Call for proposals:
Providing the evidence needed to transform prostate cancer diagnosis and deliver screening

Introduction

The current diagnostic pathway for prostate cancer is failing men. Every year, over 9000 men across the UK are diagnosed after their cancer has metastasised and spread widely around their body. Those men, as a result of their late diagnosis, miss any opportunity for curative treatment and have a very significantly reduced life expectancy compared to men diagnosed with cancer that is still contained within the prostate (or even prostate cancer that has spread but only within the pelvic region).

It is clear from evidence reviews undertaken by the National Screening Committee, and pathway and health economic modelling commissioned by Prostate Cancer UK that we will not improve this situation through additional lobbying, or even through minor tweaks to the existing diagnostic pathway. We need to make significant changes to the current pathway to deliver more benefit (find more clinically important prostate cancers before metastasis) and do less harm (fewer unnecessary biopsies, and fewer diagnoses of clinically insignificant prostate cancers that result in anxiety and overtreatment).

There are promising approaches that have evidence of performing better than the current PSA-dominated diagnostic pathway. However, the quantity and quality of evidence needed to change practice is lacking. To radically change the diagnostic pathway, it is clear that a major investment is needed to test the most promising approach (or approaches) in a large-scale prospective trial that provides definitive answers upon which to base future practice change.

In designing this call for proposals, we have consulted widely through both informal conversations and a formal survey-based consultation period where we sought specific feedback about the parameters of this call. Two things have become clear through that consultation process:

- Firstly, that there are multiple different approaches that appear to be better than the current diagnostic pathway but without complete consensus on which is the front runner. Therefore, the trial we fund will have to be flexible enough to generate definitive evidence for or against multiple different approaches (interventions, sequences or combinations), either at the outset or through adaptations and additions that happen after the core trial begins. This will enable us to gather the evidence needed as quickly and efficiently as possible, and more quickly than would be possible with simple trials running separately in sequence.

- Secondly, even the best of the current approaches may not give the performance needed to bring about screening for prostate cancer. Therefore, the trial must be flexible enough to add new comparisons as diagnostic approaches emerge so that those emerging approaches can be validated at definitive scale prospectively in as timely a way as possible. The trial must also be associated with collection of biosamples from the men recruited in order to power future discovery and allow us to test assays not yet ready for trial in this well designed and large cohort to provide retrospective data about their performance before prioritising them for future prospective validation.

Prostate Cancer UK is now seeking to fund this research: a modern trial designed to provide definitive evidence for diagnostic approaches that could replace the current pathway, with flexibility to include or add future interventions or comparisons (or elements downstream of initial diagnosis, such as refinements to our ability to prognosticate or predict optimum treatments), and the collection of biosamples to power discovery and future-proof the trial.

We intend to fund one large collaborative effort and encourage researchers to come together to inform, design and deliver this ambitious programme. To enable this we have worked with the National Cancer Research Institute (NCRI) to support a consortium and protocol development meeting to be held on 24 May 2022. More details about the meeting are available here.

We look forward to the research community joining us in this mission.

Our ambition for this funding call

We believe that the best way to make the profound and rapid progress we need in diagnosis of prostate cancer is to fund a single large collaborative effort. Taking inspiration and learning from the successful STAMPEDE governance arrangements we anticipate a core leadership group, plus larger investigator group, with multiple workpackages each led by one or more members of that team. We anticipate that the trial, or platform, set up initially will be large enough, ambitious enough and flexible enough to answer multiple questions either from the outset and/or through the addition of supplementary arms / comparisons or studies with additional funding from Prostate Cancer UK or other funders before the end of the initial trial.

Details on the research we wish to fund through this call

1. Overall aim

The European Randomised Screening trial has already demonstrated that, with sufficient follow up, regular PSA testing in men over 50 delivers a significant (20%) and robust reduction in prostate cancer mortality. However, achieving this mortality reduction through PSA-based screening comes with an unacceptably high level of harm in the form of unnecessary biopsies (which modelling suggests remains high even with the addition of mpMRI pre-biopsy), and the detection of too many clinically insignificant prostate cancers which cause psychological harm and potentially overtreatment for the men diagnosed. We also know that our current PSA-based diagnostic pathway also generates many false negative results which drive the late diagnosis suffered by some men.

The long-term aim of this funding call is to generate evidence needed to implement a diagnostic pathway that maintains or (ideally) improves on the 20% reduction in prostate cancer specific mortality delivered through PSA screening in the ERSPC while reducing the number of men harmed through unnecessary biopsy or diagnosis of clinically insignificant prostate cancer. It is essential that the pathways proven to deliver this are cost effective, practical and acceptable to men in order to ensure that wide-scale implementation across the UK is possible. This should also be considered by applicants.

