

# Effects of Intermittent Cryo-Compression Therapy in Primary Total Knee Arthroplasty Patients

## A Prospective, Single-Blind Randomized Controlled Trial

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**Objective** Compare the effects of standard cryotherapy (ice) with static compression to a novel cryotherapy device with adjustable intermittent pneumatic compression on the post-operative rehabilitation of total knee arthroplasty patients via a multi-site, prospective, randomized controlled clinical trial.

**Summary** The belief that cold and compression benefits patients recovering from orthopedic injury is long-standing. But proof of this benefit has been elusive. Studies describing the use of cryotherapy with static compression for orthopedic postoperative recovery have yielded mixed results, possibly due to variance in study design, evaluated modalities, and methods. We present a unique and robust study with substantive interim data representing treatment results from approximately 38% (n = 89) of an intent-to-treat subject pool (n = 236) of patients with osteoarthritis who were scheduled for unilateral, single-incision total knee arthroplasty (TKA). Patients were randomized to a cold and intermittent pneumatic compression test device (Game Ready® Injury Treatment System) or to ice and static compression (ice and compression bandage) and were stratified according to BMI and whether they had had a TKA on the contralateral knee. Researchers and/or physical therapists gathering data from the patients were blinded to the assignment of the device. The results of this preliminary report indicate a positive correlation between the use of the Game Ready Injury Treatment System and accelerated improvement in patients during rehabilitation from TKA surgery over a 6-week period compared to the results in patients using ice and an elastic bandage (static compression).

### Key Points

- Improved and accelerated complex physical functioning shortly after surgery generally is consistent with more rapid return to normal activities of daily living—and with patient expectations and/or payer and employer expectations.
- The Game Ready group exhibited more than double the physical function abilities of the control group in both the Timed Up and Go and Six-Minute Walk Test assessments.
- More Game Ready subjects (> 20%) were able to perform complex weight-bearing physical activities by six weeks than were control subjects.
- Game Ready subjects reported improved pain relief over time at both the two- and six-week follow-ups compared to control subjects.

### Rationale

This study was designed to support an adequately powered, single-blind, randomized controlled evaluation of two different cold and compression modalities in patients who are recovering from a standardized, orthopedic procedure. The purpose of the study was to generate strong, clinically relevant evidence to guide clinicians and payers in their postoperative management and payment decisions. Total knee arthroplasty (TKA) has become the standard for surgical management of end-stage osteoarthritis of the knee. It is generally considered a uniform operative procedure and, thus, offers a normalized forum for a thorough investigation of the effectiveness of these two postoperative orthopedic rehabilitation therapies.



There has not been a study of this magnitude or of this rigor evaluating the benefits of cold and intermittent pneumatic compression (IPC) in primary TKA patients. Primary objectives of this study involved specific functional parameters that could translate into physical and economic benefits for patients their employers and payers. The measures of these functional parameters included: physical function (as measured by the six-minute walk test and a timed up and go test) and the ability to reach defined physical therapy milestones by the end of the 6-week follow up period. Secondary objectives include other functional measurements that are common, expected measures, but are characterized by inherent variability: active range of motion, swelling, and visual analog scale (VAS) for pain and pain medications taken (note that medications data are not included in this interim analysis).

These variables can be quantified in terms of health economics that benefit both patient and payer. For example, the value of lost workdays is approximately \$200/day for an average wage earner (\$50,000/yr). In 2002, the Work Loss Data Institute (WLDI) issued a report based upon data from the Centers for Disease Control & Prevention (CDC) that lost-time costs exceeded associated medical costs.<sup>1</sup> The WLDI concluded that allowing for indirect costs, lost-time costs exceed medical costs by a substantial margin. Clearly, the sooner a patient can get back to "normal" living, the greater the reduction in medical care costs, and the greater the productivity and financial independence of the patient.

With the final analysis of this study, these cost benefits can be more succinctly quantified, and it is expected that some measurable savings will be realized.

