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Design considerations for the development of neuromuscular electrical stimulation (NMES) exercise in cancer rehabilitation

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ABSTRACT
Aim: The aim of this narrative review is to explore design considerations for effective neuromuscular electrical stimulation exercise prescription in cancer rehabilitation, with simultaneous consideration for fundamental principles of exercise training and the current state of the art in neuromuscular electrical stimulation technologies and application methodologies.

Method: Narrative review.

Results: First, we consider the key neuromuscular electrical stimulation exercise design considerations, with a focus on training objectives and individual training requirements and constraints for individuals with cancer. Here, we contend that concurrent, low and high frequency neuromuscular electrical stimulation exercise, individually prescribed and progressed may be optimal for enhancing physical function. Second, we review the appropriate literature to identify the most appropriate stimulation parameters (pulse frequency, intensity, duration and duty cycle) to deliver effective neuromuscular electrical stimulation in cancer rehabilitation.

Conclusions: We propose an informed and innovative neuromuscular electrical stimulation exercise intervention design and provide practical information for clinicians and practitioners who may work with and implement neuromuscular electrical stimulation exercise in cancer.

IMPLICATIONS FOR REHABILITATION
- Neuromuscular electrical stimulation is an emerging technology in cancer rehabilitation to help provide an aerobic and muscle strengthening exercise stimulus.
- Neuromuscular electrical stimulation may help improve aerobic exercise capacity, muscle strength and augment quality of life.
- Current prescription in cancer lacks adherence to the fundamental principles of exercise training, which may negatively affect adherence.

Introduction
Neuromuscular electrical stimulation (NMES) involves the delivery of a pulsed current to motor nerves supplying a muscle, usually applied using cutaneous surface electrodes positioned in close proximity to the muscle motor point. The intensity of the current delivered is sufficiently high enough to depolarise the underlying motor nerve and evoke a visible muscle contraction [1,2]. Depending on the current parameters selected, two main modalities are now possible:
- Muscle strengthening via high frequency (>20 Hz) tetanic contractions for healthy and clinical populations since its chronic application may augment neuromuscular function or preserve muscle mass and function during periods of muscle disuse [1,3,4];
- Aerobic conditioning via low frequency (< 6 Hz) sub-tetanic contractions for healthy and clinical populations since its chronic application may increase the metabolic capacity of the target muscle [5], and lead to augmented cardiorespiratory fitness or preserved aerobic conditioning [6], during periods where an individual may be incapable of participating in dynamic exercise which has a greater ventilatory demand than NMES.

Due to its capabilities as an "exercise mimetic", interest within clinical applications for populations with barriers to dynamic exercise such as breathlessness, fatigue and profound muscle weakness has grown. In oncology, whilst undergoing treatments such as chemotherapy, many patients can experience a rapid decline in their functional capabilities due to multi-system deconditioning that affects cardiorespiratory and neuromuscular systems [7,8]. Despite strong evidence supporting voluntary exercise (including aerobic and resistance exercise) as an adjunct therapy to offset these treatment toxicities [9], the symptom burden of cancer pathology and treatment can be exercise limiting. A common conclusion from systematic reviews investigating the effects of NMES exercise in clinical populations is that NMES exercise is perhaps best suited to individuals who are the most deconditioned [10,11]. Therefore, its application within cancer rehabilitation...
appears intuitively appealing with NMES exercise perhaps uniquely placed to optimise cancer rehabilitation in those unable to access dynamic exercise due to physical limitations.

The use of NMES exercise in cancer rehabilitation to date has been inconclusive. A recent systematic review which investigated the pooled effect of NMES exercise on physical function and quality of life concluded that although NMES exercise may enhance quality of life, it did not demonstrate large effects on function. The authors concluded that the prescription of NMES exercise in cancer currently used may be inappropriately designed [12]. A common observation relating to studies included in this systematic review was that the NMES exercise prescriptions were not guided by the fundamental principles of exercise training (e.g., specificity, individualisation, progression, rest/recovery). These principles are currently recommended to optimise exercise training in a cancer setting [13], and may optimise NMES exercise delivery and enhance adherence [14]. In addition, adopting current state of the art NMES paradigms such as “multipath” NMES might allow for higher current intensities at lower levels of discomfort [15], often a key determinant of NMES effectiveness in those who may not tolerate conventional NMES exercise delivery [16].

