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The adapted Zelen was a feasible design to trial exercise in myeloma survivors

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The adapted Zelen was a feasible design to trial exercise in myeloma survivors

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Abbrevs:
MASCOT = Myeloma Advancing Survival Outcomes in Cancer Trial
PA = physical activity
QoL = quality of life
RCT = randomised control trial
S.D = standard deviation
MM = multiple myeloma
Abstract

Objective

We utilised a method rarely seen in cancer behavioural trials to explore methods of overcoming difficulties often seen in randomised controlled trials. We report our experiences of the adapted-Zelen design, so that other researchers can consider this approach for behavioural trials.

Study Design & Setting

The adapted-Zelen design was used to explore the effects of exercise on multiple myeloma patients fatigue, quality of life and physical outcomes. All participants consented to an observational cohort study of lifestyle factors, but were unaware of subsequent randomisation to remain in cohort only group or be offered an exercise intervention requiring second consent.

Results

Due to lower than expected uptake rate to the exercise offered group (57%), the length of recruitment increased from 24 to 29 months to ensure power was reached. At enrolment patients were unaware of the potential increased commitment and as a result 62% of participants allocated to the intervention declined due to the extra time/travel commitment required. This emulates clinical settings and suggests improvements in intervention delivery are required. Dropout rates from the cohort only group were similar to designs that provide the control with the intervention. Our results from the main study do not suggest contamination occurred despite some anecdotal evidence.

Conclusion

Future use of this design warrants careful consideration of the study resources and recruitment time frames required but holds potential value in reducing contamination,
control group dissatisfaction and resulting drop out. Adapted-Zelen design reduces
selection bias and therefore gives clinicians a better understanding of acceptability in
clinical settings. Future studies should evaluate control group experiences of the
design and formally record contamination throughout the study to confirm its
acceptability.

**Keywords:** 6

Research Design; Exercise-Oncology; Exercise; Physical Activity; Multiple Myeloma;
Post Randomization Consent.
1. Background

There is growing interest in using alternative study designs to address pitfalls associated with traditional designs. In this article we describe our experience of using an ‘adapted-Zelen’ design within an exercise oncology setting in patients with a haematological cancer: multiple myeloma (MM).

The randomised controlled trial (RCT) has long been accepted as the ‘gold standard’ for testing clinical interventions. Pragmatic RCTs (which aim to inform routine health decision making) compare an intervention to usual care / standard care. All patients undergo ‘fully’ informed consent – that is to say – prior to randomisation to groups, all potential trial participants are informed that they may be randomly selected to the intervention group and offered a non-standard (new/ experimental) treatment or usual care/ standard care. This can pose significant challenges because it is not possible to blind participants to their group allocation in behavioural studies [1]. Participants who take part in standard RCTs will make a judgement of their preferred treatment and often expect/hope to be allocated to the treatment group [2]. If this does not occur, it can be followed by dissatisfaction, discontent with the research process and distrust in those who approached them to take part [3] particularly when target patients are highly motivated to engage in self-management strategies [4]. In particular cancer patients are becoming increasingly aware of potential benefits of exercise, especially in relation to recovery from their treatment [5] and is a key motivator for them to enrol in RCTs of exercise interventions [6].

Consequently, randomisation to a ‘no exercise’ or control group may lead to dropout after allocation, or self-initiation of exercise having been alerted to it in the trial information sheet [6]. This creates a bias which dilutes the true intervention effect, (contamination of the control group) which is likely to be a major contributing factor to
the often small to moderate effect sizes observed in cancer exercise RCTs [7]. For example, an exercise study among colorectal cancer survivors found no significant differences between the control and exercise intervention group, and attributed this to the high contamination rate (51% of control group engaged in >60 minutes of moderate to strenuous exercise) [4].

Several methods have been utilised in cancer exercise trials to attempt to minimise contamination and dropout in control groups. A systematic review of 40 studies addressing this concluded that a trial design that offered the control group an alternative intervention during the study, or offered the intervention to them at a later stage in a cross-over or wait-list control design, could be an effective way of minimising contamination and dropout [7]. However these designs are time-consuming, expensive and limit the possibility of testing intervention effects long-term, as they are no longer ‘true’ controls.

