admissions (14.7%)</td>
</tr>
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<td>66 resulted in injury of any sort, 32 of which caused mild patient injuries</td>
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<tr>
<td>(Lesar, Briceland, Delcoure, Parmalee, Masta-Gornic, &amp; Pohl 1990)</td>
<td>289,411 medication ordered in 1 US hospital in 1989</td>
<td>0.31% detected error rate across all written orders</td>
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<td>0.18% significant errors</td>
</tr>
<tr>
<td>(Classen, Pestotnik, Evans, &amp; Burke 1991)</td>
<td>36,653 patients admitted to 1 US hospital over 18 months</td>
<td>1.8% of all admissions</td>
</tr>
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<td>(Hallas, Harvald, Gram, Grodum, Brosen, Haghfelt, &amp; Damsbo 1990b)</td>
<td>333 admissions to a medical ward in Denmark</td>
<td>10.8% drug-related hospitalizations</td>
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<td>2.4% avoidable</td>
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<tr>
<td>(Hallas, Haghfelt, Gram, Grodum, &amp; Damsbo 1990a)</td>
<td>366 admissions to a cardiology ward in Denmark</td>
<td>4.1% drug-related hospitalizations</td>
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<tr>
<td></td>
<td></td>
<td>2.8% avoidable</td>
</tr>
<tr>
<td>(Hallas, Jensen, Grodum, Damsbo, &amp; Gram 1991a)</td>
<td>328 admissions to gastroenterology ward in Denmark</td>
<td>7.9% drug related hospitalizations</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0% (zero) avoidable</td>
</tr>
<tr>
<td>(Hallas, Worm, Beck-Nielsen, Gram, Grodum, Damsbo, &amp; Brosen 1991b)</td>
<td>294 admissions to a geriatric department in Denmark</td>
<td>13.3% drug-related hospitalizations</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2.4% avoidable</td>
</tr>
<tr>
<td>(Hallas, Davidsen, Grodum, Damsbo, &amp; Gram 1992a)</td>
<td>313 admissions to a respiratory medicine ward in Denmark</td>
<td>7.8% drug-related hospitalizations</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1.3% avoidable</td>
</tr>
<tr>
<td>(Bates, Leape, &amp; Petrycki 1993)</td>
<td>2967 patient days in 1 US hospital</td>
<td>1 actual event per 110 inpatient days</td>
</tr>
<tr>
<td></td>
<td></td>
<td>56% avoidable</td>
</tr>
<tr>
<td>Study</td>
<td>Population</td>
<td>Findings</td>
</tr>
<tr>
<td>-------</td>
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<td>----------</td>
</tr>
<tr>
<td>(Einarson 1993)</td>
<td>49 hospitals in 36 articles published between 1966 and 1989 identified in systematic review</td>
<td>5.1% of all admissions attributable to adverse drug events 3.7% of adverse events resulted in deaths</td>
</tr>
<tr>
<td>Willcox (Willcox, Himmelstein, &amp; Woolhandler 1994)</td>
<td>6171 over 65 years old Americans living in community</td>
<td>23.5% of sample prescribed contraindicated drugs</td>
</tr>
<tr>
<td>Cullen (Cullen, Bates, Small, Cooper, Nemeskal, &amp; Leape 1995)</td>
<td>55 adverse drug events in 1 US hospital in 1993</td>
<td>28% avoidable</td>
</tr>
<tr>
<td>(Bates, Cullen, Laird, Petersen, Small, Servi, Laffel, Sweitzer, Shea, Hallisey, &amp; et 1995a)</td>
<td>10,070 medication orders in 1 US hospital</td>
<td>5.3% error rate 0.9% of medication order errors not detected and resulted in actual adverse events</td>
</tr>
<tr>
<td>(Bates, Cullen, Laird, Petersen, Small, Servi, Laffel, Sweitzer, Shea, Hallisey, &amp; et 1995a)</td>
<td>4031 admissions to 2 US hospitals</td>
<td>6.5 adverse drug events per 100 non-obstetric admissions 28% preventable</td>
</tr>
<tr>
<td>(Schneitman-McIntire, Farnen, Gordon, Chan, &amp; Toy 1996)</td>
<td>62,216 visits to US HMO emergency department in 1992-93</td>
<td>1.7% of visits due to medication misadventure 14.1% of misadventures resulted in hospital admission</td>
</tr>
<tr>
<td>(Cullen, Sweitzer, Bates, Burdick, Edmondson, &amp; Leape 1997)</td>
<td>4,031 admissions to 2 US hospitals</td>
<td>1.9 preventable and potential adverse drug events per 100 inpatient days in ICUs 1.0 preventable and potential adverse drug events per 100 inpatient days in non-ICUs</td>
</tr>
<tr>
<td>(Lesar, Briceland, &amp; Stein 1997)</td>
<td>52,707 medication orders in 1 US hospital</td>
<td>0.4% medication order error rate</td>
</tr>
<tr>
<td>(Lesar, Lomaestro, &amp; Pohl 1997)</td>
<td>11,186 medication errors in 1 US hospital, 1987-1995</td>
<td>*</td>
</tr>
<tr>
<td>(Phillips, Christenfeld, &amp; Glynn 1998a)</td>
<td>All US deaths giving medication error as cause of death, 1983-1993</td>
<td>1 in 131 outpatient deaths in 1993 1 in 854 inpatient deaths</td>
</tr>
<tr>
<td>(Lazarou, Pomeranz, &amp; Corey 1998)</td>
<td>39 US studies identified in systematic review</td>
<td>6.7% serious adverse drug reaction rate</td>
</tr>
<tr>
<td>(Wilson, McArtney, Newcombe, McArtney,</td>
<td>682 admissions to a UK hospital</td>
<td>1 actual medication error per 5.8 admissions</td>
</tr>
<tr>
<td>Reference</td>
<td>Studies</td>
<td>Outcomes</td>
</tr>
<tr>
<td>-----------</td>
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<td>----------</td>
</tr>
<tr>
<td>Gracie, Kirk, &amp; Stuart (1998)</td>
<td>14 Australian studies identified in systematic review</td>
<td>2.4% to 3.6% of all hospital admissions drug related, 32% to 69% definitely or possibly preventable</td>
</tr>
<tr>
<td>(Roughead, Gilbert, Primrose, &amp; Sansom 1998)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Gandhi, Weingart, Borus, Seger, Peterson, Burdick, Seger, Shu, Federico, Leape, &amp; Bates 2003)</td>
<td>661 outpatients in 4 US primary care practices</td>
<td>25% adverse drug events, 11% of adverse drug events preventable</td>
</tr>
<tr>
<td>(Gurwitz, Field, Harrold, Rothschild, Debellis, Seger, Cadoret, Fish, Garber, Kelleher, &amp; Bates 2003)</td>
<td>30,397 person-years of observation on US Medicare enrollees over 12 months 1999-2000.</td>
<td>50.1 adverse drug events per 1000 person-years, 13.8 preventable adverse drug events per 1000 person-years.</td>
</tr>
</tbody>
</table>
Primary care

Far less attention has been paid to errors and adverse events in primary care than in secondary care. One structured (not systematic) review has been performed on published research into the frequency and nature of error in primary care. (Sandars & Esmail 2001) This review identified only 12 empirical studies relevant to the review, and of these only 4 reported an error or adverse rate: these are summarized in Table 4.

Bhasale and colleagues (1998) used a non-random sample of 324 Australian general practitioners (GPs) who anonymously submitted incident reports over the period October 1993 to June 1995. (Bhasale et al. 1998) A total of 805 incidents was reported, of which 76% were considered to be preventable, and of which 27% were considered to have been serious enough to potentially cause severe harm. 51% of the reported incidents concerned pharmacological management and 34% (non-exclusive categories) concerned diagnosis. Because of the methodology used, an overall incident/error rate was not reported.

Fischer et al (1997) also used an incident reporting methodology, and analysed all adverse events entered on risk-management database between January 1991 and June 1996 by eight primary health care clinics. (Fischer et al. 1997) Two independent reviewers assessed each incident, and those classified as adverse events were then analysed to determine cause, preventability, and outcome. They identified a total of 35 adverse events, giving an overall incidence rate of 3.7 adverse events per 100,000 clinic visits over the study period, of which 29 (83%) were considered as attributable to medical error and preventable. The main causes were diagnostic errors (26%) and treatment errors (31%). 14% of the preventable errors resulted in a permanent, disabling injury and 3% resulted in death.

Ely et al (1995) conducted interviews with 53 US family physicians, and was primarily concerned to get them to attribute cause to their most memorable errors. (Ely et al. 1995) No overall error rate was reported, although they did report an average of 10.7 errors per professional lifetime of approximately 16 years, of which an average of 1.2 resulted in death.

Kriisa (1990) examined 184 complaints concerning district physicians in Sweden between 1987 and 1988, but was primarily concerned to identify reasons for complaint and any reprimands issued; the study did not report an overall complaint rate. (Kriisa 1990)

The remaining three empirical studies identified in this section were concerned with prescribing errors by primary care physicians. Neville et al (1989) examined prescriptions issued by group of eight principal general practitioners working in the same health centre in the UK over a 3 month observation period, to
assess error rates. (Neville et al. 1989) They found a total of 504 errors from 15,916 prescription items (3.2%) during the study period. Prescription errors were also examined by Hawksworth et al (1999), but their main focus was on ascertaining the frequency with which 14 community pharmacists had to contact the prescriber when dispensing the prescription. (Hawksworth et al. 1999) Over a sample period of one week per month for a year a total of 1,503 clinical pharmacy interventions were made out of 201,000 items dispensed, suggesting an overall error rate or inadequate rate of 0.75%. Panel assessment of each intervention that between 71 (0.04% of the total items dispensed) and 483 (0.24%) of the interventions could have prevented harm, and that between 19 (0.01%) and 242 (0.12%) interventions had the potential to avert a drug-related hospital admission. Finally, Buurma et al (2001) conducted a prospective case-control study in which prescriptions which had to be modified by the dispensing pharmacist were compared with prescriptions that did not require any modification. (Buurma et al. 2001) The study was conducted in 141 Dutch community pharmacies on a single sample day between February and March 1999. The overall rate at which prescriptions had to be modified was 4.3%, with 72% of modified prescriptions concerning fairly simple clarification, but 22% involving dose errors (13%) or other errors (9%) that were considered as potentially having clinical consequences. This gives an overall rate of potential harmful error of around 1.2%.

