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Review of the Joint Global Health Trials funding scheme

Final Report

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Peter Varnai Maike Rentel Anoushka Davé

Kelly Simpson

Costanza Tiriduzzi

Emma Pottinger

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1 Executive summary

The Joint Global Health Trials funding scheme (JGHT) was established in 2009. It is a partnership of four funders, the UK Medical Research Council (MRC), the Department for International Development (DfID), Wellcome and the Department for Health and Social Care (DHSC). The overall aim of the JGHT is to support the best proposals to generate new knowledge about interventions that promise to contribute to the improvement of health in low- and middle-income countries (LMICs), addressing a major cause of mortality or morbidity.

The funders commissioned an external review to understand the impact of the JGHT scheme, its potential for future impact and to inform the design of future funding programmes. The review was carried out by Technopolis from October 2018 to October 2019, information by desk research, database analysis, and consultations through surveys and interviews with Principal Investigators (PIs), co-investigators, and global health experts and funders ('Key opinion leaders').

The evidence reviewed demonstrates that the JGHT is delivering on its core aim and has achieved tangible outcomes and impacts: JGHT-funded research has generated new knowledge about interventions which in turn are starting to contribute to improving health in LMICs.

Overview of the JGHT portfolio

The scheme includes two strands of funding through annual calls: *Full trial awards*, which support latestage and health intervention trials (Phase III/IV) to evaluate efficacy and effectiveness, and – starting from Call 5 – *Development awards*, which enable studies to carry out formative work preparing for a full trial.

In Calls 1-7, the JGHT scheme funded a portfolio of 63 full trial and 33 development awards (of which 28 and 22 had closed by June 2019, respectively), representing an investment of £138.8m. Research addressed a broad range of health issues, with strong emphasis on infectious diseases in the earlier calls, and an increase in mental health research from Call 5. Trial sites are located in 47 countries; 75% of trials include sites in Africa, 30% of trials have sites in Asia, and 8% in Central and South America.

The largest share of full trial awards (63%) were led by principal investigators (PIs) affiliated with institutions located in high-income countries (HICs), compared to 13% of awards led by researchers from LMIC institutions and 24% led by researchers at 'joint units' (programmes or institutes funded by organisations from HICs located in LMICs₁). Around one third of awards was led by female PIs.

The majority of PIs engaged with policy makers during the design and/or implementation of the project (87% of PIs of full trials and all development awards surveyed). 39% of PIs interviewed had engaged with community groups and advisory boards, community leaders, and individuals such as patients who shared their experiences. Several researchers highlighted the importance of joint units in this respect, as these have established engagement structures which researchers are able to draw on.

The JGHT is delivering against its policy and health objectives

Research funded by the JGHT has influenced policy and led to health outcomes.

Of the 28 closed full trial awards, 32% have resulted in policy influence, and a further 36% have a high potential for success, based on the trials' findings and the level of stakeholder engagement by the study team. Three of these trials provided important evidence by informing decisions to *not* change a policy or implement an intervention. In addition, three active full trials have already influenced policy. Policy outcomes included direct influence on the World Health Organisation (WHO) guidelines; addition of

¹ Joint units include: KEMRI Wellcome Trust Research Programme, Kenya; Mahidol Oxford Research Unit, Thailand; Malawi-Liverpool-Wellcome Trust Clinical Research Programme, Malawi; Mwanza Interventions Trials Unit, Tanzania; MRC Unit The Gambia; MRC/UVRI Uganda Research Unit, Uganda; Oxford University Clinical Research Unit, Vietnam.

products to the WHO Essential Medicines list; influence on WHO policies in other ways, e.g. lending confidence to a guideline under scrutiny, uptake into a best practice strategy paper; influence on national policies; and influence on strategy of international donors and shifting funding priorities.

Nine full trials and one development award likely led to the implementation of a health intervention. Four interventions were recommended by WHO guidelines, at least two of which have been purchased by governments via the Global Fund. Four further interventions have been, or are starting to be, implemented by national governments as part of public health programmes. One intervention is being implemented by an NGO with support from the national government.

In addition, the implementation of JGHT-funded research itself has led to direct and indirect benefits, e.g. through improved standard of care and access to care, education and awareness, for study participants and the wider community. For example, two trials alone have led to direct health benefits for around 450,000 trial participants.

Four key enablers of policy and health outcomes arising from JGHT-funded research were identified:

- 1. The topic of the trial is timely and under debate in the policy arena, and hence key policy makers have strong interest in the research evidence.
- 2. The trial addresses a neglected health issue, and little research evidence was available before the trial. The trial thus substantially increased the level of robust evidence on which to base policy decisions.
- 3. Collaboration with policy makers and key stakeholders in the health system during research planning and implementation, e.g. by embedding the trial within local health programmes.
- 4. Active engagement with policy makers to inform and influence relevant policies. This is facilitated by researchers holding advisory functions, e.g. as members of guideline committees, or key policy makers holding advisory functions related to the research, e.g. as members of the trial steering committee.

The JGHT is funding high-quality research, leveraging additional funding, building capacity, and fostering collaboration

The majority of the 28 closed full trial awards have either published the main trial findings₂ (20), submitted them for review (3), or are in the final analysis stage, indicating a high trial completion rate of 89%. 60% of JGHT awards reported on ResearchFish® that they had received substantial additional funding (co-funding and follow-on funding), capturing around £160m in total. Most of this funding was provided by Wellcome, EDCTP, NIHR, BMGF and US NIH₃ (in order).

Of 22 closed development awards funded so far, at least 23% have led to full trials - one funded by the JGHT, and four by other funders, including DfID, US NIH and EDCTP.

JGHT-funded research has built capacity, in HICs and LMICs, and fostered collaboration. 82% of coinvestigators from full trial and development awards (140 of 170) felt that the JGHT-funded project had positively impacted their scientific knowledge, and 50% indicated their knowledge of local health needs had improved. Publications of main findings of full trial awards named investigators affiliated with 106 distinct institutes; over half of these institutions were located in LMICs (57), indicating a high level of involvement in the delivery of the trials. The lead authors of a quarter of publications (27%) were based at LMIC institutions, comparable to the shares of lead authors affiliated with joint units (31%), and institutions in HICs (27%). JGHT awards have also led to new collaborations (e.g. as reported by 50% of co-investigators) and allowed researchers to start participating in collaborative networks (30%).

² i.e. relating to the primary outcome of the trial

³ European & Developing Countries Clinical Trials Partnership; National Institute for Health Research; Bill and Melinda Gates Foundation; US National Institutes of Health

The design and promotion of the JGHT are appropriate

Researchers and key opinion leaders were predominantly positive regarding the design and promotion of the JGHT, and no major issues emerged in the consultation. A range of additional activities were highlighted by PIs and co-investigators which the JGHT could support to help it achieve its aims. These included funding for training and other types of research such as implementation and laboratory studies; dissemination and knowledge exchange. Key opinion leaders highlighted the potential for additional support for applicants from LMICs. While researchers appreciated the 'light-touch' monitoring arrangements, many researchers felt that reporting beyond ResearchFish® should be put in place to improve tracking of outcomes and impacts.

Of PIs who described a weakness, 29% considered the amount of funding available insufficient, both in terms of the size of awards and the lack of funding for additional aspects such as dissemination, capacity building or student fellowships (e.g. as provided by the EDCTP and US NIH). Despite the fact that the JGHT calls for proposals do not state a budget or time limit, comments by several researchers indicated that the JGHT is perceived to provide funding of about £2-3m for a duration of 3 years.

The partnership of JGHT funders provides added value

The partnership of JGHT funders is working well. It has resulted in a variety of benefits to both funders and researchers, such as the ability to pool budgets and de-risk investment, closer cooperation and sharing of expertise between funders, and a de-fragmentation of the funding landscape. The partnership is considered to have helped maintain the UK's international leadership in producing high quality research of relevance to LMICs. However, international funders consulted were not aware of the scheme.

The JGHT represents value for money (VfM) in a variety of ways, thereby maximising the impact of the investment

The JGHT represents value for money (VfM) in a variety of ways, maximising the impact of the investment by its funders. The scheme is acknowledged to fill a gap in the global research landscape and delivers research with strong relevance to health issues of disadvantaged populations in LMICs. This is achieved through a partnership of funders, leading to sharing of expertise and risk and to efficiency gains. Its flexible scheme management approach has enabled trials to complete and thus avoid 'research waste', leading to 89% of closed awards completing trials and publishing their main results. The value generated by the JGHT includes scientific knowledge and capacity, which has contributed to further scientific work and strengthened the wider research ecosystem. In addition, financial benefits have already been achieved or are anticipated based on current award monitoring data:

- Research cost savings achieved from development awards de-risking full trials
- Additional research funding leveraged on the basis of the JGHT award
- Anticipated cost savings for LMIC health systems and improved health outcomes, partly due to increased education and awareness of health issues
- Direct employment effects of researchers, trial staff and supply chains for the UK and LMIC

Recommendations to increase the value gained from JGHT-funded research

The review concluded that the JGHT is delivering on its core aim and has achieved tangible outcomes and impacts. Underpinned by the evidence gathered, five recommendations to further increase the value gained from the JGHT-funded research have been developed:

- 1. Keep the overall design of the JGHT, but clearly communicate the scheme's award parameters to potential applicants, and re-focus researchers on applying for appropriately sized budgets to answer the research question (rather than fitting to the perceived funding envelope).
- 2. Provide additional support for stakeholder engagement, both pre- and post-award, to avoid challenges during trial implementation and enable pull-through of research findings into policy and practice. This could include small grants for 'partnership workshops' and/or an expansion of the

development award scheme, as well as additional funding to cover engagement activities after the award has closed. Funders should explore options for how to maximise opportunities for dissemination and engagement for findings with high potential for policy influence and health impact. This could involve taking an active role in these efforts, e.g. by targeting media and convening meetings, or providing support for a team of specialists for this function.

- **3**. Increase support for LMIC researchers, including resources to assist with proposals, providing detailed feedback to unsuccessful LMIC applicants, promotion of JGHT calls in LMICs, and 'match-making' activities to facilitate access to expertise and infrastructure.
- **4**. Agree on key criteria for project selection among JGHT funders, defining how to balance between the size of the health need addressed, the risk of interventions tested not proving effective, and the likelihood that a trial leads to policy influence and health outcomes.
- 5. Launch additional project monitoring, enabling better tracking of progress and outcomes and identify options to support dissemination of findings and engagement with policy makers.

2 Introduction

2.1 Context and the case for intervention

2.1.1 Global health trends and impact on economic growth

A recent analysis of global mortality rates concluded that between 1950 and 2017, life expectancy increased from approx. 48 years to 71 years for men and from 53 years to 76 years for women (Dicker et al. 2018). Despite this overall progress, there remains substantial variation in life expectancy at birth in 2017, with a gap of nearly 40 years between men in the Central African Republic (at 49.1 years) and women in Singapore (at 87.6 years). And while the greatest progress across age groups was for children younger than 5 years, with mortality of under-5s dropping from 216 deaths per 1000 livebirths in 1950 to 39 deaths per 1000 livebirths in 2017, an estimated 5.4 million children younger than 5 years died in the world in 2017. In addition, progress in life expectancy has been less pronounced and more variable for adults. Much progress has also been made reducing the impact of poverty-related neglected disease. These included a 40% reduction in new HIV infections, 37% reduction in the malaria incidence rate, and a 41% reduction in TB prevalence rates over the 2000-2015 period₄.

Health also underpins economic growth. A lack of effective health systems, including effective, affordable and accessible treatments and products, can affect the ability of individuals, communities and societies to achieve growth and develop. A recent study confirmed previous analyses that population health has positive and significant effect on both real income per capita as well as its growth₅. Around 11% of economic growth in low- and middle-income countries (LMICs) from 1970-2000, as measured in their national income accounts, was due to reduction in mortality₆. Enhanced investments to scale up interventions and health technologies is expected to lead to a fall in infectious, child, and maternal mortality rates in LMICs, matching those presently seen in the best-performing middle income countries. Relative to a scenario of stagnant investments and no improvements in technologies, this would prevent around 10 million deaths in 2035. In addition to new technologies, there is a need to (re-)assess the safety, efficacy, and efficiency of existing interventions, as many treatments, drugs, vaccines and diagnostics do not work as anticipated.

Despite progress, further efforts are still sorely needed. Children born into poverty are almost twice as likely to die before the age of five as those from wealthier families₇. The proportion of mothers that do not survive childbirth compared to those who do in developing regions is still 14 times higher than in the developed regions, and only half of women in developing regions receive the recommended amount of health care they need. At the UN Summit in September 2015, the Sustainable Development Goals (SDGs) were formally adopted, including goal 3, to: 'ensure healthy lives and promote well-being for all at all ages'. Some of the stated targets are, by 2030, tos:

- reduce the global maternal mortality ratio to less than 70 per 100,000 live births
- end preventable deaths of newborns and children under 5 years of age, with all countries aiming to reduce neonatal mortality to at least as low as 12 per 1,000 live births and under-5 mortality to at least as low as 25 per 1,000 live births
- end the epidemics of AIDS, tuberculosis, malaria and neglected tropical diseases and combat hepatitis, water-borne diseases and other communicable diseases
- reduce by one third premature mortality from non-communicable diseases through prevention and treatment and promote mental health and well-being
- strengthen the prevention and treatment of substance abuse, including narcotic drug abuse and harmful use of alcohol
- halve the number of global deaths and injuries from road traffic accidents (by 2020)

6 Jamison DT & Summers LH (2013) Global health 2035: a world converging within a generation. The Lancet 382:1898–1955.

⁴ https://www.mdgmonitor.org Accessed 15 Oct 2019

⁵ Sharma R (2018) Health and economic growth: Evidence from dynamic panel data of 143 years. PLoS ONE 13(10): e0204940

⁷ https://www.un.org/sustainabledevelopment/health/ Accessed 15 Oct 2019

⁸ https://www.un.org/sustainabledevelopment/health/ Accessed 15 Oct 2019

• support the research and development of vaccines and medicines for the communicable and noncommunicable diseases that primarily affect developing countries

There is a large unmet need for effective, affordable and safe treatments to achieve these goals. If progress against health-related SDG targets were to continue at the same rate as for the 1990-2017 period, most countries are projected to have a higher health-related SDG index in 2030 than in 2017 (a measure of progress against 41 of 52 health-related SDG indicators)₉. However, country-level probabilities of attainment by 2030 vary widely by indicator: Goals related to under-5 mortality, neonatal mortality, maternal mortality ratio, and malaria indicators are projected to be achieved by a high proportion of countries (with at least 95% probability of target attainment). For other indicators, including mortality from non-communicable disease and suicide mortality, no countries are projected to meet the corresponding SDG targets if progress continues at the current pace. For some indicators, including child malnutrition, several infectious diseases, and most violence measures, the annualised rates of change required to meet SDG targets far exceeded the pace of progress achieved by any country in the recent past.

2.1.2 Trials to address health needs in LMICs

Many unanswered questions remain about the efficacy₁₀, effectiveness₁₁, safety and cost-effectiveness of new as well as some existing interventions. Randomised controlled trials (RCTs) are the gold standard method of assessing health interventions, producing clear and numerical measures of their benefits - or the lack thereof. Almost all new advances in health have to be tested employing a rigorous trials methodology and within the required ethical, legal and regulatory frameworks. Trials are hence a core component of later stage development of health innovations and an essential step before implementation of a change in practice, or commercialisation of a new technology, providing definitive answers to the trial question. They can also lead to cost savings when providing evidence that an intervention does not work, and answer questions of cost-effectiveness by demonstrating that cheaper alternatives are equivalent to more expensive interventions (most cost-effectiveness and cost-benefit analyses in healthcare rely on trial data₁₂).

Under-representation in global health trial platforms continues to contribute to sustained health inequity in LMICs, despite the fact that the shortage of funds in developing countries increases the need for reliable healthcare evidence to prioritise the use of their scarce resources. Diseases of relevance to high-income countries are investigated in trials seven to eight times more often than diseases whose burden lies mainly in LMICs₁₃. In addition, researchers in developing countries face a number of barriers (on top of those their developed country counterparts encounter). A recent literature review on barriers facing clinical researchers in LMICs for conducting trials identified the following factors₁₄:

- lack of financial and human capacity (both, lack of skilled personnel and lack of awareness and of motivation to participate)
- ethical and regulatory system obstacles, especially long delays in the review process
- lack of suitable research infrastructure, research materials for conducting trials, and/or a conducive scientific atmosphere (including policy)
- operational barriers, such as an administrative environment characterised by lengthy and complex logistic and financial systems that hamper the conduct of trials
- competing demands on research staff

 $_9$ GBD 2017 SDG Collaborators (2018) Measuring progress from 1990 to 2017 and projecting attainment to 2030 of the health-related Sustainable Development Goals for 195 countries and territories: a systematic analysis for the Global Burden of Disease Study 2017. The Lancet 392:2091–138

¹⁰ Performance of an intervention under ideal and controlled circumstances. Efficacy trials can overestimate an intervention's effect when implemented in clinical practice.

¹¹ Performance of an intervention under 'real-world' conditions, accounting for external patient-, provider-, and system-level factors that may moderate an intervention's effect.

¹² Department for International Development (2013) Joint Global Health Trials Scheme - Business Case

¹³ Røttingen, JA et al (2013) Mapping of available health research and development data: what's there, what's missing, and what role is there for a global observatory? 382(9900):1286-307

¹⁴ Alemahehu, C et al (2018) Barriers for conducting clinical trials in developing countries- a systematic review. International Journal for Equity in Health 17:37

As trials generally carry a high cost (especially in Phases III and IV), the private sector, as the key actor in product development, has limited incentives to invest given that innovations may be neither patentable nor commercially exploitable. Much of the research in this field has therefore been supported by the public sector and philanthropic sector, through universities and other research institutions, and public-private partnerships. (A more detailed description of other funders and programmes operating in the JGHT's research funding environment is provided in section 6.1).

2.1.3 Impact on health – requirements for implementation and scale-up

For interventions to have an impact on health, they must be implemented and become readily available to the target population, e.g. through the health service. Here, context plays an important role, as this requires that:

- the intervention is *efficacious* in the local target population, if different from trial population. Other context-dependent factors include the ability to manufacture and/or transport the intervention under local conditions; local capacity to diagnose the underlying indication; and the availability of any infrastructure/equipment/staff required to deliver the intervention.
- the intervention is *affordable* to the health system or the individual who needs it
- the intervention is *adopted into policy*, e.g. by inclusion in national and international clinical guidelines (recommending which intervention healthcare professionals should employ for specific indications). It thus needs to be visible to and a focus for national policy makers.
- the intervention is *taken up into practice*, e.g. by health professionals. Such users thus need to be aware of the intervention, trained in its application, and willing to take it up, e.g. recommend a treatment to their patients.
- *patients/end users accept, and adhere to, the intervention.* Some interventions may come up against social or cultural barriers, either directly on the part of the end user, or the wider community/family (e.g. reproductive health; competing local traditional treatments; lack of patient education). End users also need to be able to access the intervention (which may depend on frequency of administration and distance to treatment site). Other factors affecting adherence include potential side effects of the intervention and the length of treatment course.

To ensure that the trialled interventions have the potential to deliver benefits to end users, these factors need to be taken into account during the planning and implementation of the trial.

Achieving maximum impact requires scale-up of policy influence, implementation and adoption of health interventions, i.e. through the process of expanding their coverage and geographical reach, thus benefitting more people. While some trials may address specific local health needs, most interventions are likely to be suitable for transfer to other locations, potentially with some adaptation to other contexts. This process can be accelerated by conducting multi-site trials, testing the intervention in multiple locations and various contexts (as well as engagement with relevant policy makers in other geographies); however, these trials not only need a larger budget, they also require researchers to navigate multiple administrative, ethical and legal frameworks.

The final level of health benefits will be dependent on a number of factors, including the following:

- The relative prevalence of the problem, disease or condition targeted by the intervention
- The impact of the problem, disease or condition on quantity/quality of life
- The size of the affected population for which the intervention is suitable, acceptable, and accessible
- The effectiveness of the new intervention compared to existing practice

2.2 The Joint Global Health Trials Initiative (JGHT)

2.2.1 History and stated aims of the scheme

The Joint Global Health Trials Initiative (JGHT) was established in 2009, with co-funding from the UK Medical Research Council (MRC), the Department for International Development (DfID), and the Wellcome Trust. Following the launch of the UK's aid strategy in 2015, which changed the distribution of ODA funding across departments, the Department of Health and Social Care (DHSC) established its global health portfolio in 2016. As part of this effort, the DHSC/National Institute for Health Research (NIHR) joined as a funder of the scheme, with effect from financial year 2016/17.

The partnership was preceded by various joint bilateral relationships between the MRC, Wellcome Trust and DfID. At the time, the global health trials landscape was described as a 'patchwork' of opportunities; investigators applied to multiple programmes in order to obtain funding for their proposed trials. The JGHT combined the various funding strands, and brought the review process under a single committee. In addition, this pooling of resources allowed the funders to support larger or more expensive trials, while reducing the risk for individual funders (making it possible to support some trials in new areas / with novel approaches). Joint working has since led to deepening of the funders' partnership and a better understanding of remaining gaps; e.g. in 2011, the funders of the JGHT at the time (MRC, Wellcome Trust, DfID) and the ESRC came together to address an identified funding gap and develop a 'sister scheme' addressing health systems research (the Joint Health System Research Initiative, JHSRI).

The overall aim of the scheme is to support the best proposals to generate new knowledge about interventions that promise to contribute to the improvement of health in LMICs, addressing a major cause of mortality or morbidity. As one funder representative put it: "The aim is to provide clear, definitive evidence if an intervention works or not, and what the next steps should be. [...] The ultimate goal is a trial which leads to policy or practice changes." The scheme hence gives priority to proposals that are likely to produce implementable results and that are designed to address the major causes of mortality or morbidity in LMICs; it is hence focused on late-stage and health intervention trials (Phase III /IV) evaluating efficacy and effectiveness, with the potential for impact over a 5-10 year timeframe. The review process takes into account whether the intervention has the potential to be sustainable and scalable (even if the proposal relates to a single country trial), and whether it shows engagement of local stakeholders, such as local policy makers. The JGHT also considers earlier phase trials of major relevance to the objectives of the call.

Studies funded through the JGHT have to be based in LMICs, with the principal investigator (PI) employed either by a research institution in the UK or in a LMIC; co-investigators can be located in any country. In the specifications for Call 8, the funders highlight that applications can focus on either a single or multi-country assessment as long as research takes place in LMICs. Trials are led by academic groups, but can include collaborations with commercial companies.

The scope of the scheme is broad and includes behavioural interventions, complex interventions, disease management, drugs, vaccines and hygiene and diagnostic strategies. From Call 4, the funders encouraged (but did not require) applications addressing chronic non-communicable diseases and reproductive, maternal and newborn health; from Call 7, mental health was added to this list.

While the scheme is aimed at funding trials, other types of methodologies, such as economic evaluations and social science research, are encouraged alongside the trial to explore implementation and operational issues and to pave the way to implementation and impact. From the outset (i.e. in Call 1), health economics was highlighted as an area to consider in the project design; the Call 3 specifications note that social science and implementation research could be conducted alongside trials (with the aim of providing information relevant for scale up). From Call 7, call specifications encourage applications trial designs other than Randomised Controlled Trials (RCTs), i.e. innovative trial methodologies and adaptive designs that are more complex and can carry a higher risk. The specifications for Call 8 give a stronger steer and set out that applications have to show engagement with the potential users of research (e.g. policy makers) throughout the research process in order to ensure trial results are implementable, scalable and in line with policy needs. Call 8 also emphasises that the funders have an interest in funding complex interventions delivered in community settings, including primary health care.

From 2010, the scheme published annual calls, with up to £20m per year available. In Calls 3 and 4, a number of applications for full trials were considered of high quality and promising, but in need of additional preparatory work. These were awarded smaller 'development grants', enabling the

researchers to test the feasibility of interventions and trial design that could ultimately lead to the design of credible, appropriately powered, competitive, full trials. From Call 5, the Development Award programme was fully established as a separate funding track, with generally up to £150,000 available per award. Development awards are aimed at studies to₁₅:

- Generate specific data that is needed to inform the trial design, such as to determine the sample size, outcome measures, recruitment strategy, follow-up strategy, appropriate monitoring activities and timings
- Work to understand the likelihood of contamination within the trial e.g. in a cluster randomised trial, and how that contamination might be handled.
- Work to inform design of the trial intervention, for instance feasibility and acceptability issues in a public health intervention

The JGHT was described in an overarching programme model, encompassing the theory of change of the intervention (points 7; 9-12; 14-15), the process elements which allow the programme to be delivered (points 1-3; 5-6; 8; 13), and external factors that may affect the intervention (point 4; other factors) (Figure 1).



Source: Provided by JGHT funders

2.2.2 Outline of investment to date

The funders committed up to £120m for the first six (annual) calls (2011-2016, with funded projects expected to conclude by 2020/21).

The original agreement between the funders¹⁶ set out that DFID will contribute up to £48m (40%), and each of the other three funders will contribute up to £24m (20% each). In 2017, the four funders signed a new MoU, making available up to £100m in funding for the five-year period from 2016-2020 (Calls 7 – 11, up to £20m per call). The expenditure is to be split evenly between funders, each providing up to £25m. Some of the committed funding can be used to hire two full time support staff, on MRC contracts, to work across both the JGHT and the Joint Health Systems Initiative.

By 2018, seven calls had been completed, and 96 awards were made: 63 full trial awards and 33 development awards.

2.2.3 Scheme management

The funders have taken on different roles to manage the JGHT.

- The MRC is the lead administrative partner, responsible for putting out the calls for proposals, handling preliminary and full applications, arranging external referee reports and providing oversight for studies post-award. Once the proposals have been selected, the MRC administer and account for contributions and manage the grants.
- The Wellcome Trust leads on the administrative arrangements relating to the Joint Funders Review Committee meetings, supports referee selection, and convenes the review panel (which shortlists outlines for invitation to submit full proposals, and selects full applications for funding). The Wellcome Trust, alongside other funders, also provides expertise and due diligence on issues relating to commercial or product development partners, clinical trials sponsorship, insurance and indemnity, intellectual property rights and on regulatory issues.
- DfID and DHSC provide strategic oversight and financial resources.

In addition, all full trials are monitored by a trial steering committee, a data monitoring committee, and an ethics committee, to supervise the trials and ensure they are carried out to the appropriate standards₁₇. The outputs and outcomes of JGHT-funded studies are currently monitored through investigators' submissions to ResearchFish_® (required annually for five years after awards completion).

2.2.4 The review process

The review committee meets twice per year, once to review proposal outlines for full awards and development award proposals, and a second time to review the full proposals for the full trial awards. For Call 8, the committee comprised 19 experts in global health and trials.

- The application process for full trial awards is a two-stage process. After review of the outline applications by the review committee, a selection of applicants is invited to submit full proposals. The full trial proposals are sent for external peer review. Full comments are shared with applicants invited to submit full proposals, so these can be adjusted before re-submission to the review committee. Some generic guidance is also shared with applicants that do not pass the outline stage, e.g. on problems that were commonly encountered in unsuccessful proposals.
- The application process for the development award scheme is a single stage process. The application is shortened compared to the full trial form, and there is no external peer review.

The JGHT funding committee panel reviews applications and assigns scores according to pre-set criteria (e.g. see Table 1, Call 8 for full trial awards). For full trial awards, decisions are informed by the external review, but are not bound by the recommendations.

¹⁶ MoU Amendment letter, February 2018

¹⁷ The Medical Research Council (MRC) Guidelines for Good Clinical Practice (1998) define a three-committee oversight structure: the Trial Management Group (TMG), the Data Monitoring Committee (DMC) and the executive Trial Steering Committee. The TMG is responsible for the day-to-day delivery and conduct of the trial; the DMC role is to review safety and efficacy data and make recommendations to an executive group; and the TSC is the executive decision-making group that considers the recommendations from the DMC.

After review of the applications, the funding committee may request additional information or changes to proposals before making a final decision, with the primary focus on funding the best science (e.g. rather than capacity building) and on addressing health needs of LMICs (both, global and local unmet needs). Unsuccessful applicants are provided with more general feedback on proposals, providing the opportunity to improve the project design for future funding applications.

Scoring criteria	Description
Track record of applicant	Experience of conducting trials to a high standard in the proposed setting, Publication record of outputs from trials, Evidence of uptake of findings; changes in policy and practice, Balance of expertise to undertake the trial (e.g. are clinical, methodological, social, health systems, economics, cultural issues covered), Links with local research/health institutions and involvement of investigators from low and middle income countries
Importance of the question/need for the trial	Is there a need for such a trial now for this condition or group of patients in the proposed location(s), How important is the problem being addressed? Novelty and innovation: Have similar trials been done previously or are any underway now?
Study design and feasibility	Is the design of the study appropriate to answer the question? Are the methods and study designs competitive with the best in the field?, Is the recruitment strategy appropriate and feasible? , Is the timeline realistic and achievable?, Are there any ethical concerns?, Have major scientific, technical or organisational challenges been identified, and will they be tackled well?
Impact	How important an advance would this be? Will the findings be generalizable? What is the likelihood that the findings will be taken up and implemented? Can the intervention be scaled up; is it cost effective? Is it likely to lead to significant improvements in health?
Financial Aspects	Does the study represent value for money, are the costs realistic and reasonable, do the majority of funds requested support the costs in the low- or middle-income country where the trial will be conducted, are there any financial dependencies e.g. co-funding arrangements

Table 1 Points to consider by JGHT funding committee (full trial proposals)

2.3 Objectives for the JGHT evaluation

The funders of the JGHT commissioned an external review to understand the impact of the JGHT programme (retrospective) and its potential for future impact (prospective), and to inform the design of future funding schemes. The study was to gather evidence relating to awards made in Calls 1-7 of the JGHT. It was carried out by Technopolis between October 2018 and October 2019.

The four main objectives for the review were:

- 1) to assess whether and how the JGHT scheme has delivered on its core aim i.e. the generation of new knowledge about an intervention and its contributions to improving health in LMICs
- 2) whether tangible outcomes and impacts have been achieved from the funded research
- 3) to identify ways in which the value gained from this type of research/research programme can be increased
- 4) to provide guidance on future monitoring of the scheme.

The specification for the JGHT review sets out a range of evaluation research questions to be addressed, falling into six categories:

- 1) Scientific outcomes of the JGHT
- 2) Impacts of the JGHT
- 3) Value for Money (VfM)
- 4) Location of the JGHT in the wider global health funding landscape
- 5) Research funding through the JGHT
- 6) JGHT management and evaluation

In the scoping phase of the review, the funders of the JGHT emphasised that the main objective was to determine the outcomes and impacts achieved by JGHT-funded activities; review activities were focussed accordingly.

3 Evaluation methodology

The evaluation employed a mix-methods approach, involving multiple strands of data collection and analysis which cut across the study's evaluation questions.

