2016/17 Major Award STHLM3 UK Validation: Guidance Notes

Introduction

Prostate Cancer UK has launched an ambitious 10 year Research Strategy, to tame prostate cancer in 10 years. A key focus to this strategy is to improve earlier diagnosis of aggressive prostate cancer, and in order to achieve this we need to act upon promising emerging research from both the UK and internationally which may help us achieve this.

STHLM3

Prostate-specific antigen (PSA) is used to test for prostate cancer but is considered to have a high false-positive rate that translates into unnecessary prostate biopsies and over-diagnosis of low-risk prostate cancers. The STHLM3 study aimed to develop a model for prostate cancer screening with better test characteristics than PSA alone.

STHLM3 was a prospective, population-based, paired screen-positive diagnostic study. It investigated whether the predefined STHLM3 Model, a combination of plasma protein biomarkers, genetic polymorphisms and clinical variables, could substantially reduce the proportion of men biopsied whilst maintaining the same sensitivity to diagnose Gleason Score ≥7 prostate cancer as PSA ≥3 ng/ml. The STHLM3 study was conducted in Stockholm, Sweden during 2012-2014.

58,818 men aged 50-69 who had no prior diagnosis of prostate cancer participated in STHLM3, with 7,113 men undergoing subsequent prostate biopsy. All variables used in the STHLM3 Model were statistically significantly associated with Gleason Score ≥7 prostate cancers ($p<0.05$) in the multivariate analysis. Using the same sensitivity as PSA≥3 to diagnose Gleason Score ≥7 prostate cancer, the STHLM3 Model reduced the number of biopsies by 32% (95% CI 24%-39%) and avoided 44% of the negative biopsies (95% CI; 35%-54%). The number of Gleason Score ≤6 cancers was reduced by 17% (95% CI; 7%-26%), all of which had a total cancer length ≤10mm.

In summary, the STHLM3 Model could have reduced unnecessary biopsies without compromising the ability to diagnose Gleason Score ≥7 prostate cancer, and is a significant step towards personalized risk-based prostate cancer diagnostic programs.

The STHLM3 Study was conducted in a homogeneous population of mainly Caucasian heritage in a very controlled trial setting. Thus, there is a need to validate the STHLM3 Model in more diverse populations. Further validation is also required to demonstrate whether the STHLM3 model is feasible for use in pragmatic settings in other health care systems.

Remit

Prostate Cancer UK is calling for proposals from the research community to prospectively validate the exciting results of the STHLM3 study in a UK setting. A funding envelope of **up to £750k will be made available**. In addition to validating the results of STHLM3, we welcome additional suggestions from applicants as to how the STHLM3 model could be enhanced, or made more adoptable in the UK provided those additions fall within the total budget window and do not detract from the primary purpose of this funding. We would strongly advise potential applicants to consider a collaborative approach involving primary and secondary care and how the pathology expertise required fits within the overall study.

Below is a proposed draft design of such validation study based on the results from the STHLM3 Study. However, as the STHLM3 study was tightly controlled by the investigators, we would advise potential applicants to discuss any substantive changes to the original model with the investigators of the original study before submitting their bid.

Proposed study design

The Prostate Cancer UK-STHLM3 UK Validation Study is intended to validate the findings of the Stockholm trial in a UK-representative population. It is also designed to test the feasibility of applying this diagnostic test at scale through normal NHS provision. Therefore it will need to include a significant prospective element. Validation should follow a paired screen-positive design as used in Stockholm. Two diagnostic methods, PSA and the STHLM3 Model, will be tested in each study participant. Referral to secondary care for prostate biopsy (see also section titled ‘mpMRI to rule out biopsy’ below) will be recommended if either PSA and/or STHLM3 is above a set cutoff. In all instances clinical care (either PSA testing or subsequent testing) should be delivered as per current UK best practice guidance (the PCRMP guidance and NICE guideline for ‘Suspected cancer: recognition and referral’ [NG12]).

As per the PCRMP guidance, the proposed cutoffs for “positive on PSA” is 3.0 ng/ml for men aged 50-69. The proposed cutoff for “positive on STHLM3” is 10%.

Men 70+ will not be included as the Healthcare Effectiveness Data and Information Set (HEDIS), as well as the United States Preventive Services Taskforce (USPSTF), recommend against testing in these ages. Additionally, the PCRMP guidance sets no PSA for men older than 69.

A paired screen-positive design adds safety as all men with positive results on either of the test will be recommended a biopsy.

