FIVE CALLS FOR APPLICATIONS / LETTERS OF INTEREST IN COLLABORATION:

RESEARCH ON THE VULNERABILITY OF PREVENTIVE CHEMOTHERAPY OF HELMINTH INFECTIONS TO EMERGENCE OF DRUG RESISTANCE

Submission deadlines – see individual calls below

The mandate of the TDR Intervention and Implementation Research (IIR) Team includes research for evidence-based strategies to sustain the effectiveness of interventions for the treatment, control and/or elimination of neglected tropical diseases (NTDs).

Taking into account the recommendations from TDR’s scientific advisory groups and the research priorities identified by the TDR Disease Reference Group on Helminth Infections¹, TDR is expanding support for research on key determinants of sustained effectiveness of preventive chemotherapy for schistosomiasis, soil transmitted helminths (STH), lymphatic filariasis and onchocerciasis: the probability, potential impact and detection of the emergence of resistance to the drugs used.

Planned research activities are grouped into two projects:

- Vulnerability of schistosomiasis, STH, onchocerciasis and lymphatic filariasis control to emergence of drug resistance and its consequences (TDResist, 3 calls, available funding: US$ 260 000)

- Integrated capacity building and research for ivermectin resistance surveillance and definition of *O. volvulus* transmission zones by onchocerciasis control programmes (CARIRS, 2 calls, available funding: US$ 400 000).

Grants will be awarded on a competitive basis between proposals in response to a particular call as well as across all calls.

External advisors will use the criteria for the scientific assessment found on the TDR website http://www.who.int/tdr/grants/application_reporting_forms/application_assessment_form_sample.pdf

Funding decisions will also take into account the potential for building and using research capacity in endemic countries as well as present or potential synergies with other funded or planned projects.

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1 OBJECTIVES AND RATIONALE

Vulnerability of schistosomiasis, STH, onchocerciasis and lymphatic filariasis control to emergence of drug resistance and its consequences (TDResist)

The long-term objective is to assemble and generate data related to the potential emergence of parasite resistance to the respective preventive chemotherapy drugs to inform further research, funding decisions and control programme practice.

Different activities are designed to collectively achieve this objective. Each activity has its own call for proposals.

1.1 Determinants of parasite drug response and transmission (TDResist-Depart)

Parasite, vector and host characteristics as well as environmental, social, and control-programme factors determine parasite response and/or transmission of ‘progeny’ of a parasite exposed to a drug/drugs. Consequently, these factors collectively determine the potential for selection and preferential transmission of parasites with low susceptibility/resistance to the drug(s).

A thorough understanding of these factors and their interactions can inform decisions on appropriate control and elimination strategies. It can furthermore be used to assess whether currently available transmission models could benefit from inclusion of additional parameters.

The call for applications to perform a literature review including identification of knowledge gaps is provided in section 2.1.

1.2 Quantitation of the variability of response to the drugs for preventive chemotherapy of schistosomiasis, STH, onchocerciasis, lymphatic filariasis (TDResist-QuoVadis)

Concern that resistance to preventive chemotherapy drugs has already emerged has been raised. For example, presence of individuals in areas with long term community directed treatment with ivermectin with skin microfilariae repopulation faster than considered ‘normal’ or ‘adequate’ has been suggested as indicating *O. volvulus* resistance to the embryostatic effect of ivermectin.

The extent to which low level responses to treatment justify concerns about emerging or already emerged drug resistance depends on a number of factors. These include whether the level of response is outside the ‘normal range’ and whether its frequency has increased since implementation of preventive chemotherapy.

Quantitation of parasite response has to date been conducted primarily based on mean responses (and some measure of dispersion) observed in different studies. It did not include quantitation of ‘outliers’, i.e. individuals/parasites with a very low or high level of response/drug susceptibility.

Analysis of the variability of response using individual subject data is needed to define the range of responses and their frequencies before or early on during mass treatment programmes for comparison with levels of response and their frequencies after long term mass drug administration.

This activity will be conducted in two steps:

1. Call for letters of interest in collaboration and contribution of individual subject data on parasite load before and at least once after a treatment round. The call for letters of interest in collaboration is provided in section 2.2.

