Author’s response to reviews

Title: A Feasibility Randomised Controlled Trial of Short-Term Fasting Prior to CAPOX chemotherapy for Stage 2/3 Colorectal Cancer: SWiFT Protocol

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Author’s response to reviews:

Reviewer reports:

Reviewer #1:

Shingler and colleagues designed this feasibility trial to investigate 36-hour fasting as an intervention to assist mitigate adverse effects of CAPOX chemotherapy for stage II/III colorectal cancer patients. Overall, this is a trial which could potentially add important prior knowledge to future large trials. I have a few comments which I am expecting to be addressed by the authors.

Major comments:

1). The authors may consider explaining more on the adoption of 36-hour plan instead of other plans like 24, 48 plans. In the study by Dorff et al. [1], the investigators reported both significant and non-significant trend favouring plans of longer span (>48 hours) in terms of DNA damage and neutropenia. Although the authors stated that longer hours may lead to poor adherence, is there any evidence supporting a significant difference of adherence between 36- and 48-hour plans? If this time span of 36 was selected arbitrarily, and there has not been much evidence, this ought to be discussed a bit more in the discussion section on how the benefit and adherence is balanced.

Author Response:

The 36 hour fast was chosen over longer term fasts for pragmatic reasons. It is the shortest term fast in which we would expect to see a reduction in IGF-1, whilst limiting potential patient burden which may be associated with longer term fasts. The 36 hour fast was also chosen after the research team received feedback of concern among clinicians over the length of fast when recruiting sites to run the trial. The following text has been added at line 194 to provide further clarification for this:

The 36 hour fast was chosen over longer term fasts for pragmatic reasons. It is the shortest term fast in which we would expect to see a reduction in IGF-1, whilst limiting potential patient burden which may be associated with longer term fasts. The 36 hour fast was also chosen after the research team received feedback of concern among clinicians over the length of fast when recruiting sites to run the trial. The following text has been added at line 194 to provide further clarification for this:
“A decrease in IGF-I levels in response to a short-term fast in humans is seen within 36–120 hours of fasting[3]. As previous research has suggested that longer fasts may be subject to poorer adherence[7], we have selected a 36-hour fast prior to each of the first 3 cycles of chemotherapy. This aims to find the balance between implementing a fast that is long enough to alter metabolic pathways whilst keeping participant burden to a minimum.”

2). This is more of question than comment. The primary aim for this study is to evaluate the feasibility instead of the effect of fasting on chemotherapy-related side effects. In this context, do we really need a blank control arm (standard diet arm in this study) if it is very underpowered to detect any treatment effects? It is mentioned in the text that this can better inform the sample size calculation for future trials although underpowered. However, the incidence rates or other metrics on the adverse effect for stage II/III patients with normal diet can be readily found in other large trials. Then why not just a single-arm design which would generate larger sample size to estimate the adverse events rate more accurately for the fasting arm?

Author Response:

This is an interesting point and it is true that adverse events for this chemotherapy treatment have been published previously. As well as providing reassurance that published estimates apply to our specific patient group, the control arm will serve several purposes in this trial. Firstly, there is little or no published data on usual dietary intake during CAPOX treatment. Secondly, it will allow us to see whether there is any cross-over between the treatment arms that would need to be taken into account in a full-scale trial. Finally, it will confirm whether this population are specifically willing to be randomised into the trial, with the potential for entering the trial as a control, where they will have to supply dietary data without making any active changes.

Minor comments:

1). Line 62-63: A reference needs to be inserted here to support the narrative.

Author Response:

References added

2). Table 1: what is the difference between C1 D-1 and C1 D1?

Author Response:

We apologise for the confusion. C1 D-1 refers to the day before the first chemotherapy administration when the fast begins, whereas C1 D1 refers to the day of the first chemotherapy administration. Table footnote updated to: “D = Day, where -1 is the day prior to chemotherapy and 1 is the day of chemotherapy;”

Reviewer #2:

Thank you for the opportunity to review the article, "A Feasibility Randomised Controlled Trial of Short-Term Fasting Prior to CAPOX Chemotherapy for Stage 2/3 Colorectal Cancer: SWiFT Protocol submitted by Shingler and colleagues. This is an interesting and relevant
study as many patients inquire about this type of intervention during chemotherapy but evidence is lacking. Overall the manuscript is well-written. I have provided details for minor revisions below.

