**Supplementary File 1: Sample Search Strategy – Medline**

|  |  |  |  |
| --- | --- | --- | --- |
| **PICO Framework** | **PICO Search Ideas** | **Search Terms including Mesh**  | **Search Number** |
| Population | Randomised Cancer trials | Cancer:"neoplasms[MeSH Terms] OR cancer[Text Word]” Randomised:Randomi\*"Randomized Controlled Trials as Topic"[Mesh] AND "Randomized Controlled Trial" [Publication Type] AND "Surveys and Questionnaires"[Mesh] AND "Random Allocation"[Mesh] AND "Pragmatic Clinical Trials as Topic"[Mesh] AND "Controlled Clinical Trials as Topic"[Mesh] AND "Controlled Clinical Trial" [Publication Type] AND "Intention to Treat Analysis"[Mesh] AND "Pragmatic Clinical Trial" [Publication Type]AND "Prostate"[Mesh] | #1 |
| Intervention | Any researched cancer treatment  | "therapy"[Subheading] OR "therapeutics"[MeSH Terms] OR treatment [Text Word] | #2 |
| Comparator | PlaceboSham deviceStandard of careDrug comparator | "Placebos/therapeutic use"[Mesh]) AND ( "Therapeutics"[Mesh] OR "Neoadjuvant Therapy"[Mesh] OR "Therapies, Investigational"[Mesh]  | #3 |
| Outcome | No specific outcome required for search  | N/A | N/A |

**Supplementary File 2: Burden, justifications and assumptions**

|  |  |  |
| --- | --- | --- |
| **Burden**  | **Data Category**  | **Justifications and assumptions for inclusion** |
| Cancer Diagnosis | PhysicalPsychological | Can be an extremely distressing aspect of disease progression and is often termed in Stages 1-4. * The potential of a positive prognosis decreases, the higher the stage of cancer at diagnosis.
* It is assumed that the higher the stage of PC in participants at recruitment to the trial, the higher the burden of participation.

eg. Stage 1 (Low Burden), Stage 2/3 (medium Burden) Stage 4 (High Burden). |
| Side effects | Physical | This assumption that side effects of the intervention/active comparator on participants can be measured by the rate of AE’s in the intervention arm. The scaling is based on NHS Scale but will be restricted to very common/common/uncommon as the trials included do not exceed 1500 participants. Side effect is:* Very common: more than 1 in 10 people are affected (High Burden)
* Common: between 1 in 10 and 1 in 100 people are affected (Medium Burden)
* Uncommon: between 1 in 100 and 1 in 1,000 people are affected (Low Burden)
 |
| Invasive procedures | Physical | The more physically invasive a procedure, the higher the scale number. Blood specimens are frequent in trials of prostate cancer where biomarkers play a huge role in monitoring and measuring treatment. * Often part of routine medical check-ups and is therefore considered minimally invasive (Low Burden)
* If more than one set of bloods is taken, an extra mark will be allotted to adjust for the excess burden.

Biopsies are often taken at PC trial end to determine treatment effect and are an invasive medical procedure (Medium Burden)* Often participants will have a pre-trial diagnostic biopsy but are required to provide a fresh biopsy to meet inclusion criteria for participation.
* This would be considered an excess burden, as they may already have a diagnosis and the biopsy could be avoided, therefore one extra mark is given for multiple biopsies present in a trial. (+1 Mark up in Burden)
 |
| Clinic Visit Frequency | PhysicalPsychological | Clinic visit frequency can have implications for a participant’s personal life as the requirement to attend a multiple clinic visits can clash with:Home life balance * Can increase the requirement of childcare
* Reduce the amount of spare time available to spend with family

Work life balance* Can interrupt working schedule which can affect pay and annual leave entitlements