Population

Age: 50-69 in normal risk men and 45-69 in higher than average risk men (Black ethnicity or positive family history of prostate cancer where the first degree relative was diagnosed at age <65) in coherence with the PCRMP and Prostate Cancer UK's PSA consensus statements.

Ethnicity: The cohort studied should be broadly representative of the UK population in terms of ethnicity. However, given the higher incidence rate of prostate cancer in Black men in the UK (1 in 4 Black men will be diagnosed, compared to 1 in 8 White men), applicants should explore whether it is appropriate and feasible to enrich the number of those men in the cohort in order to ensure that the results are sufficiently powered for that sub-group.

Exclusion criteria will include:

- Previous prostate cancer diagnosis or other severe illness.
- Men on 5-alpha reductase inhibitors, and
- PSA of 10 or above.

Selection and invitation of participants

In the Swedish STHLM3 trial, tax registers were used to identify men of the correct age profile and an electronic invitation was sent to each man inviting him to attend for screening. In the UK, other routes to identify and invite trial participants will be required. Applicants will be asked to specify their method for inviting men for initial eligibility screening and justify their selection.

Primary endpoint

Reduction in prostate biopsies without compromising the diagnosis of clinically significant cancer (i.e. two co-primary endpoints: non-inferior sensitivity and superior specificity).

The definition of clinically significant prostate cancer in the original STHLM3 study was Gleason Score 7+ cancer. Applicants should clearly state their definition of 'clinically significant cancer' with respect to current (or anticipated) UK clinical practice.

Secondary endpoints

We expect the study to include a health economic analysis to inform a potential roll out in the UK. Applicants should clearly state any additional outcome measures that they propose to measure in this trial.

Prostate Biopsy and Pathology protocols

A standardized protocol for systematic post-referral investigations is required. In the original STHLM3 Study a 10-12 core biopsy protocol was reinforced (based on the prostate volume). Applicants should detail the proposed process for post-referral investigation in the UK and are advised that a process which differs greatly from current UK clinical practice (or from practice that is expected to become standard within the next 2 years) is likely to impact negatively on adoptability, is therefore likely to be viewed unfavourably by the assessors, and so should be very carefully justified if proposed.

mpMRI to rule out biopsy

In the original STHLM3 study any participant positive on either PSA or the STHLM3 model was referred for a prostate biopsy. We are aware of an emerging body of evidence in favour of using mpMRI to rule out biopsy as part of UK clinical practice. However, this is not yet standard practice across all parts of the UK and in all trusts. Applicants are encouraged to consider and detail their approach to integrating mpMRI within this trial.

Variables in the STHLM3 Model

Clinical variables:	Age, ethnicity, family history (need strict definition) previous biopsies (year of biopsy, number of cores obtained), 5-alpha reductase inhibitors,
Genetic biomarkers:	New SNPs need to be added to reflect the ethnic diversity
Protein biomarkers:	Total-PSA, free-PSA, intact-PSA, HK2, MSMB and MIC-1
Prostate exam:	DRE and prostate volume during biopsy.

Applicants may suggest modifications to this set of variables (either exclusion or addition) in order to better facilitate adoption of the model in the UK. However, any changes will need to be fully justified and should be discussed with the original STLHM3 study investigators before application.

Additional Partners

Prostate Cancer UK will continue to negotiate with Thermo Fisher Scientific regarding the provision of equipment and reagents for the biomarkers analysis. As the costs for this element of the project are not yet known applicants should exclude this from their costings. Supplementary funding will be provided by Prostate Cancer UK if necessary. Applications will be sent to Thermo Fisher for feedback prior to assessment by representatives from the Prostate Cancer UK Research Advisory Committee.

Eligibility criteria

The application must come from the prospective Principal Investigator. To apply to this call, the following criteria must also be met:

- Awards are available to established researchers working within a recognised academic or clinical institution in the UK (including N. Ireland).
- Lead Applicants will normally hold tenured or tenure-track academic appointments, or for clinical applicants, they should hold an honorary academic contract at a recognised academic institution.
- Funds requested in your proposal must be in accordance with our Finance Eligibility Guidelines.

Please note that we will NOT accept applications that:

- Do not fit our Research Strategy or the remit of this scheme
- Are intended solely or primarily to purchase substantial equipment and/or infrastructure
- Are led and submitted by researchers based entirely or primarily outside the UK
- Are submitted by commercial organisations
- Are incomplete or have been completed incorrectly

If you have any queries about completing the application form please contact the Research Team **in advance** of the submission deadline (email: research@prostatecanceruk.org, or phone: 0203 310 7037).