Recently, an NMES intervention which adopted these considerations demonstrated safety and feasibility when implemented in a small, heterogenous group of patients with cancer and a single case of a rare cancer type [17,18]. Therefore, the aim of this narrative review is to review the literature and explore design considerations for effective NMES exercise prescription in cancer rehabilitation, with simultaneous consideration for the fundamental principles of exercise training and the current state of the art in NMES technologies and application methodologies. To conclude, we propose an informed and innovative NMES exercise intervention design, and provide practical information for clinicians and practitioners who may work with and implement NMES exercise in cancer.

Methods

Whilst guidelines exist to inform the reporting of systematic reviews, no such guidelines exist for narrative reviews [19]. A narrative review differs in that it may address one or more question, provides interpretation and critique, and is traditionally non-systematic [20]. However, Ferrari [19] contends that narrative reviews can benefit from adopting the methodological rigour of systematic reviews. Therefore, in the present narrative review, a comprehensive search of relevant studies was conducted in electronic databases (Google Scholar and PubMed) through October 2019. Study selection was made using combinations of keywords and Booleans including (neuromuscular electrical stimulation OR NMES OR electrical muscle stimulation) AND (cardiorespiratory fitness OR aerobic capacity OR exercise tolerance OR muscle strength OR fatigue). Articles identified after the first search were scrutinised for further references. Only articles published in English were included. Exclusion criteria were studies where the full text was not available. We have judiciously selected the most appropriate articles by which to explore, summarise and critique which design considerations should be considered in the development of NMES exercise for cancer rehabilitation.

NMES exercise design considerations

Exercise training objectives

Voluntary exercise-based guidelines for cancer survivors recommend regular aerobic and resistance exercise to maintain and augment cardiorespiratory fitness (CRF) and muscle strength [9]. NMES exercise prescription in cancer rehabilitation to date has attempted to target both aerobic and muscular fitness components, using only tetanic high frequency NMES (HF-NMES, 50-63 Hz) exercise [12]. However, whilst HF-NMES has a documented strengthening effect [3], repeated high intensity tetanic muscle contractions have negligible effects on increasing the aerobic capabilities of the target muscles and inducing a central aerobic exercise response [21–23]. Different adaptations can be expected following voluntary aerobic and resistance exercise [24], and the training prescription should reflect this with specificity in the training stimulus [25]. Training specificity is the training principle which states that the adaptation in the component of physical fitness is specific to the training stimulus undertaken [25].

Similarly, distinct training responses and adaptations have been observed following sub-tetanic low frequency NMES (LF-NMES, 4–5 Hz) and HF-NMES exercise [5,26]. Although repeated HF-NMES can enhance muscle strength and structure, repeated exposure to LF-NMES has been shown to enhance aerobic energy metabolism [27], which can lead to improvements in functional endurance [28] and peak oxygen uptake (VO2peak) in healthy and clinical patient populations [21,29]. However, despite NMES having these capabilities, current NMES exercise prescription in cancer does not meet exercise recommendation guidelines for enhancing physical function and health. Therefore, when designing an NMES exercise protocol for cancer rehabilitation to target both CRF and muscle strength, adopting a concurrent approach (LF + HF-NMES) should be considered.