1. Zelen Design

One way of eliminating the aforementioned challenges is through the use of the Zelen design. The original Zelen design involved randomisation prior to consent, with consent only required from those allocated to the intervention, whilst the control group receive their usual care [8]. One of the main features of the original Zelen design is that informed consent is not required from the control group. Baseline characteristics and outcomes are collected from medical records (with ethical approval). However, it is not possible to have interaction with the control group during follow-up as they are not informed of their presence in a study, this can reduce possible bias introduced by the nature of study participation and undergoing additional assessments, but could be considered unethical [9]. To overcome this
issue, an alternative Zelen design which uses a double consent process: an ‘adapted-Zelen design’ (described below) [8, 10].

The adapted-Zelen has two stages to consent. In the first stage, informed consent is sought from all participants to a cohort lifestyle study. They are then randomised without knowledge and in the second stage only participants who have been assigned to the intervention are re-approached and given information about it. At this stage if they agree to participate they are asked to give second informed consent for the intervention, those who decline remain in the cohort study. Those in the cohort only group are not informed about the randomisation or the intervention trial. The design has made an important contribution to evidence-based medicine [10]. However, it has rarely been used in exercise trials, and has mixed support [6, 10, 11]. Campbell et al. (2005) conducted a Zelen study of a physiotherapy intervention nested within an observational study for patients with chronic arthritis. They found it an acceptable method, with a 64% participation rate, which they reported as higher than conventional RCTs in the field. They successfully avoided contamination in the control group and had negligible loss to follow-up [11]. We have only found one cancer exercise trial using the Zelen design. Velthuis et al (2012) investigated the effect of physical activity (PA) on cancer-related fatigue and QoL on 64 breast and colon cancer patients [6]. However, due to the ethics committee deeming it not ethical that participants are not aware of the randomisation process they had to modify the design and consent patients to baseline assessments in addition to postponement of information about the study at the end. They concluded that the Zelen design with consent to postponed information at the end of the study was not any better than conventional randomisation, due to a high dropout from the
intervention and low overall participation in the study which they attributed to postponed information [6, 12]. These mixed findings highlight the need to evaluate the double consent Zelen design in other oncology exercise trials. This report describes these challenges and our experience of trying to overcome them using an ‘adapted-Zelen’ design in a trial of an exercise intervention in patients with MM.

2. Development of ‘MASCOT’

There is strong evidence that exercise improves outcomes following a cancer diagnosis in patients with breast, prostate and colorectal cancers [13, 14]. However, it is unclear if exercise is also beneficial in haematological cancers, such as multiple myeloma (MM). We previously undertook a pilot study in 37 patients which suggested that exercise intervention improved quality of life (QoL), fatigue, upper and lower limb strength, these preliminary data require confirmation with a larger randomised controlled trial (RCT) [15]. Therefore we conducted The Myeloma Advancing Survivorship Cancer Outcomes Trial ‘MASCOT’ (ISRCTN 38480455) which tested the hypothesis that a physiotherapist-led individually-tailored exercise programme would improve symptoms of cancer-related fatigue when compared to usual care, as well as explore its effect on several clinical, physical and psychosocial outcomes [16].

However, the challenges of traditional RCTs were likely to be particularly pertinent in MM, an incurable cancer that is associated with bone destruction, pain, fractures and deconditioning [17]. For most patients, response to initial combination chemotherapy can be followed by a prolonged period (median 2-3 years) where disease is stable. Patients are generally highly motivated to undertake strategies that can help them recover from the effect of treatment [18]. Considering a pilot study had been conducted at the centre previously we believed our patients may have some
awareness of the benefits observed and we therefore believed that randomisation to a no exercise arm would result in patient distress and consequently lead to high dropout rates and contamination [19]. A cross-over or waitlist control was deemed not feasible due to the time, cost and desire to follow patients up longer term.