• Scoping exercise

The evaluation started out with a scoping exercise, to allow orientation in relation to the key strategies and parameters of the JGHT, and development of an impact logic model and evaluation framework (evaluation questions set against indicators). This phase consisted of an initial meeting between Technopolis and the JGHT funders, a review of documentation available relating to the JGHT, and scoping interviews with the JGHT funders (7 interviews in total). (A further interview with one of the funding organisations was conducted as part of the key opinion leader programme of interviews.)

• Document review and desk research

Portfolio analysis: Information for the portfolio analysis was provided by the funders, including data on both funded and rejected proposals (latter anonymised). Data on funded projects was completed with additional information, such as assigning country, continent, and LMIC status for each research organisation that applied to the JGHT, the indication the award addressed and the target group for each award, the trial methodology employed, and the type of research question addressed. For full trials, the relevant trial registry number was gathered. An extended portfolio analysis is available in Appendix B.

Funding landscape review: A review of the funding landscape was conducted. This involved identification of relevant websites and reports in targeted online searches of funders and relevant programmes, including those mentioned in scoping interviews and detailed on G-FINDER. Emphasis was placed on gathering and analysing evaluation reports and evaluation frameworks and indicators to inform the development of an impact evaluation framework for the JGHT review. Extended information is available in Appendix G.

• Database analysis

Analysis of ResearchFish® *data*: 84 of the 96 awards had submitted entries to ResearchFish® in 2019, leaving 12 awards that have not done so (11 full trial awards, one development award). Of the latter, eight are Call 7 awards, and started in 2018. The data was analysed for the following categories: Publications, Further funding, Skills, Dissemination, Policy, Tools, Databases, Software, Artistic products, IP and Products. Where necessary, duplicate entries and outliers were excluded from the analysis. An extended analysis is available in Appendix C.

Bibliometric analyses: Data for publications of main findings (i.e. on the primary outcome of the trial) for 22 full trials were extracted from the Scopus database to a) determine the number of citations and b) identify the institutes authors and co-authors are affiliated with.

Analysis of clinical trials databases: Clinical trial registration entries were extracted from the World Health Organisation (WHO) ICTRP registry. This database was chosen as it collates entries from several trial registries including clinicaltrials.gov, ISRCTN, EU clinical trials register, Pan-African, and many other national registries. Searches were carried out for trials registered between 1 January 2005 and 31 December 2018 and for specific indications (in the 'title' and 'condition' fields). Data for all search hits was extracted and duplicates removed. Early-stage (Phase 0 to II) trials and studies other than interventional studies were excluded from the analysis. A full analysis is available in Appendix D.

• Primary data collection: Surveys and interviews

Survey of all PIs and co-investigators: Three surveys were developed to gather information from: 1) PIs of open full trial awards; 2) PIs of development awards; and 3) Co-investigators of all awards. The surveys were implemented using an online survey tool, SurveyMonkey. Full questionnaires are available in Appendix A.

The survey was sent to contacts contained within the JGHT grants database (24 PIs of open full awards; 27 PIs of development awards; 556 co-investigators). E-mail addresses where the survey invitation was returned as 'undeliverable' were updated through online searches. The survey remained open for 30 days, with non-respondents receiving 2 reminders.

Programme of interviews: Two interview programmes were conducted, aimed at 1) all PIs of completed full trial awards and 2) other key stakeholders.

- Interviews of PIs of completed full trial awards: The objective of this interview programme was to gather information for the impact and process evaluations; for the case studies; and to inform the wider global health landscape review. PIs of completed full trial awards were approached (28 projects). As one researcher was PI of two trials, a total of 27 individuals were contacted. In addition, six PIs of open full trials were contacted, and interviews conducted; five of these had been selected to gather additional in-depth insights from researchers located at institutions in LMICs. Similarly, three PIs of JGHT development awards based in LMICs were contacted. Of the total of 36 individuals contacted, 29 were consulted (23 closed full trial PIs, 6 open full trial PIs, 1 closed development award PI), including three PIs who provided information in writing rather than by interview.
- Interviews of key opinion leaders: The objective of this interview programme was to gather perceptions of the JGHT and its impact, and views of the design and implementation of the JGHT funding scheme; to validate case study findings and provide further context; and to inform recommendations for enhancing the JGHT's potential for impact. A total of 19 key opinion leaders were interviewed, including international funders (6), review committee members (5), and researchers in leading positions such as Heads of joint units (7).
- Impact case study development

JGHT-funded projects that had led to impact on policy, practice, and further research were identified from the information gathered in interviews and the survey, and selected for impact case studies. 16 of these were developed through extensive desk research. PIs were consulted directly and given the opportunity to verify the accuracy of the final case study in all cases but one (the Devries case study is based on desk research only). Case study summaries are presented in this report, with the full case studies available in a separate document.

• Analysis and recommendations

Evidence gathered from multiple sources and perspectives, was used to triangulate and verify findings, and to formulate recommendations.

4 The JGHT Funding Scheme Evaluation Framework

4.1 Impact logic model

A logic model provides a structured approach to look at a programme or intervention. It is based on the idea that there is a linked chain of logic that shows how the inputs to an intervention (e.g. funders' budget, programme management) and the resulting activities (e.g. research projects, stakeholder engagement) are expected to produce immediate outputs (e.g. new evidence, skills and collaborations). These in turn are connected to medium-term outcomes (e.g. change in local practices) and longer-term outcomes (e.g. change in practices beyond the project site) and eventually the realisation of the objectives - the impacts (e.g. improvement in health of target population). Anticipated outputs, outcomes, and impacts can be linked to a set of indicators that evidence whether, and to what degree, the programme is progressing against its objectives.

In order to describe the intervention of the JGHT funding scheme, we developed an impact logic model, tracing the causal chain of connections between the inputs, activities, outputs, outcomes, and impacts to achieve the stated aims. This was informed by a review of the available policy documents setting out the rationale for the programme, interviews with representatives from the funders (scoping interviews) and an outline of the process through which it was expected to deliver its intended outputs, outcomes and impacts. The logic model expands on the elements related to outcomes and impacts of the JGHT programme model (Figure 1), and is presented in Figure 2.



Figure 2 Programme logic model for the Joint Global Health Trial funding scheme

In italics: outputs/outcomes in research domain; normal: outputs/outcomes in health domain. In peach: potential barriers to uptake and implementation and JGHT elements addressing these. In green: activities linking outputs to outcomes and impacts, and JGHT elements supporting these. In red: activity and output specific to JGHT development award scheme

The model also sets out a number of spill-over effects that do not directly relate to the objectives of the scheme, but support the environment within which the programme takes place and can enhance progress towards impact. For example, while capacity building is not an explicit goal of the JGHT, the funded activity can be expected to enhance the skills of researchers and trial staff through their involvement in the project or directly through training courses, which in turn can benefit future research activity. In addition, the model illustrates external factors required to achieve the stated impacts or impeding progress (barriers). While these factors are beyond the remit and scope of the programme itself, funded activity can be informed by, or targeted at, key external factors to facilitate 'downstream' effects (i.e. beyond the project outputs).

It should be noted that the linear nature of a programme logic model is helpful for testing causal links and assumptions, but represents a simplification of the actual effects of a programme (e.g. information and learning from outputs and outcomes can be expected to feed back into the programme's activities).

4.2 The JGHT scheme evaluation framework

The main objective of this review was to determine the outcomes and impacts achieved by JGHT-funded activities to date. To guide the review, the study team developed an evaluation framework setting out indicators for the outputs (Table 2), outcomes (Table 3) and impacts (Table 4) presented in the logic model. Evidence against each of the indicators within the framework was collected, and is presented in this report. (Some of the indicators are annotated with comments in square brackets, [...], to indicate any divergence from the original study plan.)

Outputs - Research domain	Indicators		
Successfully completed Phase III/IV trials	Number and percentage of completed trials resulting in a definitive answer to the research question ₁₈ ; nature of intervention		
	Evidence that trial advanced trial methodology*; number of projects using novel trial methodologies, by type		
Evidence on interventions that are appropriate, acceptable and feasible for improving the health of disadvantaged populations and suitable for implementation in LMICs settings	Number of trials with a relevant definitive answer and a clear path to implementation at conclusion of study, including (where relevant) manufacture, access, and implementation [the elements in italics were found to require stakeholder engagement and utility of data, and are covered in the impact section of the report]		
Dissemination of research results	Number of articles published (primary trial results / other project findings)		
High quality research results	Evidence that trials contributed to a shift in the body of evidence and influenced research activity*		
	[this indicator was addressed by outlining the research landscape for four selected diseases]		
Sufficient evidence to design and implement full trials (for development awards)	Number of development awards that have led to successful full trial applications (JGHT / other funding)		
New collaborations between researchers in the UK and LMICs	Number of new collaborative partnerships (UK-LMIC / LMIC-LMIC)		
Enhanced research skills in the UK and/or LMIC	Number of researchers involved in JGHT projects (faculty members, postdoctoral researchers, postgraduate students, technicians)		
[Survey respondents and interviewees were asked to indicate the extent to which skills	Number of researchers who received trial management (or other) training for the JGHT award		

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¹⁸ The definition of 'definitive answer' used throughout the evaluation framework is: "A conclusive answer to the research question the trial was designed to address". This definition does not extend beyond the trial question itself, i.e. it does not require an answer to the question "which is the best intervention to prevent/treat health issue X in target group Y."

had been enhanced, rather than provide numbers, to allow sufficient time for questions with higher priority]	
Enhanced research infrastructure and tools	Number and type of research tools developed
in UK and/or LMIC	Number and type of new/improved research infrastructure established
New collaborations between researchers and stakeholders relevant for implementation	Number stakeholders engaged during the trial design phase, by type; level and frequency of engagement (descriptive)
	Number of stakeholders engaged during the project phase (by type); level and frequency of engagement (descriptive)
Key decision makers aware of research and receptive to findings	Level of awareness of key decision makers of JGHT project at the end of project
Health benefits for trial participants	Number of trial participants that have received health services beyond their usual level of care

*addresses evaluation question set out in the ITT. In italics: Data against this indicator was collected in aggregate form

Outcomes - Research domain	Indicators		
Further research informed by research results	Evidence that research findings have informed further work by the research team and/or the wider research community		
	Field normalised citation score [this score could not be determined as most main trial papers were too recent]		
New /strengthened international research networks	Increased number of collaborative partnerships and expansion of relevant research communities		
	Number of joint proposals and funded projects beyond the JGHT award		
Enhanced research environment	Number of investigators reporting an increase in the priority of health research in their organisation		
[these indicators were added]	Number of investigators reporting an enhancement of research governance structures at the participating LMIC institution		
	Number of investigators reporting an increase in LMIC researchers' research leadership capabilities		
	Number of investigators reporting an increased motivation of health professionals at LMIC institutions to become research leaders		
	Number of investigators reporting a reduction in cultural or operational barriers to health research		
Outcomes - Health domain			
Change in policy related to health interventions at the trial location(s), and	Number of trials resulting in a policy change at / beyond the trial location(s); number of organisations/countries involved		
beyond the trial location (scale-up)	Number of citations in local/national/international clinical guidelines		
	Nature of policy change (descriptive)		
Change in implementation of effective health interventions at the trial location(s), and	Number of trials resulting in the implementation of new effective health interventions at / beyond the trial location(s)		
beyond the trial location (scale-up)	Nature of the implemented intervention and implementing organisations		
	Number of people/patients benefitting from the new intervention		
	Level and nature of benefit to the target population (descriptive)		
	Number of trials resulting in cost savings for LMIC health system		

Table 3 Evaluation framework - Outcomes of JGHT-funded projects

Improved cost-effectiveness of healthcare provision, leading to cost savings for LMIC health systems	Nature and level of cost savings (descriptive)
Key decision makers more receptive to research evidence	Key decision makers feel more informed of the nature and value of research evidence, seek evidence from researchers to inform policy making, or consider research evidence available when taking policy decisions

Table 4 Evaluation framework - Impacts of JGHT-funded projects

Impact	Indicators	
Improved population health in LMICs	Decreased levels of mortality and morbidity in relevant LMICs, for health issues addressed by JGHT awards; increase in associated QALYs	
Improved health equality	Availability of interventions addressing the needs of disadvantaged population groups	
Improved health equity	Improved accessibility to interventions for disadvantaged population groups	
Progress towards health-related SDGs	Evidence of progress towards health-related SDGs	

5 Evaluation of the JGHT funding scheme

5.1 Inputs and activities - the JGHT portfolio

5.1.1 Inputs and activities funded

A total of 96 awards were made as part of Calls 1 - 7 of the JGHT, representing an investment of £138.8m. 63 of these awards were for full trials, with a budget of £133.8m, and 33 were development awards, with a budget of £5.06m. 28 full trial awards had closed by the end of May 2019, with 35 remaining active₁₉. Of development awards, 22 had closed and 11 remained active (Table 5).

Award status	All awards	Full trial awards	Development awards
Active	46	35	11
Closed	50	28	22
Total	96	63	33

Table 5 Number of JGHT awards (Call 1 - 7), by type and status

Source of data: MRC grants database

The number of full trial awards ranged from a low of 6 awards in Call 6, to a high of 12 awards in Call 2 (Figure 3). Since the development awards were established as a separate funding stream in Call 5, the number of awards was 10, 7 and 8 (Calls 5, 6 and 7, respectively).

¹⁹ The data provided included three grants with unclear status: 'payments suspended', 'grant suspended', 'terminating'. These were classified as 'closed' (1) or 'active' (2) on the basis of the 'actual end date' assigned in the data (i.e. end date before or after June 2019).





Source of data: MRC grants database

The amount of funding per call allocated ranged between a low of £15.8m in Call 7 / £16.8m in Call 3, and a high of £22.6m in Call 5 (Figure 4).



Figure 4 Total amount awarded (in £ million), per call

Source of data: MRC grants database

The average award size was £2.1m for full trial awards, and £153,500 for development awards. For full trial awards, the call with the lowest average award size was Call 2, at approx. £1.8m, and the call with the highest average was Call 6, at £3m. The five largest full trial awards amounted to between £4m and £5m (two in Call 1, and one each in calls 2, 3 and 6); the smallest were under £1m (Figure 5a). For development awards, the lowest average award size was in Call 6, at £129,000, and the highest average was in Call 7, at £161,000.

The size of full trial awards was more evenly distributed in Calls 1-4, with around one quarter of awards below £1m, between £1-2m, between £2-3m, and larger than £3m (9, 10, 10 and 8 of 37, respectively) (Figure 5b). In Calls 5-7, the largest share of awards was between £2-3m (38%, 9 of 24), following by 29% (7) between £1-2m, and 28% (6) larger than £3m. This may indicate that researchers are 'converging' on proposing trials with a £2-3m budget, or that the review panel considers this size award more competitive.

The average size per full trial award was the same for awards held by institutions in high income countries (HICs) and 'joint units' (HIC-funded programmes or institutes located in LMICs20), at £2.2m, and lower for awards held by institutions in LMICs (£1.7m).









*Calls 1 and 2 funded one award of under £300,000 each; given that the separate development award scheme had not been established, these awards were omitted from these figures. Source of data: MRC grants database

²⁰ Joint units include: KEMRI Wellcome Trust Research Programme, Kenya; Mahidol Oxford Research Unit, Thailand; Malawi-Liverpool-Wellcome Trust Clinical Research Programme, Malawi; Mwanza Interventions Trials Unit, Tanzania; MRC Unit The Gambia; MRC/UVRI Uganda Research Unit, Uganda; Oxford University Clinical Research Unit, Vietnam. The actual figure for applications from these units may be higher, as the names of investigators for unsuccessful applications were not provided. For awards, each investigator name was checked against the individual's institution website to determine were the researcher is based (as often only the UK institutions was named, e.g. 'University of Oxford' for researchers based at the Oxford University Clinical Research Unit in Vietnam). It is however possible that a number of investigators based at joint units in LMICs were counted as UK-based, as not all websites contained information on location.

5.1.2 Applications and funding requested

The applications process for full trial awards involves two stages, an outline stage followed by a full proposal stage.

Across all 7 calls, the JGHT received a total of 599 project outlines for full trial awards (an average of 86 outlines per call) (Figure 6). Of these, 160 were invited to prepare full proposals (26.7%), 144 full proposals were submitted, and 63 awards were made. This represents an overall success rate of 10.5% from outline to award, and of 43.8% from full proposal to award.

The development award scheme operates a one-step application process. 115 applications for development awards were received for Calls 5-7, at an average of 39 applications per call. Of these, 25 were successful, representing a success rate of 21.6%.



Figure 6 Success rates for full trial and development award applications

Source of data: provided by MRC

The average number of outlines per call was 85.6, with the largest number of outlines received in Call 1 (142), followed by Call 4 (112), and the smallest number of outlines submitted in Call 6 (55). A total of £910m was requested, ranging between £102m in Call 2 and £169m in Call 4, at a mean of £130m per call. The average award size requested by outlines was relatively steady between Calls 2 and 7, ranging between £1.5m (Calls 2 and 4) and £1.9m (Call 6).

The success rate from outline to award was highest in Call 2 (17.9%), and lowest in Call 1 (7.0%) and Call 4 (8.9%) (Figure 7). Outlines requesting a total of approx. 2.5 times the available budget are shortlisted; the number of invitations to submit full applications is hence under the control of the funders, and ranged between 40% and 50% across the seven calls.

The average number of development award applications for Calls 5-7 was 38.7, with success rates between 17.9% in Call 6 and 27.8% in Call 5_{21} (Figure 7). Since the introduction of the Development award scheme, the amount of funding requested under this strand has steadily increased, from £4.4m in Call 5, to £5.3m in Call 6 and £6.8m in Call 7.

²¹ For Calls 3 and 4, a separate Development Award scheme had not yet been established, and all applications followed the same application process. At the decision meetings of these calls, it was determined that while some of the full trial applications were of high quality, they were not yet ready for a full trial award. These applications were provided with 'development award' funding (8 awards in total), at an apparent 'success rate' of 100%, and are hence not included in Figure 7.



Figure 7 Success rates (Calls 1-7)

Source of data: MRC grants database

Two full trial proposals that had been rejected at the second stage of the application process went on to successfully apply for a JGHT development award to gather additional evidence.22, 23

Applications and awards, by lead PI affiliation (HIC, LMIC or joint unit) 5.1.3

More than half (57.6%) of all full trial award applications (second stage₂₄) were led by PIs affiliated with institutions in high income countries (HICs), compared to 27.1% of applications led by PIs from institutions in LMICs and 13.9% from joint units (Table 6). Applications led by PIs at institutions in HICs accounted for the largest share of applications across all calls; the share of applications led by PIs at LMIC institutions (excluding joint units) was highest in Call 4 (41.7%), and lowest in Call 7 (15.8%).

Applications led by PIs affiliated with joint units had the highest success rate, at 75%, securing 15 of 63 awards across Calls 1-7. This was followed by PIs from HIC institutions, with a success rate of 48.2%, leading 64% of awards. Applications led by PIs from LMIC institutions had an overall success rate of 20.5% (securing 8 awards); however, none of the applications in Calls 6 and 7 were successful (Figure 8).

The total share of full trial awards led by PIs at HIC institutions was 63.5% (40), 23.8% for PIs at joint units (15) and 12.7% for PIs at LMIC institutions (8).

Led by PIs affiliated with institutions in:	Share of applications (n=144 applications)	Success rate	Share of awards (n=63 awards)
HIC	57.6% (83)	48.2%	63.5% (40)
LMIC	27.1% (39)	20.5%	12.7% (8)
Joint unit	13.9% (20)	75%	23.8% (15)

Table 6 Full trial award applications (second stage) and success rates, by location of lead PI

In parentheses: number of awards; Source of data: MRC grants database

22 Data excerpt provided by MRC; a third PI whose full trial application to Call 7 was rejected secured a development award in Call 9 (i.e. outside the scope of this review).

23 As information on rejected full trial outlines (stage 1) was not available, the MRC database data does not contain information on the overall number of rejected full trial proposals at outline stage that then went on to apply for a development award.

24 This information was not available for outline awards.



Figure 8 Success rate for full trial award applications (second stage), by location of lead PI and call

Source of data: MRC grants database

For development awards, 50.4% of applications were led by PIs affiliated with institutions based in LMICs, 46.1% in HICs and only 2.6% at joint units (Table 7)₂₅. Lead PIs affiliated with joint units again achieved the highest success rate, with 2 of 3 applications funded (66.7%). 26.4% of applications led by from PIs from institutions in HICs were successful, compared to 15.5% of applications from PIs at institutions in LMICs.

Across all three calls, applications led by PIs at HIC institutions had a higher success rate than applications led by PIs from LMIC institutions, ranging between 37.5% and 22.2%, compared to 22.2% and 14.3% for LMICs (Figure 9). PIs from joint units submitted only one application per call, and secured one development award each in Calls 7 and 8.

Including awards made in Calls 3 and 4, the total share of development awards led by PIs at HIC institutions was 54.4% (18 of 33), 36.4% for PIs in LMICs (12) and 9.1% for PIs from joint units (3) (Table 7).

Led by PIs affiliated with institutions in:	Share of applications (calls 5-7, n=115 applications)	Success rate (calls 5-7, 25 awards made)	Share of awards (calls 3-7, n=33 awards)
ніс	46.1% (53)	26.4% (14)	54.4% (18)
LMIC	50.4% (58)	15.5% (9)	36.4% (12)
Joint unit	2.6% (3)	66.7% (2)	9.1% (3)

Table 7 Development award applications and success rates, by location of lead PI

In parentheses: number of awards; Source of data: MRC grants database

25 This excludes awards made in Calls 3 and 4, before the launch of the development award scheme.



Figure 9 Success rate of development award applications, by location of lead PI and call

Source of data: MRC grants database

5.1.4 Applications and awards, by continent

The largest share of full trial award applications (second stage) was led by PIs affiliated with institutions located in Europe (46.9%), followed by Africa (25.0%) and Asia (15.3%) (Table 8). PIs at institutions located in Europe also led the largest share of full trial awards (60.3%), with a success rate of 46.9% from full proposal to award. Lead PIs at institutions in Africa secured 28.6% of awards (most of whom were affiliated with joint units), with a success rate of 50% from full proposal to award, while applications led by PIs at institutions in Asia had a lower success rate of 22.7%.

The largest share of development award applications (calls 5-7) were also led by PIs affiliated with institutions in Europe (44.3%) (Table 8). 27% of applications were led by PIs in Asia and 21.7% in Africa. Success rates were highest for lead PIs in Europe (27.5%), with success rates for applications led by PIs in Asia at 19.4% and in Africa at 16.0%.

Full trial awards, location of lead PI	Share of applications (n=144)	Success rate	Share of full trial awards (n=63)	
Europe	56.3% (81)	46.9%	60.3% (38)	
Africa	25.0% (36)	50.0%	28.6% (18)	
Asia	15.3% (22)	22.7%	7.9% (5)	
Development awards, location of lead PI	Share of applications (calls 5-7, n=115)	Success rate (calls 5-7)	Share of full trial awards (calls 3-7, n=33)	
Europe	44.3% (51)	27.5%	51.5% (14)	
Asia	27.0% (31)	19.4%	27.3% (6)	
Africa	21.7% (25)	16.0%	15.2% (4)	
South America	3.5% (4)	25.0%	6.1% (1)	

Table 8 Applications and success rates, by continent of lead PI

In parentheses: number of awards; Source of data: MRC grants database

5.1.5 Applications and awards, by country

Applications were received from lead PIs affiliated with institutions located in 32 countries, in 27 LMICs and five HICs₂₆.

PIs from research organisations in 21 countries applied for full trial awards (full proposal stage). More than half of these applications (55.6%) were submitted by PIs at institutions in the UK (Table 9). The highest share of applications from LMIC PIs originated in South Africa and The Gambia (7.6% each), latter reflecting the location of the MRC Gambia unit, followed by India (4.9%) and Bangladesh (4.2%). Only one application was led by a PI at an institution in South America.

Lead PIs at institutions in 15 countries were awarded a full trial award, with PIs in the UK receiving the largest number (37 58.7% of all full trial awards), followed by PIs in countries in sub-Saharan Africa: The Gambia (7 awards), Kenya (4 awards) and South Africa (3 awards)₂₇ (Figure 10). Lead PIs in India and Bangladesh did not secure any full trial awards. Of countries with 3 or more awards, applications from lead institutions Kenya had the highest success rate, of 100% (all 4 full applications funded), followed by The Gambia (64%), the UK (46%), and South Africa (27%).

Lead PIs from research organisations in 23 countries applied for development awards. In Calls 5-7, 44.3% of lead PIs were from institutions located in the UK (51 of 115), 17.4% in India (20), 5.2% from South Africa (6), and 4.3% from Nigeria (5) (Table 9). Only three PIs leading applications were from South/Central America (2 from Peru, one from Mexico) (Calls 3-7).

Across Calls 3-7, development award applications led by PIs at institutions in 10 countries were successful, with PIs in the UK holding the largest share (17 of 33 awards, or 51.5%), followed by PIs in India (4 awards, 12.1%). Lead PIs in South Africa, Kenya, China and Peru held two grants each (6.1%). For Calls 5-7 (i.e. when a separate development award scheme was in place), applications led by institutions in the UK had a success rate of 27.5%. Applications led by institutions in India had the lowest success rate, at 15.0%, of 'funded countries'. Lead PIs at South African institutions submitted 6 applications, of which 2 were funded (33.3% success rate); PIs in China and Kenya achieved a success rate of 100% (2 awards each)₂₈.

Country of lead institution	Full trial application (stage 2) (n=144)	Full trial awards (n=63)	Success rate	Country of lead institution	Develop- ment award application (n=115)	Develop- ment awards (n=25)	Success rate
UK	80	37	46.3%	UK	51	14	27.5%
The Gambia	11	7	63.6%	India	20	3	15.0%
South Africa	11	3	27.3%	South Africa	6	2	33.3%
India	7	0	0.0%	Nigeria	5	0	0.0%
Bangladesh	6	0	0.0%	Kenya	4	2	50.0%
Kenya	4	4	100.0%	Bangladesh, Brazil, Tanzania	3	0	0.0%
Pakistan, Uganda	3	1	33.3%	China	2	2	100.0%

Table 9 Applications and success rates, per country of lead institution

In parentheses: number of awards; Source of data: MRC grants database

27 All awards in The Gambia and Kenya were to the MRC unit and the KEMRI-Wellcome Trust Research Programme.

28 Both awards in Kenya were to the KEMRI-Wellcome Trust Research Programme.

²⁶ LMIC: Argentina, Armenia, Bangladesh, Brazil, China, Ethiopia, Georgia, Ghana, India, Kenya, Malawi, Mexico, Nigeria, Pakistan, Papua New Guinea, Peru, Philippines, Senegal, Somaliland, South Africa, Sri Lanka, Tanzania, Uganda, Vietnam; HIC: UK (and 'UK unit' in LMIC), Australia, Canada, Singapore, Switzerland



Figure 10 Location of lead institutions of JGHT awards (n=96)

Source of data: MRC grants database. The size of the dot corresponds to the number of PIs associated.

5.1.6 Applications and awards, by institution

PIs affiliated with a total of 42 institutions led JGHT awards.

PIs at 60 institutions applied for full trial awards (27 in HICs, 26 in LMICs, 6 joint units, and 1 global organisation). Applications led by PIs at 30 institutions were successful (18 in HICs, 7 in LMICs, and 5 joint units).

The largest number of full trial awards were led by PIs based at the London School of Hygiene and Tropical Medicine (LSHTM), with 12 awards (19%)₂₉ (Table 10). PIs at the MRC Unit in The Gambia secured seven awards (11.1%), and PIs at the Liverpool School of Tropical Medicine led five awards (7.9%). PIs at LSHTM also led the largest number of applications (28)₃₀, with a success rate of 42.9%.

PIs from LMIC institutions securing full trial awards were at the University of Cape town (2 awards), and Makerere University, Uganda; the University of Ibadan, Nigeria; Stellenbosch University; South Africa; the Papua New Guinea Institute of Medical Research; The Aga Khan University, Pakistan; and the University Cheikh Anta Diop de Dakar, Senegal (1 award each).

The largest number of applications led by PIs from LMIC institutions were affiliated with the ICDDRB in Bangladesh and Stellenbosch University (4 applications each), followed by the University of Cape Town and The Aga Khan University, Pakistan (3 applications each).

²⁹ This excludes awards made to LSHTM-associated

³⁰ However, as noted above: Names of PIs for unsuccessful applications were not available, the primary location could not be verified. PIs based at joint units in LMICs are often listed under the associated UK university; the number of applications reported per UK institution here may hence be higher than the actual number, and the success rate lower than the actual success rate.

Lead institution	Number of full trial awards	Share of full trial awards (n=63)	Number of applications	Success rate
London School of Hygiene and Trop Med	12	19.0%	28	42.9%
MRC Unit, The Gambia	7	11.1%	11	63.6%
Liverpool School of Trop Med	5	7.9%	10	50.0%
University College London	4	6.3%	6	66.7%
KEMRI/Wellcome Trust Research Programme, Kenya	4	6.3%	4	100.0%
University of Oxford	3	4.8%	9	33.3%
University of Cape Town OUCRU Vietnam The University of Manchester University of Liverpool	2	3.2%	3	66.6%

Table 10 Full trial award applications and awards, by lead institution

Source of data: MRC grants database

Lead PIs at 79 institutions applied for development awards in Calls 5-7 (26 institutions in HICs, 50 in LMICs, 2 joint units), and 24 institutions led development awards in Calls 3-7 (12 in HICs, 10 in LMICs, and 2 joint units).

The largest number of development awards was led by PIs based at LSHTM, with 3 awards (9.1%, calls 3-7), and a 18.2% success rate (2 awards of 11 applications made in calls 5-7) (Table 11). All other institutions led one or two awards only.

Table 11 Development award applications and awards, by lead institution

Lead institution	Number of development awards (calls 3-7)	Share of development awards (calls 3-7) (n=33)	Number of applications (calls 5-7)	Success rate (calls 5-7), 25 awards made
London School of Hygiene and Trop Med	3	9.1%	11	18.2%
Liverpool School of Trop Med	2	6.1%	3	66.7%
Peruvian University Cayetano Heredia	2	6.1%	1	100.0%
Sangath, India	2	6.1%	3	66.7%
University of Birmingham	2	6.1%	3	66.7%
KEMRI/Wellcome Programme, Kenya	2	6.1%	2	100.0%

Source of data: MRC grants database

5.1.7 Trial locations

The 63 full trials were implemented at trial sites located in 47 countries₃₁ (indicated by their clinical trials database registrations₃₂). One third of trials involved sites in more than one country (32%, 20 of 63), with 13% (8) involving sites on more than one continent₃₃. The majority of trials included trial sites in Africa (74.6%, 46 trials). Fewer trials included sites in Asia (30%, 19 trials) and Central/South America (7.9%, 5 trials) (Figure 11).

Sub-Saharan countries hosted sites for the largest number of trials, headed by Uganda (14), Kenya (11) and South Africa (9). Countries hosted trials across a range of conditions. Further information on trials addressing malaria, tuberculosis, cryptococcal meningitis and podoconiosis is available in the relevant research landscapes (see Appendix G).