Matching/meeting individual training requirements and constraints

Cancer survivors demonstrate considerable fluctuations in daily functioning, particularly during cancer treatment cycles. Fluctuations in fatigue, depression, sleep and activity levels in the days following treatments such as chemotherapy may impact on their daily readiness to train [30,31]. Common clinical applications of NMES exercise typically involve 5 × 30 min – 1 h NMES exercise sessions per week from the offset [32]. However, such high volume NMES exercise poses a risk of disengaging the patient and adversely affecting training adherence. An individually tailored and flexible approach to NMES exercise prescription may help facilitate adherence during a time in which the magnitude of treatment symptom severity may fluctuate on a daily basis [33]. Individualization of the treatment protocol allows for the customization of the training stimulus through considerations for the baseline capacity and limitations of the patient. This approach has been reported previously as a viable solution for overcoming potential barriers to deployment of NMES in patients with chronic airway limitation [34].

The current standard method of progressing NMES exercise in cancer is to increase inter and intra-session stimulation intensity to maintain a maximum tolerable level [12]. Here, we propose a progressive approach to prescribing training parameters such as the duration (minutes) and frequency (times per week) of training sessions, particularly in the early stages of the protocol which may have a positive impact on adherence and effectiveness. Habituation protocols involving 2–3 sessions over the first week of application are recommended in the literature in clinical populations unaccustomed to NMES to help improve adherence [1,35]. Progressing session duration and frequency may also confer continued physiological adaptation, through an increased training volume and stress (progressive overload) across the intervention.
Additionally, this approach introduces periods of rest/recovery, allowing the user time between sessions to recover adequately over the initial programme time-period and potentially reduce the risk of muscle damage and muscle soreness which can occur at the beginning of a training programme \[11,36\]. A visual representation of how the principles of exercise training discussed above may be adapted for NMES exercise in cancer rehabilitation is presented in Figure 1.

### Protocol requirements: stimulation parameters

#### Pulse frequency

**Sub-tetanic NMES (LF-NMES)**

LF-NMES values typically range from 2 Hz to 15 Hz \[16\]. LF-NMES utilising a pulse frequency of 10 Hz has been shown to increase \(\text{VO}_2\text{peak}\) by 12% over 5 weeks (1-h/day stimulation, 5 days/week) in patients with stable chronic heart failure (CHF) \[37\]. However, when using LF-NMES of 15 Hz in COPD patients, the peak metabolic response (34% \(\text{VO}_2\text{peak}\)) is similar to HF-NMES (75 Hz, 33% \(\text{VO}_2\text{peak}\)) \[38\] and below recommended threshold intensities (>40% \(\text{VO}_2\text{peak}\)) for improving aerobic fitness \[39,40\]. Furthermore, partial twitch fusion may be experienced with frequencies exceeding 6 Hz resulting in greater fatigue and discomfort \[41\]. As such, emerging evidence now supports the use of 4–5 Hz (30 min – 1-h/ day, 5 days/week, 4–8 weeks) at maximum tolerable intensity for elevating the aerobic capabilities of the target muscle and inducing a sustained aerobic exercise response in healthy active and sedentary populations \[6,35,41,42\] with an increase in aerobic exercise capacity reported in healthy active and sedentary populations and patients with chronic heart failure (CHF) \[21,29,43\]. These isometric, sub-tetanic contractions generated at 4 Hz may facilitate aerobic energy conversion by allowing more time for muscle fibres (Type I and Type II Fibres) to recover between pulses, whilst sustaining an elevated metabolic cost \[27\].

Early work which targeted bilateral quadriceps stimulation demonstrated exercise intensities of 3 metabolic equivalents (METs) \[27\], with equivalence to low intensity aerobic exercise \[44\]. However, subsequent work by Crognale et al. \[35\] which targeted a larger muscle area of the quadriceps and included an additional muscle group (hamstrings) demonstrated an elevated aerobic energy contribution to levels of moderate intensity. The authors reported the peak physiological response to modified sub-tetanic (4 Hz) NMES exercise which included a built-in habituation period as 53% of the participants \(\text{VO}_2\text{max}\). This training intensity (moderate: equivalent to 40–59% heart rate reserve (HRR)) was achieved and sustained for 1-h without undue discomfort in healthy volunteers. Similar training intensities have been shown to enhance \(\text{VO}_2\text{peak}\) (+7%) after 18 × 1-h sessions over 6 weeks in healthy, physically active adults \[21\], although shorter sessions (30 min) may provide a therapeutic benefit in clinical populations provided maximum tolerable intensity is achieved resulting in a steady state oxygen uptake \[41\].