## **Physiologic Models and Reported Clinical Benefits**

Total knee arthroplasty involves a relatively standard operative technique with relatively extensive tissue excision, tourniquet time, intraoperative blood loss, and postoperative edema and pain. The extensive soft tissue trauma associated with TKA sets off a cascade of inflammatory responses, including increased blood flow, edema

and passage of leukocytes into the surrounding interstitial spaces. In general, the application of cold not only produces marked vasoconstriction but it decreases the presence of leukocytes on the endothelial surfaces of capillaries, resulting in less leukocyte migration into surrounding tissues.<sup>2,3</sup> Cryotherapy has been shown to provide short-term analgesic effect, which is thought to be a combination of a decreased production of pain mediators and slower propagation of pain signals.<sup>2,4</sup>

Post-traumatic edema results from the action of the inflammatory mediators on the endothelial cells. Tissue congestion follows and reduces the availability of oxygen to mitochondria and, thus, energy for the sodium-potassium pump. Failure of the pump causes fluid within cells to increase and consequent fragmentation of DNA within the cell nucleus and, ultimately, "clumping" of chromatin. Accumulation of this protein-rich fluid within the interstitial space can lead to inelastic scar tissue.<sup>2,5</sup> Intermittent pneumatic compression has been reported to be effective in reducing this edema formation, increasing blood and lymph flow, and stimulating tissue healing.<sup>6-9</sup>

Cryotherapy in combination with IPC would hypothetically reduce the physiologic effects of traumatic tissue damage based on the models of cryotherapy and static compression therapy alone. Both Bleakley and Hubbard concluded after their reviews of the literature that cryotherapy reduces pain allowing patients to return to more participatory exercises.<sup>7,10</sup> Adie reported on the additive effect of compression with cryotherapy to increase range of motion.<sup>11</sup> In theory, reducing these physiologic effects of tissue injury should accelerate the individual's return to his/her pre-injury state of health. Improved reduction of edema and pain may well translate into earlier and more successful rehabilitative efforts with minimal (narcotic) pain medication. Early and successful rehabilitation that requires only short-term analgesic use suggests an early return to normal work or other activities and, consequently, savings for the individual, the payer, and the community. This study seeks to confirm and quantify this hypothesis.



Given the reported clinical benefits of various cold and compression therapies, CoolSystems partnered with key orthopedic surgeons to design and implement the resulting robust, single-blind randomized controlled trial (RCT) to permit a thorough evaluation of the Game Ready Injury Treatment System compared to the standard of care of record, an ice bag with static compression.

## Materials and Methods

This prospective, randomized, controlled, single-blind IRB-approved clinical trial was conducted at 11 sites. These interim data are from the two sites that enrolled the most patients in the study (Hospital for Special Surgery, New York, NY and Brooke Army Medical Center, Fort Sam Houston, TX). It was intended that the resulting data would establish physical health and economic benefit in the clinical setting in support of reimbursement. The test device, the Game Ready Injury Treatment System (CoolSystems, Concord, CA), is a cleared device and has been in commercial distribution since 2002.

The system uses ice as the source of cold. Its intermittent pneumatic compression function can be set to any one of three pre-established levels: Low, Medium or High (15, 50, 75 mmHg). Whereas both temperature and compression levels are adjustable, temperature ultimately depends upon the amount of ice in the water that supplies the wraps and can be modified from “maximum” cold to “minimum” cold, generally ranging from ~34°F to 60°F.

The protocol did not control for temperature or for compression. It was recommended that compression in non-ambulatory patients never exceed 50 mmHg.

Subjects were randomized to two different modality groups (test vs control). Blocked and

stratified computer-generated randomization schedules were carried out for each site; stratification factors were the presence or absence of TKA in the contralateral knee and BMI ≤31 and BMI >31.

