

NEGLECTED DISEASE R&D SCOPE DOCUMENT

This document sets out the neglected disease research and development (R&D) activities that are **included** within the scope of the G-FINDER survey, as well as the R&D activities that are **excluded** or **partially excluded**.

The G-FINDER scope has been defined by an expert international Advisory Committee, in line with the following three criteria:

1. The disease disproportionately affects people in developing countries*
2. There is a need for new products (i.e. there is no existing product, or improved or additional products are needed)
3. There is market failure (i.e. there is insufficient commercial market to attract R&D by private industry)

A list of the neglected diseases, products and technologies included in the G-FINDER survey scope is presented in the neglected disease R&D matrix (see section X).

* For the purpose of the G-FINDER survey, 'developing countries' means low- and middle-income countries (LMICs), as [defined by the World Bank](#).

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I. BASIC RESEARCH

Studies that increase scientific knowledge and understanding about the disease, disease processes, pathogen or vector, but which is not yet directed towards a specific product.

1. NATURAL HISTORY AND EPIDEMIOLOGY

- 1.1 Basic mechanisms of disease transmission
- 1.2 Disease prevalence in relation to human genotype, strain variation, and inoculation rates
- 1.3 Genetic diversity and phylogeny
- 1.4 Epidemiological research on the roles of human behaviour and effects of specific host genotypes on disease transmission
- 1.5 Epidemiological research on host genetic factors influencing the prevalence of disease (e.g., sickle cell, HLA type, Rh factor) or the impact of disease in select host genotypes
- 1.6 Epidemiological research on the distribution of pathogen, vectors and the prevalence of morbidity and mortality due to the disease that is NOT related to specific product development
- 1.7 Epidemiological research on antigenic variability; population studies of human immunity to the disease
- 1.8 Epidemiology of drug resistance or evolutionary studies on resistance development for established, existing drugs
- 1.9 Epidemiological research related to vector behaviour and ecology, and vector control

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2. IMMUNOLOGY OF DISEASE

- 2.1 Defining signalling pathways of immune function (mechanisms of systemic and/or mucosal immunity)
- 2.2 Interaction and impact of the signalling pathways with the pathogen
- 2.3 Development of assays or tools potentially useful for drug, vaccine, or microbicide research & development
- 2.4 Identification of immune correlates of protection, including *in vivo* and *in vitro* studies on the protective immune response (cellular, humoral, and/or mucosal)
- 2.5 Investigating the immune response to particular antigens; studies of specific antigens or immunogens proposed as vaccine candidates
- 2.6 Development of animal models to determine immune correlates of protection
- 2.7 Genetics of the immune response to the disease and effects of antigen polymorphism or genetic diversity on specific vaccine candidates (as recognised from field studies)

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3. BIOLOGY OF DISEASE

- 3.1 Structure and morphology of different developmental stages
- 3.2 Host-parasite interactions and biology of pathogen interaction with vector host
- 3.3 Biology of invasion of host cells (entry mechanisms)
- 3.4 Localisation of pathogen proteins or antigens
- 3.5 Development of culture and purification tools to assist in study of the pathogen

- 3.6 Descriptions of pathogenic species and characterisation of strains or subtypes in animal models (course of infection, susceptibility of different hosts)
- 3.7 *In vitro* studies of interactions between the pathogen and other infectious agents (e.g. Epstein-Barr virus)

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4. BIOCHEMISTRY OF THE PATHOGEN

- 4.1 Metabolism and nutrition
- 4.2 Protein sequencing, enzymology, and protein and enzyme characterisation (including antigen analysis)
- 4.3 Signal transduction; translation, processing and export of proteins
- 4.4 Glycosylation, Glycosylphosphatidylinositol (GPI) anchors, transporters, ion channels, mitochondrial metabolism, and electrophysiology studies
- 4.5 Influence of pathogen on host-cell biochemistry
- 4.6 Characterisation of antigen/protein diversity of pathogenic strains and subtypes
- 4.7 Characterisation of proteins and molecular basis for host-cell invasion
- 4.8 Analysis & characterisation of drug-resistant strains and studies probing drug resistance mechanism/s or pathways
- 4.9 Non-specific research on pathogen or host targets to identify potential drug, vaccine, or diagnostic targets (i.e. target identification)

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5. GENETICS OF THE PATHOGEN

- 5.1 Studies on chromosomes; genomic maps; genetic crosses
- 5.2 Cloning and sequencing of genes; cDNAs for functional proteins (including drug targets and vaccine candidates)
- 5.3 Expression of proteins from cloned genes; RNA analyses
- 5.4 Control and timing of gene expression; post-transcriptional processing
- 5.5 Analysis and characterisation of genes involved in drug resistance
- 5.6 Genetics of antigenic variability
- 5.7 Techniques for the genetic transformation of the pathogen
- 5.8 Tests for genotyping the pathogen for laboratory use

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6. BIOINFORMATICS AND PROTEOMICS

- 6.1 Microarray analysis
- 6.2 Genome annotation - gene predictions
- 6.3 Comparative genomics, sequence alignment, genome assembly
- 6.4 Variation, single nucleotide polymorphisms (SNPs)
- 6.5 Database applications, data mining tools
- 6.6 Structural and functional genomics
- 6.7 Structural and functional proteomics
- 6.8 Proteome analysis, protein structure alignment

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7. PATHOPHYSIOLOGY AND DISEASE SYMPTOMS

- 7.1 Clinical diagnosis and clinical observations of the disease presentation and pathophysiology in humans and in animals
- 7.2 The role of nutritional status in determining disease severity and treatment effectiveness
- 7.3 Histopathology of the disease in humans and in animals
- 7.4 The mechanisms of pathology of the disease; including, the role of the host immune system, and expression of adhesion molecules
- 7.5 Development of improved animal models to study disease pathophysiology, to evaluate the biological properties of drugs and microbicides
- 7.6 Identification of biomarkers for diagnostics or therapeutic monitoring
- 7.7 Studies of the mechanisms by which particular susceptible/resistant mammalian host genotypes exert their effect
- 7.8 Research on effects of host co-morbidities and secondary effects of pathogen invasion (e.g., research on anaemia /neurological effects of malaria)
- 7.9 Interactions between the disease and other relevant concurrent infections, including determining timing and establishment of infection

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8. VECTOR BIOLOGY, BIOCHEMISTRY, AND GENETICS

- 8.1 Characterisation of vector behaviour and ecology
- 8.2 Studies of vector susceptibility to infection; studies of parasites and pathogens of vectors (including potential biological control agents)
- 8.3 Identification of genes responsible for disruption of parasite/virus growth, genetic transformation of vectors, and insect transposable elements
- 8.4 Target identification of vector sites that may become the subject of *in vitro* screening or molecular design
- 8.5 Development of tests for vector identification, taxonomy and systematics, and for the identification of infected vectors
- 8.6 Studies evaluating resistance development, including the genetics and transmission of pesticide resistance

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II. DRUGS

Research activities and processes necessary to develop and improve new compounds specifically designed to prevent, cure or treat neglected diseases; including drug discovery or design, preclinical and clinical development and other activities essential for successful drug development and uptake.

9. DISCOVERY AND PRECLINICAL

Research activities targeted at discovering and optimising investigational compounds and including the processes needed to allow new chemical entities to proceed to human trials; including:

- 9.1 Target validation, characterisation, and selection
- 9.2 High throughput screening, lead optimisation
- 9.3 Development of analytical tests for assaying drugs, including the development of animal models
- 9.4 Research on drugs from natural products; identification and characterisation of active ingredient
- 9.5 Research on the effects of drug treatment on immune status

- 9.6 Measurement of the activity of potential drugs *in vitro* and in animal models; including safety and efficacy studies necessary to satisfy Investigational New Drug (IND) requirements
- 9.7 Studies evaluating the activity of new drugs on drug-resistant strains, their effect on genes involved in drug resistance, or their effect on resistance pathways
- 9.8 Development of tests for drug susceptibility of the pathogen for research purposes
- 9.9 Drug pharmacokinetic, toxicity and metabolism studies *in vitro* and in animal models, including bioavailability, adsorption, metabolism, and excretion (ADME) studies
- 9.10 Chemistry and synthesis of drugs, including process and scale-up manufacture, production of Good Laboratory Practice (GLP) and Good Manufacturing Practice (GMP) batch for toxicology studies; and other Chemistry and Manufacture Control (CMC) activities required to allow new chemical entities to proceed to human trials
- 9.11 Preparation of Investigational New Drug (IND) application for regulatory submission
- 9.12 Optimisation and manufacturing of new formulations to support label-extension* for new patient sub-populations (e.g. infants, pregnant women)