**Tetanic NMES (HF-NMES)**

Typical clinical applications of HF-NMES use protocols with a pulse frequency of 20–100 Hz \[45\]. Pulse frequency has a positive and linear relationship with muscle force production \[46\], with a frequency range of 30–50 Hz reported in the literature as optimal for force production \[47\]. However, higher frequencies are associated with the rapid loss of sustained muscle force due to the onset of muscle fatigue \[48,49\]. Early work by Moritani et al. \[49\] demonstrated that during different higher frequency NMES protocols (20 Hz v 50 Hz v 80 Hz), a rapid decline in force output was evident with 50 and 80 Hz applications after 30 s of stimulation suggesting the rapid onset of fatigue. The mechanisms behind this "high frequency fatigue" have been linked to metabolic changes such as the depletion of extracellular sodium (\(N^-\)) or the accumulation of potassium (\(K^+\)) which may reduce the excitability of the muscle membrane \[48\]. The authors proposed that using a pulse frequency of 20 Hz may allow for a greater maintenance of sustained muscle force output \[49\].

Indeed, work by Gorgey et al. \[50\] supports the use of a lower frequency protocol for minimising muscle fatigue. In seven healthy participants who underwent four different HF-NMES protocols of varying pulse frequency, duration and intensity (1) 100 Hz, 450 \(\mu\text{s}\), 75% maximum voluntary contraction (MVC) (2) 100 Hz, 150 \(\mu\text{s}\), 75% MVC (3) 25 Hz, 450 \(\mu\text{s}\), 75% MVC (4) 100 Hz, 450 \(\mu\text{s}\), 45% MVC, the authors demonstrated that pulse duration and amplitude did not influence fatigue, however, lowering pulse frequency (100 Hz vs 25 Hz) resulted in less fatigue (76% vs 39% of peak torque).

Similarly, Dreibati et al. \[51\] recently investigated the impact of HF-NMES frequency on muscle force and fatigue in healthy young (mean age: 23 ± 3 yrs) participants \((n = 26)\). When comparing...
pulse frequencies of 100 Hz vs 50 Hz vs 20 Hz, the authors reported that the highest frequency was more effective for obtaining a higher % of maximum voluntary contraction (100 Hz: 71% vs 20 Hz: 55%). However, the intensity of the contraction at 100 Hz declined significantly after ~5 min suggesting the rapid onset of muscle fatigue. This force decline may be directly related to the preferential activation of fatigable Type II muscle fibers, and the lack of normal physiological motor unit rotation/cycling, which is not seen during HF-NMES contractions due to limited spatial recruitment [1, 52].

Recently, the optimal frequency for HF-NMES applications has been revisited. Mettler et al. [53] compared torque output at stimulation frequencies of 20 Hz vs 60 Hz in healthy volunteers (n = 11) and demonstrated that 20 Hz preserved a significantly higher torque time integral (TTI) than 60 Hz over a 60 min session (38288.3 vs 30496.5 Nm.s, p = 0.008, when using a 10 s ON: 15 s OFF ratio) [53]. The 20 Hz group achieved a mean contraction intensity of >11% MVC over 12 contractions (target MVC: 15%). Therefore, since HF-NMES effectiveness is dictated by the strength and duration of the contraction (i.e. TTI), a frequency which may delay the onset of fatigue and preserve a high level of evoked force may have the greatest impact on muscle strength. This observation has important and clinically relevant implications for cancer rehabilitation. Fatigue, a well-documented secondary complication in cancer has also been noted as a limiting factor during the clinical application of repetitive HF-NMES and may affect adherence to NMES protocols [54]. Frequencies of 20 Hz may be a more effective and tolerable frequency parameter for HF-NMES in cancer for muscle strengthening.