Reflecting on the variation between primary care studies in the estimated frequency of medical errors, ranging from 5 to 80 medical errors per 100,000 consultations, Sandars and Esmail (2003) emphasized the wide range of different definitions, research methods and perspectives adopted in these studies.(Sandars & Esmail 2003)
Table 4: Error and adverse event rates in 4 general practice studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Sample size</th>
<th>Error/Adverse event rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>US primary care clinics</td>
<td>8 primary care clinics over 5 years, with a total of 946,000 consultations.</td>
<td>3.7 adverse events per 1000,000 clinic visits of which 83% preventable</td>
</tr>
<tr>
<td>Prescriptions issued by British GPs</td>
<td>15,915 prescription items issued by 8 GPs over 3 months</td>
<td>3.2% error rate.</td>
</tr>
<tr>
<td>Prescriptions issued by British GPs</td>
<td>201,000 items dispensed by 14 community pharmacists.</td>
<td>0.75% error rate of which 4.7% to 32% could have caused harm</td>
</tr>
<tr>
<td>Prescriptions issued by Dutch family physicians</td>
<td>46,837 items dispensed by 141 community pharmacists</td>
<td>4.3% error rate of which 22% could have caused harm</td>
</tr>
</tbody>
</table>
The costs of medical errors and adverse events

Couch et al (1981) represents one of the earliest attempts to estimate costs associated with adverse events. (Couch, Tilney, Rayner, & Moore 1981) They reported the results of a one-year prospective survey of 5612 surgical admissions to 1 US hospital, in which 36 adverse outcomes due to error during surgical care were identified, 11 of which were assessed as being directly responsible for the patient’s death and a further 5 of which resulted in the patient leaving the hospital with serious physical impairment. The study calculated the total cost of these 36 patients at $1,732,432, but did not attempt to separately identify the additional costs incurred as a result of errors.

In 1992, Johnson et al (1992) used interviews with a sample of 794 individuals who had been identified during the Harvard Medical Practice Study as experiencing an adverse event during medical care, in order to estimate the lifetime health care costs of dealing with the medical injuries that had resulted from the adverse event (this enabled them to calculate the potential costs of a simulated no-fault insurance scheme). (Johnson et al. 1992) They were primarily interested in estimating the total costs of such events across New York State as a whole, and their extrapolations suggested that the total cost of all adverse events in New York State would amount to $21.4 billion per annum (1989 dollars), of which $1.1b was attributable to children. Of the $20.3 billion attributable to adults, $2.5 billion was accounted for by future earnings losses, $3.4 billion by lost household production, and $14.5 billion by expected lifetime medical care costs.

An attempt was then made to separate from these gross costs the costs that could be directly attributed to the consequences of the injury rather than any underlying illness. In all, approximately 19% of the total cost, or $3.8 billion, was determined to be related to the injuries received. These figures are summarized in Table 5, which also extracts from the study enough information to calculate the cost per person (in 1989$) of lost earnings, lifetime medical care costs, and lost household production of injuries attributable to all adverse events and error.
Table 5: Total and average cost per patient of lost earnings, household production and lifetime medical care arising from adverse events, from Harvard Medical Practice Study ($1989, undiscounted)

<table>
<thead>
<tr>
<th></th>
<th>Gross cost of all adverse events</th>
<th>Costs directly attributable to injury</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total ($m) (n=90,882 adults)</td>
<td>Per person ($) (n=90,882 adults)</td>
</tr>
<tr>
<td>Earnings</td>
<td>2,453</td>
<td>26,991</td>
</tr>
<tr>
<td>Household production</td>
<td>3,379</td>
<td>37,180</td>
</tr>
<tr>
<td>Lifetime medical care</td>
<td>14,462</td>
<td>159,129</td>
</tr>
<tr>
<td>Total</td>
<td>20,294</td>
<td>223,300</td>
</tr>
</tbody>
</table>

Source: (Johnson, Brennan, Newhouse, Leape, Lawthers, Hiatt, & Weiler 1992)

These results indicate that the average lifetime gross medical care costs of all adverse events was approximately $159k in 1989 $s, but that the part of this that could be directly attributed to the injury fell to $19,861. This average of course is based on a distribution of costs that is highly skewed: in fact more than 50% of those injured in the Harvard study were estimated to have incurred expected lifetime health care costs of less than $4k.

Kalish et al (1995) used routine administrative data on 372,684 discharges from 404 Californian acute-care hospitals to estimate the additional lengths of stay and charges of patients experiencing complications during or after major surgery. (Kalish et al. 1995) They estimated that at least one potential in-hospital complication occurred for 10.8% of patients. They demonstrated that these adverse events increased length of stay on average from 5.4 to 13.5 days, and charges from $9,239 to $30,896.

Schneider et al (1995) used a retrospective chart review method to assess the additional costs associated with medication-related problems amongst 109 patients at one US hospital who were known to have had clinical consequences from an adverse drug reaction or medication error. The clinical outcomes used to evaluate intervention costs were categorized as extra laboratory tests, noninvasive procedures, additional treatments, invasive monitoring or procedures, increased length of stay, and intensive care. (Schneider et al. 1995) A total of 349 clinical outcomes associated with medication-related problems, or an average of 3 outcomes per patient, were detected. The mean cost ranged from $95 for additional laboratory tests to $2,640 for intensive care. The next most costly outcomes were increased length of stay and invasive monitoring or procedures.

Johnson and Bootman (1995) developed a probability pathway model to estimate the cost of drug-related morbidity and mortality in the US, using data from
published studies, a survey of pharmacist practitioners to determine conditional probabilities of therapeutic outcomes owing to drug therapy, and health care utilization and associated costs owing to negative therapeutic outcomes. (Johnson & Bootman 1995) They estimated that drug-related morbidity and mortality cost $76.6 billion per annum in the ambulatory setting in the US, mainly associated with drug-related hospitalizations. In sensitivity analyses the estimated cost ranged from $30.1 billion to $136.8 billion.

Classen et al (1997) used a matched case control approach to estimate the additional lengths of stay, costs, and mortality attributable to adverse drug events in hospitalized patients in one US hospital during the four years from 1990 to 1993. They found 2.43 adverse drug event complications per 100 admissions during the study period. Using regression analysis to control for all matching variables, they estimated that an ADE was associated with increased length of stay of 1.91 days and an increased cost of $2,262 (P<.001), while the increased risk of death among patients experiencing an ADE was 1.88. (Classen et al. 1997)

A detailed cost analysis was performed alongside the Utah and Colorado adverse event study, (Thomas et al. 1999) broadly replicating the approach adopted in the Harvard study by Johnson et al (1992)(Johnson, Brennan, Newhouse, Leape, Lawthers, Hiatt, & Weiler 1992), with the methodological difference that patients’ future health care utilization was estimated from patients interviews in the Harvard study but by physician experts and malpractice claims adjusters in the Utah/Colorado study. Thomas et al (1999) estimated that the adverse event rate and costs identified in the study, when extrapolated to the level of the 2 States, had a total cost of $662 million (1996 US dollars), with the preventable adverse event subset costing a total of $308 million. Health care costs alone totaled $348 million for all adverse events and $159 million for preventable adverse events, equivalent to 4.8% and 2.2% respectively of per capita health care expenditures in these states. They also extrapolated to the level of the entire USA, suggesting a figure of $37.6 billion for all adverse events and $17 billion for preventable adverse events, the former figure being equivalent to 4% of all national health expenditures in 1996.

Again it is possible to extract from this study enough information to calculate the cost per person (in 1996$) of lost earnings, lost household production, and lifetime medical care costs of injuries attributable to error, and Table 6 summarises this information.
Table 6: Total and average cost per patient of lost earnings, household production and lifetime medical care arising from adverse events, from Utah/Colorado Study ($1996, discounted)

<table>
<thead>
<tr>
<th></th>
<th>All adverse events</th>
<th>Preventable adverse events</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total ($m)</td>
<td>Per person ($)</td>
</tr>
<tr>
<td>(n=16,609)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Earnings</td>
<td>160.9</td>
<td>9,687</td>
</tr>
<tr>
<td>Household production</td>
<td>152.9</td>
<td>9,206</td>
</tr>
<tr>
<td>Lifetime medical care</td>
<td>348.1</td>
<td>20,959</td>
</tr>
<tr>
<td>Total</td>
<td>661.9</td>
<td>39,852</td>
</tr>
</tbody>
</table>

Source: (Thomas, Studdert, Newhouse, Zbar, Howard, Williams, & Brennan 1999)

From this analysis it is evident that the average lifetime medical cost care of each preventable adverse event is $17,982. Comparison with the Harvard study is not straightforward as the Harvard figures were undiscounted, are reported in a different price year, refer to adults only, and concern the proportion of total costs attributable to an injury rather than the total costs of all adverse events and all preventable adverse events presented in the Utah/Colorado study. Thomas et al (1999) suggest that when discounted and adjusted in a number of other ways to be more compatible the estimates are broadly similar.

In another cost analysis performed as part of a larger study, Bates et al (1997) examined the costs of adverse drug events identified amongst hospitalized patients in the USA. (Bates et al. 1997) They attempted to assess additional resource utilization and costs associated adverse drug events, by adopting a case-control methodology where cases were 190 patients identified as having had an adverse drug event and controls were the patient on the same unit as the case with the most similar pre-event length of stay. Adjusting for severity, comorbidity, and case mix, they found that adverse drug events were associated with an additional length of stay of 2.2 days (P=.04) and an additional cost averaging $3,244 (P=.04). For the subset of 60 cases in which the adverse drug event was classified as preventable, they found that length of stay was increased by 4.6 days (P=.03) and health care costs were on average $5,857 higher (P=.07). The estimated post-event excess costs were $2,595 for all adverse drug events and $4,685 for preventable adverse drug events. Based on these estimated costs and the adverse event rates found in the study, a 700-bed teaching hospital would annually incur the equivalent of $5.6 million for all adverse drug events and $2.8 million for preventable adverse drug events.

Rigby and Litt (2000) used the results of the Quality in Australian Health Care Study (QAHCS) study (see Hospital care section above for results of this study)
to estimate the direct costs associated with iatrogenic injuries occurring in a hospital setting. (Rigby & Litt 2000) Applying those results to a typical community hospital with 120 beds, and costing them on the basis of Australian disease related groups (DRG) mapped on to injury categories, they estimated that the 12 preventable iatrogenic injuries predicted to occur each year would cost approximately 0.25 million US dollars, equivalent to between 2% and 3% of the hospital’s annual budget. In a separately reported study, they also used the DRG costing approach to try to estimate the relative cost impact of different kinds of adverse events, again using the results of the Quality in Australian Health Care Study. (Rigby, Clark, & Runciman 1999) However, although this was presented as a possible way of informing decisions to invest resources in strategies that reduce the risk of adverse events, such decisions cannot be based only on cost information and require full economic analysis of the incremental costs and effects of specified interventions compared against current practice or some other comparator, as discussed in a separate section.