Once the deadline has passed, you will no longer be able to submit your proposal. If your application has not been submitted AND approved by all necessary parties before the deadline, then your application will no longer be considered. There will be no opportunity to debate individual circumstances. Applications which are incomplete or which do not meet the requirements detailed above will be rejected without being sent for further review.

We recognise that the outcome of your application is important to you and your staff and we will inform you of the outcome as soon as possible. However we would like to remind applicants that contacting the Research Team during this time will not speed up the process. We appreciate your patience.

Once notified of our intention to award, we will begin the contracting process immediately. It is our expectation that contracting should be completed within one month of notification of award (or once any conditions of award have been addressed and/or any financial assessment completed). In any instance, successful projects should commence within six months of completion of contracting.

Making your application

The closing date for the receipt of applications is 12pm (noon) 18 July 2016.

All applications will be peer reviewed by independent, international experts in the field, before being considered by representatives from Prostate Cancer UK's Research Advisory Committee. None of the assessors will have a formal association with the STHLM3 study. However, we have convened a management committee that has advised us on development of this call and that we expect to help guide and shape the funded project. That management committee will include members of the STHLM3 research group.

Applications are to be made using our online Prostate Cancer UK CC Grant Tracker system. You must fill out **all sections of the application form** (notes below), and once completed, **yourself**, the **Head of Department** and the **University/Institute Research**

Grants office (or finance office if not applicable) must complete the online declarations in order for your application to be accepted.

Any **Joint Lead Applicant (if applicable) and all Co-Applicants** must confirm their involvement in the proposal **and** must also approve the application before it can be submitted.

Any Collaborators need not complete an online declaration; however, they should provide a letter of support specifying and confirming their involvement in the project, which must be uploaded by the Lead Applicant within the corresponding section of the form.

Approval from the Head of Department and the Research Grants/Finance Officer will be required after the proposal has been 'submitted'. The proposal must be submitted and approved by all relevant parties in advance of the submission deadline.

The application form consists of 12 sections, each of which are outlined below:

Lead Applicant details

The Lead Applicant must be the Principal Investigator who will lead the research and be responsible for delivering the project.

Information in this section is automatically populated from your contact record. Please ensure that your CV and Basic Information are up to date via the 'Manage My Details' section in the left hand menu. Please note that this section is not accessible directly from the application form, and so to update your personal details you must first 'Save & Close' your application and then click on the 'Manage My Details' link in the left hand menu.

When updating your personal details please note the following:

- For publications please only include papers from the past 5 years
- If you have an ORCID ID, please add this to corresponding section under 'Basic Information'

Personnel

This section allows you to add the details of any Joint Lead Applicant, Co-Applicants and Collaborators involved in the proposal.

Joint Lead Applicant:

We would ordinarily expect a project to be led by a single Lead Applicant; however, in exceptional circumstances you may include ONE Joint Lead Applicant.

If you wish to include a Joint Lead Applicant on the proposal, you must provide sufficient explanation (under 'Role Description') to justify the need for Joint Lead Applicants, as well

as which aspects of the proposal each person will be leading on and why they are appropriate to lead on that aspect of the project.

To include a Joint Lead Applicant onto the proposal, click on ‘Add Joint Lead Applicant’, input their name within the corresponding search fields and either select the contact if already on our database or otherwise input their details. Once added, an email will be sent to the potential applicant inviting them to take part in this application.

The Joint Lead Applicant **must** accept this invitation to confirm their participation on the proposal. Once confirmed, their CV details will automatically be appended to the application PDF.

As with the Lead Applicant’s details, the Joint Lead Applicant must ensure that their relevant details are filled in accurately by going to the ‘Manage My Details’ section. As mentioned above, **the Joint Lead Applicant must confirm their participation AND approve the application BEFORE the proposal can be ‘submitted’**.

Co-Applicants:

Please include details of all Co-Applicants to be involved in the project. It is our expectation that all Co-Applicants must have an active role in the proposed project (any other personnel should be listed as a Collaborator).

To add their information, click on ‘Add Co-Applicant’, input their name within the corresponding search fields and either select the contact if already on our database or otherwise input their details. Once added, an email will be sent to the potential Co-Applicant inviting them to take part in this application. Repeat this procedure for all Co-Applicants on the proposal.

As above, **each** Co-Applicant **must** accept this invitation to confirm their participation on the proposal. Once a Co-Applicant has confirmed their participation, their CV details will automatically be appended to the application PDF. Again, each Co-Applicant must ensure that their relevant details are filled in accurately by going to the ‘Manage My Details’ section.

