**COVER SHEET**

TITLE: Feasibility Study: Comparison of Performance Status with Objective Physical Activity Monitors in Lung Cancer Patients

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ABSTRACT

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*Context*: Performance status (PS) is a predictor of response to chemotherapy but difficult to identify in patients with advanced lung cancer. It is measured using the ECOG scale, which relies on simple questions to assign a score. Accuracy in measurement is a concern. PS is closely related to physical activity, but they are not the same.
*Objective*: To determine the feasibility of using two activity monitoring devices to examine physical activity and relate it to the PS assessment of lung cancer patients.
*Methods*: Patients wear activPAL™ and Actigraph™ monitors for two weeks around a dose of chemotherapy.
*Results*: Two patients have been evaluated of a planned 25. Initial results are below:

| | Actigraph™ Activity (counts/day) | activPAL™ Energy Expenditure (MET-hr/day) | ECOG PS at Week 1 |
|---|---|---|---|
| Subject 1 | 46,088±4286 | 18.7±1.8 | 1 |
| Subject 2 | 176,591±5405 | 20.1±0.3 | 1 |

*Conclusions*: Actigraph™ shows a difference in activity between the two patients, but activPAL™ does not. Despite the difference in activity, both patients received an ECOG PS of 1. We hope to compare the devices and assess their correlation to PS assessment. Predictive and prognostic factors based on physical activity may then be further explored.

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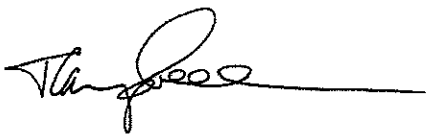

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May 16, 2010

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## Abstract

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## Introduction

Before prescribing chemotherapy treatment, an oncologist must first assess whether the patient would be able to tolerate the treatment and how the chemotherapy would affect overall

survival, particularly in older adults. The most reliable measure oncologists use to assess these questions is performance status (PS) (Jatoi *et al.*, 2003; Gridelli *et al.*, 2007). However, it is difficult to accurately identify PS in older lung cancer patients who often have comorbidities (Gridelli *et al.*, 2007; Kelly, 2004). PS is measured rather crudely by clinicians based on their perceptions and the self-reported symptoms of the patient. Two measures of PS in common use are the Eastern Cooperative Oncology Group (ECOG) PS (Figure 1) and the Karnofsky scale (Figure 2).

**ECOG PERFORMANCE STATUS**

| Grade | ECOG |
|---|---|
| 0 | Fully active, able to carry on all pre-disease performance without restriction |
| 1 | Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work |
| 2 | Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours |
| 3 | Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours |
| 4 | Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair |
| 5 | Dead |

**Figure 1**. ECOG Performance Status Scale. As published in Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P.: Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649-655, 1982.

| Karnofsky Performance Status Scale Definitions | Rating (%) | Criteria |
|---|---|---|
| Able to carry on normal activity and to work; no special care needed. | 100 | Normal no complaints; no evidence of disease. |
| | 90 | Able to carry on normal activity; minor signs or symptoms of disease. |
| | 80 | Normal activity with effort; some signs or symptoms of disease. |
| Unable to work; able to live at home and care for most personal needs; varying amount of assistance needed. | 70 | Cares for self; unable to carry on normal activity or to do active work. |
| | 60 | Requires occasional assistance, but is able to care for most of his personal needs. |
| | 50 | Requires considerable assistance and frequent medical care. |
| Unable to care for self; requires equivalent of institutional or hospital care; disease may be progressing rapidly. | 40 | Disabled; requires special care and assistance. |
| | 30 | Severely disabled; hospital admission is indicated although death not imminent. |
| | 20 | Very sick; hospital admission necessary; active supportive treatment necessary. |
| | 10 | Moribund; fatal processes progressing rapidly. |
| | 0 | Dead |

**Figure 2**. Karnofsky Performance Status Scale. As published in Crooks *et al.* (1991), de Haan *et al.* (1993), Hollen *et al.* (1994), O'Toole and Golden (1991), and Schag *et al.* (1984).