Brown et al (2002) based their cost analysis on the results of the New Zealand Quality in Healthcare Study (NZQHS) (see Hospital care section above for details), using charges to foreign patients as the basis for costing the clinical procedures and hospital bed days attributable to the 850 adverse events identified in the main study. (Brown et al. 2002) They estimated that each adverse event cost an average of $NZ 10,264 per patient, giving a total cost for all adverse events in New Zealand of $NZ 870 million or almost 30% of total public hospital expenditure, of which $NZ 590 million was associated with preventable adverse events.

Flum and Koepsell (2002), as a follow-on of a wider study of the incidence of misdiagnosis of appendicitis, (Flum, Morris, Koepsell, & Dellinger 2001) reported the results of an analysis in which they estimated the average length of stay and hospitalization charges during admissions to remove appendices that turned out to be negative for appendicitis. (Flum & Koepsell 2002) They estimated that 39,901 (15.3%) of the 261,134 appendicectomies performed in the USA in 1997 were negative for appendicitis, and that compared with patients with appendicitis these patients had a significantly longer length of stay (5.8 vs 3.6 days, P<.001), significantly higher costs per admission ($18 780 vs $10 584, P<.001), significantly higher case fatality rates (1.5% vs 0.2%, P<.001), and significantly higher rates of infectious complications (2.6% vs 1.8%, P<.001). The total cost of these misdiagnosed cases was then estimated to be $741.5 million annually.

Zhan and Miller (2003) also obtained administrative data (hospital discharge abstracts) collected by a 20% sample of all non-Federal acute-care general hospitals in the USA, and screened these using a set of patient safety indicators - consisting of 18 event categories, such as accidental puncture or laceration, obstetric trauma, or post-operative hip fracture – that were designed to identify episodes of care that
raised patient safety issues. (Zhan & Miller 2003) They then used regression analysis to estimate the excess length of stay, cost and mortality of patients experiencing each of these events in comparison with a set of control patients who shared the same hospital, sex, race, age band, comorbidities and diagnosis related group. Their analysis suggested that postoperative sepsis was the most serious event, with excess length of stay of 10.89 days, excess charges of $57,727, and an excess mortality of 22%. Based on these results, the authors estimated that the 18 categories of medical injury examined could be responsible for a total of 2.4 million extra hospital days, $9.3 billion excess charges, and 32,591 excess attributable deaths each year across the USA. This figure is fairly similar to the 36,000 deaths from errors across the USA obtained by extrapolating the results of the Utah/Colorado study, as discussed earlier. (Thomas, Studdert, Burstin, Orav, Zeena, Williams, Howard, Weiler, & Brennan 2000a)

Plowman et al (2001) reported the results of a study in which they identified all hospital-acquired infections amongst 4000 adult patients admitted to an English general hospital over the period April 1994 to May 1995, and then collected information on daily resource use by both infected and uninfected patients in order to estimate cost. (Plowman et al. 2001) 309 of the 3980 patients for whom complete data were available presented with one or more hospital-acquired infections during the in-patient period, a rate of 7.8% (95% CI; 7.0, 8.6). Infected patients, on average, incurred hospital costs 2.9 times higher than uninfected patients, equivalent to an additional UK£3,154. Extrapolated to all adult patients admitted to similar specialties at NHS hospitals in England, these results indicated that an estimated 320,994 patients per annum acquire one or more infections which present during the in-patient period, at a total cost to the hospital sector of £931 million per annum. This figure therefore represents the gross economic benefits that might accrue if these infections were prevented, but not the feasibility or cost-effectiveness of preventing them.

The cost of hospital-acquired infections was also examined by Kirkland et al (1999), who used a matched follow-up study design to examine 255 pairs of patients with or without surgical site infections in a 415-bed US community hospital. (Kirkland et al. 1999) They estimated the excess direct costs attributable to surgical site infections at $3,089, with elevated mortality rates, ICU admission rates and lengths of stay.

Vincent et al (2001), as part of their UK pilot study, also estimated the additional or excess costs associated with the 119 adverse events they identified, rather than the total costs of these patients. (Vincent, Neale, & Woloshynowych 2001) In total, they estimated that 999 extra bed days were attributable to these adverse events, of which 460 bed days (46%) were judged preventable and therefore could have been saved. Each adverse event led to an average of 8.5 additional days in
hospital, giving a total additional cost of £290,268 to the two hospitals in the study. Extrapolating these results to England and Wales, they suggested that each year approximately 5% of the total of 8.5 hospital admissions would experience a preventable adverse event, equivalent to an additional three million bed days and additional costs to the NHS of approximately £1bn.

In 2000 the Department of Health published a report entitled “An organization with a memory: report of an expert group on learning from adverse events in the NHS”,(Chief Medical Officer 2000) which drew on a number of previously published studies to estimate the approximate number and cost of adverse events in England. Using the results of the Harvard Medical Practice Study,(Brennan, Leape, Laird, Hebert, Localio, Lawthers, Newhouse, Weiler, & Hiatt 1991) with a 3.7% adverse event rate and 0.7% of inpatient episodes in which an adverse event occurred and which resulted in permanent disability or death, the report estimated that the 8.5 million NHS inpatient episodes each year would result in 314,000 potential adverse events and 60,000 potential instances of adverse event-related permanent disability or death. Using the Quality in Australian Health Care Study, (Wilson, Runciman, Gibberd, Harrison, Newby, & Hamilton 1995) which reported a 16.6% adverse event rate and 3% of inpatient episodes in which an adverse event occurred and which resulted in permanent disability or death, the report estimated that this would equate in the NHS to 1,414,000 potential adverse events each year and 255,000 potential instances of adverse event-related permanent disability or death. Finally, using the results of the pilot study by Vincent et al,(Vincent, Neale, & Woloshynowych 2001) the report estimated that the NHS in England as a whole might experience 850,000 inpatient episodes annually in which adverse events occurred, at a total cost of £2 billion in additional bed-days.

Finally, a small number of studies have tried to calculate the costs of using different screening methods to identify medical errors and adverse events. Bates et al (1995) compared the sensitivity, specificity and costs of using 15 different screening criteria for adverse events, preventable adverse events, and severe adverse events in medical patients, using 3,137 consecutive admissions to a US tertiary care hospital’s medical service over a 4-month period. (Bates et al. 1995b) First, all records were reviewed after discharge to determine the presence of an adverse event, and 341 admissions (11%) were assessed as including an adverse event, of which 274 (80%) were classified as severe and 145 (43%) as preventable. They found that prior hospitalization was the most sensitive (68%) but least specific (56%) screening criterion, that death was specific (97%) but not sensitive (9%), and that readmission was intermediate (sensitivity 28%, specificity 80%). The most sensitive screening strategy using billing information detected just 47% of adverse events, but cost only $3 per admission reviewed and $57 per adverse event detected, versus $13 per admission and $116 per adverse event detected for the strategy of
reviewing all records. The same group of researchers subsequently reported a comparison of physician reporting using email versus retrospective record review to identify adverse events in the same sample of admissions. (O’Neil et al. 1993) They found that the physician reporting method identified 89 adverse events while record review identified 85, but that the level of agreement was low, with only 41 of the same patients identified (kappa = 0.52). However, the physician reporting method did report more preventable adverse events (62.5% compared with 32%; P = 0.003) and cost approximately $15,000 compared with $54,000 for record review.
Interventions to reduce medical errors and adverse events

The vast majority of the studies documented above are descriptive studies which aim using a range of methodologies to estimate the incidence of errors and/or adverse events in different settings. A much smaller number of studies in the literature have reported studies assessing the effectiveness of interventions to reduce medical errors or adverse events. These have frequently relied on relatively non-robust study designs such as before-after comparisons, but some case control studies and randomized trials have also been performed. In addition, a small number of systematic reviews have been published in recent years, which have tried to identify all existing evidence on interventions to reduce medical errors and adverse events.

Ioannidis and Lau (2001) reported the results of a systematic review of randomized trials on behavioral, educational, informational and management interventions relating to medical errors. (Ioannidis & Lau 2001) They considered studies performed in inpatient and outpatient settings, and imposed no age or disease restrictions. They looked for studies in which the outcome was medical error, including medication, prescription, and diagnostic errors, and excluding preventive medicine errors and simple ordering of redundant tests. They found 24 nonrandomised studies, including 18 before-after studies and 6 studies with concurrent controls, and these had mainly been published prior to 1990. They also identified 13 randomized studies that qualified for evaluation, 11 of which had been published after 1990. The trials varied extensively in their patient populations, study setting, definition of errors, and interventions, making it impossible to quantitatively synthesise the results in an overall result. However, Table 7 shows some summary features of the 13 trials identified, including the error definition, intervention, risk ratio of the intervention group to the control group, and significance level of the result.

In 9 of the 13 studies, the interventions were found to be effective in reducing error rates, with evidence of harm or no significant difference in the remaining 4 studies. For example, in one of the studies showing an effect, Leape et al (1999) looked at the effect of pharmacist participation on medical rounds in the ICU of 1 US hospital on the rate of preventable adverse drug events (ADEs) caused by ordering errors. (Leape et al. 1999) The error rate was 3/75 in the intervention group and 8/75 in the control group, a risk ratio of 0.38 (p<0.001), demonstrating that a relatively simple intervention could reduce error rates by approximately 60%. Across all 13 trials identified, error rates in the control arms ranged from 10% to 63%, and the review illustrated that medical errors were frequent, and that relatively simple interventions could achieve substantial reductions in error rates, as
well as exposing the extreme scarcity of randomised trial data in this important area. However, the review also highlighted the limitations of these studies: the lack of evidence that they could be generalized from quite specific settings into more general health service use; suboptimal randomization methods leaving room for potential bias; the lack of established connection between the medical errors observed and any consequent harm or health consequences; and the lack of evidence on the net costs or cost-effectiveness of the interventions.