To address these issues MASCOT used an adapted-Zelen design of an exercise RCT embedded within a longitudinal lifestyle cohort study [16]. Patients were identified and screened by clinicians in MM clinics to assess eligibility and those eligible were approached by the research team. MASCOT had two stages of consent. In stage 1 patients were sent an information sheet inviting them to participate in a ‘Lifestyle Cohort Study’ aimed at increasing understanding of the relationship between lifestyle behaviours and symptoms such as fatigue and QoL, and how these changed over time. Details of the lifestyle cohort study are published elsewhere [16]. Importantly, this information did not mention PA and its potential benefits for MM patients as a focus of the research. After consent was obtained to the Lifestyle Cohort Study, baseline assessments were completed. Participants were then randomised, without their knowledge, to either be offered the exercise intervention (‘exercise offered) or not (‘cohort only’). In stage 2 those who were randomised into the exercise offered group, were approached by a researcher and invited to take part in a ‘second’ study evaluating an exercise intervention. Figure 1 illustrates the flow of participants through the double consent process. Those in the cohort only group were not informed about the randomisation process or existence of the exercise intervention. The measurement schedule (0, 3, 6, 12 months) and outcome measures were the same for both groups. Only the exercise intervention was part of the second consent. The intervention was delivered by a physiotherapist
in the hospital gym. During the first three months, patients attended the gym once per week and were instructed to exercise at home twice a week. During the following three months, the intensity of the intervention was reduced to one monthly gym session and three home sessions per week. During the last six months, participants were only instructed to exercise at home 3 times per week.

Full ethical approval for this methodology was provided by Queens Square Ethics Committee (13/LO/1105). Five researchers of the MASCOT team attended the ethics meeting, including a myeloma consultant (KY), behavioural scientists (AF and RB), a senior physiotherapist (BP) and the trial statistician (AH). This design can evoke strong emotions and rejection from ethicists and researchers [20] and we believe that the attendance of our diverse team providing the rationale behind the design helped mitigate a lengthy review.

4.1 Recruitment

Overall, 313 patients were invited by post to take part in the lifestyle cohort study. Of these, 80 (26%) declined, 64 (20%) never responded, 23 (7%) were medically excluded and 8 (3%) became ineligible. Between June 2014 and November 2016, 138 (44%) consented to take part. After consenting, 1 (0.3%) patient withdrew and six 6 (2%) relapsed. Therefore, 131 patients were enrolled in the lifestyle cohort study and were eligible for randomisation (Figure 1). Initially, randomisation was proposed at a 1:1 ratio. As the study progressed, the number of participants declining the intervention after randomisation was 38% which was greater than we expected given our pilot [15] which had a 20% decline rate. Thus, the randomisation allocation ratio was altered to 3:1 in favour of the intervention, to ensure that the
study maintained statistical power (34 patients were required in the exercise group to
detect an effect size of 0.69, as per the power calculation).

Of the 131 participants who were randomised, 89 were offered the exercise
intervention. Of these, 34 (38%) declined and 4 (6%) became ineligible due to
disease relapse, resulting in an uptake of 51 (57%). The main reasons for declining
the intervention were time/travel commitment (62%; n=21). Additional reasons were
patients perceiving medical problems as a barrier (12%; n=4), non-response to
invitation (9%; n=3), on long term holiday (9%; n=3) other reasons (5%; n=2),
withdrew (3%; n=1).

At three months, 1 participant (2%) withdrew from the cohort only group citing
personal family issues as the reason, 8 (19%) from the ‘exercise offered’ group (5 of
whom consent to exercise and began the intervention, 3 who had never consented
to exercise). These dropout rates are comparable to other oncology exercise studies
[7] and suggests we didn’t lose participants from the cohort only group due to
dissatisfaction of allocation. There were no differences between the characteristics of
those who agreed and declined to take part in the intervention.

3. Discussion

A double consent adapted-Zelen design method was utilised over a traditional RCT
to reduce patient distress, contamination and dropout in the cohort only group,
allowing us to explore whether exercise is a safe and effective treatment for MM
survivors. Several important learning points around recruitment, randomisation and
contamination were noted, that may aid future study design in this area.

