EVALUATION OF POINT OF CARE TESTING VERSUS CENTRAL LABORATORY TESTING IN THE CRITICAL CARE ENVIRONMENT OF A DISTRICT GENERAL HOSPITAL

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CONTENTS

LIST OF ABBREVIATIONS

A&E	Accident and Emergency
ACS	Acute Coronary Syndromes
AMI	Acute Myocardial Infacrtion
APACHE	Acute Physiological and Chronic Health Evaluation
CCU	Coronary Care Unit
CK	Creatine Kinase
CLT	Central Laboratory Testing
ECG	Electrocardiogram
IHD	Ischaemic Heart Disease
ITT	Intention To Treat
ITU	Intensive Therapy Unit
K	Potassium
LOS	Length of Stay
MWU	Mann Whitney U
Na	Sodium
NICP	Non-ischaemic Chest Pain
POCT	Point of Care Testing
PTS	Pneumatic Tube System
ROC	Receiver Operator Characteristic
TAT	Turnaround Time
TISS	Therapeutic Intervention Scoring System
TnI	Troponin I
TnT	Troponin T
UA	Unstable Angina

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ABSTRACT

The use of point of care testing (POCT) is becoming more widespread. However, it is often implemented without a comprehensive assessment of its reliability in routine clinical use or of the need for such technology in its intended setting. This study followed a step-by-step evaluation of POCT through the evaluation of the technology provided, assessment of the clinical impact and financial considerations for its use. Two prospective randomised controlled trials formed the basis of the study assessing existing analysers and novel technology. These were set in two critical care wards, the Coronary Care Unit (CCU) and the Intensive Therapy Unit (ITU), to assess the requirements of POCT in different settings. All patients admitted to the wards during the trial periods were randomised to POCT or central laboratory testing (CLT). The POCT analysers were found to have varying degrees of accuracy compared to the CLT, but were considered suitable for clinical use. Turnaround time was significantly faster for POCT than CLT, although TAT for an individual result is not necessarily the rate limiting step. No significant differences were found between the two groups for clinical impact, except in CCU where those patients identified for early discharge were found to have a reduced LOS (Mann Whitney U test: $p = 0.0256$). Cost analysis showed test costs were significantly higher for test costs for POCT than CLT, however, total hospital costs were reduced in the early discharge group. Differences were observed between the two wards indicating that POCT is not suitable for all sites. In CCU the availability of POCT had a significant impact on the management of the patients, whereas in ITU, no advantage over CLT was observed. It is essential for a full evaluation of POCT to be undertaken prior to implementation to assess the need and suitability of the technology for use in the setting for which it is intended and not just for one or two aspects to steer the decision.

CHAPTER 1 INTRODUCTION

1.1 WHY THIS RESEARCH?

Patients admitted to critical care units are dependent on the ongoing assessment of their physiological status to make, or confirm, a diagnosis or to provide a guide for therapy and management. Such assessment invariably involves biochemical analysis, which is conventionally carried out in a central laboratory. However, there has been an increasing move towards point of care testing, driven by the introduction of new technology and method development. Innovations in microchemistry, accompanied by the miniaturisation of equipment and microcomputers, have facilitated the analysis of tests near the patient, in wards, satellite laboratories, doctors' offices and in the patient's home. Advances in technology have provided many analysers for use at the point of care. These analysers have been engineered to produce rapid results that are accurate, reliable and comparable with the central laboratory analysers. They are compact instruments designed for operation by non-laboratory professionals with the minimum of training.

Many hospitals have had the facility to carry out certain analyses at the point of care for some years, primarily, glucose and arterial blood gases. However, as the use of point of care technology becomes more widespread, and the analytes available more varied, it is necessary to evaluate this technology thoroughly. Evaluation should include the need for such analysers at the point of care, in other words will their provision benefit patient management? In the critical care setting it is important to

provide reliable results in a timely fashion that reflect the current status of the patient. It is widely presumed that point of care testing will provide an improvement in turnaround time compared to the central laboratory, which will lead to appropriate interventions being carried out sooner therefore improving the outcome for the patient.

This study aims to carry out a critical assessment of the utilisation of point of care analysis, which will be systematic in its treatment of all aspects of the study. The factors relevant to the provision of point of care testing are inter-connected and no one aspect has more bearing than another. The potential benefits need to be weighed against the practicalities of providing the technology with respect to accuracy in clinical use, appropriate utilisation and financial considerations. It is important to ascertain whether the results from the point of care instruments are reliable in clinical use. This reliability must be assessed in the setting for which the instruments are intended, with the non-laboratory personnel, who will ultimately be using the technology, carrying out the analyses. The assessment of turnaround time for results should focus on the impact on patient management and outcome, and not in itself be the rationale behind point of care provision. The benefit to patient care should be the ultimate goal for this technology, although inevitably cost of its provision will be a factor when implementation is considered. The study is run in parallel at two critical care sites, intensive therapy unit and coronary care unit, allowing the assessment of clinical need and role of point of care in different settings.

Review of the current literature shows that a comprehensive evaluation of point of care technology has not been conducted and that this is the first study to undertake a

prospective randomised trial into the benefits of point of care testing in comparison to the central laboratory. Knowledge gained from such a study would be of considerable value when contemplating the provision of point of care analysis. It is this need for such an evaluation that has provided the motivation for the research described in this thesis.

1.2 AIMS AND OBJECTIVES

Hypothesis:

The hypothesis being tested is that point of care testing has a beneficial effect on patient management and prognosis, over and above that provided by the central laboratory, and is capable of being adopted for real time application in appropriate clinical settings.

Aims:

The overall aim of the research was to make a critical assessment of the operational and clinical impact of point of care testing in comparison with the central laboratory. In doing so, an evaluation of the technology available was to be undertaken with respect to the clinical accuracy and turnaround time of results. It was also intended to ascertain what impact the provision of point of care testing has on patient management and outcome, and whether the benefit outweighed any additional cost.

Objectives:

Given this overall aim, the research was concerned with addressing the following specific objectives –

1. *Accuracy of point of care technology being used.* Are the point of care analysers as accurate and reliable as the central laboratory analysers, both analytically and clinically, and therefore suitable for routine clinical use?

2. *Faster turnaround time.* Does point of care analysis provide a faster turnaround time for results?

3. *Impact on patient management.* Does point of care provision alter the patient management and outcome?

4. *Use of point of care analysers.* Do the healthcare personnel use the point of care analysers provided?

5. *Cost.* Is there a cost saving which would benefit the patient, or is any additional cost justifiable?

1.3 SUMMARY OF THESIS

The background to the study is described in chapter 2. Firstly the study environment is outlined to ensure the concepts of the central laboratory, point of care and the critical care are understood. The factors, which influence the decision to implement point of care testing, that have a relevance to the study objectives, are presented. Although set out under particular headings, the factors are inter-connected. This will provide the basis for the evaluation of point of care provision compared to the service provided by the central laboratory.

The literature review provides a critical assessment of the numerous studies that have been carried out into the various aspects of point of care. Many of the studies focus on one particular aspect such as analytical accuracy, turnaround time or cost; however, none carry out a systematic evaluation of all aspects. Included in this review is an overview of the current technology and analytes available for point of care use. The review will also assess those studies that are in any way similar to this study.

The study organisation and methods chapters set out how the study proceeded, what data was collected, the statistical analysis carried out on the results and the analytical methods used at both sites. The choice of two sites, while both critical care wards, allows the assessment of different settings and their point of care requirements. The data collected will cover the results provided by the biochemical analysis as well as clinical data. Analytical methods will provide information on the suitability of the point of care technology and length of time taken to provide the biochemical results.

The three results chapters provide the analysis of the data obtained during the trial. Firstly, the suitability of the analysers to provide accurate biochemical results was assessed in comparison to the laboratory results. Once the trial was underway further validation was carried out in order to provide information regarding the accuracy of the analysers in routine clinical use. The clinical data collected was analysed to firstly rule out any bias in the results due to patient population, and then to assess the impact of point of care testing on patient care over the central laboratory. The third results chapter analyses the costs incurred with point of care provision.

In chapter 9 the data obtained during the study is critically discussed. The systematic approach to the assessment of point of care implementation is examined with reference to other studies, and the particular results pertaining to accuracy, turnaround time, outcome and costs are compared to those observed by other users.

The conclusion of the study briefly outlines the findings of the study and reviews whether the objectives have been met and whether the hypothesis has been proved. It also outlines the information the study provides to knowledge and some further study required.

CHAPTER 2 BACKGROUND

The previous chapter contained a brief introduction to the study and set out the hypothesis, and the aims and objectives of the research. This chapter outlines the environment in which the study is set and looks at the factors influencing the implementation of point of care analysis.

2.1 STUDY ENVIRONMENT

2.1.1 Central Laboratory

Traditionally, biochemical tests to aid clinicians in diagnosis and management are carried out in a central laboratory sited within the hospital. Procedures employed in these laboratories were generally manual techniques until the 1960s when the first automated analysers were introduced. Automation has continued to be developed and expanded to the stage where routine analysers run almost like a production line. Individual analysers can be connected via sample conveyor belts, which are capable of processing the work from centrifugation through to storage.

Routine analysis refers to those tests commonly requested by the clinicians, such as those for renal function, liver function, and cardiac or bone disease. Analysers that measure these routine tests are discrete multichannel analysers capable of performing these tests simultaneously on each patient sample. An example is the Bayer Technicon Dax™ analyser that takes 17 minutes to analyse up to 18 analytes per sample at a rate of approximately 150 samples per hour. As the majority of

biochemical tests are not carried out on whole blood, the samples are first centrifuged to separate cells from serum. The introduction of serum separating tubes, where a gel keeps the cells separate from the serum after centrifugation, allows for analysis to be carried out on the primary tube. After analysis the laboratories usually have facilities to store the samples for up to a few days allowing the same sample to be used for further tests on other analysers, or for additional tests to be requested as necessary.

The analysers are often interfaced with the laboratory computer system allowing electronic transfer of data. Many hospitals also have ward terminals, which are linked to the laboratory system and have, at the least, access to results once available, and the potential to directly request tests at source.

Analysis in the central laboratory is carried out by trained laboratory professionals who maintain the equipment on a regular basis and maintain the accuracy of results by analysing quality control material with known values to ensure validity. They are fully aware of any errors that might occur due to the characteristics of the analyser or artefacts within the specimen.

2.1.2 Point of Care

Point of care testing (POCT) refers to any test performed outside the central laboratory, usually close to the patient. Other terminology used to describe such testing includes, 'bedside', 'near patient', alternative site', and 'decentralised'. This can be delivered in a number of ways on the wards or by technicians in satellite or

mobile laboratories, and common sites are critical care wards, emergency departments, operating rooms, clinics and the home setting.

Testing at the point of care was used, possibly for the first time in 19th Century London. Physicians would make a diagnosis of diabetes mellitus by dipping a finger in a urine sample to taste the sweetness caused by glycosuria. Technology has evolved and early instruments were produced that were smaller versions of the laboratory analysers requiring trained staff to operate. Further developments have resulted in portable, desktop or even hand held instruments for use within the wards that are self maintained and can be operated by non-laboratory professionals. Whole blood specimens are used and analysis is either carried out on the blood directly or a separation step is built into the assay. This reduces the time for the analysis and the amount of blood required.

The presence of analysers on the ward means it is possible for the clinicians to order a test, collect a specimen and analyse it immediately, producing a result in some cases in under a minute. However, not all assays can be carried out that quickly; qualitative Troponin assays take 20 minutes to run (Antmann et al, 1995; Heeschen et al, 1998), and many instruments only measure one analyte at a time; for example the Reflotron™ (Price & Koller, 1988). Those that are capable of testing more than one analyte simultaneously do not cover the whole routine profile and therefore additional blood is usually required for analysis in the laboratory as well. For example, the Abaxys Piccolo used during this study measures urea, creatinine and glucose but not sodium and potassium.

2.1.3 Critical Care

Critical care medicine requires rapid treatment decisions and clinical management. It encompasses those high dependency wards such as the Coronary Care Unit (CCU) and the Intensive Therapy Unit (ITU), in which this study is set.

The CCU consists of a patient population with ischaemic heart disease (IHD) who have been admitted with suspected acute coronary syndromes (ACS). Initial diagnosis and, therefore, the decision to admit to CCU, depends on clinical history and on electrocardiogram (ECG). However, the ECG has varying degrees of sensitivity and specificity. Where the ECG is equivocal, biochemical markers provide a diagnostic aid. Three groups of patients can be identified in CCU, those with acute myocardial infarction (AMI), other ACS and those with non-ischaemic chest pain (NICP), each of which requires different strategies for management. As prognosis is improved with rapid treatment it is important for biochemical results to be produced within a useful time frame.

The ITU consists of a heterogeneous population of patients requiring either intensive hospital care or post-operative recovery. The major concern for the ITU clinicians is the maintenance of the patients' tissue oxygenation, ventilation and normal acid-base status. Many disease entities and drug therapies undertaken in this unit may interfere with these processes, and life-threatening alterations may occur rapidly for a variety of reasons. Early detection of these changes is believed to improve patient care and therefore it is essential for a rapid method of monitoring.

2.2 ASPECTS OF POINT OF CARE TESTING

2.2.1 Accuracy

The first question to be addressed is, are the instruments analytically and clinically accurate? This really refers to results from POCT being comparable with those produced by the central laboratory. It is easy to establish analytical accuracy and precision as numerous method comparison studies can be carried out by the laboratory. However, the technology may be demonstrated as comparable under controlled conditions with trained technicians, but this may not reflect true clinical accuracy.

In the routine clinical situation, non-laboratory trained personnel will use POCT analysers. Although having undergone full training in the operation of the POCT analyser in use, the nurses and other healthcare workers do not have the background knowledge and expertise gained through laboratory experience. They are less skilled in analytical techniques and therefore operating procedures need to be simple. All operators are prone to random errors, the frequency of which increases when multiple operators, all with differing abilities, use the analysers. Correct interpretation of a result is, therefore, important in determining the validity of a result. For example, a raised glucose may be due to hyperglycaemia, but the same result can be produced by incorrect collection of the blood, such as from an arm where an intravenous infusion of glucose containing fluids is in progress, or due to an error occurring during the analysis. Sufficient training in the correct operation of

the analysers is essential to minimise these errors (Marks, 1988; Biomedical Scientist, 1999).

Many studies show variability in the quality of results produced by POCT. An example is the use of glucose meters (Chu & Edney-Parker, 1989). Even though studies have shown that precision is poor when analysis is carried out by POCT such analysers are still in widespread use. To ensure the reliability of these analysers, suitable quality control procedures should be considered and maintenance will be required to continue the effective running. The responsibility for this generally falls on the central laboratory, but if POCT becomes more widespread this may be very time consuming. Ward staff require sufficient training to maintain the instruments and troubleshoot any problems as they arise. Guidelines have been set up for the implementation of point of care testing which include consultation with the laboratory to ensure reliability of the results (Freedman et al 1993). However, where technology is used without the knowledge of the laboratory, such as in primary care, in the high street or at home, then the reliability of the results may be questionable.

2.2.2 Turnaround Time

Does analysis at the point of care result in a faster turnaround time? Firstly, turnaround time (TAT) needs to be defined, and a definition agreed upon by all users. Laboratories refer to the TAT for a result as the time taken from receipt of a sample to the reporting of the result; this corresponds to the stage of the process over which the laboratory has direct control. Clinicians, however, refer to the time from result order to availability. In practice, clinicians view result availability as the time

they access the result, though it may have been available earlier. Therapeutic TAT from result order to intervention, which encompasses the time for decisions on patient management to be taken on the basis of the result, would be the ideal measure, although difficult to quantify. It is important for all users of laboratory tests to agree on a definition in order for the speed and effect to be fully evaluated.

Table 2.1 Factors affecting TAT

PRE-ANALYTICAL	ORDER OF TEST TO BLOOD COLLECTION	When was order made- 1. In advance for morning ward round 2. Stat request - during routine day - out of hours
	COLLECTION TO TRANSPORT	1. Wait for porter 2. Take samples to pneumatic transport system 3. Samples stay with phlebotomist until - all patients on ward bled - all round completed
	DELIVERY TO LABORATORY	Depends on – 1. Distance from laboratory 2. Porter or pneumatic tube system 3. Workload of pneumatic tube system
ANALYTICAL	RECEIPT TO ASSAY	1. Input request on laboratory computer system 2. Centrifugation 3. Primary tube or separation of samples
	ANALYSIS	1.Length of assay 2.Batch with other urgent requests – depends on time of day
	REPORTING OF RESULT	Validation of results from analyser
POST ANALYSIS	REVIEW OF RESULTS	Review of results once available - phoned - viewed on ward terminal by nurse/doctor - viewed from notes
	REVIEW TO ACTION	Time taken to act on the results - inform doctor of results - wait for consultant ward round - follow care protocol - depends on time of day

Pre-analytical factors encompass: the time from request order to collection, time from collection to transport, time to deliver samples to point of analysis. The time delay from order to specimen collection depends on the time of day and who will be drawing the blood. Phlebotomists will often do a morning ward round to bleed all those patients requiring blood analysis, for which the clinicians will have the orders ready, sometimes from the previous day; whereas tests ordered out of hours may have the required samples collected as soon as the request is made by the nurse or even the clinician. Often, nurses will wait for all the patients on the ward to be bled before sending the samples to the laboratory, resulting in a delay. Delivery to the laboratory by pneumatic tube system (PTS) takes only seconds, but delays in taking samples to the PTS port will also affect TAT. The use of PTS assumes that samples are not affected by the system, which from the literature seems to be the case, at least for analytes dealt with in this study (Weaver et al, 1978; Pragay et al, 1980). Obviously further delays will occur should the PTS not be working and porters have to be relied upon to deliver the samples to the laboratory, and in the workload of the PTS. In POCT, transport of the specimen is at a minimum as the analyser is situated on the ward, and so in theory, at least, samples can be analysed as soon as they are collected.

Analytical TAT refers to the time taken to process the sample once it has been received at the point of analysis. In POCT this will simply be the time taken for the analyser to measure the sample. Urgent requests are usually fast tracked through the laboratory system, but in practice delays will still occur. On receipt requests have to be entered onto the laboratory computer system and then the sample is centrifuged to

separate the cells from the serum. With individual urgent requests this time will be at a minimum, however, samples from the critical care wards will often arrive together resulting in a delay as all requests are dealt with as a batch. Modern laboratory analysers allow for the use of primary tubes (specimen collection tubes placed directly on the analyser), thus avoiding time taken to aliquot the samples prior to analysis. The length of analysis is assumed to be faster on POCT analysers but this is not always the case. As examples, the rapid troponin T assay used in POCT takes 15 minutes to run whereas in the laboratory the troponin T method takes 9 minutes. Also, the biochemical profile on the ward and in the laboratory both take 12 minutes. In addition, analysis of multiple specimens results in the laboratory measuring twenty samples in the time taken for the ward to analyse two, which would correspond to all the critical care unit bloods.

Post-analytical factors include: validation of the results, time taken to review results and inform the clinician, and time before interventions are undertaken. Delays in validation will occur when requests are dealt with in a batch as described previously. Once validated, the results are immediately available for review via the ward terminal. It is difficult to assess the time taken for result review and time to intervention; the computer does not record the time at which the results are accessed. The nurses may record the results in the patients' notes as soon as they are available, but when the clinicians review them is not known, nor the time taken before any interventions are carried out. Similarly, in POCT the time taken from result availability to interventions depends on the clinicians. This is obviously greatly reduced should they remain on the ward while the tests are carried out, but this is often not practicable.

2.2.3 Clinical Decisions

While accurate results are obviously important, so is clinical relevance. Biochemical data needs to reflect the status of the patient when the request was made. It may be more desirable to have a rapid bedside result which notes the trend of the analyte than a more precise result provided later (Geyer, 1995; Watts, 1995). For example, glucose constantly varies within the blood. To aid insulin administration the patient requires to know if the levels are low, normal or raised. British Association of Clinical Biochemists recommend a 10% error for POCT devices, while the clinicians regard 20% as satisfactory (Fuhrman et al, 1995). However, what degree of imprecision would ultimately be acceptable?

The clinical significance of a result also requires the correct interpretation. Results from the laboratory are only made available to the clinicians when the laboratory staff are satisfied that the result reflects the status of the patient and is not due to contamination or some other artefact. Raised potassium may be due to renal failure or other disease state. However, haemolysis or contamination of the sample by anti-coagulant or intravenous infusion into the arm from which the sample was drawn may produce a similar result. Is there an understanding of the analyte being measured? Ionised calcium, available on some blood gas analysers, may give rise to confusion when compared with laboratory results of total calcium.

It is widely believed that POCT provides a faster turnaround time for results, due to the shorter analysis time provided by POCT instruments. While this may be true, does the ability to provide a rapid result have any benefit to the patient? Are the

results acted upon as soon as available? The biochemical analysis may not be the rate-limiting step. Other tests such as X-rays or scans may be required before any decision can be made. Potentially appropriate interventions or transfer of the patient to a step down unit may be carried out sooner if the results are available, but are appropriate interventions carried out on the basis of POCT or do the clinicians still wait for confirmation from the laboratory? Clinicians do not have 100% confidence in the results produced by POCT (Lamb et al, 1995) and, therefore, delays in clinical decision-making may ensue while 'official' results are obtained from the laboratory. If earlier treatment occurs does this have any benefit to the patient? In patients with AMI, early treatment with thrombolytics has a beneficial effect on the prognosis (Fibrinolytic Therapy Trialists, 1994) and if AMI can be ruled out earlier then step down to a general ward bed and possible reduced hospital stay may be the result.

2.2.4 Cost

Cost is always an important consideration when evaluating instrumentation and protocols for biochemical analysis. Purchasing POCT equipment will initially incur an additional cost to either the ward or the laboratory budget. Reagents and consumables, which are directly attributable to the patient analysis, are considerably higher for POCT than for central laboratory testing (CLT) (Cresce et al, 1995). Duplication of analysis where the tests are carried out by both POCT and by CLT will obviously increase the cost. Once purchased the POCT instruments may lay idle most of the day while the laboratory analysers will be running continuously (Watson, 1980). So what benefit would the technology provide? Will the analysis provide vital information that will outweigh the expenditure?

A fast TAT will provide results which reflect the current status, therefore avoiding repeat testing due to delayed results. This is particularly relevant for analytes, which change rapidly in the blood, such as arterial blood gases. Earlier results will provide information for suitable interventions and also prevent unnecessary expensive treatment being carried out. This will not only reduce financial costs but also reduce the distress to the patient of unneeded treatment. Similarly, if patients can be moved out of expensive high dependency units to general wards sooner, costs and stress will be alleviated.

2.2.5 Use

Laboratory tests are used in both the diagnosis and monitoring of clinical conditions. Troponin T aids diagnosis of AMI allowing for appropriate treatment or step down to a low dependency ward. Arterial blood gas measurements are important in critical care to monitor disease states and the interference in acid-base status and ventilation by drug therapy. POCT should be tailored to meet the needs of each individual clinical situation. Most clinicians would not consider haemoglobin or haematocrit warranting POCT, as they do not alter rapidly enough. However, it is considered by some to be of use in cardiac bypass surgery (Reasoner et al, 1996). Generally a faster TAT is required for biochemical analysis in critical care than in low dependency wards. While it is theoretically possible to measure any analyte by POCT some tests are simply not relevant to real time clinical processes. Many analytes do not change rapidly enough, nor result in acute life threatening situations.

If POCT were to be made available, would the technology actually be used and acted upon? A survey in the UK showed most consultants do not use the POCT already available and would rather the central laboratory carried out the analysis providing an adequate TAT was available for urgent requests (Gray et al, 1996). Do the clinicians trust the analysis enough to rely on it? If results are always being checked in the laboratory this leads to unnecessary duplication that does not benefit the patient or the hospital.

Providing analysis by POCT assumes the healthcare professionals are willing to carry out the testing. In most cases this falls to the nurses on the wards. However, patient care duties may make it difficult to find time to perform the tests and do they want to take on a function for which they are not trained? Laboratory personnel undergo long-term training in correct analytical procedures and result interpretation, the intensity of which would be difficult to add to the nurses schedule. Without suitable knowledge the nurses may feel it would be inappropriate to take on a task that will ultimately affect the patient.

This chapter has aimed to outline the environment in which this study will be undertaken and to examine the factors that influence the implementation of POCT. The following chapter takes a critical look at the current literature with a particular focus on studies in which these factors influence the research undertaken.

CHAPTER 3 LITERATURE REVIEW

The previous chapter outlined the background to the study. This chapter will review the current literature concerning biochemical analysis carried out at the point of care. It will review those studies, which compare point of care testing (POCT) with central laboratory testing (CLT) as well as those dealing exclusively with POCT. Initially, the technology available to provide rapid results will be examined, including innovations in point of care technology and facilities for rapid transport of samples to the laboratory. The factors that influence the decision to implement POCT will be reviewed to ascertain those areas of study the researchers view as important and which have been the main focus for studies. Finally, this chapter will review those studies, if any, which are similar to this thesis and have previously evaluated all aspects of POCT in one study.

3.1 AVAILABLE TECHNOLOGY

3.1.1 Analytes and Technology

Performing analyses outside the central laboratory has been receiving increased interest over the last two decades. There have been a number of reviews into the current status and trends for the future of POCT (Kost & Hague, 1995; Gilbert & Vender, 1996; Hicks, 1996; Dirks, 1996). The emphasis of each review is based on the area of expertise of the author, rather than on a general overview. There is also a difference between the European and American views, with American studies

influenced more by fiscal considerations, due to a different approach to costing strategies and funding mechanisms (Statland & Brzys, 1990).

Certain analytes have been measured at the point of care, either by the bedside or in satellite laboratories, for many years. Blood glucose monitoring, urine screening and blood gas analysis are probably the most common. A survey carried out in the Trent and North West Thames Regions in 1996 indicated 43% of acute hospitals in those areas performed glucose by POCT, 26% urine screens and 24% blood gases (Gray et al, 1996). It is now possible to analyse a large number of tests traditionally performed by the central laboratory by POCT, though no single device can be used for all tests. Table 3.1 indicates some of those analytes currently available (Zaloga, 1990; Kost & Hague, 1995). It is by no means a complete list, but covers those tests of particular interest to critical care.

Table 3.1 Some analytes available by POCT

Analyte	Technology	Instruments		Use	Ref
Blood gases pCO_2, pO_2, pH	Electrodes	Desk Top	Corning 800 series Radiometer ABL	Critical	
		Portable	Nova Gem Premier	Care	1 2
	Optical sensors	ex vivo in vivo	CDI 2000 PB 3300	Units	3 4
Glucose	Colorimetric Dry Chemistry	Numerous		A&E	5
Cardiac Markers	ELISA Dry Chem GLORIA Dry chemistry	Creatine Kinase TroponinT Troponin I	Reflotron Cardiac Readers Spectral Strips	CCU A&E	6 7 8
Coagulation	Dry Chemistry	Coag 1/2 Ciba Corning 512		Theatres	9 10
Urine	Dry Chemistry	Multistix		A&E	11

References referred to in this table – 1. Jacobs et al, 1993; 2. Zaloga et al, 1996; 3. Shapiro et al, 1993; 4. Larson et al, 1994; 5. Jones, 1994; 6. Romer et al, 1992; 7. Muller-Bardorff et al, 1999; 8. Heeschan et al, 1998; 9. Sane et al, 1992; 10. Ansell et al, 1991; 11. Belsey et al, 1986

A number of studies have reviewed the technological advances that have allowed the use of analysers for POCT. Such technology includes solid phase chemistry, electrochemical sensors, ion selective and substrate specific electrodes, biosensors and biomonitors, and the miniaturisation of instruments and microprocessors (Misiano et al, 1990; Smith & Vender, 1995; Gilbert & Vender, 1996; Dirks, 1996).

