Reviewer’s report

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

Version: 0 Date: 13 Feb 2019

Reviewer: Denise Gabrielson

Reviewer's report:

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.

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.

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…"

Background:

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

Page 4, Line 62: Please include references.

Methods:

Overall clear description of primary and secondary outcomes measures.

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

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

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

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.

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

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.

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

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

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.

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.

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.
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.

Page 8, Line 166: Typo - SPIRT vs SPIRIT

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

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

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?

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An article of importance in its field

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