Using the adapted-Zelen we aimed to overcome the selection bias so often reported
in exercise trials (i.e. trials tend to enrol self-selected participants who are motivated
to exercise [4]. However, recruitment to the lifestyle cohort study had a lower uptake (44%) than expected, based on the rate of 80% in the earlier single-arm pilot exercise trial we anticipated more patients would take up the intervention [15]. Possibly potential participants for the lifestyle cohort study may have perceived little benefit from enrolling in the study. In addition, only 57% then agreed to participate in the exercise intervention arm (although this is in line with a systematic review of 65 cancer exercise trials using a standard RCT design where uptake was estimated at 63% (range 33-80%) [21].

As a specialist centre many of our participants had to travel considerable distances to attend the intervention. Despite reimbursement for travel, 62% of those who declined the exercise intervention felt the increased time and number of visits were a barrier to taking part as they were not expecting this increase in commitment. These reasons are similar to those cited in other cancer exercise trials [3]. Velthuis et al (2012) who utilised the Zelen design reported a low inclusion rate of 40% of eligible patients. They attributed it to similar reasons to those of the MASCOT study, with their participants also citing lack of information regarding the increased efforts expected of them [6].

Whilst it could be argued that the rate of declining to take part in the intervention in our study was fairly high, this may suggest lack of awareness of the randomisation and low expectations of engagement were an unforeseen barrier to recruitment. The Zelen design enables researchers to see the acceptability of the intervention in real world settings by reducing selection bias. Our results suggest that our intervention was within similar uptake ranges to other exercise trials and the reasons provided for declining the intervention in our study were similar to a standard RCT design [22]. It should highlight that it may not only be due to a fault in the Zelen design but could
also be down to the fact that interventions are not accessible or attractive to patients and needs to be addressed.

During the trial, we realised that the target sample size would not be reached because of the low uptake of the intervention. Therefore, we changed the randomisation process to have unequal allocation, which Avins (1998) argues the loss of power or total numbers of required subject is small with ratios of 2:1 and only slightly more for 3:1 [23]. The allocation ratio was specified as 3:1 favouring the exercise intervention, based on the observed uptake rate, thereby allowing us to complete recruitment. We anticipated 24 months to recruit which ended up being 30 months. Researchers should be made aware that using an adapted-Zelen may require a longer than expected recruitment period, and should be cautious when estimating uptake.

Risk of contamination in control groups has been reported in exercise trials. Persoon et al (2017) investigated the effect of a supervised exercise intervention on physical fitness and fatigue in myeloma and lymphoma patients following autologous stem cell transplant. There were no significant differences reported between groups in a range of outcomes and the authors described likely contamination with 47% of the control group reporting participation in 10 or more sessions of physiotherapy during the trial period. This was attributed to a recent increase in cancer patients’ awareness of cancer rehabilitation in the Netherlands [24].

An advantage of the adapted-Zelen is to reduce contamination. However, this is compromised if the control group becomes aware of the intervention and therefore the same threats as seen within RCTs of dropout or initiation of exercise can still occur [25]. We had anecdotal reports of contamination from the cohort only group
who reported discussing MASCOT with one another at weekly myeloma outpatient
clinics and support groups that are run at our centre. Consequently, participants may
have been aware of the exercise study before consenting to the lifestyle cohort. This
was captured within the qualitative studies we undertook as part of the main study
(Box 1).

Velthuis et al (2012) reported similar problems with patients meeting in
chemotherapy day care and discussing the study whilst Campbell et al (2005) did not
report any contamination [6, 11]. In the latter study, patients with arthritis were
contacted by phone in the community which meant they did not meet other
participants, thus reducing the opportunity to be made aware of the full study [11].
However, our results do not suggest that the cohort only group were meaningfully
affected by contamination as there were significant improvements in leg strength in
favour of the intervention group and PA levels in cohort only group reduced at each
time point (data to be published). There is no formal documentation from other Zelen
studies about the level of contamination in the control group to assess potential
dilution of effect size. We did not document evidence for contamination in this study
but this is warranted in future studies utilising similar design.

