PART 1
The Theory of Monitoring

CHAPTER 1

An introduction to monitoring therapeutic interventions in clinical practice

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'Know which abnormality you are going to follow during treatment. Pick something you can measure.'
—CLIFTON MEADOR, *A Little Book of Doctors' Rules*

1.1. Introduction

Monitoring is repeated testing aimed at guiding and adjusting the management of a chronic or recurrent condition [1]. As the opening quote suggests, monitoring is a central activity in the management of patients and a major part of the ritual of routine visits for most chronic diseases. Measuring the patient's current state and responses to treatment is central to managing hypertension, diabetes mellitus, thyroid disease, asthma, depression, chronic pain and a host of other long-term conditions. Although managing acute diseases may begin with diagnostic testing, the focus should soon shift to monitoring. For example, much of the activity of intensive therapy or high-dependency units is monitoring, such as the repeated measurement of blood gases and electrolytes in a patient with trauma, or the tracking of glucose and other variables in diabetic ketoacidosis. The principles of monitoring are similar in both cases.

Although neglected as an area of research, monitoring is a substantial part of the clinical workload. Chronic conditions account for 80% of consultations by general practitioners (GPs, primary-care physicians), and such visits usually involve interpreting a set of monitoring tests and perhaps ordering some more. In the UK, the use of monitoring has accelerated as many of the quality indicators for GPs have involved monitoring, for example the targets and

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intervals of blood pressure, Hb_{A1c} (Chapter 16), cholesterol (Chapter 18), TSH (Chapter 19), FEV_1 and drugs such as lithium, aminoglycosides and digoxin [2]. The costs of such monitoring are substantial and not all of them are clearly worthwhile. Despite weak evidence for the effectiveness of self-monitoring in type 2 diabetes [3], the costs of blood glucose monitoring strips alone in 2002 in the UK was £118m—larger than the expenditure on oral hypoglycaemic agents [4]. However, despite financial and emotional investment in monitoring, many patients are poorly controlled. For example, in a UK study before the new GP contract was introduced in 2006, only 14% of 21,024 patients with newly diagnosed hypertension had met the target blood pressure after 12 months [5], and among treated patients about 40% of INR measurements are outside target ranges, compared with the ideal of 5% [6].

Intuitively, monitoring should obviously be beneficial. Nevertheless, clinicians forgo monitoring in many areas; for example, aspirin is used for preventing stroke without assessing aspirin responsiveness by measuring platelet aggregation. Deciding whether and how to monitor is clearly of central interest to both good clinical care and to the wise use of resources. In this book, we outline the principles needed to guide better monitoring and then illustrate those principles with examples. In doing so, we have built on what is known, but have also found many unexplored areas in which we have attempted to outline the problems and suggest directions for both clinical practice and research. In this chapter, I shall review the problems involved in monitoring and provide a guide to how these are dealt with in the other chapters in this book.

1.2. Is monitoring always helpful?

To be useful, a monitoring test must pass criteria similar to those for a good screening test:
- it should be accurate and simple;
- it should guide a strategy for achieving a target;
- achieving the target should improve patient outcomes.

The question of whether monitoring is helpful can be rephrased: Is a specific monitoring regimen better than no testing? Actually, there is never 'no testing', as a patient's symptoms and signs provide a default monitoring strategy. For some interventions this may be adequate; for example, phenytoin and digoxin toxicity both cause symptoms that may be sufficient for monitoring, and additional testing is required only for clarification. For other conditions, such as diabetes or thyroid disease, there may be a long silent phase, and hence some specific monitoring is desirable.

Figure 1.1 illustrates some of the possibilities. The arrows at the bottom indicate three monitoring tests that are done at regular intervals. The test at (i) does not detect the abnormal state in any of the four scenarios, but the tests at (ii) and (iii) do, at least in some of them.

