CHAPTER 4

4.0 MEASUREMENT OF NON COMPLIANCE

Identifying effective methods of enhancing compliance requires accurate methods of measuring compliance (Melnikow and Kiefe, 1994).

Two and a half thousand years ago, Hippocrates stated that the physician should remain aware of the fact that patients often lie when they state that they have taken certain medicines (Haynes, Taylor & Sackett, 1979; Tebbi, 1993).

In these early times the measurement of patient compliance with medicines was obviously not sophisticated. Hippocrates' remarks seem to be based on physician observation, as the factor of patient report is seen as less significant because he feels he cannot rely on it, i.e. patients often lie. Even at this early time and even with, we assume, the minimum of effective measurements , he saw this as a serious problem of sufficient magnitude to cause concern (Tebbi, 1993).

In looking at the statistics on non-compliance, it is important to note, at the same time, the measurements used. Obviously these are becoming more and more sophisticated as time goes on; but it is probably a major part of the reason for the disparity in compliance studies. As Melnikow and Kiefe (1994) point out, readers of the medical literature should consider how compliance was measured and analyzed when interpreting the results of clinical trials .

Urquhart (1994a) feels that compliance is now shown as a great deal poorer in clinical trials than has been revealed by the older methods due to the fact that the measurement of compliance has become increasingly more scientific and accurate.

Grymonpre, Didur, Montgomery and Sitar (1998) in studying pill count, self-report, and pharmacy claims data to measure medication adherence in the elderly, gives the warning that using medication adherence as a process measure, the researcher and practitioner should be aware of the limitations unique to the data source they choose, and interpret data cautiously.

There are many methods for measuring compliance to prescribed drug therapy. Ideally, the measurement used in the normal course of care should be practical, readily accessible and of sufficient sensitivity to identify as many non-compliers as possible (McKenney, 1979).

Gordis (1979) also writing more than 20 years ago and therefore unaware of some of the new methods of assessing non-compliance, differentiates between direct and indirect measurements of compliance. Under "direct" measurements he includes blood levels and urinary excretion of medication, metabolite and marker (tracer). Under "indirect" methods he includes: therapeutic or preventive outcome; the "impression" of the physician (predictability); the patient interview; the filling of the prescription and the pill count. Gordis' (1979) data indicated that the physician's estimate of patient compliance was of very limited value, both in research studies of compliance and in practical applications in the day-to-day delivery of health services. He felt that it was clear from the outset that methods of measuring compliance, current at that time, left much to be desired. Nevertheless, the direct methods

often permitted an approximation of compliance.

Fletcher, Pappius and Harper (1979) discuss the interview method, even though already doubted from the time of Hippocrates, one of the main tools at that time for assessing compliance. They point out that the single greatest difficulty with the interview technique for measuring medication compliance is its validity. Almost all studies comparing interview with measurements of biologic fluids (a direct method) have found that the interview method overestimates compliance. An important point he makes, though, is that the interview appears to be valid to the extent that when a patient admits non-compliance it is likely to be true .

Steiner and Vetter (1995) also distinguished between direct and indirect procedures. Questionnaires offered to patients, 'pill-counting', 'appointment-keeping' as well as registration of drug effects represent indirect methods. The direct approach include measurement of drugs or metabolites in urine or serum.

However there are difficulties even in the direct markers. The assessment of non-compliance to a medication on which research is being conducted is an important issue in the evaluation of clinical trials of self-administered drugs. Traditional methods for evaluating the compliance of subjects include self-reported questionnaires and pharmacologic assays of drug levels in randomly-drawn blood samples, but each of these has important limitations. When non-compliance begins shortly before the last observation of the marker process, these (as well as any other) estimators cannot reliably distinguish non-compliance from compliance (Kim & Lagakos, 1994). This could possible also be influenced by Urquhart (1994a) concept

of "white coat compliance" (referring to the tendency of patients to take their medicine correctly only a day or two prior to their appointment with the doctor. This was especially true, he felt, before the late eighties.).

Compliance may not always be easily defined or accurately measured. No single method of measuring compliance with appointments or medication is applicable in all settings (Melnikow and Kiefe, 1994).

Gomes, Maia Filho and Noe (1998), in studying anti-epileptic drug intake adherence found that the evaluation of blood drug measurement alone, except in cases of extreme low adherence and variability of drug intake, is not enough for the recognition of incorrect drug intake. But the clinical markers and the self-reported adherence also have to be also considered for this sort of evaluation, thereby suggesting of a multi measurement approach.