The study population consisted of patients diagnosed with osteoarthritis and scheduled for a unilateral, primary TKA procedure. Inclusion criteria included men and women

- Ages  $\geq 18 \leq 85$  years with
- BMI  $\leq 40$  and a
- Diagnosis of primary osteoarthritis of the knee who have not had a
- TKA in the contralateral knee < 6 months from the scheduled TKA of the study knee

Exclusion criteria included: rheumatoid arthritis, severe pitting in the ipsilateral limb, history of thrombophlebitis in the lower extremities, active systemic disease (eg, AIDS, HIV, hepatitis), immunologically suppressed or is/has received steroids daily for more than one month in the past 12 months, or pregnant or planning to be-

**Table 1** Subject demographics at baseline (*n* = 89).

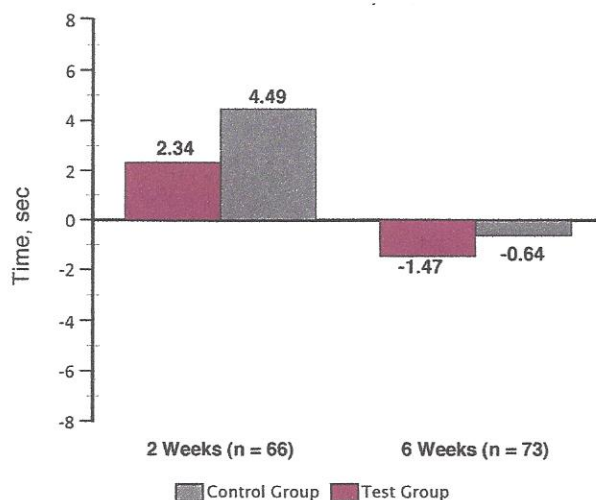
	Test	Control
<b>Randomization</b>	<b>48 (54%)</b>	<b>41 (46%)</b>
Male	26 (54%)	21 (51%)
Female	22 (46%)	20 (49%)
Age at surgery, mean; y (min, max)	64 (40, 79)	64 (32, 83)
BMI, mean (min, max)	29.9 (20.0, 47.6)	29.7 (21.6, 38.9)
Previous TKA	9 (19%)	8 (20%)
Ethnicity		
White	38 (79%)	28 (68%)
African American	7 (15%)	3 (7%)
Hispanic	3 (6%)	8 (20%)
Native Hawaiian		1 (2%)
Not declared		1 (2%)

come pregnant during the study period (pre-operative through 6 weeks postoperative).

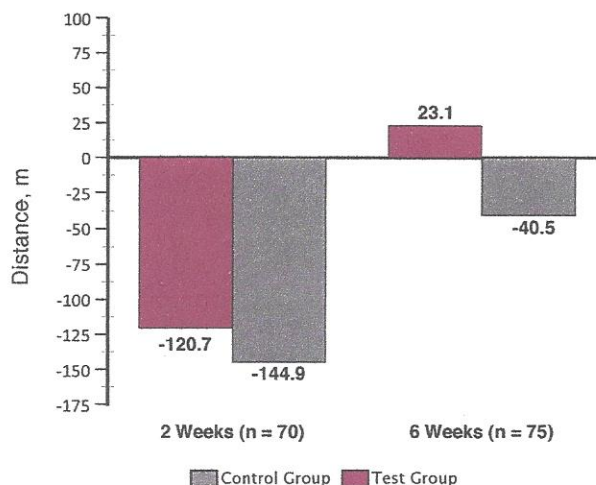
The test group and the control group used the same protocols for cryotherapy as soon as possible following surgery but no later than 3 hours after the end of the surgery.

- Game Ready was applied to the operative knee of each test subject. The device was cycled on for  $60 \pm 20$  minutes and cycled off for at least  $120 \pm 20$  minutes while the subject was awake and still in-hospital. This on/off cycle was repeated at least 4 times each day, to allow for other in-hospital protocols (e.g., physical therapy, wound management, etc.). This approach was intended to account for the presence of a very thick dressing, through which cold would have to pass. After discharge, with a much thinner dressing in place, the duration was reduced to  $30 \pm 10$  minutes, and cycled off for  $60 \pm 10$  minutes. Subjects were instructed to repeat this cycle at least 4 times each day for two weeks.
- For each control subject cryotherapy with static compression (an ice bag in a pillowcase secured to the patient with a compression bandage) was applied to the operative knee immediately after surgery in the recovery room. Ice with compression was applied according to the same on/off cycling times, durations and frequencies as were carried out with the test device both in-hospital and post-discharge for two weeks.
- After two weeks, both test and control subjects were required to stop the cryotherapy protocol, (return the Game Ready Injury Treatment System to the hospital) and, if they still desired periodic cold therapy, they could use ice or gel packs as needed.

