PART B
STUDY DESCRIPTION

Title of Protocol	**The Use of Dantrolene to Improve Analgesia in Posterior Lumbar Surgery**
Principal Investigator	Richard J. Pollard, MD

B1. PURPOSE OF PROTOCOL

The purpose of this study is to determine whether administration of a non-centrally acting muscle relaxant will improve the Overall Benefit of Analgesia Score (OBAS)[1], and Richmond Agitation Sedation Scale (RASS)[2] scores in patients undergoing lumbar decompression and/or fusion.

Hypothesis: This randomized controlled trial will test the primary hypothesis that 25 mg of Dantrolene given twice a day for two days improves the benefit of postoperative analgesia after surgery.

B2. SIGNIFICANCE AND BACKGROUND FOR THE STUDY

Major surgical operations on the spine result in significant post-operative pain.[3,4] This is in part due to the use of surgical techniques that directly impact the musculature of the posterior spine column. As a result, muscle spasm is often a limiting factor in the early mobilization and discharge of these patients. Effective pain management is essential in order to facilitate early mobility, reduce postoperative pulmonary complications, shorten hospital length of stay, and enhance patient satisfaction.

A quality assurance review of patients undergoing lumbar spinal fusion at Beth Israel Medical center (BIDMC) showed that patients undergoing lumbar spinal surgery received on average 354 mg of morphine equivalent doses (MED) in narcotics during the period after surgery. The same patients received the equivalent of greater than 30 mg of Diazepam during the same period. The primary complaint in this patient population is muscle spasm. This finding hinders the early mobilization of this population and their rapid discharge from the hospital. The current management of these patients does not facilitate early mobilization of this population, this is despite multiple studies with differing surgical and pain control approaches.[5,6,7,8,9,10,11]

Dantrolene was originally synthesized by Snyder and his co-workers in 1967 [12]. It was found to have skeletal muscle relaxant properties after intravenous administration in animals. Studies revealed that these relaxant properties are due to depression of excitation– contraction coupling. This complex process enables skeletal muscles to transform a chemical signal at the neuromuscular junction into a muscle contraction [13]. Dantrolene is now thought to work by affecting calcium flux across the sarcoplasmic reticulum of skeletal muscle. This is made possible by the drug binding to a specific N-terminal region of type-1 ryanodine receptor (RyR1) involving residues 590 to 609 within the skeletal muscle cells.[14] This reduces RyR1-dependent calcium flux in vesicle studies [15] and dihydropyridine receptor and RyR1 coupling in muscle cells. [16] Recent evidence indicates that the inhibitory effect of dantrolene on RyR1 channel activity requires calmodulin binding to RyR1. [17] Additional studies suggest that dantrolene reduces RyR1-dependent calcium influx via store-operated calcium entry,[18] although this may not be due to a direct inhibition of store-operated calcium entry channels. [19]

Dantrolene was initially used as a muscle relaxant in the long-term treatment of skeletal muscle spasticity [20]. Today Dantrolene is used in the management of malignant hyperthermia [21], the neuroleptic malignant syndrome, heat stroke, muscle spasticity, hemiplegia, cerebral palsy, muscular dystrophy and multiple sclerosis.

Properties of the Study Medication

Multiple studies have identified and quantified the effects of dantrolene on humans. After oral administration, 70% of a dose of dantrolene is absorbed.[22] Significant variations in plasma concentrations are seen, peaking at about 6 hours [23]. Meyler et al.[24] studied the mean steady state plasma concentrations of dantrolene and its metabolites after oral administration daily for two weeks. The doses studied were 50, 100, 200, or 400 mg daily. 50 and 100 mg daily were able to obtain a mean plasma concentration of between 0.35 and 0.6 mg/L.

Distribution

Animal studies have shown dantrolene to be distributed widely, with the highest concentrations in the intestines and liver.[25] However, as dantrolene is lipophilic it would be expected to cross cell membranes, the placenta and the blood-brain barrier.

Metabolism and Elimination
Dantrolene is metabolized by liver microsomes to 5-hydroxydantrolene, which itself acts as a skeletal muscle relaxant. Reduction of the nitro moiety of the benzene ring leads to the formation of amino-dantrolene, which is metabolized to the reduced acetylated derivative of dantrolene [26]. Dantrolene and its metabolites are excreted mainly via urine and bile.[27,28] Dantrolene has structural similarities to both hydantoin and some local anesthetics, but has neither anticonvulsant nor anesthetic properties [29].