Figure 11 Locations of trial sites (n=63)

Source of data: Clinical trial databases: ISRCTN, ICTRP and clinicaltrials.gov. Two trials received co-funding to conduct parallel trials involving sites in HICs and LMICs (MR/M009211/1 and MR/N006127/1); HIC sites are not included in the map.

Including both, full trial and development awards, 41 countries were cited as trial locations within the 'Case for Support' documents ($n=93_{34}$). The original project plans saw Uganda hosting the largest number of projects (19), followed by India (16), Kenya and South Africa (12 each) and Malawi (10)₃₅. The largest number of studies plans involved sites on the African continent (62; 69%), followed by sites in Asia (37 studies; 39%). 29% of awards planned to involve sites in more than one country (27 of 94). This proportion was higher for full trial awards (35%, 22 trials) than for development awards (16%, 5 awards), as would be expected given the scope and size of full trials. 10 studies (11%) intended to involve sites located on more than one continent.

 $_{31}$ Two trials (MR/M009211/1 and MR/N006127/1) included sites in HICs funded through alternative sources. These sites were excluded from this analysis.

³² http://www.isrctn.com; http://apps.who.int/trialsearch/; https://clinicaltrials.gov

³³ Some projects received co-funding to conduct parallel trials in HIC and LMIC countries. For this reason, the registration of these trials listed HIC locations as trial sites, but these were not funded by the JGHT.

³⁴ Case for Support (CfS) documents were available for 62 of 63 full trial awards, and 32 of 33 development awards. One award (MR/M009211/1) indicated only 'worldwide' in the CfS, and is hence not included in this analysis. It should be noted that the CfS set out initial project plans and were subject to change as the project is implemented.

³⁵ Studies with sites in multiple countries are counted multiple times

5.1.8 Trial settings

The largest share of full trials were set in the community (35%, 22 of 63), followed by hospitals (33%, 21) and in the home (10%, 6) (Figure 12).



Figure 12 Trial settings of full trials (n=63)

Source of data: Clinical trial databases - registration data

5.1.9 PIs and co-investigators

In total, 647 individuals (PIs and co-investigators of the JGHT, Calls 1 - 7) were listed in the MRC grant database, affiliated with a total of 212 organisations₃₆. 88 individuals were in the role of PI in at least one JGHT award, with 9 individuals PIs of more than one award.

Half of the 212 organisations are located in LMICs (49.1%, 104), 41% (87) are located in HICs, and 5.7% (12) are joint units₃₇ (Figure 13). The UK hosted the largest share of institutions (21.1%, 45), followed by the USA (7.1%, 15), South Africa (6.6%, 14), Uganda (5.2%, 11) and India (4.7%, 10). Just under 30% of organisations were located in Africa and Europe each, 22.2% in Asia and 9.0% in North America. Across the African continent, countries in East and far West Africa are strongly represented.

Individuals at the London School of Hygiene and Tropical Medicine were involved in more awards than any other organisation (41.7%, 40 awards). This was followed by the Liverpool School of Tropical Medicine and University College London (14.6% each), and KEMRI Wellcome Trust Research Programme in Kenya (10.4%). The LMIC organisations involved in the largest number of awards were The Aga Kahn University, Pakistan, and the University of Malawi, Malawi, each involved in 6 awards (6.3%). Organisations located in high income countries other than the UK were John Hopkins University, USA (involved in 6 awards) and the Institute of Tropical Medicine Antwerp, Belgium (5 awards).

³⁶ Contact details for PIs and co-investigators of JGHT awards (from the MRC's grant database) were analysed as an indication of affiliation and geographical location of the individuals involved in delivering JGHT projects. It should be noted that:

- The level of contacts available is likely to differ between awards, with some providing information on all researchers at all sites, whereas others only list the main contributors
- Contact details reflect the planned study team at the start of the award, and are not updated over the course of the project. Any changes to the team composition after the start of the award are hence not reflected.
- The team composition may have changed from the original study plan set out in the CfS: 22% of PIs of full trial and development awards indicated that the study team had changed compared to the CfS (9 of 40).
- ³⁷ Botswana Harvard AIDS Initiative Partner, CDC Botswana BOTUSA, Eijkman Oxford Clinical Research Unit, Epicentre Mbarara Research Base, KEMRI CDC, KEMRI Wellcome Trust Research Programme, Mahidol Oxford Research Unit, Malawi-Liverpool-Wellcome Trust Clinical Research Programme, Mwanza Interventions Trials Unit Tanzania, MRC Unit The Gambia, MRC Uganda, Oxford University Clinical Research Unit Vietnam



Figure 13 Locations of institutions of PIs (blue) and co-investigators (red)

Source of data: MRC grants database. The size of the dot corresponds to the number of PIs associated.

An analysis of author affiliation, limited to publications of the main trial findings₃₈, of 22 closed full trial awards₃₉ showed a similar distribution. Investigators from a total of 106 institutes were named as coauthors. Over half of the institutions were located in LMICs (53.8%, 57), 34% were located in HICs (36) and 11.3% are joint units (12)₄₀ (Figure 14). This indicates that the contribution of investigators at the (many) LMIC trial sites is indeed being recognised.

The largest number of institutes were located in the UK (16%, 17), followed by Viet Nam (10.4%, 11), Kenya (7.5%, 8) and the USA (7.5%, 8). A third of the institutes were located in Africa (34.9%), 29% in Asia, 23.6% in Europe, 9.4% in North America and 2.8% in Oceania.

The London School of Hygiene and Tropical Medicine was listed as an author affiliation on the greatest number of publications (36.4%, 8 publications). This was followed by the University of Oxford (27.3%, 6 publications) and Malawi-Liverpool-Wellcome Trust Clinical Research Programme, Liverpool School of Tropical Medicine and KEMRI Wellcome Trust Research Programme (22.7%, 5 publications each). The LMIC organisation listed as an affiliation on the largest number of publications was Makerere University, Uganda (3 publications). Other HIC institutes listed were Radboud University Medical Centre, Netherlands, Menzies School of Health Research and Charles Darwin University, Australia and University of California, San Francisco (listed on two publications each).

³⁸ i.e. a peer-reviewed publication reporting on the primary outcome(s) of a trial

³⁹ Publications of main trial findings from a further two awards could not be included as one (very recent) publication had not yet been indexed in Scopus (MR/M009211/1) and co-author indexing was not available for the other (G1100570).

⁴⁰ Eijkman Institute for Molecular Biology, KEMRI, Malawi Epidemiology and Intervention Research Unit, Malawi-Liverpool-Wellcome Trust Clinical Research Programme, Medical Research Council Unit Gambia, Dignitas International Malawi, Infectious Diseases Research Collaboration Uganda, Joint Clinical Research Centre Uganda, MRC UVRI Uganda Research Unit on AIDS, Mwanza Medical Research Centre, Oxford University Clinical Research Units Viet Nam, Mahidol-Oxford Tropical Medicine Research Unit



Figure 14 Locations of institutions of PIs (blue) and co-authors (yellow) of main trial finding publications

Source of data: Author and co-author affiliations for 22 publications. Red lines connect publication authors and co-authors.

• PI gender balance

The overall gender balance of the 96 JGHT-funded awards was 67% male to 33% female (63 and 33 of 96, respectively). The balance for full trial awards, with 37% of female-led trials (23 of 63) was similar to that of development awards, with 30% of female-led projects (10 of 33).

Gender balance varied significantly from call to call. The largest share of female-led awards occurred in Call 3 for full trials (71%, 5 of 7), and in Call 7 for development awards (50%, 4 of 8) (Figure 15). The smallest shares were in Call 6 for full trial awards (17%, 1 of 6) and Call 5 for development awards (10%, 1 of 10). The share of female-led full trials was relatively low in Calls 6 and 7, but increased again in Call 8_{41} (43%, 3 of 7).



Figure 15 Gender of PI of JGHT awards: share of female PIs per call

Source of data: MRC grants database, desk research

The share of female PIs was higher for institutions located in HICs (41%, 25 of 61 awards) than for institutions in LMICs (26%, 5 of 19). Only 19% of awards to joint units were led by a female PI (3 of 16). There were also differences between disease areas: While 43% of awards related to TB and HIV were led by female researchers (6 of 14), this was the case for only 19% of awards addressing malaria (3 of 16).

⁴¹ i.e. after the time period covered by this review

5.1.10 Health areas addressed

Across all full trial and development awards, the largest share of awards was in the area of 'Infection', at 44.4% (Figure 16), which was addressed in 48 awards₄₂. This was followed by 'Reproductive Health and Childbirth' (15.3%) in 21 awards, 'Mental Health' (9.0%; addressed in 9 awards) and 'Cardiovascular' (8.9%; addressed in 13 awards).



Figure 16 Share of HRCS classification₄₃ (all awards)

Source of data: MRC grants database. HRCS health codes

The relative shares of health area addressed varied from call to call: The share of 'Infection' awards was highest in Call 1, at 70%, but fell to around 30% in Calls 5 and 7 (Figure 17). The area 'Mental Health' increased its share, from no awards in Calls 3 and 4, to 36% in Call 7. 'Reproductive Health and Childbirth' and 'Cardiovascular' remained relatively steady.



Figure 17 Share of awards by health area addressed, per call (all awards)

Source of data: MRC grants database. HRCS health codes

⁴² Health Research Classification System (HRCS) Health codes; see https://hrcsonline.net

⁴³ For the 'JGHT lifetime' analysis, all shares of HRCS codes were added up *per code*, and expressed as the percentage of *all codes added for Calls 1-7*. For the analysis of individual calls, all shares of HRCS code were added up *per code*, and expressed as the percentage of *all codes for the call in question*.

For full trial awards, the overall share of awards addressing 'Infection' was even higher, at 61%, and remained between 42% (Call 7) and 79% (Call 6). All other areas remained at 25% or below, except 'Mental Health' in Call 7, at 33%. The health area 'Infection' also received the largest amount of funding for full trial awards over Calls 1-7 accounting for £91.2m (70.6%)₄₄ (Figure 18). This was followed by 'Reproductive Health and Childbirth' (£11.9m), 'Cardiovascular' (£8.2m), 'Mental Health' (£5.8m), and 'Injuries and Accidents' (£2.8m). All other areas accounted for 2% of the budget or less.

Figure 18 Funding allocated per health area (HRCS code)



Source of data: MRC grants database. HRCS health codes. 'Other' includes Cancer, Generic Health Relevance, Other, Respiratory, Inflammatory and Immune System, Oral and Gastrointestinal, and Metabolic and Endocrine

For development awards (Calls 3-7), the share of projects addressing 'Infection' was much lower, at only 11%. 'Reproductive Health and Childbirth' accounted for the highest share, at 21%, followed by 'Mental Health', 'Cardiovascular', 'Infection', and 'Oral and Gastrointestinal' at 9%-13%. There was no clear trend in health area coverage over time.

Compared to full trial awards, development awards covered a broader range of health areas, with an average of 8 HRCS codes per call for Calls 5 - 7. This compares to an average of 4.4 health codes covered for Calls 1-7, and an average of 4.7 codes for Calls 5-7, for full trial awards (Figure 19).



Figure 19 Number of HRCS health codes addressed, per call

Source of data: MRC grants database. HRCS health codes

⁴⁴ Methodology: Funding was allocated by share of HRCS Health code share, i.e. if an award was assigned to two codes, the award budget was split equally between the two research areas. Award MR/R006121/1, £2.7m, is not coded, and was hence not included in this analysis.
The Case for Support documents, and registration data in clinical trials databases, provided information on the specific diseases/issues addressed by the proposed research, and the types of intervention tested.

A quarter of all full trial awards were related to malaria (25.4%, 16), mostly concerned with disease transmission (Figure 20). 14.3% of trials addressed aspects of TB. As these awards were on average larger than all other trials, at \pm 3.1m, funding dedicated to addressing TB accounted for around 20% of the total full trial award budget (Figure 21). Other indications addressed by several full trial awards include respiratory disease and HIV-related fungal infections.





Source of data: Cases for support. Data labels indicate number of awards and total funding allocated. HIV-related fungal infections: Cryptococcal meningitis and talaromycosis; Sexual and reproductive health includes Human Papilloma Virus.

Figure 21 Share of total full trial award funding, by issue addressed



Source of data: Cases for support and MRC grants database. Data labels indicate average award size.

The largest number of development awards addressed issues related to nutrition (5 of 33; 15.2%), receiving funding of £689,000, followed by interventions addressing cardiovascular disease, diabetes, and tobacco use (3 awards each; 9.1%) (Figure 22).



Figure 22 Development awards, by issue addressed

Source of data: Cases for support and MRC grants database. Data labels indicate number of awards. Nutrition includes both prevention of malnutrition and of obesity.

5.1.11 Type of research conducted

Over the lifetime of the JGHT (Calls 1–7), the largest share of research fell into the broad area of 'Treatment evaluation' (46.0%), followed by 'Prevention' (34.3%), 'Health and social care services' (9.6%) and 'Management of diseases' (7.4%) (Figure 23). Shares for full trial awards and development awards were broadly similar, with a stronger emphasis on 'Treatment evaluation' in full trial awards (49.6% of full trial awards vs. 39.1% of development awards), and a stronger emphasis on 'Prevention' in development awards (43.8% of development awards vs. 29.4% of full trial awards). While relative shares of research activity differed across the seven calls, no clear trends were discernible.

Figure 23 Share of research area (HRCS research classification codes, all awards)



Source of data: MRC grants database. HRCS research classification codes

More specifically, the largest share of research fell into the class 'Pharmaceuticals' $(32.2\%)_{45}$. This was followed by 'Primary preventions interventions to modify behaviours or promote well-being' (16.6%), 'Interventions to alter physical and biological environmental risks' (9.4%) and 'Psychological and behavioural' (8.5%).

The relative shares differed between the full trial award and the development award portfolio: While full trial awards fell predominantly into the 'Pharmaceuticals' research class (42.3%), the share was much lower for development award portfolio (12.5%) (Figure 24). Conversely, one third of development awards addressed the research class 'Primary preventions interventions to modify behaviours or promote well-being' (33.9%), with only 7.7% of full trial awards in this area. Vaccines were part of the full trial award portfolio (8.1%) but not the development award portfolio, while 'Psychological and behavioural' research took a larger share of development awards (14.1%) compared to full trial awards (5.6%).



Figure 24 Share of HRCS research classification, all calls

Source of data: MRC grants database. HRCS research classification codes

The share of research class per call varied considerably (Figure 25). The research class 'Interventions to alter physical and biological environmental risks' was represented in Calls 1 - 4, but accounted for only a small share in Calls 5-7. On the other hand, 'Psychological and behavioural' received no funding in Calls 1-4, a very small share in Call 5, and substantial shares in Calls 6 and 7 (34.6% and 21.4%, respectively).

45 HRCS research classification codes (i.e. second level of research classification group)



Figure 25 Share of HRCS research classification, per call

In parentheses: number of awards; Source of data: MRC grants database. HRCS research classification codes

• Project team expertise

The expertise involved in each project as reported by the PI is illustrated in Figure 26. As can be expected, experts in clinical trial methodology (18 of 20), data management (18 of 20), clinical trial management (19 of 20), and statistics (all trials) were involved in nearly all active full trials. Experts in clinical trial methodology and data management were also involved in most of the development awards (17 of 20). 75% of full trials included experts in health economics, and approximately half of the trials experts in socials science and in health policy. Social science was the only expertise represented in a larger share of development awards than full trial awards (75% vs 50%), informing preparatory work such as feasibility and acceptance studies and stakeholder consultation. Approximately one third of full trial awards involved experts in health systems and in knowledge brokerage (e.g. for stakeholder engagement and network building), but less than 20% of development awards did so.

Figure 26 Expertise included in the project (full trials: n=21; development awards: n=20)



Source of data: Survey of PIs of full trials (active) and development awards (all)

5.2 Stakeholder engagement

Stakeholders are an important factor in the success of a project. By communicating and consulting with stakeholders, researchers can:

- tailor the study to fully address local conditions, needs, and cultural preferences
- generate buy-in to enable the project to progress smoothly and minimise opposition (e.g. participant recruitment)
- raise awareness and understanding of the intervention and its potential for implementation (e.g. among policy makers and healthcare providers)

Engagement can occur in the design and during the implementation of the JGHT-funded activity, and/or through dissemination activities following the funded project. While all trials require approval from the national authorities, e.g. obligatory engagement on trial plan and conduct, a different set of relationships and engagement activities are likely to be required to influence national health policy.

5.2.1 Level of stakeholder engagement

PIs reported they had engaged with a range of stakeholder groups during the design and implementation phases of their projects.

In the design phase, most PIs of active full trials and development awards reported that they had engaged with LMIC health care professionals (71%)₄₆, followed by implementing organisations/NGOs (59%). Fewer PIs pointed to engagement with policy makers from international agencies (32%) and community organisations (29%) (Figure 27). Approximately one quarter of projects included experts in knowledge brokerage, such as stakeholder engagement and network building, which would have supported wider engagement. Stakeholder engagement activity during the project was broadly

⁴⁶ It should be noted that not all trials involve interventions relevant for health care professionals (e.g. toolkits for violence prevention in schools). In addition, some teams include local clinicians and health care providers who feed directly into the study design (limiting the need for external consultation on study design).

consistent with engagement activity in the design phase, with an additional 5-15% of projects engaging with all stakeholder groups except LMIC healthcare providers.

While engagement with policy makers was reported for 87% of full trials (41 of 47_{47}), six PIs of full trials (5 of 25 active, 1 of 22 closed trials) indicated that they had not engaged with policy makers during the design or implementation phases of the study or after the conclusion of the study₄₈, and only one of these had engaged with implementing organisations/NGOs. 20% of development award PIs (4 of 20) indicated that they had not engaged with policy makers during the design phase of the project; however; all had done so during the implementation phase.



Figure 27 Stakeholder engagement by JGHT-funded research projects (n=41)

Source of data: Surveys and interviews with PIs of development awards and active full trials. * Other includes engagement with scientific and technical experts (1), policy makers from state government (1) and details of how research was disseminated (2)

All PIs indicated that they had engaged with stakeholders via a direct approach (Figure 28). Other common engagement modes were seminars (54%) and workshops (51%).

Figure 28 Method of stakeholder engagement (n=37)



Source of data: Survey of PIs of full trials (active) and development awards (all) *Other includes participant groups, teleconferences and visits to trial sites.

⁴⁷ The review team did not receive information on stakeholder engagement of the remaining 16 full trials, predominantly because PIs did not respond to the request for information or because PIs held more than one award (with interviews focussing on the earlier trial). In one case, the shortened interview did not cover this topic.

⁴⁸ It is possible that due to prior work, (some of) these teams are already embedded within the relevant policy arena, or have included policy makers within the study team; this information is not conveyed in the survey responses.

In interviews, PIs provided further detail on stakeholder engagement activity, the rationale for engagement, and engagement modes $employed_{49}$.

5.2.2 Engagement with policy stakeholders

Of 28 PIs interviewed, eight PIs reported engagement with international policy organisations, foremost WHO (global offices in Geneva and country offices), with two PIs directly involved as members of WHO guideline committees. Two PIs explained that many countries base their national programmes on WHO recommendations, which warrants that "first, in terms of policy impact we need to [target] the international level. That can then trickle down to local national level". A smaller number of PIs talked about engagement with the implementation funders, such as The Global Fund, UNICEF, BMGF, and The President's Malaria Initiative. For example, one trial included representatives from The Global Fund and The President's Malaria Initiative on the trial steering committee (see Case study 7).

Nearly two thirds of PIs (61%, 17 of 28) stated that they had engaged with government in countries where trial sites were located - predominantly national ministries of health, but also provincial/county government offices. Several PIs had embedded their trials within national public health programmes, e.g. mass drug administration campaigns (see Case study 9) and national malaria control programmes (see Case study 7); others kept relevant policy makers informed in regular targeted meetings (see case Davey) or by setting up dedicated policy liaison groups (see Case study 11 and Case study 13). One PI created an international advisory group headed by a high-profile individual, as well as national advisory committees in each country, with the aim of enabling scale up across countries after the conclusion of the trial. In five cases, PIs or study team members were members of government committees or government employees. One PI explained that the study team had been selected specifically to include collaborators who served on national advisory committees in the trial countries. Where this was not possible, very high-profile senior investigators were approached. PIs from the MRC-LSHTM unit in The Gambia pointed out the institute's strong relationship with the Ministry of Health, based on a 70-year history of conducting research in the country. This includes frequent exchange with the national health programme managers and regular updates to the Minister for Health.

In general, PIs considered engagement with policy makers important, making national decision makers aware of the research while it was being implemented, rather than 'surprising' (and possibly embarrassing) them with the publication of trial findings after the conclusion of the study. However, one PI highlighted that engagement with national public health programmes can also be difficult and potentially counter-productive: Local officers can "sometimes be incredibly conservative, and instead of facilitating your work, they can put blocks in your way". A co-investigator, commenting on issues encountered during a trial, pointed out that full integration with government health programmes not only paves the way for policy change, but also increases communities' buy-in: "In hindsight, I would have better engaged with the Ministry of Health, not only to secure their buy-in (which we did secure), but also their active involvement in the trial implementation. This would ensure that the community views [the research] as part of government interventions rather than a parallel programme. We would also look at integration with ongoing programmes.".

Two PIs specifically stated that they had not engaged with policy makers in the design, implementation, or post-trial phases. One of these PI explained that the question the trial addressed would not have been of interest to policy makers, and that the choice to not engage had hence been appropriate. The other PI had not engaged with WHO and national policy institutions during the trial, and did not have the resources to actively engage post-trial. While trial findings were highly supportive of a change in policy (and have been published), policy makers are not aware of the evidence and it has not (yet) been taken up.

⁴⁹ While an indication of the number of PIs reporting engagement with different stakeholder groups is provided, these represent the minimum (rather than absolute) number. Interview discussions did not always cover all stakeholder groups, focussing in more depth on the groups and engagement modes considered most relevant by the PIs.

Likewise, seven PIs felt there was a need for dedicated funding after the completion of the trial to support dissemination and engagement activities and thus help translate findings into policy change. One PI explained that at the time of the trial, the study team focussing entirely on "getting the study finished", with no resources left at the end of the grant. Another PI stated: "I think funders are very unrealistic on the whole about how long dissemination takes and how long it's going to take to get the results together and get papers out. It's difficult because the money to do that should come from project funding. But that can be very difficult because you're under pressure to close the project and terminate the contract."

Another PI explained that after the trial had completed, she attempted to set up meetings with the regional WHO offices and governments of neighbouring countries to develop a policy statement, which would have increased access and use of the superior treatment (see Case study 1). However, she was unable to identify adequate funding to allow her to engage in these activities, and policy change remains limited to the country in which the trial was conducted.

Key opinion leaders broadly agreed that engagement with policy stakeholders is crucial to achieve impact. As one interviewee explained: "We have to pay much more attention to the political and policy interface. If we do RCTs and pragmatic trials but we don't bring policy makers with us, we waste a lot of money on interventions that never go to scale because we never spoke to the government or policy makers about these things. [...] It all depends on how good you are at bringing policy makers along. And if you do that the sky is the limit.".

5.2.3 Engagement with LMIC healthcare providers

Several PIs (6 of 28) specifically mentioned engagement with LMIC healthcare professionals (e.g. see Case study 1). One project organised workshops to develop the intervention involving district health management teams, clinicians, community health workers, and technology partners as part of the JGHT-funded trial₅₀; another engaged healthcare providers through Theory of Change workshops. Two PIs engaged with professional bodies in country to secure support.

5.2.4 Community and participant/patient engagement

Engagement with communities and participants aims to generate buy-in and minimise opposition, thus facilitating participant recruitment, and enables researchers to tailor studies to fully address local conditions, needs, and preferences. Supporting this intention, a study on the effect of community sensitisation meetings conducted as part of a JGHT-funded trial in The Gambia found that individuals who went to these community meetings were more interested in participating than those who were completely unaware of the study $_{51,52}$.

More than a third of interviewed PIs (39%, 11 of 28) reported that they had engaged with community groups and community advisory boards, community leaders, and individuals such as patients who shared their experiences. Several PIs working with culturally sensitive interventions, or in communities that had not previously been exposed to research activity, described how they had prepared their studies through extensive community engagement. Specific examples of successful engagement included the following:

• At the start of one study, the team conducted extensive consultation with community leaders in the area, to discuss the trial, generate buy-in, and uncover potential issues. To this end, the team organised information events in the region, which were well-attended and gave participants the opportunity to ask question about the disease and how to manage it. Once in the implementation stage, the study hired local community health workers, living within the community, to deliver

⁵⁰ Githinji S et al (2015) Development of a text-messaging intervention to improve treatment adherence and post-treatment review of children with uncomplicated malaria in western Kenya. Malar J. 14: 320

⁵¹ Sensitisation meetings are organised by research staff to make information on the research available in the villages from which potential research participants may be recruited.

 $_{5^2}$ Dierickx S et al (2018) Community sensitization and decision- making for trial participation: A mixed- methods study from The Gambia. Dev World Bioethics 18: 406-419

intervention in primary health clinics - an important aspect as patients had to self-present to the clinics. Given the trial took place in a complex ethical landscape, the team had tailored the consent process to be very clear and transparent, laying out the aim of the study and the 'safety net' in place for the control arm (composed of regular check-ups, facilitated referral in case of complications, free of cost treatment). The trial did not encounter issues with recruitment, and few potential participants opted out.

• Another team conducted a Rapid Ethical Assessment (REA) prior to starting the trial, to "map the ethical terrain" of communities that had not previously been involved in health research₅₃ (see Case study 5). The team gathered local knowledge, e.g. on how the community operates, what the community understands about research, and their views on trial characteristics. Specific suggestions were incorporated into the preparatory phases of the trial or used during the course of the trial itself to avoid potential issues. For example, in one trial location, misinformation spread by a local individual alarmed patients. Acting on suggestions made during the REA, the trial coordinator and data manager arranged an emergency district meeting to negotiate with gatekeepers and prevent further rumours being spread.

Conversely, the PI of a trial which encountered major issues with recruitment and compliance due to cultural barriers felt that these might have been avoided by community engagement through an acceptability study.

Researchers highlighted the importance of joint units in building sustained local relationships. Through their long-term presence, these units established field sites and engagement structures which researchers are able to draw on. As one PI explained: "The value of long-term investment in overseas sites, e.g. by Wellcome Trust and the MRC, was priceless in this context. At the village level, there was an awareness of [the research process], such as the concept of randomisation and why and how data might be collected e.g. by electronic data capture or by devices. These established field sites are very important for quality." Another PI compared the relative ease of community engagement for a JGHT-funded trial in a location near a joint unit (with well-established engagement processes), with the challenging situation the study team had encountered when preparing for implementation in a region without these advantages.

One PI outlined the benefits arising from community engagement for the JGHT-funded trial and beyond: "Engagement with service users and carers drove the co-development of the project through a participatory approach, giving those affected the opportunity to have a voice and choice in the development of interventions in their country. In addition to supporting the trial itself, wider engagement with the general public and health professionals has also been a crucial means of tackling stigma and strengthening the research infrastructure within [the LMIC]".

5.3 Challenges to trial implementation

5.3.1 Overview of challenges to trial implementation

Overall, the main challenges during trial implementation were prolonged and complex administrative processes, particularly in relation to regulatory and ethical approval, difficulties with trial recruitment, and local capacity issues, all of which caused delays and at times required additional budget (Figure 29).

PIs of 65% of full trial awards (31 of 48) and 60% of development awards (12 of 20) reported issues with administrative processes and requirements at the trial site(s), including approval processes (35% of full trial PIs, 17; 25% of development award PIs, 5) and contracts/financial transfers (15% of full trial PIs, 7). Both types of awards reported issues with hiring and retaining staff with the required skills at trial sites (35% of full trials, 17; 45% of development awards, 9), whereas recruitment was a challenge for a

⁵³ Negussie H et al (2016) Preparing for and Executing a Randomised Controlled Trial of Podoconiosis Treatment in Northern Ethiopia: The Utility of Rapid Ethical Assessment. PLoS Negl Trop Dis 10: e0004531

larger share of full trial PIs (48%, 23). Civil unrest, such as tribal wars and government coups, and worker strikes had caused challenges for seven full trial awards and 3 development awards (15% each).

In line with the effect of these challenges, nearly half of co-investigators who in hindsight would make changes to the project design pointed to changes to the study timeline (42%, 26 of 62), with many highlighting the challenges and unpredictability of working in an LMIC environment, and the need to allow more time for recruitment of participants.



Source of data: Data on 20 PIs of active full trial awards and 20 PIs of development wards from surveys; data for 24 closed and 5 active full trials from interviews and desk research. As one trial was not implemented, it was not counted toward the total number of full trials in this analysis. Full analysis includes 48 full trial and 20 development awards.

5.3.2 Complex approval processes and administrative requirements

Several PIs of full trial awards commented that the time required for approval processes and contractual arrangements has increased in recent years. Countries in Eastern and Southern Africa have changed their requirements, leading to prolonged and at times multi-stage applications. One PI reported that approvals can take over 200 days at some sites; others explained that the process of obtaining all required ethical and regulatory approvals can involve three or four separate applications and committees in each country, each with varying capacity, requests, and demands. As one PI commented by survey: "There are so many unexpected extra layers of 'bureaucracy' that cannot be anticipated. It takes time to navigate through these things. I could fill a book with the number of unexpected administrative things that come up in projects like this."

Two PIs also pointed to delays in obtaining approvals from their UK institutions which were not experienced in dealing with research conducted at sites in LMICs, and two PIs from LMICs highlighted the challenge of knowing how to obtain approval from a UK institution for LMIC-led trials. One PI suggested the funders could help overcome this barrier by providing support, or a centralised process, for UK trial sponsorship. To cope with delays caused by slow approval processes, a few PIs mentioned that they had applied for no-cost extensions (and highlighted the importance of this flexibility in the funding programme). One PIs explained that having a local study team member engage directly with key decision makers had helped to progress the process.

Two PIs partnered with NGOs already set up in-country to handle financial transactions and administration. For example, one PI partnered with an NGO already established in the country and active in the (remote) area where the trial was to be implemented. The NGO was able to oversee all financial transfers, which would have been very difficult and time-consuming to manage directly

between the UK and the local research institutions. In addition, the NGO supported trial logistics in terms of consumables transport and assisted in hiring of local staff. While comprise had to be found between the NGO's strict operating processes and the unpredictability of timing in research projects, the PI summarised the partnership with: "It was a real really helpful step. It was easier to go through them, financially and with contracts that needed to be put in place – much easier." In return, the NGO benefitted from the recognition and the experience of assisting with a research trial.

A few researchers mentioned that insurance can be difficult and costly to obtain, due to change in local requirements or because of a lack of precedence. To mitigate against this problem, one co-investigator suggested the funders arrange for global insurance for all its trials through a central company, securing better rates in this way.