2. Depending on the number of collaborators and individual subject data available for analysis, a decision will be made on the feasibility of quantitating the variability of response for particular parasites and identification of principal investigator(s) for the statistical analyses.
1.3 Modelling the spread of parasites with low drug susceptibility within and between parasite and human populations (TDResist-Model)

The extent to which the presence of individuals/parasites with low response/drug susceptibility needs to raise concern about the sustained effectiveness of control strategies, also depends on the probability that parasites with low drug susceptibility will increase in frequency in the course of preventive chemotherapy programmes. Both, probability and speed of such an increase will depend on a number of factors of the vector-parasite-host-environment complex and on social and control-programmatic factors and their interactions.

Modelling can be used to estimate the probability and speed of transmission (i.e. increase in frequency) of parasites with low drug susceptibility within and beyond a particular parasite and human population. Transmission models can also be used to assess the effectiveness of current and alternate control programme strategies in reducing the probability and speed of increase in the frequency of parasites with low drug susceptibility.

Consequently, modelling can help to assess the vulnerability of specific control programmes to the emergence of resistance and the utility of different strategies to minimize it.

The call for proposals is provided in section 2.3.

Integrated capacity building and research for ivermectin resistance surveillance in onchocerciasis control programmes (CARIRS)

This project was initiated in 2009 in collaboration with the African Programme for Onchocerciasis Control (APOC) with the following objectives:

1. Answer the question whether the ‘suboptimal response’ of O. volvulus to the embryostatic effect of ivermectin reported from Cameroon and Ghana is due to selection of parasites with a genotype which confers low susceptibility to that effect.

2. If the answer to this question is yes, develop a genetic marker-based tool for the surveillance of the frequency of such genotype(s) suitable for use by onchocerciasis control programmes.

3. Build capacity in onchocerciasis endemic countries to conduct research for genetic markers of resistance, to develop genetic marker-based tools for detection of resistance and for the utilisation of the tool(s), if applicable.

Based on the results obtained to date, the project has evolved into two different directions:

1.4 Research for genetic markers of response to ivermectin (CARIRS-Markers) and, if applicable, development of a genetic marker based surveillance tool.

This continues to address the three original objectives of the project.

The call for proposals is provided in 2.4.

1.5 Research for genetic markers of O. volvulus population structure, and, if applicable, development of a genetic marker based tool for defining transmission zones (CARIRS-Mission).

This project expands upon results on O. volvulus population structure obtained in the context of the original project and addresses a need of the onchocerciasis control programmes in Africa as they move towards elimination.

The call for proposals is provided in 2.5.
2 CALLS

2.1 CALL FOR APPLICATIONS: Literature review of determinants of parasite drug response and transmission for diseases controlled by preventive chemotherapy (TDResist-Depart)

Submission deadline - 31 August 2014, 23:59 (Geneva)

2.1.1 Eligibility

Applicants can be individual researchers or collaborative groups of researchers from within one or different institutions.

We encourage applications from women scientists, scientists from endemic countries and collaborative groups with scientists from the different relevant disciplines.

2.1.2 Guidance on proposal content

Please include the following information

- Prior experience with comprehensive literature reviews and/or research with the parasite/disease for which the review is planned.

- Plans/budget for publication of the results in an open access, peer reviewed journal.

The research grant application form (see link below) should be used with section II adapted as appropriate for a literature review.

2.1.3 Funding

A decision on funding is anticipated for end of October/Early November 2014.

Up to 10 000 USD may be awarded for the review on one parasite/disease. The final report for TDR and the manuscript for submission to an open access, peer reviewed journal should be available within 6 months of receipt of the funding.

Should a grant for review for more than one parasite/ disease be awarded to the same individual/group, the funding duration will be adapted to allow 6 months/parasite.

2.1.4 How to apply

The research grant application form is attached to the DataCol and also available at this web page: http://www.who.int/tdr/grants/application_reporting_forms/en/

The completed research grant application form should be uploaded to the DataCol submission site.