Table 7: Summary data from 13 randomised trials of interventions to reduce medical errors

<table>
<thead>
<tr>
<th>Study</th>
<th>Error definition</th>
<th>Intervention</th>
<th>Risk ratio</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Klassen et al. 1993)</td>
<td>Missed fracture</td>
<td>Brand protocol by triage nurse</td>
<td>harm</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>(McCarthy et al. 1990)</td>
<td>Patient not recognizing illness as serious</td>
<td>Teaching acute illness observation to mothers</td>
<td>2.00</td>
<td>NS</td>
</tr>
<tr>
<td>(Attard et al. 1992)</td>
<td>Wrong management (operate or not)</td>
<td>Pain relief for acute abdominal pain</td>
<td>0.22</td>
<td>0.051</td>
</tr>
<tr>
<td>(Sakr et al. 1999)</td>
<td>Significant clinical management error</td>
<td>Nurse practitioner versus junior doctor</td>
<td>0.86</td>
<td>0.2</td>
</tr>
<tr>
<td>(Overhage et al. 1997)</td>
<td>Error of omission</td>
<td>Computerised reminders of corollary orders</td>
<td>0.47</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>(Owens et al. 1990)</td>
<td>Inappropriate drug choice</td>
<td>Multidisciplinary approach</td>
<td>0.53</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>(Ley, Jain, &amp; Skilbeck 1976)</td>
<td>Medication error</td>
<td>Antidepressant easy leaflet</td>
<td>0.17</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>(Barker et al. 1984)</td>
<td>Medication error</td>
<td>Tranquillizer easy leaflet</td>
<td>0.39</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>(McMahon, Rimsza, &amp; Bay 1997)</td>
<td>Prescription error</td>
<td>Automated bedside dispensing</td>
<td>0.67</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>(Bates et al. 1998)</td>
<td>Serious medication error (nonintercepted)</td>
<td>Syringe/demonstrated dose</td>
<td>0.26</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>(Pereles et al. 1996)</td>
<td>Medication error</td>
<td>Team intervention</td>
<td>1.40</td>
<td>NS</td>
</tr>
<tr>
<td>(Buchanan et al. 1991)</td>
<td>Prescription error</td>
<td>Self medication programme</td>
<td>0.61</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>(Leape, Cullen, Clapp, Burdick, Demonaco, Erickson, &amp; Bates 1999)</td>
<td>Prescription error</td>
<td>Pharmacist participation in rounds</td>
<td>0.38</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Source: (Ioannidis & Lau 2001), tables 1 & 3.

In a separate systematic review published in 2003, Kaushal et al searched the literature for studies (randomized & nonrandomized controlled trials, and
observational studies)) that had evaluated the effects of computerized physician order entry (CPOE) and clinical decision support systems (CDSSs) on medication error rates. (Kaushal, Shojania, & Bates 2003) They found 5 studies assessing computerized physician order entry, 2 demonstrating a marked decrease in the serious medication error rate, 1 an improvement in corollary orders, 1 an improvement in prescribing behavior, and 1 an improvement in nephrotoxic drug dose and frequency. They also found 7 studies assessing clinical decision support systems, 3 of which demonstrated statistically significant improvements in antibiotic-associated medication errors or adverse drug events and 1 an improvement in theophylline-associated medication errors. The remaining 3 studies had nonsignificant results. However, the size, study design and overall quality of these studies were generally not adequate to draw robust conclusions.

A systematic review by Walton et al (2002) focused on interventions using computerised advice on drug dosage for a limited range of medications (theophylline, warfarin, heparin, aminoglycosides, nitroprusside, lignocaine, oxytocin, fentanyl and midazolam), in a secondary care setting only. (Walton RT 2002) Fifteen trials involving 1229 patients were identified, in which interventions usually targeted doctors, and all took place on acute medical conditions in hospital settings. Only two studies reported a sample size calculation and most were underpowered. The overall results indicated that computer support for drug dosage gave significant benefits, reducing adverse reactions by 6%, (95% CI 12% to 0%), as well as shortening time to achieve therapeutic control, reducing toxic drug levels, and possibly reducing hospital stay, with a parallel tendency for computer support to result in higher doses of drugs.

In 2001 the US Agency for Health Care Research and Quality published a detailed evidence based report which reviewed all aspects of patient safety practices and included interventions such as the role of the clinical pharmacist and protocols for high-risk drugs in primary care. (2001) They defined patient safety practices as those that reduce the risk of adverse events related to exposure to medical care across a range of diagnoses or conditions. They then identified 79 potential patient safety practices for detailed review, by means of initial literature surveys and expert consultation, focusing mainly on hospitalized patients but including nursing home and ambulatory patients. These practices were then ranked according to the strength of the evidence base for each. Practices with the strongest supporting evidence were generally found to be clinical interventions that decreased the risks associated with hospitalization, critical care, or surgery, and the 11 rated most highly for widespread implementation were:

1. Appropriate use of prophylaxis to prevent venous thromboembolism in patients at risk
2. Use of perioperative beta-blockers in appropriate patients to prevent perioperative morbidity and mortality
3. Use of maximum sterile barriers while placing central intravenous catheters to prevent infections
4. Appropriate use of antibiotic prophylaxis in surgical patients to prevent postoperative infections
5. Asking that patients recall and restate what they have been told during the informed consent process
6. Continuous aspiration of subglottic secretions (CASS) to prevent ventilator-associated pneumonia
7. Use of pressure relieving bedding materials to prevent pressure ulcers
8. Use of real-time ultrasound guidance during central line insertion to prevent complications
9. Patient self-management for warfarin (Coumadin) to achieve appropriate outpatient anticoagulation and prevent complications
10. Appropriate provision of nutrition, with a particular emphasis on early enteral nutrition in critically ill and surgical patients
11. Use of antibiotic-impregnated central venous catheters to prevent catheter-related infections.

The report illustrated how an evidence-based approach could help identify practices that are likely to improve patient safety, but did not explicitly address the issue of the costs or cost-effectiveness of these practices.

Most recently, a review group within the Cochrane Collaboration has been formed with the objective of updating elements of the reviews cited above and expanding the area of interest to include other interventions related to the reduction of medication-related error in primary care. (Smeaton L 2003)

A small number of additional studies did not fit the criteria of the reviews discussed above or were published subsequently. Kovner et al (2002) did not use an experimental study design at all, and instead estimated the association between nurse staffing levels and adverse event rates as measured by four postsurgical adverse events - venous thrombosis/pulmonary embolism, pulmonary compromise after surgery, urinary tract infection, and pneumonia - using hospital level data from up to 13 US States between 1990 and 1996. (Kovner et al. 2002). They found an inverse relationship between registered nurse hours per adjusted inpatient day and pneumonia (p<0.05) for routine and emergency patient admissions, but no significant relationship with the other measures of adverse event. Their results suggested that improvements in nurse staffing could reduce adverse events, but clearly some form of interventional study would be required to test this hypothesis.
Pittet et al (2000) used a well-designed before-after study to estimate the effect of a hand-hygiene campaign on overall compliance with hand hygiene during routine patient care in a teaching hospital in Geneva, Switzerland, using data from 7 hospital-wide observational surveys performed twice yearly from December, 1994, to December, 1997. Secondary outcome measures were nosocomial infection rates, attack rates of methicillin-resistant Staphylococcus aureus (MRSA), and consumption of handrub disinfectant. They found that compliance improved progressively from 48% in 1994, to 66% in 1997 (p<0.001), that hand hygiene improved significantly among nurses and nursing assistants, but remained poor among doctors, and that overall nosocomial infection decreased from 16.9% in 1994 to 9.9% in 1998 (p=0.04), MRSA transmission rates decreased from 2.16 to 0.93 episodes per 10,000 patient-days (p<0.001), and consumption of alcohol-based handrub solution increased from 3.5 to 15.4 L per 1000 patient-days (p<0.001), suggesting that the campaign produced a sustained improvement in compliance with hand hygiene, and was associated with a reduction of nosocomial infections and MRSA transmission.

Cost-effectiveness studies

The relatively small number of randomized trials assessing the effectiveness of interventions to reduce medical errors or adverse events has already been commented on. It is even more noticeable that there are virtually no studies assessing the cost-effectiveness of such interventions. The only study identified in the literature that is explicitly concerned to consider the costs and effects of such an intervention is Wang (1998), who reported the results of what is described as a cost-benefit study to analyze the financial effects of electronic medical record systems in ambulatory primary care settings from the perspective of the health care organization. In this study, data were obtained from 1 hospital and the published literature, and the electronic record was compared with the traditional paper-based medical record. The primary outcome measure was the net financial benefit or cost per primary care physician for a 5-year period. The estimated net benefit from using an electronic medical record for a 5-year period was 86,400 US dollars per provider. However, the main benefits quantified in the study were savings in drug expenditures, improved utilization of radiology tests, better capture of charges, and decreased billing errors, rather than any impact on adverse events of patient outcomes.
Methodological aspects of empirical studies in medical error and adverse events

It is evident that the empirical research documented above to quantify the size of the different categories shown in Figure 1 has adopted a wide range of methodologies, but these can be broadly categorized as follows:

Surveys of clinicians and other health care providers

One methodological approach is to ask clinicians, pharmacists, surgeons or other health care providers via face-to-face or telephone interview or by postal survey to estimate the number of times errors, adverse events or preventable adverse events occurred. Such surveys are typically retrospective: for example, Blendon et al (2002), reported a national survey in which 831 practicing physicians were asked by mailed questionnaire to respond to questions concerning the frequency and causes of preventable medical errors over a previously defined period. (Blendon et al. 2002) Similarly, Meinberg et al (2003) reported a survey in which 1,560 hand surgeons were sent by mail a confidential questionnaire requesting information about the frequency of wrong-site surgery over their working career. (Meinberg & Stern 2003) Gawande et al (2003) approached 45 surgeons to investigate by means of confidential interview the incidence and characteristics of surgical adverse events arising from errors in clinical management. (Gawande et al. 2003) An early example of this approach is given by Cooper et al (1978), who conducted 47 interviews with staff and resident anesthesiologists at one US hospital, obtaining descriptions of 359 preventable incidents. (Cooper, Newbower, Long, & McPeek 1978) In a variant of this approach, Macpherson et al (2001) reported a survey in which 1,848 professional acupuncturists were asked to record prospectively on standardised self-report forms details of adverse events following treatments they provided over a four-week period. (MacPherson, Thomas, Walters, & Fitter 2001)

The advantages of the survey approach are that it is relatively cheap, and that it provides some information on near misses that might otherwise be difficult to detect. The main disadvantages are that the response rate may be low and biased, that the responses are not validated, and that clinicians may not always be aware that they are committing errors, or know whether adverse events have occurred as a consequence of an episode of care in which they were involved.
Surveys of patients

The retrospective survey method has also been used to obtain information from patients on the frequency and severity of adverse events.