In scenario (a) a test may detect the abnormal state before the event, and it may never have been detected by symptoms; for example, an abnormal
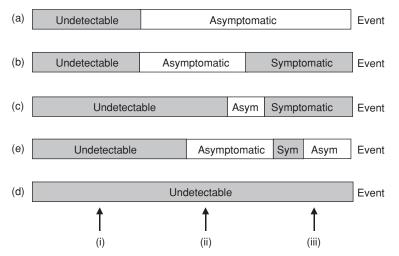
Figure 1.1 Four different scenarios that affect the frequency and timing of monitoring (see text for discussion).

prothrombin time (INR) in someone taking warfarin may be asymptomatic until a major bleed (the event).

In scenario (b) a test may detect an abnormal state, but symptoms would also detect it, albeit a little later. Hence, the question is whether early detection is clinically advantageous; for example, monitoring peak expiratory flow rate may detect a pending exacerbation of asthma a little early, but not early enough to make a difference to alterations in therapy.

In scenario (c) the asymptomatic period is too short to be feasibly detectable; for example, patients taking stable carbimazole treatment can suddenly develop neutropenia and soon afterwards develop symptoms such as a sore throat, but this happens too rapidly to be feasibly detectable by routine haematological monitoring.

In scenario (d) the asymptomatic period is too short to be detectable and does not occur at times of routine monitoring; for example, with stable lithium treatment, changes that alter lithium excretion (e.g. a fever or diarrhoea) can lead too rapidly to toxicity to be detectable by routine screening of serum lithium concentrations; routine monitoring misses the critical periods, which can only be detected by monitoring at times when the risk of toxicity is identifiably increased.

In scenario (e) the abnormal state is never detectable—that is, the current measurements do not provide a warning before the event; for example, we currently have no feasible means of detecting a period before the occurrence of ventricular fibrillation (implantable defibrillators detect this when it occurs and respond by defibrillation).

Proving that there is clear benefit, particularly in the prevention of long-term outcomes, often requires a randomized trial. Unfortunately, there are few

of these. However, in the few good monitoring studies that have been done there have been surprises. For example, Swan–Ganz catheters for monitoring pulmonary artery pressure have been standard in intensive-care monitoring for decades, but a pooled analysis of over 5000 patients in randomized trials showed no impact on either mortality or length of stay [7]. On the other hand, B-type natriuretic peptide (BNP), which has become important in the diagnosis of heart failure, may also be useful for monitoring. Two randomized trials have shown reductions in hospitalizations from heart failure with BNP monitoring [8, 9]. And a meta-analysis of comparisons of self-monitoring of INR with usual care showed not only that it was safe, but also that it led to a greater reduction in all-cause mortality [10]. Table 1.1 lists some examples of monitoring strategies that have been subjected to randomized trials. One lesson from these trials is that it is not easy to predict whether monitoring will provide benefit.

Monitoring can optimize the benefits of therapy, by tracking a surrogate marker for benefit (e.g. adequate blood pressure control). It can also detect adverse effects (e.g. the toxic effects of methotrexate); the principles are similar to those outlined above, but there are some important differences, as discussed in Chapter 15.

1.3. The five phases of monitoring

To help with thinking about the elements of monitoring, it is helpful to break monitoring down into five phases as shown in Table 1.2. The central phase of monitoring is maintenance in stable control (phase 3), but this must be preceded by the establishment of a baseline—and the diagnosis—followed by a titration phase. Chapters 6–9 focus on elements of these phases. Titration requires assessment of the initial response to treatment, but detecting that response within the 'noise' of our usual unreliable measurements can prove a challenge. Sometimes checking for an adequate response is crucial and sometimes it is completely unnecessary, depending on the predictability of the response and our ability to detect important individual deviations from the average. The maintenance phase involves setting up a schedule of regular measurements (Chapter 8), and there are guidelines for deciding when a measurement or sequence of measurements suggests that a patient has drifted too far from the target range (Chapter 7). Some methods borrowed from industrial process control are worthy of further development here. Finally, when we have detected a deviation, we need to consider the options for adjusting treatment (Chapter 9).