5.3.3 Participant recruitment

Half of full trials (23) reported that recruitment had been slower or more difficult than expected. Where reasons were provided, these mainly related to a lower disease incidence than expected. This was the case especially in trials addressing malaria in low transmission settings, where year-on-year variation and enhanced roll out of transmission control or treatment can reduce the number of infected patients ahead of the trial. In other cases, recruitment was slow due to social stigma attached to the intervention (3), because healthcare staff found it difficult to change routine care to accommodate the intervention (1), or due to individuals opposing the trial in the community (2). PIs were able to address these issues by increasing the number of trial sites (8), scaling down the trial (2), moving sites/shifting recruitment targets between sites (3), or moving to a continuous enrolment model (2). In one case, investigators from different LMICs shared their approaches to recruitment, resulting in an uplift in recruitment at 'slower' sites (see Case study 2).

Several PIs (5) working with culturally sensitive interventions, or in communities that had not previously been exposed to research activity, highlighted that they had prepared their studies through extensive community and stakeholder engagement (see section 5.2.4). These tended to report fewer issues with recruitment. One study reported that recruitment for a trial addressing a severely stigmatised condition was initially challenging, but was ultimately achieved by further increasing community engagement, involvement of stakeholders including service users and carers, and awareness raising activities. Conversely, the PI of a trial with major recruitment and compliance issues throughout the study felt that these might have been avoided by community engagement to better understand cultural barriers ahead of trial implementation.

5.3.4 Capacity shortages

Issues with staff at trial sites included both high turnover and a shortage of staff with the required expertise. While a degree of training is expected as part of any trial, PIs commented that high turnover of clinical and field staff at trial sites required frequent re-training (10). Reported capacity shortages at LMIC sites included trial coordinators, social scientists, health economists, and data managers. Especially projects involving new trial centres, with no or little prior experience of implementing RCTs, had to provide substantive training.

A number of PIs provided examples of how they overcame challenges. For example, one project was delayed due to the high turnover of trial staff and the need to retrain new staff members. The project team therefore developed an online training module to facilitate a quicker orientation and training process. In two other projects where staff with the required level of skills was not available, the PIs recruited less qualified individuals with the 'right' characteristics (e.g. motivated, committed, smart) and provided ongoing training and mentoring to help them to gain additional skills.

Two PIs specifically called out the important role of UK-supported research units in LMICs ("joint units") in providing capacity. As one PI explained: "Without [this unit], we would never have been able to conduct the trial, because we do not have this clinical trial unit support in this country. The unit has experts in clinical trial design, in data management, it has clinical trial monitoring teams, clinical research managers...all of these people. It's like the whole machinery has already been built in the country, and we were now in a position to work with local institutions to deliver the trial. I think that

without such a unit, it would be very tough for an LMIC to deliver on their own because they lack the clinical trial capacity."

5.3.5 Other challenges

Other challenges facing JGHT-funded projects included:

- Unstable political environment, such as tribal warfare, coups, and workers strikes (10)
- Roll out of national interventions interfering with the trial (2)
- Currency fluctuations (decrease in the value of the GBP), leading to budgetary challenges (2)
- High turnover of government staff, making it difficult to interface with local public health officers and public health interventions (1)
- Challenges relating to suppliers and manufacturers of intervention (4). In two cases, this led to delays in access; in one case, the product was no longer produced and the trial had to make major adjustments.

5.4 Outputs

5.4.1 Completed full trials and main trial finding publications

Main trial findings, i.e. those that relate to the trial's primary research question, have been published for 24 full trial awards (20 of 28 closed full trial awards; 71.4%) and 4 open full trial awards. One trial followed a 2x2x2 factorial design and has published three papers describing the findings for each of the three interventions tested (see Case study 3), bringing the total number of publications of main trial findings to 26.

Of the eight closed full trials that have not published the main results, three have submitted papers for publication, two are in the final analysis stage, and one trial did not take place due to unforeseeable external circumstances. There is no information on the status or intent to published for remaining two trials.

The majority of findings were published in 2018 and 2019 (7 and 8 publications, respectively) (Figure 30), with six papers appearing between June and October 2019. The short timeframe since publication can be expected to affect the level of outcomes and impacts achieved.



Figure 30 Number of main trial findings published in scientific journals, by year

Source of data: Desk research - 26 main trial findings publications, stemming from 24 full trial awards (20 closed, 4 active)

5.4.2 Definitive answer to the research question

An analysis of results based on the main trial publication indicates that 12 trials confirmed the trial hypothesis (including two Phase II trials), and 8 trials disproved the hypothesis. The trial testing three interventions confirmed the trial hypothesis for one and disproved it for the other two. The remaining trials were:

- A trial which was stopped as the intervention was found to cause harm to participants (see Case study 2)
- A full trial comparing two interventions (rather than stating a specific hypothesis), and found a significant difference between the two (see Case study 1)
- A feasibility study, funded in Call 1, which led to a full trial award in Call 5 (see Case study 10)

A number of PIs increased the sample size during the implementation of the trial (5), and one of the PIs interviewed reported that in hindsight, they would increase the participant size to increase the power of the trial. For one of the trials which reported a significant difference in primary outcome, one co-investigator nevertheless stated that it was 'underpowered'.

5.4.3 Trial methodologies

The JGHT has an interest in advancing trial methodologies, and call specifications starting with Call 7 encourage applications trial designs.

Methodologies employed in full trials funded in calls 1-7 were mostly standard two-arm blinded or nonblinded individually randomised or cluster randomised controlled trials. Four trials included four arms, and two trials included three arms. Four trials employed factorial designs (one each of 2x2x2, 2x2, 3x2 and factorial design). While these are not novel, PIs explained that they were not often used in LMIC settings. Two development awards employed stepped-wedge study designs. One trial followed a novel trial methodology, using a multi-arm multi-stage (MAMS) framework (see Case study 14).

5.4.4 Publication of findings

Research projects reported on a variety of study findings in addition to results related to the primary research question (main trial findings). These include the trial protocol developed, social and economic studies, validation of assays and diagnostic tests, and epidemiological studies and surveys. In addition, PIs and co-investigators may publish literature reviews and opinion pieces, as well as conference abstracts and book chapters.

71.4% of closed full trial awards (20 of 28) and 4 open full trial awards have published the main findings of the trials, publications for a further three trials are under review, and one trial is in the final stages of analysis. For development awards, 45.5% of PIs of closed awards (5 of 11) reported that they had published findings; publications of a further four PIs were under review. The remaining two PIs indicated that the project was still ongoing. In addition, one of the nine active awards had published results, and another active award had a publication under review.

The ResearchFish® database contains self-reported outputs and outcomes data on most of the JGHT awards (84 of 96). 70% of award holders (59 of 84) reported 772 publications related to their JGHT-funded research, while 25 awards (including all active development awards) did not report any publication. Notably, 338 of these publications were reported for one award. While this is a very long-running award, it represents an outlier compared to the rest of the data. Hence, we excluded this award to avoid skewing the analysis of remaining data.

After excluding the outlier from the analysis, 434 publications were reported for 58 awards, coming to a mean of 7.5 publications per award (see Figure 31). Of these, the vast majority (94%) are journal articles. As would be expected, the smaller development awards that are funded for a shorter period produce fewer publications on average (mean of 4.1/award) than the full trial awards (mean of 8.6 and 9.1 for active and closed awards respectively). For detailed analysis of publications reported in ResearchFish®, see Appendix C.





Source of data: ResearchFish®

Table 12 shows journals (12) in which JGHT awardees most frequently published their research findings (according to ResearchFish®), as well as all journals in which main trial findings of full trial awards have been published. Of these, nine are open access journals; the remaining offer immediate open access to specific articles on the payment of a fee (hybrid open access) and/or to all articles after 6 months (delayed open access).

Journal	Open Access?	All publications* (number)	Main trial findings ** (number)
PLoS One	Yes	21	
The Lancet	Hybrid/Delayed	17	7
Trials	Yes	17	
Clinical Infectious Diseases	Hybrid	16	1
BMJ Open	Yes	15	1
The Lancet Global Health	Yes	15	5
Wellcome Open Research	Yes	13	
The Lancet Infectious Diseases	Hybrid/Delayed	12	3
BMC Public Health	Yes	11	
International Journal of Tuberculosis and Lung Disease	Hybrid/Delayed	11	
Malaria Journal	Yes	11	1
The New England Journal of Medicine	Delayed	11	5
The Lancet HIV	Hybrid/Delayed		1
PLoS Medicine	Yes		1
EBio Med	Yes		1

Table 12 Top journals for publications

Source of data: *ResearchFish \otimes ; **Desk research

5.4.5 Development awards leading to full trial funding

The aim of the development award scheme is to develop trial application ideas into robust and competitive proposals by conducting feasibility studies and obtaining preliminary data. Following on from a development award, one investigator was awarded a full trial (see Case study 13). A smaller award in Call 1 funded a feasibility study which led to a full trial award in Call 5 (see Case study 10). Six PIs who had led development awards reported that they had obtained funding for further studies, including at least for four full trials, from other funders (see section 5.5.2)₅₄. Hence, of 22 closed development awards funded so far, at least 23% (5) have led to a full trial.

The scheme is also used by PIs who were not successful in securing a full trial award to gather additional data - two full trial proposals that had been rejected at the second stage of the application process went on to successfully apply for a JGHT development award; a third was successful in Call 9_{55} .

An increase in applications from development award holders (and potentially successes) can be expected in the future: Of the development award PIs consulted who had not yet secured further funding, 40% (6 of 15) indicated that the study had been successful and that they were in the process of applying for a full trial award. At the same time, the scheme is also serving to avoid failure of expensive full trials: Three PIs indicated that the development award had demonstrated that the plans for the full trial needed to be significantly changed, and that further preliminary data needed to be collected.

5.4.6 New collaborations

PIs from active full trial awards and development awards reported working with new partners during their JGHT funded project (86%, 18 of 21 of full trials; 75%, 15 of 20 of development awards). Most projects had started to collaborate with partners located in LMICs (77%, 16 full trial awards; 65%, 13 development awards) (Figure 32). Half of the PIs of closed trials (11 of 22) reported that their project had involved new HIC-LMIC or LMIC-LMIC partnerships.



Source of data: Survey of PIs of full trial awards (active) and development awards

The majority of PIs of active full trial and development awards indicated that they either have plans to collaborate in future (38%, 8 of 21; 15%, 3 of 20, respectively) or do not have currently plans but would be open to future collaborations (62%, 13; 75%, 15, respectively). Most full trial PIs wanted to engage in

⁵⁴ As information on rejected full trial outlines (stage 1) was not available, the MRC database data does not contain information on the overall number of full award outlines submitted following a development award.

⁵⁵ As information on rejected full trial outlines (stage 1) was not available, the MRC database data does not contain information on the overall number of rejected full trial proposals *at outline stage* that then went on to apply for a development award.

'regular information exchange and advice' (71%, 15) and half intended to work on joint proposals (52%, 11). The largest share of development award PIs planned to develop a joint proposal (45%, 9).

Half of co-investigators consulted thought that the JGHT project they were involved in had given them contacts for future work (53%, 92 of 172) and reported that collaborations started through a JGHT project were ongoing, beyond the JGHT-funded research (50%, 86 of 172) (see section 5.5.2).

5.4.7 Enhanced knowledge and skills in the UK and/or LMIC

Investigators are likely to gain knowledge and experience through participating in the design and implementation of a study.

70% (120 of 172) of co-investigators from both LMICs and HICs reported that they had either been involved in all aspects of the design of the project, or had made substantial contributions to some aspects of the study. This share was similar for co-investigators from LMICs and HICs (Figure 33). Nearly three quarters of PIs of UK-led active full trials or of development awards (73%, 16 of 22) also indicated that LMIC researchers had been engaged throughout the project, including project design and implementation.

As reported in section 5.1.9, an analysis of author affiliation of publications of 22 full trial awards showed that investigators from a total of 106 institutes were named as co-authors. Over half of these institutions were located in LMICs (53.8%, 57). While this does not suggest the level to which LMIC researchers were involved in trial design and data analysis, it indicates that the contribution of investigators in LMICs is being recognised. 31% of first authors of these publications (8 of 26) were affiliated with joint units, and 27% (7) with LMIC institutions and HIC institutions, each. Two first authors held dual appointments at institutions in HICs and LMICs, and one was a researcher from an LMIC sponsored to complete a PhD at a UK institution to implement the JGHT-funded trial.





Source of data: Survey of co-investigators

The majority of co-investigators indicated that the JGHT-funded project had positively impacted their scientific knowledge (82%, 140 of 170). In particular, the research had provided co-investigators in LMICs and HICs with scientific knowledge that they were able to use for their further work (71%, 121 of 170) and on the basis of which they were able to secure additional funding (28%, 48) (Figure 34). A number of PIs reported that LMIC researchers and clinicians were promoted or offered opportunities for career advancement as a result of the experience gained by participating in the JGHT study (11).

Knowledge of the context in which the research was carried out was also enhanced, particularly knowledge of local health needs (reported by 49% of all co-investigators (83 of 169); 60% of LMIC and 45% of HIC investigators) and knowledge related to the local health system (40% of LMIC and HIC investigators).



Figure 34 Knowledge impacts of JGHT-funded research (co-investigators)

Source of data: Survey of co-investigators. The number of respondents for each question was: Scientific knowledge LMIC n = 65, JU n = 25, HIC n = 75; context knowledge LMIC n = 66, JU n = 24, HIC n = 74.

39% of co-investigators reported that the JGHT-funded research had influenced the work of others in their organisation (66 of 168). This view was more common among co-investigators from LMICs (55%, 36 of 66) (Figure 35). Other benefits included increased knowledge of LMIC researchers beyond the study team (42%, 67), new contacts made by the institute (33%, 56) and securing of further funding by the organisation (26%, 43). Across all categories (except LMIC researcher skills), a larger share of LMIC investigators reported impacts (and a smaller share of LMIC investigators reported 'no impact').

For example, an investigator based in an LMIC reported that "the information gathered and the wealth of experience has made [our] organisation attractive for other research donors and partners and has strengthened the relation with the Ministry of Education and Health". Another respondent explained that "our research organisation is now recognised at the national level for high quality research that informs policy on maternal and child health programmes in the country". As a result of a partnership developed through the JGHT-funded research, one investigator reported that a grant application was underway to formally link clinical trial units at an LMIC and a UK institution; another organisation had established a partnership with two of [the country's] leading medical schools and the local government department of health.

Figure 35 Impact of JGHT-funded project on co-investigator institute



Source of data: Survey of co-investigators; LMIC: n = 66, JU: n = 25, HIC: n = 72

Of closed full trial PIs who discussed skills and knowledge acquired, 65% highlighted that the research had enhanced trial capacity at the trial site(s) (13 of 20), including through training in trial methodology and data management. Five PIs mentioned training of laboratory technicians as part of their trials, and another five emphasised the trial's extensive training of field workers in the delivery of the intervention and data collection, including via electronic capture. A few PIs pointed out that at many hospital trial sites, doctors and nurses are trained to establish a suitable standard of care in the control arm, and to allow implementation of the intervention to be tested.

Three PIs highlighted that the JGHT-funded research enabled trial sites to build up expertise and networks they can draw on for further research. For example, a trial investigating the effect of cleaner cookstoves on pneumonia in children was able to develop expertise on chronic lung disease at the trial site, which has since been used in other studies. Other trials led to expertise in, and platforms for, studies involving infants and studies on maternal vaccination.

5.4.8 Enhanced research tools and infrastructure

Consulted by survey, 29% of PIs of full trials (6 of 21) and 30% of PIs from development awards (6 of 20) reported that new tools had been developed. Examples included tools such as treatment manuals, consent tools, and tools to assist data collection and patient enrolment.

PIs of closed full trials described a number of tools developed for use in the trial itself which have been used for further research. One trial developed a barcoding system for drug packaging to reduce the risk that the intervention and placebo is interchanged between participants⁵⁶, another developed a survey tool and platform which is now being used by the local health officials, a third improved the design of a

 $_{\rm 56}$ Novel at the time of the trial, has now been superseded by more advanced approaches

fly trap used for research. There were a few examples of sample collections (e.g. blood and stool samples) which are being used for follow-on research.

More than a third of co-investigators based at LMIC institutions reported by survey that the JGHT award had allowed their institution to establish new infrastructure (38%; 25 of 66) (Figure 35). This share was much higher than for institutions in HICs (8%, 5 of 75) and joint units (7%, 2 of 25) (as can be expected, since by definition, JGHT research is carried out in LMICs). In interviews, PIs provided examples of infrastructure established, including diagnostic equipment and laboratories and research platforms (e.g. processes and systems).

In ResearchFish®, PIs of 44 awards indicated that they had developed at least one new research tool, research method, database or software, with 149 new tools reported (see Appendix C). These included databases/data collections, improvements to research infrastructure and new physiological assessment or outcome measures for trials (Figure 36).



Figure 36 Type of tools developed by type of award

Source of data: ResearchFish®

Examples of databases/data collections reported in ResearchFish® mainly relate to databases of data collected in the JGHT studies. Other examples include a database of SMSs appropriate for pregnant teenage girls, a database of treatment reported for community-based deworming and datasets containing costing or household records. Research infrastructure developed in JGHT awards includes electronic medical record systems, data forms and questionnaires, and establishment of new trial sites. New physiological assessment or outcome measures include a household ventilation assessment method for nurses, a quality of life questionnaire for people affected by TB living in shantytowns and an adapted Internalized Stigma of Mental Illness Scale (ISMIS) to measure TB self-stigma.

Only about a quarter of the new tools, databases and software were available to others outside the research team. While the impact of the tools was largely unknown, some types of impact cited include improvement in skills and knowledge, enabling of research through use of research tools and methods by others outside the research team, and better and more accurate data collection and management through the use of databases.

5.4.9 New collaborations between researchers and implementation stakeholders

45% of active full trial PIs (9 of 20) and 35% development award PIs (7 of 20) reported that they had worked with new policy and implementation partners as part of the JGHT-funded research (Figure 37). The main examples of organisations PIs had started to engage with were WHO, LMIC ministries of health (or equivalent), and NGOs. Most PIs reported either an ongoing partnership with the policy makers and implementation partnerships developed under the JGHT award (50% of full trial PIs; 40% of development award PIs) or the intention to partner again in the future (25% and 30%, respectively). A smaller number reported that they do not envision a future partnership (20% and 15%, respectively).

A detailed analysis of stakeholder engagement activity as part of JGHT-funded research is provided in section 5.2.

Figure 37 Policy/implementation partnerships



Source of data: Survey of PIs of full trial awards (active) and development awards

5.4.10 Stakeholder awareness and buy-in

Key decision makers, such as international or national policy organisations, need to be aware of the findings of JGHT-funded trials and understand the implications of the research in order to inform policy decisions and, if suitable, effect policy change.

The majority of PIs of closed, implemented full trials indicated that key decision makers at national level (generally, Ministries of Health), or international level (WHO) were aware of the project and its findings (where available) (75%, 20 of 27₅₇). This was a result of stakeholder engagement during the trial (see section 5.2), as well as continued efforts, such as presentations and targeted discussions, following the closing of the award. Only one PI thought that key decision makers were unaware of the trial's findings. (It should be noted that these findings are limited in strength as they are based solely on the perceptions of PIs, rather than on the views of relevant key decision makers.)

5.4.11 Health benefits to study participants

Health research can have direct as well as indirect benefit on the health of study participants. PIs of both full trials and development awards indicated that this was often a result of participation itself, irrespective of the intervention tested, providing participants with improved access to (standard) care and medication, enhanced monitoring and diagnostics, receiving information pertaining to the condition of interest, enhanced awareness of the problem in the community, and upskilling of those delivering an intervention.

⁵⁷ Findings of a further two trials are probably known to key decision stakeholders, indicated by the context information provided by the PI in interview, but was not directly confirmed. The situation for 4 trials is unknown.

Two (large) trials alone have led to *direct* health benefits for around 450,000 individuals. The TUMIKIA trial reduced the prevalence and transmission of helminths in clusters treated at a community-level, rather than through school-based deworming (see Case study 9). With 100,000 households participating in the effective treatment arms, and an average Kenyan household size of four₅₈, around 400,000 individuals will have benefitted from participating in the trial. Another trial investigated the effectiveness of a novel insecticidal net and indoor residual spray interventions (see Case study 7). A total of 45,000 of the novel bed nets were distributed, reducing the prevalence and transmission of malaria, for those using the nets as well as more widely in the villages. Another trial prevented more than 3 deaths for every 100 people starting anti-retroviral therapy, saving the lives of around 30 participants receiving the intervention as part of the trial (see Case study 3).

Most PIs described indirect benefits for the broader community, through an improved standard of care as a result of training of healthcare providers as part of the JGHT-funded study, due to greater awareness/education about the condition, or as a result of the effectiveness of the intervention. For example, one PI explained that individuals beyond the trial intervention clinics are likely to have benefited because the study had raised awareness of the disease in all of the settings. Another highlighted that 140 health professionals were trained in a technique relevant to the disease the trial addressed, but that this technique could also be applied assist with other clinical problems. A third explained that a lot of training and engagement was carried out locally to ensure an appropriate standard care, as per WHO and national guidelines, for all study participants – a standard that was not generally reached by the trial hospitals prior to the study. On the other hand, a key opinion leader explained that while trials often enhance the standard of clinical care during the trial, this standard suddenly drops after the trial finishes. Additional support would therefore be required to sustain this benefit.

In the survey, 90% of PIs of active full trials (18 of 20) reported that their research had led to health benefits for study participants, with the remaining 10% indicating that benefits had not arisen yet, but were likely to do so over the course of the project. Similarly, 75% of PIs of development awards indicated that the research had led to health benefits (15 of 20), with a further 15% (3) reporting that benefits were likely to arise over the course of the project. Of the 20 PIs who were asked about health benefits to research participants, only one indicated that there had not been any.

5.5 Scientific outcomes

5.5.1 Further research informed by project findings

Nearly all closed full trials have published, or are preparing publication of their main findings (93%, 25 of 27, with one additional trial ongoing). A simple analysis of citation data shows that eight papers published between 2015 and 2018 have been cited more than 20 times, and two papers more than 70 times, indicating that findings are used by the wider research community₅₉.

Given the short time period since most of the trials reported, a full citation analysis comparing citation rates of JGHT publications with those publications in the same research field is not yet possible. Indications are that citation impact is high, as shown by an analysis of the six highest-cited papers₆₀:

- Adjunctive dexamethasone in HIV-associated cryptococcal meningitis, NEJM 2016: Total of 113 citations, Field-Weighted Citation Impact: **23.5**
- A cleaner burning biomass-fuelled cookstove intervention to prevent pneumonia in children under 5 years old in rural Malawi, The Lancet 2017: Total of 83 citations, Field-Weighted Citation Impact: **23.2**

⁵⁸ United Nations Department of Economic and Scoial Affairs (2017) Household size and composition around the world. Popfacts No. 2017/2

⁵⁹ Status 16 October 2019.

⁶⁰ Field-weighted citation impact (FWCI) is a metric that compares a given document to similar documents; a value greater than 1.0 means the document is more cited than expected according to the average over a three-year window. It takes into account the year of publication, document type, and disciplines associated with its source. Date of analysis: 14 Nov 2019

- The Good School Toolkit for reducing physical violence from school staff to primary school students, The Lancet • Global Health, 2017: Total of 53 citations, Field-Weighted Citation Impact: 8.3
- Enhanced prophylaxis plus antiretroviral therapy for advanced HIV infection in Africa, NEJM 2017: Total of 49 citations, Field-Weighted Citation Impact: 13.4
- Effectiveness of a long-lasting piperonyl butoxide-treated insecticidal net and indoor residual sprav interventions, separately and together, against malaria transmitted by pyrethroid-resistant mosquitoes: a cluster, randomised controlled, two-by-two factorial design trial. The Lancet 2018: Total of 39 citations, Field-Weighted Citation Impact: 24.0
- Rapid urine-based screening for tuberculosis in HIV-positive patients admitted to hospital in Africa (STAMP): a pragmatic, multicentre, parallel-group, double-blind, randomised controlled trial, The Lancet 2018: Total of 34 citations, Field-Weighted Citation Impact: 20.3

The Field-Weighted Citation Impact (FWCI) of these six publications is already far above average, despite the fact that only the first publication listed was published more than three years ago (and has hence accumulated the full number of citations). The FWCI of the other publications can be expected to increase as they accrue further citations before they reach the three-year point.

Around one third of PIs of closed development awards (36%, 4 of 11) reported that their project findings or outputs have been taken up by other researchers, while 45% did not know whether the findings had been used (Figure 38). Of active awards, 38% of PIs of full trials (8 of 20) and 22% PIs of development awards (2 of 9) reported that their project findings or outputs have been taken up by other researchers.



Figure 38 Uptake of research findings

Source of data: Survey of PIs of full trial awards (active) and development awards; Full active trial: n=20, Development award active: n=9, Development award closed: n=11

5.5.2Follow-on funding

According to ResearchFish®, 50 of 84 (60%) JGHT awards have received substantial additional funding (grants of more than £10,000). However, it was not possible to reliably distinguish between funding received to supplement the JGHT award (co-funding) and follow-on funding within the data available in all cases. Further funding was mainly in the form of research grants (83% of the total). Full awards reported more additional research grants and fellowships/studentships than development awards (Figure 39). JGHT awards captured a total of around £160m in further funding from other organisations. This corresponds to a mean of $\pounds_{3,2m}$ further funding per JGHT award (n=50).





Source of data: ResearchFish®

Table 13 shows the funders who have provided three or more grants to JGHT projects. 39 other organisations provided 1-2 grants. The major funders were MRC, Wellcome Trust and BMGF, in that order. Funders did not award more than two grants for the same JGHT award with the exception of the MRC that awarded three additional grants to two full awards. The Wellcome Trust, EDCTP, NIHR, BMGF and the NIH provided on average larger grants than the other funders.

Table 13 Funders pr	oviding further	funding to JGHT awards
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Funder organisations	Number of grants awarded	Number of JGHT awards that received grants	Average amount of grant (x 1000 GBP)
Medical Research Council (MRC)	18	14	639
Wellcome Trust	11	10	4932
Bill and Melinda Gates Foundation (BMGF)	11	10	2395
Grand Challenges Canada	6	5	78
National Institute for Health Research (NIHR)	6	6	3338
European and Developing Countries Clinical Trials Partnership (EDCTP)	5	4	4176
National Institutes of Health (NIH)	5	5	1413
International Development Research Centre	3	2	513
Total	65	36	269

Source of data: ResearchFish®

Nearly half of the PIs of full trials and development awards (48%, 24 of 50; 45%, 10 of 22, respectively) reported in the survey and interviews that they had secured additional funding for research related to the JGHT award. Approximately a quarter were developing or had submitted proposals (26% and 23%, respectively). As for the ResearchFish® data, the main funders reported to support work based on JGHT awards were the MRC, BMGF, EDCTP, Wellcome, and NIHR/DfID.

The nature of follow-on funding secured by JGHT award PIs fell into four broad categories:

- 1) Funding for a full trial following a development award
- 2) Funding for a further full trial
- 3) Funding for other types of studies building on the JGHT award
- 4) Funding for networks and consortia

1) Funding for a full trial following a development award

PIs of seven development awards reported that they had secured further funding. One PI received a full trial award from the JGHT (see Case study 13)₆₁. At least four of the other six development grants PIs secured funding for a *full trial* from other funders. For example, the findings of a development award on reducing antibiotic over-prescribing in China informed the design of a larger RCT trial funded by DfID through the Communicable Diseases (COMDIS) Health Services Delivery Research Consortium (see Case study 15). Other follow-on funding was secured from the NIH Research Project Grant Program (USD2,500,000), the EDCTP (€5,977,299), and the Administrative Department of Science, Technology and Innovation (Columbia) (£301,000). (Two of these had originally applied for a JGHT full trial award, but were not successful.)

2) Funding for a further full trial

Following the JGHT project, a number of full trial project teams have been awarded funding to conduct new trials that build upon the work of the JGHT project. This includes six full trial PIs who secured a second (or third) JGHT full trial award. There was one example of a PI being awarded a JGHT development award after the full trial to address a barrier to intervention.

Other examples include:

- The DeWorm3 trial, which is extending the findings generated in the JGHT TUMIKIA trial (see Case study 9). DeWorm3 is funded by the Bill & Melinda Gates Foundation and led by the Natural History Museum London (USD895,068). Funding was also awarded by the EDCTP (€4,899,488) for an additional clinical trial (STOP) that will incorporate the same research team involved in the TUMIKA trial.
- A trial funded jointly by MRC, DFID and NIHR, taking the same intervention used in the JGHT trial and adapting it for a different population (adolescents instead of adults)₆₂. The new study will draw on the networks and partnerships developed during the JGHT project.
- The PI of a JGHT-funded trial will be involved in a related trial investigating the effect of the same intervention but targeted to a specific age group. The trial is funded by the BMGF (USD6.5m).

3) Funding for other types of studies building on the JGHT award

PIs reported funding for a range of studies that build on evidence and materials generated during the JGHT project. These studies ranged from smaller funding pots of USD25,000 to larger grants over £1M and varied greatly in nature (Table 14). For example, a development award PI received a small grant from the Arts & Humanities Research Council / MRC to develop qualitative interview tools to explore participants experience of the trial (£41,235). A member of the REALITY trial team received an MRC grant (£813,361) for pathogen testing of blood and faecal samples collected during the trial (see Case study 3). A development grant PI (see Case study 16) is co-investigator on a NIHR grant which provides funding for a stakeholder engagement workshop designed to inform a scale up of the development award.

⁶¹ In addition, a feasibility study funded before the development scheme was established received a full trial award (see Case study 10).

⁶² https://gtr.ukri.org/projects?ref=MR%2FR022461%2F1

Study type	Funders	Count of projects
Feasibility/additional baseline data, social studies	Wellcome Trust, DFID, Arts & Humanities Research Council (AHRC), UKRI, MRC, NIHR	5
Community/stakeholder engagement	NIHR, Wellcome Trust	2
Microbiological studies	NIHR, MRC	2
Epidemiological studies	Bill & Melinda Gates, MRC	2
Other - Assessment of case definitions, drug safety	Bill & Melinda Gates, Medicines for Malaria Venture (MMV)	2

Table 14 Types and funders of extension studies

Source of data: PI surveys and interviews

4) Funding for networks and consortia

A number of JGHT awards led to funding for research networks and consortia. These were typically large grants to support the development of research collaborations, infrastructure, and largescale stakeholder engagement. The role of JGHT funded projects in securing these grants was less direct than for other types of follow-on funding, but PIs reported that their contribution had been important. In one example, the PI of a full trial reported that networks built during the JGHT project were instrumental in the project team being awarded a \pounds 7M grant for the IMPALA project, a research unit on Lung Health and Tuberculosis in Africa under the NIHR Global Health Research Programme. Similarly, JGHT-funded research supported a successful bid by the University of Sussex to establish an NIHR Global Research Unit (for \pounds 5.7m, 2017-21) (see Case study 5). A JGHT trial on Severe Acute Malnutrition (SAM) in infants helped to secure funding for the Childhood Acute Illness and Nutrition Network (CHAIN), a global research network funded by the BMGF (USD18.7m).