All Co-Applicants must confirm their participation AND approve the application BEFORE the proposal can be ‘submitted’.

You **must** then detail how **each** Co-Applicant will be involved in the project. To do so, click on 'Add Co-Applicant Role', select the relevant name from the dropdown list provided and input their role in the corresponding section. Please repeat this for all Co-Applicants on this proposal.

Collaborators:

To include a Collaborator onto the proposal, click on ‘Add Collaborator’ and follow the same procedures as with adding a Co-Applicant (detailed above). Repeat this procedure for all Collaborators on the proposal.

Collaborators are not required to confirm their participation via the on-line system; however, each Collaborator will receive an email to inform them that they have been selected to be involved on this application and will be asked to provide the Lead Applicant with a supporting letter.

You **must** then detail how **each** Collaborator will be involved in the project, as with the Co-Applicants. A letter of support from each Collaborator must be uploaded via this section, alongside the corresponding Collaborators' role. Please repeat this for all Collaborators on this proposal.

Project summary

Provide a concise scientific title as well as a lay title for your project, and include the duration of the research project (in months) as well as a proposed start date. Please note that it is our expectation that successful projects should commence within six months of completion of contracting (please see above).

Within this section you must also indicate which one (or more) of the Prostate Cancer UK priority areas your project shall address (please refer to our Research Strategy for further details). You must then select up to 6 keywords from the list provided which best describe the project, and provide a brief scientific abstract (in no more than 300 words), outlining the background to the application, the proposed aims of the research to be undertaken and the expected outcomes. All proposals must clearly state how the planned research aims to improve the health and wellbeing of men affected by prostate cancer.

Please be aware that your abstract will be sent to potential peer reviewers to establish their ability to review the proposal, and if funded, the abstract will also be shared with the National Cancer Research Institute (NCRI) and the International Cancer Research Partnership (ICRP).

Therefore, please do not include any confidential or commercially sensitive information in this section.

Project description

It is our expectation that this project will follow a similar trial design to that of the original STHLM3 study, as outlined in the '**Proposed Study Design**' section above. However, we would like you to explain why you are most suited to carry out this study and to also detail any changes to the above design you believe would strengthen the project. In particular, you will be asked:

Are you proposing any changes to the above trial design? (up to 1,000 words)

Please provide further detail as to *your* trial design, in particular highlighting and justifying any changes you would make to the proposed study design detailed above. Please also include a brief timetable of milestones and targets. Any references referred to in this section should be listed in the next section under 'References' (50 maximum).

Patient Recruitment (up to 1,000 words)

Please detail the number of patients you intend to recruit to this study (including power calculations). You should also describe you planned recruitment strategy along with the number of centres you intend to be involved.

What is your experience of delivering trials of this nature? (up to 500 words)

So that the reviewers can assess your suitability of leading a study of this nature, please describe your experience of delivering trials of this nature.

What unique quality will your team bring to this study? (up to 500 words)

Explain here why this team is most suited to host this project and what unique qualities you and your colleagues would bring to this study.

Do you intend to supplement the prospective cohort by testing existing samples? If so, please provide further details (up to 1,000 words)

Please provide further details if you intend to supplement this study through the addition existing patient samples and what additional benefit this will provide.

Potential problems and contingency plans (up to 500 words)

We understand that research projects often do not run entirely to plan. Please highlight the problems this project is mostly likely to encounter and explain how they will be dealt with.

Patient & Public Involvement (up to 500 words)

Prostate Cancer UK is supportive of the active involvement of patients and the public in research activities as it can ensure that the research remains patient focused. You should describe whether men with prostate cancer, or their relatives/partners etc., will be involved in the design, planning or management of this research, and if so, what their role will be. Please note, we do not consider the recruitment of patients to take part in a study as involvement in research.

Please detail the plans for obtaining ethical approval (including timings) (up to 500 words)

Funding will not be released to successful applicants until all regulatory approvals for the project are in place. Please describe your plans and proposed timescales for obtaining the necessary regulatory approvals.

References

You may include up to 50 full references (Vancouver format) here that you have referred to in the 'Project Description' section.

Gantt chart

Insert a Gantt chart detailing the main goals, milestones, deliverables and associated major costs for the grant duration. These will be the key goals and timelines from which the progress of your project shall be measured against, so please ensure they are achievable within the given timeframe. Attach as a MS Word or PDF document.