1.4. Development and evaluation of monitoring

The final decision to monitor must take into account the balance of the benefits against the harms, such as inconvenience and cost, and the impact of false-positive results and false-negative results, which can lead to inappropriate or

Table 1.1 Examples of monitoring strategies subjected to randomized trials

Clinical area	Evidence	Results
Monitoring appears to be helpful		
Anticoagulation: INR self-monitoring for patients taking warfarin	Systematic review of eight randomized trials [9]	Self-monitoring reduces all-cause mortality compared with usual clinical care
Intensive follow-up of colorectal cancer after curative surgery	Systematic review of five randomized trials [11]	A one-third reduction in mortality
BNP and monitoring of heart failure	Two randomized trials [7, 8]	BNP monitoring reduces hospitalizations in severe heart failure
Temperature monitoring for diabetic foot ulcers	Randomized trial of 173 patients [12]	Temperature monitoring led to an 80% reduction in ulcers
Nitric oxide monitoring for asthma	Systematic review of three randomized trials [13, 14]	Nitric oxide monitoring improves control, with less use of medications
Monitoring not helpful or equivocal		
Pulmonary artery pressure in intensive care	Systematic review of randomized trials [7]	No impact of monitoring on length of stay or mortality
Peak expiratory flow rate (PEFR) monitoring in asthma	Systematic review of six randomized trials, and one later trial [15, 16]	Self-management based on PEFR was equivalent to self-management using symptoms
Urine or blood sugar monitoring for non-insulin dependent (type 2) diabetes	Systematic review of randomized trials [2]	Neither blood or urine self-monitoring affected Hb_{A1c}
Foetal heart rate monitoring during labour	Systematic review of randomized trials [17]	Equivocal results, with a reduction in seizures, but no difference in foetal mortality, and an increase in caesarean and forceps deliveries

delayed actions. Hence, establishing patient's benefit is important, but evaluation must be preceded by the development of a good monitoring strategy.

A monitoring test may be simple, but a monitoring strategy is a complex intervention, involving multiple components and adaptive decision-making on the part of the clinician and patient. The UK's Medical Research Council has proposed a framework for the development and evaluation of such complex interventions [18]. Chapter 2 considers the processes and elements needed

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Table 1.2 The objectives of the five phases of monitoring*

Phase	Monitoring objectives	Optimal monitoring interval
1. Pre-treatment	• Check need for treatment • Establish a baseline for determining the response and change	Short; based on the within-person variability and analytical variation
2. Initial titration	• Assess the individual response to treatment • Detect immediate adverse drug reactions • Achieve control	Medium; based on both pharmacokinetics (for example, drug half-life) and the pharmacodynamics (physiological impact time)
3. Maintenance	• Detect drift from control limits • Detect long-term harms	Long; based on rate of random and systematic 'drift'
4. Re-establish control	• Bring value back within control limits	Medium; as for phase 2
5. Cessation	• Check safety of cessation	Medium; as for phase 2

Note: *Modified from [1].

to develop an optimal testing regimen and to evaluate it. These elements are expanded in subsequent chapters.

1.5. A few general principles

In this chapter I shall not attempt to give a complete overview of monitoring, but it is useful to draw together some of the pitfalls and lessons that emerge from the discussion in the succeeding chapters. These will necessarily be briefly mentioned here—the detailed background to these lessons will be covered in the chapters themselves.

1.5.1. Avoid the 'ping-pong' effect

Chasing random fluctuations can be dangerous. A common error when adjusting treatment is over-adjustment—changes in treatment that are too large can increase the variation in the monitored variable. A sequence of false alarms and inappropriate changes leads to increasing fluctuation and instability. This type of 'ping-pong' effect with subsequent overshoot (see Figure 9.1) has been observed in clinicians' adjustment of INR [1]. A typical sequence might be as follows:
- the INR is above the target range, but is in fact not significantly so;
- the clinician misunderstands this and reduces the dose of warfarin;
- the adjustment is too large;
- the INR falls below the target range;
- the clinician re-adjusts the dose, etc.

It is generally best to be cautious in making changes and when making changes to make small ones. Chapter 7 discusses some methods of more accurately sorting out real from spurious changes, and Chapter 9 gives details on the options for appropriate adjustment.