Of note, higher stimulating frequencies (60 vs 20 Hz) may provide a greater stimulus for initiating an anabolic response: that is, a greater upregulation of genes involved in muscle protein synthesis (+30% mTOR phosphorylation) [55]. Given that most individuals with cancer may experience some degree of muscle atrophy in response to the direct and indirect effects of treatment, a potential progression strategy once the user is suitably habituated to the uncustomed sensation of non-physiological contractions which are synchronous, spatially fixed, and superficial compared with physiological muscle contractions [1] may involve progressing stimulation frequency (e.g., 20 Hz > 60 Hz) to further target muscle strength and to initiate a greater molecular level protein synthetic response. However, the level of muscle protein synthetic response does not always correlate with muscle hypertrophy [56]. In addition, interventions which combine muscle building strategies with appropriate nutritional support would likely have the greatest effect in preserving muscle mass [57].

Stimulation intensity

Sub-tetanic & tetanic NMES

NMES exercise intensity is generally regarded as the most important parameter dictating training effectiveness [16]. Because the response to NMES exercise can be heterogeneous, encouraging the user to achieve the maximum tolerable intensity may likely lead to the best results. To achieve positive adaptations in CRF and muscle strength using concurrent LF & HF-NMES exercise, two fundamental practical recommendations must be met. During LF-NMES; visible, rapid short-duration rhythmic contractions and a central aerobic exercise response (i.e., increased HR, VO2) are required and during HF-NMES strengthening applications a visible and maximum tolerable muscle contraction achieved [54, 58]. To meet these criteria, the maximum tolerable intensity should be sought. During early LF-NMES exercise sessions, a primary goal should be to achieve, at minimum, a low to moderate aerobic exercise intensity (i.e., 30–59% heart rate reserve (HRR)) where possible [40]. Reporting the intensity of HF-NMES as a % of maximum voluntary contraction (MVC) is a best practice standard. However, this method is not always rigorous (e.g., very weak patients) or possible (e.g., critically ill patients) [54]. Therefore, a clinically acceptable alternative is ensuring a visible muscle contraction and the periodic increase in inter and intra session maximum tolerable intensity to account for improved tolerance and accommodation [54].

Pulse duration

Sub-tetanic NMES

The pulses used in NMES are commonly biphasic, such as that illustrated in Figure 4, where both phases have the same duration. The pulse or phase duration is the total time for both phases in addition to the interval between them. The literature often uses the term pulse width when referring to phase duration. To date, no research has investigated the manipulation of phase duration in LF-NMES application. Explicit reporting of phase duration used in LF-NMES exercise studies is often lacking in the literature. Studies which have reported phase durations have used ranges from 600 to 760 μs [35, 41, 59, 60]. Higher phase durations (>600 μs) are associated with greater muscle recruitment and may be optimal for targeting a greater amount of muscle massments and activating a greater number of motor units. As such, the response to long phase durations with a low frequency pulse (4 Hz) have been observed to lead to a greater oxidative energy contribution in the activated muscle, enhancing the cardiorespiratory response [27].

Tetanic NMES

Early work established that phase durations of 20–200 μs were sufficient for motor stimulation [61]. However, research into phase duration manipulation during HF-NMES application has demonstrated that higher phase durations may be optimal, leading to greater levels of muscle activation and higher torque output. Indeed, Gorgey et al. [62] measured the activated cross-sectional area of the quadriceps femoris in seven healthy participants and reported a 40% greater level of motor unit recruitment when comparing 150 μs and 450 μs phase durations. Higher motor unit recruitment logically translates to increased muscle force production. In support of this, Hultman et al. [2] demonstrated that increasing phase duration from 150 to 500 μs achieved a 40% greater torque output. In addition, when comparing low (200 μs) and high (500 μs) phase durations, healthy young individuals have been shown to tolerate and generate higher force tetanic muscle contractions (45% vs 49% maximum voluntary contraction (MVC)) with a higher phase duration [63]. However, many HF-NMES applications use phase durations of <300 μs [3], despite the evidence supporting the use of higher phase durations for muscle strengthening applications.