Elimination Half-life
Plasma concentrations remain stable within the therapeutic range for approximately 5 hours after administration. The plasma elimination half-life time is estimated to be 12 hours. In the only pharmacokinetic study in patients with malignant hyperthermia the mean elimination half-life following administration of intravenous dantrolene 2.5 mg/kg over a 10- to 30-minute period was 12 hours.[30]

Implications
Given its muscle relaxing properties, Dantrolene seems to be an ideal candidate to be studied for treatment of postoperative muscle spasms, with the potential to reduce postoperative pain following lumbar surgery.

B3. DESCRIPTION OF RESEARCH PROTOCOL

A. Study Design – Overview, Methods, Procedures

Study Design
This is as a prospective, randomized, placebo-controlled triple-blinded trial of patients undergoing lumbar spine decompression and/or fusion at BIDMC. Patients meeting inclusion criteria with no exclusions will be approached to obtain written informed consent. Patients who decide to participate will receive either Dantrolene (25 mg PO) or placebo twice daily for two days commencing pre-operatively. Data will be collected in order to determine whether there is a difference in OBAS scores following surgery.

Randomization and Medication Administration
Enrolled subjects will be randomized before surgery to one of the two study groups, in a 1:1 randomization ratio. The randomization schema will be generated by an unblinded statistician and sent to the research pharmacy, who will prepare and dispense the study medications.

Patients will be randomized to receive either oral Dantrolene or placebo at a dose of 25 mg PO preoperatively. Use of placebo is a standard control procedure in clinical trials and will allow for the assessment of unbiased quantitative data on the efficacy across all treatment groups. The patient, clinicians and the study team members will all be blinded for the group. In case of an emergency the randomization can be obtained from the research pharmacy. The patients will receive either Dantrolene (25 mg PO) or placebo twice daily for a total of four doses at the following time points:

Dose	Administration Time	Details
1	One Hour Before Surgery (Time 0)	*This will be administered preoperatively one hour of surgery.*
2	12 Hours Postoperatively	*The study medication will be administered 12 hours (± 1 hour to accommodate pharmacy scheduling) after time 0.*
3	24 Hours Postoperatively	*The study medication will be administered 24 hours (± 1 hour to accommodate pharmacy scheduling) after time 0.*
4	36 Hours Postoperatively	*The study medication will be administered 36 hours (± 1 hour to accommodate pharmacy scheduling) after time 0.*

Standard Therapy (Usual Care)
All preoperative care and intraoperative management, including medication administration, will follow the current standard of care in all study participants and will be at the discretion of the treating clinician. The intraoperative and postoperative anesthetic management will not be determined by this research protocols with one exception. The use of neostigmine (an acetylcholinesterase antagonist) has been associated with impairment of genioglossus muscle activity (upper airway dilator function) [31,32,33], which could potentially lead to respiratory insufficiency in the

immediate postoperative period. In this study the neuromuscular blocking agent Rocuronium will therefore be used. This is due to the presence of a selective relaxant binding agent (Sugamadex) that does not have the potential to cause muscle weakness. Additionally, the following concomitant medications will be prohibited while taking Dantrolene: non-dihydropyridine calcium channel blockers including verapamil and estrogen therapy.

Data Collection, Outcomes and their Measurement
Patient comorbid conditions, surgery and anesthetic medications administered during surgery used will be obtained from the patient's medical record and the Anesthesia Information Management System. Data related to outcomes such as pain scores, opioid doses, results of physical and occupational therapy consults, duration of stay and complications will be obtained from the medical records.

Additional data will be collected directly from patients including the Overall Benefit of Analgesia Score (OBAS), and Richmond Agitation Sedation Scale (RASS), and ICU Mobility Score at the time intervals specified below. This data will be recorded on paper data collection forms. Results of the questionnaires will not be made part of the patient's medical record, nor will they be made available to treating clinicians. *Please see Section B11 and the attached questionnaires for details*.

	Baseline (1 Hour Before Surgery)	**After Surgery**	
		24 Hours *(± 1 hour)*	***48 Hours*** *(± 1 hour)*
Pain Score Assessed	**X**	**X**	**X**
OBAS	**X**	**X**	**X**
RASS		**X**	**X**
ICU Mobility Questionnaire		**X**	**X**

Pain is routinely assessed in the postoperative period by nurses on an 11-point scale (i.e. patients are asked to rate their pain on a scale of 0 to 10). If a pain score is not documented at the intervals required per protocol, we will ask the patient directly. The total dose of opioids consumed in the 48 hours post-operative period will be obtained from the patient's medical records. This will be converted to morphine equivalents for standardization of the outcome and for ease of analysis.