For example, Fenn et al (2002) asked a random population sample of 8206 individuals if they believed that over the last three years they had suffered some illness, injury or impairment that in their opinion was caused by their medical treatment or care, and further detailed questions of those who gave a positive response to this filter question. Blendon et al (2002) conducted a similar but smaller study of 1207 members of the public, using telephone interview after selection by random-digit dialing to obtain information on the perceived frequency of preventable medical errors. Blendon, DesRoches, Brodie, Benson, Rosen, Schneider, Altman, Zapert, Herrmann, & Steffenson 2002) Some surveys have adapted this study design to use a prospective methodology. For example, Gandhi et al (2003) prospectively asked 1202 outpatients who had received at least one prescription during a four-week period to record any adverse events that occurred, and then performed case reviews to try to ascertain the cause and preventability of the adverse event. Gandhi, Weingart, Borus, Seger, Peterson, Burdick, Seger, Shu, Federico, Leape, & Bates 2003)

As with surveys of clinicians, patient surveys are relatively cheap to perform, and may also provide some information on adverse events that the health care system has no knowledge of. However patients may be unaware of errors that do not result in an adverse event, or may not know that an adverse event had in fact occurred, and may also find it difficult to know whether an adverse event of which they are aware was preventable or indeed negligent.

Retrospective reviews of cases

The most common methodological approach in the literature on medical errors and adverse events is the use of some type of case note review. This may take many different forms. In the most widely quoted study of the incidence of adverse events, the Harvard Medical Practice Study, 30,251 patient records were selected at random from 51 randomly selected hospitals, and each case record was then reviewed to ascertain whether an adverse event had occurred and, if so, its nature, severity and other characteristics. Brennan, Leape, Laird, Hebert, Localio, Lawthers, Newhouse, Weiler, & Hiatt 1991) A similar approach was adopted with 15,000 randomly selected patients from hospitals in Utah and Colorado, (Thomas, Studdert, Burstin, Orav, Zeena, Williams, Howard, Weiler, & Brennan 2000a) in a pilot study of 1014 medical records from British hospitals, (Vincent, Neale, & Woloshynowycz
Case review typically relies on a small number of individuals reviewing each record according to some predefined criteria, and a substantial literature has developed on the reliability and validity of different methods of reviewing and classifying records. Bates et al (1995) reported an evaluation of the sensitivity and specificity of individual screening criteria to identify adverse events. Bates, O’Neil, Petersen, Lee, & Brennan (1995b) reported high levels of agreement between a two-stage review procedure involving record administrators and physicians guided by an event analysis form and review by senior physicians. Brennan, Localio, & Laird (1989) found substantial disagreement between physicians assessing 7533 medical records as part of the Harvard Medical Practice Study. (Localio et al. 1996) Working independently, 127 physicians each had to assess records for the existence of an adverse event, and the type of adverse event when one was assessed. In fact, in 12.9% of cases (971 of 7533), the two physicians in a pair had extreme disagreement about the occurrence of an adverse event. These cases outnumbered those in which both reviewers found an adverse event (10%; n = 757). Agreement was highest for wound infections and lowest for adverse events attributed to failure to diagnose or lack of therapy.

Similarly, Thomas et al (2002) found substantial differences between reviewers in the number of adverse events and negligent adverse events they detected in medical records. (Thomas et al. 2002)

An alternative method avoiding the need for individual case note review is to use routinely collected data, such as inpatient records, in which codes are assigned to adverse events or conditions associated with adverse events. Kalish et al (1995) used data from 404 Californian acute-care hospitals to estimate the additional lengths of stay and charges of patients experiencing complications during or after major surgery. (Kalish, Daley, Duncan, Davis, Coffman, & Iezzoni 1995) O’Hara et al (1997) used a similar approach, obtaining routine inpatient data from all acute-care hospitals in Victoria, Australia to estimate the adverse event rate by hospital type and specialty, and to examine death rates and other variables associated with adverse events. (O’Hara & Carson 1997) Zhan and Miller (2003) also used routine hospital discharge summaries in a large sample, of US hospitals, and then applied a screening algorithm to identify types of episode that were likely to involve medical error. (Zhan & Miller 2003)

Review of records has been used particularly widely in studies of medication error. In general these have taken the form of individual review or semi-automated review of medication records, and because it is possible to define fairly simple criteria for error – such as incorrect doses or incorrect drug combinations – some
very large studies have been undertaken. For example, Lesar et al (JAMA 1997) were able to survey 289,411 medication orders,(Lesar, Briceland, & Stein 1997;Lesar, Lomaestro, & Pohl 1997) and Folli et al (1987) examined 101,022 medication orders.(Folli, Poole, Benitz, & Russo 1987)

An advantage of studies based on written records is that they may capture errors that did not result in adverse events: this is particularly likely to be the case in medication studies, where at least some types of error are relatively easy to define. Record review is also likely to provide more detailed information on sequences of events, the context within which adverse events and errors occurred, and other characteristics such as setting and staff involved. The major disadvantage of studies based on written records is that they will not capture the occurrence of events or errors that are undocumented. In addition, adverse events which become apparent after an episode of care has been completed will not be captured. Reliance on routinely recorded data has the advantage of low cost, but suffers from the additional disadvantage that there is unlikely to be any information on the severity of any adverse events.

**Observational studies**

A small number of studies have adopted an observational methodology to investigate adverse events, relying on the likelihood that staff involved in care will discuss amongst themselves aspects of care including errors and adverse events. Andrews et al (1997) demonstrated this approach, conducting ethnographic research during which trained researchers attended ward-rounds, nursing shift changes, case conferences and other meetings, recording all adverse events discussed.(Andrews, Stocking, Krizek, Gottlieb, Krizek, Vargish, & Siegler 1997) This may capture events that have not been documented, but is expensive and time-consuming to do.

**Economic studies**

The economic studies identified above typically have attempted to quantify the total costs of errors and/or adverse events, normally using samples of individual patient records, but sometimes based on administrative data sets.(Kalish, Daley, Duncan, Davis, Coffman, & Iezzoni 1995), (Flum & Koepsell 2002), (Zhan & Miller 2003) From these estimates, a number of studies have then extrapolated to the hospital, State, regional or national level to calculate the likely total costs of such events. Most of the studies identified attempted to identify the additional costs associated with adverse events, either by using a case-control (e.g. (Classen, Pestotnik, Evans, Lloyd, & Burke 1997), (Bates, Spell, Cullen, Burdick, Laird,
Petersen, Small, Sweitzer, & Leape 1997) or regression based approach (e.g. (Zhan & Miller 2003)) to identify excess costs, or by apportioning bed-days, tests, procedures and other aspects of resource use of an episode in which an adverse event occurred (e.g. (Johnson, Brennan, Newhouse, Leape, Lawthers, Hiatt, & Weiler 1992), (Schneider, Gift, Lee, Rothermich, & Sill 1995), (Brown, McArthur, Newby, Lay-Yee, Davis, & Briant 2002)).

The studies identified here have mainly looked at costs occurring at or around the time of the adverse event. In some cases analyses have also included costs of adverse events that occurred prior to a particular study period: for example, Brown et al (2002) examined hospital admissions in 1998 associated with adverse events which could have happened during that admission or prior to it: in fact approximately 20% of the adverse events had occurred prior to 1998. (Brown, McArthur, Newby, Lay-Yee, Davis, & Briant 2002) But very few studies have tried to examine the longer term consequences of adverse events, exceptions being the Harvard medical Practice Study and the Utah/Colorado study, both of which attempted to quantify the lifetime medical costs associated with adverse events. (Johnson, Brennan, Newhouse, Leape, Lawthers, Hiatt, & Weiler 1992), (Thomas, Studdert, Newhouse, Zbar, Howard, Williams, & Brennan 1999)

No economic studies were identified that tried to quantify the actual or potential costs of actions to avert medical errors or adverse events, and only one partial economic evaluation of an intervention to reduce medical errors or adverse events was found. (Wang, Middleton, Prosser, Bardon, Spurr, Carchidi, Kittler, Goldszer, Fairchild, Sussman, Kuperman, & Bates 2003)

**Summary: methodological issues**

It is evident that a wide range of methodologies have been used to estimate the incidence and characteristics of medical errors and adverse events, and that each method has different advantages and limitations. As a result, no single approach is likely to provide reliable information on the size of all the categories of interest identified in Figure 1: some methodologies (e.g. patients surveys) will provide little or no information on errors that do not give rise to adverse events, while others (e.g. analysis of medication records) may provide information on errors but little or no information on adverse events.

A limitation of most of the study methodologies noted above is the difficulty of reliably estimating the consequences of medical errors. In particular, it has been argued that clinicians find it difficult to estimate accurately the number of deaths that are attributable to serious medical errors. In part this has been attributed to a tendency to overestimate the survival prospects of patients had they received error-
free care. (Hayward & Hofer 2001) In turn this may reflect an over-optimistic view amongst clinicians of the effects of care: Christakis and Lamont (2000), for example, in a study which compared doctors’ predictions of survival amongst terminally ill patients referred to hospices with actual duration of survival, found a low level of correlation and systematic over-estimation. (Christakis & Lamont 2000) Other studies have demonstrated high levels of discordance between clinical and autopsy diagnoses of malignant neoplasms, (Burton, Troxclair, & Newman 1998) again suggesting that it may often be difficult to state the consequences of an adverse event with any certainty.

A final issue affecting many different methodological approaches to medical error and adverse events is the difficulty of categorizing adverse events as preventable or not. This raises a more general issue about the framework within which errors and the concept of preventability should be viewed, on the subject of which the clinical/epidemiological and the economic literatures are divergent. The next section of this report begins this task, by providing an outline of the economic approach to adverse events and medical errors.
An economic approach to adverse events, negligence and preventability

Introduction

The literature reviewed above has been concerned primarily to define the incidence, character and cost of medical errors and adverse events, with much less attention paid to interventions that might reduce adverse events. This section sets out an economic approach to adverse events, negligence and preventability, and suggests that cost-effectiveness methodology offers a useful framework for considering these issues.