Solid phase chemistry has been utilised in POCT since the use of urine test papers for the detection of sugar and albumin in the 1880s, though the 'stick tests' as we know them today were first introduced in 1956 (Voswinckel, 1994). The methodology for all solid phase analysis is similar in that the lyophilised reagents are immobilised on a test pad and are reconstituted on the introduction of a sample. Usually the result is indicated by colour development of a dye that can be read qualitatively or by an analyser that converts the colour development into a concentration. Such technology is used in a number of POCT instruments. The simplest devices are the qualitative test strips such as those used to measure troponin T and I (Antman et al, 1995; Heeschen et al 1998). However, readers have been developed to quantitate these strips (Muller-Bardorff et al, 1999). There are a variety of meters, which quantitate glucose, many are outlined by Jones (Jones, 1994). Much has been written concerning the performance of these instruments with differing outcomes as to accuracy and reliability (Chu & Edney-Parker, 1989; Bain et al, 1991; Frishman et al, 1992). A number of other analytes are capable of quantitation from solid phase chemistry strips. The Roche Reflotron™, Vitros Ektachem™ and Ames Seralyser™ (Horder et al, 1991; Romer et al, 1992) can measure up to eleven analytes including sodium & potassium, glucose, and creatine kinase, though only one analyte per sample at a time. More recent instruments allow simultaneous analysis of a number

of analytes. The Alpha DX™ measures a cardiac profile including the MB isoenzyme of creatine kinase, myoglobin and troponin I, and the Piccolo™ analyses a biochemical profile including alkaline phosphatase, glucose, total bilirubin, though not as yet sodium and potassium (Miller EA et al, 1998; Schembri et al, 1995).

Interestingly, the use of dry chemistry has been applied to the central laboratories with the production of large multi-parameter automated analysers that utilise dry chemistry technology (Theodorsen, 1993).

Electrochemical sensor technology incorporating ion selective and substrate specific electrodes has been developed into POCT analysers (Misiano et al, 1990; Dirks, 1996). Blood gas analysers have used this technology for some time. Then sodium and potassium electrodes were developed, and more recently other analytes such as ionised calcium and lactate have been incorporated. Further development revolves around reducing the size of the instrumentation and maintenance requirements (Salem et al, 1991; Jacobs et al, 1993; Zaloga et al, 1996). Current literature is concerned with the development of biosensors (Kost & Hague, 1995; Smith & Vender, 1995). A number of new portable instruments that incorporate biosensors into their methodology are capable of measuring blood gases and sodium, potassium, chloride, glucose and creatinine, though on two separate cartridges (Jacobs et al, 1993; Erickson & Wilding, 1993). They are also being developed as monitors that can be placed in tubing (ex vivo) (Shapiro et al, 1993; Shapiro, 1994) or directly in the patient (in vivo) (Larson et al, 1994). There are advantages to these systems such as information in 'real time', no blood draw and no pre-analytical errors. At present only blood gases can be measured in this way and in the case of ex vivo only those

patients with arterial lines in place. However, blood is still required for other tests and there is also the question of evaluating this technology against the 'gold standard'.

In conclusion many POCT instruments have been introduced into the market over the last decade that make use of the technology available, and there are several studies that document their accuracy and reliability in comparison to the central laboratory methods.*

3.1.2 Pneumatic Tube Systems

Transport of specimens to the central laboratory is one of the factors that influence the decision for POCT. Rapid results are important for urgent samples, especially from the critical care areas. The introduction of pneumatic tube systems (PTS) to deliver specimens to the laboratory has shown to reduce specimen transport time to the central laboratory (Keshgegian & Bull, 1992; Johnston et al, 1997). One study stated that prior to installation of PTS, urgent samples took between 30 and 120 minutes to arrive in the laboratory. This was reduced to a maximum of 2 minutes post PTS (Nosanchuk & Salvatore, 1997).

* Horder et al, 1991; Salem et al, 1991; Romer et al, 1992; Jacobs et al, 1993; Downie et al, 1993; Shapiro et al, 1993; Erickson & Wilding, 1993; Shapiro, 1994; Larson et al, 1994; Schembri et al, 1995; Zaloga et al, 1996; Miller EA, et al 1998

Another study compared TAT for blood gases from the central laboratory with a satellite laboratory (Winkleman & Wybenga, 1994). TAT data were recorded by the hospital computer system. The central laboratory reported a mean TAT of 6 minutes (including any repeats). Transport time was less than 1 minute. In this study, the transport time was considered to be the rate-limiting step and, therefore, when reduced to a minimum the clinicians preferred to rely on the central laboratory for results.

More recently the introduction of an air tube system at St. Thomas' Hospital, London as an alternative to POCT has been evaluated (Johnston et al, 1997). Transport time was reduced by an average of 26 minutes, which was the time it took the porters to deliver the specimens from the Accident & Emergency (A&E) department to the laboratory, to a 'negligible amount', as stated in the report.

All these studies indicated that the introduction of PTS helped to reduce TAT from the central laboratory and together with other measures such as electronic data reporting, and urgent procedures within the laboratory TAT is reduced sufficiently such that POCT is not necessary.

The use of PTS for the transport of blood samples to the central laboratory assumes that the specimens are not affected by the system. Early studies carried out into the effect of pneumatic transport concluded that the majority of analytes are not affected (Weaver et al, 1978; Pragay et al, 1980). In the late 1970s a study assessing the common analytes tested by biochemistry and haematology concluded that lactate dehydrogenase (LDH) was the only analyte affected (Weaver et al, 1978). This was

thought to be due to ruptured red blood cells when the specimen tubes were incompletely filled. Two years later a similar study evaluated those tests affected by damage to blood cells (Pragay et al, 1980). It concluded the increase in LDH estimation did not outweigh the advantages offered by the use of PTS. More recently, evaluations on modified and upgraded PTS models have shown that even LDH is not significantly affected (Keshgegian & Bull, 1992; Winkleman & Wybenga, 1994).

3.2 FACTORS AFFECTING POCT

3.2.1 Quality/Accuracy of Results

Several studies have specifically set out to demonstrate that results produced by POCT instruments are accurate in comparison with the laboratory analysers (Horder et al, 1991; Jacobs et al, 1993; Antman et al 1995), and that they are equally reliable when carried out by non-laboratory personnel (Nanji et al, 1988; Salem et al, 1991; Zaloga et al, 1993; Erickson & Wilding, 1993). One recent study showed that the use of rapid dry strip cardiac markers gave reliable results when carried out by the Coronary Care Unit nurses (Sylven et al, 1998). However, another study concerning the i-STAT™ analyser had to abort the haematocrit comparison due to the marked increase in levels by POCT when testing was carried out by non-laboratory staff (Parvin et al, 1996). Although clinically acceptable, greater variability is seen when tests are carried out by non-laboratory personnel (Belsey, 1987; Romer et al, 1992; Nichols et al, 1995). While demonstrating accuracy under laboratory conditions is

important, it is essential that the reliability of the POCT instruments be validated with the personnel who will be using them.

Quality control, both internal and external, is an essential part of the central laboratory. These same stringent standards should be adhered to by POCT to ensure reliability of the results that will be used in clinical decision making (Marks, 1988; Freedman et al, 1993). Some reports have suggested that the clinicians are happy to sacrifice quality for timely results, depending on the context in which the results are to be used (Geyer, 1995). In Diabetes blood glucose levels are important in determining the dose of insulin to be administered, however as levels in the blood vary constantly, it is considered '.. more desirable to have a bedside test with rapid results than to have a more precise result provided at a later time' (Watts, 1995). However, there is little further evidence that clinicians would be happy to sacrifice precision. It is clinical relevance, and therefore timeliness, which is important.

Some of the literature sets out guidelines and recommendations for the use of devices near the patient. They include adequate training of non-laboratory personnel and quality control of the assays (Burnett & Freedman, 1994). Crook sets out recommendations for minimum standards to be achieved, including training and regular reassessment of all users in quality control (Crook, 1996). Similarly, in 1981,the Royal College of Pathologists and the Associations of Clinical Pathologists and Clinical Biochemists, set out guidelines for the performance of tests outside the laboratory (Anderson et al, 1981). However, it has been observed that while traditional quality control methods are effective for detecting systematic errors, they cannot detect the random errors more likely to occur with POCT due to the operator

(Baer & Belsey, 1993). It would be more appropriate to test the validity of results as part of the testing procedure to confirm correct operation of the instrument. For example, tests for potassium should perhaps also measure haemoglobin to indicate haemolysis. This would be important for users to interpret the results from POCT analysers (McConnell, 1998).

3.2.2 Turnaround time

Turnaround time (TAT) appears to be the most important factor for the researchers when assessing the outcome of POCT. Often the assumption made is that a faster result will be of greater benefit to the decision making process (Fleischer, 1993; Tsai et al, 1994; Fleischer & Schwartz, 1995). Clinicians argue that TAT for urgent work does not meet their expectations (Steindel, 1995). However, there is a lack of consensus regarding the several interpretations of TAT, and the many factors that influence it (Fleischer & Schwartz, 1990; Saxena & Wong, 1993; Bailey et al, 1997).

Laboratory staff define TAT as the time from receipt of sample to reporting the result. Clinicians refer to time of ordering test to result. Much of the literature reflects this difference (Saxena & Wong, 1993; Kilgore et al, 1998). In addition there are three phases that constitute TAT that are often referred to in the literature. Pre-analytical, the time from ordering test to receipt in the laboratory; analytical, equivalent to the laboratory TAT definition; and post-analytical, time from reporting of result to management of the patient (Refer to Table 2.1) Therapeutic TAT is considered the most appropriate as it covers the time from ordering to patient management, so including all three phases. Though it is often difficult to assess TAT

outside the laboratory, formal assessment of therapeutic TAT would improve the studies, as would a standard measure of TAT.

Delays in the pre-analytical phase will increase the TAT (Howanitz et al, 1992; Saxena & Wong, 1993). This phase can be divided into three stages; time from order to collection; time from collection to transport; and time to transport specimens to the laboratory (Saxena & Wong, 1993). Transport time to the central laboratory can be significantly reduced by the introduction of PTS. Fleischer reported a 23-minute reduction in pre-analytical time from 37 minutes to 14 after PTS was introduced (Fleischer & Schwartz, 1995). However, as PTS took only 50 seconds delays must arise from the other two stages from order to transport. Fleischer's report also suggest sample type has an influence on TAT. Blood gas samples are dealt with immediately, however, serum samples may wait for all the ward requests before being sent for analysis. The healthcare professional drawing the blood can also have an effect. A College of American Pathologists Q-probe (Quality-probe) study into TAT at the emergency department reported an average TAT for haemoglobin results as 23 minutes when blood was drawn by a phlebotomist from the laboratory; 34 minutes when drawn by a nurse; and 56 minutes by the doctor (Howanitz et al, 1992).

With electronic data transfer, results, once reported, are immediately available to the clinicians. Therefore post-analytical TAT will be dependent on the communication of the result to the decision maker. Time from result availability to inquiry, for urgent tests, was reported with a median of 35 minutes (range 15 - 90) in a study by Winkleman et al (1997). This may either indicate the real need for the result, or that clinicians expect a longer delay from the laboratory. Similarly, Saxena reported that

delay in review of results by the doctors was the longest component in overall TAT (Saxena & Wong, 1993). These studies do not measure the post-analytical TAT incurred by POCT, but assume it would be instantaneous. Bedside testing would seem to be more efficient when no decision making by the clinicians is required and the analysis and appropriate interventions are carried out by the nursing staff according to protocols, therefore, reducing post-analytical time (Kilgore et al, 1998).

The analytical phase or laboratory TAT has attracted many of the studies, probably as it is easy to quantitate. The majority of analysers available for POCT allow for analysis on whole blood within a few minutes (Jacobs et al, 1993; Downie et al, 1993; Erickson & Wilding, 1993). This is an obvious reduction in TAT compared to the laboratory which has to allow time for clotting and centrifugation before analysis. This is clearly demonstrated in a number of reports. Tsai reported analytical TAT as 8 minutes for POCT compared with 59 minutes for the central laboratory, though this included 25 minutes for transport time (Tsai et al, 1994). Similarly, Fleischer reported 8 minutes for POCT and 30 minutes for CLT (Fleischer & Schwartz, 1995).

Clearly, therapeutic TAT would be the best indicator of the difference between POCT and CLT. One method may produce a faster result, but this does not necessarily translate into an advantage for the patient. The information required from TAT studies is whether POCT results in quicker intervention and therefore benefits the patient. Kilgore suggests bedside analysis produces more frequent interventions on the basis of the result than CLT (Kilgore et al, 1998); 21% of laboratory results compared to 57% of satellite laboratory and 26% of POCT analyser results, however, the comparison was made using different tests. CLT measured blood gases, which

were generally used in monitoring and therefore fewer interventions required, and the satellite laboratory and POCT measured glucoses. Another study by Becker compared the use of activated partial thromboplastin time from bedside instruments with the laboratory during monitoring of patients receiving heparin, and concluded the therapeutic TAT and the time to achieve therapeutic levels were substantially decreased with POCT (Becker et al, 1994). However, a comparison of clinical outcome was not analysed.

To ascertain if a reduced TAT for results is beneficial to patient care the studies need to follow through to the outcome of the patient, in respect of

- decision making concerning their care
- length of stay on high dependency wards and in the hospital and
- overall outcome to patient.

3.2.3 Patient Outcomes

Providing results in a shorter time than CLT seems to be the aim for POCT, and many studies have evaluated this on the assumption that producing a faster result equals better care and therefore POCT is superior to CLT. However, what happens once a result is available? Does having a result quicker actually affect patient outcome? In an observational study, where POCT TAT was shown to be faster than the CLT, clinicians were questioned concerning their opinion of the outcome of patients based on the laboratory tests (Tsai et al, 1994). Of the 210 patients involved in the study, 59 patients (28.1%) were discharged or admitted on the basis of the results. The clinicians considered that 40 patients (19% of total) would have benefited from earlier

results. However, 75% of these (30 patients) had to wait for other procedures before the decision could be made. Another study, which took the form of a prospective randomised trial, considered that changes in management occur in 59 out of 859 (6.9%) patients (Kendall et al, 1998). Time until clinicians were aware of results was 86 minutes less for POCT than for CLT. However, there was no difference in the time spent in A&E, admission rates, or the length of stay as an in-patient or mortality.

A report by Rainey lays out some of the difficulties in quantifying the outcome for patients, based on the results of biochemistry tests (Rainey, 1998). He points out that medical interventions directly affect the outcome not laboratory tests. Therefore finding the link between test results and interventions is imperative in the study of POCT and patient outcomes. Hobbs suggested C-reactive protein measurement in primary care may enable clinicians to avoid unnecessary prescription of antibiotics by distinguishing between viral and bacterial infections (Hobbs, 1996), while another study reported the time to achieve therapeutic heparin concentrations was substantially shortened by POCT (Becker et al, 1994).

The length of stay (LOS) during the hospital encounter may be directly altered by a reduced TAT for results. Zaloga demonstrated that mean LOS could be significantly reduced from 2.5 to 1.4 days in patients with diabetic ketoacidosis who had bedside glucose measurements (Zaloga, 1990). Parvin on the other hand observed no reduction in LOS in the patients whose analysis was carried out by POCT during the experimental period of the study (Parvin et al, 1996). A median LOS of 209 minutes for those patients whose results came from the laboratory compared to 201 minutes with POCT. However, of the 1722 patients who had POCT, 1631 also had to have

other tests done in the laboratory that the POC analyser did not provide. The median LOS for those having POCT was reduced to 164 minutes. Keffer also pointed out this potential flaw in Parvin's study and suggested modifying the urgent profile to fit the tests provided by the POCT analyser (Keffer, 1997). A change in patient management was reported in one study where coagulation monitoring was available by POCT (Despotis et al, 1995). However, the study also incorporated a change in protocol and therefore the altered heparin therapy could not be directly attributed to the POCT.

3.2.4 Costs

While analytical and clinical factors affecting the provision of biochemical analysis by POCT are important in assessing the benefit to the patient, the cost of its provision also requires justification. However, it is difficult to describe costs incurred by POCT and CLT. Direct costs associated with providing the analysis can easily be quantified, but assigning values to indirect costs such as subsequent interventions, improved patient outcomes, or projected expenditure are often subjective (Watson, 1980; Keffer, 1995). Many studies only take into account those costs that they see as relevant to their particular study, or more accurately those they can quantify (Keffer, 1995).

When calculating costs it is important to assess the same factors for both sites. Zaloga reports cost of glucose analysis by POCT as $0.45 compared to $3.50 for CLT, however the same categories of costings were not used for both sites (Zaloga, 1990). Only the cost of the reagent strips was quoted for POCT whereas for CLT

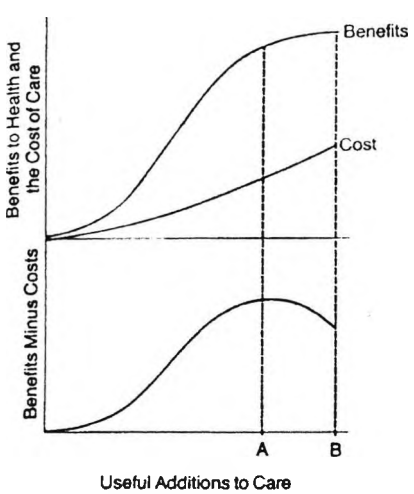
labour and fixed costs were also included. Similarly, Lee-Lewandrowski only quotes costs for labour and consumables for the POCT, whereas for the CLT, instrument and overheads are also included (Lee-Lewandrowski et al, 1994).

A study by Tsai found the cost of POCT to be $16.15 compared to $20.62 for CLT (Tsai et al, 1994). However, the same analytes were not being measured. The POCT analyser measured haematocrit and 5 biochemical tests whereas the laboratory was measuring a full blood count (FBC) and an additional two biochemical tests. Requests for an FBC or either of the extra tests would incur an additional cost.

Generally fixed costs are higher for CLT than for POCT, but variable costs are much lower for CLT (Cresce et al, 1995). Changes in workload have little effect on the costs of CLT but have a marked influence on POCT. Laposta quotes $3.84 for the cost of CLT and between $3.50 and $18.00 for POCT (dependent on the number of tests performed) (Laposta & Lewandrowski, 1995). When only one test is carried out per day 85% of the cost results from indirect costs such as quality control and training. The study concludes that provided greater than five tests are performed per day there is little difference in cost between POCT and CLT. However, in common with similar studies, no attempt was made to estimate the financial impact of moving some tests from the CLT to the ward. For instance, in the case of glucose analysis moving from CLT to ward, would CLT costs would be reduced by the full $3.84 per test or would costs such as labour, instrument maintenance and depreciation still be accountable? In the laboratory the instruments run continuously providing analysis for other sites and other tests whereas on the wards the POCT equipment may lie idle for the majority of the time (Watson, 1980).

Although many clinicians feel POCT likely to have a significant impact on outcome and resources, most studies are unable to report whether the reduced TAT provided by POCT results in a superior medical outcome, which would outweigh the cost increase (Nosanchuk & Keefner, 1995; Fleischer & Schwartz, 1995). Most studies indicate higher running costs for POCT than CLT (Watson, 1980; Tsai et al, 1994; Nosanchuk & Keefner, 1995; Cresce et al, 1995). Winkleman reported the cost of POCT was $6.62 compared to $3.30 for CLT and suggested a one off expense for the provision of pneumatic tube recovered from savings by avoiding the high cost of POCT (Winkleman et al, 1993). However, the higher cost for POCT does not necessarily rule out its use. Donabedian illustrates the relationship between cost and benefit (Fig. 3.1) (Donebedian, 1988). He suggests that as additions to care are made actual improvements become progressively smaller though costs will increase, therefore providing these additions result in substantial improvements to patient care the increase in cost will be justifiable. There is a point however, where the improvements made are so small that they are outweighed by the increased costs.

Fig 3.1 Relationship between Cost and Benefit of Care (Donabedian, 1988)



A. Optimum effective care

B. Maximum effective care

A reduction in TAT may provide results which reflect the current status of the patient and reduce the need and cost of repeating tests which have been delayed in the laboratory (Zaloga, 1990). Zaloga reported that bedside testing with a Gem blood gas analyser reduced the length of hospital stay, and average hospital costs related to weaning patient from ventilators, as more rapid treatment received by the POCT group (Zaloga et al, 1989). Becker suggests many patients with chest pain could be cared for in less intensive wards if myocardial infarction could be reliably ruled out (Becker, 1995). CCU beds are more expensive than those on general wards and therefore the reduced bed cost would repay the additional analytical costs (Collinson, 1998). However, reduced hospital costs as a result of POCT are difficult to document, especially if other factors influence the LOS (Kendall et al, 1998; Brogan & Bock, 1998).

3.2.5 Use

In the majority of cases, POCT is expected to be carried out by the nursing staff (Zaloga et al, 1993). A survey in America indicated that although the nursing staff saw POCT could be helpful to patient management, they would prefer laboratory personnel to take responsibility for POCT (Lamb et al, 1995). This was particularly true of those nurses who were not involved with any POCT. In the UK, a survey questioned the clinicians' view of POCT results. Only 34% trusted the results enough, without any laboratory backup, to act on them. It was observed that there was no doubt concerning the need for blood gases in Intensive Therapy Unit or glucose on the wards, but 71% said POCT was not needed if transport was available to the laboratory (Gray et al, 1996).

3.3 SIMILAR STUDIES TO THAT DESCRIBED IN THIS THESIS

A search of the literature was undertaken to review any other studies that were in any way similar to this thesis, in respect of being a systematic approach covering all aspects of POCT or run as a prospective randomised trial where the 'real time' of POCT was assessed. Many of the evaluations of POCT in comparison with CLT centre on the assessment of particular analysers and their accuracy. Romer undertook a complete method evaluation of three portable POCT instruments, including linearity and interference studies (Romer et al, 1992). Samples were selected to cover the measuring range, then they were split and analysed in parallel by laboratory staff. The study concluded no fundamental differences between the POCT analysers and the laboratory's. Similarly, another study carried out a method evaluation of glucose meters (Nicholls et al, 1995). These types of study are useful in defining the operating characteristics of the analysers, but not the performance by POCT, nor are they relevant to the disease prevalence in the population where POCT is used. Both studies did include a phase where the analysis was carried out by non-laboratory personnel, the results of which showed that the technical staff produced a better quality. Neither of these studies were carried out in 'real time' but were retrospective.

Prospective studies, where all samples from a population are analysed, provide a better measure of performance (Ball et al, 1994; Schembri et al, 1995; Rumley, 1997). In these studies the users of POCT were aware that their results were checked in the laboratory. However, the studies still focused on the accuracy of the analyser, not on the impact on the management of the patient.

There have been a few studies comparing POCT with CLT where the benefit to the patient is measured, mainly in the field of coagulation monitoring (Becker et al, 1994; Despotis et al, 1994; Despotis et al, 1995). Despotis studied transfusion requirements in coronary by-pass patients and concluded that the use of POCT for coagulation analysis reduced transfusion requirements, re-operation rates and post-bypass recovery time (Despotis et al, 1994). Becker concluded that the time to achieve therapeutic levels and time to dose adjustment was shorter in the POCT group (Becker et al, 1994). A study based in the A&E department reported 6.9% of those patients randomised to POCT had changes in management due to the timely delivery of the result. However, there was no difference in LOS, or in mortality rates between patients randomised to POCT or CLT (Kendall et al, 1998). All these studies used dedicated personnel to perform the analysis.

This chapter has reviewed the current literature pertaining to POCT. The majority of the studies have focused on the reliability of the analysers to produce accurate results and on the improvement in TAT over the central laboratory. Few take this further and assess the benefits POCT may have on patient management and outcome, and of those that do, none undertake a thorough evaluation of POCT in comparison with CLT, nor include a prospective randomised controlled trial to assess the impact of POCT in routine clinical use.

CHAPTER 4 ORGANISATION OF THE STUDY

The previous chapters laid out the rationale behind this study and reviewed the current literature pertaining to point of care testing. This chapter sets out the organisation of the study. The setting where the study takes place is outlined along with the study protocol and procedures for the collection and analysis of the data.

4.1 STUDY SETTING

The study was run as a single centre prospective randomised trial carried out in a large District General Hospital consisting of 850 beds and serving a population of 320,000. The focus of the study was on the critical care wards, comprising the Intensive Therapy Unit (ITU) and the Coronary Care Unit (CCU). Between them they had 10 beds, 6 in ITU and 4 in CCU. Sometimes there was overflow from CCU into ITU, which could be managed due to the proximity of the wards to one another. All sequential admissions were enrolled during the study period.

For phase 1 the ITU already had access to a Ciba Corning 850 (Chiron Diagnostics, UK) blood gas analyser situated in a satellite laboratory on the ward, which could also analyse electrolytes, sodium (Na) and potassium (K). This analyser had been in routine use for two years and so all the current nurses on these wards had previously been fully trained in its operation. The CCU was supplied with a Reflotron (Boehringer Mannheim, Lewes, UK) analyser for the measurement of creatine kinase (CK). This analyser was situated within the CCU itself. The nurses on this ward had

to be trained in its use. For Phase 2 both wards were supplied with new analysers for which all nurses required full training. ITU were supplied with a portable analyser, which measured a biochemical profile including urea, creatinine and alkaline phosphatase (ALP). CCU had a new analyser to measure CK and two qualitative devices for the measurement of troponin T and I. The biochemistry laboratory staff were responsible for maintaining the equipment and ensuring quality control.

There was a link to the central laboratory from these units via a pneumatic air tube system (ASCOM GmbH, Keven, Germany) for the rapid transfer of specimens. This system had been in routine use for the previous 2 years. It was situated in the ITU and shared by 5 other users within the surgical block of the hospital, with the ITU port having priority over the other users. All samples arriving in the laboratory from these wards were automatically considered urgent and dealt with accordingly. The analysers were interfaced with the laboratory computer system and both wards were also linked electronically to the laboratory via ward-based terminals, allowing access of results as soon as they were available.

The patient population involved in the study were those admitted to the critical care units, ITU and CCU. The ITU comprised a heterogeneous group of patients that included, acute medical problems requiring intensive interventions, long-term therapy such as dialysis, and short-term post-operative patients requiring monitoring before returning to their own wards. There were typically 250 cases per year. In CCU the population was more homogenous, the majority of patients having acute coronary syndromes (ACS). This included acute myocardial infarction (AMI), angina, both stable and unstable, and also those with non-ischaemic chest pain (NICP) being ruled

out for AMI. The hospital admits and investigates 5000 patients a year with ACS, of whom 500 are admitted to CCU.

In both these wards the specialised nursing staff carried out the routine patient management, referring to junior medical staff where unexpected deviations from patient plans occurred. There were no condition-specific protocols in the ITU due to the heterogeneity of the patient population, though there were general guidelines on ventilator and fluid management. The consultant ward round scheduled at 11:00 a.m. reviewed patients on a daily basis. The patient management in CCU followed care protocols based on clinical findings, electrocardiogram (ECG) results and biochemical markers. The cardiac team reviewed the patients at 09:00 am on a daily basis.

4.2 STUDY PROTOCOL

The study was carried out in the form of a prospective randomised controlled trial. It was a two phase study comprising two consecutive trials (ITU and CCU). The first phase utilised existing technologies and routine analysers. The second phase introduced innovative point of care testing (POCT) developments. These were all to be compared with the central laboratory's existing analysers and protocols. The tests to be investigated are outlined in Table 4.1

Ethical approval for the study was obtained from the Hospital Ethics Committee and the study complied with the Declaration of Helsinki.

Table 4.1 Analysers and tests to be run during the study

		Analyser	Tests
Phase 1 Existing Technology	ITU	Ciba Corning Gas Analyser	Na & K
	CCU	Boehringer Mannheim Reflotron	CK
Phase 2 Novel Technology	ITU	Abaxys Piccolo	Urea, creatinine, calcium, bilirubin, albumin & ALP
	CCU	First Medical Inc. Alpha Dx Dry Chemistry Sticks	CK Troponin T & I

Both phases were split into 3 stages -

Stage 1 Analytical Validation

An evaluation of the POCT technology was carried out to ensure the suitability of the analysers for use in the clinical setting prior to the start of the trial. This involved comparative studies using the central laboratory methods as 'gold standard'. In addition, evaluation of the loop from sample draw to return of results was performed to ensure accuracy from request to result. This first stage addressed part of the first objective of the study, namely to assess the accuracy and reliability of the POCT analysers. Clinical accuracy would be assessed from the data collected during the prospective trial. Once their suitability was established the next stage could continue.