1.5.2. Do not remeasure until there is a chance of a real change

This follows from the principle of the ping-pong effect. If a patient is in a relatively stable condition, measuring too frequently can be misleading. There will have been little chance for the condition to change, but the random fluctuations in many clinical measurements may mislead us into changing therapy. Chapter 8 discusses the problems of developing an appropriate monitoring schedule and Chapter 18 looks at the specific example of cholesterol concentration monitoring. In the latter, it is suggested that we currently monitor cholesterol far too often, and would be better to shift to monitoring only every 3–5 years. This seems counter to clinical experience, since changes in cholesterol concentration occur in a short time, but most of this apparent change is due to short-term biological variation and analytical variation. The true underlying cholesterol changes only very slowly, unless there is a dramatic change in diet or drug therapy. However, other conditions fluctuate more, and earlier detection in the asymptomatic phase can be useful; for example, exhaled nitric oxide appears to be a good marker of airways inflammation in asthma and can signal a need for increased treatment [19, 20].

1.5.3. Sometimes we can 'hit and run'

Usually, we need to check whether the patient has had a sufficient response to treatment. However, if there is little or no individual variation in response, we can assume the average response instead. In fact, when there is no individual variation and the measure has considerable variation, trying to monitoring for a response can be misleading. In this case we can use a 'hit and run' strategy, i.e. measure once and not again. Of course, the patient's symptoms are a form of monitoring, and the hit and run strategy may rely on them for the trigger to change treatment. Chapter 6 discusses how we can decide when to hit and run, when we need to check repeatedly, and how to interpret the resulting checks.

1.5.4. There are several ways of adjusting therapy

If a patient's condition is not sufficiently well controlled, there are three basic strategies for improving the outcome:
1 *Intensify* treatment; for example, increase the dose or increase the frequency of administration.
2 *Switch* treatments; for example, to another similar agent or a different class of therapy.
3 *Add* a different therapy; for example, a low dose of an additional drug or another form of adjuvant therapy.

Different disease areas seem to concentrate on different options. For example, treatment of hypertension has been dominated by stepped care (option 1), but others have suggested using a switching option (option 2), and still others have suggested a 'Polypill' approach (option 3, with low doses of multiple agents) [19]. It is helpful to be aware of these generic options to avoid being trapped by a local paradigm.

In the case of over-treatment, with adverse effects, the opposite strategies apply:

1 *Reduce* treatment. For example, reduce the dose or decrease the frequency of administration; temporary withdrawal of treatment may be necessary before restarting at a lower total dose.

2 *Switch* treatments.

3 *Withdraw* the treatment altogether.

1.5.5. Understand the relation between dose and effect

When titrating and adjusting treatment, it is helpful to understand how the effect varies with the dosage. For drugs, this is an understanding of the pharmacological (pharmacokinetic and pharmacodynamic) properties of a drug, which are more fully discussed in Chapter 3.

1.5.5.1. Pharmacokinetics: the processing of the drug by the body

Detailed discussion of pharmacokinetics [20] is beyond the scope of this book. However, there are a few simple principles that are relevant. After the start of therapy with a regular dose of a drug, it takes about four half-lives for a steady state to be reached. The same is true after a change in dose (both an increase and a reduction); a new steady state takes about four half-lives to achieve. Knowing the half-life of a drug therefore helps to predict how long it will take before a change can be expected and whether to use a loading dose to produce the change more quickly. Knowing whether the drug is eliminated by the kidneys or the liver helps to predict the effects of renal or hepatic disease. Knowing the mechanisms of hepatic elimination helps in understanding drug interactions that involve inhibition of drug metabolism.