In many studies there has been poor correlation between the measurement methods used. Smyth and Judd (1993) assessed compliance with antibiotic prophylaxis after urinary tract infection in 32 children, using a parent questionnaire, and a urine test for antibacterial substances. In 31 (97%) cases, parents reported giving the antibiotics every day but only 22 (69%) of urine tests were positive. Cureton, Regennitter and Yancey (1993) studied the role of the headgear calendar in headgear compliance. There was a poor correlation between the number of hours the patient said he wore his headgear compared with the actual number of hours worn.

Even the assessments of the physicians and of the health workers can be inaccurate when compared with other methods. The existence of poor compliance levels often surprises health workers, to whom such behaviour appears illogical. Physicians overestimate the degree of cooperation achieved in their practices (Becker, 1985; Blackwell, 1976). Physician prediction was not found to be an accurate method of identifying prenatal patients at risk for missing appointments (Feierabend, 1996.) Though some physicians may cherish the illusion that they can intuitively detect drug defaulters, the evidence indicates otherwise. Skilled psychiatrists have been shown to err in up to 20 per cent of their predictions concerning which out-patients are taking their drugs, though it is interesting that 71 per cent of mistakes were in the direction of believing that patients were not taking their drugs when in fact they were (McClellan & Cowan, 1970).

Goldberg, Cohen and Rubin (1998), in a study of how physicians evaluate patient compliance, practitioner judgments were compared to the self-reports of 138 adult patients receiving treatment for pulmonary diseases at an outpatient clinic. The research found no significant relationship between physician evaluations of compliance and accounts given by the same patients. The conclusions of physicians regarding patient compliance proved to be influenced by their views on the seriousness of the condition and the effectiveness of treatments, but patient reports were different. They concluded that physicians clearly have difficulties in appraising the compliance behavior of their patients.

Wagner, Schnoll and Gipson (1998) and Rushe and McGee (1998) have developed scales and questionnaires to assess adherence to self-monitoring of blood glucose and adherence to renal

treatment respectively.

4.1 Measurement Methods Used

Edelman, Eitel, Wadhwa, Friend, Suh, Howell, Cabralda, Jao & Aprile-Forlenza (1996) assessed the methods used by nurses to rate patients' compliance and to make accurate assessments. They found that nurses relied heavily on medical records, and also used several individual indicators (lab values etc.) to rate overall dietary compliance. At the same time, however, while assessments did not seem to be biased by personal factors such as nurses' perceptions of patients' education levels, it seemed that nurses did rely on personal knowledge when rating non-compliant patients.

One of the current methods used to measure treatment compliance in a clinical drug trial is through the use of a patient diary (van Berge Henegouwen et. al., 1999). Arici, Altun, Usalan, Ulusoy, Erdem, Yasavul Turgan and Caglar (1998) felt that unanticipated control of biochemical indices might contribute to the actual assessment of compliance in hemodialysis patients. Naik, Vartak and Sequiera (1994) working under field conditions in 112 leprosy centres in Maharashtra, used a simple but effective method of assessing the patient's adherence to the medication by testing the urine samples for dapsone.

Karbwang, Fungladda, Pickard, Shires, Hay and Feely (1998) finding it necessary to monitor non-compliance, used low-dose phenobarbital as an indicator of compliance with anti-malarial drug treatment. Thilothammal, Krishnamurthy, Banu and Gandhimathy (1995) assessed

compliance in drug-taking by what they called a simple bed side method. Using riboflavin as a urinary marker is a simple and rational method. Identifying riboflavin in the urine by fluorescence on exposure to ultraviolet (UV) rays or torch light is being used in medical practice but not extensively though it seems to have potential as a simple and inexpensive way of assessing compliance.

Dumortier, Lochu, Zerrouk, Van Nieuwenhuyse, Colen de Melo, Roche Rabreau and Degrassat (1998) found that saliva concentrations appeared to be useful for checking compliance to treatment, in particular among outpatients.

Baril (1998) used indinavir assays in the hair of patients to assess the level of absorbed medication. Uematsu, Nakashima, Fujii, Hamano, Yasutomi, Kodaira, Kato, Katoake, Oka and Masuike (1996) measured 5-fluorouracil in scalp hair as a possible index of patient compliance with oral adjuvant chemotherapy.