These narrow scales leave little room for precision of measurement, and in particular, the difference between an ECOG score of 2 and 3, often used as the cut-off for prescribing anti-cancer treatment, has anchors of "symptomatic, up and about more than 50% of waking hours" and "symptomatic, up and about less than 50% of waking hours." It is likely that persons falling within a single grade have a very wide range of physical function. Additionally, oncologists and patients alike are subject to the tremendous emotions around treatment decisions, which create

the possibility to over or underestimate a given patient's PS, leading to inappropriate treatment. Despite these limitations, however, PS remains powerfully predictive.

Although physical activity is not the same as performance status, the two are closely related such that people with higher levels of activity have better physical function (Johnson *et al.*, 2009; Visser *et al.*, 2005; Brach *et al.*, 2004; Visser *et al.*, 2002; Miller *et al.*, 2000). Since physical function is difficult and time-consuming to measure objectively in a clinic, the SF-36 physical function scale which is based on patient self-reporting, is often used. However, recent advances have led to the invention of portable physical activity monitors that allow for an objective measurement of a patient's physical activity. These physical activity monitors will provide physicians with a concrete measurement of activity, which may help clarify the relationship between activity and PS, leading to a possible objective assessment of PS.

Two such physical activity monitors are activPAL™ and Actigraph GT3X™. The activPAL™ (PAL Technologies Ltd, Glasgow, UK, <http://www.paltech.plus.com/products.htm>) is a matchbook-sized (53 x 35 x 7 mm), light (20g) accelerometer, which can measure the amount of time the wearer is lying or sitting versus standing, and ambulating. When ambulating, it measures the speed at which the wearer is moving. These measurements can be used with the accompanying software to calculate energy expenditure. The device is easily attached to the front of the patient's thigh with a non-irritating adhesive sticker and can capture and store up to one week's worth of continuous data silently. The device has been shown to measure time spent on dynamic versus static activities of daily living, to accurately record steps taken and cadence during walking in older adults (Grant *et al.*, 2008), and to appropriately not count motion during vehicle travel (Maddocks *et al.*, 2008). One study to date has used the activPAL™ to compare the activPAL™ measures and ECOG scores

of patients (mean age ≈ 60 yrs) with advanced upper gastrointestinal cancer to controls (Dahele *et al.*, 2007). As expected, controls spent less time sitting/lying each day, and had significantly greater steps/day and energy expenditure.

One limitation of the Dahele *et al.* (2007) study is that the design precluded direct comparisons within levels of the ECOG scale. This preclusion was unfortunate because the range of energy expenditure and steps/day within individual ECOG scores was quite high. However, both energy expenditure and steps/day decreased as expected with increasing ECOG score.

The Actigraph™ GT3X (Actigraph™, LLC, Fort Walton Beach FL, <http://www.theactigraph.com>) is a small (~1.5 x 1.5 x 0.5 inches), light (1.5 ounces), and highly sensitive accelerometer that can record acceleration information in selected epochs. The device records vertical acceleration as an activity count, which provides an indication of the intensity of bodily movement, and can also quantify steps taken. It also contains an inclinometer for the measurement of body position. The device is worn on an elastic belt worn around the waist, and is reasonably unobtrusive. Accelerometers have been used since the 1980's as reliable and valid measures of dynamic activities. The Actigraph™, in particular, has proven to be a dependable device for the assessment of active behaviors, particularly more ambulatory light and moderate-vigorous activities (Matthews, 2005). Recently this instrument has been used to evaluate both active and sedentary behaviors in a national sample in the United States (Troiano *et al.*, 2008; Matthews *et al.*, 2008).

We believe activPAL™ and Actigraph™ can dramatically enhance our ability to objectively determine physical activity and, correlatively, PS. Our study is a pilot feasibility study to evaluate the ability of activPAL™ and Actigraph™ to accurately provide measures of

physical activity, to compare these measures to the PS scores of lung cancer patients receiving chemotherapy, and to understand the ability of patients to tolerate the device. If tolerated, these devices could be further explored for use for both predictive and prognostic purposes and serve as a platform for studying activity interventions.

We hypothesize that the ECOG, Karnofsky, and SF-36 scores will correlate positively with energy expenditure, steps/day, and number of times the subject rises per day, and negatively with percent of time spent sedentary. We do expect, however, that the correlations will be relatively weak, and that for the ECOG scale in particular, we predict a wide range of physical activity at any given ECOG score. We also hypothesize that measures of physical activity (energy expenditure, steps/day, number of times/day arisen) will decrease from pre- to post-chemotherapy, and that percent of time sedentary will increase over the same time period.