All applications must be submitted online using the WHO DataCol portal form found on this link: https://extranet.who.int/datacol/survey.asp?survey_id=2990

The log-in credentials are:
Username: Depart
Password: Depart-2014

Only applications submitted through this online portal can be considered.
2.2 CALL FOR LETTERS OF INTEREST IN COLLABORATION on the

Quantitation of variability of response to the drugs for preventive chemotherapy of schistosomiasis, soil-transmitted helminthiasis, onchocerciasis, lymphatic filariasis:

Step 1 – Identification of collaborators willing to share data for pooled analysis (TDResist-QuoVadis)

Submission deadline: 12 January 2015, 23:59 (Geneva)

2.2.1 Eligibility

Individual researchers, leaders of groups of researchers from within one or several research institutions/control programmes or collaborative groups of researchers from within one or several research institutions/control programmes, control programme staff.

We welcome collaboration not only with researchers but also with control programmes.

2.2.2 Information requested from Collaborators

The information on the individual subject data requested is listed below. The Excel sheet appended to the DataCol (see below) can be used to provide this information.

Please provide as much of the information as possible. Availability of all information is not a prerequisite for the data sets to be included in the analyses.

1. Parasite
2. Location where samples were obtained (country, district/county, name of MDA implementation unit (e.g. district, CDTI project name), village)
3. Sampling context (clinical trial, community study, Control programme surveillance activity, other)
4. Approvals
   • If applicable: Ethics Committee approval for sampling (Name(s) of Ethics Committee(s) who provided sampling protocol approval, Year of EC approval)
   • Reason/sampling context if EC approval was considered non-applicable and not requested.
   • If applicable: other approvals (e.g. MoH / Control Programme head)
5. Methods
   • Time points relative to treatment for which individual subject data are available
   • Number of samples per individual and time point
   • Method for quantitation of parasite number in samples
6. Information on individuals for whom individual subject data are available (age, sex)
7. Treatment context
   • Year(s) of sampling
   • Drug(s) administered
   • Drug administered under observation or not
   • Drug administered with/shortly after food intake or not
   • Number of prior treatments of individuals from whom samples were obtained
   • Number of rounds of MDA in the study area
8. Type of data available
   - Raw data
   - Calculated parasite loads
   - Data formats (scanned hard copy, electronic files)

9. References for publication of the data, if applicable

10. Names of leader of the project/activity in which the samples were obtained

Appendices
   - Ethics Committee and other approvals (or information on the committees/organizations which approved the work and anticipated time of provision of the approval documents to TDR) should be uploaded to the DataCol.

2.2.3 How to inform WHO/TDR of interest in collaboration

Ideally, letters will be sent online using the WHO DataCol portal form found on this link and the filled in spreadsheet can be uploaded:

https://extranet.who.int/datacol/survey.asp?survey_id=2991

The log-in credentials are:
Username: QuoVadis
Password: QuoVadis-2014

Alternatively, letters of interest and information on the data available for the samples / the filled in excel sheet can be e-mailed to kuesela@who.int. Note that e-mails with a size of > 6 MB will be rejected by the WHO e-mail system and neither the sender, nor the intended recipient will be notified of this rejection.

We will follow up with you via e-mail and phone/Skype to discuss the collaboration framework in detail.
2.3 CALL FOR APPLICATIONS: Modelling the spread of ‘low response’ parasites within the population of a ‘transmission zone’ (TDResist-Model)

Submission deadline: 31 August 2014, 23:59 (Geneva)

2.3.1 Eligibility

Applicants can be individual researchers, research groups from within one institution or collaborative groups of researchers from different institutions including at least one researcher from an onchocerciasis endemic country.

We encourage applications from women scientists and scientists from endemic countries.

2.3.2 Guidance on proposal content

Please include

- Information on potential synergies between the proposed work and other projects you are currently working on or planning/applying for
- Information on your ongoing or planned collaborations with other groups working on transmission modelling.
- Plans/budget for publication of the results in an open access, peer reviewed journal.
- Proposed distribution of funds requested for the first year across three payments, taking into account that the first payment should not exceed 50% of the total funds requested for that year.

2.3.3 Funding

A decision on funding is anticipated for end of October/Early November 2014.