Stage 2 Trial Run

Prior to the actual study period a trial run, lasting a period of one month, was undertaken in which the conditions of the true study were examined. During this period any necessary training of the ITU and CCU staff was carried out with particular care taken to ensure correct operational procedures of the analysers, the identification of possible erroneous results and the consequent appropriate action to be taken. Data collected during this trial run were assessed and any problems that arose were resolved prior to the start of the randomised controlled trial. All the healthcare workers, involved in the trial, were made familiar with its requirements and any additional training was provided as required. Once the logistics of the trial were finalised the actual study could begin.

Stage 3 Prospective Randomised Controlled Trial

Sequential randomisation of consecutive patients for routine investigations, by POCT or central laboratory testing (CLT), was carried out over a period of eight months. Patients were randomised on admission to the ward. All analysis for the tests involved in the study was then carried out at the testing site assigned. Data was collected prospectively which would be analysed in order to address the objectives laid out in the introduction. Where additional investigations were required urgently, samples were analysed either by POCT or CLT, regardless of the patients' randomisation, at the physician's discretion.

4.3 DATA AND SAMPLE COLLECTION

4.3.1 Randomisation

The randomisation sequence for the study was obtained from formal tables and supervised by Professor Derek Cramp. The sequence was duplicated in order that both wards could maintain their own separate process. As patients were admitted to the ward they were assigned to testing by POCT or CLT. Numbered sealed envelopes, containing the analysis site (POCT or CLT), were opened by the nurses on admission of the patient to the ward. Each patient's name and analysis mode were recorded to ensure no envelopes were omitted and the analysis method was also stated in the patients' notes.

4.3.2 Sample Collection

Blood gas samples were taken from arterial lines into pre-heparinised syringes (Mieno Corp, Tokyo, Japan). On the ITU, the samples were analysed within 5 minutes of blood draw. Samples for CLT were sealed in clear plastic envelopes and placed into a canister and dispatched to the laboratory via the pneumatic transport system. On receipt the samples were analysed immediately.

Samples required for laboratory analysis of electrolytes, CK, full biochemical profile and troponins were collected into vacutainer tubes containing serum separator gel (SST, Beckton Dickenson, Oxford). Patients randomised to CLT did not require any additional samples during the study. However, those having analysis by POCT

required further samples to be drawn in addition to those already going to the laboratory (Table 4.2).

Table 4.2 Additional samples required for POCT

		Samples required	Comment
Phase 1	ITU	None	
	CCU	Lithium Heparin Tubes	Taken at 0, 4 & 8 hours post admission
Phase 2	ITU	Lithium Heparin Tubes	Stored at 4°C until analysis carried out
	CCU	EDTA * tubes (CK) Lithium Heparin (Troponins)	0, 4 hours (&12-24hrs if required) 12 – 24 hours

* Ethylene-diamino-tetra-acetic acid

4.3.3 Data recording

A clinical proforma was completed prospectively for each patient randomised into the study. This included demographic data for patient identification, date & time of admission, date and time of discharge from the critical care ward and from the hospital, clinical diagnosis and relevant history, and any interventions carried out. ITU patients had their admission Acute Physiological and Chronic Health Evaluation (APACHE) III scores and daily Therapeutic Intervention Scoring System (TISS) recorded, and for patients on the CCU, onset of chest pain was recorded along with ECG findings and whether thrombolytic therapy was undertaken.

Patients had a 6-month follow up to ascertain their outcome. Any hospital readmissions were noted (not including elective surgery), any invasive cardiac

interventions subsequently performed, such as Percutaneous Transluminal Coronary Angioplasty (PTCA) or Coronary Artery Bypass Graft (CABG), and, where necessary, date of death. The final diagnosis obtained during the study was concluded by the consultant chemical pathologist and a cardiologist based on a retrospective review of the data, or from the discharge letter contained in the patients files. The final diagnosis was categorised according to International Classification of Disease (ICD) 10 codes for ITU and World Health Organisation (WHO) criteria (Table 4.3) for CCU.

Table 4.3 WHO criteria

AMI	Characteristic ECG changes: ST elevation or Q waves Confirmed by significant changes in biochemistry (CK 2 x ULN / cTnT >0.2 µg/l)
High Risk Unstable Angina (UA)	1. Without ECG change 2. Non specific ECG: ST depression or T wave inversion (cTnT >0.2 µg/l) 3. Symptoms suggesting cardiac disease (cTnT >0.2 µg/l) 4. Continuing chest pain with or without non-specific ECG
Stable Angina (SA)	cTnT <0.2 µg/l and either positive stress test, positive radionucliede scan or CAD on angiography
NICP	Follow up investigations allow exclusion of above or source of chest pain found.
ULN Upper limit of normal CAD Coronary Artery Disease	

4.4 DATA ANALYSIS

4.4.1 Evaluation of the POCT technology

Direct method comparison between POCT and the central laboratory analysers was undertaken using Passing and Bablok regression analysis and Altman and Bland plots. Similarly, routine clinical accuracy during the trial run in was assessed. Passing & Bablok regression analysis takes into account deviations arising from both methods instead of comparing one to an assumed absolute perfect method as with linear regression. It also has an advantage over Deming's regression analysis as it does not fix the degree of error. The Passing and Bablok graphs used throughout the thesis all follow the same format. Points are plotted for POCT results (y-axis) compared to the CLT results (x-axis) and the line of regression is drawn. Where possible the scales on the axes are the same except where the difference in result range is marked, such as for the Troponin I comparison. Altman & Bland plots indicate the degree of bias produced by one method compared to the other and whether any bias is constant or changes over the measured values. This is achieved by plotting the difference between the results against the mean of the results. Bias is indicated by the position of the plotted points and mean line relative to zero.

The differences between the methods were analysed by the Mann Whitney U test, which is a non-parametric test allowing the analysis of independent random samples of different sizes to assess whether the samples derive from the same population. In other words is the accuracy of the methods comparable?

The diagnostic accuracy was assessed by the construction of receiver operating characteristic (ROC) curves where clinical cut-off points were available. These compare the diagnostic test by plotting the sensitivity against 1- specificity. The area under the curve is a measure of how good the test is at distinguishing between patients with or without a particular condition. Therefore, the greater the area, the better the test.

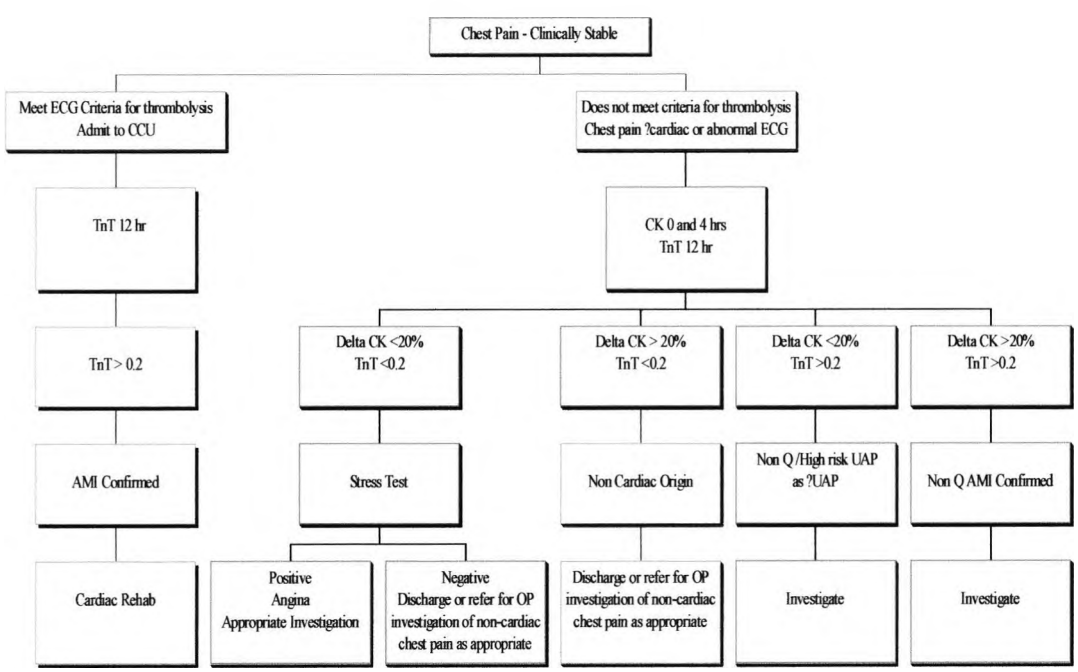
The time recorded for turnaround time (TAT) in this study was from blood draw to availability of result, either displayed on the POCT analyser or available for access on the laboratory computer database via the ward based terminal. This was assessed by the Mann Whitney U test.

4.4.2 Clinical Impact

The patient demographics obtained during the trial were analysed to ascertain whether the two groups (POCT and CLT) came from the same population and thereby rule out any differences observed between the testing sites deriving from differences in the patient groups. Where the data obtained was categorical, such as sex, ethnic origin and previous history, Chi^2 test was used to assess it. This is a non-parametric test, which analyses the difference between actual and expected values between categorical variables. In the cases where the sample data was small, the Fisher exact probability test was used instead. Both tests indicate the probability that the data from each category is the same. All other demographical data were analysed by the Mann Whitney U test.

Analysis of the length of stay was undertaken in both wards as a measure of clinical outcome. Each patient had three measures of stay recorded - duration of stay from admission to critical care unit to step down (or death); non-critical care to hospital discharge (or death); plus the total duration from initial admission to discharge. Standard hospital discharge time of 12:00 was used when no other record was present. In addition, TISS scores and documented action on receipt of results were recorded for ITU, and Intention to Treat (ITT) analysis, based on the time taken to reach a management decision according to the WHO criteria (Table 4.3) and the CCU protocol (Fig. 4.1), was assessed in CCU. The ITT data was collated by the clinical assistant cardiologist on a daily basis and is the time when the final decision regarding the patients' condition and subsequent treatment could have been made. This was the time when sufficient data was available to make that decision. From this data patients who could have been rapidly discharged from the CCU, and moved to a lower dependency ward or sent home, were identified.

Fig 4.1 CCU Protocol Phase 2



Other indicators of clinical impact related to morbidity and mortality; incidence of complications recorded from data records and follow up readmission rates and deaths occurring during critical care stay, in-patient and six month follow up. These were all assessed using the Fisher exact probability test.

4.4.3 Operational Impact

Information regarding all costs was obtained from the hospital finance department by retrospective analysis of actual departmental budgetary expenditure for both the laboratory and patient.

The components for test costs were divided as follows: -

Fixed Costs

These include hospital and departmental overheads. Hospital overheads are apportioned to the individual departments according to a formula based on floor space. These were not included in the overall test costs as they are top sliced and do not appear in the departmental budgets. Departmental costs, incorporate such costs as contracts for information technology licences and de-ionised water provision. These were also not included as the percentage shift from the laboratory to POCT in critical care is minimal (0.5% of total annual workload).

Semi Fixed Costs

Semi fixed costs change in increments depending on the workload. Small changes in workload have little affect on the overall cost, unlike a large change which increases

or decreases the cost in steps. These include staffing costs and maintenance contracts. Staff costs were calculated using the mid point on the pay scale of a Biomedical Scientist grade 1 and a D grade Nurse. Maintenance contracts with the instrument providers are fixed within certain test volumes.

Variable Costs

The cost of consumables (reagents, vacutainers, quality control material etc) is directly dependent on the number of tests performed, as the workload increases so the cost decreases.

Opportunity Costs

These costs include the cost of providing beds to the patients. General medicine ward beds are less expensive than the high dependency units of CCU and ITU. The length of patient stay will have a direct bearing on the total cost of an episode of care, including the number of tests required.

The costs evaluated in this thesis were based on the workload experienced during the period of the study and where necessary annual costs extrapolated.

All the data were recorded onto an ACCESS®database and all statistical data were analysed using ASTUTE® add-in for EXCEL® (Microsoft). Details of the analysis will be presented in chapters 6, 7 & 8.

CHAPTER 5 ANALYTICAL METHODS

Chapter 4 described the organisation of this study, outlining the setting, study protocol and data collection. This chapter will outline the analytical methods used to obtain the biochemistry data. The methodology used in the point of care technology is important when comparing the suitability of the results with those obtained from the central laboratory. As the study was split into two phases corresponding to existing and novel technologies, so this chapter will be arranged. However, as much of the central laboratory analysis was carried out on one main analyser, these methods will be dealt with together.

5.1 PHASE 1 EXISTING TECHNOLOGY

The first phase of this study involved the evaluation of existing point of care testing (POCT) technology. In the study setting, the Intensive Therapy Unit (ITU) already had technology in use and the Coronary Care Unit (CCU) was supplied with an appropriate analyser from another setting. The evaluation for this phase, therefore, was concerned with the analysis of the electrolytes, sodium and potassium, which were available on the ITU blood gas analyser, and creatine kinase, which the CCU analyser was set up to measure.

5.1.1 ITU Blood Gas Analyser for Electrolytes

Arterial whole blood is collected into heparinised syringes and analysed on the ward using a Ciba Corning 850™ blood gas analyser (Chiron Diagnostics, Halstead,

Essex). 110µl of blood is introduced into the analyser via aspiration (not injected), and all measurements are carried out at 37°C. The instrument provides blood gas analysis and simultaneously measures sodium (Na) and potassium (K). They are measured directly using ion selective electrodes with membranes specific for the ion being measured. A potential develops across the membrane that is compared to an external reference electrode. The Na electrode consists of a silver/silver chloride (Ag/AgCl) wire surrounded by an electrolyte of fixed Na and Cl ions, and a glass membrane. The K electrode has a valinomycin membrane, and an Ag/AgCl surrounded by an electrolyte solution of fixed K ions. See Table 5.1 for the between batch coefficient of variation (CV) and the reference ranges.

Table 5.1 CV % and reference range for Na and K

SODIUM		POTASSIUM	
mmol/l	%CV (n = 84)	mmol/l	%CV (n = 84)
115.7	2.1	2.9	1.1
132.8	1.3	4.9	1.5
157.9	0.9	6.9	3.7
Reference Range	133 – 145 mmol/l	Reference Range	3.3 – 4.5 mmol/l

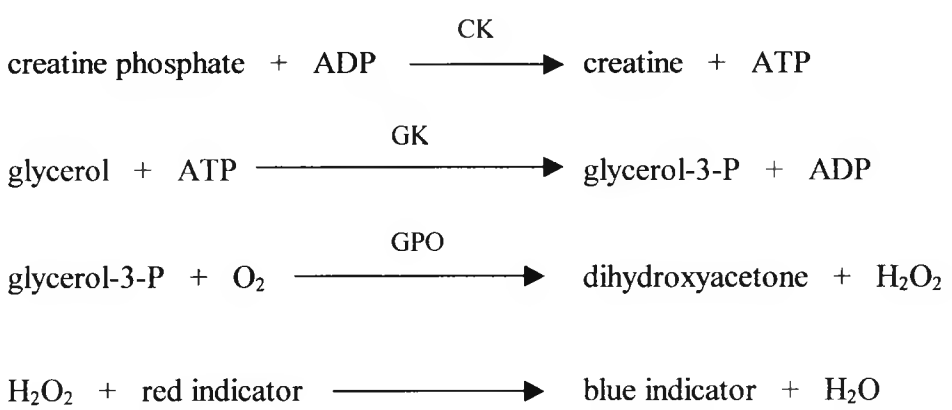
CV% data quoted by the manufacturer

Each analyte has a reference range within which, the level of that analyte measured in a patient sample is deemed to be within normal limits. The range usually has a 95% confidence limit, so allowing 5% of patients with normal levels to have values outside this range. Reference ranges for each analyte are method and population dependent and are therefore not fixed. Each laboratory should determine their own ranges. Those applicable to the analysis in this study will be quoted as appropriate. The

percentage CV is an indicator of the imprecision of the analyser. A low CV shows that the analysis is very precise. Values of less than 5% are considered good methods and those <10% are considered reasonable. Assuming the method is precise the CV% should decrease as the number of tests increase.

5.1.2 CCU Creatine Kinase Analysis

Creatine kinase (CK) activity was determined in the CCU by a member of the nursing staff with a dry chemistry system, the Reflotron (Roche Diagnostics, Lewes, Sussex). This was a small bench top analyser capable of performing a range of analyses using bar coded solid phase reagent strips. 32µl of heparinised whole blood was applied to the test pad using a fixed volume pipette. The strip is then inserted into the Reflotron, which identifies the test and carries it out at 37°C. CK in the sample reacts with creatine phosphate and adenosine diphosphate (ADP) to form adenosine triphosphate (ATP). In the next step this ATP reacts with glycerol in the presence of glucose kinase (GK), the product of which then reacts with glycerol phosphate oxidase (GPO) forming hydrogen peroxide. The hydrogen peroxide converts a red indicator to blue. This colour change is measured kinetically at 642nm and a result is displayed within 190 seconds.



The Reflotron is linear up to 1400 IU/l, though will produce results up to 1800 with a linearity flag. Samples exceeding this limit were first repeated to confirm the result, then recorded as >1400 IU/l, while the sample was then sent to the central laboratory for analysis. The manufacturers supplied the quality control material and the laboratory staff carried out the quality control analysis along with the daily maintenance. The reference range was 0 – 160 IU/l.

5.2 PHASE 2 NEW TECHNOLOGIES

A range of POCT instruments have been and are being developed. The trend is towards smaller instruments that are capable of analysing a number of analytes. In this phase, the study looks at two new instruments that were made available to the project. In the ITU a small portable analyser for measuring a range of biochemical tests simultaneously was evaluated, and in the CCU rapid stick tests for Troponin measurements, as well as an instrument undergoing pre-market trials capable of analysing a cardiac profile, were assessed.

5.2.1 ITU Biochemistry Analyser

The ITU was supplied with a portable instrument for analysing a range of biochemical tests. The Piccolo™ (Abaxis, Sunnyvale, California) was a precalibrated, spectrophotometric analyser that could measure a panel of 11 tests using solid phase reagents held on a rotor. Between 90 - 120 µl of heparinised whole blood is pipetted into the rotor via an application port. The rotor is inserted into the instrument and the analysis begins. The rotor spins during the assay, which separates the plasma

from cells and reconstitution of the reagents takes place to process the sample. The assay takes 15 minutes to run.

Eleven analytes were available, these being, albumin, alkaline phosphatase (ALP), alanine aminotransferase (ALT), amylase, bilirubin, calcium, cholesterol, creatinine, glucose, total protein and urea. All the results are printed on the result card. However, total protein and ALT were not assayed routinely in the main laboratory and therefore were not included in the study. The methodologies for the remaining 9 analytes were as follows;

Albumin A dye binding end point reaction using bromocresol purple (BCP) at an acid pH. The amount of BCP-albumin complex formed is proportional to the concentration of albumin in the sample. The end point reaction is measured as the difference in absorbance between 600nm and 550nm.

$$\text{BCP} + \text{Albumin} \xrightarrow{\text{Acid pH}} \text{BCP-Albumin complex}$$

ALP A modified International Federation of Clinical Chemistry (IFCC) method using *p*-nitrophenyl phosphate (*p*-NPP) as the substrate, which is hydrolysed by ALP in a metal ion buffer. ALP activity is proportional to the rate of increase in absorbance difference between 405nm and 500nm.

$$p\text{-NPP} \xrightarrow{\text{buffer}} p\text{-Nitrophenol} + \text{phosphate}$$

Amylase Amylase reacts with 2 chloro 4 nitrophenyl maltotrioside (CNPG3) releasing CNP creating a change in colour, which is directly proportional to the

amylase, activity in the sample. The reaction is measured bichromatically at 405nm and 500nm.

$$\text{CNPG3} \xrightarrow{\text{Amylase}} \text{CNP} + \text{D-maltotrioside}$$

Bilirubin An enzymatic method where bilirubin is oxidised by bilirubin oxidase (BO) into biliverdin, which is then oxidised to various purple compounds. A cuvette blank is measured and subtracted from the final absorbance reading.

$$\text{Bilirubin} + O_2 \xrightarrow{\text{BO}} \text{Biliverdin} + H_2O$$

$$\text{Biliverdin} + O_2 \longrightarrow \text{purple compounds}$$

Creatinine Coupled enzymatic reactions using tribromohydroxybenzoic acid (TBHBA) and 4-aminoantipyrine (4AAP) as substrates.

$$\text{creatinine} + H_2O \xrightarrow{\text{creatinine amidohydrolase}} \text{creatine}$$

$$\text{creatine} + H_2O \xrightarrow{\text{creatine amidinohydrolase}} \text{sarcosine} + \text{urea}$$

$$\text{sarcosine} + H_2O + O_2 \xrightarrow{\text{sarcosine oxidase}} \text{glycine} + \text{formaldehyde} + H_2O_2$$

$$H_2O_2 + \text{TBHBA} + \text{4AAP} \xrightarrow{\text{peroxidase}} \text{Red quinoneimine dye} + H_2O$$

Potassium ferrocyanide is also added to reduce the interference from bilirubin. Ultimately a red quinoneimine dye is formed, the intensity being proportional to the creatinine in the sample, once endogenous creatinine has been subtracted.

Cholesterol Cholesterol esters are hydrolysed to free cholesterol with cholesterol esterase (CHE), which in turn is oxidised by cholesterol dehydrogenase (CHDH)

coupled with the reduction of nicotinamide adenosine dinucleotide (NAD^+) to NADH. The absorbance is measured bichromatically at 340nm and 405nm.

$$\text{cholesterol esters} + H_2O \xrightarrow{\text{CHE}} \text{cholesterol} + \text{fatty acids}$$

$$\text{cholesterol} + NAD^+ \xrightarrow{\text{CHDH}} \text{cholesterone} + NADH$$

Glucose Glucose reacts with ATP catalysed by hexokinase (HK) to glucose-6-phosphate (G-6-P). G-6-P dehydrogenase catalyses G-6-P to 6 phosphogluconate coupled to reduction of NAD^+ to NADH.

$$\text{Glucose} + ATP \xrightarrow{\text{HK}} \text{G-6-P} + ADP$$

$$\text{G-6-P} + NAD^+ \xrightarrow{\text{G-6-PDH}} \text{6-phosphogluconate} + NADH$$

Urea Urease hydrolyses urea to ammonia, which then reacts with oxoglutarate and glutamate dehydrogenase (GLDH) to oxidise NADH to NAD^+. The rate of change in absorbance between 340 and 405nm is proportional to the amount of urea in the sample.

$$\text{urea} + H_2O \xrightarrow{\text{urease}} NH_3 + CO_2$$

$$NH_3 + \text{2-oxoglutarate} + NADH \xrightarrow{\text{GLDH}} \text{glutamate} + H_2O + NAD^+$$

Calcium A dye binding reaction with arsenazo III. A calcium-dye complex is formed, the amount of which is proportional to the calcium in the sample. This is an endpoint reaction monitored at 3 wavelengths.

$$Ca^{2+} + \text{Arsenazo III} \longrightarrow Ca^{2+}\text{-Arsenazo III complex}$$

For the between batch CV% (n = 80) quoted by the manufacturer of these methods please refer to Table 5.2.

Table 5.2 CV% for Piccolo™ Portable Analyser

ALBUMIN		ALP		AMYLASE	
g/l	CV%	IU/l	CV%	IU/l	CV%
37	2.9	39	5.8	46	5.7
56	2.1	281	3.1	300	3.8
BILIRUBIN		CALCIUM		CHOLESTEROL	
µmol/l	CV%	mmol/l	CV%	mmol/l	CV%
13.7	9.3	2.15	2.9	5.27	3.4
88.9	2.8	2.94	3.4	6.49	3.5
CREATININE		GLUCOSE		UREA	
µmol/l	CV%	mmol/l	CV%	mmol/l	CV%
97.2	13.1	3.67	1.6	6.8	2.1
460	5.2	15.4	1.4	23.2	1.8

The reference ranges used were the same as the main laboratory (Table 5.3).

5.2.2 CCU Troponin and CK Assays

Troponin T (TnT) was determined on the ward using qualitative Trop T test sticks (Roche Diagnostics, Lewes, Sussex). 150µl of heparinised whole blood sample is pipetted into the well of the test stick using a fixed volume sample pipette (supplied by the manufacturers). These pipettes are capable of puncturing the rubber seal on a vacuum-sealed blood collection tube, therefore, avoiding additional handling of the specimen. A biotinylated monoclonal antibody and a gold labelled monoclonal antibody, both TnT specific, form a sandwich complex with TnT present in the

sample. Red blood cells are removed and the plasma passes along the detection zone. The TnT sandwich complex accumulates along a line of immobilised streptavidin and appears as a red line. Excess gold-labelled antibodies migrate further long the detection zone and accumulate along a control line. Providing a red line is visible at the control point a positive result for TnT is indicated by the presence of a red line at the sample detection point. Intensity is proportional to the concentration of TnT in the sample. The test takes 15 minutes to run.

Troponin I (TnI) was analysed on the ward, concurrently with TnT, using a qualitative dry chemistry stick, the Spectral Cardiac STATus Troponin I Rapid Test (Spectral Diagnostics Europe, GmbH). 200µl of whole blood is applied to the sample well of the measuring stick. Plasma is transferred onto the region containing two antibodies, a monoclonal anti TnI - dye conjugate, and a polyclonal anti TnI antibody labelled with biotin. These antibodies bind to TnI present in the sample to form sandwich complexes that then migrate through the detection zone. These complexes are captured by immobilised streptavidin while unbound substances migrate to the control area. A positive result requires the presence of two purplish lines formed in the detection zone. This test also takes 15mins to run.

CK concentration in the second phase of the study was analysed in the CCU by a member of the nursing staff using the Alpha DX (First Medical Inc., California, USA). This is another small bench top analyser, utilising dry chemistry discs and a wet washing solution. It simultaneously measures Total CK, CK-MB, TnI and Myoglobin. Results for the other three analytes were recorded though not used in the evaluation or available to the clinicians. Whole blood samples, anti-coagulated with

ethylenediaminetetraacetic acid (EDTA), were introduced into the analyser via the specimen collection tube, the analyser then drew from this sample the volume required for analysis. While the cardiac markers are being analysed the instrument also measures packed cell volume to convert the whole blood measurements to serum values, which are reported.

CK in the sample is mixed with a CK specific antibody labelled with fluorescein. The disc is spun and under centrifugal force the immune complex mixes with a monoclonal CK specific antibody conjugated to streptavidin and becomes linked to biotin, which is immobilised on the test disc surface. Any unbound substances are removed and a third antibody (Cy5 labelled monoclonal anti-fluorescein antibody) is used to enhance the signal reaction with the immobilised sandwich complex. This is measured at 633nm; the intensity of excitation being proportional to the concentration of CK in the sample. The reference range is 0 -160 μg/l.

5.3 CENTRAL LABORATORY METHODS

The POCT methods were compared to those available in the central laboratory. Much of the actual methodology was similar, but the central laboratory analysers are much larger multichannel analysers with a throughput of 120 samples per hour.

5.3.1 Electrolytes, CK and Biochemistry Profile

All the following biochemical analytes were determined in the laboratory on a discrete multichannel analyser, the Technicon Axon (Bayer, Basingstoke, UK). Samples were

collected into serum separating tubes and after centrifugation placed directly on the analyser. The instrument pipettes the required volumes of sample into reaction chambers and then adds the reagents. The analytes were measured using the following methodologies at 37°C and the reference ranges were determined by the laboratory. The between batch CV% and reference ranges are summarised in table 5.3.

Table 5.3 CV% for Technicon Axon Multichannel Analyser

NA		K		CK	
mmol/l	CV%	mmol/l	CV%	IU/l	CV%
116	0.8	3.5	2.5	137	5.2
143	0.8	7.5	2.2	572	3.8
Ref. range 132 – 145 mmol/l		Ref. range 3.4 – 5.2 mmol/l		Ref. Range 0 – 200 IU/l	
ALBUMIN		ALP		AMYLASE	
g/l	CV%	IU/l	CV%	IU/l	CV%
23	2.9	65	5.1	56	2.3
51	2.2	501	2.0	383	0.8
Ref. Range 30 – 45 g/l		Ref. Range 80 – 300 IU/l		Ref. Range 15 – 90 IU/l	
BILIRUBIN		CALCIUM		CHOLESTEROL	
µmol/l	CV%	mmol/l	CV%	mmol/l	CV%
17.1	5.2	1.72	2.0	3.3	2.2
233	2.1	2.77	2.0	5.9	2.3
Ref. Range <20 µmol/l		Ref. Range 2.05 – 2.65 mmol/l		Ref. Range <5.2 mmol/l	
CREATININE		GLUCOSE		UREA	
µmol/l	CV%	mmol/l	CV%	mmol/l	CV%
141	2.5	4.0	2.2	6.4	4.3
654	1.6	20.3	1.7	21.1	2.4
Ref. Range 45 – 120 µmol/l		Ref. Range <7.0 mmol/l		Ref. Range 2.5 – 6.7 mmol/l	

N.B. The CV data quoted by the manufacturer was collected in duplicate from 1 –2 runs per day over 20-23 days, except ALP and calcium which were collected over 10 days.