Title:

Clearly states that it is a protocol for a feasibility RCT, and clearly states the intervention and study population. Capitalize 'chemotherapy' for consistency.

Author Response:  We have made this change

Abstract:

Overall the abstract is clear and concise. Please see some minor comments below:

Page 2, Line 20 and Line 23: "Short term" should be hyphenated.

Author Response:

We have made this change on both lines

The abstract should not only state that it is not known whether it is feasible for patients to follow a short-term fast but should also indicate the lack of evidence supporting efficacy of the intervention. For example, "Evidence/RCTs demonstrating efficacy of short-term fasting in protecting against chemotherapy-related toxicities in humans is lacking however, it is not known whether people due to undergo chemotherapy will be able to follow a short-term fast. Preliminary data confirming this…"

Author Response: We have changed the sentence as follows: “However, there is a lack of evidence to support the efficacy of short-term fasting in protecting against chemotherapy-related toxicities in humans, and it is not known whether people due to undergo chemotherapy will be willing and able to follow a short-term fast.”

Background:

Page 4, Lines 48-50: These two sentences are repetitive, consider re-wording.

Author Response: The two sentences have been merged as follows: “During times of nutrient scarcity, normally functioning body cells have the ability to switch from a state of growth and development to a state of maintenance and repair, which enables cells to conserve energy.”

Overall, I feel that the background could use more detail in describing effects of calorie restriction and potential mechanisms (cell vs animal vs human studies), a broader range of references, and a broader review of the literature to support why the study is being done.

Author response:

We have added references to the pre-clinical research as well as the following text to the
Background section:

“The exact mechanisms behind DSR are not fully understood. It is believed they may be partially mediated by the reduction in blood glucose and growth factors such as Insulin-like Growth Factors (IGFs) brought about by fasting. Within healthy cells, this negatively regulates downstream cellular pathways such as the Ras/MAPK and P13K/Akt pathways which are promoters of cellular proliferation (3). This allows the cells to cease growth and convert energy to cell maintenance. Another mechanism through which DSR may protect healthy cells is through increased autophagy. Calorie restriction activates the enzyme “AMP activated protein kinase” which increases autophagy. Autophagy can target defective organelles to be degraded into substrate for use in energy production and repair(3). Cancer is often associated with a defect in autophagic capacity as oncogenes Akt and P13k inhibit autophagy while the tumour suppressor gene PTEN, which loses function in tumour cells, would usually upregulate it. The decrease in growth factors associated with fasting may therefore lead to upregulation of autophagy in normal cells but not in cancer cells, allowing them to degrade organelles for energy use(6).”

Page 4, Line 62: Please include references.

Author response:

References added

Methods:

Overall clear description of primary and secondary outcomes measures.

Page 5, Line 85: Hyphenate "36 hour".

Author response:

We have made this change

Page 5, Lines 93-99: Regarding adherence to intervention, this is a water only fast yet participants will be considered to have adhered to the fast if they consume less than 14% of their BMR. Please provide a reference that this calorie approximation should keep participants in a fasted state. I think it should be stated more clearly why there is flexibility the water only fast allowing up to 14% of BMR i.e. to manage any adverse symptoms experienced with fasting. Would macronutrient distribution/composition of the foods influence participants remaining in a fasting state irrespective of being under 200 kcal/24h? Could compliance/keeping participants in a fasted state be encouraged by providing a suggested list of specific foods to relieve adverse symptoms associated with fasting?

Author response:

Further information on the use of this cut off has been provided at line 114:

“The aim of using a cut-off of 14% BMR is to allow participants to consume small amounts of food if they need to mitigate any side effects of fasting, whilst keeping the participant in
the metabolically altered state associated with fasting. This cut off has been used in previous trials of fasting(10). To encourage participants to only consume a small number of calories, a list of 50kcal snacks will be provided.”

Page 6, Line 103: Hyphenate "in depth”.

Author response:
We have made this change

Page 6, Line 110: Hyphenate "Patient reported”.

Author response:
We have made this change

Page 6, Line 110-111: It is a strength of the study protocol that side effects will be captured on day 1, 3, and 7 of each cycle. Will participants need to make an extra trip to the hospital for this or will it be assessed over the phone? Extra hospital visits may decrease retention/data completion.