A physical therapist or independent researcher, who was blinded to the patient's treatment method evaluated the subject's physical function at baseline (ie, pre-operatively), within 24-hours pre-discharge, and weekly ( $\pm 3$  days) from 2 weeks to 6 weeks postoperatively. The study was designed to replicate a conventional



**Fig. 1A** Timed Up and Go Test: timed transition from sit to stand and return to chair, compared to baseline.



**Fig. 1B** Six-Minute Walk Test: timed six-minute walk, measured in meters, compared to baseline.

**Figures 1A and 1B** Physical Function Assessment.

or “real world” setting. Thus, there were no prescriptions on type of physical therapy program. Whether in-hospital or post-discharge, each physical therapy program was asked to limit the patient measurements to the same observer, if possible.

Primary assessments evaluated the subject's weekly change in physical function from pre-operative levels to postoperative levels beginning at 2 and continuing for 6 weeks post-surgery according to his or her ability to transition from sit to stand, walk 3 meters, turn, return to the chair,



and sit down again (“Timed Up and Go” [TUG]) as well as the ability to walk as far as possible during a timed 6-minute, 60-meter course on a flat surface (“6-Minute Walk Test” [6MWT]). Primary assessments also measured the subject’s achievement of certain physical therapy milestones:

- Transition from sit to stand without assistance, have
- Full active extension (0 degrees measured with a goniometer while supine) and
- Full active flexion (110 degrees measured with a goniometer while supine), and
- Walk without limping and without an assistive device (if the subject did not use one pre-operatively)

Secondary assessments detailed the subject’s change in active range of motion, self-reported pain on a 100-mm Visual Analog Scale (VAS), and swelling measured at 10 cm above mid-patella, mid-patella, and 10 cm below mid-patella.

## Results

The following summary, tabular and graphical results represent preliminary data collected for 89 patients in the study out of the total population of 236 subjects enrolled and entered into the database at the time of this interim analysis. Summary subject demographics are presented in Table 1 and reflect successful randomization.

Graphical analyses of the study outcomes in terms of physical function, active range of motion, pain, and swelling and edema are presented in Figures 1, 2, 3 and 4, respectively. Physical therapy milestones are listed in Table

2. The evaluated endpoints were the differences between the 2- and 6-week postoperative measurements and the baseline pre-operative measurements. The summarized data represent only those data that have been collected and verified to date; thus, there could be additional as of yet unverified and/or uncollected data that are not included for these same subjects.

### Primary Assessments

Both test and control subjects took longer to complete the TUG test at two weeks post-procedure than they did pre-operatively (Figure 1A). However, the test group completed the TUG test substantially faster (+2.34 sec versus +4.49 sec) than the control group did at the two-week

**Table 2** Physical therapy functional milestones (*n* = 89).

	Test ( <i>n</i> = 48)	Control ( <i>n</i> = 41)
<b>Sit to Stand</b>		
Number successful	34	21
Percent successful	71%	51%
Time to success, d, mean; (min, max [SD])	25 (2, 48 [11.8])	22 (3, 43 [12.7])
<b>0° Extension</b>		
Number successful	29	27
Percent successful	60%	66%
Time to success, d, mean; (min, max [SD])	30 (13, 46 [11.5])	26 (2, 47 [14.1])
<b>110° Flexion</b>		
Number successful	18	15
Percent successful	38%	37%
Time to success, d, mean; (min, max [SD])	30 (14, 43 [8.5])	36 (13, 48 [11.3])
<b>Ambulation Without Antalgia</b>		
Number successful	33	19
Percent successful	69%	46%
Time to success, d, mean; (min, max [SD])	28 (4, 43 [11.1])	30 (13, 47 [10.3])