5.5.3 New /strengthened international research networks

JGHT awards have contributed to the formation of international research networks and helped to secure funding to support these (see section 5.5.2).

Co-investigators also reported an increase is their collaborative partnerships and participation in research networks. Half of the survey respondents, from both LMICs and HICs, indicated that the JGHT project had given them contacts for future work (53%, 92 of 172) and that collaborations formed during the JGHT project had continued after (or outside) the project (50%, 86 of 172) (Figure 40). 30% (52) reported that the JGHT project led them to become active in new research networks; this share is higher among co-investigators from LMICs, at 40% (26 of 66). A high share of LMIC co-investigators also indicated that they had established new collaborations with implementation partners (35%, 23 of 66), compared to 13% of researchers from HICs (10 of 76).



Figure 40 Collaboration and networks impacts of JGHT trial on co-investigators

Source of data: Survey of co-investigators. Number of respondents: LMIC n = 66, JU n = 25, HIC n = 76

Referring to the impact on collaborations and networks at the project site, 40% of co-investigators (65 of 161) reported that the JGHT-funded research had built up, or expanded, an international network of researchers, with more researchers in HICs pointing to this effect (50%) (Figure 41). A third of investigators considered that the JGHT award had expanded local researcher networks (34%, 35 of 161).

Figure 41 Collaboration and networks impacts of JGHT trial at project site



Source of data: Survey of co-investigators. LMIC n = 64, JU n = 25, HIC n = 68

5.5.4 Enhanced research environment

JGHT research assisted in shaping the environment for health research to facilitate future studies.

Both full trial and development award PIs reported that the project had increased the priority of health research within LMIC institutions (50% of full trial PIs, 10 of 20; 30% of development award PIs, 6 of 20), reduced cultural and operational barriers for future health research (45%, 9 of 20; and 30%, 6 of 20, respectively), and convinced decision makers and practitioners of the value of health research (40%, 8 of 20; and 30%, 6 of 20, respectively).

Co-investigators reported a range of effects of the JGHT awards at the research location, i.e. beyond the JGHT-funded study team (Figure 42). Just over one third each thought the research had helped convince practitioners and decision makers of the value of global health trials and health research, and

increased LMIC researchers' leadership capabilities (35%, 54 of 161₆₃). 28% (45) thought the research had reduced operational barriers to future health research. The share of co-investigators indicating that LMIC institutions' research governance structures had been improved was twice as high among individuals located in LMICs compared to those in HICs (26%, 17 of 64; vs 13%, 9 of 68). Further explaining the nature of wider impacts, several co-investigators pointed to the building of stronger relationships between researchers and policy makers (12).





Source of data: Survey of co-investigators. Number of respondents: LMIC n = 64, JU n = 25, HIC n = 68

⁶³ This percentage is likely to be higher, as the survey included co-investigators of studies that started only recently, and who indicated 'no/not yet' to answer the question. Some of these projects are likely lead to impacts as they progress to a later stage.

5.6 Policy and health outcomes

5.6.1 Influence on policy related to health interventions

Eight full trial awards have informed policy and are cited in guidelines or policy documents, with evidence from a further three trials incorporated into policies to be soon released.

• Influence on WHO policy

There were ten instances of where JGHT-funded trials influenced WHO policy₆₄. Four trials have had a direct influence on WHO guidelines (e.g. see cases Day, Gibb, Rowland), with one other expected to do so in the next weeks. Two trials informed the WHO Essential Medicines list and one has lent confidence to a current WHO recommendation that had experienced concerns over safety (see Case study 3 and Case study 4). A further trial has contributed to a WHO recommendation of a diagnostic test (see Case study 8), and another trial was taken up in a WHO best practice strategy paper (see Case study 6).

WHO guidelines are 'automatically' adopted by (many) countries, and do not require a policy scale-up as such₆₅. Further research can scale policy impact in terms of the target population; for example, one project team is now working on adapting an intervention developed for primary schools for use in secondary schools (see Case study 6). Further research can also provide evidence to refine the policy recommendation; e.g. one study team is now involved in a further trial to determine the effect of an intervention on a smaller sub-population.

• Influence on national guidelines

Evidence from three trials influenced national guidelines⁶⁶: One trial was taken up into national guidelines in Vietnam, and also cited in a WHO guideline (but did not affect the recommendation) (see Case study 1). Two other trials provided evidence for national strategies, both of which are expected to be published in the coming months (see Case study 5 and Case study 9). All three trials have the potential to scale their policy influence on LMICs, with two PIs actively pursuing this goal. The third PI reported she had no resources (time and budget) to engage policy makers. A researcher involved in a fourth trial reported that it had influenced national strategy. This trial has not yet published the main findings, and no further information is available.

• Other: One trial informed the strategy of WHO and international donors and shifted funding priorities

Factors supporting these trials to achieve policy ('enablers') impact fell into four categories:

- 1) The topic of trial is currently under debate in the policy arena, and key policy makers have strong interest in the research evidence (6 trials)
- 2) Little researched health area, hence little evidence available on the indication addressed by the trial (e.g. talaromycosis, podoconiosis, cryptococcal meningitis), including a lack of an established standard of care. JGHT studies substantially increase the level of robust evidence on which to base policy decisions (3 trials)
- 3) Collaboration with policy makers and key stakeholders in the local health system during planning and implementation of the research (3 trials). This includes embedding the trial within local health programmes (see Case study 9)

⁶⁴ Release of one policy expected soon; the policy guidelines on the use of azithromycin as a child survival strategy have not yet been published but review of a late draft suggests that the results of the trial will have had a major influence on the final WHO policy recommendation (personal communication, Prof Brian Greenwood, 21 Oct 2019)

⁶⁵ "A WHO guideline is any document developed by WHO containing recommendations for clinical practice or public health policy. A recommendation tells the intended end-user of the guideline what he or she can or should do in specific situations to achieve the best health outcomes possible, individually or collectively. It offers a choice among different interventions or measures having an anticipated positive impact on health and implications for the use of resources." WHO Handbook for Guideline Development (2012)

⁶⁶ Two of these policies are expected to be published in the next months.

4) Active engagement with policy makers to inform and influence relevant policies. This is facilitated by researchers holding advisory functions, e.g. as members of WHO guideline or national strategy committees, or key policy makers holding advisory functions related to the research project, e.g. as members of the trial committee (2 trials)

All trials that influenced policy were underpinned by at least two of these enablers. (Further details on enablers and barriers is provided in Table 15 and accompanying description).

There was no clear difference in the ability to influence policy whether a trial was conducted in one country or more. Two trials addressing issues of people living with HIV involved four or more countries (one of which in Africa and Asia), two trials were conducted in two countries, and six trials in one country. The topics of the latter ranged from diseases with limited geographic distribution, such as talaromycosis and podoconiosis, to violence prevention in schools and clean stoves to reduce childhood pneumonia, to helminth transmission and novel insecticidal malaria nets.

Factors enabling <u>policy scale up</u> were continued engagement of the PI or co-investigators, both in the policy (see Case study 5) and research (see Case study 9) arena.

Barriers to policy scale up were a lack of resources, preventing the PI from actively engaging with policy makers in neighbouring countries (see Case study 1), and the need for further research evidence form multiple countries/contexts and over longer periods of time (see Case study 9).

5.6.2 Implementation of effective health interventions

Eight trials have led to some degree of implementation of health interventions. These are:

- Novel nets to control malaria transmission are being made available in areas of confirmed insecticide resistance across Africa. The Global Fund has placed purchases, e.g. in January 2019 for Burkina Faso, with a transaction value of USD4.2m. The full extent to which countries have implemented the nets is not known. (see Case study 7)
- In Ethiopia, an estimated 100,000 podoconiosis patients have been trained to self-treat with this a simple, inexpensive care package that reduces the frequency and duration of severe symptoms of podoconiosis. The training was predominantly financed and delivered by an NGO, but also included a financial commitment from the Ethiopian government. In addition, 300 health professionals in Ethiopia as well as neighbouring countries have been trained (see Case study 5).
- In Vietnam, all patients with talaromycosis are now given the superior treatment (amphotericin B), compared to only 30% of patients before the trial. This has cut the death rate in half, saving the lives of around 35 individuals every year (see Case study 1)
- In Kenya, the government's Breaking Transmission Strategy 2019-2023, which was informed by the JGHT-funded trial, targets soil-transmitted helminths with a new, more effective, package of interventions. The strategy is currently being introduced across three counties, in preparation for national roll-out (see Case study 9).
- The Good Schools Toolkit, an intervention shown to reduce violence in schools, is being used in more than 1000 schools across Uganda, Tanzania, Kenya and Rwanda (see Case study 6).
- A JGHT-funded trial on prevention TB-MDR in children and adolescents developed a paediatric formulation of the drug tested in the trial. This has informed inclusion of the formulation on the WHO Essential Medicines List in February 201867. There is evidence that countries have started to purchase this formulation, e.g. the Global Fund placed purchase orders for Ethiopia, Pakistan, Tajikistan and Tanzania from June 2018 for a total of USD120,00068.

⁶⁷ https://extranet.who.int/prequal/news/first-dispersible-paediatric-levofloxacin-tablet-prequalified Accessed 12 Oct 2019

⁶⁸ https://public.tableau.com/profile/the.global.fund#!/vizhome/PQRTransactionSummary_V1/TransactionSummary Accessed 12 Oct 2019

In addition, in some instances, impact was assumed but information to assess the extent of implementation was not available. This was the case where interventions and products tested as part of three JGHT-funded trials were recommended by WHO:

- WHO recommends that the antimicrobials cotrimoxazole and isoniazid are taken as part of preventative therapy against tuberculosis for people living with HIV. However, access to isoniazid remained poor and few people were receiving this treatment. Underpinned by evidence from the JGHT-funded trial, a co-formulated pill combining was added to the WHO Essential Medicines list. The polypill should enhance access and adherence; however, the current level of distribution and use of the pill is unknown (see Case study 4).
- Evidence from a JGHT-funded trial contributed to the body of evidence that led to WHO to recommend a new version of a TB diagnostic test, given its higher sensitivity than the previous version. The level of use of this new test is not known (see Case study 8).
- Similarly, the extent to which recommended changes in treatment strategy are implemented is difficult to ascertain. For example, based on evidence from a JGHT-funded trial, a WHO recommendation included as an option the provision of a package of antimicrobial drugs when people with HIV and low immunity levels start anti-retroviral treatment. The extent to which this option is being used is unknown.

Evidence from a further three trials also informed decisions to <u>not</u> implement an intervention, or to alleviate concerns about a current recommendation:

- Findings of one trial led to the recommendation to <u>not</u> provide cryptococcal meningitis patients with dexamethasone due to safety issues (see Case study 2)
- The finding that cleaner cook stoves provided to rural households with children did not improve children's lung health steered WHO and donor organisations away from focussing solely on this approach and towards a shift to also tackle other sources of air pollution.
- Another trial provided confidence that the recommended intervention was effective and safe, alleviating concerns about the currently recommended anti-retroviral drug class (see Case study 3).

In addition, two trials have led to implementation of an intervention while research is still ongoing, and one development award also reported changes in practice:

- One trial led to the implementation of an intervention before the conclusion of the trial, i.e. before an assessment of the effectiveness of the intervention. The Jamaican government decided to implement a toolbox to prevent violence in schools, developed as part of the JGHT-funded project and tested in the trial₆₉. This decision was based on the strong relationships the research team had cultivated, working with the national ministry and providers. For example, as the trial progressed, the team shared information on the toolbox and how it was being applied as part of the trial in ongoing presentations and discussion with these key stakeholders. The study team also developed a one-day teacher-training programme based on the toolbox and trained technical staff of the Jamaican Ministry of Education to conduct this training. It has since been conducted with all grade 1 teachers in 2016 and all grades 2 and 3 teachers in 2017 a total of approximately 5200 teachers, reaching up to 120,000 children per year.
- Researchers working on another (active) award have developed expertise in conducting patient cost surveys as part of the trial. Publications on this aspect of the study are referenced in the WHO handbook for conducting TB patient costs surveys, and the study team has helped to roll out such cost surveys in 15 countries (see Case study 12).

⁶⁹ MR/M007553/1 The "Irie Classrooms Toolbox": a cluster randomised trial of a universal violence prevention programme in Jamaican preschools. Professor Baker-Henningham, Bangor University

• A development award has also led to adoption of an intervention: The research team adapted the WHO Caregivers Training Skills (CTS) programme to educate and support caregivers of children with developmental disorders to the Ethiopian context. CST is now used in Ethiopia's state-run child mental health clinics and rolled out to all caregivers who attend these (see Case study 16).

PIs of several trials reported that the research led, or contributed, to impact on health beyond trial participants as a result of the implementation of the trial, rather than as a result of the main trial findings. In most cases, training of healthcare staff led to upskilling and a sustained increase in the quality of care. One example is a JGHT-funded trial that, based on the experiences with trial participants, led to the development of resources to help patients with brain infections settle back into their communities and cope with disability after being discharged from hospital. The project, which concluded recently, has modified a major local hospital's approach to discharge planning, and is now being rolled out by a local NGO (see Case study 2). Meetings with policy stakeholders, started through development award and continued through the following full trial, evolved into a regional forum on NCD (Policy Forum on Hypertension and Cardiometabolic Diseases-Impact on Health Systems in Sri Lanka, Bangladesh, Pakistan, and Regional Countries) where government officials present their countries' strategies and plans to tackle the burden of NCD. This legacy of the development trial enables governments to learn from each other and supports alignment of actions between countries (see Case study 13).

In summary, enablers of implementation for interventions tested in JGHT trials included:

- Donors covering the cost of interventions recommended by WHO (see Case study 1, Case study 3, Case study 7). PIs of trials that influenced WHO policy did not report that they continued to be involved in promoting implementation of the intervention.
- Involvement of an investigator with an implementing NGO (see Case study 5)
- Embedding of research within the local health programme (see Case study 9)

Barriers to implementation included:

- Lack of funds to cover the cost of interventions, where donors do not take these on. In one case, a change in ODA status of the country concerned (Vietnam) endangered availability of the intervention in the future, as PEPFAR would be withdrawing its support over the next years (see Case study 1).
- The need for further evidence to expand the implementation area (scale-up) (see Case study 9). This was being addressed through additional research, funded by BMGF.

5.6.3 Improved cost-effectiveness of healthcare

The cost-effectiveness of interventions was examined as part of four trials that have published their main findings and have reported policy influence.

For one trial, a preliminary analysis published as part of the findings publication suggested that the intervention would be cost-effective (see Case study 3). The full cost-effectiveness analysis for this trial, as well as two other trials, is currently being prepared for publication.

The potential for improving health equity and equality were specifically determined as part of a trial investigating interruption of helminth transmission through community-wide de-worming treatment. The study found that the community delivery platform tested in the trial resulted in comparable coverage and effects of the interventions across important demographic and socioeconomic subgroups (i.e. equity) (see Case study 9).

5.6.4 Future potential for impact on policy and implementation

The majority of JGHT-funded trials have not yet concluded or published results (38 of 62), or have only published their main findings very recently (e.g. 8 trials in 2019).

Bearing in mind the enablers and barriers reported by trials with outcomes (as described in sections 5.6.1 and 5.6.2), and drawing on further information from consultation and desk research, the 15 trials that have published their main findings were assessed for their potential for policy influence, implementation and scale up. (It should be noted that this assessment is based on a limited level of information, in particular for trials where researchers had no or very limited input into the review.)

• Seven trials which have published their main findings were considered to have clear potential for policy influence, based on the evidence they provide and/or the continued level of engagement with policy makers by the PI or research team. One trial is very close to being taken up in policy, with a draft national strategy awaiting endorsement from the ministry (see Case study 10). Five trials resulted in findings with potential for take-up, but published their findings recently (in 2019); all for PIs continue to engage with policy makers and disseminate the results. One trial saw only a small level of benefit across the entire participant population, but showed stronger benefits in sub-groups. As the PI continues to be engaged with national policy makers, there is opportunity for these findings to inform policy. Findings of one trial, confirming the trial hypothesis, were published very recently (October 2019).

An *eighth* trial has potential for impact, but uptake into policy is not currently actively pursued. The trial resulted in findings with clear potential for take up (simpler and lower cost intervention was more effective). However, as policy makers had not been engaged during the research, and there were no resources (time or budget) for engagement after the award closed, the finding may have limited influence on, or is at a minimum delayed in influencing, strategy going forward without further action. (The publication is currently being incorporated into an updated Cochrane review, and may influence practice in this way.)

- Seven trials were considered to have <u>limited potential for policy influence</u>. Three trials encountered barriers as a result of research and policy developments outside the trial (e.g. FDA did not approve drug tested, intervention tested for safety was shown to not be effective). The findings of the remaining five trials did not result in a clear option for policy change; four of these reported no difference in the treatment and control arms.
- Six closed full trial awards have <u>not yet published their main findings</u>, but three of these have submitted the main publications for review, and one is in the final stages of analysis. Depending on the results, all three have potential for influencing policy, as the PIs have engaged policy makers throughout the design and implementation of the trials.

5.6.5 Success of the JGHT full trial award scheme in influencing policy

Taking 'policy influence' as a key performance indicator, the following estimate of the 'success rate' for the <u>closed</u> full trial awards of the JGHT can be made:

- 32% of JGHT-funded closed full trials (9 of 28) have resulted in success: Eight closed trials have achieved, or are about to achieve, policy influence. In addition, one feasibility study is close to influencing policy and has resulted in a JGHT-funded full trial, and was therefore counted within the group.
- 36% of JGHT-funded closed full trials (10 of 28) have high potential for success: Six closed trials were scored as having a high potential for policy influence. In addition, four closed trials for which the main findings have not yet been published were counted towards this group, as all PIs continue to be engaged with policy makers (with level of influence depending on trial outcome).

The final figure could hence be more than 70% of closed full trials resulting in policy influence.

5.6.6 Enablers and barriers

Table 15 summarises the enablers of and barriers to policy influence, implementation, and scale-up that emerged from the JGHT researcher consultation. This list only includes factors encountered by PIs and co-investigators of the JGHT *so far*. As more trials report their results and reach the point where these can be taken up into policy, implemented, and scaled, it is likely that additional factors emerge.

Enablers of and barriers to policy influence fell into two broad categories:

- Utility of the research evidence for policy making: This aspect focusses on how useful the evidence generated is, a function of the nature of the research question investigated, the quality and scale of investigation, and existing evidence within the area of research. Interventions in complex (real world) settings, affected by a large number of environmental, systems and cultural factors, were subject to many outside influences on the trial result, and are hence particularly challenging in this respect. The expected level of utility of evidence can be assessed at the start of the research project; however, challenges during implementation and developments in the research or policy fields can have (unexpected) impacts.
- Policy makers' knowledge of the research evidence and willingness to act on it: This aspect focusses on policy makers, including their level understanding of the research and the implications of the findings for policy and implementation, their attitude to the research (e.g. lack of buy-in), and their awareness of and interest in addressing the health need the research relates to. Some of these aspects can be assessed prior to the start of the research project, and a stakeholder engagement plan can be formulated on the basis of this assessment (and active engagement may need to precede the research).

Some of the enablers and barriers are linked. For example, if policy makers are not aware of a health problem, and it is hence not considered a high priority, it is likely to limit opportunities and willingness to engage on research and policy. In these cases, efforts to raise awareness could help to pave the way for constructive engagement (see cases Phillips-Howard and Davey). Alternatively, strong research evidence demonstrating that a change in policy would be beneficial and/or save costs could be used as an effective tool to generate awareness and engagement. In this case, there is a need for active (and potentially prolonged) policy engagement after the research has concluded. Latter may be hindered by a lack of resources to provide investigators with the necessary time and budget; alternatively, investigators may not be in a position (or willing) to focus on policy engagement due to competing priorities (such as further research projects).

Enablers of and barriers to implementation were related to:

- The cost of implementation, including whether the cost is covered by donor organisations (e.g. a barrier where the research has not (yet) influenced WHO recommendations) or is taken on NGOs. Enablers of impact were active engagement, and even involvement, with 'implementers'.
- The ability of the health system and structures at the site of implementation to take up a change into practise. This was facilitated by close working with local government and embedding trials within local health programmes and delivery structures.

Enablers of and barriers to scale-up were similar to enablers and barriers of policy influence:

- The level of knowledge of policy makers in relation to the research evidence, and awareness of / willingness to address the health issue concerned. This is facilitated by active engagement with relevant policy makers.
- The utility of the data in contexts beyond the trial location. This can be addressed through additional research in other settings.

Table 15 Enablers and barriers

	Enablers	Barriers	
Policy influen	ce		
Utility of research evidence to policy makers (Nature, quality, and scale of research)	 Research provides a clear evidence supporting or rejecting a policy change, especially if: Question the trial addresses is actively debated by policy makers ('hot topic'). Policy makers have strong interest in the result of the trial Little evidence is available for the indication addressed by the trial. JGHT-funded research substantially increases the level of robust evidence on which to base policy decisions. 	 Research results not conclusive, and do not point to a clear course of action for policy Intervention is not compatible with existing policies, or in conflict with other policy concerns Need for further research, e.g. implementation pilot (delay) 	
Knowledge of research & willingness to act (Stakeholder engagement)	 PI and/or co-investigators actively engage with policy makers on <i>research</i> (planning and implementation), e.g. Extensive consultation in planning stages, and regular updates during implementation Policy makers are part of research team Trial embedded within local health programme 	Low level of engagement with policy makers on <i>research</i>	
	 PI and/or co-investigators actively engage with policy makers on <i>policy</i>, e.g. PI and co-investigators are members of/advisors to national/international policy committees Policy makers are members of the trial steering committee 	 Low level of engagement with policy makers on <i>policy</i> implications during trial Lack of resources (time/budget) for policy engagement following close of trial; competing priorities 	
	PI and/or co-investigators continue to engage with policy makers to achieve policy influence (after the trial)	Timeline: Trial results were published only recently; policy makers have not yet been able to consider and act	
	PI and/or co-investigators actively engage in activities to raise awareness of health problem	 Low awareness of health problem Cultural barriers inhibiting debate / policy action 	
Implementati	on		
Cost	Donors cover cost of intervention	Cost of implementation (if not covered by donors)	
Ability of system to take up change	 PI and/or co-investigators actively engage with 'implementers', e.g. NGOs Full buy-in of policy makers and practitioners, e.g. as a result of engagement during planning and implementation of trial Trial intervention was delivered through local health programme 	 Lack of awareness of policy change/intervention Issues with intervention in practice (e.g. shortened shelf life) 	
Scale-up			
Knowledge of research & willingness to act (Stakeholder engagement)	 PI and/or co-investigators actively engage with policy makers in other relevant countries/regions to scale up policy influence PI and/or co-investigators actively engage in activities to raise awareness of the health problem at international level 	Lack of resources (time/budget) for international policy engagement	
Utility of data in different contexts	PI and/or co-investigators conduct research to expand geographic range of results or to include additional target populations (e.g. additional age groups)	Need for additional research to demonstrate trial findings also apply in other contexts	

Source: PI interviews and surveys, desk research

The conditions enabling policy and health outcomes is further abstracted in a model presented in Figure 4370. The model separates enablers into two categories:

- Enablers driven by utility of data and external conditions, dictating whether research evidence '**can**' (in principle) be used and implemented
- Enablers driven by human factors (awareness, understanding, and buy-in), dictating whether individuals involved in the process '**want to**' respond to the change warranted by the research evidence

Awareness, understanding, and buy-in of decision makers is hence a key factor for achieving policy and health outcomes. Engagement with research is likely to enhance these aspects not only with the project at hand but also for future research. Indeed, as discussed in section 0, JGHT-funded studies have helped to raise decision makers' awareness of and in research evidence: 35% of PIs (14 of 40) and co-investigators (54 of 161) surveyed reported that the trial had convinced decision makers of the value of health (including 38% of co-investigators working at LMIC institutions).

	Policy	Implementation	Scale-up
	"Can use"	"Can implement"	"Can scale up"
Utility of research evidence	 Research evidence: Demonstrates conclusive option for uptake into policy Is not in conflict with existing evidence (low level of evidence available) OR Is of sufficient strength to demonstrate superior policy option, over conflicting evidence (scale and scope of research findings) To avoid delay in uptake: Is reported at the right point in the policy cycle 	 Implementing organisation: Can afford the intervention (cost) Can deliver the intervention within the existing health system or other relevant structure, incl.: community acceptance availability of necessary infrastructure healthcare worker skills training suitability of product, technology or care delivery mechanism for local conditions secure conditions, e.g. no war, environmental disasters 	 Research evidence: Is relevant to and can be applied to other contexts (expanded geographic contexts; other target populations)
r	"Want to use"	"Want to implement/adopt"	"Want to scale up"
Stakeholder knowledge and buy-i	 Policy makers: Are aware of / involved in research and understand options for take up into policy Are aware of the health need the research addresses Have prioritised the policy addressed in research, with structures in place Feel a level of ownership over research and policy option (buy-in) 	 Implementing organisation: Can overcome potential resistance to change within the system (including from practitioners and target population) Has bought into the policy change; feels a level of ownership 	 Policy makers and implementing organisations outside the study context: Are aware and interested in intervention Can overcome potential resistance present in other contexts

Figure 43 Model of conditions enabling policy and health outcomes

⁷⁰ The model includes aspects reported to have directly affected JGHT projects, as well as points raised in general discussion in researcher and key opinion leader interviews.

5.7 Impact on health

As reported in sections 5.6.1 and 5.6.2, some of the JGHT-funded research has influenced policy and led to the use of research findings and implementation of interventions tested. At this point in the programme, health impacts are still limited to relatively modest numbers of beneficiaries, and the impact at the level of LMIC populations is too small to be detectable. However, the short timeframe since publication of trial findings has to be borne in mind: half of the main trial publications were published in 2018 and 2019 (13 of 26), with just under one quarter published in 2019 (6 of 26) (see Appendix F).

There is potential for impact reflected in population-level statistics once roll-out of interventions and adoption of policy changes into practice have occurred. For example, roll-out of the Kenyan government's strategy to break transmission of soil-transmitted helminths, which was informed by a trial co-funded by the JGHT, has potential to impact on the prevalence of infection and associated morbidity at national level and, if scaled up as a result of a current larger trial, in multiple countries (see Case study 9). In Ethiopia, 100,000 patients suffering from podoconiosis have already been trained in how to self-treat with a simple foot care package, shown to be effective in reducing severe symptoms of podoconiosis by a JGHT-funded trial. With an estimated 1.6 million Ethiopians affected by podoconiosis, this already represents 6.3% of the patient population; further roll-out can be expected to further decrease the level of disability and social effects as a result of the disease (see Case study 5).

Other trials have the potential to avert a deterioration of the current situation. For example, while 'standard' insecticidal nets have led to a dramatic reduction in the burden of malaria across sub-Saharan Africa₇₁, this progress is now threatened by an increase in insecticide resistance. The new generation of nets tested in a JGHT-funded trial in Tanzania may help to stem this risk, and there is evidence that governments have started to purchase these (see Case study 7). The final impact will depend on many additional factors, including effective distribution and appropriate use of nets.

To fully determine the level of impact of health interventions to which the JGHT funding scheme contributed, further assessment at a later point is required. As one key opinion leader explained: "A lot of the trials tend to think that inclusion in guidelines, for example if clinical recommendations changed in the WHO guideline, would have extremely high impact. Yet the reality is, as experts in implementation science and knowledge translation will tell you, that it is going to be another 15-20 years before [the change] even makes it into common practice.". At that point, however, the level of impact will be determined not only by the research evidence and its influence on policy and its utility for implementation, but also by a complex set of external factors (e.g. changes in the local context, sustained focus of decision makers on health need addressed at and beyond the trial location), and is hence beyond the scope and responsibility of JGHT-funded researchers.

5.8 Progress towards health-related SDGs

At the UN Summit in September 2015, the new Sustainable Development Goals (SDGs) were formally adopted, including goal 3, to: 'ensure healthy lives and promote well-being for all at all ages' (see also section 2.1.1). SDGs include a broad range of health-related targets, to be reached by 2030. The WHO Global Health Observatory tracks health-related statistics, organised to monitor progress towards the SDGs, including indicators for the specific health and health-related targets of the SDGs. JGHT-funded research has addressed, or is addressing, a broad range of these indicators (Table 16).

The attainment of SDGs is likely to require a variety of interventions, research and otherwise; and is hence a tall order for any one trial, or small number of trials, to achieve. Key opinion leaders considered the JGHT to contribute to progress towards the SDGs by addressing the wider health goals (but could not point to the scheme having specifically addressed gender equality). At the same time, the contribution can be expected to be limited; as one key opinion leader elaborated: "To achieve impact on SDGs, multifactorial problems would need to be addressed. JGHT trials are focused and their design

⁷¹ WHO. World malaria report 2016. Geneva: World Health Organization, 2016.
does not easily accommodate multifactorial problems such as environmental destruction, malnutrition, lack of energy in poor communities.".

Information from the trial database registrations showed that most studies (78%, 49 of 63) enrolled both male and female participants. Of the 14 studies that enrolled only female participants 50% (7) were related to reproduction/sexual health.

SDG health and health-related targets	WHO Global Observatory statistics	
3.1 Maternal mortality	Maternal and reproductive health	
3.2 Newborn and child mortality	Child health	
	Child mortality	
3.3 Communicable diseases	HIV/AIDS	
	Tuberculosis	
	Malaria	
	Neglected tropical diseases	
	Cholera	
	Influenza	
	Meningitis	
	Other vaccine-preventable communicable diseases	
	Sexually transmitted infections	
3.4 Noncommunicable diseases and mental health	Noncommunicable diseases	
	Mental health	
3.5 Substance abuse	Alcohol and Health	
	Prevention and Treatment of Substance Use Disorders	
3.6 Road traffic injuries	Road safety	
3.7 Sexual and reproductive health	Universal access to reproductive health	
3.8 Universal health coverage	Universal health coverage data portal	
3.9 Mortality from environmental pollution	Public health and environment	
	Joint effects of air pollution	
3.a Tobacco control	Tobacco control	
3.b Essential medicines and vaccines	Essential medicines	
	Priority health technologies	
	Immunisation	
3.c Health financing and health workforce	Health financing	
	Health workforce	
3.d National and global health risks	International Health Regulations	
2.2 Child malnutrition	Child malnutrition	
16.1 Violence	Violence prevention	
	Violence against women	

*Table 16 SDG health targets and WHO statistics on health-related targets*⁷² Indicators addressed by JGHT-funded research are shaded in light blue.

5.9 Impact case study – summaries

The following section presents 14 impact case studies to illustrate the range of scientific and health outcomes achieved, and the activities that have enabled the project to be implemented and the findings to be taken up. Two additional case studies were presented in preceding sections (see sections 5.4.3 and 5.5.2). An overview of all 16 case studies is provided in Table 17, cross-linked to the relevant case. The full case studies are available in a separate document (Review of the JGHT – Impact Case Studies).