Author response:
We apologise that this was not clear within the text. We have revised the text to say:

“Patient-reported side effects will be collected on day 1 of each cycle (prior to chemotherapy administration) and at home on day 3 and day 7 (via participant-completed questionnaires), to capture the transient nature of side effects.”

Page 6, re: Markers of cellular metabolism: Please specify how far in advance baseline samples will be collected.

Author response: Text updated to clarify timings of samples:
“Baseline samples will be collected prior to fasting, when participants attend for routine pre-chemotherapy blood tests (approx. 4 days prior to cycle 1). Follow-up samples will be collected immediately prior to chemotherapy administration at cycles 1 and 3.”

Page 6, re: Sarcopenia: How far from the third cycle of chemotherapy will follow-up CT scans take place? If the follow-up CT scan occurs long after the last cycle of intervention, it will limit interpretation of any changes in body composition/lean body mass and whether they may be attributed to the intervention as participants would have a longer period of time for repletion. Regarding hand grip strength, please specify who on the research team will conduct this and the training. If multiple individuals completing this measurement, how will you optimize inter rater reliability.

Author Response:

Follow-up scans are expected to take place around the 3rd or 4th cycle of chemotherapy, so within weeks of the 3rd cycle. If there is too much variation in this, it will be recognised through the feasibility study and a timed protocol can be adopted for any further trials.
It is likely only one member will be taking hand grip strength but for cases of holiday cover, etc, a SOP has been developed which the local site team will be trained in. The following text has been added to the sarcopenia section:

“Measurements will be taken by the research site’s clinical trial officer/research nurse who will be trained in following the trial’s Standard Operating Procedure for measuring hand grip strength.”

If space permits, providing a brief rationale for each primary and secondary outcome would provide greater clarity.

Author response:

The rationale has been included for the primary outcomes and some of the secondary in the initial draft. Further text has been added to clarify the rationale for the secondary outcomes:

“The secondary outcome measures aim to provide further information on possible outcomes of interest in a definitive trial. Including these in the feasibility trial will allow for the data collection methods to be assessed as well as providing information on the variance of each outcome. The impact of fasting on these measures could then be tested in a suitably powered trial. The secondary outcome measures are:

Side effects of chemotherapy – Measured using the Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE™)[15], Full Blood Count (FBC) and blood chemistry analysis. Short term dietary fasting may result in differential stress resistance between normal and tumour cells, which may render tumour cells more susceptible to chemotherapy than normal cells. Patient-reported side effects will be collected on day 1 of each cycle (prior to chemotherapy administration) and at home on day 3 and day 7 (via participant-completed questionnaires), to capture the transient nature of side effects. Data will also be recorded on whether participants completed their first 3 cycles of chemotherapy and reasons for dose reductions/delays/early termination if they occurred.

Quality of Life (QoL) – Measured using the EQ-5D-5L health related quality of life instrument[16]. This would be used to explore whether fasting, or its impact on chemotherapy side effects, increases QoL. Haematologic toxicities – Assessed using routine FBC data collected prior to each round of chemotherapy and classified according to CTCAE criteria[17]. Markers of cellular metabolism – Measures will include glucose, insulin, IGF-I, IGF-II, IGF binding protein (IGFBP)-2 and IGFBP-3. These will be used to study the effect of the fast on markers of cellular metabolism. They will also be considered in conjunction with self-reported dietary intake to explore adherence to the intervention, as the level of these markers would be expected to be reduced in adherent participants. Baseline samples will be collected prior to fasting, when participants attend for routine pre-chemotherapy blood tests (approx. 4 days prior to cycle 1). Follow-up samples will be collected immediately prior to chemotherapy administration at cycles 1 and 3.

Markers of inflammation – C-reactive protein (CRP) will be measured at baseline (pre-fast) and prior to chemotherapy administration at cycles 1 and 3. In a full powered trial this would be used to explore whether fasting reduces inflammation.