2.3.4 How to apply

The research grant application form is attached to the DataCol and also available at this web page: http://www.who.int/trd/grants/application_reporting_forms/en/

The completed research grant application form should be uploaded to the DataCol submission site.

All applications must be completed and submitted online using the WHO DataCol portal form found on this link:

https://extranet.who.int/datacol/survey.asp?survey_id=2989

The log-in credentials are:

Username: Model
Password: Model-2014

Only applications submitted through this online portal can be considered.

The Research grant application form should be appended to the DataCol.
2.4 CALL FOR APPLICATIONS: Research for genetic markers of *O. volvulus* response to ivermectin and development of an onchocerciasis control programme surveillance tool (CARIRS-Markers)

Submission deadline: 31 August 2014, 23:59 (Geneva)

2.4.1 Eligibility

Applicants can be individual researchers, research groups from within one institution or collaborative groups of researchers from different institutions including at least one researcher from an onchocerciasis endemic country.

Individual researchers and research groups from institution(s) in non-onchocerciasis endemic countries need to document that they have established a collaboration with researchers in or from an onchocerciasis endemic country or a collaboration with an onchocerciasis control programme.

We encourage applications from women scientists, scientists from onchocerciasis endemic countries, from previous TDR grantees and those having established collaborations with the previous TDR grantees or APOC/MDSC collaborators on this project (Dr. W. Grant, Australia; Dr. S. Wanji, Cameroon, Dr. R. Prichard, Canada, Dr. M. Wilson and Dr. D. Boakye, Ghana; Dr. G. Adjami, WHO APOC/MDSC Burkina Faso).

2.4.2 Guidance on proposal content

Please include information on the following:

a. Collaborations with other researchers/institutions relevant to this project

b. Availability of parasite samples or plans on how to obtain the samples during the project.

- If already available parasite samples are to be used, the grant application should include
  - Source, number and phenotypic characterization of the samples
  - Ethics Committee (EC) approval of the protocol under which they were obtained. A copy of the Ethics Committee approval(s) should be appended.
  - Signed confirmation of those involved in sample collection and phenotypic characterization that samples and phenotypic characterization will be made available for the analyses. Such confirmation is required even in cases when the researchers involved in sample collection and phenotypic characterization are part of a group submitting the proposal.

- If parasite samples from people are to be obtained during the research for which funding is requested:
  - Due consideration needs to be given to the requirements and time needed to obtain Ethics Committee (EC) approval, including from the WHO Ethics Review Committee (ERC) (http://www.who.int/rpc/research_ethics/review_process/en/, http://www.who.int/rpc/research_ethics/guidance/en/), for the protocol under which sampling will occur.
  - Funding for research which requires WHO ERC approval will be provided only after WHO ERC approval has been obtained. WHO ERC approval is contingent upon National/local EC approval.
  - Note: sufficient details on the plans for sample collection need to be included in the proposal to allow external advisors to assess the plan and associated budget. However, a protocol suitable for submission to WHO ERC and National ECs is required only after the grant has been awarded.
c. Prior experience and/or training in research on genetic markers.

d. Plans/budget for publication of the results in an open access, peer reviewed journal.

e. Synergies with other ongoing or planned activities
   
   • Researchers working on related projects funded by other organisations should include
     information on the synergies created through the simultaneous work on related projects as
     well as the amount of funding from other organisations which will, through these synergies,
     indirectly contribute to the work to be funded by TDR.

   • Researchers submitting proposals for this as well as other Calls for Applications within
     TDResist or CARIRs should include information on synergies and potential cost-savings
     through simultaneous work on more than one of activity.

f. Proposed distribution of funds requested for the first year across three payments, taking into
   account that the first payment should not exceed 50% of the total funds requested for that year.

2.4.3 Funding

A decision on funding is anticipated for end of October/Early November 2014.

2.4.4 How to apply

The research grant application form is attached to the DataCol and also available at this web page:
http://www.who.int/tdr/grants/application_reporting_forms/en/

The completed research grant application form should be uploaded to the DataCol submission site.

All applications must be completed and submitted online using the WHO DataCol portal form found
on this link:
https://extranet.who.int/datacol/survey.asp?survey_id=2992

The log-in credentials are:
Username: Markers
Password: Markers-2014

Only applications submitted through this online portal can be considered.