## Methods

*Trial Design*

Our study is a cross-sectional study on lung cancer patients recruited from the University of Wisconsin Cancer Center. One week prior to the initiation of chemotherapy (Day -7), subjects are evaluated by a physician to indicate their clinical judgment of the patient's ECOG and Karnofsky scores, complete an SF-36 questionnaire, and receive activPAL™ and Actigraph™ devices to wear for one week (Figure 3). Subjects receive a new activPAL™ and Actigraph™ at Day +1 of their chemotherapy cycles to wear for week two.

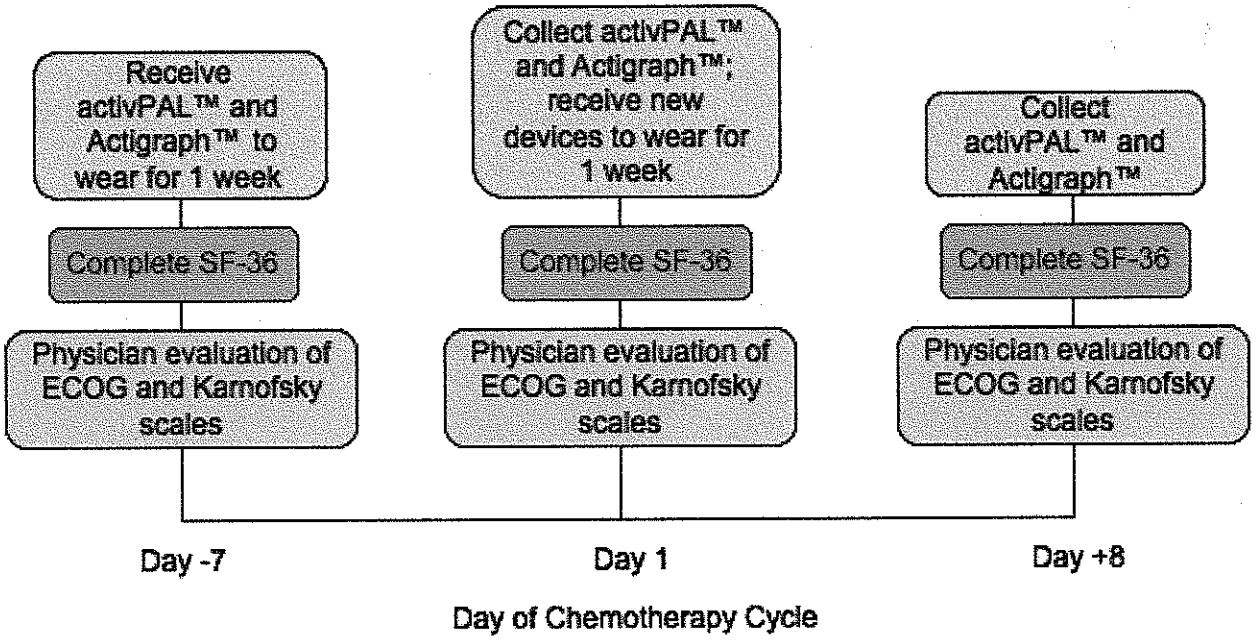


**Figure 3**. Study Design Timeline.

*Subject Population*

We aim to enroll 25 lung cancer patients that are receiving chemotherapy. To date, two subjects have participated. Inclusion criteria for enrolling patients includes having confirmed lung cancer, a Worse Daily Pain Rating of <4/10, an ECOG PS score of 0, 1, or 2 and receiving any cycle, any line or current or planned cytotoxic chemotherapy. Those patients with known brain metastases, receiving concurrent radiotherapy and receiving only targeted therapy are not eligible to participate in our study.

*Interventions*

Subjects are asked to wear the devices throughout the day, from the time they wake up in the morning until the time they go to bed at night, but asked to remove the monitors if they will

get them wet (e.g. showering or bathing). Subjects also complete an activity log to indicate the times they wore the devices and any activities for which they removed them.