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10. CLINICAL DEVELOPMENT

Research activities and processes associated with clinical testing of investigational new drugs so as to demonstrate safety and efficacy in human subjects (as needed for regulatory approval), together with other costs required to support such clinical trials; including:

- 10.1 Phase I pharmacokinetic, toxicity and metabolism studies in healthy human subjects
- 10.2 Phase II testing of drugs and drug combinations in human patients to establish safety and efficacy including dose-finding, and proof of principle studies
- 10.3 Phase III clinical trials for registration purposes
- 10.4 Regulatory standard clinical trials that support a formal registration for label-extension* of an existing drug to a new disease or patient group (e.g. paediatric patients, pregnant women or HIV-positive patients)
- 10.5 Regulatory standard clinical trials that support formal registration for label-extension* of an existing drug to a new use, such as intermittent preventative therapy and pre-exposure prophylaxis
- 10.6 Infrastructure and site development costs **directly** associated with the conduct of clinical trials for drug development in **endemic countries** (e.g. refurbishment of hospital wing, vehicle purchase, generators, training and community relationship building)
- 10.7 Further pharmaceutical development to generate the final clinical formulation, dosage form and other Chemistry and Manufacture Control (CMC) activities required for regulatory submission
- 10.8 Compiling of all non-clinical and clinical data for submission of a New Drug Application (NDA) to regulatory authorities
- 10.9 Behavioural research **during clinical trials** relating to risk assessment, factors affecting adherence to protocol, and product acceptability

* Label-extensions refer to changes to drugs or their labels after they have been approved. This includes changes in manufacturing, recommended patient population and/or formulation. To change a label, market a new dosage or strength of a drug, or change the way a drug is manufactured, the company must submit a supplemental new drug application (sNDA) to regulatory authorities to obtain marketing approval

- 10.10** Protocol development, investigator meetings, Good Clinical Practice (GCP)-monitoring, quality control, data management, analysis and reporting, establishing a Data Safety Monitoring Board (DSMB), and trial audits

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11. PHASE IV / PHARMACOVIGILANCE

Studies relating to the detection, monitoring, evaluation, and prevention of adverse events associated with newly approved drugs so as to bridge the gap between highly controlled clinical trials intended for regulatory approval and the largely uncontrolled use of new drugs by patients. Also includes studies conducted after regulatory approval that assess drug effectiveness in the wider population or which are necessary to support product use in developing countries.

- 11.1** Pharmacovigilance and post-registration studies of newly registered drugs to assess adverse reactions, toxicology and safety
- 11.2** Effectiveness studies and head-to-head comparator studies of newly registered drugs (with other therapies or interventions)
- 11.3** Cost-effectiveness studies of newly registered drugs
- 11.4** Treatment interactions and population level studies (of newly registered products e.g., pharmaco-epidemiological and resistance studies)
- 11.5** Behavioural research **post-registration** of new drugs relating to risk assessment, factors affecting adherence to protocol, provider compliance, and product acceptability
- 11.6** Case history reports and assessment of long-term prophylaxis using newly registered drugs in communities in endemic areas

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12. BASELINE EPIDEMIOLOGY

Studies evaluating potential trial site populations to confirm disease incidence, prevalence or exposure risk, and which serve as the foundation for determining the optimal collection, analysis, interpretation and presentation of clinical trial data, including:

- 12.1** Epidemiological studies **directly** linked to the conduct or support of clinical trials of products in development, in order to assess or validate the epidemiology of disease, disease incidence, or health of target populations at trial sites
- 12.2** Preliminary studies of morbidity and mortality at potential clinical trial sites, where these studies are directly linked to planned product trials
- 12.3** Pre-trial activities designed to understand trial site conditions before the commencement of trials and to facilitate engagement

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III. PREVENTIVE VACCINES

Research activities and processes necessary to develop and improve investigational vaccines specifically intended to prevent infection; including vaccine design, preclinical and clinical development and other activities essential for successful vaccine development and uptake.

13. DISCOVERY AND PRECLINICAL

Research activities targeted at discovering and optimising investigational vaccines and including the processes necessary to allow a candidate vaccine to proceed to human trials; including:

- 13.1** Studies supporting novel vaccine design, including target validation & candidate optimisation
- 13.2** Development of animal models to assist in vaccine design and testing

- 13.3 Evaluation of vaccine technologies (e.g. adjuvants, delivery systems) to improve the immunogenicity of an identified candidate
- 13.4 Preclinical safety and immunogenicity studies with candidate vaccines, including use or development of functional assays
- 13.5 Preclinical animal studies, challenge models and addressing the correlation between *in vitro* models, animal models and field results
- 13.6 Studies on the genetics of the immune response to selected antigens as vaccine candidates, optimisation of animal models and correlates to clinical results
- 13.7 Manufacturing scale-up and consistency of manufacture, including production of Good Laboratory Practice (GLP) and Good Manufacturing Practice (GMP) batches for regulatory toxicology studies and other Chemistry and Manufacture Control (CMC) activities required to allow a candidate vaccine to proceed to human trials
- 13.8 Research on safety and regulatory considerations (e.g. validation of preclinical assays to permit registration)
- 13.9 Preparation of an Investigational New Drug (IND) application for regulatory submission
- 13.10 Optimisation of vaccine candidates for global use (cheaper, more stable, ease of administration, addition of developing country-specific strains)

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14. CLINICAL DEVELOPMENT

Activities and processes associated with clinical testing of investigational vaccines so as to demonstrate safety, immunogenicity and efficacy in human subjects (as needed for regulatory approval), together with other costs required to support such clinical trials, including:

- 14.1 Phase Ia studies assessing safety, dosing, and immunogenicity in human volunteers; Phase Ib studies assessing safety, dosing, and immunogenicity in clinically exposed or high-risk populations
- 14.2 Phase IIa challenge studies; Phase II safety and preliminary efficacy studies in exposed populations or those at high-risk of infection
- 14.3 Phase III expanded efficacy, effectiveness and safety studies required for registration purposes, including implementation, retention and follow-up of volunteers
- 14.4 Infrastructure and site development costs associated with the conduct of clinical trials for vaccine development in **endemic countries** (e.g. refurbishment of hospital wing, vehicle purchase, generators, training and community relationship building)
- 14.5 Further biological/product development to generate the optimal clinical formulation and dosage form, and other Chemistry and Manufacture Control (CMC) activities required for regulatory submission
- 14.6 Compiling all non-clinical and clinical data to obtain a Biologics License from regulatory authorities
- 14.7 Behavioural research **during clinical trials** relating to risk assessment, factors affecting adherence to protocol, and product acceptability
- 14.8 Protocol development, investigator meetings, Good Clinical Practice (GCP) monitoring, quality control, data management, analysis and reporting, establishing a Data Safety Monitoring Board (DSMB) and trial audits

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15. PHASE IV / PHARMACOVIGILANCE

Studies relating to the detection, monitoring, evaluation, and prevention of adverse events associated with newly approved vaccines so as to bridge the gap between highly controlled clinical trials intended for regulatory approval and the largely uncontrolled delivery of new vaccines. Also includes studies conducted after regulatory approval that assess vaccine effectiveness in the wider population or which are necessary to support product use in developing countries.

- 15.1 Pharmacovigilance and post-registration studies of newly registered preventive vaccines to assess adverse reactions, toxicology and safety
- 15.2 Effectiveness studies and head-to-head comparator studies of newly registered preventive vaccines (with other therapies or interventions)
- 15.3 Cost-effectiveness studies of newly registered preventive vaccines
- 15.4 Treatment interactions and population level studies (of newly registered preventive vaccines e.g., pharmaco-epidemiological and resistance studies)
- 15.5 Behavioural research **post-registration** of new preventive vaccines relating to risk assessment, factors affecting adherence to protocol, provider compliance, and product acceptability
- 15.6 Case history reports and assessment of long-term prophylaxis using newly registered preventive vaccines in communities in endemic areas

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16. BASELINE EPIDEMIOLOGY

Studies evaluating potential trial site populations to confirm disease incidence, prevalence or exposure risk, and which serve as the foundation for determining the optimal collection, analysis, interpretation and presentation of clinical trial data, including:

- 16.1 Epidemiological studies **directly** linked to the conduct or support of clinical trials of preventive vaccines in development, in order to assess or validate the epidemiology of disease, disease incidence, or health of target populations at trial sites
- 16.2 Preliminary studies of morbidity and mortality at potential clinical trial sites, where these studies are directly linked to planned preventive vaccines trials
- 16.3 Pre-trial activities designed to understand trial site conditions before the commencement of trials and to facilitate engagement

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IV. THERAPEUTIC VACCINES

Research activities and processes necessary to develop and improve investigational vaccines specifically intended to treat infection; including vaccine design, preclinical and clinical development, and other activities essential for successful vaccine development and uptake.