junction, performing 47.9% better than the control group. At six weeks post-procedure, both groups achieved faster TUG mean times than they did pre-operatively, with the test group continuing to out-perform the control group by a nominal 275% faster time (-1.47 sec versus -0.64 sec). The same functional trend is suggested by Figure 1B, which summarizes the groups’ ability to walk. Unlike the control subjects, who fell short of their mean pre-operative distance

by 40.5 meters at the 6-week follow up, the test subjects exceeded their average pre-operative distance by 23.1 meters. The interim results of these two tests indicate improved functionality for complex physical movements in the Game Ready patients compared to those treated with ice and static compression by significant margins. The test group exhibited more than double the physical function abilities of the control group in both assessments.

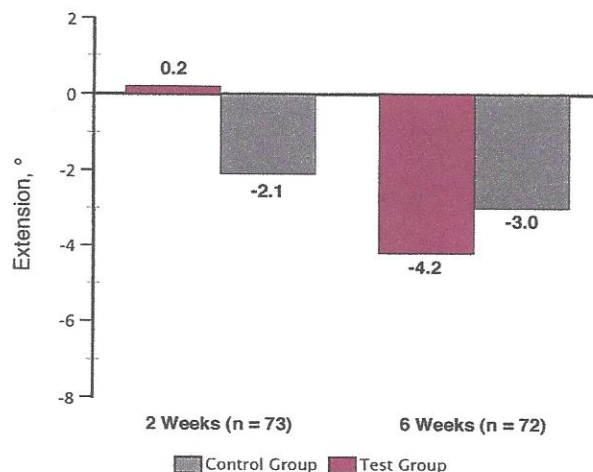
Even though there were no detectable differences in flexion and extension between test and control (Table 2), approximately 20% more test (Game Ready) than control (ice) patients met the sit-to-stand and the ambulation without limping milestones, which were reached by a larger percentage of the Game Ready subjects compared to the control subjects, indicate that the former achieved greater functionality than their control counterparts.

Collectively, these findings (TUG, 6-minute walk test, sit-to-stand and limp-free ambulation) indicate that more Game Ready subjects were able to perform complex weight-bearing physical activity, representative of the activities of independent daily living, such as getting in and out of a chair, and walking some distance (including turning) without limping (antalgia). The Game Ready group, unlike the control group, exceeded their pre-operative functional levels at the 6-week follow-up in the six-minute walk test. Both groups improved upon their pre-operative function by 6 weeks for the timed up and go test; however, the test group achieved more than double the improvement over the control group in the TUG test.

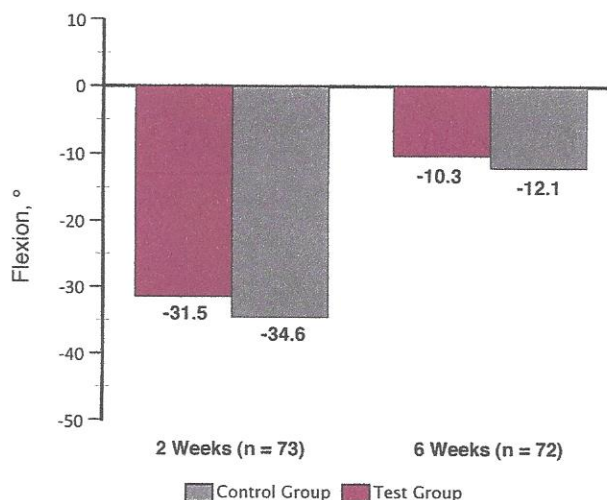
### Secondary Assessments

Flexion and Extension were also measured throughout the course of the 6-week study follow-up period and were compared as a measure of progress from baseline (pre-operative).