In the occasion that a patient has been discharged prior to their 48 hour time point, the follow-up pain assessment and additional data collection questionnaires may either occur in the PACU or at home via telephone.

Data will be collected and stored in REDCap or on password protected computers. Any data collected on paper will be stored in locked study offices or file cabinets.

Adverse Event Reporting
Our patient population is by definition undergoing high risk surgery and is therefore critically ill. It is expected that they will have a number of unrelated adverse health events during the course of their hospital stay. Therefore, we will limit the scope of our AE monitoring and reporting to the following:

- All Serious Adverse Events, including unexpected death, believed to be related to the study
- Unexpected, Non-serious Adverse Events believed to be possibly or probably related to the intervention

Evidence for adverse events will be assessed daily during the hospital stay, for a maximum of four postoperative days, which well exceeds the half-life of the study medication. Additionally, adverse events will be periodically reviewed by a safety committee, as specified in Part P.

B. Statistical Considerations

Sample Size Justification
A difference in a mean OBAS score of less than three points is considered a clinically meaningful difference.[34] This represents 10% of the range of the OBAS scale. Thus, the study must have the power to detect a difference of three points to reject the null hypothesis the Dantrolene treatment is superior to placebo treatment. Using a 2-tailed alpha of 0.05, a standard deviation of 5 and a power of 80% power to detect a standardized effect size of 0.6 with two-sample t test, 45 patients are needed per group, 90 patients in total. Due to more withdrawals than originally anticipated, we will increase our sample size by 45%, enrolling a total of 130 patients.

Data Analysis
Analyses will be conducted by a statistician at BIDMC using SAS version 9.4 (SAS Institute Inc., Cary, NC) or later. Descriptive statistics of the data will be performed. Continuous data (e.g. age, pain scores, and opioid consumption) will be represented using mean (± standard deviation) or median (interquartile range) for variables not normally distributed and compared using parametric or non-parametric t-tests as appropriate. Categorical data (e.g. benzodiazepine use, incidence of nausea/vomiting) will be presented as frequencies or proportions and analyzed using a chi-square or Fishers Exact test. Linear and logistic regression will be employed as necessary to adjust for potential differences between groups that persist after randomization. Repeated measures analyses will be employed to assess the trajectory and changes in continuous variable (OBAS, RASS, NRS) over time. All two sided p-values < 0.05 will be considered statistically significant.

The primary outcome of the study, OBAS score at 24 hours, will be patient reported and assessed for differences between those who received at least one dose of placebo versus Dantrolene.

Other secondary outcomes include:
- OBAS scores at 48 hours
- Richmond Agitation Sedation Scale (RASS scores) at 24 and 48 hours
- ICU Mobility Score at 24 and 48 hours
- Pain Scores using a Numeric Rating Scale (0 [no pain] to 10)
- Any incidence of adverse events including vomiting, nausea, oxygen desaturations (<95%, or >5% of baseline) or need for supplemental oxygen requirements
- ICU length of stay
- Hospital length of stay
- Benzodiazepine use postoperatively
- Postoperative narcotic administration and morphine equivalent dose

Electronic data will be stored on password-protected computers behind the BIDMC firewall or in REDCap directly. All analyses will be performed on an intention to treat basis.

C. Subject Selection

Inclusion Criteria
- 18 – 80 years of age (inclusive)
- Presenting to BIDMC for lumbar decompression and/or fusion (instrumented fusion of the lumbar spine) with a posterior approach, under general anesthesia, and scheduled for same-day admission or inpatient admission
- Procedure should involve ≥ 2 vertebrae levels
- American Society of Anesthesiologists (ASA) Category 1, 2 or 3

Exclusion Criteria
- Known allergy to Dantrolene, morphine or other opioids, benzodiazepines that causes a reaction of hives, anaphylaxis, shock, unconsciousness/fainting, rashes/blisters, irregular heartbeat, fever, swelling, shortness of breath, wheezing, serum sickness, drug induced anemia, drug reaction with eosinophilia and systemic symptoms, or nephritis
- Patient being treated with any of the following medications:
    - Non-dihydropyridine Calcium Channel Blockers including verapamil

