Exercise and nutrition interventions to improve treatment-related outcomes in cancer survivors (Clinical Trial Required)

Frank Perna, Tanya Agurs-Collins, and Joanne Elena on behalf of the Obesity & Cancer Working Group
Background

- Adverse physical consequences among survivors can increase risk for treatment interruptions
  - Adiposity/low muscle mass, poor fitness, and diet can lead to worse outcomes in survivors, including dose interruptions and toxicities
  - 35% of US cancer survivors are obese and <17% meet general physical activity guidelines

- Exercise and nutrition interventions:
  - Improve fitness, body composition, and nutritional status
  - Are generally well-tolerated and can be tailored
  - Can be delivered in conjunction with cancer therapies

- Few studies have focused on:
  - The time period shortly before or during cancer treatment
  - Treatment-related outcomes
Purpose of this RFA

• To understand how exercise and nutrition interventions (alone or combined) affect treatment-related outcomes for curative/life-extending therapies
  • Treatment-related outcomes include:
    • Dose interruption, reduction, or delays
    • Related healthcare utilizations (e.g., hospital admissions, length of stay, ED visits)
    • Severe adverse events (e.g., CTCAE ≥ 3, dose-limiting and organ-specific toxicities)

• To address research gaps concerning:
  • Specific exercise and nutrition interventions across cancer sites and treatment protocols

• Goal: to help patients successfully complete planned treatment with good overall outcomes
Exercise Intervention

• ACSM Exercise Guidelines for Cancer Survivors:
  • Reviewed existing literature
  • Exercise deemed safe and provided considerations

• Strength of evidence
  • Strong: improved fitness, lean mass, fatigue, QOL, and functioning
  • Safe/moderate benefit: lymphedema and bone health
  • Requiring further study: cardiotoxicity, peripheral neuropathy, treatment tolerance

• Limitations: studies of treatment-related outcomes
  • Secondary data analyses of a parent trial
  • Lacked specificity regarding exercise guidance ("dose") by Frequency, Intensity, Time, and Type (FITT) and determination of optimally-effective exercise level
### Nutrition Interventions Before and During Treatment

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<thead>
<tr>
<th>Before Treatment “Prehab”</th>
<th>Results</th>
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| Nutritional interventions (some with exercise) prior to colorectal surgery (Gillis et al. 2018) | ↑- presurgical functional capacity and lean body mass  
↓- length of hospital stay                  |

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<tr>
<th>During Treatment</th>
<th>Results</th>
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| Protein Supplementation (colorectal cancer patients during 5-fluorouracil-based chemotherapy) (Mazzuca et al. 2019) | ↓ - hematological and gastrointestinal toxicities  
↑ - nutritional status                  |
| Fasting-mimicking diets in combination with therapies were associated with: (Bauersfeld et al. 2018, Nencioni et al. 2018) | ↑- treatment efficacy and tolerability  
↓- toxicities                        |
| High-fiber diet (compared with habitual-fiber intake) during pelvic radiotherapy (Wedlake et al. 2017) | ↓- gastrointestinal toxicity                |
Required Elements of RFA

- Identify the gaps in knowledge to be addressed
- RCT, initiated before or during cancer treatment, with power to test intervention effects on a treatment-related outcome as the primary endpoint and secondary endpoints i.e., patient reported outcomes
- Justify the biological plausibility of the intervention on the treatment-related outcomes
- Specify population of cancer survivors treated for curative or life-extending intent
- Include robust treatment data - planned and delivered dose and type for all treatment modalities, and where appropriate, supportive care measures (e.g., anti-emetics)
- Include validated measures of body composition, diet, general physical activity, and where appropriate, metabolic biomarkers
- Cooperate with Coordinating Center in identification of common data elements and standardization procedures

Additional Requirements: Studies with Exercise Component

- Specify details of exercise prescriptions (e.g., FITT criteria)
- Include validated measure of exercise adherence and exercise-related biomarkers relevant to treatment outcomes (e.g., CRF, functional status)
Possible Research Questions

• What is the minimally and optimally effective “dose” of exercise to mitigate organ-specific toxicity in cancer survivors receiving a specific therapy?

• Does exercise and/or access to medical nutritional therapy improve immediate post-surgical outcomes, including length of hospital stay and readmissions?

• Does a tailored weight loss intervention for overweight/obese cancer survivors that is designed to preserve muscle improve completion of the planned course of treatment in cancer survivors?

• Does intermittent fasting around the time of chemotherapy improve ability to deliver the planned course of treatment?
RFA Justification

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<th>U Mechanism</th>
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<td>• Focuses work to address the research gap identified in the portfolio and ensure studies are aligned with NCI priorities</td>
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<td>• Promotes trans-disciplinary exchange and collaboration among awardees</td>
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<td>• Facilitates NCI expertise and involvement</td>
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<td>• Requires collection and harmonization of common measures and standardized procedures across projects to maximize opportunities for data pooling and pilot projects</td>
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<th>Research Coordinating Center</th>
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<td>• Supports collection of common data, standardization of platform and procedures for the collection, pooling, and analysis of common data across projects for current and future use</td>
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<td>• Provides expertise to support collection of novel data (e.g., cost or implementation feasibility)</td>
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<td>• Facilitates communication within the cooperative group and serves as a resource for extramural community</td>
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Budget: $1.275M total cost per grant per year. 5 research sites and 1 coordinating center.
Reviewer Comments and Clarifications (Drs. Robison, Seewaldt, & Colditz)

- Remove age ≥ 18-years as requirement
- Include patient report outcomes as a secondary outcome
- Collect, where appropriate, supportive care measures (e.g., anti-emetics, pain medication)
- Clarification of responsive study design features
  - **Study population**
    - Overweight/obesity status is a consideration but not a required sample selection criterion
    - Inclusion of minority and socioeconomically underserved populations strongly encouraged
  - **Study design**
    - Study enrollment initiated shortly before or during treatment, but intervention may extend beyond treatment
    - Collect common data elements facilitated by Coordinating Center:
      - metabolic biomarkers/profile of participants and set of patient reported outcomes
      - Collection of intervention implementation and feasibility data
  - **Coordinating Center**
    - Establish common data terms, definitions, platforms and standardized procedures for common data collection and harmonization across all projects to facilitate future data pooling and analysis
    - Support collection of novel data (e.g., implementation feasibility, cost) and data analyses