We believe that regulator support and buy-in is crucial through the programme from inception to delivery. Prostate Cancer UK has engaged with the National Screening Committee whilst scoping this call for proposals and will continue to work with relevant groups through to (and beyond) funding of the trial. We will expect applicants to work in partnership with the charity, screening committee and other regulators to ensure the research we fund delivers results that can change practice.

2. Accelerating future diagnostic development and discovery through sample collection

The collection of relevant biosamples from men recruited to this trial is a key requirement for Prostate Cancer UK to power future discovery, accelerating the speed that new diagnostic approaches are developed, validated and moved into definitive prospective trials. We believe that by funding an associated biorepository alongside this trial we can power that future development and also future-proof the main trial should it return a negative initial result. Applicants will be required to detail their plans for collection, storage and provision of access to the samples collected (and full costings) as part of the application.

3. Definition of clinically significant prostate cancer and improving prognostic classification of prostate cancer

We agree with the consensus that has emerged since the introduction of MRI to guide biopsy that genuine Gleason Grade Group 1 prostate cancer (previously Gleason 3+3 disease) is extremely unlikely to become symptomatic or metastasize. Therefore, we believe that the trial we fund should test the ability of the pathways, tests and assays incorporated to detect clinically significant cancer (Gleason Grade Group 2+, any Gleason pattern 4) rather than detection of “any” prostate cancer. The detection of clinically insignificant disease should be reported as this is an important consideration in cost/benefit and harm/benefit calculations.

We are aware of ongoing discussions regarding the clinical significance of Gleason Grade Group 2 cancers. On the basis of the evidence we currently have, and for the purposes of this trial, we consider those cancers to be clinically significant and in need of detection.

We recognise that this definition is likely to misclassify some cancers as either high risk or low risk and that it could be improved. While the primary purpose of this call is to improve diagnosis (as opposed to our ability to prognosticate beyond this current classification of insignificant vs significant) it is likely that the samples and data collected – especially with long term follow up through data linkage – could provide opportunities to develop more effective definitions of what makes a cancer aggressive / significant and even help to define predictive biomarkers or characteristics that enable better selection of treatments for individual men. We encourage applicants to consider these opportunities either upfront or as future additions to the core trial platform.

4. Timescale, endpoints and follow up

We wish to see progress, and introduction of new, better diagnostic pathways as quickly as possible. However, we recognize that it may require evidence of events that happen 10 years or more after initial diagnosis to provide the definitive evidence needed. Applicants will be required to present a feasible, costed method for data linkage from all participants recruited to the trial to ensure that long-term clinically-relevant events are captured and analysed. Early engagement with NHS Digital and other custodians of routine clinical data that will be needed to track these events after the trial has concluded will be essential.

We also encourage applicants to consider whether there are endpoints that can indicate futile approaches that should be discontinued at an early stage, and also whether there are opportunities to use, validate or develop surrogate endpoints for survival in this screening setting that may allow us to change practice more quickly.

5. Patient cohort

We expect the trial we fund to recruit a cohort of patients that is representative of the UK population. In particular, we know that prostate cancer disproportionately affects black men and so, ideally, we would like to see over-representation of black men within the cohort. Applicants will be asked to address how they plan to achieve representative recruitment in the application form. Prostate Cancer UK will also use the charity's communication channels and networks where this supports the research team to achieve this.

6. International collaboration

We recognise that bringing in collaborators from abroad could offer many benefits in terms of speed, robustness and impact of this programme. We see significant merit in this approach and will work with successful applicants and relevant international funders to explore this post-award. However, in the first instance, we believe it is important to design a trial that is deliverable in the UK and reflects current and feasible future UK clinical practice. We therefore encourage consideration of international collaborations **after** funding.

Budget

Improving diagnosis of prostate cancer is a cornerstone of Prostate Cancer UK's research and overall strategy. We believe radical change is needed in order to deliver this ambition and that the change required will only be possible through large scale and sustained investment in research. Proposals must be designed to deliver results that could change clinical practice, and address all other elements detailed in this call. **Applicants should request the amount of funding required to deliver that proposal.**

By comparison with other trials that have sought to address similar knowledge gaps in other diseases we believe this programme of research may require funding of around £20m across its entire life cycle. We are confident that we will be able to raise funds and engage partners to build a funding pot of at least that scale (and more if required) to deliver the change we wish to see. In practical terms, we have £5m of funds restricted to diagnosis research already in hand and will be able to commit a first tranche of funding of at least that amount.