Table 17 Case studies

Case study category	Case study	Award details
JGHT-funded trials with	Case study 1	G1100682/1, Thuy Le, Call 1
evidence of policy influence	Case study 2	G1100684/1, Jeremy Day, Call 1
	Case study 3	G1100693/1, Diana Gibb, Call 1 (2 cases)
	Case study 4	G1100693/1, Diana Gibb, Call 1
	Case study 5	MR/K007211/1, Gail Davey, Call 2
	Case study 6	MR/L004321/1, Karen Devries, Call 3
	Case study 7	MR/L004437/1, M Rowland (active), Call 3
	Case study 8	MR/M007413/1, David Meya (active), Call 4
	Case study 9	MR/N00597X/1, Rachel Pullan, Call 5
Trials with potential for policy	Case study 10	G1100677/1, P Phillips-Howard, Call 1 (and Call 5)
influence, PIs actively engaged	Case study 11	G1100654/1, Feiko Ter Kuile, Call 1
	Case study 12	MR/K007467/1, Carlton Evans (active), Call 2
Full trials, main trial findings	Case study 13	MR/N006178/1, Tazeen Jafar, Call 3 (and Call 5)
not yet published	Case study 13	MR/L004356/1 Angela Crook, Call 3
Development awards with	Case study 15	MR/M022161/1. Xiaolin Wei. Call 5
evidence of outcomes	Case study 16	MR/P020844/1, Rosa Hoekstra, Call 7

5.9.1 JGHT-funded trials with evidence of policy influence

Case study 1

A Randomised, Open-Label, Comparative Study of Itraconazole vs. Amphotericin B for the Induction Therapy of Penicilliosis (G1100682, Call 1)

Funding period: 01/08/2011 - 31/03/2017

Funding amount: £1,540,178

Lead PI: Dr Thuy Le

Lead institution: Oxford University Clinical Research Unit (OUCRU) Vietnam

- The 'Itraconazole versus Amphotericin B for Penicilliosis' (IVAP) trial was the first trial to compare the relative effectiveness of two treatments, amphotericin B and itraconazole, for talaromycosis, a common fungal infection among HIV-positive persons endemic to southeast Asia. The trial was conducted at five major referral hospitals in Viet Nam, and was led by Dr Thuy Le, Oxford University Clinical Research Unit (OUCRU), Ho Chi Minh City, Viet Nam.
- Before the trial, international guidelines recommended treatment with amphotericin B but were based on poor evidence. The trial showed that amphotericin was more effective than itraconazole, providing robust evidence to underpin the treatment recommendations. The trial's findings were taken up into national guidelines in Viet Nam, and also described in WHO guidelines.
- The trial led to health impacts by changing treatment of talaromycosis patients in Viet Nam, where amphotericin B is now provided to all patients, compared to only 30% of patients before the trial. This has cut the death rate in half, saving the lives of around 35 individuals every year.
- Locating the trial within the Vietnamese health system was crucial in securing buy-in from practitioners and enabling changes in policy and practice.

Le T et al (2017) A Trial of Itraconazole or Amphotericin B for HIV-Associated Talaromycosis. NEJM 376:2329-2340

Case study 2

A clinical trial of dexamethasone to reduce mortality in cryptococcal meningitis (CryptoDex) (G1100684/Call 1)

Funding period: 01/10/2011 - 31/03/2017	Funding amount: £4,217,875
Lead PI: Prof Jeremy Day	Lead institution: Oxford University Clinical Research Unit (OUCRU), Ho Chi Minh City, Vietnam

- The Cryptodex trial determined whether addition of dexamethasone to standard treatment would improve survival among adults with HIV-associated cryptococcal meningitis. It was led by Professor Jeremy Day, Oxford University Clinical Research Unit (OUCRU), Ho Chi Minh City, Viet Nam, and involved 13 centres in 6 countries (Vietnam, Thailand, Indonesia, Laos, Uganda, and Malawi).
- The trial showed that dexamethasone is unlikely to benefit survival in patients with HIV-associated cryptococcal meningitis and its findings were taken up by WHO in the 2018 Guidelines on Cryptococcal Disease in HIV-infected adults, adolescents, and children.
- During the trial, researchers from participating centres in Africa and Asia were able to exchange experiences and share learning, e.g. on delivering interventions in relatively lower setting and approaches to patient recruitment.
- The CryptoDex trial has also helped to inform improvements in the hospital discharge protocol for patients with brain infections, and developed resources to assist patients to cope with disability and re-integrate into their communities. These resources are now being made available through an NGO, and the Hospital for Tropical Diseases, Ho Chi Minh City, Vietnam has already modified their approach to discharge planning.

Beardsley J et al (2016) Adjunctive Dexamethasone in HIV-Associated Cryptococcal Meningitis, NEJM 374: 542-554

Case study 3

Reduction of EArly mortaLITY in HIV-infected African adults and children starting antiretroviral therapy: REALITY trial (G1100693/Call 1)

Funding namiad. Oct costs. Man cost	Euroding amounts Co. ob(= 16
Funding period: Oct 2012 - Mar 2016	Funding amount. £3,960,740

Lead PI: Prof Diana Gibb

and institution. University College

Lead institution: University College London / MRC Clinical Trials Unit

- The REALITY trial aimed to address the question of how to reduce the high early death rates when HIVinfected individuals with low immunity start antiretroviral therapy (ART). The trial tested three different approaches, at trial centres in Zimbabwe, Uganda, Malawi, and Kenya. It was led by UCL / MRC CTU.
- The trial showed that taking a package of antimicrobial drugs at the same time as starting ART reduced the rate of death by 3.3%, from 12.2% to 8.9%, i.e. saving 3 lives for every 1000 patients treated.
- The antimicrobial prophylaxis package was taken up into WHO guidelines as an option but currently not as a first line treatment recommendation. Work to address concerns about antimicrobial resistance and cost-effectiveness of the intervention is ongoing and is expected to inform the next WHO guideline update.
- The trial also showed that giving extra food to those starting on ART, or adding an integrase inhibitor (a new type of antiretroviral drug) to ART did not have an effect on mortality. Latter alleviated concerns over the safety of integrase inhibitors in HIV-infected individuals with very low immunity and lent confidence to the current WHO guidelines recommending integrase inhibitors as the preferred treatment.

Hakim J et al (2017) Enhanced Prophylaxis plus Antiretroviral Therapy for Advanced HIV Infection in Africa. NEJM 377:233-245

Kityo C et al (2018) Raltegravir-intensified initial antiretroviral therapy in advanced HIV disease in Africa: A randomised controlled trial. PLoS Med 15: e1002706

Mallewa J et al (2018) Effect of ready-to-use supplementary food on mortality in severely immunocompromised HIVinfected individuals in Africa initiating antiretroviral therapy (REALITY): an open-label, parallel-group, randomised controlled trial. The Lancet HIV 5: PE231-E240

Case study 4

Reduction of EArly mortaLITY in HIV-infected African adults and children starting antiretroviral therapy: REALITY trial (G1100693/Call 1)

Funding period: Oct 2012 - Mar 2018Funding amount: £3,986,746Lead PI: Prof Diana GibbLead institution: University College London / MRC Clinical Trials Unit

- WHO recommends preventative therapy against tuberculosis for people living with HIV, including the antimicrobials cotrimoxazole and isoniazid. However, access to isoniazid remained poor and few people were receiving this treatment.
- To increase access and adherence, Cipla Ltd developed a co-formulated pill, combining cotrimoxazole and isoniazid. The enhanced prophylaxis arm of the REALITY trial provided an opportunity to test Q-TIB and gather data on adherence and acceptability, to contribute to submission for WHO pre-qualification.
- In 2017, Q-TIB was included on WHO essential medicines list and its use recommended in WHO guidelines. It is now available on the market.

Case study 5

Randomised controlled trial of podoconiosis treatment in northern Ethiopia (GoLBeT) (MR_K007211_1/Call 2)

Funding period: 01/02/2013 - 30/05/2017	Funding amount: £777,890
Lead PI: Prof Gail Davey	Lead institution: Brighton and Sussex Medical School, University of Sussex

- Podoconiosis is a form of lymphoedema (leg swelling) in people who walk barefoot on volcanic soil in highland tropical areas. The GoLBet trial was the first trial to measure the effects of a simple foot care package on ADLA, the most severe consequence of podoconiosis, an acute inflammation of skin, tissue, lymphatics, and lymph nodes. The trial was led by Prof Gail Davey, University of Sussex, and conducted in rural communities in the East Gojjam Zone, Ethiopia.
- The trial showed that the simple, inexpensive care package was effective in reducing the frequency and duration of ADLA. The package is now set to be incorporated into the next 5-year Ethiopian Neglected Tropical Diseases masterplan (2020-2025).
- So far, an estimated 100,000 podoconiosis patients have been trained to self-treat with the foot care package in Ethiopia, including through a financial commitment by the Ethiopian government for training in 2018. In addition, the University of Sussex working with NGOs has trained 200 health professionals in endemic areas.
- The GoLBeT team have also started working in neighbouring countries, e.g. in Rwanda, where the foot hygiene package will be referenced in the national Strategic Plan for 2020-2025, and in Uganda and Cameroon where approx. 40 health professionals where trained.
- A Rapid Ethical Assessment ahead of the trial was important to lay the groundwork for the trial. Gathering local knowledge through community consultation facilitated patient recruitment and enabled the trial team to effectively address challenges encountered during the trial.

Negussie H et al. (2018) Lymphoedema management to prevent acute dermatolymphangioadenitis in podoconiosis in northern Ethiopia (GoLBeT): a pragmatic randomised controlled trial. Lancet Glob Health 6:e795–e803

Case study 6

The Good Schools Study: A cluster randomised controlled trial of an intervention to prevent violence against children in Ugandan primary schools (MR/L004321/1, Call 3)

Funding period: 31/12/2013 - 30/12/2015 Funding amount: £664,266

Lead PI: Karen Devries

Lead institution: London School of Hygiene and Tropical Medicine

- Physical, sexual or psychological violence is a global health problem affecting 1 billion children worldwide every year. The problem is particularly acute in Ugandan primary schools with more than 90% of children reporting some form of physical violence from school staff.
- A team led by Dr Karen Devries at the London School of Hygiene and Tropical Medicine tested The Good Schools Toolkit, a behavioural intervention developed by a Ugandan NGO Raising Voices, in primary schools in Uganda in a two-arm cluster-randomised controlled trial. A qualitative study, economic evaluation, and process evaluation were also included in the study.
- Trial results showed that the intervention was effective at reducing violence towards children by 42% in the space of 18 months. This evidence informed WHO violence prevention guidelines. Moreover, 434 of the children participating in the trial were referred to Child Protective Services. Thus, the study itself has had an impact on the health and wellbeing of children.
- The Good Schools Toolkit is now being used in Tanzania, Kenya and Rwanda in addition to Uganda. It is also being adapted for secondary schools and a randomised controlled trial of this new toolkit is planned for 2020.

Devries K et al (2015) The Good School Toolkit for reducing physical violence from school staff to primary school students: a cluster-randomised controlled trial in Uganda. The Lancet Global Health 3: PE378-E386

Case study 7

Combination interventions for controlling malaria transmitted by pyrethroid resistant mosquitoes: A novel bed net with synergist and IRS formulation (MR/L004437/1/Call 3)

Funding period: 01/03/2014 - 31/01/2019	Funding amount: £2,551,857
Lead PI: Prof Mark Rowland	Lead institution: London School of Hygiene and Tropical Medicine

- Abundant use of pyrethroid-based insecticides has driven an increase in pyrethroid-resistant mosquitoes, threatening the future success of these control strategies.
- The JGHT-funded trial evaluated the use of two alternative control products in the prevention of malaria transmission in Tanzania: insecticidal nets combining pyrethroid with piperonyl butoxide (PBO LLIN) and an indoor residual spray (IRS) formulation of a non-pyrethroid insecticide. The reference arm (the current standard of care) was pyrethroid-only LLIN. The study was led by the London School of Hygiene and Tropical Medicine in collaboration with two research institutes in Tanzania.
- The trial demonstrated that both products independently reduced malaria infection and transmission compared to standard control strategies. Use of both prevention tools in conjunction did not provide any additional benefit. It was the first trial to measure the impact of PBO LLIN in humans.
- The trial's findings on PBO LLINs were incorporated by WHO into policy, recommending their use in areas where pyrethroid resistance has been confirmed. PBO LLIN are being made available and scaled up across Africa.

Protopopoff et al (2018) Effectiveness of a long-lasting piperonyl butoxide-treated insecticidal net and indoor residual spray interventions, separately and together, against malaria transmitted by pyrethroid-resistant mosquitoes: a cluster, randomised controlled, two-by-two factorial design trial. The Lancet 391: P1577-1588

Case study 8

Evaluation of a rapid test for tuberculous meningitis: Adjunctive Sertraline for the Treatment of HIV-Associated Cryptococcal Meningitis (MR/M007413/1, full trial /Call 4)

Funding period: 01/03/2015 - 28/02/2018	Funding amount: £888,672
Lead PI: Dr David Meya	Lead institution: Makerere University, Uganda

- The JGHT-funded ASTRO-CM trial aimed to evaluate whether addition of the drug sertraline to standard treatment improved survival of HIV patients with cryptococcal meningitis. The trial was led by Dr David Meya, Infectious Diseases Institute in Uganda. The trial results showed that adjunctive sertraline did not improve survival.
- Data collected as part of a study nested within the trial, but not directly related to the issue the trial addresses, has informed WHO policy: During screening of potential trial participants for Cryptococcal meningitis, the ASTRO-CM team also compared diagnostic TB tests and found that the new TB Xpert Ultra assay detected significantly more tuberculous meningitis than the other tests. This contributed to an update of a WHO recommendation in March 2017.

Bahr, NC et al (2018) Diagnostic accuracy of Xpert MTB/RIF Ultra for tuberculous meningitis in HIV-infected adults: a prospective cohort study. Lancet Infect Dis 18: 68-75

Case study 9

Interrupting transmission of soil-transmitted helminths: cluster randomised trial evaluating alternative treatment strategies in Kenya (TUMIKIA) (MR_N00579X_1/Call 5)

Funding period: 01/11/2015 - 31/10/2018

Funding amount: £1,027,818

Lead PI: Dr Rachel Pullan

Lead institution: London School of Hygiene and Tropical Medicine, UK

- Soil-transmitted helminths (STH) are among the most common infections worldwide and affect the poorest and most deprived communities.
- The TUMIKIA trial investigated whether it is possible to interrupt the transmission of STH, evaluating the impact of school-based and community-based treatment on the prevalence and intensity of STH infection. It was co-funded by the Government of Kenya, the Children's Investment Fund Foundation, and the Bill and Melinda Gates Foundation. The trial was led by Dr Rachel Pullan, LSHTM and included collaborators from the Kenya Medical Research Institute (KEMRI) and other investigators at LSHTM.
- The trial found that community-wide treatment was more effective in reducing hookworm prevalence and intensity than school-based treatment, with little additional benefit of treating every 6 months compared to once per year.
- The results fed into the development of the Breaking Transmission Strategy of the Kenyan government for 2019-2023, which targets STH, and other NTDs, with a package of interventions. Implementation is currently being piloted to prepare for nation-wide roll-out. TUMIKIA findings are also informing WHO discussions on community- vs school-based treatment, and on effective monitoring and surveillance strategies.
- Broadening coverage is faced with a key challenge: Deworming programmes are mainly driven by donations that are limited to children in their use. Unless donor programmes chose to purchase drugs, only a shift in this limitation will enable broader uptake of community-based deworming.
- A longer-term study in Malawi, Benin, and Sri Lanka the DeWorm3 trial funded by BMGF and led by the Natural History Museum London is currently expanding on the trial's results. Findings are likely to guide BMGF strategy and inform WHO and other international organisations

Pullan RL et al (2019) Effects, equity, and cost of school-based and community-wide treatment strategies for soil-transmitted helminths in Kenya: a cluster-randomised controlled trial. The Lancet 393: 2039-50

5.9.2 JGHT awards with potential for policy influence, PIs actively engaged

Case study 10

Menstrual solutions in adolescent school girls in western Kenya: an acceptability, feasibility and safety study (G1100677/1/Call 1)

Funding period: 01/04/2012 - 30/09/2013	Funding amount: £716,200
Lead PI: Penelope Anne Phillips-Howard	Lead institution: Liverpool School of Tropical Medicine

- Little evidence is available on Menstrual Health Management (MHM) by schoolgirls in LMICs and its impact on education and health outcomes. The JGHT-funded feasibility study responded to this gap and compared three different approaches to MHM (menstrual cups, sanitary pads, no intervention). The study was led by the London School of Hygiene and Tropical Medicine, with partners in Kenya and the UK.
- The feasibility study provided important evidence for the design of a full trial, subsequently funded by the JGHT (ongoing). For example, the full trial's primary outcome measure was shifted from the level of absenteeism to the level of school drop-out and level of sexually transmitted infections, as the feasibility study showed this to be a more reliable indicator. The study also stimulated further international research activity on the topic.
- Expertise developed through the JGHT award enabled the study team to contribute to committees and fora addressing issues in MHM, both in Kenya and internationally. This has included feeding into the Kenyan National Menstrual Hygiene Management Policy and Strategy, currently under development by the Kenyan Ministries of Health, Education and Gender.

Phillips-Howard P et al (2016) Menstrual cups and sanitary pads to reduce school attrition, and sexually transmitted and reproductive tract infections: a cluster randomised controlled feasibility study in rural Western Kenya. BMJ Open 6:e013229

Case study 11

Intermittent screening and treatment or intermittent preventive therapy for control of malaria in pregnancy in Indonesia (G1100654/1 /Call 1)

Funding period: 01/10/2011 - 30/06/2017

Lead PI: Prof Feiko ter Kuile

Funding amount: £2,426,004

Lead institution: Liverpool School of Tropical Medicine

- Infection with malaria in pregnancy (MiP) can have severe consequences for both mother and baby. Interventions recommended by WHO for the control of MiP are largely based on findings from sub-Saharan Africa; the Asia-Pacific region on the other hand does not have a standardised strategy for the prevention of MiP.
- The JGHT-funded study was the first trial in Indonesia to determine the effectiveness of several strategies designed to prevent malaria in pregnancy. It was led by the Liverpool School of Tropical Medicine, in collaboration with researchers from institutions in the UK, Indonesia, and Australia.
- Comparing the current strategy with two alternatives revealed that intermittent preventive treatment (IPT) was most effective in a high transmission setting to prevent MiP in Indonesia.
- The Indonesian Ministry of Health was engaged throughout the project and has now requested support from the research team to conduct and evaluate a pilot implementation of IPT in the Indonesian healthcare system (subject to LSTM obtaining funding).
- Nested acceptability and systems effectiveness studies were conducted as part of the JGHT award. These provided additional information that will support the implementation of IPT in terms of key priority areas that need to be addressed in the implementation pilot.

Ahmed R et al (2019) Efficacy and safety of intermittent preventive treatment and intermittent screening and treatment versus single screening and treatment with dihydroartemisinin–piperaquine for the control of malaria in pregnancy in Indonesia: a cluster-randomised, open-label, superiority trial. Lancet Infect Dis. S1473-3099(19)30156-2

5.9.3 JGHT awards, main trial findings not yet published

Case study 12

Community randomised evaluation (MR/K007467/1/Call 2)	of socioeconomic	intervention	to	prevent	ТВ
Funding period: 01/10/2012 - 01/10/ 2021	Funding amount: £3,168,12	5			
Lead PI: Carlton Evans	Lead institution: Imperial C	ollege London			
• Tuberculosis (TB), one of the top 10 causes of death worldwide, is associated with poverty. Therefore, socioeconomic interventions have a large role to play in addressing this problem.					

- A team led by Professor Carlton Evans (Imperial College London; Universidad Peruana Cayetano Heredia, Peru) is evaluating a combined socioeconomic intervention aimed at tackling TB in the CRESIPT trial in Peru. The intervention comprises household visits, community meetings and conditional cash transfers towards TB-associated costs.
- The findings so far show that households receiving the intervention are less likely to incur catastrophic costs, uptake of preventive therapy among household contacts is increased and TB treatment success in TB patients is improved.
- The trial team has engaged with local, national and international stakeholders; influenced the training of health professionals; empowered recovering patients to become community leaders and contributed to improved understanding of TB in the community. Publications emerging from the project have been referenced in WHO's handbook for conducting TB patient costs surveys and the team has helped to roll out such cost surveys in 15 countries.

Case study 13

Primary Care Strategies to Reduce High Blood Pressure: A Cluster Randomised Trial in Rural Bangladesh, Pakistan and Sri Lanka (COBRA-BPS) (MR/N006178/1/Call 5)

Funding period: 01/09/2015 - 30/11/2019	Funding amount: £2,233,623 (COBRA-PBS), £201,806 (feasibility study)
Lead PI: Prof Tazeen H. Jafar	Lead institution: Duke-National University of Singapore Medical School, Singapore

- Hypertension is a leading risk factor of cardiovascular disease, a major cause of mortality and disability. Many affected people in rural South Asia remain undiagnosed and undertreated and are at risk of serious adverse effects. A potential strategy to reduce rates of hypertension is a multicomponent intervention (MCI).
- Professor Jafar, from the Duke-National University of Singapore Medical School, led a feasibility study funded by the JGHT to optimise the delivery of an MCI designed to be embedded in the existing healthcare infrastructure. It encompassed screening and referral of at-risk individuals, family education on mitigation strategies, training of healthcare providers, and a financing model.
- The feasibility study indicated that a full-scale trial in the rural settings of Pakistan, Bangladesh and Sri Lanka was viable. It also supported the development of training manuals and protocols needed to deliver the intervention. Comprehensive stakeholder engagement ensured the intervention was supported by local and national healthcare officials.
- The full-scale COBRA-BPS trial was undertaken following the feasibility study. The final trial results will be published shortly; however, a number of other publications have already emerged including a qualitative assessment of the barriers to accessing healthcare. The stakeholder engagement, established during the feasibility study, has since developed into a regional policy forum centred on cardiovascular disease and hypertension.

Case study 14

Two-month Regimens Using Novel Combinations to Augment Treatment Effectiveness for drugsensitive Tuberculosis: the "TRUNCATE-TB" trial (MR/L004356/1 / Call 3)

Funding period: Nov 2014 – Mar 2022 Funding amount: £5,012,977

Lead PI: Angela Crook

Lead institution: University College London, UK

- Tuberculosis (TB) presents a high disease burden worldwide, particularly in LMICs. Furthermore, multidrug resistant TB (MDR-TB) has emerged as a serious threat to health security. Patients often fail to adhere to treatment, leading to poor outcomes and drug resistance. Therefore, alternative management strategies are the need of the hour.
- Dr Angela Crook from University College London is leading a team of researchers from the UK and Singapore to test a new management strategy comprising a variety of novel 2-month combination drug regimens against the current 6-month treatment in the TRUNCATE-TB trial. The trial is being conducted in Indonesia, the Philippines and Thailand.
- The TRUNCATE-TB trial is one of the first trials to use the multi-arm multi-stage (MAMS) design in the context of global health trials. This design allows researchers to test multiple intervention arms against a single control arm and drop unpromising intervention arms as well as add new ones part way through the trial. Hence, this approach is more efficient and cost-effective than a traditional two-arm trial and offers a greater chance of finding an effective treatment.
- The study is still ongoing, and findings are yet to emerge. However, the trial has already contributed to enhancing the scientific knowledge, technical skills and professional networks of the researchers working at the trial sites, and stakeholders are being engaged.

5.9.4 Development awards with evidence of outcomes

Case study 15

Develop an interventional study on reducing antibiotic over-prescribing among children with Upper Respiratory Tract Infections in rural Guangxi, China (MR/M022161/1, Call 5 – Development award)

Funding period: 01/04/2015 - 31/12/2017

Funding amount: £151,260

Lead PI: Prof Xiaolin Wei

Lead institution: Shandong University

- Overuse of antibiotics promotes the development of antimicrobial resistance, a major global health problem. Antibiotic over-prescription is widespread in the treatment of upper respiratory tract infections (URTIs) and this challenge is particularly pressing in LMICs.
- A JGHT-funded pilot study aimed to inform the design of a randomised controlled trial aiming to reduce antibiotic over-prescription in the treatment of URTIs in children in rural Guangxi, China. The pilot study tested the feasibility of a multidimensional intervention consisting of clinical guidelines, training material and workshops in two groups (clinicians only; clinicians and caregivers) against a control group.
- Findings of the pilot study informed the design of a full trial which was funded by DfID. This trial showed that the intervention reduced the antibiotic prescription rate by about a third (29%) and that the effect was sustained for at least a year in the intervention hospitals.
- Implementation of the interventions as part of the feasibility study and the full trial had a positive impact in reducing over-prescription of antibiotics regionally.

Case study 16

WHO's Parent Skills Training for developmental disorders: Piloting task-shifting to non-specialists in Ethiopia (MR/P020844/1, Call 7)

Funding period: 01/08/2017 - 30/04/2019	Funding amount: £147,849
Lead PI: Dr Rosa Anna Hoekstra	Lead institution: King's College London

- Developmental disorders are common yet under-resourced in LMICs. To address this gap, WHO has developed a Caregivers Training Skills (CTS) programme to educate and support caregivers of children with developmental disorders. The programme, designed to be delivered by non-specialists, had not been adapted to or tested in the Ethiopian context prior to this study.
- A pilot study led by King's College London, funded by a JGHT development award, aimed to evaluate whether CST can be implemented in the Ethiopian context and determine if the measures to assess its impact are reliable and appropriate. The full results are not yet published, but the qualitative study indicates that the CST is acceptable and can be implemented in Ethiopia.
- The study team placed emphasis on local stakeholder engagement, ensuring that the project became locally owned. The CST has since been taken up by the community: It is now used in Ethiopia's state-run child mental health clinics and rolled out to all caregivers who attend these.
- The research team is currently collaborating with a team in Kenya to conduct a full multi-country randomised control trial. Findings from the pilot study will feed directly into this planned work.

[Tekola, B. et al (2019) Adapting and pre-testing the World Health Organization's Caregiver Skills Training programme for autism and other developmental disorders in a very low-resource setting: Findings from Ethiopia. Autism: https://doi.org/10.1177/1362361319848532]

5.10 Value for money

The JGHT represents value for money (VfM) in a variety of ways, maximising the impact of the investment.

• Partnership of funders

Delivery of the JGHT through a partnership of funders has represented efficiency gains for both funders and applicants by:

- Reducing duplication of effort. A unified review process avoids unnecessary time investment by
 researchers in submitting proposals to multiple schemes and avoids duplication of effort by
 review panels. In addition, funders are able to draw on their respective expertise to inform the
 review process, ensuring a high quality of projects selected (e.g. as evidenced by the high
 completion rate of trials, see below). Efficiencies are also achieved through centralised scheme
 management.
- Enabling a strategic view of the scheme's direction and the JGHT portfolio funded, ensuring that any gaps or duplications are identified (a risk if individual funders work in silos)
- Enabling large-scale global health trials to be funded from pooled resources and at the same time reducing the risk of investment for individual funders

This view was also expressed by key opinion leaders when asked about aspects that contribute to the scheme's VfM: half (3 of 6) pointed to the set-up of the programme itself and highlighted the added value achieved by running the JGHT as a partnership of funders.

• Flexible scheme management

The flexibility of the scheme's management is contributing to value for money of the research budget. Research in LMICs is facing a variety of risks, from delayed approval processes to civil unrest, jeopardising researchers' ability to complete the studies. While an accurate assessment of time and cost at the proposal stage is preferable, the flexibility of the JGHT has ensured that research efforts were not 'wasted' by allowing for non-costed, as well as some costed extensions. This aspect has contributed to the high trial completion rate (see below).

• Support for high-quality research

The JGHT has funded high quality research projects, including 63 full trials addressing health issues of disadvantaged populations in LMICs. Of the 28 closed full trial awards, the majority have published or are in the process of publishing the main trial results (23) with another two in the final analysis phase, indicating that at least 89% of these trials have completed. This compares favourably with reported figures for trial completion rates in a study of 114 trials in the UK, which indicated that only 31% met enrolment goals₇₃, and is in line with a recent analysis of Phase III and Phase IV trial completion rates, at 85% and 87%, respectively₇₄.

• Filling a gap in the wider global health research landscape

Evidence from desk research and stakeholder consultation underpins the finding that the JGHT fills an important gap in the global research landscape. The scheme is unique in that is provides funding for global health trials across health areas relevant to LMICs and across all countries, and in that it is open to lead PIs from LMICs. While there is overlap between the JGHT and the EDCTP, they also complement each other: JGHT covers areas, both disease and geographical areas, not covered by EDCTP, and EDCTP funds activities not covered by JGHT e.g. capacity building and early stage trials.

• Research findings with strong relevance to health issues of disadvantaged populations in LMICs

JGHT-funded research is generating essential evidence that has been, or has the potential for being, utilised world-wide to support development. For example, 39% of JGHT-funded closed full trials (11 of 28) have already influenced policy at a local or international level, with a further 36% (10 of 28) showing high potential for doing so (based on the conclusiveness of the research results and the PIs level of stakeholder engagement) (see section 5.6.1). The final figure could hence be as high as 75% of closed full trials resulting in policy influence.

Despite the relatively short time since completion of most of these trials, some impacts on health have already been achieved (see section 5.6.2). For example, in Ethiopia, 100,000 patients suffering from podoconiosis have already been trained in how to self-treat with a simple foot care package, shown to be effective in reducing severe symptoms of podoconiosis. With an estimated 1.6 million Ethiopians affected by podoconiosis, this already represents 6.3% of the patient population (see Case study 5). Further roll-out can be expected to further decrease the level of disability and social effects as a result of the disease. In addition, the trials themselves have resulted in health benefits, both direct and indirect, to study participants and their wider communities (see section 5.4.11). For example, the TUMIKIA trial reduced the prevalence and transmission of helminths in clusters treated at a community-level, rather than through school-based deworming (see Case study 9). With 100,000 households participating in the effective treatment arms, and an average Kenyan household size of four₇₅, a minimum of 400,000 individuals have benefitted from participating in the trial. In addition, research activity has increased participants' and their communities' knowledge and awareness of risks factors, health issues and ways to address them, leading to potentially positive behaviour change and health outcomes.

⁷³ Bower P et al (2009) Improving recruitment to health research in primary care. Fam. Pract. 26:391–397

⁷⁴ Wong CH et al (2019) Estimation of clinical trial success rates and related parameters. Biostatistics 20: 273-286

⁷⁵ United Nations Department of Economic and Social Affairs (2017) Household size and composition around the world. Popfacts No. 2017/2

• Leverage of additional resources and economic benefits

JGHT-funded research has led to a range of benefits for researchers in LMICs and HICs, such as enhanced scientific knowledge which has been used for further work (e.g. as reported by 71% of co-investigators, 121 of 170), strengthening the wider research ecosystem. This has also helped to leverage additional funding, as reported by 28% co-investigators (48 of 170). For example, the findings of a development award on reducing antibiotic over-prescribing in China informed the design of a larger RCT trial funded by DfID through the Communicable Diseases (COMDIS) Health Services Delivery Research Consortium (see Case study 15). Another development award led to funding for a full trial from the EDCTP (€5,977,299).