With a traditional RCT design, participants may drop out due to disappointment at
their allocation and a systematic review into control group dropout rates in cancer
exercise trials showed that the largest mean percentage dropout was found in
studies where no intervention was provided to the control group 11.2% (S.D 8.1) [7].
Whilst we did not provide any treatment to the cohort only group, our dropout rate at
three months was 5% which is comparable with the study design which reports the
lowest drop outs by providing some form of an intervention to the control group after
the study (5.8% S.D 5.0) [7]. This may be a promising indication that the adapted-
Zelen could potentially reduce dropout rates due to treatment allocation without providing the intervention.

To the best of our knowledge, there are no studies reporting cancer patients’ thoughts about the Zelen design. Qualitative data from participants in a neonatal clinic elicited mixed attitudes towards Zelen randomisation with participants evenly split between accepting and not accepting the design. Some reported that they found the Zelen design underhand yet acknowledged if you were in the control group it was kinder than an RCT as you weren’t aware you had not received a potentially desirable treatment [26].

We utilised this design over a standard RCT because we felt it would cause patient distress if they were not allocated to the exercise intervention and may lead to contamination and participants to drop out. However, it is worth acknowledging that historically this design has previously led to ethical criticism because whilst it spares emotional distress for the participant, it raises questions as to whether it is ethical for patients to be randomised without knowledge or consent [19].

Reporting an alternative study design similar to Zelen, Gal et al (2019) used a “trials within cohort randomised controlled trial” within an exercise oncology setting [27]. In the first stage, participants enroll to a cohort study and provide broad consent to be approached for any experimental interventions or to be a control for multiple studies that may be undertaken during the cohort study period. In the second stage, informed consent is only sought in those randomly allocated to the intervention. The third stage all cohort participants are informed of the multiple RCT results. Kim et al (2018) report it is ethically superior to the adapted Zelen design because patients are fully informed they will be randomised [28]. Gal et al (2019) report no contamination
and this design also mitigates patient distress because they remain unaware of the interventions unless they are selected [27]. This design is suggested to overcome the ethical disadvantages of the Zelen design and provides advantages over traditional study designs and researchers may want to explore this as an alternative to the Zelen design.

It is important to note that in the adapted-Zelen design the control patients are not deprived of any other treatments and are managed as per usual clinical practice. Behavioural interventions are generally expected to only lead to small to moderate benefits. Therefore, the negative impact of contamination can be substantial, and this can only be mitigated by a Zelen type of design. We only interviewed patients who took-up the exercise intervention but whilst the majority of participants were not aware that they had been randomised as a result of consenting to the lifestyle study, one participant did report that they thought it was perverse (Box 1). It is possible that in those motivated to exercise in our study we may have reduced potential distress for the patient at the time of enrolment but it remains unclear whether it caused delayed distress once those who were randomised to the cohort only group realised they were not fully informed. We would recommend researchers considering using the Zelen design collect data on control participants experience to assess its acceptability within cancer trials and aid the ethical debate.

1. Conclusion

The adapted-Zelen presents an alternative way to reduce risk of contamination and bias in exercise oncology research where blinding participants to their allocation and the intervention they receive is difficult. By reducing selection bias it provides real world acceptability of an intervention.
Further work is warranted to explore the experiences of participants in both arms to gather a greater understanding of its strengths and applicability.

Box 1. Qualitative interview quotes from MASCOT participants.

| Participant | Exercise study with others | Q: Would you recommend taking part in the study to discussing other people? |
|-------------|---------------------------|-------------------------------------------------------------------------|
|             | A: “Yeah. Yeah. I have done.” | Q: You have done? Is that other people that you’ve met?                  |
|             | A: “Through the clinic, yeah, through the hospital here.” |                                                           |

| Participant | Exercise awareness of the intervention | Q: When they introduced the exercise element, were you surprised? |
|-------------|----------------------------------------|-----------------------------------------------------------------|
|             | A: “You, you mean the every week one? Um, yeah, I guess to a certain extent I was because [the doctor] had not suggested that [the exercise aspect of the study] at the outset and then [the researcher] suggested that it was, you know, secret, almost …um, which I found quite perverse but there we are. Um, but it took on a different dimension.” |
Authors Contribution