Electronic monitoring of peak expiratory flow rate and inhaler usage can provide early identification of patients who do not comply (Chmelik & Doughty, 1994). Yeung, O'Connor, Parry and Cochane (1994) tested compliance with prescribed drug therapy in asthma using a novel electro mechanical counter which could record MDI actuations.

4.1.1 The Medication Event Monitoring System (MEMS)

Perhaps the most significant breakthrough in the measurement of compliance has been the

Medication Event Monitoring System (MEMS).

This allows the integration of microelectronics into drug packaging, providing a continuous record of the interactions of the patient with the drug package. A microprocessor in the MEMS cap records each opening as a presumptive dose, listing the date, time, and duration of opening for later retrieval on a microcomputer. Vaur, Vaisse, Genes, Elkik, Legrand and Poggi (1999) used electronic pill boxes (MEMS) to assess the risk of poor treatment compliance. The main compliance parameters were the percentage of missed doses, the percentage of delayed doses, and the percentage of correct dosing periods.

This is discussed and used by Waterhouse, Calzone, Mele and Brenner, (1993) as they find that patient self-reports and pill counts are likely to overestimate the degree to which patients adhere to their tamoxifen regimen. Lee, Nicholson, Ledermann and Rustin (1996), using the 'intelligent' tablet bottle (MEMS), unknown to the patient, electronically recorded the times of opening, have assessed the compliance of patients with prescribed oral altretamine for ovarian cancer. Schwed et.al. (1999) in monitoring the daily compliance to a 6-month course of lipid-lowering therapy, using MEMS found that it provided some patterns of non-adherence to medication, undetectable by pill count alone.

Burney, Krishnan, Ruffin, Zhang and Brenner (1996) studied adherence to single daily dose of aspirin in a chemoprevention trial, evaluating self-report and microelectronic monitoring. They found the adherence rates for all dosing errors between self-report and MEMS significantly different. They concluded that patient self-report alone is not a reliable measure

of adherence.

In Magometschnigg's (1995) study mentioned earlier, 389 Austrian general practitioners studied compliance in 945 hypertensives, using the Medication Event Monitoring System. The patients were asked to take the ACE-inhibitor Cilacapril once a day between 7.00 a.m. and 9.00 a.m. Each package opening was registered by a microprocessor located in the cover of the drug vial. A similar study using an electronic pillbox (quoted earlier) was conducted in France by Mallion et.al.(1995) using hypertensive patients. Guerrero, Rudd, Bryant-Kosling, Middleton and Middleton (1993) also discuss electronic monitoring. They found that pill counts tend to overestimate patients' compliance rates.

Sevick, Levine, Burkart, Rocco, Keith and Cohen (1999) used a novel approach in the measurement of continuous ambulatory peritoneal dialysis prescription adherence. Patients recorded in their logs their exchange activities during the 2-week observation period. Concurrently, patients were instructed to deposit the pull tab from their dialysate bag into a MEMS bottle immediately after performing each exchange. The MEMS bottle was closed with a cap containing a computer chip that recorded the date and time each time the bottle was opened. A significant discrepancy was found between log data and MEMS data, with MEMS data indicating a greater number and percentage of missed exchanges. This implies a definite 'faking' of their records on the part of the patient, perhaps to avoid the disapproval of their doctor or perhaps significant on a deeper level of trying to move as far away as possible from a traumatic illness. It is obviously more than "forgetting" to take the medication.

Clearly, methods to measure compliance have many limitations (Kelloway, Wyatt & Adlis, 1994). There is at times a strong discrepancy between various methods of compliance measurement: It is clear that there are many different ways of measuring compliance, some extremely accurate and others with apparently minimal validity. The opinion of the health worker can either overestimate or underestimate compliance and is often inaccurate. It is important to assess the method of measurement in compliance studies and to assess the results with these in mind. There seems to be a trend that the more accurate the instrument of measurement, the less compliant the patients appear.

4.2 Summary

Non-compliance is extremely difficult to measure and people have used various methods to do this. Some are extremely effective and others not. The patient's own word has been found to be unreliable whether this is done intentionally or not, and doctors' assessments are only minimally so.

The electronic pillbox, where each opening is recorded by a microprossesor is an extremely accurate invention for measuring compliance and has, in many countries, changed the face of measurement of non-compliance. However, particularly in a country like South Africa, which has limited funds for Health care, the method is not economically viable.