17. DISCOVERY AND PRECLINICAL

Research activities targeted at discovering and optimising investigational therapeutic vaccines and including the processes necessary to allow a candidate vaccine to proceed to human trials; including:

- 17.1 Studies supporting novel vaccine design including target validation and candidate optimisation
- 17.2 Evaluation of vaccine technologies (e.g. adjuvants, delivery systems) to improve the immunogenicity of an identified candidate
- 17.3 Preclinical safety and immunogenicity studies with candidate vaccines, including use or development of functional assays
- 17.4 Preclinical animal studies, challenge models, and studies addressing the correlation between *in vitro* models, animal models and field results

- 17.5 Studies on the genetics of the immune response to selected antigens as vaccine candidates, optimisation of animal models and correlates to clinical results
- 17.6 Manufacturing scale-up and consistency of manufacture, including production of Good Laboratory Practice (GLP) and Good Manufacturing Practice (GMP) batches for regulatory toxicology studies and other Chemistry and Manufacture Control (CMC) activities required to allow a candidate vaccine to proceed to human trials
- 17.7 Research on safety and regulatory considerations (e.g. validation of preclinical assays to permit registration)
- 17.8 Preparation of an Investigational New Drug (IND) application for regulatory submission
- 17.9 Optimisation of vaccine candidates for global use (cheaper, more stable, ease of administration, addition of developing country-specific targets)

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18. CLINICAL DEVELOPMENT

Activities and processes associated with clinical testing of investigational therapeutic vaccines so as to demonstrate safety, immunogenicity, and efficacy in human subjects (as needed for regulatory approval), together with other costs required to support such clinical trials; including:

- 18.1 Phase Ia studies assessing safety, dosing and immunogenicity in human volunteers; Phase Ib studies assessing safety, dosing and immunogenicity in clinically exposed or high-risk populations
- 18.2 Phase IIa challenge studies; Phase II safety and preliminary efficacy studies in exposed populations or those at high-risk of infection
- 18.3 Phase III expanded efficacy, effectiveness and safety studies required for registration purposes, including implementation, retention and follow-up of volunteers
- 18.4 Infrastructure and site development costs associated with the conduct of clinical trials for vaccine development in **endemic countries** (e.g. refurbishment of hospital wing, vehicle purchase, generators)
- 18.5 Further biological/product development to generate the optimal clinical formulation, dosage form and other Chemistry and Manufacture Control (CMC) activities required for regulatory submission
- 18.6 Behavioural research **during clinical trials** relating to risk assessment, factors affecting adherence to protocol and product acceptability
- 18.7 Compiling of all non-clinical and clinical data to obtain a Biologics License from regulatory authorities
- 18.8 Protocol development, investigator meetings, Good Clinical Practice (GCP) monitoring, quality control, data management, analysis and reporting, establishing a Data Safety Monitoring Board (DSMB) and trial audits

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19. PHASE IV/PHARMACOVIGILANCE

Studies relating to the detection, monitoring, evaluation, and prevention of adverse events associated with newly approved therapeutic vaccines so as to bridge the gap between highly controlled clinical trials intended for regulatory approval and the largely uncontrolled delivery of new therapeutic vaccines. Also includes studies conducted after regulatory approval that assess therapeutic vaccine effectiveness in the wider population or which are necessary to support product use in developing countries.

- 19.1 Pharmacovigilance and post-registration studies of newly registered therapeutic vaccines to assess adverse reactions, toxicology and safety

- 19.2 Effectiveness studies and head-to-head comparator studies of newly registered therapeutic vaccines (with other therapies or interventions)
- 19.3 Cost-effectiveness studies of newly registered therapeutic vaccines
- 19.4 Treatment interactions and population level studies (of newly registered therapeutic vaccines e.g., pharmaco-epidemiological and resistance studies)
- 19.5 Behavioural research **post-registration** of new therapeutic vaccines relating to risk assessment, factors affecting adherence to protocol, provider compliance, and product acceptability
- 19.6 Case history reports and assessment of long-term prophylaxis using newly registered therapeutic vaccines in communities in endemic areas

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20. BASELINE EPIDEMIOLOGY

Studies evaluating potential trial site populations to confirm disease incidence, prevalence, or exposure risk, and which serve as the foundation for determining the optimal collection, analysis, interpretation, and presentation of clinical trial data; including:

- 20.1 Epidemiological studies **directly** linked to the conduct or support of clinical trials to assess or validate the epidemiology of disease, disease incidence or health of target populations at potential trial sites
- 20.2 Preliminary studies of morbidity & mortality at potential clinical trial sites necessary for product development
- 20.3 Pre-trial activities designed to understand trial site conditions before the commencement of trials and to facilitate engagement

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V. DIAGNOSTICS

Research activities and processes necessary to develop, optimise, and validate diagnostic tests for use in resource-limited settings (cheaper, faster, more reliable, ease of use in the field); including discovery and design, preclinical and clinical evaluation, and other activities essential for successful deployment for public health use.

21. DISCOVERY AND PRECLINICAL

*Research activities targeted at discovering and optimising **low-cost**, stable, easy-to-use diagnostics for neglected diseases and including the processes necessary to allow a potential product to proceed to clinical evaluation including:*

- 21.1 Validation, characterisation, and selection of targets suitable for diagnostic use
- 21.2 Validation of new diagnostic markers or biomarkers
- 21.3 Development and testing of **low-cost**, stable, easy-to-use diagnostic tests (e.g. simpler microscopy, improved sample collection/preparation, cheaper ELISA assays), including manufacturing design
- 21.4 New or improved diagnostics for disease staging and therapy decisions
- 21.5 New or improved diagnostic tools to identify resistant pathogens
- 21.6 New or improved diagnostics to identify specific target populations
- 21.7 Tailoring diagnostic tools for developing country use, including improved point-of-care tests (rapid test), local laboratory test, reference laboratory tests and central laboratory tests
- 21.8 Creation of reference material banks

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22. CLINICAL EVALUATION

Activities and processes associated with clinical evaluation of investigational diagnostic tools so as to demonstrate sensitivity and specificity in human subjects, together with other costs required to support such clinical trials; including:

- 22.1 Clinical efficacy trials
- 22.2 Small-scale testing in humans to establish sensitivity and specificity and utility
- 22.3 Technical evaluation of tests and studies evaluating product performance
- 22.4 Establishment of product specifications, kit development and quality assurance
- 22.5 Submission of relevant data to regulatory authorities for approval
- 22.6 Assessment & validation of trial sites to carry out product trials
- 22.7 Infrastructure and site development costs **directly** associated with the conduct of clinical trials for diagnostic development in **endemic countries** (e.g. refurbishment of hospital wing, vehicle purchase, generators, training and community relationship building)

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23. OPERATIONAL RESEARCH FOR DIAGNOSTICS

Operational procedures and implementation activities associated with novel diagnostic tools, which are necessary to support World Health Organization recommendations for global public health use including:

- 23.1 Larger-scale demonstration studies (assessing specificity, sensitivity and utility of the diagnostic test in endemic countries)
- 23.2 Cost-effectiveness studies assessing the diagnostic test
- 23.3 Identification of pitfalls of the technology and studies of safety measures needed to support the technology
- 23.4 Studies to determine at what level of the health care system the technology is applicable (e.g. reference labs, regional labs)
- 23.5 Identification of training needs
- 23.6 Collecting evidence for expanding the use of a diagnostic tool in different countries
- 23.7 Development of equipment and customer support documents
- 23.8 Head-to-head comparator studies (with current gold standard) and in the context of existing diagnostic algorithms
- 23.9 Behavioural research relating to risk assessment, factors affecting diagnostics use, and user acceptability (patient and provider)
- 23.10 Epidemiological studies to assess or validate the epidemiology of disease, disease incidence or health of target populations at potential trial sites, and which are **directly** linked to clinical trials of a new diagnostic

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VI. MICROBICIDES

Research activities and processes necessary to develop and improve topical microbicides specifically intended to prevent HIV transmission; including microbicide discovery or design, preclinical and clinical development, and other activities essential for successful microbicide development and uptake.