- Hormonal replacement therapy
- Current or past medical history of any of the following:
    - Hepatic impairment (including history of transplant)
    - Renal impairment or chronic renal disease (including history of transplant)
    - Heavy alcohol use (defined as consuming more than 4 drinks for females or 5 drinks for males in 2 hours on more than 5 occasions per month)
    - Chronic respiratory disease (i.e. chronic hypoxia or hypercapnia, COPD) that creates an increased risk to the participant per clinician assessment
- Recent history of aspiration (within the last 3 months)
- Patients with any history of neuromuscular dysfunction that creates as increased risk to the participant per clinician assessment
- Weight > 140 kg
- Known or suspected pregnancy
- Actively breastfeeding
- Inability to provide written informed consent
- Staged procedures
- COVID-19 positive test result

Drop-out Criteria

- Oxygen saturation < 94% in pre-op holding unless all prior readings have been normal and/or in the clinical judgement of the investigator, the low reading is spurious

We will enroll patients without regard to gender, race, or ethnic distribution.

B4. POSSIBLE BENEFITS

There are no guaranteed health benefits to the patient being included in this study. An improved understanding, and potentially information as to whether or not this medication can provide symptom relief, may improve comfort after lumbar surgery for other patients in the future.

B5. POSSIBLE RISKS AND ANALYSIS OF RISK/BENEFIT RATIO

Risks of the Study Medication

The most frequently occurring side effects of Dantrium have been drowsiness, dizziness, weakness, general malaise, fatigue, and diarrhea. These are generally transient, occurring early in treatment, and can often be obviated by beginning with a low dose and increasing dosage gradually until an optimal regimen is established.

Effects on the Central Nervous System

In Flewellen et al.'s study [30] patient's central nervous system function was altered subjectively in all subjects. Description of this effect varied among dizzy, floating, and lightheaded. Subjects rated the alteration from minimal to marked after the last dose of Dantrolene (cumulative dose of 2.5 mg/kg IV). Nausea and vomiting occurred in 1 subject (8.3%), while bilateral ptosis was noted in 8 patients (66.67%). These effects were noted with doses ranging from 6 – 7 times the proposed dose in this study.

Effects on Skeletal Muscle

Dantrolene has no effect on calcium-induced contraction,[35] but was shown to diminish myoplasmic calcium concentration.[36] Though it is categorized as a muscle relaxant, total paralysis cannot be obtained regardless of the dose, a fact attributed to its poor water solubility.[37] Studies have shown that even with doses of 10 – 14 times the oral dose suggested in this study there would be minimal effects on muscle strength. [38 39]

Effects of Twitch Height

Dantrolene has a dose-dependent effect on both twitch height and grip-strength. Flewellen et al. [40] noticed an

exponential relationship between the percentage of depression of twitch tension and cumulative dose of Dantrolene. Maximal twitch depression was noted at doses of between 2.2 – 2.5 mg/kg IV (Mean 2.4 mg/kg or 6-7 times the dose proposed in this study). Percent twitch depression at the doses indicated in this study (approximately 0.3 – 0.4 mg/kg) would be approximately 20%.

Effects on Respiratory Function
The respiratory effects of dantrolene appear to be negligible in spite of its muscle relaxant effects. In Flewellen et al.'s. study, peak expiratory flow rate, vital capacity, end-tidal carbon dioxide, and respiratory rate did not change significantly with high-dose Dantrolene administration (2.4 mg/kg or 6-7 times the proposed dose in this study).

Dantrolene Doses noted in Medical Management
The first therapeutic use of oral dantrolene was for the treatment of spasticity[41]. The aims of therapy are functional improvement, prevention of expected functional disabilities, pain reduction and facilitation of nursing [42]. Dantrolene is still an effective anti-spastic drug, as are diazepam, baclofen and tizanidin[43]. Adults initially receive oral dantrolene 25 mg per day, with doses increasing every 3–7 days. The maximum dose should be no more than 100 mg four times a day. This is will be within the range of medication suggested in this study.