Na and K These electrolytes are measured indirectly by mixing the sample with an ion specific electrode (ISE) buffer solution. This maintains the pH and ionic strength. The buffered sample passes the ISEs causing a change in electrical potential, which is compared to a reference electrode. The membranes of the electrodes are specific for Na and K respectively.

CK CK activity in the sample reacts with creatine phosphate and ADP to form ATP that in turn reacts with glucose in the presence of hexokinase producing G-6-P. NADPH is generated when G-6-P and $NADP^+$ react together, catalysed by glucose phosphate dehydrogenase (GPD). The increase in NADPH is measured at 340nm and is directly proportional to the CK activity. These reactions are N-acetylcysteine (NAC) activated, which restores the CK activity in the sample.

$$\text{creatine phosphate} + \text{ADP} \xrightarrow{\text{CK}} \text{creatine} + \text{ATP}$$

$$\text{D-glucose} + \text{ATP} \xrightarrow{\text{HK}} \text{ADP} + \text{G-6-P}$$

$$\text{G-6-P} + \text{NADP} \xrightarrow{\text{GPD}} \text{6-phosphogluconate} + \text{NADPH}$$

Bilirubin Bile pigments in serum react with a diazo reagent at an acid pH producing azobilirubin. Absorbance of the end product is measured at 540nm and is proportional to the bilirubin concentration in the sample.

$$\text{sulfanilic acid} + \text{sodium nitrite} \longrightarrow \text{diazo sulfanilic acid}$$

$$\text{diazo sulfanilic acid} + \text{bilirubin} \longrightarrow \text{azobilirubin}$$

Albumin Albumin in the sample combines with bromocresol green (BCG) dye at pH 7.0 forming a stable complex. The absorbance of this complex is measured at 600nm and is proportional to the albumin concentration.

$$\text{Albumin} + \text{BCG} \longrightarrow \text{Albumin-BCG complex}$$

ALP ALP hydrolyses *p*-NPP, in a buffered solution of constant pH, to *p*-nitrophenyl. The rate of formation of this yellow product is proportional to ALP activity in the sample.

$$p\text{-NPP} + \text{AMP buffer} \xrightarrow{\text{ALP}} p\text{-nitrophenol} + p\text{-AMP}$$

Amylase Amylase hydrolyses CNP-maltotrioside to CNP. The rate of the reaction is accelerated with potassium thiocyanate. The amylase activity is proportional to the rate of CNP formation.

$$\text{CNP-maltrotrioside} \xrightarrow{\text{amylase}} \text{CNP} + \text{maltotriose}$$

Cholesterol Cholesterol esterase hydrolyses cholesterol esters to free cholesterol. This cholesterol then reacts with oxygen and cholesterol oxidase to form hydrogen peroxide, which in turn combines with aminoantipyrine and a phenol derivative to form a red quinoneimine dye.

Creatinine Creatinine is measured utilising the original Jaffe method. In this, creatinine reacts with picric acid in an alkaline medium to produce a red coloured complex. The rate of complex formation is measured at 505nm and is proportional to creatinine concentration.

Glucose Glucose is phosphorylated by ATP in the presence of hexokinase and magnesium ions to G-6-P. This in turn is converted by G-6-P dehydrogenase in a coupled reaction where NAD^+ is reduced to NADH. NADH formation is proportional to glucose concentration.

$$\text{Glucose} + \text{ATP} \xrightarrow{\text{HK}} \text{G-6-P} + \text{ADP}$$

$$\text{G-6-P} + \text{NAD}^+ \xrightarrow{\text{G-6-PDH}} \text{6-phosphogluconate} + \text{NADH} + \text{H}^+$$

Urea Urea in the sample is hydrolysed to ammonia by urease. Ammonia then reacts as a substrate with NADH, which is catalysed by glutamic dehydrogenase to NAD^+. The rate of NAD^+ formation is measured at 340nm.

$$\text{urea} + \text{H}_2\text{O} \xrightarrow{\text{urease}} \text{NH}_3 + \text{CO}_2$$

$$\text{NH}_3 + \text{ketoglutarate} + \text{NADH} \xrightarrow{\text{GLDH}} \text{glutamate} + \text{H}_2\text{O} + \text{NAD}$$

5.3.2 Troponins

TnT was determined in the central laboratory by electro-chemiluminescence immunoassay (ECLIA) using the Elecsys 1010™ analyser (Boehringer Mannheim, Lewes, Sussex). Two monoclonal TnT specific antibodies, one labelled with biotin, the other with a ruthenium complex are mixed with 15µl sample. TnT in the sample forms a sandwich complex with the antibodies. Streptavidin coated microparticles are added which bind the complex to the solid phase. The microparticles are then magnetically attracted to the surface of the measuring cell, and any unbound

substances are removed by washing. A voltage is applied creating a chemiluminescent emission, which is measured by a photomultiplier. The length of the assay is 9 minutes. The detectable cut off point is <0.1µg/l.

TnI was determined on archived frozen samples stored until analysis was carried out on an ACS:180™ (Bayer Diagnostics). The method involves a two site sandwich immunoassay where the solid phase consists of a monoclonal mouse anti-cTnI antibody coupled to paramagnetic particles, and the detection antibody is polyclonal anti-cTnI labelled with acridinium ester. 100µl of sample is required which is mixed with the antibodies, the reaction is measured by chemiluminescence and takes 15 minutes. CV% at 2.49µg/l is quoted as 5.5% and at 26.7µg/l as 5.4%

Outlined in this chapter are the various analytical methods used in this study. When comparing the results from the two testing sites any differences observed might be due to the different methodologies utilised by the instruments. Results from the evaluation of the POCT technology stage of the study are presented in the following chapter.

CHAPTER 6 POCT TECHNOLOGY EVALUATION RESULTS

The previous chapter laid out the analytical methods that were used during this study at the point of care and in the laboratory. The next three chapters will detail the results collected during the study in order to answer the objectives set out in the introduction. This chapter contains the results from the evaluation of the technology, assessing the accuracy and therefore the suitability of the analysers for use at the point of care, and the turnaround time for results. The evaluation was carried out in comparison with the central laboratory.

The first objective of this study was to assess the accuracy of the point of care testing (POCT) technology being used. Is the instrumentation as accurate and reliable as central laboratory testing (CLT)? To answer this, two validation processes were carried out. Initially, an analytical validation stage, where the instruments were assessed for accuracy prior to the trial, was undertaken in order to establish their suitability for use in sample analysis. Then, during the main trial period, data were collected so that accuracy while in routine clinical use could be determined.

6.1 ANALYTICAL VALIDATION

6.1.1 Intensive Therapy Unit Phase 1

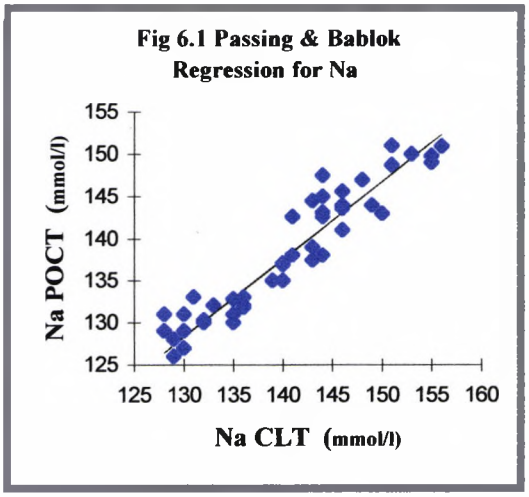
Samples for analysis of sodium (Na) and potassium (K) by POCT were measured as part of the routine blood gas analysis. Blood was taken from those patients with arterial lines into pre-heparinised syringes and analysed immediately on the blood

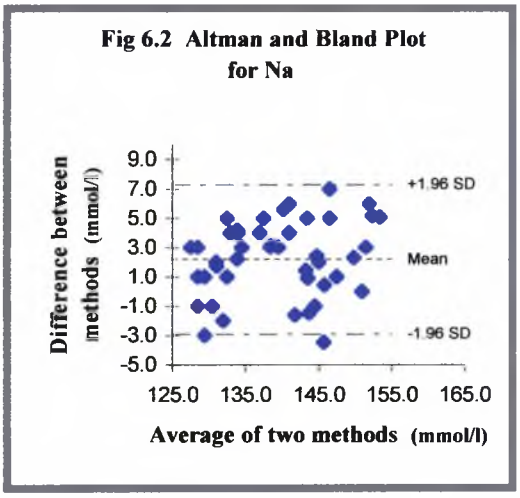
gas analyser. Parallel samples for routine analysis by the central laboratory were taken into serum separating tubes (SST) and sent to the laboratory.

Table 6.1 Analytical comparison data for Na and K

	Sodium		Potassium	
	CLT	POCT	CLT	POCT
min	128	126	3.1	2.8
median	141	138	4.1	3.7
max	156	151	5.8	5.1
Pearson's Correlation	$r = 0.9459$		$r = 0.9046$	
Passing & Bablok Regression	Slope	Intercept	Slope	Intercept
	0.925	8.0625	0.7692	0.5627
Mann Whitney U	U = 980	$p = 0.207$	U = 685.5	$p = 0.0006$

The regression analysis data showed good agreement between the POCT and CLT methods for sodium (Fig 6.1). These regression data were applied to the CLT reference range to ascertain whether an adjusted range would be required for use with the POCT analyser. This was achieved by taking the slope (m) and intercept (c) values obtained from the regression analysis and substituting these values into the equation for a straight line: y = mx + c, where x is the CLT value. In the case of sodium little difference was found and therefore an adjusted range was not used.





The Altman Bland plot in Figure 6.2 also indicated a good overall agreement between the two methods, though a slight negative bias in the POCT values was observed. Results of the Mann Whitney U test (MWU) showed that any difference in the two methods was not statistically significant. The regression analysis for potassium showed fairly good agreement between the two methods (Fig 6.3); however, significantly lower values were observed on the POCT analyser. The Altman & Bland plot in Figure 6.4 shows a significant negative bias, which is proportional as the bias increases with increased K values. Similarly to sodium the regression data were applied to the CLT reference range resulting in a corrected range being required for use in the ITU. This corrected range was 3.2 – 4.6 mmol/l, which is much lower at the upper limit than the CLT range of 3.4 – 5.2 mmol/l.

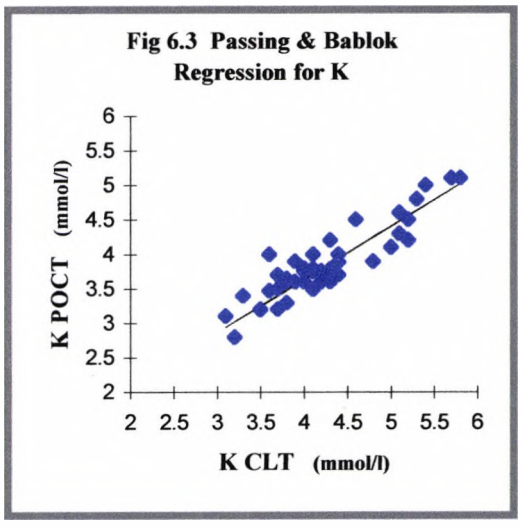


Fig 6.3 Passing & Bablok Regression for K

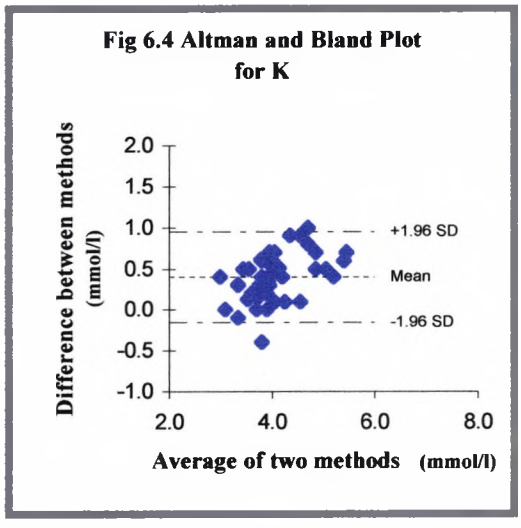


Fig 6.4 Altman and Bland Plot for K

6.1.2 Coronary Care Unit Phase 1

In phase 1, 25 samples were drawn for the analytical stage of creatine kinase (CK) analysis. Blood was collected into SST vacutainers as part of the routine investigations and sent to the laboratory. Parallel samples for the analysis of CK on

the ward were drawn into vacutainers containing lithium heparin anti-coagulant. Data from the analytical comparison are summarised in Table 6.2.

Table 6.2 Analytical comparison data for CK – phase 1

				Passing & Bablok		MWU	
	min	median	max	slope	intercept	U	*p*
CLT	42	183	1313	0.8214	-2.649	250	0.2252
POC	35	169	1190				

The Passing & Bablok regression data showed good correlation between the POCT and CLT methods although the POCT values were lower (Fig 6.5). This is supported by the MWU test, which indicates no significant difference between the two methods. The Altman & Bland (Fig. 6.6) plot shows a proportional bias indicating the difference in values between the two methods is increasing, as the values get higher and approach the linearity limit of the POCT analyser. Applying the regression data, as before, to the existing laboratory reference range (0 – 200 IU/l) a corrected range, of 0 – 160 IU/l for use with the POCT was required.

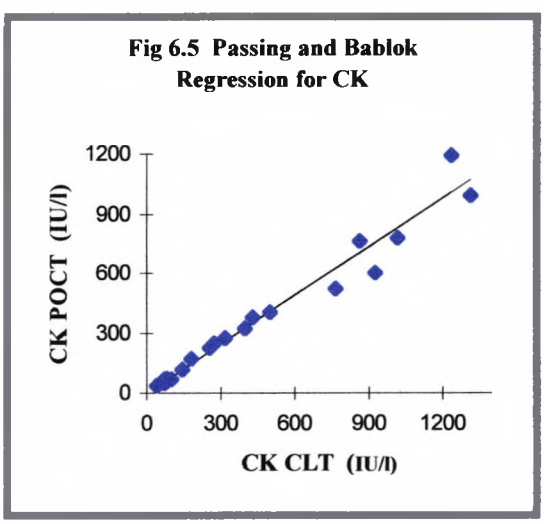


Fig 6.5 Passing and Bablok Regression for CK

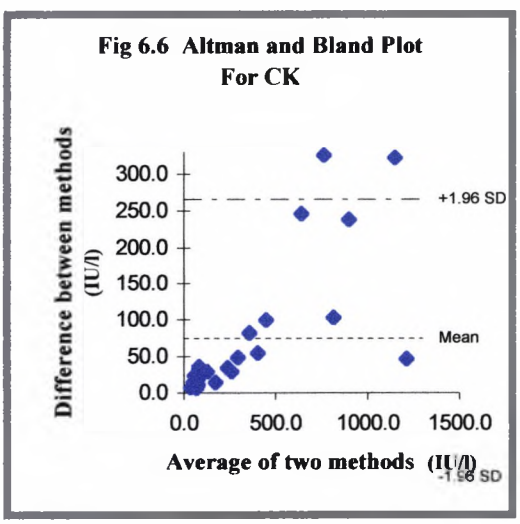


Fig 6.6 Altman and Bland Plot For CK

6.1.3 ITU Phase 2

Samples were obtained in parallel on 30 patients for the analytical comparison of the Piccolo™ POCT instrument. Blood for the laboratory was drawn into SST vacutainers and for the POCT into vacutainers anticoagulated with lithium heparin. The results are summarised in Table 6.3.

Table 6.3 Analytical data comparison for Piccolo™

					Passing & Bablok		MWU	
		min	median	max	Slope	intercept	U	*p*
Albumin	CLT	17	24	42	1.333	-5.1667	313	0.0424
	POCT	17	27.5	46				
ALP	CLT	65	212	1686	0.4061	-1.1878	190	0.0001
	POCT	25	89	667				
Amylase	CLT	16	70	198	1.0556	-3.722	445.5	0.9469
	POCT	12	68	202				
Bilirubin	CLT	4	12.5	75	0.8421	2.9211	416.5	0.6199
	POCT	6	13	59				
Calcium	CLT	1.65	2.05	2.5	1.0968	-0.3361	282.5	0.0133
	POCT	1.43	1.88	2.34				
Cholesterol	CLT	0.7	2.35	6.8	0.9643	0.0446	449	0.9882
	POCT	0.6	2.4	6.6				
Creatinine	CLT	54	90	253	0.6826	-13.1258	141.5	<0.0001
	POCT	23	44.5	198				
Glucose	CLT	3.4	6.2	33.2	0.9	0.14	378.5	0.2902
	POCT	3.0	5.75	32.3				
Urea	CLT	3.2	9.65	26.3	0.9444	0.3139	401	0.4688
	POCT	2.7	8.25	25.9				

The Passing & Bablok regression analyses of the analytes (Figs 1 – 9; Appendix 1) show good correlation between the two methods for amylase, bilirubin, cholesterol, glucose and urea. Alkaline phosphatase (ALP) and creatinine have produced much lower results by the POCT method, whereas albumin and calcium have more

scattered results. This is supported by the MWU test that indicates significant differences observed with ALP, albumin, creatinine and calcium. The Altman & Bland plots (Fig 10–18 Appendix 1) indicate a bias in the results for glucose and urea as well as ALP, albumin, creatinine, and calcium. In all except albumin the bias was negative. The other tests do not appear to have any bias. In order to maintain the same reference ranges for POCT and CLT, ALP, creatinine and calcium values were adjusted for POCT using a conversion factor to normalise them to the CLT range. After discussion with the ITU consultants, the difference in values observed with albumin was not considered to be of clinical significance and so the values were not adjusted.

6.1.4 CCU Phase 2

In phase 2, CKs were measured on a beta test prototype Alpha Dx™ analyser. It was supplied for clinical testing with preliminary analytical validation data. The main focus of this phase in the CCU was the troponin analysis; therefore it was considered unnecessary to carry out further analytical validation on CKs, but to obtain data for the clinical validation.

The POCT method for qualitative troponin T (TnT) determination had previously been validated within the study setting as part of a number of multi centre clinical trials and hence was introduced into the study without the need to perform any further analytical validation. Similarly it was deemed unnecessary to perform analytical validation on the qualitative troponin I (TnI) method. TnI was also

available on the Alpha Dx™ and values were obtained for clinical validation during the trial, but were unavailable for clinical use by the health care workers.

6.2 CLINICAL VALIDATION

Having carried out the method comparison between the POCT analysers and the laboratory methods, it was concluded that the instruments were analytically valid. Corrected reference ranges were provided where appropriate or correction factors applied to the results in order to use the same reference ranges for both methods.

6.2.1 ITU Phase 1

During the randomised clinical trial samples were collected randomly into both SST vacutainers and lithium heparin syringes for the comparison of Na and K analysis in routine clinical use. 433 samples were analysed on the POCT instrument, of which 69 had parallel measurements carried out in the laboratory. These were used to assess the clinical validity of the analyser. The data (Table 6.4) obtained from this stage was similar to that obtained in the analytical study.

Table 6.4 Clinical validation data for Na and K

	Na		K	
	CLT	POCT	CLT	POCT
min	122	121	3.2	2.5
median	135	133.5	4.4	4.0
max	155	151	5.8	5.6
Passing & Bablok Regression	Slope	Intercept	Slope	Intercept
	1.00	-3.00	1.00	-0.40
Mann Whitney U	U = 1978	p = 0.1454	U = 1220	p = <0.0001

The regression analysis (Fig 6.7 & 6.9) indicate a greater scatter of values than was observed during the analytical stage. Sodium had a similar tendency to a slight negative bias (Fig 6.8) and potassium, as expected, was significantly different, though not such a proportional bias (Fig 6.10) was observed.

Fig 6.7 Passing & Bablok Regression for Na

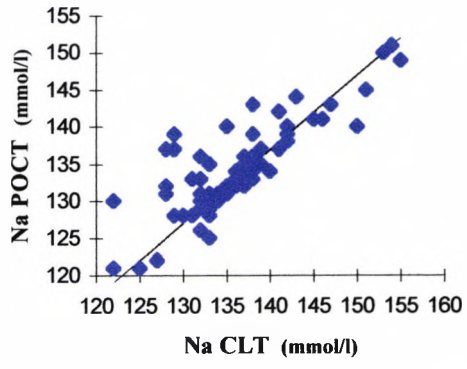


Fig 6.8 Altman and Bland Plot For Na

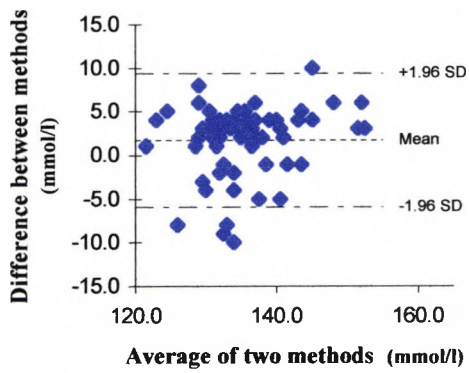


Fig 6.9 Passing & Bablok Regression for K

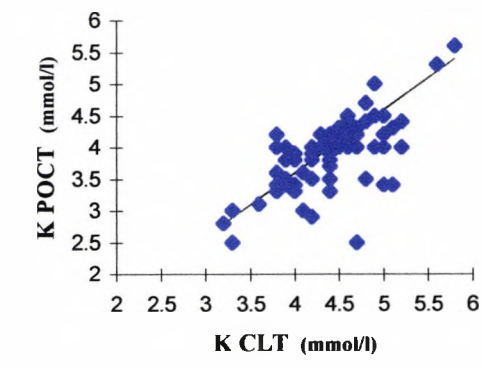
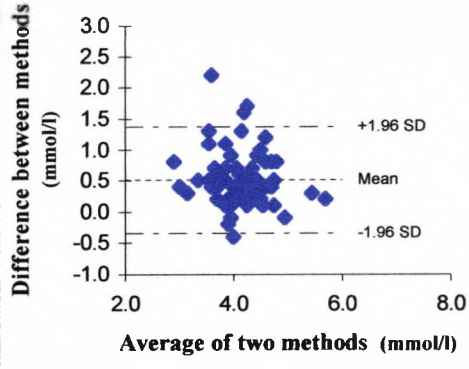


Fig 6.10 Altman and Bland Plot For K



6.2.2 CCU Phase 1

In phase 1, a total of 222 POCT CK determinations were carried out on the Reflotron during the randomisation trial stage of the study. Of these 42 also had parallel analysis carried out in the laboratory. Eight samples exceeded the measuring range of the instrument of 1400 IU/l, and so were excluded from the clinical validation data. Good correlation between the two methods was again observed (Table 6.5), the MWU test indicates no significant difference but a greater scatter was observed than during the analytical stage (Fig 6.11). The Altman & Bland plot indicates a proportional negative bias (Fig 6.12).

Table 6.5 Clinical validation data for CK – phase 1

				Passing & Bablok		MWU	
	min	median	max	slope	intercept	U	*p*
CLT	40	195.5	1957	0.8966	-1.3621	534.5	0.5936
POCT	44	178.5	1680				

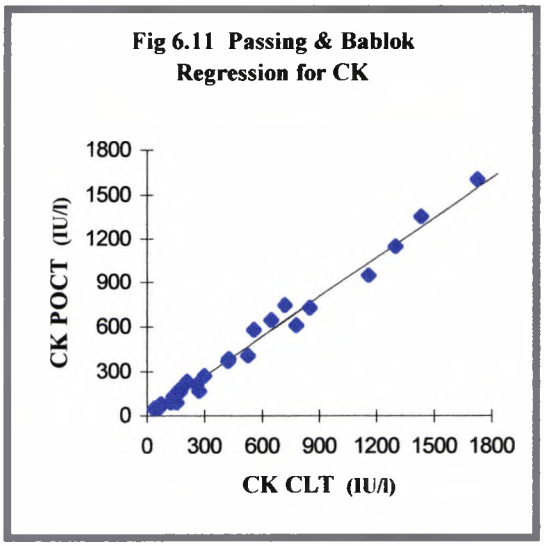


Fig 6.11 Passing & Bablok Regression for CK

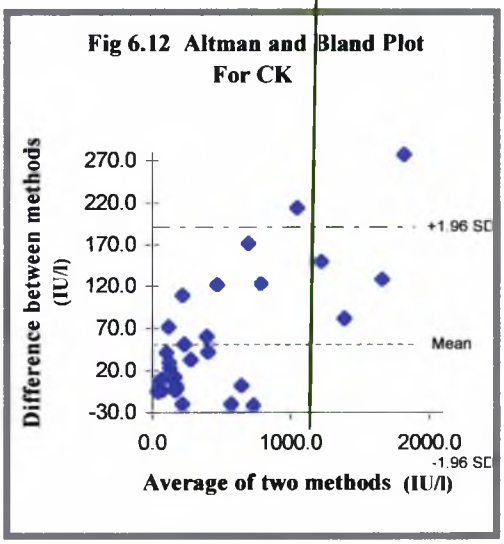
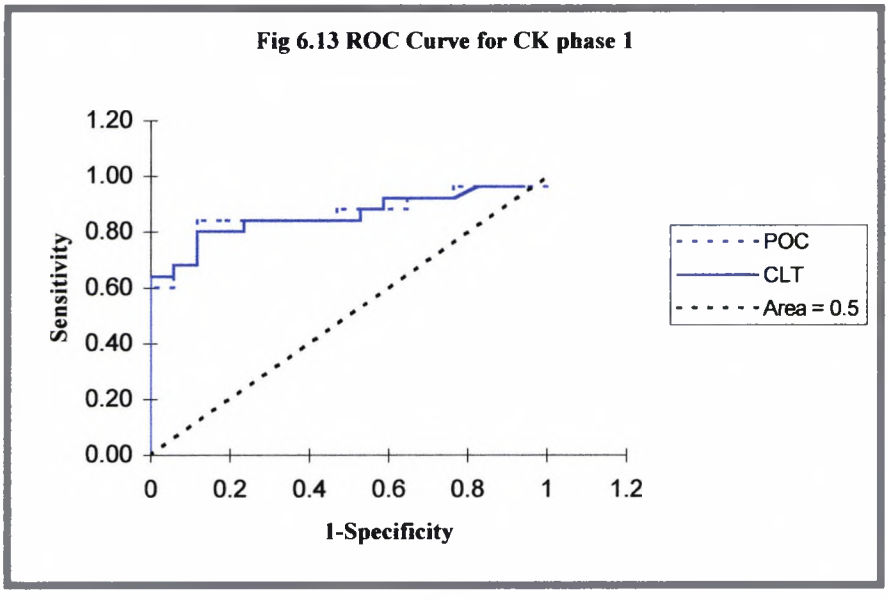


Fig 6.12 Altman and Bland Plot For CK

Comparison by receiver operator characteristic (ROC) analysis (Fig 6.13) showed the two methods gave an identical clinical outcome, with no significant difference in the areas under the curves (0.8588 CLT and 0.8612 POCT).