24. DISCOVERY AND PRECLINICAL

Research activities targeted at identifying, optimising, and characterising investigational microbicides and including the processes necessary to allow lead compounds to proceed to human trials including:

- 24.1 Specific research aimed at discovery of topical applications for microbicide use (e.g. vaginal defence enhancers, surfactants, entry/fusion inhibitors and replication inhibitors)
- 24.2 Target validation, characterisation and selection
- 24.3 Preclinical evaluation of microbicide candidates including determination of acceptable formulation and delivery modes
- 24.4 Studies supporting safety & immunogenicity testing in animal models and looking at *in vitro* correlates of *in vivo* protective response
- 24.5 Developing reagents and standardised methods to assess microbicide-induced immune response in animals and humans
- 24.6 Optimisation of microbicide candidates, bioprocess development, formulation and mode of delivery of novel prevention tools for broad international use (cheap, easy to produce, stable, easy to administer) including production of Good Laboratory Practice (GLP) and Good Manufacturing Practice (GMP)-grade product for regulatory toxicology studies
- 24.7 Preparation of an Investigational New Drug (IND) application for regulatory submission

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25. CLINICAL DEVELOPMENT

Activities and processes associated with clinical testing of investigational new microbicides to demonstrate safety and efficacy in human subjects (as needed for regulatory approval), together with other costs required to support such clinical trials, including:

- 25.1 Phase I trials of novel microbicide products aimed at determining early safety and efficacy in healthy human subjects
- 25.2 Phase II clinical trials that evaluate safety and efficacy of the microbicide in a controlled setting, including dose-finding and proof-of-principle studies
- 25.3 Phase III trials of novel microbicide products aimed at confirming efficacy and safety in expanded populations
- 25.4 Infrastructure and site development costs associated with the conduct of clinical trials for microbicide development in **endemic countries** (e.g., refurbishment of hospital wing, vehicle purchase, generators, training and community relationship building)
- 25.5 Further microbicide development to generate the final clinical formulation, dosage form and other Chemistry and Manufacture Control (CMC) activities required for regulatory submission
- 25.6 Compiling of all non-clinical and clinical data for submission of a New Drug Application (NDA) to regulatory authorities
- 25.7 Behavioural research **during clinical trials** relating to risk assessment, factors affecting adherence to protocol and product acceptability
- 25.8 Protocol development, investigator meetings, Good Clinical Practice (GCP) monitoring, quality control, data management, analysis and reporting, establishing a Data Safety Monitoring Board (DSMB) and trial audits

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26. PHASE IV / PHARMACOVIGILANCE

Studies relating to the detection, monitoring, evaluation, and prevention of adverse events associated with newly approved microbicides so as to bridge the gap between highly controlled clinical trials intended for regulatory approval and the largely uncontrolled delivery of new microbicides. Also

includes studies conducted after regulatory approval that assess microbicide effectiveness in the wider population or which are necessary to support product use in developing countries.

- 26.1** Pharmacovigilance and post-registration studies of newly registered microbicides to assess adverse reactions, toxicology and safety
- 26.2** Effectiveness studies and head-to-head comparator studies of newly registered microbicides (with other therapies or interventions)
- 26.3** Cost-effectiveness studies of newly registered microbicides
- 26.4** Treatment interactions and population level studies (of newly registered preventive microbicides e.g., pharmaco-epidemiological and resistance studies)
- 26.5** Behavioural research **post-registration** of new microbicides relating to risk assessment, factors affecting adherence to protocol, provider compliance, and product acceptability
- 26.6** Case history reports and assessment of long-term prophylaxis using newly registered microbicides in communities in endemic areas

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27. BASELINE EPIDEMIOLOGY

Studies evaluating potential trial site populations to confirm disease incidence, prevalence or exposure risk, and which serve as the foundation for determining the optimal collection, analysis, interpretation and presentation of clinical trial data, including:

- 27.1** Epidemiological studies **directly** linked to the conduct or support of clinical trials of microbicides in development, in order to assess or validate the epidemiology of disease, disease incidence, or health of target populations at trial sites
- 27.2** Preliminary studies of morbidity and mortality at potential clinical trial sites, where these studies are directly linked to planned microbicide trials
- 27.3** Pre-trial activities designed to understand trial site conditions before the commencement of trials and to facilitate engagement

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VII. VECTOR CONTROL PRODUCTS

Research and development activities and processes necessary to develop and improve vector control approaches intended to prevent infection and block transmission of a neglected disease from vector and/or animal reservoirs to human; including novel chemical vector control products, biological vector control products and reservoir targeted vaccines.

28. CHEMICAL VECTOR CONTROL PRODUCTS

*This product category **ONLY** includes chemical active ingredients and formulations intended for global public health use and which specifically aim to inhibit, kill and/or repel indoor and outdoor vectors associated with neglected disease transmission. This includes new insecticides and formulations in LLINs/IRS; insecticide-based bait and traps; spatial repellents; and chemical larvicides.*

*Predation measures, habitat control and infrastructure measures are **EXCLUDED** from the G-FINDER scope.*

28.1 Primary and secondary screening and optimisation

Laboratory-based design, synthesis and testing of potential insecticides, chemical larvicides, molluscides, trypanocides etc. and generation of data sufficient to allow developers to proceed field testing, including:

- 28.1.1 Primary and secondary screens (e.g. *in vitro* and *in vivo* screens, chemical screens, whole insect screens)
- 28.1.2 Target validation and characterisation
- 28.1.3 Lead optimisation, synthesis optimisation

- 28.1.4 Early toxicology screens (e.g. acute oral toxicity, eye and skin irritation studies, AMES/mutagenicity studies)
- 28.1.5 Applied laboratory research and small-scale field trials, including *in vitro* and glass house efficacy testing
- 28.1.6 Acute toxicology and ecotoxicology studies (e.g. animal studies, exposure studies, fish and wildlife studies)
- 28.1.7 Metabolism and stability studies in plants and animals including mode of action, residue analysis and cross-resistance studies
- 28.1.8 Environmental effect and decomposition studies in soil, water and air

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28.2 Development

Pre-registration activities and processes associated with clinical testing of investigational chemical vector control products so as to generate data sufficient to allow developers to proceed to product roll-out & dissemination and including other costs required to support such clinical trials.

- 28.2.1 Small-scale efficacy studies, residue plots and field studies necessary for product optimisation and registration
- 28.2.2 Acute and long-term toxicology and ecotoxicology studies
- 28.2.3 Metabolic and residual fate studies, crop residue and exposure data
- 28.2.4 Environmental assessment and environmental chemistry data
- 28.2.5 Generation of hazard data in humans, domestic animals and non-target plants and animals
- 28.2.6 Compiling of all laboratory and field data necessary for submission to regulatory authorities
- 28.2.7 Behavioural research conducted **pre-registration** relating to risk assessment, factors affecting adherence to protocol, and product acceptability
- 28.2.8 Manufacturing process development, formulation and scale-up

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28.3 PQ listing and regulatory approval

PQ assessment processes and post-registration research activities that comprise entomological, quality, safety and epidemiological evaluation (where appropriate) and development of specifications required for application of insecticide products for use in international public health programmes, including:

- 28.3.1 PQ assessment of laboratory studies (e.g. determining intrinsic insecticidal activity, diagnostic concentration, irritant or excito-repellent properties, cross-resistance to other insecticides, efficacy and residual activity on relevant substrates)
- 28.3.2 PQ assessment of small-scale field trials (e.g. efficacy and persistence under different ecological settings, dosage of application, handling and application, perceived side-effects)
- 28.3.3 PQ assessment of large-scale field trials (e.g. community level efficacy and residual activity, operational and community acceptance)
- 28.3.4 Assessment & validation of trial sites **directly** linked to product trials
- 28.3.5 Infrastructure and site development costs associated with the conduct of field trials for pesticide development in **endemic countries** (e.g. refurbishment of hospital wing, vehicle purchase, generators, training and community relationship building)
- 28.3.6 Behavioural research conducted **post-registration** relating to risk assessment, factors affecting adherence to protocol, provider compliance and product acceptability
- 28.3.7 Studies that confirm efficacy, improve product uptake or confirm safety (e.g. studies to measure impact, usage levels, contamination potential or storage and disposal needs)

- 28.3.8 Surveillance studies directly linked to the conduct of field trials for vector control products; including studies that determine prevalence, track distribution, abundance, or significant habits of target vectors or the vector-borne pathogen

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29. BIOLOGICAL VECTOR CONTROL PRODUCTS†

*This product category **ONLY** includes research and development of innovative biological control interventions that specifically aim to kill or control vectors associated with transmitting neglected diseases (e.g. microbial/bacteriological larvicides, sterilisation techniques, and genetic modification measures).*

Biological control interventions comprise the use of natural enemies or "engineered" products to manage vector populations either through the introduction of natural parasites, pathogens or predators of the target, or via the introduction of modified vector species to compete with natural sources.