A recent study of the value NIHR clinical research has added to the UK economy found substantial direct and indirect economic benefits⁷⁶. Economic benefits related to direct employment, effects on the UK and LMIC supply chains, the provision of free-of-cost treatment by commercial organisations, and through spending by trial staff within the economy can also be expected to have accrued as a result of JGHTfunded research, both in the UK and LMICs.

Findings of JGHT-funded research have also led to, or have the potential to lead to, cost savings. This includes:

- Learning from development awards which have 'de-risked' full trial awards, both by tailoring the intervention to be tested and building stakeholder support (see Case study 10 andCase study 14).
- Potential cost savings for LMIC health systems. For example, the TUMIKIA trial (see Case study 9) found that the community delivery platform tested in the trial resulted in comparable coverage and effects of the interventions across important demographic and socioeconomic subgroups (i.e. equity). This has implications for the intervention tested (de-worming) as well as for other treatments delivered via the community. Another trial has led to cost savings by steering away from a treatment approach involving a harmful intervention (e.g. see Case study 2). However, most studies are still in the process of completing their full cost-effectiveness assessments (see section 5.6.3), and the potential for cost savings through implementation of JGHT findings is not yet known.

5.10.1 Opportunities to improve VfM

There are a number of opportunities to improve the JGHT's VfM. These are outlined below, and taken up in more detail in the review recommendations (see section 8.2).

- While researchers appreciated the 'light-touch' reporting requirements of the scheme, additional monitoring would enhance the funders' ability to track outcomes and impacts, identify any patterns (both positive and negative, e.g. in relation to outcomes of, or challenges to, specific research areas or research in particular countries), and pinpoint opportunities for sharing learning more widely to optimise the value derived from funded research.
- Funders could ensure that opportunities for further stakeholder engagement are available, both preand post-award, in order to ensure full pull-through of research findings to policy and implementation. This could include partnering with other funders or across funding schemes, e.g. with the EDCTP.
- Expansion of the development award scheme (in overall budget, and size of awards available), to derisk the larger trial and ensure that the stakeholder environment is conducive to take up of research findings.

⁷⁶ KPMG (2019) Impact and value of the NIHR Clinical Research Network

6 The global health trials funding landscape

6.1 Organisations funding global health trials

In interviews, researchers and key opinion leaders noted that in addition to the JGHT scheme, funders and programmes such as the European & Developing Countries Clinical Trials Partnership (EDCTP), Bill and Melinda Gates Foundation (BMGF), US National Institutes of Health (NIH), the MRC and the Wellcome Trust were important sources of funding for global health trials.

6.1.1 European & Developing Countries Clinical Trials Partnership

EDCTP is the closest to JGHT in that it provides funding specifically for global health trials. However, its scope is limited to research on interventions for poverty-related infectious diseases₇₇ taking place in sub-Saharan Africa. On the other hand, EDCTP funds all clinical trial phases (I-IV) – not only late-stage trials – including research investigating health services optimisation as well as capacity strengthening and networking activities such as PhD, MSc and career development fellowships₇₈. Nonetheless, the majority of trials funded are Phase II and III studies (58% in EDCTP2₇₉). EDCTP is also a larger scale partnership than the JGHT, both in terms of budget (€655m since 2003; average €5.2m for research grants in EDCTP2₈₀) and partners which include the European Union and 16 African and 14 European countries including the UK₈₁.

Other funders such as BMGF, NIH, Canada's International Development Research Centre (IDRC) and the Research Council of Norway (RCN) fund global health trials through programmes or funding mechanisms that have a much wider scope, for example, product development or health innovation to address health-related challenges in LMICs. Moreover, their strategic priorities and aims determine the scope of the activities they fund and the manner in which they are funded.

6.1.2 Bill and Melinda Gates Foundation

The BMGF aims to reducing health inequalities in developing countries. As such, it has adopted a challenge-driven approach and fosters the development of new treatments and strategies to decrease the burden of infectious disease and the leading causes of child mortality. Thus, it funds clinical trials as part of a host of activities including discovery and translational research, therapeutic development, vaccine development and surveillance focussing on high burden diseases and areas of unmet need in LMICs such as enteric and diarrheal diseases, HIV, malaria, maternal and new-born health, neglected tropical diseases, pneumonia and TB. Moreover, there is no specific requirement for BMGF-funded trials addressing global health issues to be conducted in LMICs.

BMGF has a more directed approach towards awarding funding. Ideas for proposals are identified by programme officers in consultation with stakeholders including researchers and policy makers⁸². These ideas are further developed into proposals for research through direct solicitation, discussion with one or more organisations who are then invited to submit a proposal and public/private requests for proposals.

Some BMGF funds for global health research are distributed through specific programmes such as Grand Challenges ($USD_{450m_{83}}$) and Grand Challenges Explorations. The former started in 2003, is

⁷⁷ HIV, tuberculosis, malaria, neglected infectious diseases, diarrhoeal diseases, lower respiratory tract infections, emerging or re-emerging infectious diseases of particular relevance for Africa such as Ebola virus disease or yellow fever

⁷⁸ EDCTP. Strategy and work plans. http://www.edctp.org/see-work/strategy/ Accessed 20 Oct 2019

⁷⁹ Among interventional trials funded by EDCTP2. Data provided by EDCTP.

⁸⁰ Clinical trials and implementation research grants funded 2016 to 2018. Data provided by EDCTP.

⁸¹ EDCTP. Get to know us. http://www.edctp.org/get-know-us/ Accessed 20 Oct 2019

⁸² BMGF. How we work. https://www.gatesfoundation.org/How-We-Work Accessed 20 Oct 2019

⁸³ BMGF. Grand Challenges. https://gcgh.grandchallenges.org/about Accessed 20 Oct 2019

funded in partnership with the NIH, Canadian Institutes of Health Research (CIHR) and the Wellcome Trust, and consists of a programme of initiatives wherein each initiative focuses on innovation towards addressing a specific global health or development challenges₄. The latter was initiated in 2007 and invites high-risk, high-reward proposals from innovators on a biannual basis₅. Successful applicants are initially awarded USD100k with successful projects potentially receiving up to USD1m of follow-on funding.

6.1.3 The US National Institutes of Health

In contrast to the JGHT and EDCTP, the US NIH does not have specific programmes for funding global health trials. The agency funds global health trials worldwide (including in LMICs) through its standard funding mechanisms and specialist institutes such as the National Institute of Allergy and Infectious Diseases (NIAID). There is no defined remit in terms of trial areas or phases, and thus topics such as bioethics, non-communicable diseases, infectious diseases, implementation science, mobile health, mental health and maternal and child health are all covered.

NIAID funds clinical research in one of two ways86:

- through *extramural grants*, where outside entities (typically universities or academic institutions) are funded to conduct research. This usually takes place in the context of existing NIH/NIAID-funding networks such as the AIDS Clinical Trials Group, the Immune Tolerance Network and the Vaccine Treatment and Evaluation units, which ensures that relevant infrastructure is available (e.g. for regulatory support, biostatistics and training). Proposals can be for investigator-initiated (unsolicited) or NIAID-requested (solicited, in predefined areas) research⁸⁷.
- through *intramural grants* where NIAID scientists work in partnership with investigators in LMICs. The grant comes from the NIAID scientist's sustained funding allocation (block grant)₈₈.

Most NIAID clinical trials are funded in response to solicitations from NIAID where the topic and scope is predetermined (NIAID-requested research)₈₉. Some calls allow LMIC researchers to apply either independently or in partnership with a US institution. In 2018, NIAID funding for clinical research in LMICs was USD443m₉₀.

6.1.4 Other funders

Funders such as IDRC (Canada), Grand Challenges Canada (GCC) and the RCN/Norwegian Agency for Development Cooperation (Norad) fund trials as part of innovation programmes with a global health focus.

- IDRC has two programmes for health-related innovation Food, Environment and Health (covering nutrition, infectious and non-communicable diseases) and Maternal and Child Health₉₁. In addition, the agency has partnered with the Canadian Institutes of Health Research (CIHR) and Global Affairs Canada on a third programme Innovating for Maternal and Child Health in Africa. These programmes fund projects on a competitive basis through calls with their own specific eligibility requirements and thematic focus. Trials form a small proportion of the activities funded (6 of 438 projects; total spend CAD13m) and include testing of vaccines (e.g. Ebola) and prevention
- 84 BMGF. Grand Challenges. https://gcgh.grandchallenges.org/history Accessed 20 Oct 2019
- 85 BMGF. Grand Challenges. https://gcgh.grandchallenges.org/about Accessed 20 Oct 2019
- 86 Personal Communication, Dr Clifford Lane (8 October 2019)

88 Personal Communication, Dr Clifford Lane (8 October 2019)

⁸⁷ NIAID. Types of Funding Opportunities. <u>https://www.niaid.nih.gov/grants-contracts/types-funding-opportunities</u> Accessed 20 Oct 2019

⁸⁹ NIAID. Clinical Trial Research. https://www.niaid.nih.gov/grants-contracts/clinical-trial-research. Accessed 20 Oct 2019

⁹⁰ Personal communication, Joyelle Dominique (12 October 2019)

⁹¹ IDRC. https://www.idrc.ca/en/what-we-do/programs Accessed 20 Oct 2019

interventions $_{92}$. All trials within these programmes were/are being conducted in LMICs, with half of the trials led by LMIC researchers.

- GCC is an independent, not-for-profit organisation funded by the Canadian government and other partners (including DFID, BMGF, USAID and Johnson & Johnson). It supports innovators in LMICs and Canada to develop innovations that will save and improve lives in LMICs₉₃. GCC awards grants and zero interest loans for targeted challenges (e.g. maternal and child health, mental health, hypertension, point-of-care diagnostics), innovator-led proposals and challenges related to scaling up promising innovations. Between 2010 and 2018, GCC spent CAD269m on these programmes₉₄; the proportion of funding awarded for trials is not clear. So far, about 150 different interventions have been tested in product development or implementation trials₉₅. Grants are solicited through open calls for proposals, each defining the scope of what will be funded. PIs can be based anywhere in the world, but funded activities have to take place in an LMIC.
- The Global Health and Vaccination Research (GLOBVAC) programme is the main global health research programme in Norway, jointly funded by RCN and Norad since 2006. It has an annual income of about NOK122m (about £10m)₉₆ and primarily aims to support high-quality research with potential for high impact on health and health equity in LMICs₉₇. Funding is available for research on interventions to prevent, treat and diagnose communicable diseases and to promote reproductive, maternal and child health, including clinical trials of such interventions. Research can be conducted in Norway or LMICs and proposals are solicited through open calls for proposals.

The research funding landscape, and the JGHT's role within, was determined for a selection of four conditions: malaria, tuberculosis, cryptococcal meningitis and podoconiosis. JGHT-funded research accounted for a small share of funding for malaria- and TB-related research, funding around 2% of trials registered in these disease areas between 2011 and 2018 (16 of 833 and 9 of 662, respectively). The scheme played a much bigger role in the "smaller" disease areas of cryptococcal meningitis, accounting for 23% of trials funded (3 of 13), and podoconiosis, accounting for one of three trials in this area (33%). A detailed analysis of each disease area is available in Appendix G.

6.1.5 Product development partnerships

Several funders also support development of innovations for prevention, diagnosis, or treatment of infectious diseases through Product Development Partnerships (PDPs). Examples include the International AIDS Vaccine Initiative (IAVI), European Vaccine Initiative (EVI), Medicines for Malaria Venture (MMV) and Foundation for Innovative Diagnostics (FIND)₉₈. PDPs received USD508m in 2017₉₈ mainly from government agencies such as the UK's DHSC and DFID, the US NIH, USAID, the European Commission, the German Federal Ministry of Education and Research (BMBF), the Australian Department of Foreign Affairs and Trade and the Swiss Agency for Development and Cooperation as well as organisations such as the BMGF and UNITAID. The extent of private sector engagement varies from partnership to partnership.

92 IDRC. Available at:

https://www.idrc.ca/en/search?f%5B0%5D=type%3Aidrc_project&f%5B1%5D=field_program%3A16837&f%5B2%5D=field_program%3A16836&f%5B3%5D=field_program%3A16826. Accessed 20 Oct 2019

93 Grand Challenges Canada. Annual report 2017-18. Available at: <u>https://www.grandchallenges.ca/wp-content/uploads/2018/10/Annual_Report_2017-2018_FINAL.pdf</u> Accessed 20 Oct 2019

⁹⁴ Ibid.

⁹⁵ Grand Challenges Canada. Discover our innovations and results. https://www.grandchallenges.ca/who-we-are/discover-ourinnovations-and-results/ Accessed 20 Oct 2019

⁹⁶ Technopolis (2016) Mid-term evaluation of second programme for Global Health and Vaccination Research (GLOBVAC2)

⁹⁷ https://www.forskningsradet.no/prognett-globvac/About_the_programme/1224697869303 Accessed 20 Oct 2019

⁹⁸ Policy Cures Research (2019) G-Finder 2018 report

PDPs are able to combine the strengths of the public and private sector. The majority of the partnerships work as virtual organisations supporting R&D activities that fit their scope and strategy. They target one or more 'neglected diseases' (i.e. HIV/AIDS, tuberculosis, malaria and neglected tropical diseases) and use a portfolio management approach for developing products. Clinical trials are funded as part of the product development pipeline. For instance, EVI conducts early stage clinical trials and hands over promising candidates to partners for mid-stage clinical development₉₉.

6.2 Outputs, outcomes and impacts of other funding global health programmes

Most funders undertake monitoring of outputs, outcomes and sometimes impacts at a programme level to assess if they are meeting their objectives. Programme evaluations are also commissioned, often from independent, external groups. Most funders use evaluation frameworks and both qualitative and quantitative indicators for monitoring, gathering evidence via a mixed-methods approach (see Appendix G). However, the variation in objectives and timelines, investment and scope of funded activities between funders and programmes limits the level to which outcomes and impacts can be compared across initiatives.

6.2.1 EDCTP

EDCTP funded 96 grants (€395m) for clinical research (including observational studies) between 2004 and 2018_{100,101}. From these grants, 216 clinical trials (interventional studies) have been funded; however, the proportion of funding spent on clinical trials as opposed to observational and other types of studies is not known. EDCTP1 projects (about 180, 2004–13) have generated over 750 peer-reviewed publications (between 2005 and 2019)₁₀₂. In addition, four regional Networks of Excellence and a Pan-African Clinical Trials Registry were established₁₀₃. Some examples of impact achieved from EDCTP1 include the following₁₀₄:

- The CHAPAS trials (CHAPAS-1, 2005–09, €1.2m; CHAPAS-3, 2010–11, €5m) contributed to the approval of specific HIV medicines (Triomune Baby/Junior) by the US Food and Drug Administration in 2007, WHO recommendations on optimal drug ratios for fixed-dose combinations and on appropriate dosage according to weight, the WHO recommendation of abacavir-containing combinations for first-line antiretroviral therapy in children, and applications for regulatory approval for new scored efavirenz tablets
- The Kesho Bora study (2006–10, €2.7m including €1.1m EDCTP funding) informed the development of revised WHO guidelines, which recommended more extensive use of antiretrovirals in pregnant and breastfeeding women. More generally, the results highlight the potential achievability of elimination of mother-to-child transmission
- The WANECAM trial (2009–14, €9.3m including €4.8m EDCTP funding) showed that two antimalarial drug combinations, dihydroartemisinin-piperaquine (DP, Eurartesim®) and pyronaridine-artesunate (PA, Pyramax®) remain safe and efficacious even when used repeatedly. Trial results were used to support successful applications to the European Medicines Agency to extend use of PA to treatment of multiple episodes of malaria

⁹⁹ EVI. Available at: http://www.euvaccine.eu Accessed 20 Oct 2019

¹⁰⁰ Technopolis (2014) Assessment of the performance and impact of the first programme of the European & Developing Countries Clinical Trials Partnership (EDCTP)

¹⁰¹ EDCTP2 data provided by EDCTP

¹⁰² EDCTP1 data provided by EDCTP

¹⁰³ EDCTP. Tackling infectious disease in sub-Saharan Africa. <u>http://www.edctp.org/web/app/uploads/2018/09/Tackling-infectious-disease-in-sub-Saharan-Africa_EDCTP-funded-clinical-studies-for-medical-interventions-2003-2018-4.pdf</u> Accessed 20 Oct 2019

¹⁰⁴ EDCTP. Tackling infectious disease in sub-Saharan Africa. <u>http://www.edctp.org/web/app/uploads/2018/09/Tackling-infectious-disease-in-sub-Saharan-Africa_EDCTP-funded-clinical-studies-for-medical-interventions-2003-2018-4.pdf Accessed 20 Oct 2019</u>

and for a paediatric formulation; both formulations are now on the list of WHO- prequalified medicines

The European Commission's interim evaluation of the second phase of EDCTP (from 2014-2016) noted a number of successes related to researcher participation from Sub-Saharan Africa which included (but were not limited to) the following₁₀₅:

- More than 40 countries in Sub-Saharan Africa were involved in activities initiated by EDCTP participating states (14 European and 14 African countries). 50% of these activities involved up to 4 countries and approximately 10% involved a minimum of 10 countries
- Scientists from nearly 30 sub-Saharan countries were represented in applications for funding
- 73% of funded grants (including research grants, fellowships, coordination and support grants) were led by scientists from sub-Saharan Africa

While EDCTP has many similarities with JGHT and has had some notable successes, outcomes are not directly comparable owing to the difference in scope in terms of disease areas, geography and trial phases. Moreover, a comparison of the enablers of outcomes between the JGHT and EDCTP would require further research and analysis to understand differences between the research and stakeholder engagement carried out by these programmes.

6.2.2 Product development partnerships

A selection of PDPs has also been evaluated on behalf of individual funders (DFID/BMBF106, the Australian Government107 and the Dutch Ministry of Foreign Affairs108). Findings on outputs and outcomes that emerged from these evaluations and from desk research (PDP websites) are as follows:

- Since 2003, FIND has developed 24 new diagnostic tools for neglected diseases, 17 of which have been recommended by WHO₁₀₉. It has supported 71 clinical trials and published 241 scientific articles₁₁₀. Over 50 million FIND-supported products have been provided to 150 LMICs since 2015₁₁₁. The total expenditure for research activities was USD55m in 2018₁₁₂.
- Since its inception in 1999, MMV and its public and private partners have brought forward 10 new antimalarials and have helped save an estimated 1.9 million lives through medicines they have supported₁₁₃. MMV's expenditure in 2017 and 2018 totalled USD159m which covers all R&D activities including clinical trials.
- The TB Alliance is currently conducting three Phase III trials and one paediatric Phase IV trial¹¹⁴. It previously funded two Phase III studies. In 2018, TB Alliance submitted its first new drug

¹⁰⁵ Evaluation of the Second European and Developing Countries Clinical Trials Partnership Programme (2014-2016). Experts Group Report. 2017

¹⁰⁶ Boulton et al (2015) Evaluation of the Product Development Partnerships (PDP) funding activities

¹⁰⁷ Ramchandani and Bulc (2017) Final evaluation of Australia's investment in Product Development Partnerships (2013-2018): Evaluation findings and options for future DFAT investment. Specialist Health Service.

¹⁰⁸ Technopolis (2014) Review of the Product Development Partnerships Fund 2011-2014. Final report to the Dutch Ministry of Foreign Affairs.

¹⁰⁹ FIND. Available at: https://www.finddx.org/ Accessed 20 Oct 2019

¹¹⁰ FIND. Annual Report 2018. Available at: https://www.finddx.org/wp-content/uploads/2019/10/FIND_Annual-Report-2018_WEB-final-cpr.pdf Accessed 20 Nov 2019

¹¹¹ Ibid.

¹¹² Ibid.

¹¹³ MMV at a glance. <u>https://www.mmv.org/sites/default/files/uploads/docs/publications/MMV_at_a_glance_EN_2019.pdf</u> Accessed 20 Nov 2019

¹¹⁴ TB Alliance. Our pipeline. https://www.tballiance.org/portfolio/trials Accessed 15 Oct 2019

application, for pretomanid, to the US Food and Drug Administration (FDA)¹¹⁵. Total R&D expenditure for 2018 was USD48m¹¹⁶.

PDPs cover the whole spectrum of R&D activities from basic research and translation to product development. Clinical trials form a small proportion of these activities. Moreover, the amount of funding that they put towards clinical trials is unclear. Hence, a direct comparison with JGHT is not possible.

6.2.3 GLOBVAC

An evaluation of RCN and Norad's GLOBVAC programme conducted in 2016 found that GLOBVAC is a reasonably efficient and effective research support mechanism that fills an important gap in the Norwegian funding landscape₁₁₇. Between 2006 and 2015, about NOK900m (approximately \pounds 76m) was spent on the programme which had led to:

- 1,239 scholarly publications; 15 products, 42 prototypes and 12 process or service innovations; 12 patents and 1 licensing agreement; 16 new businesses
- creation of new research collaborations and partnerships within Norway and internationally; capacity development in low and lower-middle income countries
- Phase II and III trials that had provided crucial evidence with regard to interventions against, for example, transmission of HIV from mother to baby through breastfeeding, HIV-1 infection (Vacc-4x vaccine), rotavirus (ROTAVAC® vaccine) and Ebola (rVSV-ZEBOV vaccine)

While GLOBVAC has been evaluated¹¹⁸, it funded very few large-scale trials, which does not allow a meaningful comparison with the JGHT.

6.3 Advantages / disadvantages of the JGHT compared to other funding programmes

Researchers and key opinion leaders pointed to a range of strengths that set the JGHT apart from other programmes, including the fact that:

- Researchers are driving the research rather than the funders
- A substantial amount of funding is available at a sufficient scale to conduct a large late-stage trial
- The scheme's remit covers various conditions including NCDs, mental health and violence, and not just infectious diseases
- All LMICs are in scope and the research can be led by an LMIC researcher
- Grant management and reporting requirements are realistic and do not burden researchers

EDCTP was mentioned by all interviewees as a comparator programme to the JGHT, although significant differences between the two programmes were highlighted (see section 6.1.1). Two interviewees commented that the application process for EDCTP is much more cumbersome than that for the JGHT, which they saw as more straightforward. However, the availability of funding from EDCTP for networking and to translate research results into policy was viewed favourably.

BMGF was also seen as a major funder by the interviewees with the main difference being that although it funds very large trials, it does so with a top-down and directive approach, rather than funding an investigator-initiated trial. According to one key opinion leader, this means that BMGF exerts closer control on trials, including in terms of monitoring progress and milestones and sitting on the trial

¹¹⁵ TB Alliance. Developing new treatments. Available at: <u>https://www.tballiance.org/annualreport2018/developing-new-</u> <u>treatments</u> Accessed 15 Oct 2019

¹¹⁶ TB Alliance. Annual report 2018. Available at: https://www.tballiance.org/annualreport2018/financials Accessed 20 Nov 2019

¹¹⁷ Technopolis (2016) Mid-term evaluation of second programme for Global Health and Vaccination Research (GLOBVAC2) ¹¹⁸ Ibid.

steering committees, which "is suboptimal and inhibits flexibility". BMGF's end-to-end approach was seen as an advantage in that all the questions that need to be answered before a policy decision are identified in advance and policy makers (e.g. WHO and country level policymakers) are involved before a clinical trial is even started. This means that the research undertaken is directly relevant to the needs of the health systems in LMICs. In addition, qualitative research and research for countries to identify what will be required for implementation is often undertaken in parallel to the trials, which shortens the timeline for implementation and impact.

The NIH was described as being very 'US-centric' in its approach. However, one interviewee stated that its large resources, better costing models and trial networks in LMICs offer distinct advantages over the JGHT. In addition, its other capacity building efforts e.g. through the Fogarty International Center allows early career researchers from LMICs as well as the US to build professional networks and gain the necessary skills and experience to apply to international global health research programmes.

Opportunities offered by other funders and programmes to engage with policy stakeholders in LMICs were a key distinction for a few interviewees. Examples cited included

- Wellcome Trust, where researchers can apply for public engagement funds when applying for a grant, which can be useful to bring relevant LMIC stakeholders together
- DFID, where programmes are tailored to local needs and local stakeholders are engaged, increasing the likelihood of getting implementable results from the research funded
- NIHR, which has recently offered small development grants to hold consultations with ministries of health in LMICs to identify the priority research questions in the local context

The lack of a specific disease focus in JGHT in contrast to both EDCTP and BMGF was viewed very positively by several interviewees. A disease focus was seen as somewhat limiting as research proposals falling outside the funders' areas of interest will not be funded, leaving gaps in the funding landscape. It was also noted that as individual funders are pooling their resources in the JGHT, researchers are able to access larger amounts funding, and hence can deliver larger trials.

6.4 Current gaps in the global health trial funding landscape

Researchers and key opinion leaders reported a number of gaps in the research funding landscape.

The majority of PIs (89%, 34 of 38) and co-investigators (94%, 124 of 132) surveyed indicated that there were critical gaps in the global health funding landscape, with 30-40% of researchers referring to a gap in the type of research funded, a gap in funding for critical research infrastructure, and a gap in funding for capacity building and training. PIs of development awards (67%, 8 of 12) more commonly held the view that their health field/intervention was underfunded compared to PIs of full awards (24%, 4 of 17). 17% of PIs (5) and 30% of co-investigators (22) indicated a gap in follow-on funding to support implementation of trial findings, policy engagement, and funding during the manuscript writing stage. This was seen as a barrier to impact; as one respondent summarised: "In many, cases studies are funded and have to operate on stringent budgets. After the end of the trial there are minimal funds left for publication. As such, policy makers may receive results alongside the international community. They are often very minimally engaged in the analysis and interpretation of these results. This may impact ownership as well as utilisation of results moving forwards".

Gaps reported by researchers and key opinion leaders in interviews fell into four categories:

- Implementation research, taking results from a successful trial and understanding how to scale up the intervention across different locations
- Lack of sufficient funding for research on NCDs in LMICs
- Capacity building in LMICs, e.g. support for junior PIs, funding for graduate students and training in statistics and health economics
- Funding for smaller Phase II trials, to enhance the design of Phase III trials: "These are very valuable and cheaper (i.e. more value for money), but there are few mechanisms to support these. It means that some researchers jump prematurely into Phase III trials in order to secure funding."

7 JGHT funding scheme - design and management

7.1 The design of the JGHT funding scheme

7.1.1 Overall impressions of the design

Researchers and key opinion leaders were predominantly positive regarding the design of the JGHT.

Positive aspects mentioned included:

- The broad range of topics funded under the scheme, e.g. 69% of PIs (24 of 35) and 53% of coinvestigators (55 of 104) surveyed expressed positive views of the type of research funded.
- The researcher-led, bottom-up approach to funding, e.g. 81% of key opinion leaders (13 of 16) felt this was a crucial aspect of the scheme
- The substantive level of funding available, e.g. several researchers and key opinion leaders (5) specifically highlighted that the JGHT was one of a handful of schemes that supported (expensive) RCTs
- The opportunity for LMIC institutions to apply directly
- Geographical coverage, without limitation to specific countries or continents, including support for multi-country trials
- The focus on impact, with projects positioned 'at the implementation-end of the research spectrum'.

The scheme's emphasis on stakeholder engagement (such as policy makers) throughout the research process and involvement of social science and health economics experts in the trial team were commended, as both elements were seen to facilitate policy influence and health impact. However, a small number of PIs explained that the requirement for health economic and social science studies as part of the project was not appropriate for all trials. For example, one researcher explained: "We did it because it was required, but it wasn't really necessary in our situation.". A key opinion leader commented that the cost of some interventions can be driven down after an intervention has been shown to be effective; current costs should hence not dictate whether a piece of research is undertaken or not.

Nearly all PIs (97%, 37 of 38) and the majority of co-investigators (84%, 121 of 144) surveyed agreed that the design and requirements of the JGHT enabled the scheme to attract high-quality proposals, and more than half of PIs (57%, 21 of 37) and three quarters of co-investigators (79%, 115 of 146) felt there were no aspects of the JGHT design or requirements that could be improved. Researchers and key opinion leaders consulted in interviews were also mainly positive about the scheme.

Conversely, 29% of PIs (8 of 28) and 18% of co-investigators (15 of 83) surveyed stated that the JGHT did *not* have any obvious weaknesses when specifically asked about these. 29% of PIs (8 of 28) considered the amount of funding available a weakness, both in terms of the size of awards (3) and the lack of funding for additional aspects such as dissemination, capacity building or student fellowships (4). 18% of PIs highlighted issues pertaining to administrative factors (e.g. timeline, fund transfer logistics) (5).

Among co-investigators, the most common weaknesses reported were related to award administration, such as lengthy processes and limited communication with funders (24%, 18 of 76). A higher share of co-investigators working at LMIC institutions (40%, 12 of 30) considered these problematic compared to respondents from HICs (Figure 44). Other issues raised were the lack of funding for capacity building and follow-on studies (18%, 14 of 76), and the JGHT's bias towards established and UK-based PIs (16%, 12; 20% of co-investigators from LMIC institutions). A number of interviewees added that this bias may (at least partially) be due to a lower level of English language skills, less experience in and precedents for writing a 'polished' proposal, and a low level of knowledge of the UK research system (including its ethical review process).





Source of data: Survey of co-investigators. ^'Award administration' includes lengthy application time and lack of communication with the funders.

7.1.2 Size of awards

Several researchers and key opinion leaders raised issues with the size and length of JGHT awards. While the JGHT was appreciated as one of few funding programmes that provide substantial grants to finance RCTs, the grant sizes were nevertheless too small to appropriately cover the cost of full global health trials. In addition, a few researchers and key opinion leaders considered that the awards were of insufficient duration. Other funders – the EDCTP, US NIH and BMGF - were cited as offering much larger awards and (at least in the case of the EDCTP) over longer periods of time.

Comments by a number of researchers implied that they perceived the JGHT to fund a certain size of award (£2-3m, possibly £4m), over a certain period (around 3 years). In order for the proposals to be competitive, two interviewees reported that they had scaled down their original trial designs to reduce trials costs and enhance their chance of success. As one researcher explained: "You've always got to try to squeeze [the research] into what you think is going to be the correct funding envelope. So there's never enough dedicated time at the end for writing up. It's always trying to do things on the cheap. [...] I think the expectations of funders in terms of how much money trials should cost is unrealistically small". On the same point, two other researchers asked for more clarity around the budget range and funding ceiling for full grants. Other aspects mentioned were a clarification of the preferred duration of trials, and the need to include a health economics and qualitative study. On this point, one PI expressed the view that health economics and qualitative studies may not be beneficial as part of the trial in all cases and could be realised at a later stage.

7.1.3 Design of the development award scheme

Researchers and key opinion leaders were overall positive about the development award scheme. All but one of the 14 key opinion leaders who discussed this funding stream were complimentary of it (93%), highlighting its importance in preparing the ground for full trials: By collecting baseline and feasibility data, the awards were expected to underpin the design of the full trial, giving confidence to sample size, outcome measures and implementation aspects. In addition, it could serve to forge strong relationships with stakeholders.