Drug Interactions
The potential effects of dantrolene and verapamil has been noted.[44,45] For this reason any patient being treated with verapamil will be excluded from the study. In addition, dantrolene depresses excitation–contraction coupling without interfering with neuromuscular transmission or electrical properties such as resting or action potentials. However, since Dantrolene decreases the force of skeletal muscle contraction, some synergistic effects with drugs blocking neuromuscular transmission have to be expected. A marked prolongation of the neuromuscular junction recovery has been reported after vecuronium has been given in combination with Dantrolene [46]. This may be caused by decreased transmitter release at the neuromuscular junction as a result of attenuated calcium release from the cholinergic terminal calcium storage sites. For this reason vecuronium will not be used as a muscle relaxant during this phase of the trial.

Risk of a Confidentiality Breach
Any patient participating in a research study runs a small risk of breach of confidentiality. All study staff for this trial are well trained in HIPAA regulations and BIDMC confidentiality standards. Patient data will stored in locked cabinets and will be password protected computers on BIDMC network secure servers or in REDCap directly.

Risk/Benefit Ratio
The medication used in this study is approved by FDA for controlling the manifestations of chronic clinical spasticity. When administered at recommended safe dosages and when monitored in the appropriate setting, the risks of toxicity associated with Dantrolene are overshadowed by the potential benefits of decreased pain and enhanced recovery following lumbar surgery.

B6. RECRUITMENT AND CONSENT PROCEDURES

Recruitment

Prescreening will be accomplished by reviewing the operating room schedule and surgical consult lists for patients presenting with acute, musculoskeletal or back pain, lumbar stenosis or lumbar fracture. Patient medical records will be reviewed for inclusion and exclusion criteria. All patients who meet inclusion criteria with no exclusions will be approached for a pre-consent discussion that will occur over the phone prior to their preoperative admission testing appointment to determine patient's interest. Then they will be approated in PAT their surgeon's clinic or in the preoperative holding area for full written informed consent.

Consent

Written informed consent will be obtained prior to the scheduled surgery in a private, secure location, with the option of utilizing the secure electronic e-consent system in REDCap in necessary. In the event that the patient cannot come to PAT, we will conduct written consent over the phone, where the patient will sign and send the consent back electronically. Consent will be obtained by one of the participating researchers of the study. At the time of consent, all study procedures will be explained in detail, including the associated risks and benefits. The subjects will have the opportunity to ask any and all questions, and will be reminded that participation is voluntarily. All subjects will be consented with curtains drawn or the door closed, assuring patient privacy. Written informed consent will then be obtained prior to surgery and initiation of any research procedures. If the consent is signed electronically through REDCap, copies of the signed consent will be provided to the patient via email and filed in the medical record.

Please see Part A and the attached HIPAA waiver of authorization for additional information.

Subject Protection

It is unlikely that patients will be vulnerable to coercion or undue influence in this study. Patients will be informed that their decision to participate or not to participate will in no way affect their relationship with their health care provider. Patients will have the ability to discontinue their participation at any time.

B7. STUDY LOCATION

Privacy

All efforts will be taken to ensure patient privacy. Patient interactions including consent will take place in private clinical settings with curtains/doors closed so as to provide privacy and comfort. In addition, administration of the study medication and questionnaires will occur at the bedside in private rooms. Throughout the study, only the minimum required information will be collected, assuring patient privacy during the study protocol as with usual patient care. Data collection from chart extraction will occur only on password-protected computers secured by the BIDMC firewall or in REDCap directly. Data collected will be limited to only the minimum necessary to accomplish the stated research purposes.

Physical Setting

Consent will be obtained from eligible patients in private clinical settings with curtains/doors closed. Study procedures, including medication administration and questionnaire administration will occur at the bedside in private PACU locations or patient rooms. Only in the occasion a patient has been discharged prior to their 48 hour time point will follow-up assessments occur over the phone. Data will be abstracted from the patients' chart and will be stored on password-protected computers behind the BIDMC firewall or in REDCap directly. All data collected on paper will be maintained in locked study offices accessible to only the study team. Study investigators have been trained to maintain PHI in a secure and compliant manner.

B8. DATA SECURITY

Data will be stored on password-protected computers behind the BIDMC firewall and entered into a computer database (REDCap). Computers and data collected on paper will be stored in locked rooms. For all analyses subjects will be identified only by their unique coded study ID number assigned for the sole purpose of this project. Limited information will be retained on patients who are prescreened and do not qualify, or who are approached and declined, for the purposes of generating a CONSORT diagram for the trial.