*Predation measures, habitat control and infrastructure measures are **EXCLUDED** from the G-FINDER scope.*

29.1 Phase I

Laboratory studies of novel biological vector control techniques

- 29.1.1 Development of intervention concept and target product profile (TPP) that also specifies the intended product claim (e.g. target vector, entomological effect etc.)
- 29.1.2 Molecular, genotypic, physiological and behavioural characteristics research in genetically modified vectors
- 29.1.3 Activities related to generating transgenic vector lines, checking stability of the transgene and its phenotype and studies related to the rate of spread of a transgene in laboratory cage populations
- 29.1.4 Ecological modelling to assess environmental risk
- 29.1.5 Quality control to ensure new biological materials are well characterised, stable and detectable
- 29.1.6 Phenotypic evaluation research of transgenic endemic strains, including testing for adverse effects on target or non-target species
- 29.1.7 Laboratory assays to establish mechanism of action
- 29.1.8 Small-scale laboratory studies for efficacy and safety
- 29.1.9 Laboratory-based studies on efficacy and safety in larger population cages
- 29.1.10 Establishment of standard operating procedures for genetically modified vector production and release
- 29.1.11 Activities related to site preparation and hazard containment (risk analysis and risk management)
- 29.1.12 Activities related to data analysis as required by regulators
- 29.1.13 Modelling of expected cost of protection per person

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29.2 Phase II

Semi-field tests or small-scale field trials (in physical or ecological confinement) to assess the entomological efficacy of the approach‡

† Unlike the universally accepted definitions for the drug, vaccine and diagnostic R&D pathways, definitions for the biological control product R&D pathway are not firmly established. It is possible that the terminology may change over time as the scientific field develops, and as new biological control products undergo regulatory approval. Please note that the activities listed under each stage are not exhaustive but are intended to illustrate the most critical R&D activities within each stage.

‡ Reduction in the likelihood of disease transmission due to vector population characteristics

- 29.2.1 Physically confined (large cage, greenhouse or screen-house type facility that simulates the disease-endemic setting) field trials or semi-field tests to assess entomological efficacy (biological and functional)
- 29.2.2 Ecologically confined (geographic/spatial and/or climatic isolation) small-scale field trials to assess entomological efficacy (biological and functional)
- 29.2.3 Ecological modelling to assess environmental risk
- 29.2.4 Compiling all entomological and epidemiological efficacy data as required by regulators
- 29.2.5 Activities related to site preparation and hazard containment (risk analysis and risk management)
- 29.2.6 Initial cost analysis of prototype or approach
- 29.2.7 Continued monitoring of molecular quality control

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29.3 Phase III

Large-scale staged field trials to assess the epidemiological efficacy of the approach[§]

- 29.3.1 Staged, open, large-scale randomised control trials to determine epidemiological efficacy (e.g., reduced disease prevalence, population suppression of target vector)
- 29.3.2 Ecological modelling to assess environmental risk
- 29.3.3 Trial site selection and preparation
- 29.3.4 Baseline studies such as ovitrap surveillance
- 29.3.5 Rearing and sorting of genetically modified vectors
- 29.3.6 Continued monitoring of molecular quality control
- 29.3.7 Activities related to data management and statistical analysis
- 29.3.8 Projection of cost per person protected and cost-efficacy of prototype or approach

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29.4 Phase IV

Studies, in real-world conditions, that validate the effectiveness of a newly-developed biological vector control product, or post-implementation surveillance of safety and quality

- 29.4.1 Pilot implementation studies
- 29.4.2 Post-implementation studies to validate feasibility, acceptability and cost-effectiveness
- 29.4.3 Post-implementation surveillance studies to measure mechanism of distribution, molecular quality control, efficacy and safety (including ecological safety) that are NOT part of routine disease or demographic surveillance activities

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30. RESERVOIR TARGETED VACCINES

*This product category **ONLY** includes research and development of veterinary vaccines specifically designed to prevent animal to human transmission of neglected diseases. Vaccines developed and used solely for veterinary purposes are excluded from this product category.*

30.1 Discovery and preclinical

Research activities targeted at discovering and optimising investigational vaccines and including the processes necessary to allow a candidate vaccine to proceed to animal trials; including:

- 30.1.1 Studies supporting novel vaccine design, including target validation and candidate optimisation
- 30.1.2 Development of animal models to assist in vaccine design and testing

[§] Reduction in the incidence of infection or disease in human populations

- 30.1.3 Evaluation of vaccine technologies (e.g. adjuvants, delivery systems) to improve the immunogenicity of an identified candidate
- 30.1.4 Preclinical safety and immunogenicity studies with candidate vaccines, including use or development of functional assays
- 30.1.5 Preclinical animal studies, challenge models and addressing the correlation between *in vitro* models, animal models and field results
- 30.1.6 Studies on the genetics of the immune response to selected antigens as vaccine candidates, optimisation of animal models and correlates to clinical results
- 30.1.7 Manufacturing scale-up and consistency of manufacture, including production of Good Laboratory Practice (GLP) and Good Manufacturing Practice (GMP) batches for regulatory toxicology studies and other Chemistry and Manufacture Control (CMC) activities required to allow a candidate vaccine to proceed to human trials
- 30.1.8 Research on safety and regulatory considerations (e.g. validation of preclinical assays to permit registration)
- 30.1.9 Preparation of a Veterinary Biological Product License application for regulatory submission
- 30.1.10 Optimisation of vaccine candidates for global use (cheaper, more stable, ease of administration, addition of developing country-specific strains)

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30.2 Clinical development

Activities and processes associated with clinical testing of investigational vaccines so as to demonstrate safety, immunogenicity and efficacy in animals including animal to human transmission (as needed for regulatory approval), together with other costs required to support such clinical trials, including:

- 30.2.1 Phase Ia studies assessing safety, dosing, and immunogenicity in animals; Phase Ib studies assessing safety, dosing, and immunogenicity in clinically exposed or high-risk animal populations
- 30.2.2 Phase IIa challenge studies; Phase II safety and preliminary efficacy studies in exposed animal populations or those at high-risk of infection
- 30.2.3 Phase III expanded efficacy, effectiveness and safety studies required for registration purposes
- 30.2.4 Infrastructure and site development costs associated with the conduct of clinical trials for vaccine development in **endemic countries** (e.g. vehicle purchase, generators, training and community relationship building)
- 30.2.5 Further biological/product development to generate the optimal clinical formulation and dosage form, and other Chemistry and Manufacture Control (CMC) activities required for regulatory submission
- 30.2.6 Compiling all non-clinical and clinical data to obtain a Biologics License from regulatory authorities
- 30.2.7 Behavioural research **during clinical trials** relating to risk assessment, factors affecting adherence to protocol, and product acceptability
- 30.2.8 Protocol development, investigator meetings, Good Clinical Practice (GCP) monitoring, quality control, data management, analysis and reporting, establishing a Data Safety Monitoring Board (DSMB) and trial audits

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30.3 Phase IV/pharmacovigilance

Studies relating to the detection, monitoring, evaluation, and prevention of adverse events associated with newly approved vaccines so as to bridge the gap between highly controlled clinical trials intended for regulatory approval and the largely uncontrolled delivery of new vaccines. Also includes studies conducted after regulatory approval that assess vaccine effectiveness in real world settings or which are necessary to support product use in developing countries.