At six weeks, the test group evidenced improved mean extension to  $-4.2^\circ$  and the control group to  $-3.0^\circ$ . Both test and control groups showed improved flexion by the end of 6 weeks as compared to their flexion at 2 weeks ( $-10.3^\circ$  versus

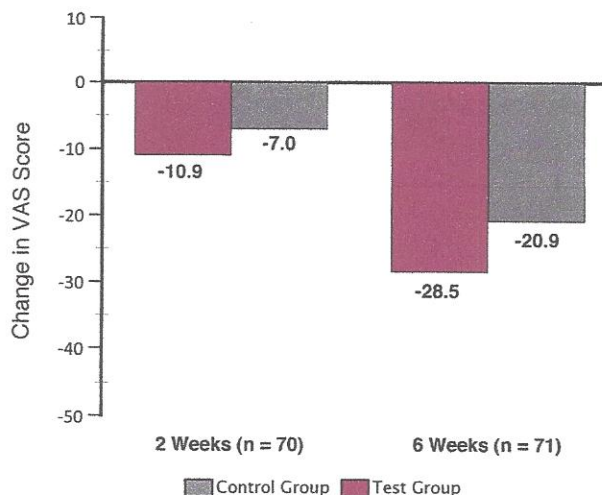


**Fig. 2A** Change in degree of extension since pre-operative measurement.



**Fig. 2B** Change in Flexion Since Baseline

**Figures 2A and 2B** Active Range of Motion Assessment.



**Figure 3** Secondary Assessment: Change in mean VAS Pain Score reported by patients.



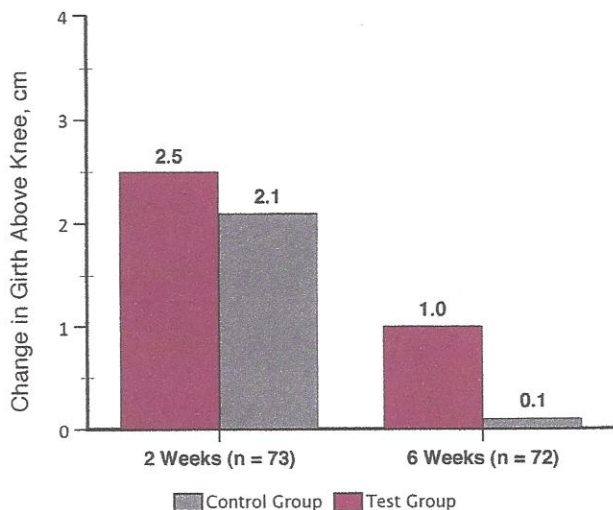


Fig. 4A Change in girth measured 10 cm above mid-patella.

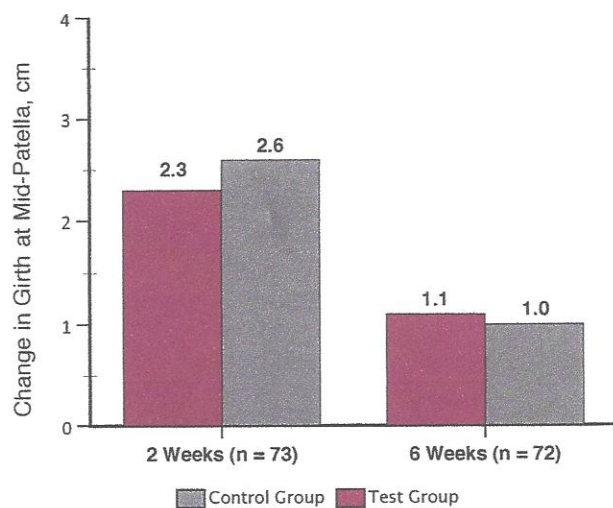


Fig. 4B Change in girth measured at mid-patella.