Appetite – Self-reported on visual analogue scales[18]. As chemotherapy can alter taste and appetite[19], measuring appetite is of interest to explore whether fasting negates reduced appetite through decreased treatment side effects.
Sarcopenia – Assessed using Computerised Tomography (CT) and hand grip dynamometer[20]. Single axial images of the third lumbar (L3) level muscle mass, taken from pre-chemotherapy staging and follow-up CT scans conducted as part of routine care, will be analysed for body composition using SliceOMatic software[21]. Hand grip strength will be measured three times in the dominant hand, while the participant is in a seated position, arms supported at right angles and feet on the floor. Measurements will be taken by the research site’s clinical trial officer/research nurse who will be trained in following the trial’s Standard Operating Procedure for measuring hand grip strength. The mean of the three measures will be used to assess hand grip strength, using cut-off values defined by the European Working Group on Sarcopenia in Older People (EWGSOP) to identify low grip strength[22]. These measures will allow us to inform future trials on the prevalence of sarcopenia in this population and explore the safety of fasting in relation to this condition.”

Page 7, Line 143: Please specify what scale is being used for performance status. ECOG vs WHO?

Author response:
Updated so that ECOG has been specified.

Page 7, Line 144: Please specify what criteria will be used to determine whether a participant has cachexia and would thus exclude them from participation in the study.

As there is currently no uniform criteria for diagnosing cachexia, a pragmatic approach is to exclude those who have been given this diagnosis by their treating clinicians. Therefore the wording has been updated to:

“People will be excluded if they have a clinical diagnosis of cachexia”

Page 7, Line 144: Re: exclusion criteria, the current criteria does not account for patients who may have sarcopenic obesity, who may be at higher risk for adverse effects of fasting. These patients may also be at higher risk for chemotherapy-related toxicities.

Author response:

The authors acknowledge that this is a very interesting point. As we are assessing sarcopenia, we will have the opportunity to assess the degree of sarcopenic obesity within our trial population and therefore inform future trials on the prevalence of sarcopenic obesity and the effect (including safety) of short term fasting on this group. See additional text added as per the above query on measurement rationale.

Page 8, Line 161: Can you provide details regarding the rationale for selecting a 36-hour fast as the intervention rather than a 48-72 hour fast? In the pilot study by de Groot et al, the intervention was 48 hours. In this study, they did not see a benefit of short-term fasting on chemotherapy-related side effects and attributed this to the fasting period of 48 hours being potentially too short and discuss that previous studies have shown that a longer fasting period is required.

Author Response:
Please see author response to Reviewer #1, Comment #1.

Page 8, Line 163: Regarding "standard dietary guidance/advice as per local standard practice", are local standard practices the same at both sites? Can you elaborate on what this may entail? Do patients receive general nutrition and chemotherapy education at the start of chemotherapy? Is there equal access to dietitians for the management of nutrition impact factors during chemotherapy? If some patients receive dietitian assessment and nutrition and chemotherapy education at first visit and some do not, some participants who understand the importance of maintaining nutritional status during chemotherapy and have received diet education may be better able to compensate after the fasting intervention and may be better able to replete weight/muscle mass between cycles.

Author response: Practice may vary between sites and even between clinicians. We are therefore going to collect data through the qualitative interviews on what, if any, nutritional advice was received by those in the control arm. This will help to inform whether future trials will require a standardised approach for those in the control arm across study sites. Line 208 has been updated to clarify this:
“Interviews will follow a topic guide, which covers topics such as dietary guidance received, experience of randomisation, tolerability of the intervention/experience of taking part as a “control” and experience of the data collection methods.”

Page 8, Line 166: Typo - SPIRT vs SPIRIT

Author response: We have changed SPIRT to SPIRIT

Page 8, Line 167: "patient attends their" vs "patient attends for their".

Author response: We have removed ‘for’

Page 10, Line 218: Hyphenate "short term".

Author response: We have made this change

Page 14, Trial schedule: The 36-hour fast appears to start D-1 overlapping to D1. Please be more specific in how many hours will participants be fasting prior to receiving the chemotherapy and how many hours after infusion. Repeat HGS appears to fall on C3, D-1 but there are no other measurements on this day. Will participants be required to make a trip to the hospital to measure HGS? Could this occur on C3, D1 to minimize participant burden?

Author Response: The entire 36 hour fast will take place prior to receiving chemotherapy.

HGS measurement has been moved to coincide with the other follow-up measures on C3 D1.