- 30.3.1 Pharmacovigilance and post-registration studies of newly registered preventive vaccines to assess adverse reactions, toxicology and safety
- 30.3.2 Effectiveness studies and head-to-head comparator studies of newly registered preventive vaccines (with other therapies or interventions)
- 30.3.3 Cost-effectiveness studies of newly registered preventive vaccines
- 30.3.4 Treatment interactions and population level studies (of newly registered preventive vaccines, e.g. pharmaco-epidemiological and resistance studies)
- 30.3.5 Behavioural research **post-registration** of new preventive vaccines relating to risk assessment, factors affecting adherence to protocol, provider compliance, and product acceptability
- 30.3.6 Case history reports and assessment of long-term prophylaxis using newly registered preventive vaccines in endemic areas

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30.4 Baseline epidemiology

Studies evaluating potential trial site animal populations to confirm disease incidence, prevalence or exposure risk, and which serve as the foundation for determining the optimal collection, analysis, interpretation and presentation of clinical trial data, including

- 30.4.1 Epidemiological studies **directly** linked to the conduct or support of clinical trials of vaccines in development, in order to assess or validate the epidemiological impact on disease, disease incidence, or health of target animal populations at trial sites
- 30.4.2 Preliminary studies of morbidity and mortality at potential clinical trial sites, where these studies are directly linked to planned vaccines trials
- 30.4.3 Pre-trial activities designed to understand trial site conditions before the commencement of trials and to facilitate engagement

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VIII. CAN NOT BE ALLOCATED TO ONE DISEASE

31. MULTI-DISEASE VECTOR CONTROL PRODUCTS

This category **ONLY** applies to vector control product R&D that is not yet targeted at a specific neglected disease, or is explicitly targeted at multiple vector-borne neglected diseases. Disease-specific investment associated with R&D of vector control products with multi-disease potential (e.g. assessment of the epidemiological efficacy of *Wolbachia* carrying mosquitoes *in reducing dengue incidence*) **DOES NOT** fall under this category.

Example:

- i. Design and synthesis of new mode-of-action chemicals for controlling mosquitoes of various species (*Anopheles*, *Aedes* and/or *Culex*)
- ii. Development of a sterile-insect technique for controlling mosquito-borne diseases

31.1 Multi-disease chemical vector control products

- 31.1.1 See section 28 for the full outline of R&D activities included under this product category

31.2 Multi-disease biological vector control products

- 31.2.1 See section VII.29 for the full outline of R&D activities included under this product category

31.3 Multi-disease reservoir targeted vaccines

- 31.3.1 See section VII.30 for the full outline of R&D activities included under this product category

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32. CORE FUNDING OF A MULTI-DISEASE R&D ORGANISATION

*This category applies to organisations that disburse core funding or non-earmarked funding to an organisation that researches and develops products for multiple neglected diseases, and **where it is unknown how the funding has been allocated within the recipient organisation.***

Example:

- i. Core funding has been allocated to an organisation that researches tuberculosis, Buruli ulcer and leprosy, but the donor does not know how much has been allocated to each disease

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33. PLATFORM TECHNOLOGIES

33.1 ADJUVANTS AND IMMUNOMODULATORS

Adjuvants and immunomodulators are compounds or structures that aim to improve, modulate or potentiate the immune response. These include compounds such as CpG oligonucleotides, lipopolysaccharide derivatives, Toll-like receptor agonists, chemokines and cytokines.

This category has **strict restrictions**:

33.1.1 **ONLY** includes funding for R&D which meets the following conditions:

- a) It is conducted by public, philanthropic or not-for-profit entities
 - b) It is research that is not directed towards a specific disease or product
 - c) It is aimed at developing safer, cheaper, more immunogenic adjuvants and immunomodulators suitable for use in developing country products
 - d) The resulting research findings or leads **MUST** be accessible to organisations developing pharmaceutical or biological products for neglected diseases
- *If the adjuvant or immunomodulator is being developed as part of a specific product, this investment is included under the relevant disease and product category (e.g. adjuvant R&D as part of a malaria vaccine construct is included under malaria vaccines)*

Examples of R&D for adjuvants and immunomodulators **INCLUDED** in the survey scope:

- i. Understanding the innate or adaptive immune response, e.g. studies of Toll-like receptors for the purpose of adjuvant discovery
- ii. Strategies for targeting the cellular immune response to improve the quality of known adjuvants
- iii. Developing a systematic approach to adjuvant discovery (e.g. predictive *in vitro* assays)
- iv. High throughput screening to identify potential adjuvants

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33.2 DELIVERY TECHNOLOGIES AND DEVICES

Delivery technologies and devices comprise mucosal delivery tools, vaccine carrier systems, and alternative delivery technologies that facilitate the successful delivery of pharmaceutical or biological products in a resource-limited setting (e.g. dendritic cell systems, emulsions, novel viral vectors, sprays, patches and needle-free devices).

This category has **strict restrictions**:

33.2.1 **ONLY** includes funding for R&D which meets the following conditions:

- a) It is conducted by public, philanthropic or not-for-profit entities
- b) It is research that is not directed towards a specific disease or product
- c) It is research aimed at developing cheaper, faster, more user friendly delivery technologies and devices, intended for use in resource-limited settings.

Examples of R&D for delivery technologies and devices **INCLUDED** in the survey scope:

- i. Development of an intra-nasal vaccine delivery platform or the development of a plant-based sub-unit vaccine delivery system
- ii. Discovery and optimisation of mechanisms for controlled release

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33.3 GENERAL DIAGNOSTIC PLATFORMS

This category has **strict restrictions**:

- 33.3.1 ONLY includes funding for R&D which meets the following conditions:
- It is conducted by public, philanthropic or not-for-profit entities
 - It is research that is not directed towards a specific disease or product
 - It is research aimed at developing cheaper, faster, more user friendly diagnostic platforms or technologies, intended for use in resource-limited settings

Examples of R&D for general diagnostic platforms **INCLUDED** in the survey scope:

- Simplification of a diagnostic approach to reduce costs e.g. lateral flow tests for malaria
- Re-designing tests/ equipment to use cheap, standard reagents
- Work to make standard tests cheaper and simpler e.g. simpler ELISA assays; simpler Nucleic Acid Amplification tests; simpler DSTs

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34. UNSPECIFIED R&D

*The unspecified R&D category is for funding disbursed or received for research and development efforts that simultaneously focus on two or more neglected diseases, **and which therefore cannot be apportioned to the specific disease categories.***

Examples of unspecified R&D:

- Research into the interaction between HIV and tuberculosis
 - If research is part of the normal development path of a product for a specific disease (e.g. testing new TB drugs in special populations such as AIDS patients), it is included under the specific disease and product category where the product will be used (e.g. TB drugs)
- Development of a diagnostic to differentiate between different causes of fever (e.g. between malaria and meningitis)
- Development of a multi-disease diagnostic (e.g. the test can identify tuberculosis, malaria or sleeping sickness depending on the reagents used)
- Development of a multi-disease vaccine (e.g. a combination pneumonia/meningitis vaccine)

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IX. OUT OF SCOPE (EXCLUDED FROM THE SURVEY)

35. GENERAL EXCLUSIONS

The G-FINDER survey only captures investments that support pharmaceutical R&D where products aimed at preventing, treating or curing neglected diseases for patients in developing countries either do not already exist, or are inappropriate for developing country contexts.

*The following categories are therefore **EXCLUDED** from the survey:*

35.1 Non-pharmaceutical tools

- 35.1.1 Adult male circumcision, cervical barriers, HSV-2 prevention, untreated bed nets, traps, water sanitation tools

35.2 General supportive, nutritional and symptomatic therapies

- 35.2.1 Oral rehydration therapy
35.2.2 Micronutrient supplementation, vitamins
35.2.3 Anti-pyretics, painkillers

35.3 Products developed and used for veterinary purposes

35.4 In-kind contributions

- 35.4.1 In-kind R&D contributions are excluded from the survey due to the difficulty in quantifying their value; however a sample of these contributions is highlighted in G-

FINDER reporting. Typical in-kind contributions would include training of developing country scientists, sharing of expertise or access to compounds

35.5 Additional exclusions for private sector investment

- 35.5.1 Industry overhead costs, capital costs and opportunity costs are excluded, due to the difficulty of quantifying these and allocating them to the neglected disease investment. However, the published report will acknowledge the role of these in contributing to costs

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36. NON-PRODUCT R&D EXCLUSIONS

*The intention of the G-FINDER survey is to capture investments into **neglected disease product development** as accurately as possible.*

*The following R&D activities are therefore **EXCLUDED** from the survey:*

36.1 Clinical studies not linked to development of a NEW product

- 36.1.1 Protocol studies and clinical trials using established, available products (not linked to formal label-extension trials of new products)
- 36.1.2 Epidemiological surveillance and monitoring studies that are not directly linked to product development. For example, routine DSS (Demographic Surveillance System) activities

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36.2 Health services and access research

- 36.2.1 Any clinical study not linked to development of a product - disease management, studies of community attitudes, knowledge and practice in relation to neglected disease treatment and control programs
- 36.2.2 Health care service studies in relation to delivery of neglected disease treatment and control measures
- 36.2.3 Design of treatment and control programs appropriate to local prevailing conditions
- 36.2.4 Implementation and evaluation of large-scale neglected disease treatment and control programs operated through health care services, government ministries, non-governmental organizations (NGOs), etc.
- 36.2.5 Roll-out of proven vector control products (e.g. traps and nets, DDT)
- 36.2.6 Advocacy, community education and policy activities related to use, access, or roll-out of new products

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36.3 Operational programme assessment

- 36.3.1 Reviews on the status of neglected disease product development
- 36.3.2 Studies on the economic impact of neglected disease morbidity and mortality on communities
- 36.3.3 Studies on the economics of neglected disease prevention and control measures
- 36.3.4 Mathematical modelling of the disease (e.g. transmission, immune response)
- 36.3.5 Fostering collaboration between academia, industry, government agencies, and NGOs.