6.2.3 ITU Phase 2

Table 6.6 Clinical Validation data for the Piccolo™

						Passing & Bablok		MWU	
		n	min	median	max	Slope	intercept	U	*p*
Albumin	CLT	92	15	22	36	1.3077	-2.384	2592.5	<0.0001
	POCT	92	17	25	42				
ALP	CLT	82	44	202	1032	1.0154	-18.207	2967.5	0.1945
	POCT	82	31	178	950				
Bilirubin	CLT	83	1	18	327	0.8	2.0	3428.5	0.9588
	POCT	83	2	17	255				
Calcium	CLT	80	1.49	1.97	2.47	1.4468	-0.798	2396.5	0.0061
	POCT	80	1.38	2.05	2.56				
Creatinine	CLT	103	42	89	946	1.2867	-26.72	4982	0.4509
	POCT	103	25	92	1161				
Urea	CLT	104	1.9	7.9	52.6	0.9290	-0.366	4797	0.1592
	POCT	104	1.0	6.85	47.1				

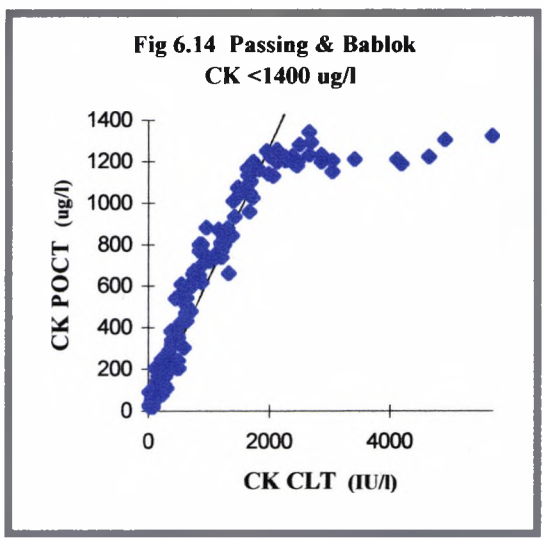
Data obtained during routine clinical use of the POCT instruments are summarised in Table 6.6. The data for calcium creatinine and ALP is based on the adjusted results. Albumin again showed markedly different results between the two methods; though no bias was indicated on the Altman & Bland plot (Fig 25 Appendix 2). Allowing for the use of correction factors for ALP and creatinine there was no significant difference observed between the CLT and POCT methods. However, even with a conversion, calcium had a significant difference. Urea and bilirubin were not statistically different, bilirubin particularly showed good agreement. The bias observed in the POCT methods during clinical use were different than that observed during the analytical validation stage. ALP now only has a slight negative bias, calcium has a slight positive bias and urea has none. Both creatinine and bilirubin have a proportional bias, which increases as the values increase. See Appendix 2 for the Passing & Bablok regression (Fig 19-24) and Altman & Bland (Fig 25-30) plots. Amylase, cholesterol and glucose were not included in the clinical stage because either the analytes were not frequently requested for laboratory analysis (amylase and cholesterol) or an alternative POCT method was already in routine use (glucose).

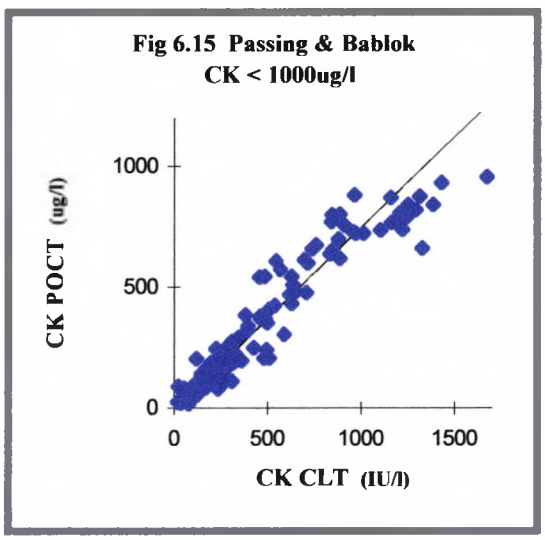
6.2.4 CCU Phase 2

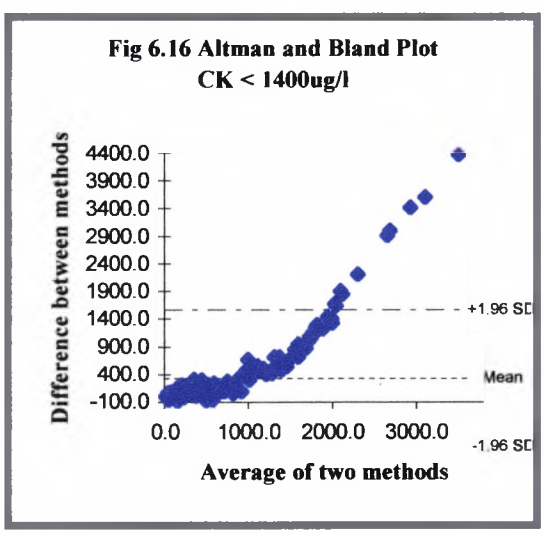
Table 6.7 Clinical validation data for CK – phase 2

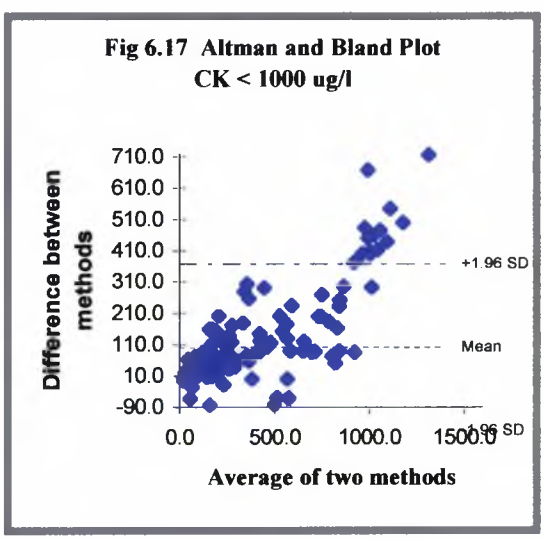
				Passing & Bablok		
	min	median	max	excluding values	slope	intercept
CLT	19	284	5686	>1400 µg/l	0.6358	3.4851
POCT	17	205	1342	>1000 µg/l	0.7552	-8.6203

In phase 2, CK was analysed on an Alpha Dx™. Table 6.7 summarises the data. 246 determinations were carried out in parallel, of which 27 were excluded from the clinical validation data as they exceeded the detection limit of the analyser (<1400). Initial data from the Alpha Dx™ suggested the detection limit was up to 1400 µg/l. Clearly from the regression analysis (Fig 6.14) and the Altman & Bland Plot (Fig 6.16) the limit was much lower. With a revision of this limit to <1000 µg/l the regression data was much improved (Fig 6.15), though a proportional negative bias was still apparent (Fig 6.17). However analysis by MWU indicates a significant difference in the two methods even when the linearity limit was adjusted (CK <1400 µg/l MWU = 12562, $p = 0.0013$ and CK <1000 µg/l MWU = 19528, $p = 0.0008$).



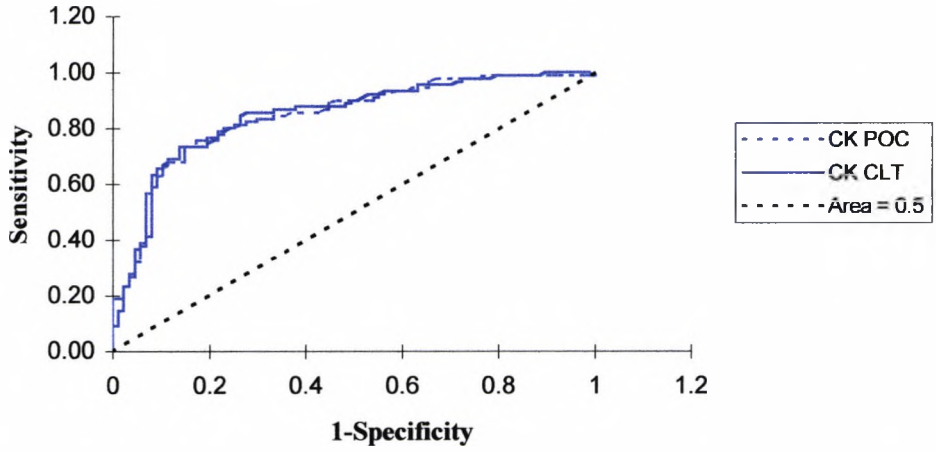






Comparison of the two methods by ROC analysis showed diagnostic equivalence with areas under the curve of 0.8448 for CLT and 0.8434 for POCT (Fig 6.18).

Fig 6.18 ROC Curve for CK phase 2



Parallel analysis was carried out on 152 determinations of Troponin T (TnT) and 120 determinations of Troponin I (TnI). Diagnostic performance of the POCT measurements was examined in two ways. Firstly, the number of positive and negative results was plotted against intervals of troponin values obtained in the central laboratory (Figs 6.19 & 6.20).

Fig 6.19 Qualitative TnT results compared to Elecsys

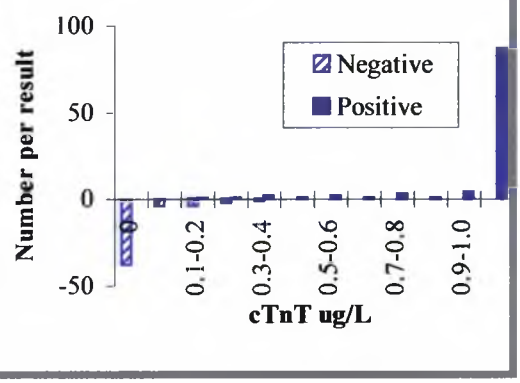
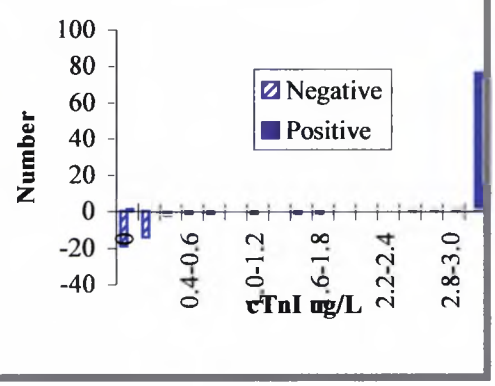
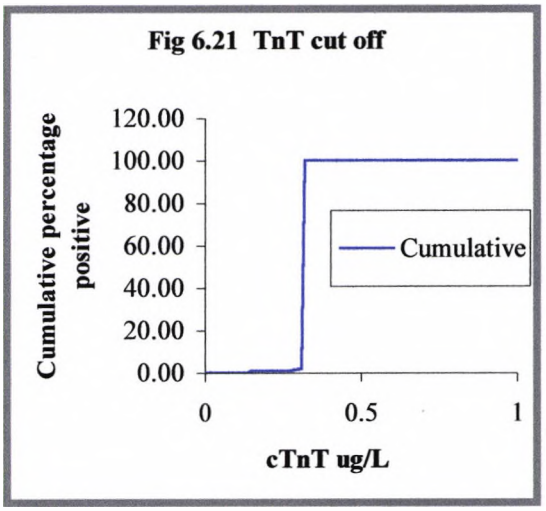
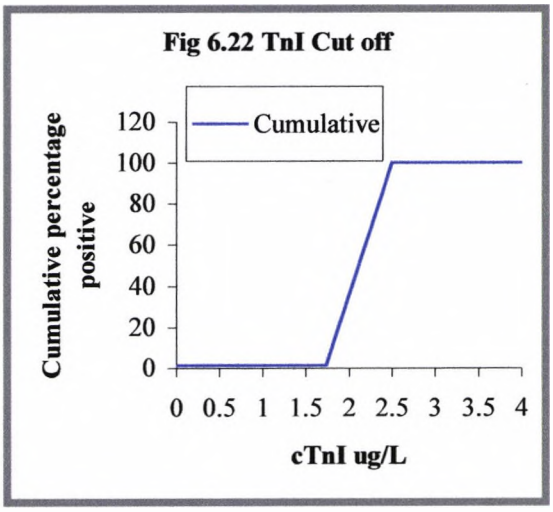


Fig 6.20 Qualitative TnI results compared to ACS:180



Secondly, cumulative percentage positive results against laboratory troponin values were plotted to examine the analytical diagnostic cut off point (Figs 6.21 & 6.22). For TnT the cut off was found to be 0.3 and for TnI 2.5.





Both the POCT devices were found to be 100% sensitive (number of acute myocardial infarctions (AMI) with positive result/total number of AMIs x 100) and the specificity (number of non-AMIs with negative result/total number of non-AMIs x 100) was also high, 84.2% for TnT and 82.5% for TnI. Comparison of the diagnostic accuracy of the two devices showed no significant differences for troponin positive results (Chi^2 0.0851, p = 0.9584) and troponin negative results (Chi^2 0.0078, p = 0.9961).

Additional data were also available from determinations of TnI on the Alpha Dx™ which were compared to those provided by analysis on an ACS:180™. The Passing & Bablok regression analysis (Fig 6.23) shows a large scatter of results between the two methods and the Altman & Bland plot (Fig 6.24) shows a proportional negative bias for the results produced from the Alpha Dx™ compared to the ACS:180™

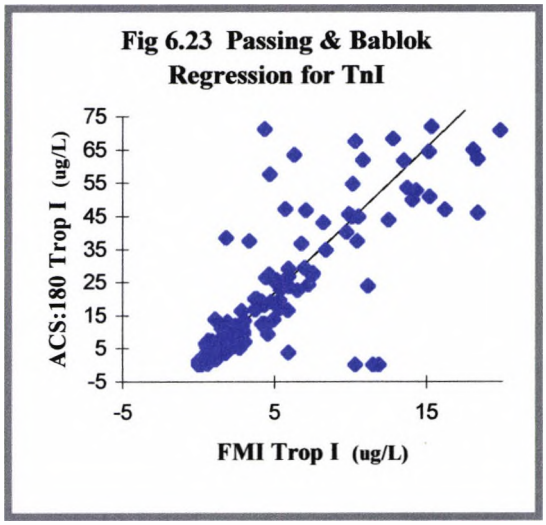


Fig 6.23 Passing & Bablok Regression for TnI

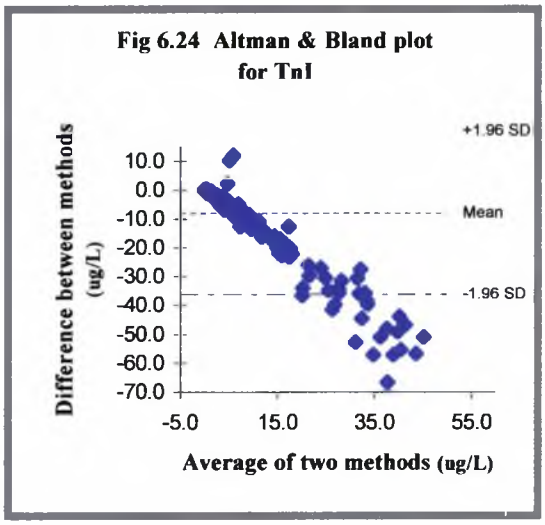


Fig 6.24 Altman & Bland plot for TnI

6.3 TURNAROUND TIME

The second objective concerned turnaround time (TAT) for delivery of results to the ward. Does analysis by POCT provide results significantly faster then the central laboratory? This was assessed by comparing the length of time taken to carry out the analysis. The TAT for POCT was measured from request order to test completion with a result displayed (or printed) by the analyser. The CLT TAT was measured from request order to the result being available on the laboratory computer system, which could be accessed via the ward-based terminals.

During phase 1, 402 electrolyte investigations were undertaken by CLT and 455 by the ITU POCT analyser. The TATs for the results of these tests were compared, and the data obtained summarised in Table 6.8. Time taken to obtain results by POCT was significantly faster than by the CLT. The maximum TAT for POCT was faster than the minimum time experienced by CLT.

Table 6.8 Turnaround Time for Na & K results

	All samples (mins)	
	TAT CLT	TAT POCT
n	402	455
minimum	21	5
25th percentile	55	5
median	70.5	5
75th percentile	91	5
maximum	277	10
	Mann Whitney U	
	U	0
	p	<0.0001

In the CCU, 334 samples were randomised to CLT and 332 to POCT for CK analysis in phase 1. However, 110 of the POCT samples were analysed by CLT instead. TAT was compared for the total number of CLT tests and for those randomised to CLT, with tests carried out by POC (Table 6.9). The POCT results were significantly faster than CLT, with 175 of the total number of tests (79%) taking less than 10 minutes to perform.

Table 6.9 Turnaround Time - CK Phase 1

	Total CLT tests (mins)	Randomised to CLT (mins)	POCT (mins)
n	444	334	222
minimum	18	18	5
25th percentile	52	51	7
median	69	69	7
75th percentile	98.5	98	10
maximum	1435	1435	68
		Mann Whitney U	
		Total CLT	Randomised to CLT
	U	1464	1150.5
	p	<0.0001	<0.0001

In the second phase of the ITU study, all samples randomised to POCT had parallel samples taken for analysis by CLT. A total of 136 samples were randomised to POCT, of which 108 were actually analysed, and 118 samples randomised to CLT. TAT was significantly faster for POCT than CLT both in the comparison with the randomised samples and those taken in parallel. The data are summarised in Table 6.10

Table 6.10 Turnaround Time - ITU phase 2

	Randomised to CLT (mins)	Parallel samples (mins)	
		CLT	POCT
n	118	108	108
minimum	21	27	35
25th percentile	187	192	85.5
median	206	206	115.5
75th percentile	220	223.5	150
maximum	495	316	210
		Mann Whitney U	
		Randomised to CLT	Parallel samples
	U	1869.5	1270.5
	p	<0.0001	<0.0001

Table 6.11 summarises the TAT data for both CK and TnT in CCU during phase 2. A total of 345 samples were measured by POCT (301 CK and 138 TnT), and 377 analysed by CLT (356 CK and 138 TnT). Of the CK samples 189 had parallel analysis carried out in the laboratory. Results for TAT are similar to CCU in phase 1 and to both phases of the ITU study in that POCT produces significantly faster results for CK and TnT analysis than CLT.

Table 6.11 Turnaround Time for CK & TnT

	All CK Samples (mins)		Parallel CK samples (mins)		TnT samples (mins)	
	CLT	POCT	CLT	POCT	CLT	POCT
n	356	301	189	189	138	138
minimum	20	20	25	20	25	20
25th percentile	45	22	71	22	51	20
median	72	22	136	22	79	20
75th percentile	108.5	25	290	25	110	22
maximum	1123	60	1368	38	1018	38
	Mann Whitney U		Mann Whitney U		Mann Whitney U	
	U	274	U	17	U	23
	p	<0.0001	*p*	<0.0001	*p*	<0.0001

This chapter aimed to provide data for the comparison of POCT technology involved in this study with the CLT methods. The analysers that were analytically validated proved to have varying degrees of accuracy compared to the laboratory methods, but were deemed suitable for use on the wards. In routine clinical use the trends observed during the analytical stage were accentuated, which highlights the importance of carrying out evaluations under routine conditions. TAT for POCT, as expected, proved to be significantly faster than the CLT per individual test. The next chapter contains the results of the clinical data collected during the trial, which aims to address the clinical impact of analysis using POCT technology.

CHAPTER 7 CLINICAL RESULTS

The previous chapter presented the results of the evaluation of point of care testing (POCT) technology used on the wards during the trial. This involved the assessment of analytical and clinical accuracy of the analysers, and turnaround time (TAT) for result availability, in comparison with central laboratory testing (CLT). This following chapter will be concerned with the clinical results obtained during the trial in order to test the clinical impact POCT had on patient management and outcome.

7.1 INTENSIVE THERAPY UNIT PHASE 1

7.1.1 Patient Population

Prior to carrying out data analysis on the clinical results obtained from the trial it was necessary to assess whether the patients randomised to testing by CLT or POCT, were from the same population. This would exclude population bias that might affect the assessment of clinical impact.

A total of 80 patients (47 CLT, 33 POCT) were enrolled onto the Intensive Therapy Unit (ITU) trial during phase 1 over a period of 8 months. As can be seen from the following tables, there was no significant difference in sex, ethnic group (Table 7.1), or age (Table 7.2) between those randomised to CLT or to POCT.

Table 7.1 Sex and Ethnic Groups – ITU phase 1

	Female	Male		Afro Caribbean	Caucasian	Asian
CLT	20	27	CLT	1	41	5
POCT	11	22	POCT	2	30	1
Fisher Exact Probability	two tailed		Chi^2	2.3254		
	p	0.5501	df	2		
			p	0.3126		

Table 7.2 Age - ITU phase 1

	Age (years) CLT	Age (years) POCT
n	47	33
minimum	17	28
25th percentile	51	54
median	66	67
75th percentile	76	76
maximum	86	86
	Mann Whitney U	
	U	767
	p	0.9338

Patients were assessed as to the reason for being admitted to ITU, either true admission for ITU management or planned post-operative recovery prior to return to a low dependency ward. In this study 64 patients were true ITU admissions (36 CLT and 28 POCT) and 16 were found to be post-operative recovery (11 CLT and 5 POCT). The distribution was not significantly different between the CLT and POCT groups: Fisher $p = 0.5376$ (two tailed).

On admission to the ITU the patients were evaluated, by the medical staff, for the severity of their condition and given an appropriate Acute Physiological and Chronic

Health Evaluation (APACHE) III score. This is a severity of disease classification that assigns a point score based on initial values of a number of physiological measurements, age and previous health etc. of the patient. No significant difference was observed in the APACHE III scores between the two groups (Table 7.3)

Table 7.3 Admission APACHE III - ITU phase 1

	APACHE CLT	APACHE POCT
n	47	33
minimum	14	8
25th percentile	35	31
median	57	66
75th percentile	75	82
maximum	111	113
	Mann Whitney U	
	U	713
	p	0.5411

7.1.2 Impact on Decision Making

Accuracy and fast turnaround time are important in the evaluation of POCT technology; however, the potential benefit to patient care over the service provided by the central laboratory will be assessed by the impact on patient management and outcome. In the ITU, clinical impact was measured by intensity of treatment, length of stay on the ward and in the hospital, and prognosis.

The intensity of treatment between the two groups was analysed by comparing the average Therapeutic Intervention Scoring System (TISS) for each patient. This

allows quantification of patient care by assigning a score to each intervention carried out, on a 1 – 4 basis, depending on the intensity of the treatment. Not all of the 80 patients in ITU had TISS scores recorded. Data were obtained from 75 subjects (Table 7.4). There was no significant difference between the CLT and POCT groups in terms of the intensity of their treatment. Although interventions were recorded during the study, none could be identified that occurred as a direct result of the POCT, except any unexpected abnormal results had a request for confirmation by CLT.

Table 7.4 TISS – ITU phase 1

	TISS CLT	TISS POCT
n	44	31
minimum	14.5	16
25th percentile	25	25.3
median	30.7	33
75th percentile	35.1	36.2
maximum	57.3	45
	Mann Whitney U	
	U	651.5
	p	0.7428

Three measures of length of stay (LOS) were analysed; the duration of stay on the unit (ITU stay): length of stay from step down from the unit to hospital discharge or patient death (non-ITU stay); and total hospital stay. Where there was no record of actual discharge time, a standardised time of 12:00 noon was used. Comparison of LOS data for the ITU showed no difference in ITU stay, non-ITU stay or total hospital stay between the two groups (Table 7.5)

Table 7.5 LOS Data - ITU phase 1

	ITU Stay (days)		Non-ITU Stay (days)		Hospital Stay (days)	
	CLT	POCT	CLT	POCT	CLT	POCT
n	47	33	47	33	47	33
minimum	0.67	0.67	0	0	1.2	0.67
25th percentile	2.1	1.8	0	0	7.6	3.9
median	3.9	4.9	10.1	5.6	14.4	17.5
75th percentile	7.6	12.7	24.8	30.1	30.0	48.7
maximum	34.2	65.4	165	95.9	172	101
	Mann Whitney U		Mann Whitney U		Mann Whitney U	
	U	738.5	U	723	U	757
	p	0.7176	*p*	0.6036	*P*	0.8565

The prognosis of the patients was assessed in terms of mortality of the patients during admission to the ward, while as an in-patient and 6 months after admission. No difference was observed between CLT and POCT. (Table 7.6)

Table 7.6 Mortality Rate - ITU phase 1

		Alive	Dead	Fisher	
ITU	CLT	37	10	*p*	0.9604
	POCT	25	8		
In Patient	CLT	34	13	*p*	0.2568
	POCT	19	14		
6 month follow up	CLT	32	15	*p*	0.1263
	POCT	16	17		

7.2 CORONARY CARE UNIT PHASE 1

7.2.1 Patient Population

A total of 199 patients (103 CLT, 96 POCT) were enrolled onto the Coronary Care Unit (CCU) trial in phase 1, 67 of these were female and 132 male. As can be seen in Tables 7.7 there was no significant difference between the CLT and POCT groups for sex or age.

Table 7.7 Age and Sex - CCU phase 1

	female	male		Age (years) CLT	Age (years) POCT
CLT	36	67	n	103	96
POCT	31	65	minimum	28	24
			25th percentile	51	52
Chi-square Test	Chi^2	0.0608	median	61	61
	df	1	75th percentile	72	70
	p	0.8052	maximum	85	88
			Mann Whitney U	U = 4855	*p* = 0.8265

Similarly, no significant difference was observed in their ethnic groups or previous heart related history (Table 7.8)

Table 7.8 Previous History and Ethnic Group – CCU phase 1

	Previous history	None		Afro Caribbean	Caucasian	Asian
CLT	51	52	CLT	3	82	18
POCT	47	49	POC	3	69	24
Chi^2	0.0062		Chi^2	1.7323		
df	1		df	2		
p	0.9375		*p*	0.4206		

Patients were categorised into four groups according to their final diagnosis as the reason for being admitted to the CCU. These were acute myocardial infarction (AMI), dysrhythmia, unstable angina (UA) and non-ischaemic chest pain (NICP). The occurrence of these categories in the CLT and POCT groups is shown in Table 7.9. No significant difference was observed.

Table 7.9 Patient Categories - CCU phase 1

	CLT	POCT	Chi Square Test	
AMI	57	52	Chi^2	2.8443
Dysrhythmia	5	1	df	3
UA	29	32	*p*	0.4163
NICP	12	11		

Patients admitted to the CCU typically have a history of chest pain. Admission to the ward will be to confirm this chest pain as an AMI and therefore appropriately manage, or to monitor the patient until a diagnosis is made. The time of chest pain onset and the time of the most recent episode of pain were recorded, as an indication of severity of the condition, and the data are summarised in Table 7.10.

Table 7.10 Duration of Chest Pain – CCU phase 1

	Pain from onset (hours)		Most recent episode (hours)	
	CLT	POCT	CLT	POCT
n	103	96	103	96
minimum	0	0	0	0
25^{th} percentile	3	2.8	2	1
median	5.3	5	3.4	3
75^{th} percentile	43.5	33.9	5.3	4.4
maximum	916	719	18.3	18.5

No significant difference between the CLT and POCT groups for the duration of pain since onset (Mann Whitney U test; U = 4621, p = 0.4262) was observed, however there was a difference in the duration of the most recent episode with those patients randomised to CLT having the longer period pain.(U = 4098, p = 0.0371).

7.2.2 Impact on Decision Making

Clinical impact of POCT on the CCU patients was measured by LOS and prognosis. In addition to the three measures of LOS described previously for the ITU, CCU patients were assessed according by intention to treat (ITT) analysis, which was the time at which a definitive management decision could have been made based on the CCU protocol (refer to Chapter 4 Study Organisation). Decisions were based on electrocardiogram (ECG), clinical progress, biochemical data and cardiological review. No difference in CCU, non-CCU or hospital stay was seen, however, ITT stay was significantly less in the POCT group (Table 7.11).

Table 7.11 LOS Data – CCU phase 1

	CCU Stay (hours)		Non-CCU Stay (hours)		Hospital Stay (hours)	
	CLT	POCT	CLT	POCT	CLT	POCT
n	103	96	103	96	103	96
minimum	5.8	6.1	0	0	5.8	20.1
25th percentile	36.8	39.4	48.5	93.4	123	132.1
median	60.3	53.6	137.1	150.7	193.3	214
75th percentile	90.7	79.5	259.8	298.1	336	382
maximum	269	209	740	1145	947	1208
	Mann Whitney U		Mann Whitney U		Mann Whitney U	
	U =4642	P = 0.4569	U = 4414	P = 0.1912	U = 4604	P = 0.403

Based on the ITT analysis, of the 84 patients in phase 1 who had a final diagnosis of UA or NICP, 43 patients (18 female, 25 male) were reviewed as ready for rapid discharge. This group was analysed to see whether there were any differences between those randomised to POCT or CLT. There were no significant differences in sex (Fisher p = 1.0), age and duration of pain (Table 7.12) or length of stay in CCU, non-CCU or hospital (Table 7.13). However, stay based on ITT was significantly less in the POCT group.