Therefore, the numbering system proposed is based on the theory the higher the frequency of visits the higher the burden to participants.If all visits occur in routine care (0 Burden Measured).  |
| Questionnaire/diary usage and frequency | Physical Psychological | The burden associated with questionnaire/diary usage and frequency is related to time burden. * The theory that higher the frequency of questionnaire or diary usage the higher the burden to participants so the assumption made is the more questionnaires/diary usage/frequency in a trial, the higher the burden to participants
* • Often PC trials will use multiple questionnaires which can be extremely time consuming for the participant and interrupt home/work life balance mentioned.
 |
| Comparator Arm | Psychological | The use of placebo has been shown in the literature to be a distressing aspect of trials for participants so is assumed to be the most burdensome comparator.* An active comparator can psychologically appear more appealing than standard care and therefore is considered moderately burdensome
* The use of standard care is easily justified to participants, is a minimal prerequisite and is therefore not considered as burdensome as placebo.
 |
| Symptom burden | Psychological | In this case symptom burden will be based on the mean diagnosed stage of PC of the participants in the trial. * Symptoms of PC become more prevalent as the disease progresses stages and the treatments available also become more aggressive.
* Therefore, it will be assumed the higher the stage of cancer in participants, the higher the corresponding symptom burden of the participant.
 |
| Questionnaire Invasiveness | Psychological | The use of multiple questionnaires is commonplace in trials for PC patients or PCS’s.* Questionnaires relating to routine medical information such as BMI/Demographics will be considered the least burdensome. Any personal opinions or beliefs will be considered moderately burdensome as the questions are more personal and invasive to the participant.
* Because of the effect PCa can have on sexual functioning, questionnaires based on personal information involving relationships or sexual intimacy will be considered the most invasive or burdensome as men have reported embarrassment or difficulties in disclosing their complaints with health care providers (Grondhuis Palacios et al., 2018).
 |
| Follow-up Treatment | PsychologicalEconomic | For this category we will assume that the participant would find the prospect of completing the trial that maybe contributing to positive effects on their health or wellbeing, distressing. * If there is a possibility of treatment to continue past trial completion this would be the least burdensome option for participants.
* After trial completion it is reassuring for participants to have a follow-up consultation where any potential tolerability issues post trial can be discussed.

No follow up can be considered the most burdensome aspect post trial as this period can be distressing for participants transitioning from participant to appropriate care in the healthcare system without adequate support (Cho et al., 2018) |
| Clinic Visit Travel Distance | Economic | Clinical visit travel distance is considered burdensome due to both time and financial loss to participants. * The further a participant must travel, the higher cost they pay financially and the higher the relative loss in leisure time.
* Most trials did not have the distance travelled for visits readily available retrospectively, so an assumption was made whereby the higher the number of clinics/hospitals associated with the trial the lower the burden of distance travel.
 |
| Financial Implications | Economic | Participation in trials can have an economic burden on a participant through loss of work, excess travel costs or sick leave associated with trial treatments/AEs. Financial incentives for participation, while ethically are questionable, remove the burden of financial loss for the participant while also increasing potential recruitment or attrition. * Reimbursement for travel can aid participants who may find the cost of travel as a barrier to adherence to trial visits.
* No financial assistance can put financial strain on participants as excess expenses for travel to and from trials/loss of workdays are an increased psychological and economic strain.
 |
| Participant age | Familial | Assumptions were made in respect to participants age at recruitment.18–35-year-olds:* on average, are less likely to have comorbidities and underlying conditions that increase risk of participation.
* may be more inclined to see the trial as a positive treatment avenue, therefore reducing potential burden of participation.

36–64-year-olds:* Are more likely to have dependents and active careers which can increase the burden of participation
* Childcare costs may increase, and work life balance is disrupted causing a moderate rise in burden.

+65-year-olds:* It is assumed that there will be a larger burden placed on caregivers such as partners/friends or children due to age related comorbidities.
* Increase in age may also increase the risk/benefit of treatment burden if in later stages of cancer diagnosis.
 |
| SocioeconomicClass | Familial | The assumption made in this category is the higher the socioeconomic class, the higher the treatment options and the lower the economic burden.* Often people of a lower socioeconomic standing will participate in research as it may be the only financially viable avenue for treatment.
* Therefore, the higher the class rating, the more likely the participation in the trial was completely choice and not the only opportunity to receive affordable treatment.
 |
| Caregiver Burden  | Familial | Caregiver burden is the burden placed on the partners/family/friends who care for participants while a trial is ongoing and can be considered a direct a burden relating to participants’ psyche has been seen as a ‘burden’ themselves.* The assumptions made to quantify caregiver burden is the sum of the Financial Implication and Cancer stage burden sub-categories, and this result is then scaled 1-2 Low Burden, 3-4 Medium Burden and 5-6 High Burden.