Preventability, negligence and cost-effectiveness

The Harvard Medical Practice Study defined an adverse event as “…an injury that was caused by medical management (rather than the underlying disease) and that prolonged the hospitalization, produced a disability at the time of discharge, or both”, (Brennan, Leape, Laird, Hebert, Localio, Lawthers, Newhouse, Weiler, & Hiatt 1991) p.370) a preventable adverse event as an adverse event caused by an error, and a negligent adverse event as an adverse event cause by “…failure to meet the standard of care reasonably expected of an average physician qualified to take care of the patient in question.” (Leape, Brennan, Laird, Lawthers, Localio, Barnes, Hebert, Newhouse, Weiler, & Hiatt 1991) p.377)

Proving that an adverse event was negligent requires demonstrating two things: first, that the injury was related to the medical care received (causation), and secondly, that the standard of care fell below what might reasonably be expected (negligence). Within these definitions, negligent adverse events then become a subset of preventable adverse events, as shown previously in Figure 1. Tort therefore relies on demonstrating causation and negligence, whereas a no-fault compensation system would typically be based on a strict liability rule which required only evidence of causation.

It is clear from the above that error is a necessary but not sufficient condition for proving negligence, which lies at one end of a wider spectrum of preventability. In fact, the Harvard Medical Practice Study group also introduced some conditionality into their general definition of error, by defining a preventable adverse events as “…an adverse event … caused by a reasonably avoided error, defined as a mistake in performance or thought” (Leape, Brennan, Laird, Lawthers, Localio, Barnes, Hebert, Newhouse, Weiler, & Hiatt 1991) p.377 (italics added). In discussing their results, the Harvard Medical Practice Study group developed this
approach, arguing that preventing adverse events entirely was not a feasible target because of the prohibitive costs involved, and proposing a definition of an optimal level of error based on “…a realistic assessment of the effectiveness of efforts to reduce their occurrence.” (Leape, Brennan, Laird, Lawthers, Localio, Barnes, Hebert, Newhouse, Weiler, & Hiatt 1991) p.382)

This kind of approach is sketched in Figure 2. The X-axis depicts the amount of effort required to prevent adverse events, and the cumulative quantum of harm caused is plotted on the Y-axis; if the effort is deployed logically by being concentrated on the adverse event that can be prevented most effectively, the marginal benefit of increased effort will start to decline, until eventually there is a “flat of the curve” where large amounts of effort are required to prevent relatively small additions to the total quantum of harm. Following the quote above, an optimal level of adverse event prevention would presumably aim to prevent adverse events on the steeper part of the slope and try to avoid expending effort on the flat of the curve.

**Figure 2: Diminishing returns to preventing adverse events**

This approach was further emphasized by one of the principal Harvard study investigators in 2000, as part of the debate over the Institute of Medicine report: “preventability is difficult to determine because it is often influenced by decisions about expenditures. For example, if every patient were tested for drug allergies before being given a prescription for antibiotics, many drug reactions would be prevented. From this perspective, all allergic reactions to antibiotics, which are
adverse events according to the studies’ definitions, are preventable. But such preventive testing would not be cost effective, so we did not classify all drug reactions as preventable adverse events.” (Brennan 2000)

Extending this approach, it is possible to recast Figure 2 to incorporate cost-effectiveness. The X-axis then becomes the cumulative cost of activities to prevent adverse events, and the objective becomes to arrange this expenditure so that the most cost-effective interventions are performed first: this is shown in Figure 3. The slope of the curve then shows declining cost-effectiveness, so that a given amount of expenditure produces less and less health gain.

Figure 2: Diminishing cost-effectiveness of preventing adverse events

It also then becomes possible to argue that the dividing line between negligence and other preventable adverse events can be defined in terms of cost-effectiveness: that is, the standard of care reasonably expected will include actions that could be considered broadly cost-effective to perform, and exclude those where the balance between costs and benefits is too unfavourable to constitute part of the reasonably expected standard of care. In Figure 2, for example, adverse events to the left of the vertical line might be adjudged negligent on the grounds that they could have been prevented cost-effectively but were not, whereas adverse events to the right of the line could only have been prevented at a very unfavourable cost-effectiveness ratio that would not be considered reasonable.
In the literature on the economics of tort law, a variant of this approach is sometimes referred to as the Hand rule or formula, after the American Judge Learned Hand who was most closely associated with its formulation. (Landes 1987) Hand argued (U.S. v. Carroll Towing, 1947) that an adverse event resulting in harm could only be considered negligent if the burden or cost of the precautions necessary to prevent the event was less than the probability of an adverse event occurring times the gravity or cost of that adverse event (that is, the expected cost of harm). The Hand formula is therefore a type of aggregate risk-utility test to assess social cost and benefit. For example, assume an allergy test existed which allowed GPs to ascertain whether patients were likely to suffer serious adverse reactions to a particular drug. The test costs £5 and reduces the probability of adverse reactions from 3 per 10,000 to 1 per 10,000. If an adverse reaction occurs a court is likely to make an award which values the pain, distress and other losses at £8,000. Therefore, by spending £50,000 (testing 10,000 patients at £5 each) the health service would avert 2 adverse events valued at £16,000. It would be spending £50,000 to save £16,000 and the Hand formula would assert that this could not be considered negligent. However, if a test was available for £1 per patient, the spending of £10,000 could save £16,000. This would be socially beneficial, and so not providing this test would be considered negligent.

The sum that a court decides to award in settlement of a successful negligence case may include compensation for past and future pain, suffering and disability, as well as past and future financial losses, such as lost earnings and health care costs. It is therefore clearly closely related, if not strictly equivalent, to the kinds of outcomes and costs that a cost-effectiveness analysis is attempting to quantify. So two important questions raised by this approach have to be addressed: first, how is cost-effectiveness to be estimated; and secondly, how is a reasonable level of cost-effectiveness to be defined. Some additional questions, concerning incentives to undertake cost-effective prevention and incentives to invest in research, are dealt with in the final section of the report.

**Evaluating interventions: Principles of economic evaluation**

Economic evaluation has become an important part of health technology assessment in many countries, and there has been a major effort amongst health economists to reach consensus on the methodology that should be used to conduct economic evaluations. Guidelines on good practice have been developed to guide the planning and conduct of studies, the preparation of manuscripts, and the assessment of manuscripts by journal referees and editors. (Drummond et al. 1997), (Canadian Coordinating Office for Health Technology Assessment 1997), (Gold et al. 1996), (NICE 2001)
The basic features of these are summarized below, based broadly on checklist of the Panel on Cost-Effectiveness in Health and Medicine, convened by the US Public Health Service to produce explicit guidelines on the conduct of cost-effectiveness analyses. (Gold, Siegel, Russell, & Weinstein 1996)

1) Stating and justifying the type of analysis

A small number of different types of analyses makes up the family of economic evaluations. The simplest type of study is a cost analysis, which does not provide information on health outcomes or frequently on alternative courses of action. Such studies may be of descriptive value but are otherwise of limited use, as they give no information on health outcomes or on whether the observed cost is too high or too low.

Where alternatives do exist – for example, infection control by hand-washing or by rapid isolation of patients - and there is reliable information that these are equivalent in terms of their health outcome, then it is reasonable to conduct a study to identify the least cost option. These are called cost-minimisation studies. However, it is hard to demonstrate equivalence, which requires a specific study design with enough power to demonstrate similar effects, and it is important to avoid assuming that failure to detect a hypothesised difference is the same as proof of equivalence. For this reason, the role of cost-minimisation studies is quite circumscribed. (Briggs & O'Brien 2001)

If alternative courses of action exist and their outcomes are known to be different (or not known to be the same), we enter the domain of cost-effectiveness analysis. The objective of such studies is to estimate the difference in costs between an intervention or programme and some specified alternative, and then expressing that difference as a ratio of the difference in outcomes. For example, if prescription errors could be reduced by bar coding or by computerised ordering, a cost-effectiveness analysis would calculate the difference in cost of the two strategies as a ratio of the difference in outcome, expressed as a net cost per error avoided. The outcome of interest can vary widely in cost-effectiveness analyses: e.g., the cost per case detected in screening studies, the cost per symptom free day, the cost per adverse event avoided, or the cost per death averted.

However, as discussed below, the whole point of undertaking a cost-effectiveness analysis is generally to help decide whether it is worthwhile spending money on a particular course of action compared to doing something else with the money. Consequently economists are interested in measures of outcome that allow comparisons to be made across a wide range of alternatives, and the most popular such measure at present is the quality adjusted life year or QALY, which is a composite measure of changes in survival and quality of life. Cost-effectiveness
analyses which make use of QALYs as the main outcome measure are sometimes called *cost-utility analyses*, because QALYs are trying to measure the value or utility derived from a state of health or health change.

Cost-effectiveness and cost-utility analyses are entirely premised on the assumption that the outcome – whether errors or adverse events averted, or lives saved, or cases detected – is a worthwhile objective. They address a second order question, which is ‘Accepting that it is worthwhile to attain this objective, what is the most efficient way of doing so?’ In health technology assessment, this typically means starting from an assumption that the health care system exists to improve health, and then asking questions about the best (most efficient) way of going about it. Cost-effectiveness analyses do not answer the more fundamental question: is the objective worth pursuing at all? To do this requires the use of *cost-benefit analysis*, which attempts to place an absolute monetary value on, for example, a human life. The attraction of the cost-benefit approach is that, if a life could be valued in monetary terms, then action or intervention which saved a life for less than that value – that is, where the costs were less than the benefits - would be worthwhile, while any action where the costs exceeded that value – that costs, where the costs were greater than the benefits - would not be worthwhile. The attraction of the approach is that this decision-rule is simpler than in cost-effectiveness analysis. However, it is very difficult to obtain agreement on monetary valuations of health, or even on the methods that should be used, and consequently cost-benefit analysis is not widely used in health technology assessment at present.

2) Stating the background of the intervention

Many published studies unfortunately fail to comply with this simple but important point. The background includes the size and nature of the problem, the details of the interventions being considered, including the grade and experience of staff delivering the intervention, the physical setting (e.g. the intensive care unit of a large teaching hospital or a general ward on a small general hospital), and the target population (e.g. their age, sex, and risk characteristics), which may all affect the costs and outcomes reported.

3) Specifying a comparator programme

Cost-effectiveness analysis is all about the comparison of an intervention with some alternative: it is a strictly comparative methodology. Hence the comparator that is selected is crucial to the results. If the cost-effectiveness of a new drug was to be calculated against a do-nothing alternative its cost-effectiveness would probably seem much better than if it was compared with existing treatments.
Current practice is therefore usually the appropriate comparator. However, if current practice has not itself been evaluated, it may be appropriate to try to compare an intervention against a do-nothing alternative. For example, the costs and effects of a new infection control policy involving publicity and provision of improved hand-washing facilities should be compared against the existing current practice; but current practice may contain many actions and policies that are not evidence based, in which case it may also be appropriate to compare the new policy against something other than current practice, such as a minimum set of evidence based practices.