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36.4 General capacity building (human and infrastructure)

*Capacity building activities are excluded unless they are **DIRECTLY** linked to development of a new neglected disease product.*

*The following capacity building activities are therefore **EXCLUDED**:*

- 36.4.1 Building academic research capacity; improving existing academic capacity (except where directly linked to development of a specific product)
- 36.4.2 Providing training opportunities; strengthening R&D institutional capacity; developing and maintaining personnel (except where directly linked to development of a specific product).
- 36.4.3 Major infrastructure development (e.g. design, construction and validation of large-scale manufacturing facilities)

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37. SELECTED DISEASE AND PRODUCT RESTRICTIONS

*Diseases where commercial incentives for R&D already exist (including diseases prevalent in both high-income and developing countries, where product R&D already occurs in response to high-income country markets) are **EXCLUDED** from this survey.*

37.1 Basic research

RESTRICTIONS: Basic research is **RESTRICTED** for the following diseases:

37.1.1 HIV/AIDS

ONLY includes basic research that is related to preventive vaccines (e.g. immunological responses to potential antigens) and microbicides (e.g. mechanism of mucosal transmission), or basic research that is explicitly targeted at developing country needs.

37.1.2 Bacterial pneumonia & meningitis

ONLY includes basic research related to the natural history, epidemiology, biochemistry, and genetics of *S. pneumoniae* and/or *N. meningitidis* in developing country contexts (e.g. epidemiological research on serotype/serogroup distribution in developing countries; impact of age, HIV status, and malnutrition on disease prevention strategies; impact of the nasopharyngeal microbiome on disease transmission dynamics).

EXCLUSIONS: Basic research is **EXCLUDED** for diseases that have a commercial market, based on the assumption that investments into basic research are driven by commercial markets.

*Basic research is therefore **EXCLUDED** for the following diseases:*

- 37.1.3 Diarrhoea caused by Enteroaggregative *E.coli* (EAggEC), Enterotoxigenic *E.coli* (ETEC), giardiasis or rotavirus
- 37.1.4 Trachoma
- 37.1.5 Rheumatic fever
- 37.1.6 Cryptococcal meningitis
- 37.1.7 Hepatitis C (genotypes 4, 5 & 6)
- 37.1.8 Leptospirosis

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37.2 Drugs

RESTRICTIONS: R&D for drugs is **RESTRICTED** for the following diseases:

37.2.1 HIV/AIDS

ONLY includes developing country-specific costs for label-extension** clinical trials of new drugs and reformulations for developing country use (e.g. paediatric or slow-release formulations; fixed dose combinations; low dose drug formulations for prophylaxis; long-acting injectables for treatment or prophylaxis) or preclinical research targeted at developing such products

** Label-extensions refer to changes to drugs or their labels after they have been approved. This includes changes in manufacturing, recommended patient population and/or formulation. To change a label, market a new dosage or strength of a drug, or change the way a drug is manufactured, the Company must submit a supplemental new drug application (sNDA) to regulatory authorities to obtain marketing approval.

37.2.2 Diarrhoea caused by cholera, shigellosis, cryptosporidiosis, and multiple diarrhoeal diseases

ONLY includes pharmacological interventions that target the pathogen. Supportive therapies (e.g. zinc treatment, oral rehydration therapy, or other fluid and nutritional supplements) are **EXCLUDED**

37.2.3 Hepatitis C (genotypes 4, 5 & 6)

ONLY includes developing country specific research and/or research that has been designed specifically for genotypes 4, 5 or 6 (e.g. a clinical trial that includes developing country cohorts)

EXCLUSIONS: R&D for drugs is **EXCLUDED** for the following diseases:

37.2.4 Bacterial pneumonia & meningitis

37.2.5 Diarrhoea caused by Enteroaggregative *E.coli* (EAggEC), Enterotoxigenic *E.coli* (ETEC), giardiasis or rotavirus

37.2.6 Trachoma

37.2.7 Rheumatic fever

37.2.8 Leptospirosis

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37.3 Vaccines (preventive)

RESTRICTED R&D for preventive vaccines for the following diseases:

37.3.1 Bacterial pneumonia caused by *S. pneumoniae*

ONLY includes R&D on vaccines being developed specifically for developing country needs, or in support of registration of suitable vaccines in developing countries.

Such a vaccine must at a minimum:

- a) Be designed for use in infants less than two years of age;
- b) Provide broad coverage across all *S. pneumoniae* serotypes, or focused protection against strains prevalent in developing countries (at minimum serotypes 1, 5, and 14); and
- c) Involve low-cost whole cell, non-conjugate, or combination conjugate-non-conjugate technologies.

For multi-valent vaccines covering both high-income country and developing country strains, only developing country-specific costs are included; for example, for trials, registration, and Phase IV/pharmacovigilance studies in the target developing countries)

37.3.2 Bacterial meningitis caused by *N. meningitidis*

ONLY includes R&D on vaccines specifically for developing-country registration.

Such a vaccine must, at a minimum:

- a) Provide coverage against *N. meningitidis* serotype A;
- b) Be a conjugate vaccine;
- c) Be designed for use in infants less than two years of age; and
- d) Be designed to cost less than one US dollar per dose

For multi-valent vaccines covering high-income country and developing country strains, only developing country-specific costs are included; for example, for trials, registration and Phase IV/pharmacovigilance studies in the target developing countries

37.3.3 Diarrhoea caused by rotavirus

ONLY includes developing country-specific R&D, including clinical trials, registration and Phase IV/pharmacovigilance studies in the target developing countries

EXCLUSIONS: R&D for preventive vaccines is **EXCLUDED** for the following diseases:

37.3.4 Diarrhoea caused by giardiasis

- 37.3.5 Roundworm (ascariasis)
- 37.3.6 Whipworm
- 37.3.7 Tapeworm (taeniasis/cysticercosis)
- 37.3.8 Lymphatic filariasis (elephantiasis)
- 37.3.9 Leprosy
- 37.3.10 Dengue
- 37.3.11 Cryptococcal meningitis
- 37.3.12 Leptospirosis

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37.4 Diagnostics

R&D for diagnostics is **RESTRICTED** to the development of cheap, stable, easy-to-use diagnostics suited to resource-limited settings.