The assumption is based on participants caregivers’ being directly burdened by financial and psychological burden placed on participants in clinical trials. This caregiver burden in turn affects the participants level of burden. |

**Supplementary File 3: Data extraction tables - total burden score (TBS)**

|  |  |  |
| --- | --- | --- |
| **Physical Participant Burden** | **Burden Measurement/Value** | **Burden Value (No.)** |
| **Cancer stage** | 1. Stage 1
2. Stage 2/3
3. Stage 4
 |  |
| **Side effects (mean)** | 1. Rare2. Common3. Very Common |  |
| **Invasive procedures** | 1. Blood withdrawal

(if Multiple (>2) add 1)1. Biopsies

(if Multiple (>2) add 1)1. Surgery
 |  |
| **Clinic Visit Frequency** | 1. Weekly 2. Bi-weekly3. Monthly |  |
| **Questionnaire Usage and Frequency** | 1. None2. 1-23. 2+ |  |
| **Total Physical Burden of Trial** |  |

|  |  |  |
| --- | --- | --- |
| **Psychological Participant Burden** | **Burden Measurement/Value** | **Burden Value****(No.)** |
| **Comparator arm** | 1. Standard of care
2. Use of active treatment comparator
3. Use of placebo
 |  |
| **Symptom Burden** | 1. Low
2. Moderate
3. High
 |  |
| **Clinic Visit Frequency** | 1. Weekly
2. Bi-weekly
3. Monthly
 |  |
| **Questionnaire Usage and Frequency** | 1. None
2. 1-2
3. 2+
 |  |
| **Questionnaire Invasiveness** | 1. Basic Information (Gender/age/disease)
2. Personal Opinions/Beliefs
3. Personal Information (relationships/family/financial)
 |  |
| **Cancer stage** | 1. Stage 1
2. Stage 2/3
3. Stage 4
 |  |
| **Follow up treatment** | 1. Option to continue treatment
2. Follow up check up
3. No Follow up
 |  |
| **Total Psychological Burden of Trial** |  |
|  |  |
| **Economic Participant Burden** | **Burden Measurement/Value** | **Burden Value****(No.)** |
| **Clinic Visit Travel Distance** | 1. O-10 miles
2. 10-25 miles
3. >25 miles
 |  |
| **Financial Implications** | 1. Financial Incentive
2. Financial reimbursements for travel
3. No financial aid
 |  |
| **Follow up treatment** | 1. Option to continue treatment
2. Follow up check up
3. No Follow up
 |  |
| **Total Economic Burden of Trial** |  |

|  |  |  |
| --- | --- | --- |
| **Familial Participant Burden** | **Burden Measurement/Value** | **Burden Value****(No.)** |
| **Participant age** | 1. 36-64
2. 18-35
3. 65+
 |  |
| **Socioeconomical class** | 1. High
2. Middle
3. Low
 |  |
| **Caregiver Burden**  | 1. (<=2) Low
2. (2-3) Moderate
3. (3+) High
 |  |
| **Total Familial Burden of Trial** |  |

|  |  |  |
| --- | --- | --- |
| **Social Participant Burden** | **Burden Measurement/Value** | **Burden Value****(No.)** |
| **Productive life lost** | Number of deaths under 65 per trial1. Low
2. Moderate
3. High
 |  |
| **Total Social Burden of Trial** |  |

**Note:** Randomisation has been identified as a psychological burden in the literature but will not be given a numerical range as all the included trials are RCT’s the value would not make any quantifiable difference to the trials comparable burdens (Fallowfield et al., 1998)