*Data Collection and Assessment*

ECOG and Karnofsky PS scores are evaluated by the treating physician for each subject. The SF-36 questionnaires completed by the subjects are scored for a physical composite score using the SF-36 Health Survey Scoring Demonstration (<http://www.sf-36.org/demos/SF-36.html>). The Actigraph™ device collects information that can be used to calculate a wear-time. Those days for which the device is not worn at least 10 hrs will be excluded from the calculations (Figure 4).

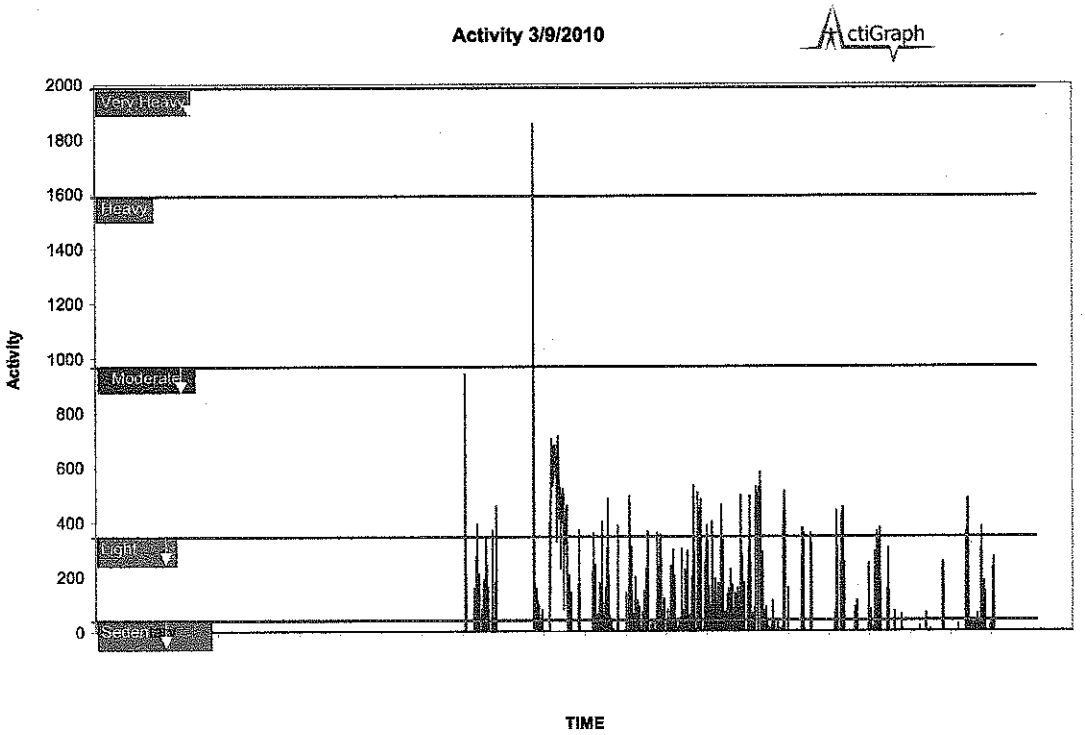


**Figure 4**. Example Actigraph™ GT3X output data. Data was used to determine which days the devices were worn for ≥10 hours. For information on software and device specifics visit www.actigraph.com.

Data from the selected days will be evaluated for average Actigraph™ activity, average activPAL™ energy expenditure, average number of steps per day as measured by both devices, and average number of times subject rose per day as measured by activPAL™ during the week. The measurements of the week prior to chemotherapy are compared to those after treatment and the physical activity data from patients with similar PS scores are also be compared.

**Results**

Two subjects have completed the study. One of the subjects did not receive chemotherapy at Day +1 and therefore, only Week One data of each subject was compared. Both patients received an ECOG score of 1. However, Subject 1 had a lower mean Actigraph™ activity count and mean number of steps per day as measured by both devices than those of Subject 2 (Table 1). Furthermore, Subject 2 rose more than twice the number of times per day than Subject 1 did. Subject 1, however, wore the devices for ≥10 hours for only 4 days of Week One.