Table 7.12 Rapid Discharge Patients - CCU phase 1

	Age (years)		All pain (hrs)		Worst pain (hrs)	
	CLT	POCT	CLT	POCT	CLT	POCT
n	22	21	22	21	22	21
minimum	28	39	0	1.5	0	0
25th percentile	47	49	2.3	3.7	2	1
median	54	61	5.3	10.5	2.8	2.3
75th percentile	65	69	73.3	43.8	5.3	4.3
maximum	82	75	740	719	11.1	9.3
Mann Whitney U	U = 194	P = 0.3680	U = 203.5	P = 0.5039	U = 188	P = 0.2956

Table 7.13 LOS Data for Rapid Discharge Patients - CCU phase 1

	CCU Stay (hours)		Non-CCU Stay (hours)		Hospital Stay (hours)	
	CLT	POCT	CLT	POCT	CLT	POCT
n	22	21	22	21	22	21
minimum	12	6.1	0	0	15.5	23.8
25th percentile	23.4	22.3	48.5	34	85.8	114
median	35.2	43.1	141	109	224	150
75th percentile	71	69.3	262	235	336	304
maximum	143	105	621	929	729	950
Mann Whitney U	U = 227.5	p = 0.9322	U = 226	p = 0.9031	U = 224.5	p = 0.8745

Prognosis was assessed by readmission or mortality rates. On the six-month follow up there were 27 heart related readmissions (19 CLT, 12 POCT), however no significant difference was observed (Fisher p = 0.7778). Neither was there any significant difference in the mortality rates between POCT and CLT (Table 7.14).

Table 7.14 Mortality Rates – CCU phase 1

		Alive	Dead	Chi Square	
CCU	CLT	98	5	Chi^2	0.0673
	POCT	93	3	df	1
				p	0.7953
In Patient	CLT	92	11	Chi^2	0.1033
	POCT	88	8	df	1
				p	0.7499
6 month follow up	CLT	83	20	Chi^2	0.0162
	POCT	79	17	df	1
				p	0.8987

7.3 ITU PHASE 2

7.3.1 Patient Population

During the second phase of the study 61 patients (26 CLT, 35 POCT) were enrolled onto the ITU trial, of these 24 were female and 37 male. The distribution of age, sex and ethnic group between the CLT and POCT groups is summarised in tables 7.15 and 7.16. As with phase 1 there was no significant difference observed between the two groups.

Table 7.15 Age – ITU phase 2

	Age (years) CLT	Age (years) POCT
n	26	35
minimum	22	18
25th percentile	50	50
median	67	64
75th percentile	75	75
maximum	86	94
	Mann Whitney U	
	U	429
	p	0.7044

Table 7.16 Sex and Ethnicity – ITU phase 2

	Female	Male		Afro Caribbean	Caucasian	Asian
CLT	10	16	CLT	1	21	4
POCT	14	21	POCT	1	30	4
Fisher Exact Probability	two tailed		Chi^2	0.2662		
	p	1.00	df	2		
			p	0.8754		

43 patients (15 CLT, 28 POCT) were true ITU admissions and 18 (11 CLT, 7 POCT) were admitted for post-operative recovery. The distribution was not significantly different; Fisher $p = 0.1091$ (two tailed). Similarly, no difference was observed in the APACHE scores of the patients in phase 2 (Table 7.17).

Table 7.17 APACHE scores ITU phase 2

	APACHE CLT	APACHE POCT
n	26	35
minimum	19	16
25th percentile	68	45
median	75.5	66
75th percentile	89	97
maximum	124	176
	Mann Whitney U	
	U	409
	p	0.5022

7.3.2 Impact on Decision Making

During the trial it became progressively more difficult to perform the POCT in the ITU. This was mainly due to staff shortages and an unwillingness to take on duties additional to their already heavy schedule. On discussion with the ITU consultants a consistent opinion was expressed that no action was taken on the POCT results as patient review occurred daily at 11:00, by which time the CLT results were all available, and any unexpected results discovered by POCT had sufficient time for CLT confirmation prior to review. As a result the ITU study was discontinued and no further analysis was undertaken.

7.4 CCU PHASE 2

7.4.1 Patient Population

During phase 2, there was an even split between CLT (132) and POCT (131) in those patients who were enrolled for CCU. Of these 86 were female and 177 male. The distribution of age and sex is summarised in Table 7.18, and previous history and ethnic groups in Table 7.19. No significant differences were observed.

Table 7.18 Age and Sex - CCU phase 2

	female	male		Age (years) CLT	Age (years) POCT
CLT	47	85	n	132	131
POCT	39	92	minimum	27	38
			25th percentile	57	57
Chi-square Test	Chi^2	0.7694	median	65.5	64
	df	1	75th percentile	73	73
	p	0.3804	maximum	86	87
			Mann Whitney U	U = 8377	*p* = 0.6626

Table 7.19 Previous History and Ethnic Group – CCU phase 2

	IHD	MI	None		Afro Caribbean	Caucasian	Asian
CLT	31	41	60	CLT	3	109	20
POCT	31	35	65	POCT	2	110	19
Chi^2	0.6699			Chi^2	0.1962		
df	2			df	2		
p	0.7154			*p*	0.9066		

As in phase 1, the patients were categorised according to their final diagnosis (Table 7.20).

Table 7.20 Patient Categories - CCU phase 2

	CLT	POCT
AMI	62	81
Dysrhythmia	22	10
UA	38	31
NICP	10	9
	Chi Square Test	
	Chi^2	7.7836
	p	0.051

Duration of pain in the second phase of the CCU trial is summarised in Table 7.21. No significant difference was observed.

Table 7.21 Duration of Pain - CCU phase 2

	Pain since onset (hours)		Most recent episode (hours)	
	CLT	POCT	CLT	POCT
n	132	131	132	131
minimum	0	0	0	0
25^{th} percentile	2	2.7	1.5	1
median	5	6.5	3	3
75^{th} percentile	17.6	20	6	7
maximum	793	500	129	43.2
	Mann Whitney U		Mann Whitney U	
	U	8023.5	U	8548
	p	0.3127	*p*	0.8737

7.4.2 Impact on Decision Making

Length of stay for phase 2 in CCU was similar to phase 1 in that no differences were observed in the CCU, non-CCU or total hospital stay, but the ITT stay was significantly less in the POCT group (Table 7.22).

Table 7.22 Length of Stay CCU Phase 2

	CCU Stay (hours)		Non-CCU Stay (hours)		Hospital Stay (hours)	
	CLT	POCT	CLT	POCT	CLT	POCT
n	132	131	132	131	132	131
minimum	8.5	4.5	0	0	14.2	4.5
25th percentile	33.6	36.5	68.2	68	140	141
median	48.4	42.2	162.2	136	217	202
75th percentile	70.7	70.3	271.3	253	325	313
maximum	202	373	1700	1093	1808	1219
	Mann Whitney U		Mann Whitney U		Mann Whitney U	
	U	8244	U	8096.5	U	8177.5
	p	0.5145	*p*	0.3727	*p*	0.4475

As in phase 1, ITT analysis identified a group of patients for rapid discharge. 96 patients had a final diagnosis of UA or NICP; of these 66 patients met the rapid discharge criteria. The data are summarised in Tables 7.23 and 7.24. No significant differences were observed in sex (Fisher $p = 0.6696$), age, duration of pain or length of CCU stay. However, there was a significantly shorter stay in the POCT group for non-CCU, total hospital and ITT stay.

Table 7.23 Rapid Discharge Patients - CCU phase 2

	Age (years)		All pain (hrs)		Worst pain (hrs)	
	CLT	POCT	CLT	POCT	CLT	POCT
n	34	32	34	32	34	32
minimum	41	39	0	0	0	0
25th percentile	54	51.5	1.7	0.7	1.5	0.37
median	63.5	63.5	3.5	5.1	2.5	2.4
75th percentile	73	72.5	12.5	27.2	4.5	7
maximum	83	85	203	459	129	43.5
Mann Whitney U	U = 533	p = 0.8877	U = 535.5	p = 0.913	U = 524	p = 0.797

Table 7.24 LOS Data for Rapid Discharge Patients - CCU phase 2

	CCU Stay (hours)		Non-CCU Stay (hours)		Hospital Stay (hours)	
	CLT	POCT	CLT	POCT	CLT	POCT
n	34	32	34	32	34	32
minimum	9.5	10.3	0	0	18.5	30
25th percentile	24	30.8	48.4	27.8	143	87.9
median	39.4	51.1	145	79.8	209	149
75th percentile	64	74.6	305	146	323	187
maximum	164	146	914	325	927	356
Mann Whitney U	U = 443	P = 0.195	U = 392	P = 0.05	U = 370	P = 0.0256

Follow up studies found 66/263 patients (34 CLT, 32 POCT) were readmitted for cardiac related problems and 29 patients (10 CLT, 19 POCT) had a Percutaneous Transluminal Coronary Angioplasty (PTCA) or a Coronary Artery Bypass Graft (CABG). Analysis by Fisher exact probability test showed a significant difference

in both cases (readmissions p = 0.0191, procedures p = 0.0385). However, no difference was found in mortality rates (Table 7.25).

Table 7.25 Mortality Rates - CCU phase 2

		Alive	Dead	Chi Square	
CCU	CLT	131	1	Chi^2	0.8311
	POCT	127	4	df	1
				p	0.3620
In Patient	CLT	128	4	Chi^2	0.8100
	POCT	123	8	df	1
				p	0.3681
6 month follow up	CLT	119	13	Chi^2	0.1726
	POCT	115	16	df	1
				p	0.6778

This chapter aimed to present the data obtained during the trial, which would assess the clinical impact of blood analysis using POCT technology. No difference was observed in the patient population between the two groups and, therefore, any differences observed in patient management or outcome would be attributable to the site of analysis. Little or no difference was found in patient management, which was assessed by the comparison of LOS between patients assigned to POCT or CLT. The following chapter provides data on the operational impact by assessing the cost of POCT provision compared to the CLT.

CHAPTER 8 RESULTS OF COST ANALYSIS

The previous chapter was concerned with the clinical results obtained during the trial that would provide information to assess the clinical impact of point of care testing (POCT) on patient care. The operational impact of POCT was assessed by the cost of POCT implementation and the use of the analysers while in routine operation. This chapter presents the cost analysis data comparing POCT expenditure with central laboratory testing (CLT). The cost analysis was carried out for Coronary Care Unit (CCU) only, as the Intensive Care Unit (ITU) arm of the trial was prematurely terminated.

Test costs were calculated from semi-fixed costs of labour and maintenance, plus the variable costs of reagents and other consumables. Labour costs were based on 10 minutes per request using the mid point of the pay scales, and maintenance and variable costs were obtained from budgetary information. During phase 1 of the study 199 patients were admitted over a period of 8 months (103 CLT, 96 POCT). Utilising the workload figures obtained during the project an extra annual cost of £2,790.00 is incurred at if all testing is carried out by POCT (Table 8.1).

Table 8.1 Test Costs (£) - Phase 1

	Per Test			CLT	POCT
	CLT	POCT			
Semi-fixed	1.65	2.69	Test cost per patient (3xCK)	6.60	15.90
Variable	0.55	2.61	Total Test costs (over trial period)	679.80	1,526.40
Total	2.20	5.30	Annual *	1,980.00	4,770.00

* Annual cost for all analysis carried out at each site assuming 300 patients admitted over 12 months.

Opportunity costs, saving in bed days, should offset the additional cost incurred by POCT. Two cost models were prepared to demonstrate this. The first was based on actual length of stay (LOS) encountered during the study and the second model based on the early discharge group identified by the intention to treat (ITT) analysis. In both cases the mean LOS was used and the bed costs, at time of the trial, were as follows-

CCU bed - £405

General ward bed - £163

The first model calculated the total costs incurred during the study for all patients enrolled in the study (Table 8.2). A difference of £189.89 per patient was found in favour of CLT.

Table 8.2 Cost of Hospital Stay - Phase 1

	LOS (days)		Hosp Cost (£)		Total inc Tests (£)	
	CCU	Non-CCU	CCU	Non-CCU	Total	Per patient
CLT (n = 103)	2.96	7.6	123,476.40	127,596.40	251,752.60	2,444.20
POCT (n = 96)	2.77	9.18	107,697.60	143,648.64	252,872.64	2,634.09
			Difference		-1120.04	-189.89

A second model was prepared for those patients suitable for early discharge. A saving of £17.47 per patient was found for the 43 patients (22 CLT, 21 POCT) in this group (Table 8.3).

Table 8.3 Cost of Hospital Stay in early discharge group – Phase 1

	LOS (days)		Hosp Cost (£)		Total inc Tests (£)	
	CCU	Non CCU	CCU	Non-CCU	Total	Per patient
CLT (n = 22)	2.16	7.69	19,245.60	27,576.34	46,967.14	2,134.87
POCT (n = 21)	2.11	7.65	17,945.55	26,185.93	44,465.38	2,117.40
			Difference		2,501.76	17.47

Although the ITT data was based on when the time when sufficient results were available for the decision to discharge low risk patients to be made it is theoretically possible for the results to be available by POCT within 24 hours (the time to carry out the required tests according to the protocol), therefore these early discharge patients could be moved after only a day on CCU. This would result in a further 53% saving on the CCU bed costs, a total saving of £19,776.15 if all tests carried out by POCT. This theoretical data is summarised in Table 8.4.

Table 8.4 Theoretical CCU bed costs – phase 1

	LOS (days)	Cost (£)	LOS (days)	Cost (£)	Difference
CLT (n = 22)	1	8,910	2.16	19,245.60	10,325.60
POCT (n = 21)	1	8,505	2.11	17,945.55	9,440.55
Total (n = 33)		17,415		37,191.15	19,776.15

Cost analysis was carried out for phase 2 based on the same budgetary information as in phase 1. 263 patients (132 CLT, 131 POCT) were randomised during this phase and costs calculated accordingly. CK costs are the same as phase 1, however, phase 2 also included Troponin analysis (Table 8.5).

Table 8.5 Test Costs (£) - Phase 2

		CLT		POCT	
		CK	TnT	CK	TnT
Costs	Semi-fixed	1.65	1.65	2.69	2.69
	Variable	0.55	3.80	2.61	6.60
	Total	2.20	5.45	5.30	9.29

As can be seen from Table 8.6 POCT costs are much higher than CLT, with an additional cost of £3,977.84 being incurred if all tests are carried out by POCT.

Table 8.6 Patient Costs (£) – Phase 2

	2 CKs plus 1 TnT	
	CLT	POCT
Test Cost per patient	9.85	19.89
Total Test Cost (during trial period)	1,300.20	2,605.59
Annual *	3,900.60	7,876.44

* Annual cost for all analysis carried out at each site assuming 396 patients admitted over 12-month period

Similarly to phase 1, two models for hospital costs were prepared. In Table 8.7 the cost of total hospital stay incurred by all the patients enrolled in the study are shown. A saving of more than £17,000 was found in the POCT group over the course of the study.

Table 8.7 Cost of Hospital Stay - Phase 2

	Length of Stay (days)		Hosp Cost (£)		Total inc Tests (£)	
	CCU	Non-CCU	CCU	Non-CCU	Total	Per Patient
CLT (n = 132)	2.44	8.73	130,442.40	187,834.68	319,577.28	2,421.04
POCT (n = 131)	2.63	7.49	139,534.65	159,933.97	302,074.21	2,305.91
			Difference		17,503.07	115.13

The potential savings were increased when looking at the second cost model (Table 8.8). A saving of over £24,000 was found in the POCT group in the patients suitable for early discharge.

Table 8.8 Total Hospital Cost for Early Discharge group – Phase 2

	Length of Stay (days)		Hosp Cost (£)		Total inc Tests (£)	
	CCU	Non-CCU	CCU	Non-CCU	Total	Per Patient
CLT (n = 34)	2.12	8.64	29,192.40	47,882.88	77,410.18	2,276.77
POCT (n = 32)	2.36	4.10	30,585.60	21,385.60	52,607.68	1,643.99
			Difference		24,802.50	632.78

Like phase 1, if the early discharge patient group could be discharged from CCU when the results by POCT should be available (within 24 hours) a similar further saving of 55% for CCU costs could be made (Table 8.9).

Table 8.9 Theoretical CCU bed costs – phase 2

	LOS (days)	Cost (£)	LOS (days)	Cost (£)	Difference
CLT (n = 34)	1	13,770	2.12	29,192.40	15,422.40
POCT (n = 32)	1	12,960	2.36	30,585.60	17,625.60
Total (n = 66)		26,730		59,778	33,048

This chapter aimed to outline the costs involved in providing analysis by POCT. Although the cost of tests at the POCT is significantly greater than for the CLT, savings can be made on the total hospital costs by taking into account the length of stay on the high dependency ward. A greater saving would be observed if patients were discharged earlier on the basis of the ITT data, however in phase 2, the data for all patients also showed a substantial saving, on the basis of bed costs, in the POCT group. In the following chapter a critical discussion of these results and those of the previous two chapters will be presented.

CHAPTER 9 DISCUSSION

The premise behind this study was the need to fully evaluate the use of point of care technology. With many more instruments becoming available for use outside the laboratory, evaluation of their impact on healthcare is essential to ensure appropriate utilisation of available resources. The study aimed to assess whether biochemical analysis by point of care testing (POCT) in real time operation was sufficiently accurate and resulted in patient management and outcome superior to that provided by central laboratory testing (CLT). From a review of the current literature it is clear there is a great interest in POCT. Most focus on the technologies and instruments available and their analytical accuracy, and the reduction in turnaround time for results. Few assess the impact on patient management and outcome.

In this chapter a critical examination of the study findings will be undertaken. Initially, it will begin by discussing the systematic approach required in the assessment of the inter-connected factors of POCT to ensure the suitability and necessity for its implementation. Specific results obtained during the trial will also be discussed in more depth, which will highlight the particular requirements and problems encountered at the study site. Information gained from this study will provide knowledge enabling the future assessment of POCT to be undertaken in an appropriate and comprehensive way prior to its implementation.

9.1 SYSTEMATIC APPROACH TO POCT

Although there is no documented evidence to support this case, POCT has often been seen as a 'good idea' and has been implemented by the clinicians without collaboration with the central laboratory, or indeed been imposed by the laboratory. A thorough evaluation is essential to prove the technology is reliable and to ensure the legal implications of its use are taken into account. Implementation of POCT requires a systematic approach to ascertain its suitability for use, and any benefit that it may provide to patient care. This assessment of the suitability of POCT must be carried out in 'real time' by the personnel who will ultimately be using the technology, and in the setting for which it is intended. Furthermore, the assessment must be a comparison with the central laboratory to ascertain whether it provides any benefit to healthcare over the existing service. In order to achieve this, the study was run by taking a systematic approach to the assessment of POCT followed by a prospective randomised trial where the routine clinical use of POCT was compared with the laboratory. The results of the analysis and the effect they had on patient management were compared with testing in the central laboratory.

The rationale behind a prospective randomised trial is that it would allow analysis of the actual affect of POCT on patient care, as decisions would be taken on the basis of the POCT results. Patients on admission were randomly selected for POCT or CLT over a period of nine months. The POCT results were available to the clinicians and therefore a direct comparison with the laboratory could be achieved. A similar study carried out in the accident and emergency (A&E) department compared the effect of POCT results with the CLT (Parvin et al, 1996). The study was segmented into three

study periods where, in the first biochemical results were available from the central laboratory; in the second some results were exclusively provided by POCT, and in the final period the testing reverted back to the central laboratory. No direct comparison was achieved as POCT and CLT was carried out at separate times. Another prospective study was carried out to assess the accuracy of a POCT analyser for use in intensive care (Salem et al, 1991). The study concluded the analyser was accurate both in the laboratory and in its intended setting; however the results were not available to the clinicians and, therefore, the effect on patient management could not be assessed. Other prospective studies have been observational. In Kilgore's study an observer recorded the time taken to process requests for biochemical analysis from the CLT, satellite laboratory and POCT instruments (Kilgore et al, 1998). A questionnaire was circulated to those users to obtain views on each testing site for turnaround time, accuracy, ease of use, etc. Tsai et al employed a research assistant to question the A&E clinicians for their opinion regarding possible earlier availability of results (Tsai et al, 1994). Neither study was able to provide actual evidence for improvement to patient care from POCT as the data was based on supposition and not fact. This study aimed to look at actual effect of the POCT in 'real time'.

During the study non-laboratory trained personnel carried out the analysis by POCT. The nurses on the wards were fully trained in the operation of the analysers prior to the start, and further training was given as necessary. Non-laboratory trained personnel are not as experienced in the correct procedures required for accurate blood analysis and a greater number of operators, all with differing abilities, will use the instruments. Therefore, the performance of the analysers when used by these

operators will indicate their suitability for clinical use. Many studies investigating the accuracy of POCT analysers are undertaken using laboratory staff to carry out the analysis and as expected these studies provide data to conclude their suitability, but do not evaluate the instruments in routine use (Horder et al, 1991; Romer et al, 1992; Fleisher & Schwartz, 1995). Zaloga clearly believes accuracy evaluations should be carried out by the personnel who will ultimately be using the instruments and for this evaluation to take place in the intended setting (Zaloga et al, 1993; Zaloga et al, 1996). In his studies Zaloga concludes the analysers are accurate under these conditions. Nichols conducted a study into the accuracy of four glucose meters, both in the laboratory and at the bedside using nursing staff (Nichols et al, 1995). A greater variance in results was reported from the bedside evaluation, in particular one operator performed poorly. Once this operator's results were removed from the data set the variance improved considerably, indicating the ability of the operator is important. A brief study, as part of a larger evaluation, also indicated that the accuracy of the Reflotron was dependent on operator skill (Romer et al, 1992). However, in Romer's study they did not validate the analysers with laboratory staff first to establish a base line, it is therefore difficult to conclude whether the problems experienced with the analysis are attributable to the analytical method or in fact the ability of the personnel. This study evaluated the analytical accuracy by using laboratory staff to carry out the analysis, and then the clinical accuracy was assessed by comparison of results obtained by nursing staff with those from the laboratory.

Clinical decisions during the trial were to be made on the basis of POCT results. Therefore the initial step in this systematic approach was the evaluation of the instruments analytical accuracy to assess their suitability for use, and their clinical

accuracy during the trial compared to the CLT methods. The central laboratory provides the 'gold standard' when comparing results obtained from POCT. Healthcare professionals and patients alike will want to be confident that POCT provides reliable results on which clinical decisions can be based. Therefore, the first objective of this study involved the evaluation of the analysers' accuracy, both in the laboratory and while in routine clinical use.

The study was set in a critical care environment as timely results are often a requirement for critically ill patients and POCT may therefore prove desirable. Two different sites were assessed simultaneously to ascertain whether all sites, given the assumed need for POCT, actually require such technology. Information obtained from an A&E study cannot be transferred to the Coronary Care Unit (CCU), as the testing requirements are not the same. A&E requires a much broader spectrum of analyses. Similarly, hospital catchment areas are not homogenous; therefore the analysers need to be assessed in the local site to ensure relevance to the case mix of the hospital population. This study evaluated the technology and its effect on patient care in its intended setting. In the CCU cardiac marker analysis was available, the clinicians and nursing staff were enthusiastic about carrying out their own tests, especially when they could obtain results out of hours and at the weekends when the laboratory did not provide these tests. In the Intensive Therapy Unit (ITU) however, the nursing staff found their already busy schedule made POCT difficult and were happier for the laboratory to carry out the tests providing the results were available for the morning ward review. Additionally, U&Es (sodium, potassium, urea and creatinine) were available out of hours from the laboratory for urgent analysis as required.

The first step in the systematic approach to POCT was the assessment of the reliability of the analysers. A laboratory based analytical comparison was undertaken to assess the methodological differences and provide a baseline of the analysers' performance. Accuracy of particular analysers is often demonstrated in various studies. The i-STAT™ is an example of new technology that has been assessed on numerous occasions, some under laboratory conditions and others using non-laboratory personnel (Erickson & Wilding, 1993; Herr et al, 1995; Murthy et al, 1997). Once the analytical accuracy has been established, it is the analysers' performance during routine clinical use that is ultimately important.

The second part of the accuracy evaluation was a clinical comparison while the CCU and ITU nursing staff were operating the analysers on a day-to-day basis. Parvin's study of the impact of POCT in the A&E department evaluated the POC analyser's accuracy in the laboratory and while in routine clinical use (Parvin et al, 1996). The analyser proved to be comparable when tested in the laboratory, but not so in routine use. The measurement of haematocrit had to be terminated, as the results were markedly different to the laboratory results. Other tests showed greater variability, though all except glucose correlated well.

Six POCT systems were used during the course of this study, three of which underwent analytical validation, to ensure their suitability, with varying results. Measurement of potassium ion concentration using the blood gas analyser during phase 1 and some of the Piccolo methods in phase 2 on ITU proved to be significantly different from the laboratory methods, whereas creatine kinase (CK)

measured on the Reflotron in phase 1 compared well. The reasons for not carrying out validations for the other systems are explained below –

- CK analysis was not initially considered as part of the study in the second phase. However, the Alpha Dx™ was supplied as part of an ongoing trial and the clinical comparisons already undertaken were considered suitable for the basis of its analytical accuracy.
- The troponin T (TnT) dry chemistry sticks had previously been evaluated as part of a multicentre trial undertaken at this hospital (Collinson et al, 1996).
- Troponin I (TnI) was being compared directly with the TnT method, and was not offered by the central laboratory.

The decision to accept the manufacturer's method comparison data for the Alpha Dx™ highlighted the need to carry out comparisons even when previous evaluations have been done. The analyser did not perform as well as predicted by the company, the results were significantly different from the laboratory results, although the method did show diagnostic equivalence. The troponin methods, however, did perform as expected.

So the POCT analysers show varying degrees of comparability with the laboratory methods, but how accurate do they need to be? CKs were comparable in the first phase but statistically different in phase two. Both phases produced lower results requiring an altered range of 0 – 160 IU/l compared to 0 – 200 IU/l for the laboratory. However, according to the WHO criteria, 2 times the upper limit of normal is characteristic of an acute myocardial infarction (AMI), therefore a raised

result of greater than 400 IU/l will be indicative regardless of analyser and greater than 320 IU/l when measured on the POCT instruments. Normal potassium concentrations fall into a much narrower range, and more importantly, small deviations outside this range produce critically abnormal states. The accuracy of potassium results is, therefore, far more critical.

Once suitability had been established the next step in this study was to assess the turnaround time (TAT) for the results. Biochemistry results need to reflect the current status of the patient and delays may render the results clinically irrelevant. Timing is of course more critical with analytes for which the concentration can change quickly in the blood. For example blood glucose concentration guide insulin administration, but as the concentration constantly change a delay will diminish the usefulness of a result (Watts, 1995).

Establishing whether POCT is significantly faster than the CLT will depend on the definition of TAT and whether the definition is measurable. This study measured CLT TAT from blood collection to result availability on the ward terminals. The POCT TAT was from collection to result display on the analyser. POCT results were available significantly faster than the CLT in both phases and at both sites. However, this definition does not measure the time from result availability to review by a clinician. Unlike data obtained from computer audit trails, time to review results is difficult to accurately measure. Tsai employed an observer to record the time from result availability to review for CLT results, however the same was not recorded for POCT, as results were not available for the clinicians (Tsai et al, 1994). Kilgore also had an observer recording steps with a stopwatch from result

availability to review but as results did not always require any decision this was difficult to assess (Kilgore et al, 1998). The assumption that POCT results will be reviewed as soon as available whereas CLT results have to wait cannot be made. This will be dependent on the protocol for result review. In the CCU a specific protocol allowed for decisions to be made, on the basis of results, by the nurses as well as clinicians (refer to CCU Protocol, Chapter 4), whereas in the ITU the results were reviewed on the daily ward round by the clinicians, or when they were alerted to abnormal or unexpected results.

The next stage in the evaluation was the assessment of the impact POCT would have on patient management and outcome. To assess this the POCT results were available for clinical review and all patients entering the ward during the nine-month study period were enrolled in the trial. Other studies have collected data over shorter periods, or selected the times during which data will be collected (Saxena & Wong, 1993; Winkleman et al, 1994). Any impact POCT has on patient care makes two assumptions; that the tests are needed and that the biochemistry tests are the rate-limiting step in clinical decision-making.