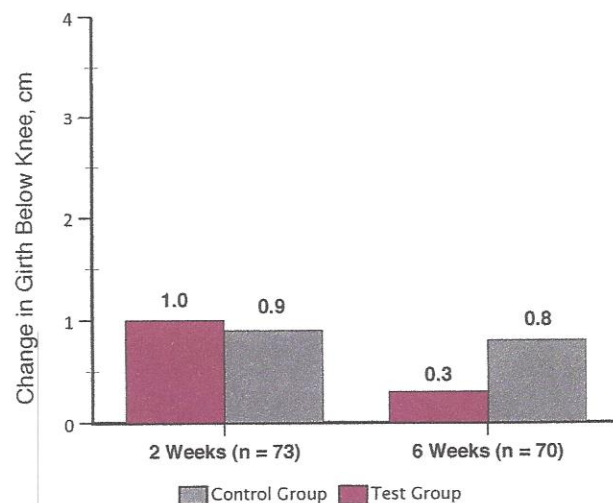


Fig. 4C Change in girth measured 10 cm below mid-patella.

Figures 4A, 4B and 4C Swelling and Edema assessed by change in girth measurements compared to baseline.

-12.1°, respectively); however, neither test nor control groups achieved pre-operative levels by their 6-week follow-up. (Fig. 2B)

Pain for both study groups was measured at the 2- and 6-week postoperative visits by the Visual Analog Scale (VAS). These scores represent the change in reported pain levels over time, thus a negative score reflects the extent to which pain levels have decreased. The mean VAS scores for both groups reported here indicate the test subjects reported a greater decrease in pain over time compared to the control subjects: -10.9 mm versus -7.0 mm at 2 weeks and -28.5 mm versus -20.9 mm at 6 weeks. (Fig. 3)

For changes in superior, midline and inferior girth overall, the control group and the test group showed comparable trends of swelling (Figs 4A-C). However, the control subjects showed less swelling/edema formation than did the test subjects in terms of girth measurements 10 cm above the mid-patella: 2.1 cm versus 2.5 cm at 2 weeks and 0.1 cm versus 1.0 cm at 6 weeks. Both midline and inferior girth measurements were comparable between both subject groups with the inferior girth measurement results indicating slightly less average swelling in the test group (0.3 cm for the test subjects versus 0.8 cm for the control subjects) at 6 weeks.

## Discussion

This is an interim analysis of a sampling of available and verified data from approximately 38% of a patient subject pool. Because these data may not represent complete sets for each subject, readers must be guarded in their assumptions. The study was designed to imitate the conventions of a "normal" postoperative and post-discharge setting. That is, the study did not control for physical therapy protocols, cryotherapy temperature or degree of compression (static versus adjustable IPC from 0 mm Hg to 75 mmHg). Blinding was constant (limited to the observer only), the applications of the test and control devices were constant in terms of time on and time off, and the two cryotherapy modalities had to be used at least 4 times each day for two weeks.

The results gathered thus far outline the distinct possibilities of improved functional performance with intermittent pneumatic compression and active cryotherapy for the patient anticipating rehabilitation after TKA.

The final data analysis will evaluate in-hospital and post-discharge use of pain medications and will look closely at the results as they might influence the economics of orthopedic post-operative recovery. However, even without the pain medication data, these interim results suggest a promising outcome for intermittent cryo-compression therapy in primary TKA patients.

## Limitations

The primary outcome measures were selected as representative of physical function necessary for return to independent function. Because they are relatively straightforward, the probability that trends suggested by these measures will hold detectable statistical significance is more likely.

The secondary measures are highly variable in

measurement and therefore have a large standard deviation. It is not certain the sample size for this study will support the ability to detect a treatment effect associated with either modality and only the final analysis will shed any light on that concern.

## Conclusion

These interim results indicate that the Game Ready Injury Treatment System may provide:

- Improved and accelerated complex physical functioning shortly after surgery.
- Reduced levels of pain postoperatively.
- Faster return to independence in daily living activities.

Collectively, these findings may allow one to anticipate reduced pain medications, reduced physical therapy time, and more rapid return to “normal” activities of daily living—consistent with patient expectations and/or payer and employer expectations.



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