B9 Multi-Site Studies

Is the BIDMC the coordinating site? ☐ Yes ☐ No ☒ N/A – Single Center Study

Is the BIDMC PI the lead investigator of the multi-site study? ☐ Yes ☐ No

B10 Dissemination of Research Results

Please explain whether you will be able to thank subjects and provide research results and, if so, how this will be accomplished. If you do not think this is feasible, appropriate or applicable to this research, please specify why.

Patients will be thanked for their time throughout the study. Because study results are likely to be published a few years after a given subject's participation, study investigators are concerned that mailing the published manuscript and an additional thank-you note years after participation risks violating subject privacy, as mailing addresses are increasingly likely to change with passing time. It is out of the scope of this study to continue tracking mailing addresses after study completion.

B11 Appendices

Table 1: Overall Benefit of Analgesia Score.[1]
The OBAS. To calculate the OBAS score, compute the sum of scores in items 1 – 6 and add '4 – score in item 7'. For example, a patient with minimal pain (NRS=0), severe vomiting (NRS=4), and no itching, sweating, and freezing who is slightly dizzy (NRS=1) and is not very satisfied with his postoperative pain treatment (NRS=1) has an OBAS of 8. Note that a low score indicates high benefit.

Please Rate the Following	**SCALE** *0 = minimum; 4 = maximum*
1. Please rate your current **pain at rest**	
2. Please grade any distress and bother from **vomiting** the past 24 hours	
3. Please grade any distress and bother from **itching** in the past 24 hours	
4. Please grade any distress and bother from **sweating** in the past 24 hours	
5. Please grade any distress and bother from **freezing** in the past 24 hours	
6. Please grade any distress and bother from **dizziness** in the past 24 hours	
7. How **satisfied** are you **with your pain treatment** during the past 24 hours	
Total Score	**___ / 28**

Table 2: Richmond Agitation-Sedation Scale[2]

Score	Term	Description
+4	Combative	Overtly combative or violent: immediate danger to staff
+3	Very Agitated	Pulls on or removes tube(s) or catheters(s) or has aggressive behavior towards staff
+2	Agitated	Frequent non-purposeful movement or patient-ventilator dyssynchrony
+1	Restless	Anxious or apprehensive but movements not aggressive or vigorous
0	Alert and calm	Spontaneously pays attention to caregiver
-1	Drowsy	Not fully alert, but has sustained (more than 10 seconds) awakening, with eye contact, to voice
-2	Light sedation	Briefly (less than 10 seconds) awakens with eye contact to voice
-3	Moderate sedation	Any movement (but no eye contact) to voice
-4	Deep sedation	No response to voice, but any movement to physical stimulation
-5	Unarousable	No response to voice or physical simulation

ICU Mobility Score[47]

Score	Classification	Definition
0	**Nothing (Lying in bed)**	*Passively rolled or passively exercised by staff, but not actively moving.*
1	**Sitting in bed, exercises in bed**	*Any activity in bed, including rolling, bridging, active exercises, cycle ergometry and active assisted exercises, not moving out of bed or over the edge of the bed.*
2	**Passively moved to chair (no standing)**	*Hoist, passive lift or slide transfer to the chair, with no standing or sitting on the edge of the bed.*
3	**Sitting over edge of bed**	*May be assisted with staff but involves actively sitting over the side of the bed with some trunk control.*
4	**Standing**	*Weight bearing through the feet in the standing position, with or without assistance. This may include use of a standing lifter device or tilt table.*
5	**Transferring bed to chair**	*Able to step or shuffle through standing to the chair. This involves actively transferring weight from one leg to another to move to the chair. If the patient has been stood with the assistance of a medical device, they must step to the chair (not included if the patient is wheeled in a standing lifter device).*
6	**Marching on spot (at bedside)**	*Able to walk on the spot by lifting alternate feet (must be able to step at least 4 times, twice on each foot), with or without assistance.*
7	**Walking with assistance of 2 or more people**	*Walking away from the bed/chair by at least 5 m (5 yards) assisted by 2 or more people.*
8	**Walking with assistance of 1 person**	*Walking away from the bed/chair by at least 5 m (5 yards) assisted by 1 person.*
9	**Walking independently with a gait aid**	*Walking away from the bed/chair by at least 5 m (5 yards) with a gait aid, but no assistance from another person. In a wheelchair bound person, this activity includes wheeling the chair independently 5 m (5 yards) away from the bed and chair.*
10	**Walking independently without a gait aid**	*Walking away from the bed/chair by at least 5 m (5 yards) without a gait aid or assistance from another person*

B12 References

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