In a systematic review of clinical applications of HF-NMES in advanced disease, phase durations of variable width (200–700 μs) were reported [32]. Recent reports, which have demonstrated improvements in muscle strength with their protocols, have utilised phase durations of 400–700 μs [64–66]. As mentioned previously, higher phase durations likely result in greater muscle activation and higher torque output. However, just as with pulse intensity and pulse frequency, higher phase duration increases the root-mean-square (RMS) current and therefore the power dissipated in the skin potentially leading to skin irritation. Skin irritation is an important clinical consideration when targeting muscle
tissue with NMES. The United States FDA advise that power dissipations greater than 0.25 W/cm² cause tissue heating. The safety standard IECC 60601-2-10 requires that the user’s attention be drawn to situations where the current density can exceed RMS 2 mA/cm². Pragmatically, in situations where skin sensation might be impaired, a current density less than RMS 0.5 mA/cm² may be preferred. For a symmetric biphasic square wave current of amplitude $I$ mA, such as shown in Figure 2, the RMS current $I_{\text{rms}}$ can be calculated as follows:

$$I_{\text{rms}} = \sqrt{2} f \tau$$

where, $f$ is the pulse frequency (Hz) and $\tau$ is the phase duration(s).

Longer phase durations typically increase the area of activated muscle but also penetrate deeper, allowing for greater muscle activation [62]. This can optimise HF-NMES delivery in those who may have higher subcutaneous adipose tissues or who have oedema. Therefore, higher phase durations during HF-NMES applications in clinical groups such as individuals with cancer may be optimal for targeting muscle tissue and producing higher torque outputs. However, it would then be advisable to reduce the pulse frequency to offset the increase in RMS current that would otherwise occur (e.g., lower pulse frequencies (20 Hz) and high phase duration (>500 μs) to help limit skin irritation, and minimise fatigue). For example, the RMS current of a 50 Hz, 100 mA biphasic pulse train with a phase duration of 500 μs is 22.3 mA, whereas for 20 Hz it is 14.1 mA.

**NMES protocol design**

**NMES equipment**

In our application, we used the INKO-RS hand held stimulator (Biomedical Research, Ireland) with four large electrodes ($17 \times 10$ cm) placed on each leg (area per leg = 680 cm², 2 × proximal/distal quadriceps, 2 × proximal/distal hamstrings). To accommodate differences in limb size amongst individuals, electrodes can be modified for individuals in whom the standard size may be too large. In keeping with recommendations from the literature, electrodes should be placed as far apart as possible on the muscle belly and should be integrated within wearable garments to assist patients with correct electrode positioning [54]. This ensures electrodes are positioned correctly consistently each session and allows the user to quickly apply and remove the electrodes, potentially improving user compliance [67].

**Multipath delivery of NMES**

Traditionally, NMES devices are designed to operate with a pair of electrodes, or even multiple pairs, where the current pulse flows within the electrodes of a pair but not between pairs. A pair of electrodes attached to the body surface can only deliver one three-dimensional current density field patterns in the body, assuming an unchanged underlying anatomy. Consequently, repeated stimulation at the same phase charge (pulse-width times current) will inevitably recruit the same motor unit pool. The only option to recruit additional motor units is to increase the phase charge, however all motor units with lower stimulation thresholds will continue to be activated. An emergent approach, addressing this short-coming, employs an array of electrodes that are not pre-assigned in pairs [15]. Instead, any combination of electrodes from the array can be dynamically selected to deliver a stimulation pulse (Figure 3) and so a greatly increased selection of current density field patterns can be created in the tissue. This permits additional motor units to be recruited and also allows motor units to be spared so that fatigue is delayed. This approach, named multipath NMES has been associated with higher evoked force generation and lower levels of reported discomfort and fatigue [67-69]. These benefits are linked to the dynamically changing current pathways, the wider current distribution via large surface electrodes, and the ability to recruit a greater number of motor units [15,67]. The larger electrodes used with multipath NMES may result in greater muscle activation due to a reduced gap between the proximal and distal electrodes. The larger electrode surface also likely reduces current density at the site of stimulation, increasing comfort levels at higher evoked force [69].