The Research grant application form should be appended to the DataCol.
2.5 CALL FOR APPLICATIONS: Research for genetic markers of *O. volvulus* population structure and potential development of a tool for defining transmission zones (CARIRS-Mission)

Submission deadline: 31 August 2014, 23:59 (Geneva)

2.5.1 Eligibility

Applicants can be individual researchers, research groups from within one institution or collaborative groups of researchers from different institutions including at least one researcher from an onchocerciasis endemic country.

Individual researchers and research groups from within institution(s) in non-onchocerciasis endemic countries need to document that they have established a collaboration with researchers in or from an onchocerciasis endemic country or a collaboration with an onchocerciasis control programme.

We encourage applications from women scientists, scientists from onchocerciasis endemic countries, from previous TDR grantees and those having established collaborations with the previous TDR grantees or APOC/MDSC collaborators on this project (Dr. W. Grant, Australia; Dr. S. Wanji, Cameroon, Dr. R. Prichard, Canada, Dr. M. Wilson and Dr. D. Boakye, Ghana; Dr. G. Adjami, WHO APOC/MDSC Burkina Faso).

2.5.2 Guidance on proposal content

Please include information on the following:

a. Collaborations with other researchers/institutions relevant to this project

b. Availability of parasite samples or plans on how to obtain the samples during the project.

- If already available parasite samples are to be used, the grant application should include
  - Source, number and phenotypic characterization of the samples
  - Ethics Committee (EC) approval of the protocol under which they were obtained. A copy of the Ethics Committee approval(s) should be appended.
  - Signed confirmation of those involved in sample collection and phenotypic characterization that these will be made available for inclusion in the analyses. Such confirmation is required even when the researchers involved in sample collection and phenotypic characterization are part of the group submitting the proposal.

- If parasite samples from people are to be obtained during the research for which funding is requested:
  - Due consideration needs to be given to the requirements and time needed to obtain Ethics Committee (EC) approval, including from the WHO Ethics Review Committee (ERC) ([http://www.who.int/rpc/research_ethics/review_process/en/](http://www.who.int/rpc/research_ethics/review_process/en/), [http://www.who.int/rpc/research_ethics/guidance/en/](http://www.who.int/rpc/research_ethics/guidance/en/)), for the protocol under which sampling will occur.
  - Funding for research which requires WHO ERC approval will be provided only after WHO ERC approval has been obtained. WHO ERC approval is contingent upon National/local EC approval.

  - **Note:** sufficient details on the plans for sample collection need to be included in the proposal to allow external advisors to assess the plan and associated budget. However, a protocol suitable for submission to WHO ERC and National ECs is required only after the grant has been awarded.
c. Prior experience and/or training in research on genetic markers.
d. Plans/budget for publication of the results in an open access, peer reviewed journal.
e. Synergies with other ongoing or planned activities
   • Researchers working on related projects funded by other organisations should include
     information on the synergies created through the simultaneous work on related projects as
     well as the amount of funding from other organisations which will, through these synergies,
     indirectly contribute to the work to be funded by TDR.
   • Researchers submitting proposals for this as well as other Calls for Applications within
     TDRResist or CARIRs should include information on synergies and potential cost-savings
     through simultaneous work on more than one of the activities.
f. Proposed distribution of funds requested for the first year across three payments, taking into
   account that the first payment should not exceed 50% of the total funds requested for that year.

2.5.3 Funding
A decision on funding is anticipated for end of October/Early November 2014.

2.5.4 How to apply
The Research grant application form available is attached to the DataCol and also available at
http://www.who.int/tdr/grants/application_reporting_forms/en/ (Research grant application form)
specifies the content.

All applications must be completed and submitted online using the WHO DataCol portal form found
on this link:

https://extranet.who.int/datacol/survey.asp?survey_id=2993

The log-in credentials are:
Username: Mission
Password: Mission-2014

Only applications submitted through this online portal will be considered.

The Research grant application form should be appended to the DataCol.

3 CONTACT FOR FURTHER INFORMATION
For further information, please contact Dr Annette C. Kuesel, kuesela@who.int