| | **Subject 1** | **Subject 2** |
|---|---|---|
| **Mean Actigraph™ GT3X Activity (counts/day)** | 46,088±4286 | 176,591±5405 |
| **Mean activPAL™ Energy Expenditure (MET-hr/day)** | 18.7±1.8 | 20.1±0.3 |
| **Mean Actigraph™ GT3X Number of Steps per day** | 1412±183 | 6189±183 |
| **Mean activPAL™ Number of Steps per day** | 1427±197 | 7600±270 |
| **Mean activPAL™ Number of Times Subject Rises per day** | 22±2 | 54±1 |
| **ECOG PS Score** | 1 | 1 |
| **Karnofsky Score (%)** | 80 | 90 |
| **SF-36 Physical Composite Score at Day +1 (%)** | 35.8 | 31.7 |
| **Number of Days Devices Worn for ≥10 Hours** | 4 | 6 |

**Table 1.** Comparison of mean Actigraph™ GT3X and activPAL™ measurements with ECOG PS and Karnofsky scores for Week One. Error represents standard error of the mean.

Since Subject 1 received chemotherapy as planned at Day +1, the data from the week prior and week after were compared. There was a discrepancy between the Actigraph™ and

activPAL™ measurements, as the former displayed a decrease in steps per day at Week Two, whereas the latter displayed an increased mean energy expenditure and number of steps per day (Table 2). Also, compliance for Subject 1 was better at Week Two compared to Week One.

| | Week One | Week Two |
|---|---|---|
| **Mean Actigraph™ GT3X Activity (counts/day)** | 46,088±4286 | 39,030±3657 |
| **Mean activPAL™ Energy Expenditure (MET-hr/day)** | 18.7±1.8 | 19.7±0.9 |
| **Mean Actigraph™ GT3X Number of Steps per day** | 1412±183 | 999±110 |
| **Mean activPAL™ Number of Steps per day** | 1427±197 | 1516±236 |
| **SF-36 Physical Composite Score at Day +1 (%)** | 35.8 | 30.6 |
| **Number of Days Devices Worn for ≥10 Hours** | 4 | 7 |

**Table 2**. Comparison of mean Actigraph™ GT3X and activPAL™ measurements of Week One and Two for Subject 1. Error represents standard error of the mean.

**Future Directions**

Since only two subjects have completed the study, the data cannot be analyzed yet using statistical tests nor to evaluate the hypotheses. However, evaluating the data of these two subjects can provide some initial results and insights into the methods of our study. For example, while Actigraph™ GT3X shows a difference in activity between the two patients, activPAL™ does not (Table 1). Furthermore, the data from Subject 1's chemotherapy cycle also indicates a difference in Actigraph™ GT3X activity, but not in activPAL™ energy expenditure (Table 2). This discrepancy between Actigraph™ GT3X activity and activPAL™ energy expenditure may suggest a possible lack of correlation between the two device measurements. It is important to recognize that the devices measure activity differently and report results in different units, which may explain the inconsistency. Additional patient data are needed in order to come to any conclusions in this area. Furthermore, SF-36 data for Subject 1 from Week One and Week Two indicates a decrease in physical function during the chemotherapy cycle (Table 2), which agrees with the demonstrated decrease in activity indicated by the Actigraph™ GT3X.

Despite any apparent difference in levels of activity, both subjects received an ECOG PS score of 1 (Table 1), indicating that a wide-range of activity may relate to PS 1.

The data from the two subjects indicates compliance issues that will be addressed with future participants. During Week One, Subject 1 wore the devices for ≥10 hours only four days of the week, while Subject 2 had 6 complete days (Table 1). We are currently formulating methods to increase compliance, such as showing subjects example data of devices prior to enrolling in the study.

These results provide the first step in evaluating the feasibility of using two easily worn devices to provide objective measures of physical activity. The activPAL™ and Actigraph™ GT3X physical activity monitors may dramatically enhance the ability of oncologists to objectively determine physical activity of cancer patients receiving chemotherapy. Future directions following this pilot study include several possibilities. Physical activity can be used as an outcome measure in studies evaluating survival, ability to return to work, ability to tolerate chemotherapy, as well as pain, shortness of breath, and fatigue. Next, physical activity may be explored for predicting life expectancy or response to chemotherapy. Finally, we envision a methodological breakthrough based on our research that can be used to measure the effects of different types of interventions, like yoga or weight-lifting, on patient response to chemotherapy using activPAL™ and Actigraph™ GT3X.