Maffiuletti et al. [15] were the first group to compare the effects of both traditional and multipath NMES modalities on evoked knee extension force and perceived discomfort. In a cross over design study, the authors investigated the evoked force and discomfort response to a ramp NMES protocol (10-50% MVC every 3 min in increments of 10%) and demonstrated in a small group ($n=10$) of healthy participants that multipath NMES was capable of eliciting a higher level of evoked force at a lower level of discomfort vs traditional NMES. Similarly, Morf et al. [69] compared multipath NMES vs traditional NMES (parameters for both: 50 Hz, 400 μs, 5 s ON: 10 s OFF) and demonstrated in 20 patients with total knee arthroplasty (TKA) that multipath NMES could generate stronger contractions (higher evoked quadriceps torque: +33%) whilst provoking less discomfort (−39%) and fatigue than
traditional NMES suggesting that multipath NMES may be more effective than traditional NMES for eliciting less fatiguing and stronger contractions at a lower given level of discomfort.

High level evidence in support of an array electrode configuration in musculoskeletal populations supports the consideration of this approach in NMES and cancer. In an early prospective, single-blinded, randomized controlled trial (RCT), Feil et al. [67] compared the effects of adding multipath NMES (50 Hz, 5 s ON: 10 s OFF, 3 sets × 10 reps, knee presses, bottle knee presses, extended leg raises, leg extensions, wall squats and hamstring curls) for enhancing physical function in older adults (55–75 yrs, n = 41) with moderate to severe knee osteoarthritis. After 6 weeks, both groups had significantly improved functional performance (25-m walk, timed stair climb, repeated chair), whilst a trend towards improved isometric and isokinetic quadriceps peak torque was observed. Interestingly, improvements in function were maintained for an additional 6-weeks. Of note, although not significant, adherence to the multipath NMES protocol was higher than resistance training (91% vs 83%) possibly due to its ease of unsupervised use at home and novelty [70].

Integrating design considerations to develop NMES protocols for cancer rehabilitation

Below we outline an NMES protocol where the design considerations and evidence base described above were taken into account. This protocol has been implemented into the rehabilitation of individuals with mixed cancer diagnoses, and a rare cancer type [17,18]. With this protocol, contractions are achieved by means of delivering a modulated pulse train, utilising a burst of four mixed frequency pulses. The waveform uses a symmetric biphasic pulse with interphase interval, operating under constant current control. The pulse frequency is selected depending on the functional objectives of the phase of the training session (Table 1). The stimulator can be programmed to deliver two separate phases (concurrent aerobic and strengthening NMES) during each training session with a maximum current output of 140 mA.

| Phase 1 – the current waveform for Phase 1 (LF-NMES) designed to generate rhythmical sub-tetanic isometric contractions using bursts of four pulses (pulse width 620 μs) delivered at a fixed frequency of 4 Hz for a duration of 13–45 min (RMS current: 9.9 mA). |
| Phase 2 – the current waveform for Phase 2 (HF-NMES) designed elicit a series of tetanic strengthening isometric contractions using a burst of four pulses (pulse width 500 μs) delivered at a fixed frequency of 20 Hz, for a duration of 15 min (RMS current: 19.8 mA). |