This study was set in two critical care sites to assess the need for POCT. Tests selected for use by POCT have to be relevant to the patient population of the setting in which they will be used, such as blood gas measurement on wards where the patients are on ventilation, or cardiac markers in coronary care where acute coronary syndromes (ACS) are suspected. Blood gas analysis was initially considered as part of this study along with the measurement of electrolytes, but research undertaken prior to the start indicated problems with transporting gas samples through the

pneumatic tube system linking ITU to the laboratory (Collinson et al; in press). In phase 2 ITU was provided with an analyser to measure a biochemical profile, which included urea, creatinine, calcium and liver function tests (LFT). Protocols on the ITU required LFTs to be assayed only twice a week, as levels in the blood do not rapidly alter. Other tests, such as amylase and cholesterol are not required on a day-to-day basis, and glucose was measured on an existing POCT analyser. That left four tests (calcium, albumin, urea and creatinine) out of a possible eleven that were of use to the ITU, however, calcium and albumin did not correlate well with the central laboratory. In practice the test profile required by the ITU, which would include sodium and potassium, is not actually compatible with the one offered by the Piccolo™. Alternative instrumentation would need to be evaluated which would provide a suitable profile of tests.

In CCU rapid biochemical analysis will help in the diagnosis of ACS. A combination of cardiac markers such as CK and TnT used in the second phase of this study, available at the bedside might benefit the decision making process. Other markers are also available on POCT devices. Myoglobin and CK-MB, for example are included in the cardiac profile provided by the Alpha Dx (Miller et al, 1998), and are also available as dry chemistry tests (Muller-Bardorff et al, 1999). Such tests would only be relevant where ACS are suspected, such as in CCU. In this particular ITU results are reviewed at a ward round at 11:00, and no evidence was found that results were reviewed any earlier. In ITU in this study TAT was not as important as accuracy and consistency. In A&E decisions can be delayed while waiting for other tests or beds to be available (Parvin et al, 1996). Similarly, in this study CCU

patients for step down to a lower dependency ward or discharge home had to wait for a bed to become available.

The actual impact of POCT on patient management and outcome was assessed by comparing the length of stay (LOS) on the critical care wards and the total hospital stay, morbidity and mortality rates between patients assigned to POCT and those whose testing was solely carried out in the central laboratory. It proved to be difficult to document whether interventions were undertaken on the basis of particular results, therefore, LOS was evaluated as the main measure of patient management. The assumption being if results are provided earlier clinical decisions and management changes will be faster and this will have a knock on effect on LOS. Retrospective analysis has indicated that if results can be available earlier then the LOS in A&E could be improved (Tsai et al, 1994). However, it is important for information to be based on fact and not supposition. A prospective study into the affect of POCT on LOS in an A&E department appears to agree with Tsai's findings (Parvin et al 1996). It does also concede, however, that the biochemical tests are not the rate-limiting factor.

The last step in this systematic approach into the impact of POCT is cost analysis. If POCT proves to be beneficial to patient management, the final decision for its implementation will be financially driven. The technology needs to be cost effective. Two measures of cost were analysed in this study. Firstly, test costs were assessed, which included the cost of labour and consumables. It is important to compare the same data for both POCT and CLT to give an accurate comparison and avoid bias. A cost analysis study of glucose testing found CLT to be considerably

more expensive than POCT. However, while labour and instruments were taken into account for the CLT, POCT costs were based only on reagents (Zaloga, 1990). Variable costs are generally higher for POCT than for CLT largely due to the lower workload, making test costs for POCT considerably higher. Therefore, the second cost data analysed in this study was the total cost to the hospital, taking the LOS data into account. Critical care beds are more expensive than general ward beds due to the intensity of the treatment required. Therefore, if LOS is reduced by provision of POCT then total hospital costs may also be reduced. Other studies have not taken hospital costs into account, but relied on tests costs only to assess the financial considerations of POCT.

9.2 EVALUATION OF THE TECHNOLOGY

9.2.1 Accuracy

The analytical and clinical accuracy of the technology used in this study was compared to the central laboratory methods. In practice three of the six POC systems underwent analytical validation; CK analysis on the Reflotron™ in CCU; the electrolyte measurement on the ITU gas machine; and the full biochemical profile on the Piccolo™. All the systems underwent clinical validation during the trial.

The results obtained from the analytical comparison of CK showed good agreement with the laboratory method. The results were slightly lower by POCT, but did not show a statistically significant difference. Similar findings were reported in other

studies (Horder et al, 1991; Romer et al, 1992). The electrolyte measurements on the gas machine in ITU proved to have a mixed response in the analytical accuracy comparisons. Sodium showed no significant differences compared to the CLT values, whereas potassium values were significantly lower on the POCT analyser, requiring an altered reference range for use in the ITU. Other studies have demonstrated electrolytes on POCT analysers compare well with the laboratory methods, however, none specifically compared the analyser used in this study. Finally, the extended biochemical profile assayed on the Piccolo™ in ITU showed good analytical comparison for those tests where the methods were similar. Statistically different results were observed for albumin, alkaline phosphatase (ALP), calcium and creatinine. A conversion factor was provided for these tests to allow the same reference ranges to be used for both POCT and CLT.

In routine clinical use some of the POCT measurements showed greater discrepancies from the CLT methods. Potassium results were again significantly lower by POCT, even accounting for altered reference range, and although not statistically different, sodium results were also more variable than in the analytical validation. The different sample matrix and blood collection site used for POCT and CLT sites could explain the poor comparison. The measurement of electrolytes in whole blood plasma obtained from an arterial line does not compare well with venous serum. Serum produces higher potassium values than whole blood, due to the hydrogen ion buffering capacities of the different matrices, serum and plasma (Fogh-Anderson et al, 1984). A difference is also observed between arterial and venous samples, an altered reference range is required when using arterial plasma (Ward et al, 1978).

Mixed comparisons were observed for the Piccolo™ during routine clinical use. Urea and bilirubin compared well with the laboratory methods and ALP and creatinine showed an improvement, however, there were marked discrepancies with albumin and calcium, much greater than was observed in the analytical validation. The differences in the methodology used for POCT and CLT can explain the poor comparison, while the increased numbers of samples collected during routine use highlights the trend seen in the analytical stage. In practice the use of conversion factors, although allowing the use of the same reference ranges as the CLT, may in itself cause problems by creating a stage where error can occur.

Measurement of CK on the Reflotron™ during routine clinical use compared well with the laboratory. A similar scatter of results was observed as for the analytical validation stage. Receiver operator curve (ROC) analysis demonstrated that the POCT method showed diagnostic equivalence with the central laboratory method. This can be explained due to the similar methodology employed by both assays, based on the colorimetric measurement of CK activity. This finding agreed with another study of CK analysis using the Reflotron™, though they found a greater variability of CK results during routine use (Horder et al, 1991). Although CK measured on the Alpha Dx™ was not initially considered, their availability as part of an ongoing trial presented this study with further analytical data. During routine use the Alpha Dx™ did not compare with the laboratory as well as expected. The manufacturers had suggested a detection limit up to 1400 µg/l, however, during the trial it became clear that the results were only linear to 1000 µg/l, but although the correlation to this limit was better the methods were still statistically different. The difference is possibly due to the method differences, unlike the Reflotron™, the

Alpha Dx™ employs a fluorescent immunoassay for the measurement of CK, which is different to the laboratory method. However, as the analytical accuracy was not assessed, it cannot be ascertained whether the poor comparison can be attributed to this methodological difference or to the analysis being carried out by non-laboratory personnel. In addition, although the results correlated well, the difference between mass and activity for CK analysis may have a direct affect on the comparison. However, while the CK results obtained by the POCT analyser were statistically different to the laboratory results, the two methods did show diagnostic equivalence. According to the WHO criteria an increase of two times the upper limit of normal for CK measurement is indicative of a possible AMI, it is the result relative to the reference range which is important in the diagnosis, therefore providing the source of the result is recorded, its diagnostic ability will be the same. Once the results approach the linearity limit of the analyser they are clearly raised and will indicate an AMI.

The measurement of cardiac TnT by the POCT qualitative device showed diagnostic equivalence to the CLT method. It yielded an analytical cut off corresponding to 0.3μg/l. A previous multicentre study of the cardiac TnT stick also found 100% analytical sensitivity at a cut off of 0.3μg/l (Collinson et al, 1996). In this study 8 patients fell in the range 0.1 – 0.3 μg/l all with a final diagnosis of either unstable angina (UA) or dysrhythmia. The recommended cut off for the diagnosis of UA is 0.1μg/l (Lindahl et al, 1996; Collinson, 1998). A subsequent new generation assay has reportedly improved the cut off to 0.1μg/l and the dry chemistry sticks can now be read quantitatively over the range 0 – 3.0μg/l on a Cardiac Reader™ (Muller-Bardorff et al, 1999). No problem arises in the comparison between POCT and CLT

for the analysis of TnT as both sites use the same methodology and antibodies. Due to patent rights one manufacturer markets all commercial assays for the determination of TnT. The POCT method is simply a dry chemistry version of the CLT method.

The story is completely different for TnI measurements. There is a lack of standardisation between the various assays available which is problematic when comparing the methods. The analytical cut off for the POCT TnI was found to be 2.5µg/l compared to the ACS:180™ and 0.35µg/l for the Alpha Dx™. Unlike TnT there are a variety of differing methods available for the measurement of TnI. Direct comparison of the Alpha DX™ with the ACS:180™ showed a good correlation, but there was a marked difference in the values. As more TnI methods are developed the situation will only become more complicated. Findings for one assay cannot be easily extrapolated to another unless calibrated to give equivalent results and have a comparable analytical performance at the same clinical decision level.

Both the POCT devices for TnT and TnI were 100% sensitive. The specificity of the methods was also similar, 84.2% for TnT and 82.5 % for TnI. This can be explained by the time samples were taken relative to the cardiac event. Samples for troponin analysis were drawn between 12 and 24 hours post-admission to CCU. Patients would have been admitted via A&E therefore a delay would be inevitable prior to sample draw. Concentrations of troponin would be increased by 12 hours post-admission to CCU if an AMI had occurred. The decision regarding the diagnosis or rule out of an AMI are made on the basis of biochemical results as part of the CCU

protocol (Fig 4.1). Therefore it is important for POCT results to be as accurate as possible and for their diagnostic ability to be equivalent to that produced by CLT.

When POCT is to be implemented the analytical and clinical accuracy need to be assessed. This is particularly necessary when the methodology is not the same, to avoid any confusion, which may arise due to the use of different reference ranges or cut off points. The different methods and sample types used in this study proved incompatible for potassium, albumin and calcium, and for potassium particularly this would cause problems when reviewing the patients' results. The qualitative analysis proved to have diagnostic equivalence with the TnT method, though the Alpha Dx™ did not compare favourably with the laboratory method. The level of accuracy for POCT needs to be assessed as well. CK was statistically different on the Alpha Dx™ however, clinically they were suitable for use.

9.2.2 TAT

It is generally expected that POCT would produce a shorter TAT than CLT, based on the perception that the length of a POCT assay is always shorter. In this study while the analysis of electrolytes and CK (Reflotron™) by POCT took 20 seconds and 3 minutes respectively compared to 12 minutes in the laboratory, not all the assays were faster by POCT. The rapid TnT and TnI methods used on CCU took 15 minutes to run per test, while the laboratory method took only 9 minutes, and the CK (Alpha Dx™) in phase 2 runs for 17 minutes compared to 12 minutes on the Axon™ in the laboratory. TAT for results from the laboratory was measured from test request to result availability on the ward computer terminal, and POCT TAT from

test request to result display (or print out) on the analyser. As expected the data did prove the TAT for POCT to be significantly shorter than the CLT. In phase 1 the median TATs for CLT and POCT respectively (in minutes) were: electrolytes 70.5 and 5; CK 69 and 5, and in phase 2 the TATs were: CK 72 and 20; TnT 79 and 20; extended profile 206 and 115.5. There are few other studies that provide empirical data for the analysis of TAT. An observational time and motion study reported a TAT of 59 minutes for CLT and 8 minutes for POCT in a study carried out in the emergency department (Tsai et al, 1994).

At first sight POCT seems significantly faster then the CLT, and this is indeed the case when looking at the TAT data for individual tests. However, the organisation of blood test requesting often leads to all patients on the ward requiring blood analysis at the same time. Phlebotomists from the laboratory carry out morning ward rounds to bleed patients for testing, this usually involves all the patients on CCU and ITU. Even in the CCU where bloods are taken relative to admission times, the 12-24 hour window for troponin analysis, while preventing patients from being woken up at 03:00, results in all tests being required in the morning. The effect of this organisation is an increase in the TAT for POCT results. For example, during phase 2 of the study, POCT CKs had a median TAT of 20 minutes per test, therefore if all 4 beds on CCU had patients requiring blood analysis to include CK it would take at least 80 minutes to complete the testing on the ward. The median TAT from the laboratory for CK analysis was 72 minutes. This would be the same for one test or all four, as the laboratory processes the CCU (and ITU) requests in a batch. Therefore the laboratory will provide the results faster than POCT. In addition the laboratory results will also include other tests which would have been requested,

such as renal or liver function tests, for which the ward would have to wait, when carrying out tests by POCT.

The minimum TATs for the CLT group indicate that it is possible for the TAT from the laboratory to be shorter than the median times suggest. During phase 2 the minimum TAT for CK in CCU and the extended profile in ITU was 25 and 27 minutes respectively. This indicates a number of pre-analytical or analytical delays must be affecting the TAT from the central laboratory. A study into the need for a dedicated stat laboratory in the emergency department found pre-analytical delays totalling 36 minutes, which was longer than the time to analyse the sample (Saxena & Wong, 1993). Transport of specimens to the laboratory is always a problem, which is reduced to a minimum by the pneumatic tube system. However, although the ITU port is set as priority, due to the high usage, specimen carriers will inevitably already be in the system and a delay will result while they are cleared to their destination. A common cause of analytical delay will be the analyser downtime while maintenance is carried out, plus the increase in workload due to the morning phlebotomy ward rounds. These problems in TAT could be alleviated by the introduction of different working practices or a dedicated analyser for urgent work in the laboratory.

Pre-analytical delays are clearly a factor with the extended biochemical profile. The analysis was carried out on the same analyser, which was used for the measurement of electrolytes and CK. The TAT would not be expected to be significantly different from the times observed for these tests (between 69 and 72 minutes). However, ITU take their morning samples at the shift change over at 7 a.m., knowing that the

samples do not get analysed until after the daily start up for the analyser is complete at approximately 9 a.m. (CCU generally take their CK samples as necessary throughout the day). Taking this 120-minute delay into account the TAT for CLT would be reduced to 86 minutes. Similarly, although the TAT for the extended profile is significantly shorter in the POCT group, the time taken is much longer than would be expected. The minimum time for POCT is actually longer than the minimum TAT for the CLT (35 minutes versus 27 minutes). As the length of the POCT assay only takes 12 minutes, other factors must be affecting the TAT. Analysis by POCT assumes that the nurses have the time to take on the additional task of analysing their own samples.

The maximum TAT from the CLT recorded for CCU (in minutes) were: 1435 (CK phase 1), 1123 (CK phase 2) and 1018 (TnT phase 2). This compares to the maximum times for electrolytes and the extended profile in ITU of 277 and 316 minutes respectively. The longer TATs in the CCU are due to CK and TnT not being available out of hours. Samples taken in the evening would be collected, sent to the laboratory where they were centrifuged and left for analysis the following day, and in the case of TnT batched for analysis in the afternoon. ITU could as necessary obtain urgent testing out of hours. The POCT in CCU allows the measurement of cardiac markers when they are not available from the central laboratory.

9.3 CLINICAL IMPACT

9.3.1 Patient Population

The aim of the study was to assess the possible benefit to the patient from having biochemical analysis carried out by POCT. There is potential for bias in the study findings from the population assigned to POCT or CLT. In order to assess any benefit that might be accrued by POCT over CLT, it is necessary to establish that both groups consist of the same population, thereby ensuring that any differences regarding clinical decisions and outcome can be attributed to the mode of analysis.

The clinical condition of the patient is influenced by such factors as age, sex and ethnic group. As patients age they are more susceptible to certain disease states, such as heart disease, and generally require more intensive treatment. Death rates from Chronic Heart Disease rise steeply in the elderly (Gillum & Feinleib, 1988). Patients of Indian subcontinent origin have a higher prevalence of diabetes, which increases their risk of coronary related disease (Shaukat et al, 1997). If either group (POCT or CLT) has a greater number of patients from a particular age group, sex or ethnic background this would influence the management and create a bias in the findings. However, the results from both phases and from both ITU and CCU indicate no statistical difference between the POCT and the CLT groups in age, sex or ethnicity.

Similarly, the reason for admission to the units will have a bearing on their management. In ITU due to hospital organisation, some patients were admitted for elective post-operative recovery. These patients ideally require a high dependency

recovery ward to monitor their condition post operatively before returning to their own ward. As no such ward was available at the hospital, patients were admitted to the ITU for monitoring. Management decisions and outcome are entirely different for this group compared to true ITU admissions and hence could influence the study if there were differences between the CLT and POCT groups. In phase 1, 23% of the CLT group were post-operative admissions compared to 15% of the POCT group, and in phase 2, 42% of CLT group were post-operative cases compared to 20% of POCT group, however, statistically there was no significant difference.

In the CCU, patients admitted to ward were categorised into four groups, AMI, dysrhythmia, UA and non-ischaemic chest pain (NICP). Those patients with AMI would require more intensive management than patients admitted with NICP. In phase 2 more AMI patients were randomised to POCT, but there was no significant difference between the two groups in either phase.

The severity of the patients' condition on admission to the ward would also affect the intensity of treatment required. Patients admitted to the ITU were assessed and given an Acute Physiological and Chronic Health Evaluation (APACHE) III score based on physiological measurements and previous history, so giving an indication of the severity of the problem and a prognostic indication of the risk of death. Any difference in these scores between the CLT and POCT groups could account for any benefit provided by analysis site observed in the study. A higher APACHE III score will indicate an increase in severity of the condition and therefore more intense treatment may result. No difference was observed in either phase.

For patients on CCU, the duration of chest pain was recorded as a measure of severity. Two lengths of pain duration were noted; time since all pain began, and time since the most recent episode. In phase 1 and 2 there was no difference in the duration of all pain, neither was there a difference in most recent pain in phase 2. However, in phase1 those patients randomised to POCT had a significantly shorter duration of most recent episode. LOS nor costs were significantly different for this group, therefore it is unlikely the difference in duration of most recent pain greatly influenced the outcome.

It can be concluded that during both phases of the study there were no significant differences between the patients randomised to the CLT or POCT groups for analysis, and therefore any benefit to the patient will be attributable to the mode of analysis.

9.3.2 Patient Management and Outcome

In the ITU, TAT for POCT results was significantly faster than CLT, however no impact on decision-making or outcome was identified. Therapeutic intervention scoring systems (TISS) were recorded but no significant difference was found between either group. However, no interventions arising directly from the electrolyte or extended biochemical profile measurements could be identified from the case note review, except where CLT results were requested for confirmation of POCT results. This reflects that biochemical results, while contributing to the long term therapy planning, do not regularly result in short term management changes. No impact on the LOS in ITU, or as an in-patient after step down from critical care

was observed as a consequence of POCT. Mortality rates were the same for both the CLT and POCT patients.

An observational study was conducted in a more intense environment than the ITU site of this study (Kilgore et al, 1998). They concluded that POCT results prompted more treatment changes than the CLT results. The satellite laboratory prompted changes in 57% of the results, and 38% of results were acted upon from the POCT analyser in the ward, whereas only 21% of the CLT results effected treatment change. However, the same tests were not being compared for each testing site. Electrolytes were rarely sent to the CLT for analysis, therefore treatment changes based on electrolyte results would be due to POCT.

For the majority of ITU patients enrolled during this study, daily electrolyte determinations were considered adequate for monitoring, except where there were large fluid shifts, such as in renal replacement therapy when more intensive electrolyte monitoring required. POCT electrolyte results would be used as a guide only, with any unexpected changes or abnormal results repeated by CLT for confirmation, therefore the POCT results were not directly acted on. The CLT results were seen as the 'gold standard', with POCT used to monitor any trends. POCT measurement of renal or liver function did not contribute to the clinical decision making process. Creatinine and urea do not change rapidly enough and renal testing is therefore requested daily on ITU. Liver function tests are carried out on alternate days, as again levels do not change rapidly, and therefore POCT is not required. In addition, the accuracy and methodological problems, together with the time required for nurses to carry out these tests, made POCT difficult.

In CCU the TAT for results was also significantly reduced in the POCT group, but no difference was found in the LOS or mortality rates between the laboratory and POCT. However, the time taken to reach a definitive management decision was evaluated by intention to treat (ITT) analysis. The provision of POCT results significantly reduced the time for a diagnosis to be reached in both phases. Patients scheduled for early discharge on the basis of ITT were those patients with UA or NICP (43 patients in phase 1 and 66 in phase 2). In phase 2 the length of hospital and non-CCU stay was significantly reduced in the early discharge group. There are two possible explanations for this. The second phase of the CCU study was noticeably busier than the first (263 patients compared to 199 patients). This may have resulted in greater pressure to discharge patients. Alternatively the availability of TnT by POCT may have facilitated the decision to rule out AMI. During phase 1 the time to obtain TnT results was the rate-limiting step as the assay was neither available out of hours nor included in the POCT. In phase 2 rapid TnT analysis was made available for POCT while the CLT still did not offer TnT out of hours. As a consequence of TnT availability by POCT these low risk patients could be transferred out of CCU earlier. Would the provision of TnT 24 hours a day from the laboratory also result in a reduced stay for these patients? It may be the availability of TnT that has effected this change and not the use of POCT itself. Other researchers have studied the use of POCT TnT measurements to identify low risk patients potentially suitable for early step down. Patients admitted without elevated ST segment on ECG trace who are troponin negative at 12-24 hours post suspected event are at a low risk of in hospital cardiac event (Collinson, 1998). POCT troponin has been retrospectively compared to the CLT for risk stratification in the emergency department. A 30-day follow up of event rates in patients with negative results were

only 1.1% for TnT and 0.3% for TnI (Hamm et al, 1997). Although the ITT analysis provides a possible scenario where hospital and non-CCU stay would be reduced, CCU stay is unaffected, due in part to a lack of general ward beds for transfer of the patients.

These findings are in agreement with other published studies. A prospective study was carried out into the effect of POCT on LOS while in A&E (Parvin et al, 1996). This concluded no decrease in LOS resulted from blood testing on the ward. Similarly, another study also concluded no effect on clinical outcome resulted from POCT (Kendall et al, 1998). In that study, 6.9% of the POCT results required changes in management in which timing was considered crucial. However, no differences were observed in LOS, admission rates or mortality. The full impact of POCT is only seen when care protocols are modified to allow treatment on the bias of the POCT results (Bailey, 1997). These studies together with the findings from this trial suggest that biochemical analysis is not the rate-limiting step. A bias will be observed where tests are available on a POCT basis but not routinely available from the CLT, such as the availability of TnT analysis out of hours on the CCU, but only during the day from the CLT.

9.4 OPERATIONAL IMPACT

9.4.1 Costs

Cost analysis was only carried out for CCU, as the ITU arm of the study was prematurely terminated. In phase 1 the cost of supplying POCT was £847.60 more than the CLT over the course of the randomised trial and in phase 2 £1,305.39 more expensive. Over a period of a year this extra cost would be £2,790.00 and £3,977.94 respectively for phases 1 and 2, based on the number of patients admitted during the trial. This is due to the higher costs for consumables for POCT, which is a direct result of the much lower workload. The higher test costs for POCT found in this study agrees with a number of others. In one study the cost of glucose measurements from finger stick specimens at the point of care was compared to the central laboratory analysis (Winkleman et al, 1993). They reported test costs for POCT and CLT of $6.62 and $3.30 respectively. Similarly, another study into cost of glucose analysis found POCT a more expensive way to deliver rapid tests than the CLT (Nonsanchuk & Keefner, 1995). Where POCT has been reported to be lower than the CLT the same criteria for cost analysis has not been used for both groups (Zaloga, 1990; Lee-Lewandrowski et al, 1994). In Zaloga's study the cost of glucose analysis by POCT was reported as $0.45 compared to the $3.50 for the laboratory cost. However, the POCT data only included the cost of the reagent strips whereas the laboratory figure also included labour and fixed costs. Similarly, Lee-Lewandrowski included the cost of the analyser and overheads in the CLT data, but this was omitted from the POCT costs. The same criteria must be used for both sites otherwise the data will be biased.

Although the study compares the cost of POCT with CLT, in practice the provision of POCT will be an additional expenditure on top of the laboratory costs. The only saving will result from the reduced reagent costs incurred by the laboratory if all the testing was transferred to the ward. The other costs of labour and maintenance will be incurred whether the CCU tests are carried out in the laboratory or not. This is due to the fact that CK and troponin analysis on CCU patients is only a very small percentage of the total laboratory workload. Therefore, the annual cost of £7,876.44, minus the reagent costs of £1772.60 (assuming laboratory data not required for results confirmation), for the provision of POCT in phase 2 will be additional to the costs incurred by the laboratory. These figures are based on the analysis of 2 CKs and 1 troponin per patient. In practice it is likely more reagents will be used, for repeat analysis or for additional tests. In addition, from anecdotal evidence other wards, especially A&E, were utilising the availability of the troponin devices, particularly at those times when troponin analysis was not available from the laboratory. This will inevitably increase the costs incurred for POCT.

Cost analysis was then carried out on the effect of POCT on the hospital bed costs. The analysis was based on the LOS data for CCU and non-CCU stay. Although for all patients enrolled on the study there was no significant difference in the LOS at either stage (CCU or non-CCU), this did result in a cost difference. During phase 1, where CKs only were measured, the total costs (bed and test costs) for POCT were £1,120.04 (0.44%) more expensive than the central laboratory. In phase 2, with the availability of POCT troponin, a saving of £17,503.07 (5.47%) was found over the laboratory costs.

This saving increased when comparing the data for those patients identified for early step down or discharge from the CCU by ITT analysis. In phase 1, 43/199 (22%) patients were identified with NICP or dysrhythmia requiring no further treatment on CCU and in phase 2, there were 66/263 (25%) patients. This translated into a cost saving of £2,501.76 (5.33%) and £24,802.50 (32%) respectively even though in phase 2 the CCU costs were in fact increased, as the LOS on CCU for the POCT group was longer than the CLT group. Further savings would be made if patients could be moved out of the high dependency CCU as soon as they have been identified for early step down, however, the availability of general ward beds meant patients often stayed in CCU until discharged. These findings of hospital cost savings cannot be compared with other studies as there have been no others, which take hospital costs into account, except those of Collinson (1998).

The difference in savings demonstrated between the two phases can be explained by the change in protocol, with the addition of troponin measurements in the second phase. However, the same reduction in costs may well be demonstrated in that troponin analysis was available from the laboratory on a 24-hour basis.

9.4.2 Use

During the study and particularly the randomised trial there was regular review and feedback from the nursing and clinical staff concerning any problems arising from the routine use of the POCT analysers. There were marked differences in the use of POCT between the two testing sites of ITU and CCU.

The initial interest in the POCT study in the ITU was not sustained. The measurement of sodium (Na) and potassium (K) on the blood gas samples were considered supplementary to those measurements performed in the laboratory. The results obtained were only of interest if deviated from the normal range or from those results expected for that patient, when requests would be sent to the laboratory for confirmation. In the second phase the provision of an analyser that measured a profile of tests did not improve the need for POCT in ITU. Although the analyser was simple to operate, it was an additional task that required nursing input without any apparent gain. The pressures on the nursing staff due to the staff shortages and nature of the care meant additional task were considered a burden and difficult to find the time to perform the analysis, demonstrated by the relatively long turnaround time for results from POCT. Despite the initial interest, the nursing staff on ITU performed few of the POCT, and subsequently felt unable to participate in the study. The clinical staff saw no benefit from POCT in terms of patient management. This may in part be a result of practices in this particular ITU in which the major ward round of the day starts at 11:00, by which time the routine CLT results were available. The POCT analyser did not provide for Na and K analysis, considered essential for most ITU patients. Therefore additional CLT results were required to redress this. Furthermore, the differences between the POCT and CLT methods required correction factors for some of the other tests leading to confusion in interpretation. Another point in favour of laboratory analysis was the availability of results 24 hours a day for renal function tests (including Na and K).