RESTRICTIONS: R&D for diagnostics is **RESTRICTED** for the following diseases:

37.4.1 Leptospirosis

ONLY includes R&D on diagnostics suited to resource-limited settings. Such a diagnostic must at a minimum:

- a) Detect the disease during the septicemic or early acute phase of disease;
- b) Be accurate, easy to interpret, with little or no processing and give the results within 1-2 hours; and
- c) Be cheap, stable, easy-to use (i.e. should not require specific equipment and/or laboratory and highly trained staff)

EXCLUSIONS: R&D for diagnostics is **EXCLUDED** for the following diseases:

- 37.4.2 Diarrhoea caused by rotavirus
- 37.4.3 Roundworm (ascariasis)
- 37.4.4 Hookworm
- 37.4.5 Whipworm
- 37.4.6 Rheumatic fever
- 37.4.7 Cryptococcal meningitis

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37.5 Microbicides

EXCLUSIONS: Some R&D for microbicides is **EXCLUDED**

- 37.5.1 Applications that may have high-income country markets or be useful for other STIs (e.g. mucosal delivery technology, adjuvants) are **EXCLUDED**

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37.6 Vaccines (therapeutic)

RESTRICTIONS: R&D for therapeutic vaccines is **RESTRICTED** for the following diseases:

37.6.1 HIV/AIDS

ONLY includes R&D on therapeutic vaccines (e.g. broadly neutralising antibodies (bNAbs) being developed specifically for developing country needs, or in support of registration of therapeutic HIV vaccines in developing countries

EXCLUSIONS: R&D for therapeutic vaccines is **EXCLUDED** for the following diseases:

- 37.6.2 Malaria (*Plasmodium falciparum*, *Plasmodium vivax*)
- 37.6.3 Bacterial pneumonia & meningitis (*S.pneumoniae* and *N.meningitidis*)
- 37.6.4 Diarrhoeal diseases (rotavirus, cholera, shigellosis, Enterotoxigenic *E.coli* (ETEC), cryptosporidiosis, Enteroaggregative *E.coli* (E.AggEC), giardiasis and multiple diarrhoeal diseases)

- 37.6.5 Sleeping sickness
- 37.6.6 Buruli ulcer
- 37.6.7 Dengue
- 37.6.8 Helminth infections (Schistosomiasis (bilharziasis), lymphatic filariasis, onchocerciasis (river blindness), hookworm (anclostomiasis and necatoriasis), tapeworm (taeniasis/cysticercosis), strongyloidiasis & other intestinal roundworms, whipworm (trichuriasis) and roundworm (ascariasis)).
- 37.6.9 Leprosy
- 37.6.10 Rheumatic fever
- 37.6.11 Trachoma
- 37.6.12 Salmonellosis
- 37.6.13 Cryptococcal meningitis
- 37.6.14 Hepatitis C (genotypes 4, 5 & 6)
- 37.6.15 Leptospirosis

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37.7 Vector control products

37.7.1 Chemical vector control products

This product category **ONLY** includes chemical active ingredients and formulations intended for global public health use and which specifically aim to inhibit, kill and/or repel indoor and outdoor vectors associated with neglected disease transmission. This includes new insecticides and formulations in LLINs/IRS; insecticide-based bait and traps; spatial repellents; and chemical larvicides. Predation measures, biological larvicides, habitat control and infrastructure measures are **EXCLUDED** from the G-FINDER scope

37.7.2 Biological vector control products

This product category **ONLY** includes research and development of innovative biological control interventions that specifically aim to kill or control vectors associated with transmitting poverty-related diseases (e.g. microbial/bacteriological larvicides, sterilisation techniques, and genetic modification measures).

Predation measures, habitat control and infrastructure measures are **EXCLUDED** from the G-FINDER scope

37.7.3 Reservoir targeted vaccines

This product category **ONLY** includes research and development of veterinary vaccines specifically designed to prevent animal to human transmission of neglected diseases.

Vaccines developed and used solely for veterinary purposes are **EXCLUDED** from this product category

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37.8 Can not be allocated to one disease

RESTRICTIONS: R&D that cannot be allocated to one disease is **RESTRICTED** for the following categories:

37.8.1 Adjuvants and immunomodulators

ONLY includes funding for R&D which meets the following conditions:

- a) It is conducted by **public, philanthropic or not-for-profit entities** (i.e. private sector investment into adjuvants and immunomodulators is **EXCLUDED**)
- b) It is research that is **not directed towards a specific disease or product**
- c) It is research aimed at developing safer, cheaper, more immunogenic adjuvants and immunomodulators.
- d) The resulting research findings or leads **must be accessible** to organisations developing pharmaceutical or biological products intended to treat or prevent neglected diseases

37.8.2 Delivery technologies and devices

ONLY includes funding for R&D which meets the following conditions:

- a) It is conducted by **public, philanthropic or not-for-profit entities** (i.e. private sector investment into delivery technologies and devices is **EXCLUDED**)
- b) It is research that is **not directed towards a specific disease or product**
- c) It is research aimed at developing cheaper, faster, more user friendly delivery technologies and devices, intended for use in resource-limited settings

37.8.3 General diagnostic platforms

ONLY includes funding for R&D which meets the following conditions:

- a) It is conducted by **public, philanthropic or not-for-profit entities** (i.e. private sector investment into adjuvants and immunomodulators is **EXCLUDED**).
- b) It is research that is **not directed towards a specific disease or product**
- c) It is research aimed at developing cheaper, faster, more user friendly diagnostic platforms or technologies, intended for use in resource-limited settings

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X. NEGLECTED DISEASE R&D MATRIX

		Basic research	Drugs	Vaccines (preventive)	Vaccines (therapeutic)	Diagnostics	Microbicides	Vector control products
HIV/AIDS		Restricted	Restricted	✓	Restricted	✓	✓	-
Malaria	<i>P. falciparum</i>	✓	✓	✓	-	✓	-	✓
	<i>P. vivax</i>	✓	✓	✓	-	✓	-	✓
	Multiple / other malaria strains	✓	✓	✓	-	✓	-	✓
Tuberculosis		✓	✓	✓	✓	✓	-	-
Diarrhoeal diseases	Rotavirus	-	-	Restricted	-	-	-	-
	Shigellosis	✓	Restricted	✓	-	✓	-	-
	Cholera	✓	Restricted	✓	-	✓	-	-
	Cryptosporidiosis	✓	Restricted	✓	-	✓	-	-
	Enterotoxigenic <i>E. coli</i> (ETEC)	-	-	✓	-	✓	-	-
	Enteraggregative <i>E. coli</i> (EAEC)	-	-	✓	-	✓	-	-
	Giardiasis	-	-	-	-	✓	-	-
	Multiple diarrhoeal diseases	✓	Restricted	✓	-	✓	-	-
Kinetoplastid diseases	Leishmaniasis	✓	✓	✓	✓	✓	-	-
	Sleeping sickness (HAT)	✓	✓	✓	-	✓	-	✓
	Chagas' disease	✓	✓	✓	✓	✓	-	✓
	Multiple kinetoplastid diseases	✓	✓	✓	✓	✓	-	✓
Helminth infections (worms & flukes)	Schistosomiasis (bilharziasis)	✓	✓	✓	-	✓	-	✓
	Lymphatic filariasis (elephantiasis)	✓	✓	-	-	✓	-	✓
	Onchocerciasis (river blindness)	✓	✓	✓	-	✓	-	✓
	Tapeworm (taeniasis / cysticercosis)	✓	✓	-	-	✓	-	✓
	Hookworm (ancylostomiasis & necatoriasis)	✓	✓	✓	-	-	-	-
	Strongyloidiasis & other intestinal roundworms	✓	✓	✓	-	✓	-	-
	Roundworm (ascariasis)	✓	✓	-	-	-	-	-
	Whipworm (trichuriasis)	✓	✓	-	-	-	-	-
Multiple helminth infections	✓	✓	✓	-	✓	-	✓	
Salmonella infections	Typhoid and paratyphoid fever (<i>S. Typhi</i> , <i>S. Paratyphi A</i>)	✓	✓	✓	-	✓	-	-
	Non-typhoidal <i>S. enterica</i> (NTS)	✓	✓	✓	-	✓	-	-
	Multiple <i>Salmonella</i> infections	✓	✓	✓	-	✓	-	-
Dengue		✓	✓	-	-	✓	-	✓
Bacterial pneumonia & meningitis	<i>S. pneumoniae</i>	Restricted	-	Restricted	-	✓	-	-
	<i>N. meningitidis</i>	Restricted	-	Restricted	-	✓	-	-
	Both <i>S. pneumoniae</i> and <i>N. meningitidis</i>	Restricted	-	-	-	✓	-	-
Hepatitis C (genotypes 4, 5 & 6)		-	Restricted	✓	-	✓	-	-
Leprosy		✓	✓	-	-	✓	-	-
Cryptococcal meningitis		-	✓	-	-	-	-	-
Leptospirosis		-	-	-	-	Restricted	-	-
Buruli ulcer		✓	✓	✓	-	✓	-	-
Trachoma		-	-	✓	-	✓	-	-
Rheumatic fever		-	-	✓	-	-	-	-

Other investment applicable to more than one neglected disease or both neglected and emerging infectious diseases				
Platform Technologies			Multi-disease vector control products	Core funding of a multi- disease R&D organisation
General diagnostic platforms	Adjuvants and immunomodulators	Delivery technologies and devices		
<u>Restricted</u>	<u>Restricted</u>	<u>Restricted</u>	✓	✓

✓ denotes a category where a disease or product is included in the survey

Restricted denotes a category where only some investments are eligible, as defined in the G-FINDER neglected disease R&D scope document