4) Stating perspective and time horizon

The perspective of an economic evaluation means the point of view from which costs and outcomes have been calculated. For example, a hospital at home scheme that encouraged more rapid discharge from hospital wards could save hospital resources, but increase costs incurred by primary care and community care services, and could allow patients to recovery return to paid employment more quickly, but also require extra informal care by the families and friends of patients. Viewed from the perspective of the hospital, or the general practitioner, or the patient, or the patients’ family, or the patients’ employer, the balance between costs and benefits may appear very different. Examples of this are not uncommon in the literature: for example an American economic evaluation of a varicella (chickenpox) vaccination programme showed that with no vaccination programme the health care system incurred annual costs of $90m, and parents incurred annual costs of $439 (mainly time off work looking after sick children).(Lieu et al. 1994) If a programme was introduced, the health system would incur the vaccination costs ($88m per annum) and some remaining treatment costs ($10m per annum), leaving it spending more than previously - $98m rather than $90m each year. But the costs to parents and/or their employers would fall from $439m to $48m each year. So they would be better off, as would society as a whole. Whether the programme makes sense may seem therefore to depend on the perspective adopted. In general economic evaluations should take a societal perspective and try to identify all winners and losers. A separate question may then have to be addressed on how winners should compensate losers, but if it is worthwhile from a societal perspective it should in principle be possible to implement the policy and leave everyone better off. The National Institute for Clinical Excellence currently advises that economic evaluations “…should be conducted from the perspective of the NHS and Personal Social Service (PSS) decision-maker. That is to say the benefits should include all clinical and health-related benefits valued from the perspective of society, and costing should include all use of NHS and PSS resources required to
achieve those benefits.” (NICE 2001) This suggests that the default position for NICE would be to exclude from consideration costs incurred by patients or their carers, or productivity losses and gains such as sickness absence, although the guidance does state elsewhere that “impacts on social productivity may be assessed if considered sufficiently important in specific cases” (but should be presented and reported separately).

This idea of perspective also includes a time dimension: some interventions – for example increasing the emphasis on hand hygiene in undergraduate medical courses - may have benefits many years in the future, when the student has entered full-time employment. Other interventions - e.g. new operating room procedures to reduce infection rates during surgery - may result in immediate changes in lengths of stay and ICU use. Both interventions may eventually result in fewer hospital acquired infections, less morbidity and less mortality. Economic evaluations should ideally adopt a time horizon that extends sufficiently far into the future to capture all these economic consequences and health outcomes. In practice this often means the lifetime of a patient.

Because the costs and benefits of different programmes may be spread out quite unevenly over time, but have to be compared at the same point in time – usually the present – economists generally adjust future costs outcomes using a discount rate which gives less weight to future costs and benefits than to present costs and benefits. There are two main reasons for discounting: first, that most individuals attach higher value to present benefits than future benefits, and prefer to postpone costs to the future rather than incur them now. This is referred to as time preference. A discount rate tries to capture this time preference. The second reason for discounting is opportunity cost: resources not spent now could be invested and will normally yield a positive rate of return which makes them worth more in real terms in the future.

Discount rates tend to vary between countries and are sometimes revised. For many years in the UK costs and outcomes were discounted at 6% per annum, which tended to work quite strongly against preventive interventions (where costs are usually incurred now and benefits are reaped many years into the future). More recently, the discount rate recommended in the UK by the National Institute for Clinical Excellence has been altered to 6% per annum for costs and 1.5% per annum for outcomes. However, it is also recommended practice to provide additional results using a range of discount rates.

5) Identifying, measuring and valuing all resources of interest

Estimating the costs of an intervention is usually done in distinct stages. First, it is necessary to identify all the resources involved in the intervention itself, and
any future resource consequences such as adverse events or an altered probability of clinical events (hence the need for a clear description of the intervention). For example, the resource consequences of hormone replacement therapy include not only the drug therapy itself but also an altered future likelihood of osteoporosis, breast cancer, endometrial cancer and possibly cardiovascular and other diseases, all of which have resource consequences. Ideally we should include not only health care resources, but also the consequences for patients, their families and society (see the discussion of the study perspective above).

Once these resource consequences have been identified, they need to be measured and then valued. The way in which they are measured will vary depending on the level of detail of the study. For example, use of hospital resources may be measured simply in terms of numbers of cases or of in-patient days, or in much more detail by documenting all the nursing and medical time, drugs and dressings, tests and consumables involved in the episode. The level of detail in turn will depend on the research question: is there reason to believe that the intensity of care in hospital may differ between interventions, for example, or is it more important simply to detect any overall difference in hospitalisation rates?

The valuation of these resources is the point at which unit costs are attached. To an economist, cost is measured in terms of the potential opportunities which are foregone when resources are committed to one purpose rather than another. The normal market price - the wage for a nurse or the price of a prescribed drug - will usually be a reasonable measure of this opportunity cost. However, prices, charges, tariffs or fees can sometimes be misleading. For example, a family planning clinic may get ‘free’ space in a hospital out-patient department; that is, it does not pay for it. But by using the space in this way, other potential benefits from using the space in a different way are sacrificed. So there is an opportunity cost, even though there is no charge. This distinction can become very important in areas such as informal care, where relatives and friends of patients may be sacrificing a great deal of work time or leisure time to caring, for no financial reward. There is no price, but the opportunity cost may be very substantial.

6) Identifying, measuring and valuing all outcomes of interest

As noted earlier, cost-effectiveness analyses can measure outcome, effectiveness or benefit in many different ways, but disease-specific or process-specific measures such as medication errors averted are not very useful as they only permit comparisons with other interventions that also reduce medication error, whereas the more important question may be whether reducing medication error is good value for money compared with reducing waiting times for knee replacements, improving nurse staffing, or introducing a stroke rehabilitation
service. Hence economics has moved towards the quality adjusted life year or QALY as the preferred measure of outcome or effectiveness. A range of methods are used for numerically estimating the value or utility which someone obtains from a health state, and the sources of these valuations (e.g. patients, the public, carers, clinicians), and these should be clearly stated, but there is increasing evidence that such valuations are fairly robust across a range of methods. (Tengs & Lin 2003) The QALY should capture interventions aimed at affecting mortality, such as avoidance of intrathecal injection medication error, but also interventions that mainly affect quality of life, including most adverse drug reactions.

7) Documenting methods and sources

Estimating costs and effectiveness is done in steps: identification, measurement, valuation. For example, to calculate the costs of an adverse event reduction programme it would be necessary to identify the types of adverse events, their resource consequences (consultations, bed-days, etc.), the unit costs and total costs of these resources, and their health consequences. It is important to set out clearly how these steps will be taken, including: the sample size for measuring resource use, the source of unit cost estimates, the source of effectiveness data, and the source of quality of life valuations.

8) Reporting costs, effectiveness, cost-effectiveness, and uncertainty

The objective of an economic evaluation is normally to provide an estimate of cost-effectiveness, such as the cost per quality adjusted life year gained. One useful way of displaying the results is in the form of a cost-effectiveness plane, for example as shown in Figure 3. The central point represents the comparator, for example current practice; the difference in effect of the new intervention against the comparator – the incremental effectiveness - is plotted along the X-axis, and the difference in cost of the new intervention against the comparator – the incremental cost – is plotted up and down the Y-axis. If the new intervention is more expensive and less effective it will be in the north-west quadrant of the figure; if it is cheaper and less effective it will be in the south-west quadrant; if it is cheaper and more effective it will be in the south-east quadrant, and finally if it is more expensive and more effective it will be in the north-east quadrant.
Figure 3: the cost-effectiveness plane

In practice most new interventions are in the north-east quadrant: that is, they cost more but are more effective. If the difference in cost and the difference in effect were both to be plotted on the figure as a point in that quadrant, the slope of the line from the centre of the figure to that point would be the incremental cost-effectiveness ratio or ICER. If the intervention was much more effective and not much more expensive (for example, point A on Figure 3), it would probably be accepted as good value for money and implemented. If it was only a little more effective and was much more costly (for example, point B), it might well be considered bad value for money and rejected.

There must therefore be some diagonal line running through the figure that represents a maximum willingness to pay for health gain: if an intervention is to the right of that line (the dashed line in the figure) it is likely to be accepted, and if it is to the left it is likely to be rejected. Where that line lies will depend on many factors, including the total amount of money available for health care. In practice, decision making agencies and reimbursement authorities tend to consider the cost-effectiveness of things already done in routine health care, and then assume that if
there is a willingness to pay for them then any new interventions that are at least as
cost-effective should also be acceptable. The deliberations and decisions of the
National Institute for Clinical Excellence in England and Wales suggest that
interventions with a cost-effectiveness of less than £30,000 per quality adjusted life-
year gained are much more likely to be accepted than are interventions with cost-
effectiveness ratios well above that figure. (Towse & Pritchard 2002)

The cost-effectiveness plane is a useful graphical device for a number of other
reasons: it allows the absolute difference in costs and effects to be shown, which
may be important for decision makers with budget constraints who are interested in
total cost as well as cost-effectiveness. And it allows the uncertainty around cost
and effect differences to be displayed, for example as error bars or as an ellipse
rather than a point estimate. (Van Hout et al. 1994)

9) Placing the results in the context of other relevant economic evaluations

As mentioned above, cost-effectiveness is a comparative methodology, which
only has meaning in comparison with other cost-effectiveness results. While the use
of an outcome measure such as the QALY permits comparison across a wide range
of other interventions, in practice it is helpful to place cost-effectiveness results in
the context of areas that compete for resources with the intervention under
investigation. This could be a specialty, age group, disease area, type of
intervention, organisational element of the health service, or ring-fenced budget.