Conceptualization & Methodology: KY, AF, RJB, BP, AH. Investigation & Data curation: JL, MH, DAK, OM, BP. Data Analysis: DAK, AH, AF, and KY. Funding Acquisition KY and AF. Project administration and supervision: KY and AF. Writing Original Draft: JL, OM, AF, KY, RJB, AH, DAK

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Role of the funding source

The funders and sponsor of the study had no role in study design, data collection, data analysis, data interpretation, or the writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.
Declaration of interest

KY reports grants from Celgene during the conduct of the study. All other authors declare no conflicts of interest.

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Stage 1
Participant Approached With Information on Lifestyle Cohort Study

Informed Consent Gained For Lifestyle Cohort Study
Including 4 study assessments over 12 months

Baseline Assessment
Lifestyle Cohort Study

Stage 2
Randomisation of all cohort study participants (n=131)

Approached with information about Exercise Study - Intervention Group (n=89)

Informed Consent Gained For Exercise Study
6 month intervention

Consented Gained: Participants undertake exercise intervention (n=51)

Consent Not Gained: Participants agree to continue in cohort study (n=31)

Continuation in Cohort Study - Usual Care Group. Unaware of randomisation or intervention (n=42)

3 month assessment
Lifestyle Cohort Study

6 month assessment
Lifestyle Cohort Study

12 month assessment
Lifestyle Cohort Study
AUTHOR DECLARATION

We wish to draw the attention of the Editor to the following facts which may be considered as potential conflicts of interest and to significant financial contributions to this work.

KY reports grants from Celgene during the conduct of the study. All other authors declare no conflicts of interest.

We confirm that the manuscript has been read and approved by all named authors and that there are no other persons who satisfied the criteria for authorship but are not listed. We further confirm that the order of authors listed in the manuscript has been approved by all of us.

We confirm that we have given due consideration to the protection of intellectual property associated with this work and that there are no impediments to publication, including the timing of publication, with respect to intellectual property. In so doing we confirm that we have followed the regulations of our institutions concerning intellectual property.

We further confirm that any aspect of the work covered in this manuscript that has involved either experimental animals or human patients has been conducted with the ethical approval of all relevant bodies and that such approvals are acknowledged within the manuscript.

We understand that the Corresponding Author is the sole contact for the Editorial process (including Editorial Manager and direct communications with the office). He/she is responsible for communicating with the other authors about progress, submissions of revisions and final approval of proofs. We confirm that we have provided a current, correct email address which is accessible by the Corresponding Author.

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Conceptulization & Methodology: KY, AF, RJB, BP, AH. Investigation & Data curation: JL, MH, DAK, OM, BP. Data Analysis: DAK, AH, AF, and KY. Funding Acquisition KY and AF. Project administration and supervision: KY and AF. Writing Original Draft: JL, OM, AF, KY, RJB, AH, DAK
What is new?

Key Findings

• The adapted-Zelen design reduces selection bias and can provide real world acceptability of an exercise intervention within a clinical service.

• Dropout rates are comparable with a cross over design without the associated costs and time.

• An advantage of the adapted-Zelen design is that no patients were lost from usual care due to dissatisfaction of allocation.

What this adds to what is known

• The adapted-Zelen design increases demand on research resources as a larger number of participants are required to achieve power than a randomised controlled trial. However, it provides an acceptable alternative study design to avoid common disadvantages found with other study designs e.g. drop outs due to dissatisfaction at allocation, contamination and low generalisability in clinical settings.

What is the implications and what should change now?

• To date there has been no qualitative work in adapted-Zelen trials for cancer patients to explore their experiences of being involved in these study designs. This study gathered brief insights from intervention group participants but its imperative further work is done to gather greater understanding of its strengths and applicability. This would aid the ethical debate surrounding this design.

• Further work is required to eliminate barriers preventing patients from accessing exercise interventions and find acceptable alternatives to face to face groups.