Finances

The total cost for this proposal should not exceed £750k. Please refer to our Finance Eligibility Guidelines for furthers details regarding cost eligibility. Budget items **MUST** be broken down in as much detail as possible and entered as separate items under the following headings:

Salary costs:

Include salary details for the personnel who will be employed directly on this project. Grants cannot be used to support students or to offset the salaries of any core-funded academic or clinical staff. Please name individuals where possible.

Research expenses:

Detail all expenses that will be directly incurred by the project. If you are including fees for the use of any core research facilities please state the cost per hour or per sample. These costs must be fully justified within the 'Justification of Budget' section.

Animal purchase & maintenance costs:

It is anticipated that there will not be any animal costs associated with this project.

Other costs:

This section should include any other costs such as conference travel, publication and dissemination costs and purchasing of equipment. Equipment should only be included if essential for the project and must be purchased within the first half of the grant and should not represent a substantial proportion of the overall budget. We encourage research findings to be freely available and disseminated as widely as possible, and so it is permissible to include a small allocation to cover the costs of open access publishing.

Any items which appear excessive or which have not been suitably justified will be queried by Prostate Cancer UK staff and may be removed from the budget if the application is recommended for funding. Please note that after funding is awarded, any changes in budget allocations must be approved in advance, in writing by Prostate Cancer UK, and increases in the total budget will not be permitted under any circumstances. Make sure you include allowances for annual pay awards and inflation – your university/institute finance office should be able to advise on appropriate inflation levels.

Applications should be costed in line with the AcoRD framework for attributing the costs of clinical research, and our standard terms and conditions regarding eligibility of certain costs apply.

Prostate Cancer UK does not pay Full Economic Costs; do not include indirect, estate or any other non-attributable overhead costs in your budget. Applications containing these costs will not be considered. Please refer to our Finance Eligibility Guidelines for furthers details.

Justification of budget:

Please also provide a brief justification of the costs that you expect to incur (in no more than 500 words). In particular you should justify the number and seniority of any staff to be employed on the project, and the inclusion of any costly equipment (or any other significant expenditure) deemed essential for the proposed project. Please also state whether the study is likely to receive support from a research network and, if so, the support that will be provided. If the amount requested does not cover the full study costs (e.g. where the work would be part funded by another grant) please also provide brief details as to how the remaining costs of the study will be met.

Declarations

The application must be approved by the Lead Applicant, the Joint Lead Applicant (if applicable), all Co-Applicants, the Head of Department and the Finance Officer who will be responsible for administering any grant that may be awarded. Both the Head of Department and the Finance Officer must be registered on the on-line Prostate Cancer UK CC Grant Tracker system to approve the application, and must complete their corresponding 'Declarations' section within the online form.

In the case of the Finance Officer, click on 'Add Finance Officer' within the 'Declaration - Finance Officer' section and follow the steps to select and invite your Finance Officer to participate (following the same procedure as with adding a Co-Applicant). They must then log into the system and access the 'Declaration – Finance Officer' section of the application form and complete the declaration question.

Please follow the same procedure with the Head of Department under the 'Declaration – Head of Department' section.

Approving the application will imply that the approver has read the terms and conditions and agrees to abide by them if a grant is awarded.

Submitting your application

Once you have completed all sections of the form you must go to the 'Validation' tab in the left hand menu of the online application. This will highlight any sections which still need completing, or that exceed the stipulated word limits or which require confirmation and/or approval from others

Please note that all mandatory sections of the form must be completed (within the stipulated word limits), and all relevant parties must confirm their involvement in the proposal before the application can be submitted. Any such discrepancies will be flagged under the 'Validation' section of the online form, and you will be unable to submit your application until these have been resolved.

When all sections are complete and all necessary approvals have been made the application is ready to be submitted. You must 'Save and Close' the application and this will then take you back to the application details page. The Submit button on the right hand side should now be activated, and you can click this to submit your proposal

The application will require approval from your Head of Department and Finance Officer after the proposal has been 'submitted'. The proposal must be submitted by the Lead Applicant and approved by the Head of Department and the Finance Officer in advance of the submission deadline. Applications which have been submitted but do not have the necessary approvals will not be accepted.

Once submitted and approved by the Head of Department and Finance Officer, you should receive an automated email confirming your submission. Please note you may also download a PDF of the submitted application via the 'View/Print' button on the right hand side of the application details screen.

Contact Us

If you have any queries regarding your application please contact the Research team at Prostate Cancer UK via:

Email: research@prostatecanceruk.org

Phone: 0203 310 7037