10) Discussing policy relevance, ethical and distributive implications

Health economists argue that decisions about resource allocation should not
be taken without considering the costs and outcomes associated with different
courses of action, and propose the cost-effectiveness approach as one way of doing
this. However, this is not to argue that cost-effectiveness criteria are sufficient to
make decisions. In practice, policy makers may have to take into account many
other factors, including fairness and justice, legal and ethical issues, and
humanitarian concerns. For example, cost-effectiveness analysis may show that
intervention X is superior to intervention Y in terms of the cost per QALY gained.
But intervention Y might be sufficiently affordable to be provided to the whole
population at risk, whereas intervention X could only be offered to section of the
population at risk; fairness might then dictate that Y is preferable to X, despite being
less efficient. Economic evaluation cannot provide answers to all decision-making
problems, but it can provide information about what is likely to be the most efficient
choice, and therefore can help quantify the implications of making a decision that is
not based solely on efficiency criteria.
The cost-effectiveness approach to patient safety

Summary of the cost-effectiveness approach

The preceding section set out the main features of the cost-effectiveness approach to evaluating health interventions. It is important to re-emphasise that the cost-effectiveness approach is a decision-making aid designed to help improve the allocation of resources, premised in the health care sector on the underlying assumption that resources are allocated to health care with the objective of obtaining as much health gain as possible. Once this framework is accepted, it no longer makes sense to assess actions in terms of costs alone: it would be cost-saving to stop treating all patients requiring renal replacement therapy, but that would result in serious health losses and would run counter to the underlying objectives of the NHS. This is what differentiates the cost-effectiveness approach from the “business case” approach advocated by analysts. Within that approach, “…a business case for a health care intervention exists if the entity that invests in the intervention realizes a financial return on its investment in a reasonable time frame, using a reasonable rate of discounting.” (Leatherman et al. 2003)

For example, a health maintenance organisation might evaluate the business case for improving the management of patients with diabetes by assessing whether the costs of the programme are likely to be more than outweighed by savings in the form of lower use of services because patients have fewer complications. If the costs are outweighed by the savings to the organisation it will go ahead, otherwise it will not. (Leatherman, Berwick, Iles, Lewin, Davidoff, Nolan, & Bisognano 2003) This approach diverges from the cost-effectiveness approach in some fundamental ways. First, the business case analysis is conducted entirely from the perspective of the payer or investor, whereas the cost-effectiveness approach considers all costs and savings across the health and social services, and potentially also recognizes social costs and savings such as productivity gains. To illustrate, there would be no business case for a Primary Care Trust investing in improved care of patients with diabetes if treating the eligible patients increased costs by £10,000 per year, even if this resulted in fewer hospitalizations and therefore saved the local hospital trust £25,000 per year. However, there might well be a cost-effectiveness argument, as all health and social care costs would automatically be included.

Secondly, the short-term time horizon of the business case approach is likely to work against many interventions that provide substantial benefits in the longer term. An HMO may decide that there is no business case for smoking cessation interventions because the savings will not outweigh the costs within the (relatively short) time frame it has adopted for its investment appraisal. (Leatherman, Berwick,
However, a cost-effectiveness approach, typically using a lifetime perspective, would almost certainly conclude that this type of intervention was extremely cost-effective and would be a very good use of health resources. (Stapleton, Lewin, & Russell 1999)

Finally, and most importantly, the business case approach does not put any value on health gain except insofar as a health improvement results in financial savings to the organisation providing the intervention. There is no business case for improving care for patients with diabetes unless the savings outweigh the costs to the provider. But this implies that the health benefits have no value. For example, if improved diabetes treatment cost a PCT £10,000 per annum, and resulted in fewer complications and so saved the hospital trust £3,000 per annum, there is a net cost of £7,000 a year and no business case. But patients will experience fewer complications and better health, and the net cost of £7,000 may well be considered a reasonable price to pay for these health benefits. To return to Figure 3, a cost of £7,000 for these health benefits may well fall below the dotted diagonal line that represents the cost-effectiveness ceiling or maximum willingness to pay for health gain. The business case in effect says that interventions are only acceptable if they are in the lower half of Figure 3: cost saving and (hopefully) either health neutral or health gaining (the south-east quadrant). This is a very hurdle to set, which would result in almost no new interventions being adopted by the NHS.

Of course, if decision makers were being asked to allocate a budget using cost-effectiveness criteria, they would start by adopting any interventions known to have positive effects on health and to be cost-saving – that is, interventions in the south-east quadrant of Figure 3. A few such interventions have been identified, (Clarke et al. 2001) and it is possible that others exist in the field of patient safety. But they would rapidly have to move on to interventions in the north-east quadrant, that had a net cost but provided health gain. They would continue until their budget was exhausted, which should approximate to the diagonal line indicating their maximum willingness to pay.

The essence of the cost-effectiveness approach applied to patient safety, therefore, is that interventions to improve patient safety should be undertaken if the cost of obtaining the health benefits is considered acceptable using the criteria in use elsewhere in the NHS: that is, if the demonstrated cost-effectiveness is below the ceiling value of willingness to pay for health gain. Some interventions may be cost-saving, and some may also meet a business case criterion, but they are likely to be a very small subset. Using only a business case approach would imply that the willingness to pay for health gain was zero.
Identifying interventions

The main features of a robust cost-effectiveness analysis, as set out above, can be applied to a wide range of different types of intervention, from population-based screening and prevention programmes to specific patient groups. Similarly, the health technologies being evaluated could include organisational and behavioural innovations as well as surgical, pharmaceutical or information technologies. As the literature review reported above illustrates, medical errors and adverse events may occur in many different settings and in many different ways, but there is no reason to think that patient safety raises methodological issues that are not amenable to the cost-effectiveness approach. The main questions are practical, and concern the identification of existing and alternative interventions, and then the collection of information on effectiveness and costs.

While economic evaluation is most typically applied to new technologies to help determine whether they should be adopted, it is important to recognise that it can and should also be applied to existing practices that are not evidence based. There are likely to be many practices in the health care sector that are notionally in place for patient safety reasons but have never been evaluated, and if evidence on their effectiveness is genuinely lacking then it should not be unethical to assess their effectiveness in an experimental way.

The selection of areas to evaluate is not straightforward. It should be evident from the preceding discussion that the basis of the cost-effectiveness approach is to identify areas in which interventions exist that are cost-effective in comparison with current practice. This may have no connection to the size of a particular problem: there may be very cost-effective ways of reducing a small problem, but no cost-effective alternatives available to reduce a large problem. This is the fundamental reason why cost of illness studies – a particular type of cost analysis that aims to determine the total cost or burden associated with a disease or problem – is of little help in deciding treatment priorities.

However, estimating the size of a problem may be helpful in making choices about research priorities. This indeed was one of the original reasons for undertaking cost of illness studies.(Pole 1974) More recently, considerable interest has been shown in the concept of Expected Value of Perfect Information (EVPI) analysis, which offers a potential way of deciding whether the benefits of obtaining more information about the effectiveness or cost-effectiveness of an intervention will be worthwhile in relation to the costs of obtaining the information.(Claxton & Posnett 1996) Clearly, the size of a problem is likely to be one important parameter in calculating the benefits of obtaining more information on interventions.

In other areas of health technology assessment, the selection of areas for evaluation is usually determined by the existence of new interventions, and by
doubts concerning the evidence base of existing interventions, especially where there are wide variations in what constitutes standard clinical practice or no clear basis on which to make choices between alternative treatments. Other methods, such as systematic reviews, horizon scanning, and public & professional elicitation of suggestions, have also been used to help identify areas for evaluation. These are likely also to be the main ways in which patient safety interventions might be identified.

Economic modelling may also play a part if helping to identify areas in which evaluation should be concentrated. In particular, simulation models can draw together the existing evidence from a wide variety of different sources, and use this to identify the main areas of uncertainty and the interventions amongst a range of alternatives that are most likely or least likely to be cost-effective. This may allow the least likely options to be eliminated and future research, such as a randomised trial, to focus on two or three most promising candidates.

**Incentives to reduce adverse events**

Most health care interventions are not cost-saving: using the cost-effectiveness plane framework set out in Figure 3, new interventions are typically located in the north east quadrant, where they are more effective than current practice but at higher cost. That is precisely why the cost-effectiveness approach is advocated: if new interventions were cost-saving as well as more effective there would be no decision making problem. In most areas of health technology assessment, therefore, the case for a new technology normally does not depend on whether it is likely to be cost-saving, but on whether any additional effectiveness is worth the additional cost. In patient safety interventions as in any other area of health care, having a cost-saving criteria would set a very high hurdle that most interventions could not hope to clear.

Advocacy for new interventions typically comes from clinicians, manufacturers, and patient groups often represented by disease-aligned charities. In addition, many other bodies produce recommendations, guidelines and policy statement on what constitutes best practice in different therapeutic areas, some of which will sometimes be underpinned by cost-effectiveness evidence – for example, most national screening recommendations. Finally, since 1999 NICE has explicitly incorporated cost-effectiveness evidence in its guidance statement, which now have statutory authority.

The adoption of most technologies in health care, therefore, increasingly depends on producing convincing evidence on effectiveness and cost-effectiveness, and may also require evidence on budget impact, meaning the total cost of adoption
and how that total cost may be distributed between different parts of the NHS. (NICE 2001) As noted above, these costs and benefits may be quite unevenly distributed: for example, adopting policies that give better blood pressure control and blood glucose control to patients with type 2 diabetes has been shown to be cost-effective to the NHS as a whole, but budget impact analysis has shown that general practices will incur most of the costs of more intensive drug therapies, while hospitals may experience some benefits in terms of having to treat fewer diabetes-related complications. (Gray et al. 2002) This may create some incentive problems general practices, but the rationale for the intervention must be, not that a conventional business case using profit-loss criteria can be made for investing in the intervention, but that patient care can be improved cost-effectively. Indeed, from this perspective, providing intensive risk factor control to patients with type 2 diabetes can be placed on a spectrum of patient safety activities, as not providing such care is not good practice and may give rise to preventable adverse events that could be interpreted as negligent.

The same broad approach should be used in assessing other interventions that may improve patient safety. Of course some patient safety initiatives may not be specialty-specific and may therefore lack organised clinical or patient advocacy; however, the same arguments concerning effectiveness and cost-effectiveness still apply.

In addition, as discussed earlier, it can be argued that adverse events that are deemed negligent are in effect instances of error which should have been cost-effectively preventable but were not prevented. Pursuing this, if hospitals are to have incentives to invest in patient safety, there needs to be some cost associated with their adverse event and negligent adverse event performance. One mechanism would be some element of experience-rating in premiums to the NHS Litigation Authority. Another would be to link premiums to the implementation of specified cost-effective patient safety interventions, rather than more general process measures.

Finally, there is substantial scope to make use of existing mechanisms such as the Health Technology Assessment programme to identify, commission, fund and monitor patient safety research, and NICE to evaluate the effectiveness and cost-effectiveness of interventions and set out guidelines on their adoption by the NHS.
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