1.5.5.2. Pharmacodynamics: the dose–response curves for benefit and harms

The pharmacodynamic effect of a drug is summed up in its dose–response curve (or concentration–effect curve), which is the central dogma of pharmacology, as important, for example, as the central limit theorem is to statistics. If you choose to titrate the dose of a drug, an understanding of the dose–response curves of its benefits and harms is vital to predicting the impact of different doses, which will depend in part on the slopes and maximal efficacies of each curve. Chapters 3, 4 and 9 explore these concepts, but a few simple ideas are worth remembering:

- Once the peak response is reached, further dose increases only cause harm.
- There is a law of diminishing returns—increasing the dose does not produce a proportional increase in benefit unless the dose is within the short segment of the dose–response curve that is approximately linear. This is because the sigmoid curve of the beneficial response is log-linearly related to dosage only for the short central segment portion.
- The dose–response curves for benefits and harms are usually different. We can take advantage of this. If a drug has toxic effects (see Chapter 15, Figure 15.4) we can generally gain benefit at low doses, while harms tend to occur at high doses, and we can select medicines with this in mind. On the other hand, if a drug has adverse effects that are due to hypersusceptibility or collateral effects, avoiding adverse reactions may be impossible (in the former case, Figure 15.2) or at least difficult (in the latter, Figure 15.3).

1.5.6. Involve the patient in monitoring

Patients are often more capable than some health-care providers think. And they are often more motivated to manage their condition. The first pregnant woman with diabetes to monitor her blood glucose at home needed to be considerably persuaded, but her success led to a change in our paradigm of monitoring. However, we should remember that patients vary considerably in their ability to self-monitor effectively for chronic conditions. Some patients are very capable at both self-testing and self-management, whereas others are poor at self-monitoring, and still others may not agree or may be incapable.

Chapter 17 looks at the specific example of INR self-monitoring for patients taking warfarin. The systematic review of trials discussed there shows that self-monitoring was more effective than conventional clinical monitoring and equally safe. However, it appeared to be most effective when patients both self-tested and self-adjusted treatment rather than merely self-testing. Clearly, self-adjustment of therapy requires more skill and training, but it is more motivating.

1.5.7. Monitoring can adjust the mind as well as the treatment

While a key aim of monitoring is to detect clinically important changes and adjust treatment in response, it is also a learning and motivational tool. Indeed, simply monitoring weight by keeping a diary, hand written or electronic, can lead patients to lose weight without any specific intervention [21]. Hence, we need to be aware that monitoring has influences beyond the clinician's adjustment of treatment. Patients can learn what causes their condition to become worse, such as dietary changes or exercise in diabetes and other conditions, or can become more motivated by seeing progress, which in turn may improve adherence. Chapters 10 and 11 explore these issues further.

1.5.8. Do not read single measurements in isolation

Because of random fluctuation in monitoring measurements, it is helpful to think of a moving average of measurements. Some statistical rules have been
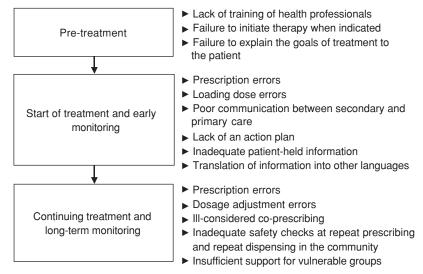
Figure 1.2 Some problems that can arise during monitoring at different stages.

developed to help interpret multiple tests. For example, one rule suggests that we can conclude that there is a real change if there is

1 a single measure 3 or more standard deviations from target, or

2 two of the last three measurements were at least 2 standard deviations from the target, or

3 four of the last five measurements were at least 1 standard deviation from the mean.

These are known as the WECO (Western Electric Company) rules. They are useful, but may not be sufficiently sensitive in some medical settings. However, the concept of using the combine deviation of several measurements is useful in clinical monitoring. Chapter 7, on control charts, discusses the various approaches to interpreting a sequence of test results.

1.6. Problems in monitoring

Some problems that can arise during monitoring at different phases are shown in Figure 1.2. The problems can be system failures, such as prescription errors or availability of translations of materials, or errors from the clinician, patient or laboratory, or the communication between these. These are discussed in Chapters 6–15.

1.7. Conclusions

Monitoring is a large and rapidly rising area of laboratory testing. However, unlike diagnostic testing there has been little interest in and development of

methods for assessing the value of monitoring tests. These methods need further development. Nevertheless, there are some simple principles, such as the eight outlined above, that can be applied to the development and evaluation of optimal monitoring strategies.

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