Pulse delivery

In this protocol, we delivered packets of four pulses repeated at a frequency of 4 Hz or 20 Hz to target CRF and strength training. Pulses were delivered to electrode arrays with a primary goal of reducing muscle fatigue [15]. Each stimulation pulse was divided into a number of time segments, called timeslots, and different electrode selections were made under software control for each timeslot. Dividing each pulse into timeslots with different electrodes selected allowed a larger electrode area and variation in the phase charge delivered to each electrode. This approach reduces the intensity of stimulation associated with each electrode and should improve tolerability and comfort levels. For Pulse 1 and 4,
there are three time slots per pulse. For Pulse 2 and 3, there are five time slots.

**Personalisation and progression**

**Sub-tetanic NMES**

The protocol is designed to slowly progress stimulation exposure over weeks 1 and 2 with the aim to habituate the current and progression is achieved through an intermittent delivery of the LF-NMES programme for each patient during week 1 of the protocol. Reduction of the pulse width from 620 to 300 μs is used as the means of introducing relative “rest” periods to the intermittent programme. This method of delivery is intuitively appealing given that patient cohorts may require a prolonged period of habituation [14], and was developed to make NMES exercise more palatable to users who are unaccustomed to the sensation of NMES exercise. In week 2, patients progress to either an extended intermittent protocol (Stage 2), or to continuous delivery (Stage 3) (Figure 4). Once tolerant to continuous LF-NMES programme, FITT principles were used to guide programme

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**Figure 4. Schematic representation of LF-NMES intermittent delivery (A) and HF-NMES duty cycle (B) progressions.**
The progression strategy involved progressively increasing the frequency and duration of NMES sessions whilst maintaining the maximum tolerable intensity. The LF-NMES session protocol involved increased weekly session duration (5–10 min per week, personalised for each patient) in accordance with the American College of Sports Medicine (ACSM) guidelines for aerobic exercise progression (minimum target 30% HRR) [40].

**Tetanic HF-NMES**

In the HF-NMES protocol, the duty cycle (ON: OFF cycle) increased weekly from 2 s:15 s to 5 s:15 s to 5 s:10 s and constant thereafter as previously reported [71]. This progression strategy was selected to slowly inure the user to the unaccustomed contractions generated. The duty cycle during the last phase of 5 s contraction (on) followed by 10 s relaxation (off), provides a total of 60 contraction cycles with a total cumulative duration of 5 min over the 15-min phase duration. The goal of this protocol was to achieve a visible muscle contraction and to reduce the duty cycle from 1:7.5 to 1:2.

**Monitoring adherence to the protocol**

To monitor protocol adherence, this protocol recommends self-report diaries to be completed by patients. Although self-report diaries have inherent limitations [72], weekly phone calls to patients carried out to identify issues and answer questions, check on protocol adherence and to reinforce the importance of accurate detailing of session data may help to trouble shoot and enhance data recording and are similarly recommended as a routine part of the protocol. In addition, with the ubiquity of digital technology, devices such as mobile phones may be used to report session data and allow for remote monitoring and support [14].

**Conclusions**

To optimally target cancer rehabilitation, we believe a personalised and progressive concurrent NMES exercise programme protocol should be developed based on established end-user needs. The proposed NMES exercise intervention design was developed to augment physical function through evidence-based parameters and methods which slowly habituate the user, minimise fatigue and facilitate adherence. The protocol guidelines developed and reported in Table 2 provides practitioners with a framework from which to prescribe personalised and progressive concurrent NMES exercise interventions in individuals with cancer. This guide for progression may help promote a more palatable method of implementing NMES exercise into the care of individuals with cancer, whilst providing a therapeutic exercise dose. Early work by our research group which has implemented this protocol has provided early safety data. However, marked attrition was noted, a problem common in cancer research lasting more than a few weeks. As such, further work is warranted prior to its clinical implementation.

**Disclosure statement**

CM is an employee of Biomedical Research Ltd., who produce NMES devices. No other conflicts of interest to declare.

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