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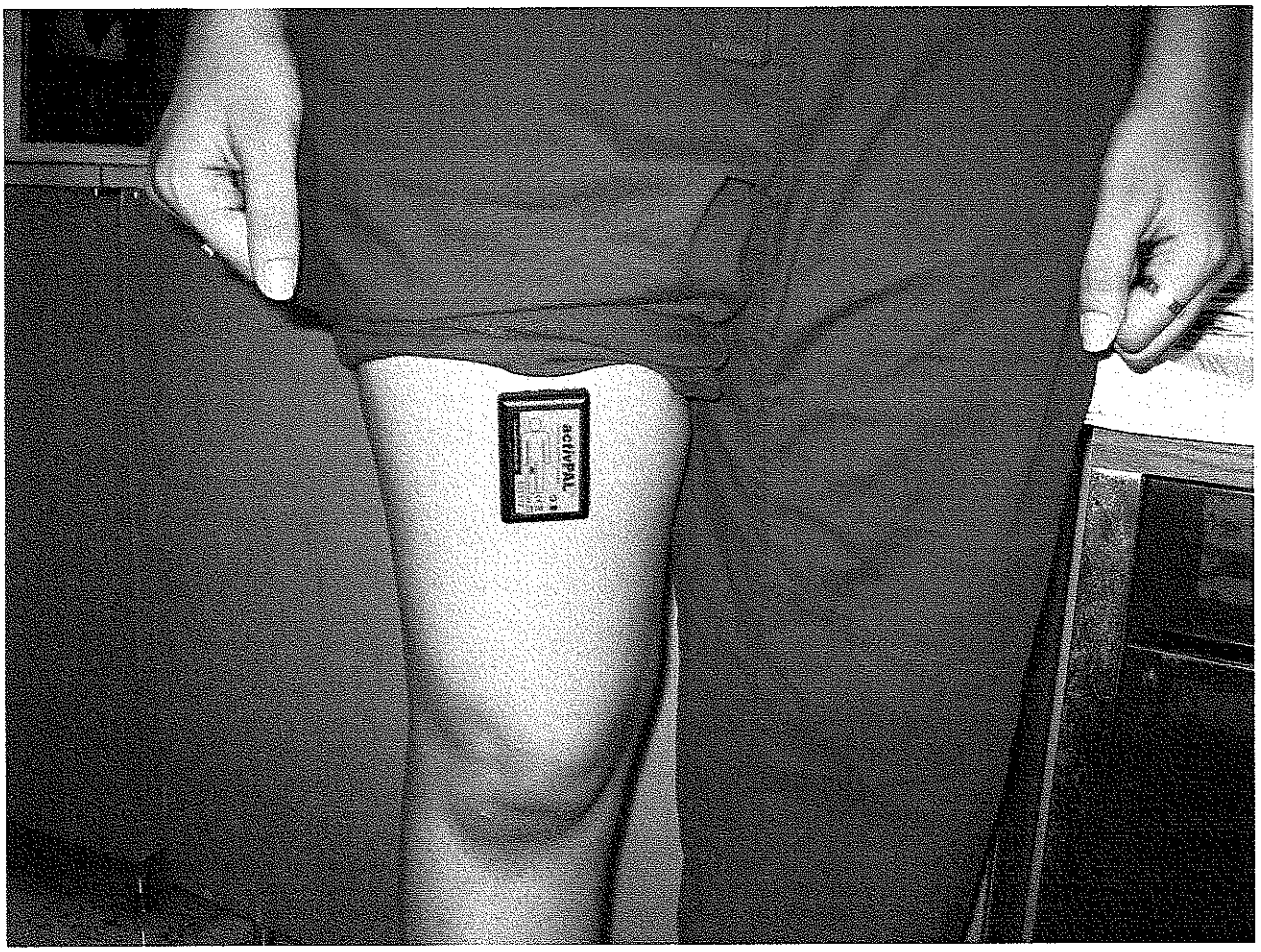
## APPENDIX I: activPAL™ Pictures


*Image from www.paltech.plus.com*



**APPENDIX II: Actigraph™ GT3X Picture**

*Image from www.theactigraph.com*