Any system, which provides POCT, needs to be integrated within current practices, such as part of the routine blood gas measurement. However, blood gas

measurement requires the patients to have an arterial line in place, which is not always necessary. Additional stand-alone systems would need to provide the required profile of tests on one analyser and yield obvious clinical benefits to ITU. Due to the heterogeneous nature of the ITU patient population in this study setting, it maybe, at present, difficult to provide such a profile on one POCT analyser. Further studies into the provision of POCT on ITU must take into account the requirements of the clinicians as well as the laboratory. An alternative solution, in this case, could be to provide a small satellite laboratory based on site and staffed by laboratory personnel.

In contrast to ITU, the nursing staff in CCU found the ability to measure their own tests valuable. They did not consider the measurement of CK or troponin on the ward as an additional or unnecessary task. Neither of these tests were available 24 hours a day from the laboratory and troponin was not available at the weekends, which therefore restricted the use of these tests in rapidly making management decisions. POCT allowed these tests to be carried out when they were not available from the laboratory, allowing decisions to be taken on morning review on the basis of all the data without delays in waiting for results to be returned from the laboratory.

9.5 SUMMARY

This chapter critically discussed the findings of this study, including the rationale behind a systematic approach to POCT assessment and the need to undertake a comparison with the laboratory in the form of a prospective randomised trial where the POCT results would be routinely available to the clinicians. The results reported for each step of the evaluation were discussed and these highlighted the need for a thorough step-by-step assessment of POCT prior to implementation.

The analytical and clinical accuracy of the POCT analysers varies depending on the methodology and the ability of the operators. Full comparison with the laboratory is essential to ensure results will be reliable in routine use and will not cause any confusion with different reference ranges or clinical cut off points. TAT must be assessed for the time taken to reach a decision on management on the basis of the results and not the analytical TAT. POCT is clearly capable of providing results in a faster time frame than CLT but there will be no advantage for POCT if the results are not reviewed and acted upon as soon as available.

The important factor in the decision to implement POCT is the impact it will have on patient management and outcome. There is little point in providing POCT if there is no benefit to the patient. Potentially LOS can be reduced in patients requiring early step down from the high dependency wards, but with the proviso that beds are available in the general medicine wards. The financial aspect of POCT certainly appears to be a benefit especially in the early discharge group, where the reduced LOS can be translated into a saving in total hospital costs. One question arising

from these findings would be if the laboratory could provide the same testing profile as provided by POCT over 24 hours, would the outcome be the same?

CHAPTER 10 CONCLUSION

The hypothesis of the study was that point of care testing (POCT) has a beneficial effect on patient management and prognosis over and above central laboratory testing (CLT), and is capable of being adopted for routine clinical use. A beneficial effect on patient management can be seen in those patients in the Coronary Care Unit (CCU) who were identified for early step down based on the Intention to Treat analysis. Their total hospital stay was reduced by the availability of troponin T (TnT) on the ward. The study also demonstrated that point of care technology is capable of being adopted for routine use providing a number of conditions are met. These being –

- Ensuring comparability with the laboratory results to avoid confusion arising from the use of different reference ranges or diagnostic cut offs for POCT.
- Ascertaining clinical accuracy by evaluating the assays with non-laboratory personnel.

Both must be undertaken in the setting for which the analysis is intended and not based on data provide by the manufacturer, so ensuring relevance to the intended population.

The importance of a systematic approach to the evaluation of POCT prior to implementation has been demonstrated. The impact on patient management must be the ultimate goal, however, full assessment of the technology and the operational aspects must be carried out to achieve the full picture. Six objectives were set out at the start of this study and they have been met with varying degrees of success. This again highlights the need for a thorough assessment of all aspects of POCT prior to implementation.

The assessment of the analytical and clinical accuracy of the analysers used in this study demonstrated the need to thoroughly evaluate potential analysers POCT use. While some assays correlated well others showed significantly different results particularly in clinical use. However, decisions regarding clinical relevance of the results can be taken before the analysers are put into use.

POCT proved to be significantly faster when providing an individual result and had the advantage of providing results on demand 24 hours a day. However, when a number of patients require analysis at the same time, the POCT turnaround time (TAT) increases by the number of requests made, whereas the laboratory TAT remains the same. In addition the tests available at the POCT may be provided in a faster time scale but other results such as renal function tests are reliant on the TAT of CLT.

In general the patient management and outcome was not altered. The same results were seen in the POCT and CLT groups. However, patients in CCU who were identified for early discharge had a reduced total hospital LOS. Stay on CCU was however increased and therefore indicates biochemical tests are not the rate limiting step. Further savings could therefore by made if patients were moved as soon as they were identified for step down, so reducing CCU bed costs. The reduction in LOS for the early discharge group in phase 2 resulted in savings in total hospital costs. This would make funds available for other facilities such as the provision of more CCU beds.

Though would have expected the need for POCT to be the same for both critical care wards this was in fact not the case. On ITU, POCT was not required as the results

from the laboratory were available in time for the morning review, and any urgent results for renal function tests were available from the laboratory as requested 24 hours a day. In addition the nursing staff found the task of performing biochemical tests difficult to fit in with their heavy workload. In CCU, the availability of creatine kinase (CK) and particularly TnT meant a diagnosis could be confirmed within 24 hours even when the tests were not available from the laboratory. The nursing staff were happy to carry out the additional task especially as the ward protocols allowed for these results to be acted upon as soon as available.

The study has proved that a systematic approach to the assessment of POCT is extremely valuable. It is not appropriate to implement POCT on the basis of the reliability of the analysers to produce accurate results, or to produce these results in as faster TAT than the central laboratory, but for the provision of POCT to have a beneficial impact on the patient management and outcome. Therefore any assessment must include a step-by-step evaluation of all aspects of POCT and include a prospective randomised trial where POCT is directly compared to CLT and is undertaken while the POCT is in routine clinical use. Any evaluation must ensure that the conditions for both testing sites are the same to avoid potential bias. This study also demonstrated that although POCT may prove beneficial in one setting, it cannot be assumed to be required in all settings.

Further research needs to be undertaken to study the use and costs of POCT in routine clinical use. Data collected regarding the number of requests made per patient by POCT and CLT and the amount of reagent and consumables used will provide information on the actual use and costs incurred and thereby ascertain whether POCT is cost effective. Further prospective randomised trials should be

undertaken in a number of situations targeting particular problems, such as, would the same results be produced if the laboratory provide a 24 hour service for cardiac markers, or, what effect would dedicated urgent analyser in the central laboratory have on patient management? In other words what effect would altering the working practice have on the outcome?

In conclusion, whenever POCT is being considered its implementation must be preceded by an assessment of the requirements of the technology and a thorough step-by-step evaluation to ascertain whether the objectives set have been met. Findings cannot be extrapolated from previous studies as results will be dependent on the intended setting, and therefore the assessment of POCT must be carried out for each individual case.

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APPENDIX 1

This appendix contains the Passing & Bablok (Fig 1-9) and Altman & Bland (Fig 10-18) plots for the ITU extended biochemistry profile for the analytical validation stage in phase 2. For ease of comparison both plots for each analyte are displayed next to one another. Conclusions regarding the data shown in these plots can be found in chapter 6 under section 6.1.3 ITU phase 2.

Fig 18 Altman and Bland Plot for Urea

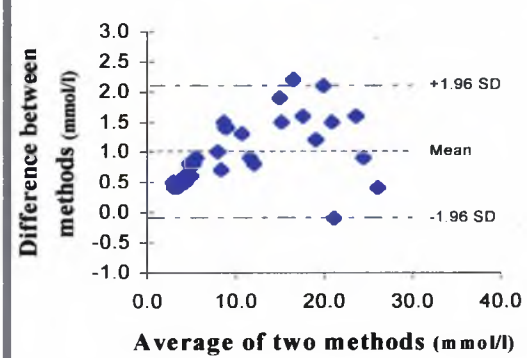


Fig 10 Altman and Bland Plot for Albumin

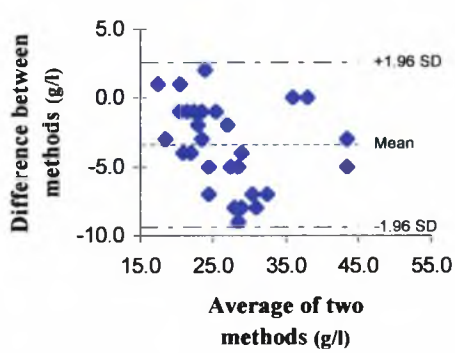


Fig 2 Passing & Bablok Regression for ALP

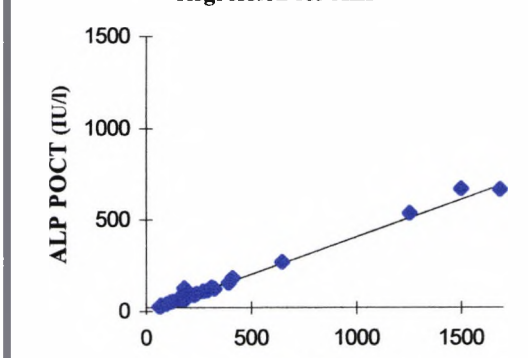


Fig 11 Altman and Bland Plot for ALP

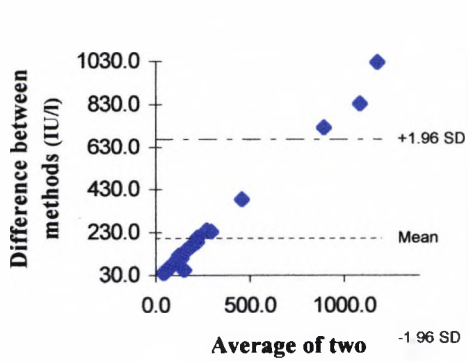


Fig 3 Passing & Bablok Regression for Amylase

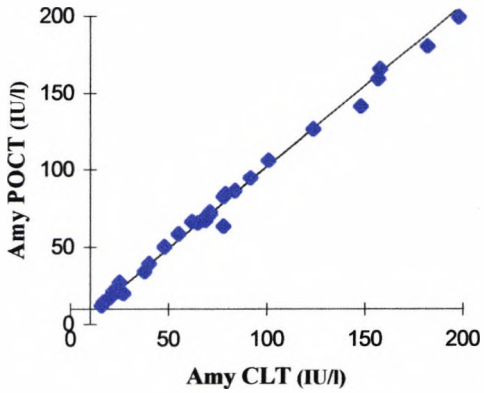


Fig 12 Altman and Bland Plot For Amylase

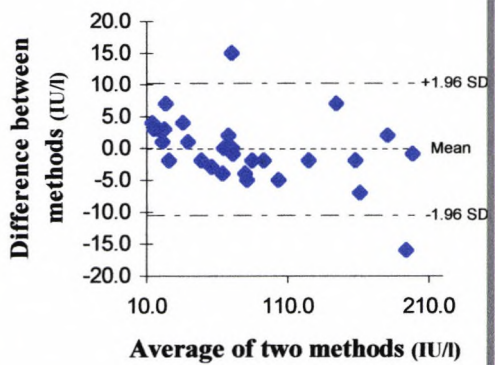


Fig 4 Passing & Bablok Regression for Bilirubin

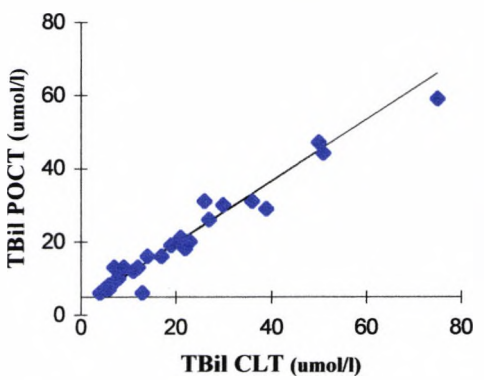


Fig 13 Altman and Bland Plot for Bilirubin

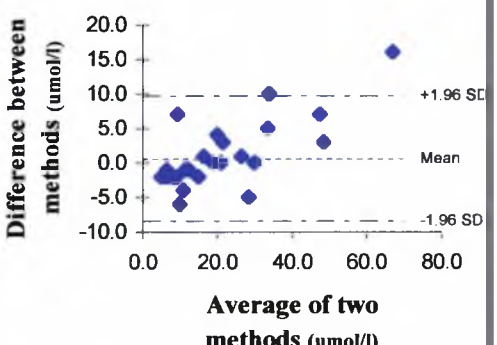


Fig 5 Passing & Bablok Regression for Calcium

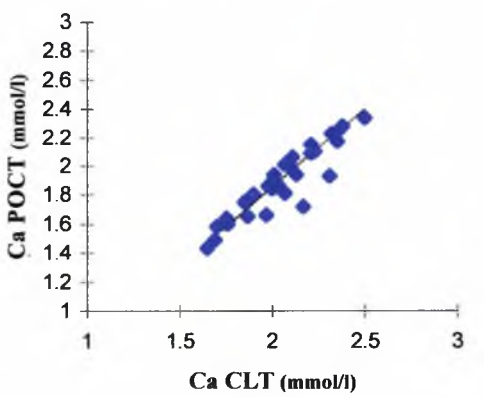


Fig 14 Altman and Bland Plot for Calcium

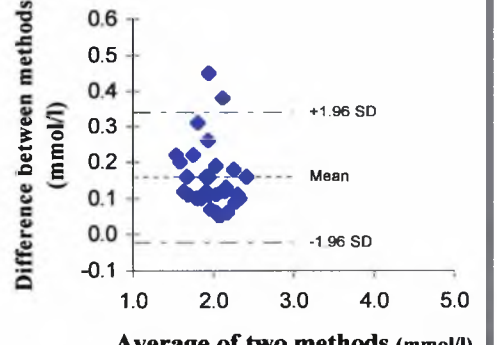


Fig 6 Passing & Bablok Regression for Cholesterol

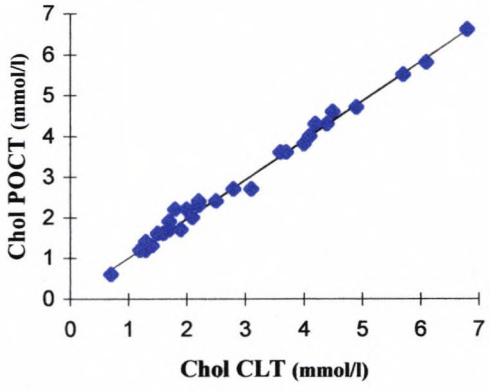


Fig 15 Altman and Bland Plot For Cholesterol

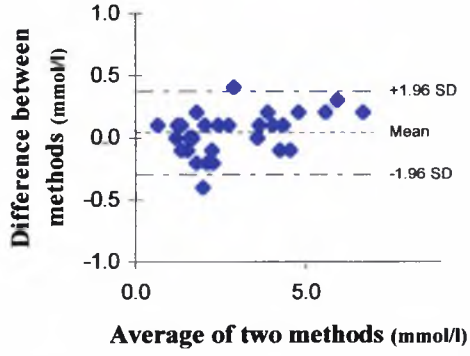


Fig 7 Passing & Bablok Regression for Creatinine

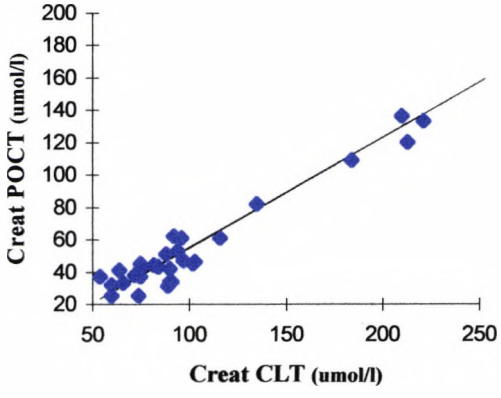


Fig 16 Altman and Bland Plot for Creatinine

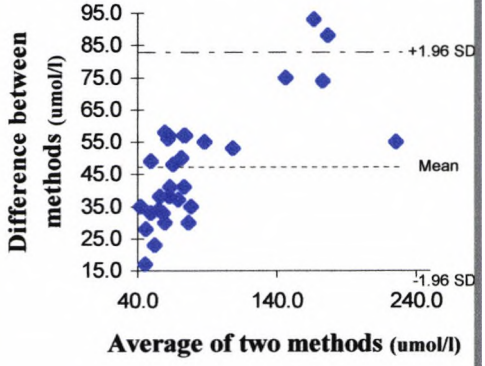


Fig 8 Passing & Bablok Regression for GLucose

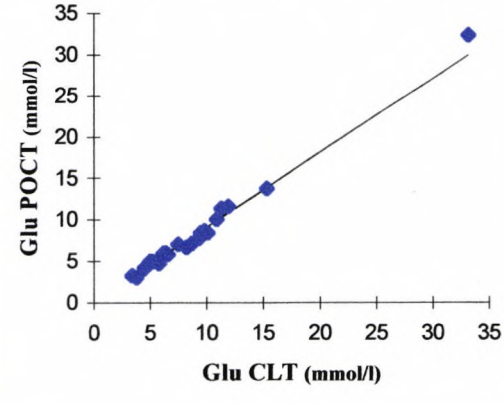


Fig 17 Altman and Bland Plot For Glucose

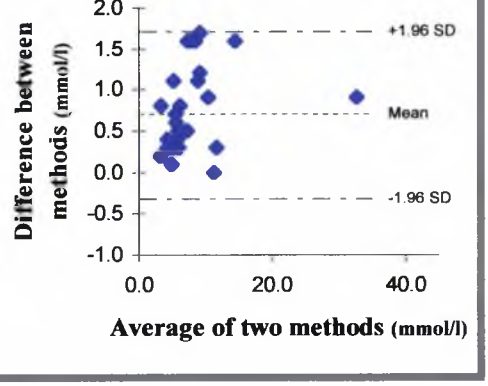


Fig 9 Passing & Bablok Regression for Urea

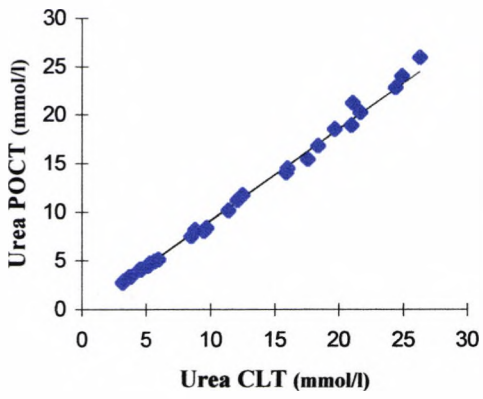
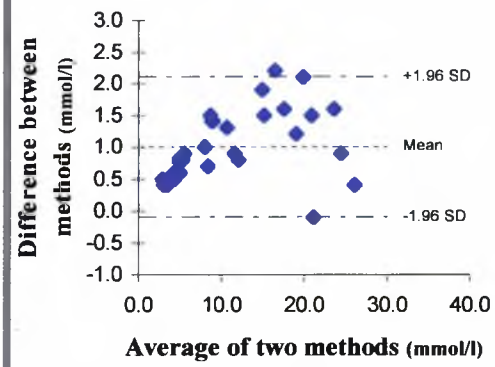
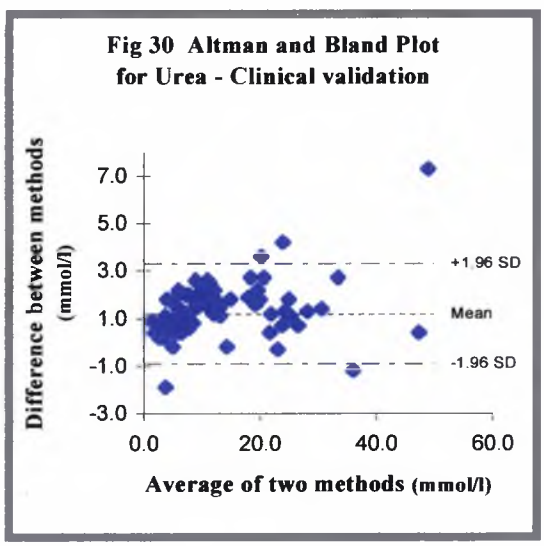


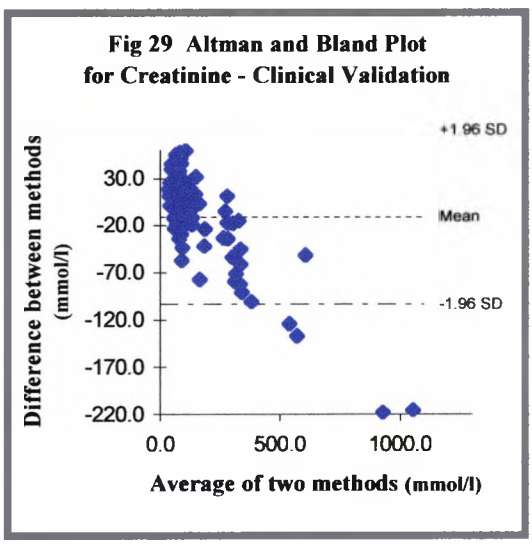
Fig 18 Altman and Bland Plot for Urea

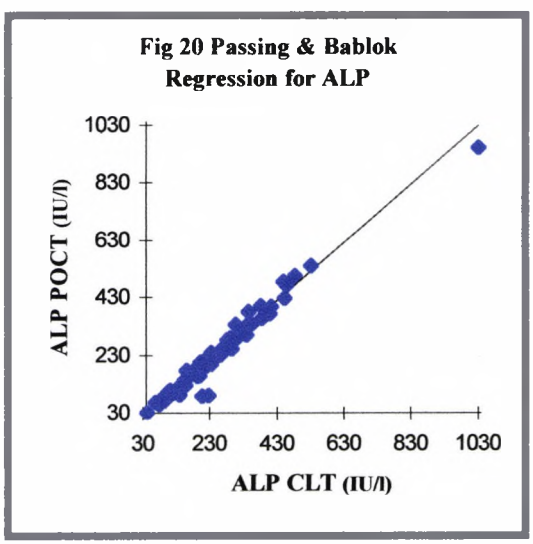


APPENDIX 2

This appendix containd the Passing & Bablok (Fig 19-24) and Altman & Bland (Fig 25–30) plots for the clinical validation of the ITU extended profile in phase 2. Only the analytes which were compared during the clinical trial are shown. Both plots for each analyte are displayed sid by side for ease of comparison. Conclusion regarding the data displayed in these graphs can be found in chapter 6 section 6.2.3 ITU phase 2.







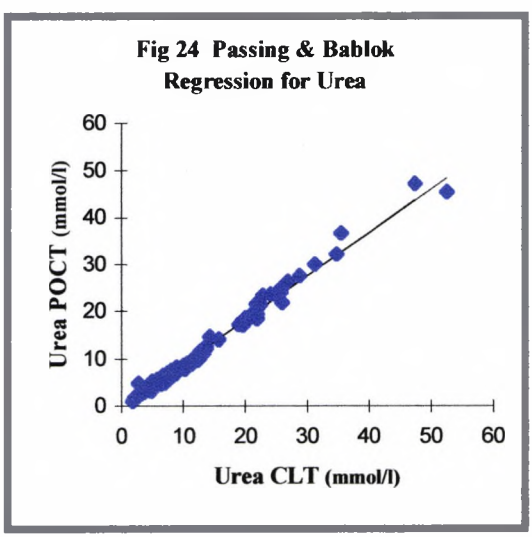


Fig 21 Passing & Bablok Regression for Bilirubin

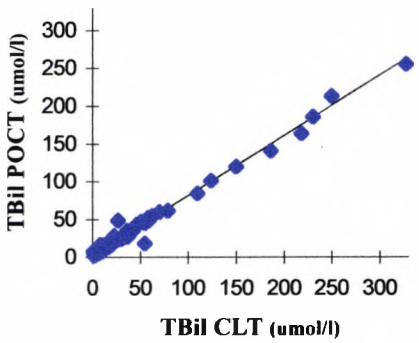


Fig 27 Altman and Bland Plot for Bilirubin - Clinical validation

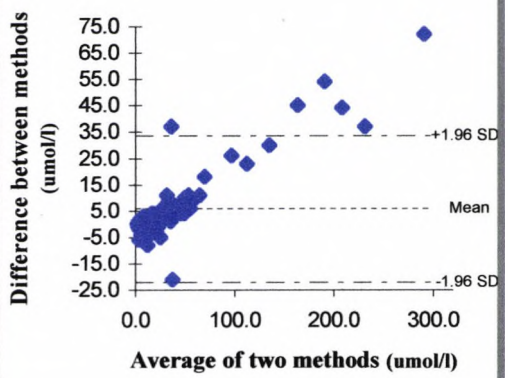


Fig 22 Passing & Bablok Regression for Calcium

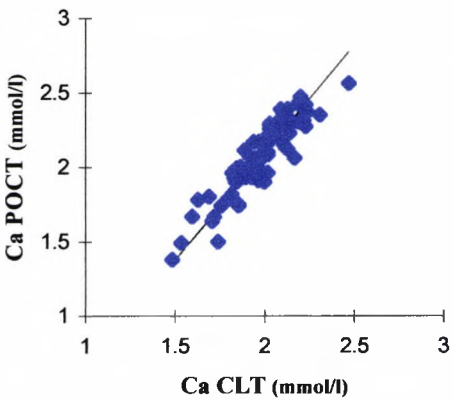


Fig 28 Altman and Bland Plot for Calcium - Clinical validation

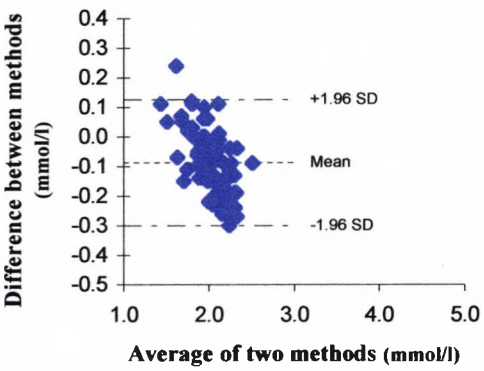


Fig 23 Passing & Bablok Regression for Creatinine

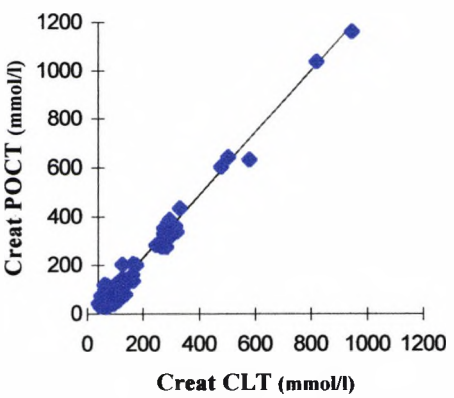


Fig 29 Altman and Bland Plot for Creatinine - Clinical Validation

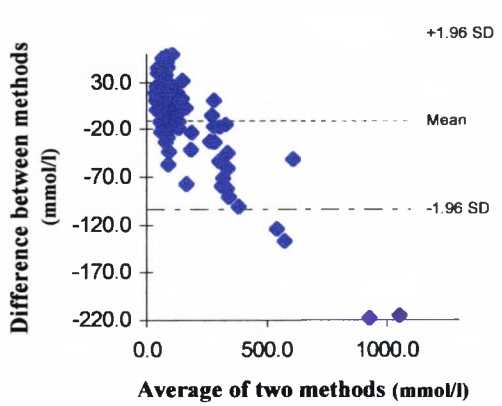


Fig 24 Passing & Bablok Regression for Urea

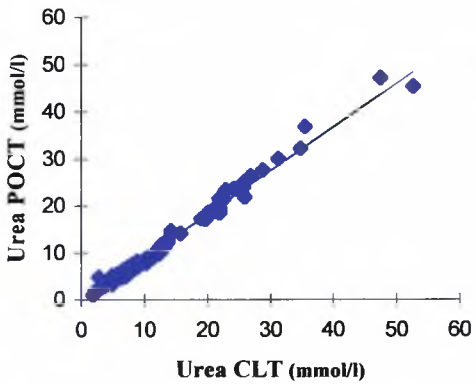


Fig 30 Altman and Bland Plot for Urea - Clinical validation