We need to understand the amount required to set this trial in motion, as well as the anticipated full long-term cost of the study. As far as possible we also would like to see the budget for the programme presented in a modular way, separating out the costs of the core trial and any complementary activities (such as health economic analysis, biobanking etc.). This will allow us to plan budgets and raise funds in order to ensure the full amount is available when required, and that the essential progress men need is not delayed unnecessarily. Milestones will be set in order to ensure that our investment is, and remains, tied to successful delivery. We encourage applicants to set out any particularly appropriate milestones in the application.

Partnerships

We are keen to make progress as quickly as possible in this key strategic area of need and believe that the way to do that is to work in partnership as widely as possible. We will continue to have funder-to-funder conversations with relevant organisations but would welcome applicants also exploring and introducing opportunities for partnerships to support this programme.

Partnerships with existing or emerging infrastructure and programmes will be essential to leverage expertise and funding already committed, reduce duplication and, crucially, maximise the likelihood of success. Part of the assessment process will be to assess whether opportunities for collaboration and partnership have been fully explored. Applicants may be required to engage or re-engage with potential partners as a condition of award if the committee concludes that that has not been the case.

We are aware that several companies have prostate cancer diagnostic assays that require further evidence from large-scale prospective trials such as this, and we are keen to engage with those companies. We believe that the ReIMAGINE study provides a good model for partnership with commercial entities. Depending on the details of the research we fund through this call we would anticipate following a similar model.

There are opportunities for commercial partners in both the initial clinical research stage and through access to samples collected from participants for future research. For the avoidance of doubt, we will expect commercial entities to cover the costs of any research which stands to add value to their intellectual property or assets, and to contribute to the overall costs of this ambitious research programme. However, we are happy to consider different models for company contribution on a case-by-case basis including but not limited to: upfront funding through financial contribution to Prostate Cancer UK, upfront funding through in-kind contributions, payback models based on returning a multiple of any initial investment by the charity based on milestones, and revenue and equity share arrangements. We encourage companies who may be interested in these opportunities to engage with the charity as early as possible so that we can discuss options, and any redlines, and put you in contact with the applicants if relevant. Applicants should be ready and willing to engage with industry partners.

In line with other comparable research programmes, our expectation is that commercial partners must be willing for full results to be published and for the academic trial team to have full access to all results and data produced through the trial. In instances where we have multiple options competing for inclusion in the trial (either academic or commercial) we will, through an access and/or independent funding committee, prioritise those options that have the best chance of implementation through the NHS and devolved nations' health systems in the shortest timeframe.

Process

Recognising that this is a very complex area and that we are proposing to fund at scale, we have already consulted on a draft version of this call and amended it (and our plans) on the basis of the feedback we received.

One of the key elements of the feedback we received was a need to enable participation in the consortium which designs and delivers this trial by as broad a range of researchers as possible. Our intention is to make this consortium as inclusive as possible and will be willing to fund a study addressing multiple questions, as well as subsequent 'bolt-on' awards after the trial is up and running, provided that the work proposed is aligned to the overall aim of producing definitive evidence to bring about screening for prostate cancer. To ensure complete openness at the outset, we are starting this process with a protocol development meeting led and delivered by the National Cancer Research Institute, and an independent chair who will not be part of the trial delivery consortium beyond the meeting. The meeting is designed to enable genuine discussion and participation and the aim is to deliver, at the end of the meeting, an initial overarching trial design (or a small number of alternative approaches), a consortium of researchers willing and able to refine the different elements of this programme, and a leadership group able to bring together those working groups and participants who are eager to drive forward the application for funding.

Applications will be assessed by a funding Committee of unconflicted experts. We anticipate an iterative process which may involve meetings between applicants and the committee. Final sign off will be by Prostate Cancer UK trustees informed by the Director of Research and the Funding Committee. We expect that through this process applicants may have to respond to (and adjust their plans to address) committee feedback. However, for clarity, our intention and our expectation is to fund. The process we design will be to identify the best option (if we receive multiple applications) and subsequently to refine that proposal to the point that our funding committee considers that it has a good chance to provide definitive evidence aligned to this call and recommends that we fund it. As we intend to fund a single large collaborative group, we may ask applicants to enter into discussion with other groups also submitting applications to avoid, if possible, multiple competing bids. If we do receive multiple applications which are assessed positively, we may also request discussions and alignment between groups after committee has met, as a condition of award.

Anticipated timeline

Consortium and protocol development meeting: **24 May 2022**

Application forms go live: **no later than 31 May 2022**

Application closing date: **31 August 2022**

Initial committee recommendation: by **mid October 2022**