Two interviewees proposed the scheme be expanded, both in its overall budget to allow a larger number of awards to be funded, as well as in the size of individual awards, e.g. to include Phase II trials. A third interviewee advocated for an extended timeline for these awards to allow iteration of research approaches and learning. A suggestion was to offer a larger, longer grants for new interventions, allowing careful development of interventions before testing in a full trial.

However, there were a small number of researchers and key opinion leaders who raised issue with the scheme. Four interviewees felt the two-step approach dragged out the timeline; another did not think this type of research should be a priority for the JGHT.

Two interviewees felt that decisions on development award proposals should take into consideration potential funding through the full trial award scheme. As a key opinion leader explained: "I think we have to be very careful. Sometimes there's a good idea, and we fund it. But when it comes around to the time of funding the full trial, we realise that it's not one of our top priorities. So we have to find a way to be able to look at the development grant application with the eye to 'would we fund a larger trial if this comes up positive'.". Accordingly, a small number of researchers who had applied for a full trial following a development award expressed some frustration that they had not been successful.

7.1.4 The application process

When asked to compare the JGHT's application process and requirements with those of related funding programmes, nearly all PIs surveyed held a positive view (97%, 29 of 30), with the majority (63%, 19 of 30) describing the JGHT as "simpler than other schemes" and "straightforward". A smaller share of co-investigators (31%, 24 of 78) considered the process simpler or advantageous, while 35% (27) felt that the process was similar to that of other funders. There were no major differences in the opinions raised between co-investigators from LMIC and HIC institutes and joint units.

A few researchers (from both LMICs and HICs) explained that the application process was less burdensome in comparison to similar programmes, and in particular when compared to the EDCTP. A small number of interviewees (3), all from LMICs, had found it difficult to understand and complete the (many) required forms and UK ethical approval process, and a number of suggestions were made to facilitate this for potential LMIC applicants (see section 7.2.5).

It was noted that the timeframe from application to award, especially for the two-stage full trial awards, was almost a year, during which the research field and conditions at the proposed trial location may already have changed.

7.1.5 Award administration

26% of PIs (9 of 35) and 34% of co-investigators (35 of 104) surveyed pointed to the administrative processes as a key strength of the programme. Programme staff was described as approachable and friendly. A few PIs from LMICs would have liked to more frequent communication and interaction with programme management.

Most interviewed researchers who raised the point of administrative processes also expressed a positive opinion on the monitoring arrangements for JGHT projects. These were described as 'light-touch', allowing PIs to dedicate more time to research. As one PI summarised: "In this particular scheme, they treat you like adults: they give you the money, they trust you to do the work, they ask you to publish, they want you to be advocates and get [your research] out there. Then you fill in your ResearchFish® and it's perfect.". However, the predominant view among key opinion leaders and representatives of the JGHT funders that current monitoring arrangements were insufficient to capture the scheme's outcomes and impacts (see section 7.8)

Researchers also commented positively on the JGHT's flexible approach to funding and openness to accommodating changes in case of unexpected changes in project circumstances. The most frequent changes in projects funded concerned the timeline of the project (projects started late needing a no-cost extension), budget allocation (projects needing to allocate funding differently from the proposal stage) and budget amount (costed extensions).

7.2 Additional activities to improve impact

When asked which additional activities the JGHT could support that would help it achieve its aims, 21% of PIs (7 of 33) and 31% of co-investigators (43 of 139) considered training an important area - especially for early/mid-career researchers and researchers from LMICs. Support for other types of research and for dissemination and knowledge exchange were both highlighted by approximately 21% of PIs (7 of 33) and 22% of co-investigators (30 of 139). Training was more commonly reported by co-investigators from LMICs (39%, 23 of 59) than co-investigators from HICs (25%, 13 of 53) (Figure 45). Conversely, a smaller share of co-investigators from LMICs (14%, 8 of 59) suggested support for other types of research compared to 23% (12 of 53) of co-investigators from HICs.



Figure 45 Additional support activities suggested by co-investigators (LMIC n = 59, JU n = 22, HIC n = 53)

Source of data: Survey of co-investigators

38% (14 of 37) of PIs and one quarter of co-investigators (25%, 36 of 143) surveyed were aware of additional activities covered by other funders that are effective to achieve impacts and health outcomes. Examples provided mainly related to the support for dissemination of results and policy engagement (e.g. as provided by EDCTP, Wellcome Trust and BMGF), for implementation or scale-up (e.g. as provided by BMGF), and for capacity building (e.g. EDCTP, Wellcome Trust-Newton Fund Collaboration, GCRF).

7.2.1 Training and capacity building

Survey respondents highlighted training and capacity building as an important element the JGHT could support to achieve impacts and health outcomes (see above).

While many PIs reported that a lack of capacity had been a challenge for trial implementation, only one of the PIs and one of the key opinion leaders interviewed felt that funding should be provided as part of the JGTHI. Others explained that while capacity building is an important outcome of the research, it should not be a major focus of the JGHT.

Two other key opinion leaders suggested that the funders encourage LMIC institutions to include junior investigators in the project, and require evidence that LMIC researchers are fully involved in developing and implementing the research, and analysing the data gathered. As one representative of a funding organisation explained: "The main way the JGHT could help build capacity is by having scientists train under the scheme and improve their scientific knowledge and skills to take forward in their career. There are many other schemes that target capacity building and meet this need, and they are better designed as capacity building schemes."

7.2.2 Funding for dissemination and engagement post-award

Interviewees broadly agreed that research impact could be enhanced by providing more support for dissemination and stakeholder engagement after the trial has concluded. With many projects overrunning, the planned timeframe shifts, leading to dissemination and engagement activities having to take place after the grant has closed. This poses a problem for investigators, who for financial reasons need to move on to a new grant and new project. This is particularly difficult for investigators working at LMIC institutions. As one key opinion leader summarised: "Researchers from LMICs don't have any institutional support via core support or tenure. [...] In LMICs, income is tied more heavily to the project grant; [investigators] do not have the flexibility and luxury to work on engaging stakeholders and writing papers once the grant closes.".

Seven PIs specifically recommended the JGHT provide funding for these tasks. The majority of key opinion leaders (70%, 7 of 10) also supported this approach. Of these, four suggested a separate funding stream (within the JGHT) that PIs could apply for. However, two key opinion leaders in favour of additional support for post-trial stakeholder engagement also cautioned that this should not become added to the responsibilities of researchers but could instead involve funders' policy departments.

Two PIs suggested a 'phased approach' to project funding, whereby "just the PI and project manager are funded right at the beginning, for the first six months. When the trial starts, the amount of funding increases. It then has a long tail at the end, just funding the PI and a project manager or someone to close out [the trial] and do all the dissemination. ".

7.2.3 Support for other types of research

Several key opinion leaders and researchers suggested that the JGHT could broaden the types of funding provided to include smaller trials (Phase II), implementation pilot studies, 'bolt on' laboratory-based work, and aspects of health systems research. There was no consensus on the additional type of research to be supported.

7.2.4 Dissemination of results through the funders' existing networks

Key opinion leaders were asked to comment on the option of disseminating research results through the funders' existing networks, i.e. funders taking an active role. The majority of key opinion leaders had a positive view of this option (86%, 6 of 7). Three interviewees felt this should not be a blanket approach, but on a case-by-case basis. Two interviewees suggested meetings with the relevant stakeholder audience to present results, and one proposed a joint forum with the EDCTP.

7.2.5 Supporting LMIC investigators during the application stage

Several interviewees pointed to a 'monopoly' of a few institutions in securing awards, with few LMIC researchers – with good and innovative ideas - able to compete. This was put down to a number of factors, including a language barrier, a lack of experience dealing with MRC application forms, and a lack of methodological and statistical expertise.

The majority of key opinion leaders (82%, 9 of 11) supported additional efforts funded by the JGHT to assist LMIC applicants in principle, but also cautioned against lowering the quality bar of the review process or awarding funding to LMIC institutions that do not have the necessary capacity and infrastructure to lead a full trial. As one key opinion leader explained: "There is no point if nice grants are written with help, but then there is not capacity to support the delivery of the trial. Support with proposals is great, but it should be done with caution."

A number of concrete suggestions for improvement were made by key opinion leaders and researchers:

• A proof-reading service for LMIC applicants, as part of the application, to identify cases in which vocabulary from the call for applications has been misunderstood. For example, one UK-based full trial PI explained that: "I recently encountered somebody who didn't know what safeguarding really was. They would have been able to do what was necessary, if they'd understood the term. But they thought it was more about financial due diligence.".

- Providing detailed feedback to unsuccessful applicants to enable them to learn the skill of grant writing as relevant to UK-funded projects. One interviewee suggested this could be targeted towards grants that received high scores and came close to being funded.
- Make available supporting resources, such as examples of successful applications and webinars explaining how to fill in the various forms.

7.2.6 Increased communication between JGHT funders and PIs

Two PIs from LMICs would have also liked to see more involvement of JGHT funders with individual projects. They expressed that, while donor representatives were present on each trial's steering committee, they were not as involved as donors in other funding programmes during the course of the project. As a PI of a full closed trial explained: "It's felt quite hands off so it would be nice to have a bit more of an ongoing dialogue about these studies on the challenges that we have been experiencing, and maybe having early opportunities for discussion".

7.3 Options for changes to the design of the JGHT

A number of options for changes to the JGHT were discussed with key opinion leaders and representatives of JGHT funders¹¹⁹ in interviews:

7.3.1 Prioritisation of health issues

Funding calls invite applications restricted to one or a small number of health issues, leading to a 'critical mass' of research in the specified area(s) to increase the potential for impact.

The majority of key opinion leaders and representatives of JGHT funding organisations disapproved of this option (81%, 13 of 16). The wide remit was described as a key strength of the scheme; restrictions would limit the flow of new ideas and lower the overall quality of funded projects. Interviewees also highlighted the fact that health needs in LMICs change and cannot be predicted; researchers and public health experts on the ground have the best understanding of the issues to be addressed. As one key opinion commented: "I think it's much better to do it this way [response-mode]. [...]. I think it's very close-minded to think that a relatively small team [the prioritising committee] can put together all the important global health questions and then limit the rest of the world to that. I think that's totally the wrong way around. Being open to whatever comes through the door is the right way to do it. Too many other funders are going the other way, believing that they're the ones who know how to save the world."

However, several interviewees supported that calls continue to encourage researchers to submit applications in certain areas, felt to be important and under-represented in the current grant portfolio.

7.3.2 Commissioned funding stream for research high priority questions

Research addressing a key question for policy makers is commissioned, leading to a definitive answer with immediate policy implications.

Views on this option were more evenly distributed, with 40% of key opinion leaders and representatives of funding organisations (4 of 10) in favour of this option, alongside the response-mode funding stream, to enable a focus on key questions. Of the six interviewees opposed to this suggestion, three are not in favour of top-down approaches (see above), two thought that commissioned research is more suitable to be picked up by other funding programmes, and one held the view that the budget of the JGHT is too low to accommodate both types of funding.

¹¹⁹ 7 representatives of JGHT funders were interviewed as part of the scoping phase, using a different interview guide. Where comments addressing the JGHT options were made, these were incorporated into the analysis.

7.3.3 Focus funding on larger, more definitive trials

To provide the strength of evidence required as a basis for global policy making, the JGHT should focus on funding larger trials that result in a definitive answer across a range of contexts.

The majority of key opinion leaders and representatives of JGHT funders were not in favour of increasing the scheme's focus on larger trials (62%, 8 of 13). Of these, three interviewees were actively opposed to larger trials, pointing to the need for multiple studies in multiple contexts and timeframes rather than one large trial to robustly inform policy. As one interviewee explained: "I'm not necessarily in favour of grants for huge trials that are definitive, because I don't actually think that science is that simple. I think it is more powerful to have multiple trials that show signals and show smaller signals than one trial as a big signal.". Five considered the flexibility of award sizes a key strength of the JGHT that should not be changed, and explained that the main focus should remain whether the study will answer the research question. This does not exclude larger awards – as one interviewee explained: "If a proposal clearly demonstrates the needs for a larger budget to answer an important question, then there would not be barriers to funding.". Another key opinion leader suggested a multi-step scheme: If a trial is successful in one location, the scheme can have a built-in option for trialling in other countries.

Of those supporting an explicit shift to larger trials, two would like to see this coupled to prioritisation of research questions to be addressed, one would like to see more multi-country trials, and another favours multi-arm trials. Three recommend that larger trials are supported by smaller Phase II studies and policy engagement support.

7.4 Promotion of the scheme

For researchers in the UK and LMICs to be aware of the JGHT and to attract the 'right' proposals, the funders need to undertake promotional activities.

Award holders broadly agreed that information on the JGHT is communicated through the right channels and that information reaches the relevant research communities. This view was expressed by 92% (35 of 38) of PIs and 73% (110 of 149) of co-investigators surveyed. However, several PIs and co-investigators, both from LMIC and HIC institutions, reported that they had not known about the scheme until collaborators had made them aware of it.

Researchers and key opinion leaders interviewed did not feel they were in a position to comment on whether the JGHT was sufficiently promoted. While the level of awareness in the UK was considered high, interviewees were not certain about the level of awareness globally. Most had the feeling that it was 'probably' adequate, with researchers in LMICs who are likely to be successful in applying being aware, but thought difficult to judge the full extent.

When asked about the scheme's promotional activities, one closed award PI based at an LMIC institution noted that he had not seen information on recent calls for proposals, and that the scheme had "somehow dropped off my radar"; another PI from an LMIC institution had heard of the scheme from a mentor but did not think others at the university were aware. A further PI commented that: "I suppose [the JGHT is communicated through the right channels], but I don't think they're very prominent. Only very well-established investigators would dare to go for those awards."

Suggestions for improvements in communication of the scheme included sending calls to all previous PIs and co-investigators, dissemination of calls via the medical literature, and activities specifically targeted at increasing awareness in LMICs and outreach to health ministries and special interest groups.

7.5 The review process

Current and former review panel consulted considered the review process to be fit for purpose, and to 'work well'. A number of PIs of full trial awards also called out the review process as one of the JGHT's strength. As one PI explained: "A major comment was made about the study design that we were proposing in Stage 1 and we changed, radically. And I appreciated that input. So I think to have two stages is great and to have really robust reviewing is important. And we all benefit from it in the end."

Committee members were described as 'very collaborative and respectful', despite a range of opinions across the panel. The meetings are well run, but broadly perceived as pressed for time. As one committee member commented: "At the end of the review process, when all of the studies are ranked, and the decision needs to be made where the cut-off should be: This step can be somewhat hurried, because it takes place at the very end of the meeting and people need to leave to catch planes etc. Ideally there should be more time dedicated to this step although it may be difficult to work out logistically how this could be done.".

Committee members highlighted that the number of proposals to review had burgeoned in recent calls, and that it was now a challenge for reviewers to master the workload this represents. Some of the forms were also considered difficult to work with, placing additional burden on the reviewer.

Views on whether the committee encompassed the required expertise varied. Provided the broad range of topics covered by the JGHT, two committee members felt that "sometimes, we don't have the right experts in the room". Others explained that this was well covered by the selection of external peer reviewers, but one nevertheless would welcome "the option to co-opt someone in, just for that particular application, so that there is a person who is knowledgeable of the subject in the discussion.". A researcher felt that more focussed programmes would have more subject-specific experts on the committee member was very positive about the trial expertise of the panel, and felt the committee was in better suited than those of other schemes: "Normally, the funding committee is made up of a mixed group of people. Only a few, if any, may have any expertise in trials. The great strength of the JGHT committee is that virtually everybody on the assessment panel has expertise in trials, so they are the best group to evaluate these.".

A few committee members and representatives from funders suggested that decision making by the panel take into account additional aspects, such as gender balance, the share of LMIC-led awards, or the level of contribution of LMIC researchers to the proposed research, and a stronger emphasis on the potential of impact of the proposed research on the top causes of mortality and morbidity.

Committee members agreed that the quality of the majority of proposals from LMIC researchers tended to be lower. Two specifically pointed to the lack of experience in proposal writing. Another highlighted that a small number of institutions were 'monopolising' the scheme, having an excellent track record of submitting 'polished' applications, but not necessarily innovative approaches.

A few researchers felt there was a lack of transparency in the review process and criteria. As two researchers explained: "As an applicant you get preliminary feedback from reviewers. And then you get a decision from a panel. And the preliminary feedback can sometimes be completely contradictory to the final decision feedback. For instance, you can get preliminary feedback that says: "I think you might have too big a sample, you should reduce it". And then you can get turned down with one of the chief criticisms being the sample size is too small.". Another pointed to an example where an application had received amazing reviews but did not get funded.

It was also suggested that the review committee appoint more women and experts from LMICs.

7.6 Perceptions of how the JGHT has evolved over time

The overarching aim of the JGHT has not changed over the past 10 years: Support for trials generating evidence which ultimately lead to policy or practice changes. Researchers and key opinion leaders alike continued to support this aim, and many key opinion leaders pointed to the scheme's successes in supporting the highest quality science to inform a broad range of health needs, and in achieving policy influence (in a number of areas they were aware of).

The JGHT was considered to fill a clear gap in the research landscape:

• At the time the it was established, sources of funding for researcher-led global health trials were limited; funding tended to be more focussed on individuals (e.g. fellowships) and awards were

smaller. Pooling of resources as a partnership of funders allowed for a cohort of 6-10 full trials to be funded.

• Today, the JGHT continues to fill a gap, notwithstanding developments in the funding environment over the past decade, such as a broadening of the scope of the EDCTP (see section 6). It is considered to be 'unique', combining a response-led approach without a focus on specific health needs and the ability of LMIC researchers to apply. In the words of a key opinion leader: "It is the only scheme with response-mode calls to fund single large Phase III-type clinical trial with the aim of changing policy.". Others highlighted specific research gaps the JGHT fills, such as research on repurposing of drugs and effectiveness studies. One interviewee summarised with "I feel [the JGHT] fills an important gap in the middle, between products being developed and then evaluated in field studies and more efficient use of existing products."

In interviews, key opinion leaders were aware that the earlier JGHT calls had supported more 'traditional' trials on infectious diseases. The (welcome) impression was that over time, the scheme had become more innovative, and expanded to address a broader range of health issues as well as more implementation-focussed trials. As one interviewee explained: "The JGHT became a signalling device that types of projects that did not perfectly fit any individual funders could receive funding. This was particularly important for some of the health systems type trials but also some of the larger trials that would be a risky for one funder to support alone.".

However, key opinion leaders also raised a number of aspects of the JGHT they felt needed addressing:

- Enhanced focus on implementation trials: The scheme was described as "still having a tendency to focus on possibly too simple interventions, as opposed to some things which are a little bit more embracing of the complex reality of health systems". While these trials are more difficult to conduct, and require a broader range of partners, they are "critical to turn research outcomes into health outcomes.". Funding for implementation research was also highlighted as a gap in the research funding landscape.
- Re-focus on definitive studies: Several interviewees (key opinion leaders and funders) felt that the scheme had 'stagnated' and needed to refresh. Researchers were writing proposals to fit the scheme (and hence maximise chances of success) rather than to conclusively address the research question and aim. There were concerns that this represented a barrier to impact, as a single trial at a single location is too small and context-specific for scale up.

7.7 Added value of a partnership of funders

The four funders, committee members, and researchers had an overall positive view of the partnership. While differences in the organisations' scopes and expertise were acknowledged, some interviewees saw this as a strength, ensuring an informed, coordinated approach across all four organisations. No other issues were raised, but a range of benefits were cited:

- Pooling budgets and de-risking investment: Pooling of budgets has allowed a larger portfolio to be supported, and de-risking investment for each organisation. This has enabled funding of larger trials as well as some more 'novel' and hence riskier areas of investigation, such as menstrual cups and interventions to reduce violence in schools.
- De-fragmentation of the funding landscape: The JGHT has provided a single point of call for researchers looking to run a global health trial. It has unified the review process under a single review committee; as one interviewee explained, in this way applications from across health fields can be compared to each other and the best ones selected for funding, raising the quality of UK-funded trials. A unified review process also avoids duplication and competition between funders for the 'best' projects. This is more efficient for researchers and funders alike, and funders can draw on their respective expertise to inform the review process.
- <u>Closer cooperation between funders</u>: Rather than each pursuing their own priorities, the JGHT allows funders to discuss and coordinate strategies. This has also led them to identify and address

other funding gaps on the path to implementation. For example, the JGHT led to a new joint scheme (health systems research), and a second scheme (implementation research) is currently in pilot stage (via the Global Alliance for Chronic Diseases, GACD). A few interviewees mentioned some tensions between the funders, as each has a different mandate. One key opinion leader alignment between the four funders might mean that certain types of research outside the JGHT are unable to access funding.

- Sharing of expertise: Several key opinion leaders highlighted that the partnership enabled funders to bring their respective expertise to the table, e.g. Wellcome for technical aspects of trial design, MRC with strong scientific background, DfID for working in LMICs and policy translation, and DHSC with a strong understanding of the UK network.
- Broadening areas of research and the research community: The establishment of a separate Development Award scheme helped to provide funds for pilot studies in global health. This is not only de-risking follow-on research, but also serves as an entry point to global health research and trials for less experienced PIs, and an avenue for preparing the ground in areas not previously involved/addressed (both geographic and in terms of health needs).

Key opinion leaders and representatives from the funders broadly agreed that the partnership had helped to maintain the UK's reputation and international leadership in producing high quality research of relevance to LMICs. As one interviewee explained: "It helps the reputation very much. We come in at scale and do the job properly.". Another pointed out that each funder has a different sphere of influence; by working together, the overall reach of the scheme is expanded.

However, it was notable that of the seven international funders interviewed, the representatives of the four North American organisations had not heard of the JGHT. Similarly, a key opinion leader reported that contacts at the US CDC did not know of the scheme. These instances may be down to the individual consulted or may indicate a general lack of awareness of the JGHT on the North American continent.

7.8 Project monitoring & evaluation

Most key opinion leaders and funders pointed to 1) research publications and 2) policy influence as the key indicators to track for JGHT awards. The small number of interviewees who mentioned measuring health impact as an indicator, e.g. changes in morbidity and mortality in the trial location and beyond, thought that this would be too difficult to track (and outside the knowledge of the PI).

In line with the MRC's reporting requirements for all funded research, award holders have to annually report outputs and outcomes via the ResearchFish® platform. This includes reporting on publications and policy influence, as well as other indicators such as funding secured, dissemination activity, and tools, databases, software, IP and products developed.

Many key opinion leaders expressed the view that monitoring via ResearchFish® was 'better than nothing', but that additional reporting should be put in place to track outcomes and impacts. Suggestions for enhanced monitoring included:

- An end-of-grant report, which is reviewed by the review panel and scored, including for aspects such as dissemination and post-trial stakeholder engagement and thus incentivising researchers to focus on these aspects. The end-of-grant could also be used by funders' communication teams to showcase some of the outcomes.
- Use of ResearchFish[®] to identify potentially interesting trials, and develop case studies for these
- Keeping in touch with the PIs after the trial, and potentially beyond the five-year ResearchFish® reporting period. One suggestion was to have a regular short phone call with PIs to discuss any developments.

This review's experience with ResearchFish[®] mirrors the view that it is good starting point, but it provides neither a complete not a rounded picture. Regarding the two key indicators of publications and policy influence:

- The category 'Publications' suffered from a 'deluge' of reporting, making it difficult to identify whether the trial has published its main findings, and a lack of clarity on the degree to which reported publications have a direct link to the funded project. Details on the main trial paper are often included clinical trial registries but not always.
- The category 'Policy' provided some valuable information, but without additional investigation, it was difficult to understand the level of influence achieved and the implications thereof. Of the ten instances in which findings from JGHT-funded trials had influenced WHO policy, six were reported on ResearchFish®, while four were not captured. Latter related to one WHO recommendation (see Case study 7), two instances where data on products used in the trial had informed WHO policy (see Case study 4 and Case study 8), and one instance where the trial had lent confidence to a contested WHO recommendation (i.e. not change). Also not reported was one instance where trial findings had informed national policy (see Case study 1)₁20.

On the basis of this experience, and resource permitting, we recommend additional monitoring of key outputs and outcomes. This could take the form of a) engaging with and developing case studies from trials reporting of outcomes in ResearchFish®, b) a light-touch end-of-grant report, and/or c) a follow-up survey requesting key information to update on progress and outputs/outcomes. Any additional monitoring has to be supported by resource on the part of the implementing funder; e.g. development of case studies. Recommendations for monitoring are further detailed in section 8.2.5.

8 Conclusions and recommendations

8.1 Conclusions

This review of the JGHT was guided by four overarching objectives:

- 1) To assess whether and how the JGHT scheme has delivered on its core aim i.e. the generation of new knowledge about an intervention and its contributions to improving health in LMICs
- 2) Whether tangible outcomes and impacts have been achieved from the funded research

The JGHT has delivered on its core aim and achieved tangible outcomes and impacts: JGHT-funded research has generated new knowledge about interventions which in turn are starting to contribute to improving health in LMICs. Eleven trials - 39% of JGHT-funded closed full trials - have informed, or are about to inform, WHO and national policies. Nine full trials and one development award have led to the implementation of a health intervention. A further 10 trials - 36% of JGHT-funded closed full trials - have high potential for success, as indicated by the nature of the finding and the level of policy engagement by the study team. As more trials complete, further outcomes can be expected.

3) To identify ways in which the value gained from this type of research/research programme can be increased

Key enablers and barriers to policy influence and implementation identified centred around two main aspects: a) the utility of data and external conditions, and b) awareness, understanding, and buy-in by those who are to take up the evidence. Section 8.2 provides a range of recommendations for how the value gained from JGHT-funded can be increased, in relation to both the type of research conducted, and the level of stakeholder engagement prior to, during, and after the award.

¹²⁰ Other national strategies informed by JGHT awards are still awaiting release.

4) To provide guidance on future monitoring of the scheme

Most researchers welcomed the 'light touch' monitoring requirements of the scheme. However, while information reported in ResearchFish® indicates outcomes 'in short-hand' for many (but not all) awards, it does not enable a full understanding of the implications for health in LMICs, nor does it identify findings with potential for policy influence / health impact that would benefit from additional support to engage with the relevant stakeholders. Section 8.2.5 makes a number of suggestions to improve future monitoring, depending on resources available: Engagement with trials identified through ResearchFish® submissions, a requirement for an end-of-grant report, and annual requests for information to complement reporting through ResearchFish®.

8.2 Recommendations

Based on evidence and opinions gathered throughout the review, five recommendations have been formulated. These are presented in Table 18 and set out in more detail in the following sections.

Table 18 Summary of recommendations for the JGHT Image: Commendation of the section of the sect

- 1) Keep the overall design of the JGHT, but clearly communicate the scheme's award parameters to potential applicants
- 2) Provide additional support for stakeholder engagement, both pre- and post-award
- 3) Increase support for LMIC researchers, including resources to assist with proposals, promotion of JGHT calls in LMICs and 'match-making' activities to facilitate access to expertise and infrastructure
- 4) Agree on key criteria for project selection, defining how to balance between the size of the health need addressed, projects' risk of interventions not proving effective, and their likelihood of policy influence
- 5) Launch additional project monitoring activities

8.2.1 Keep the overall design of the JGHT, but clearly set out the scheme's award parameters

The majority of researchers and key opinion leaders supported the current design of the JGHT, and the scheme has enabled trials that have achieved a variety of policy influence and health outcomes. An overarching change in design is not required.

However, the issue of under-funded projects and unrealistic timeframes was raised repeatedly. Delays and issues with cost were mainly due to prolonged ethical approval processes and slow recruitment. The delays then impacted on the level of engagement post-trial, as no time remained at the end of the trial. To some degree, this issue is the result of a perceived 'time and budget limit' for full trial awards, with PIs 'squeezing' their proposed trial timelines and budgets – and possibly methodologies and scale of trial - in order to be competitive.

To avoid this approach, funders should **clearly communicate that time and budget are truly flexible** and re-focus researchers on asking the right questions and proposing appropriately sized approaches to answer them. This clarification could be provided within the call text.

8.2.2 Provide additional support for stakeholder engagement

The review showed that stakeholder engagement in the design and implementation of the trial, as well as post-award, is an enabler of policy influence and health outcomes. In addition, engagement with communities affected before the trial helps to avoid challenges during its implementation. To maximise the potential for policy and health outcomes and impacts, the JGHT should consider options to further support pre- and post-award stakeholder engagement:

Pre-award

- The JGHT could support joint working between different trial institutions, and between researchers and relevant policy makers, by offering **small grants for 'partnership workshops'**, similar to the NIHR's Proposal and Partnership Development Awards (funding of up to £10,000 to support partnership development), for applicants invited to submit full trial award proposals. This will allow trial plans to be optimised and ensure that all partners are fully informed, with the opportunity to provide input and local perspectives.
- The development award scheme is acknowledged as an important source of funding to build community and policy engagement and awareness, test (and adapt) the proposed intervention, and develop a better understanding of the local context in relation to the health need (e.g. associated risk factors), the proposed intervention (e.g. acceptability), and structures for implementation of the trial (e.g. societal decision making processes). As proposed by several researchers and key opinion leaders, the JGHT could consider an **expansion of the development award scheme**, **both in terms of the amount of funding available per call, and in terms of the size of the individual awards**. While its effectiveness in preparing for full trials is not yet clear (see section 5.4.5), this could to be monitored going forward and considered when more information becomes available. If shown to be effective at de-risking full trials, an expansion of this scheme would also avoid 'costly' research mistakes, contributing the JGHT's VfM; this may be particularly important when addressing complex diseases across cultural contexts and health systems.

Post-award

- The JGHT could provide opportunities for PIs or other members of the team to apply for **additional funding to cover engagement activities after the award has closed**, as some awards are likely to require sustained engagement with policy makers and implementing organisations after the trial has closed in order to realise their full potential for policy influence and take up.
- The **funders should explore options for maximising opportunities for dissemination and engagement for trials with high potential for policy influence and health impact.** PIs may not always be in a position to continue engagement beyond the trial or may not have the right network of connections to optimise dissemination. To enhance dissemination and learning, efforts could be combined for multiple trials addressing the same health need but in different geographic locations (need-specific research-policy networks), or for multiple trials in the same geographic location but addressing different health needs (geographic networks, working within similar contexts). Meetings could also involve trialists funded from other sources, e.g. working with the EDCTP secretariat. (To enable this approach, the funders need to be informed of, or monitor, the outcomes of JGHT-funded projects – see recommendation on monitoring.).

Funders could take an active role in these efforts, e.g. by targeting media and convening meetings. Alternatively, a team of specialists could be supported to provide this function. For example, the Knowledge Translation Network Africa (KTNet Africa) was an initiative funded by the Dutch Research Council (NWO) which provided a shared platform for health systems knowledge translation in sub-Saharan Africa coordinated by the Makerere University School of Public Health¹²¹.

8.2.3 Increase support for LMIC researchers

Researchers from LMICs were described as having good ideas that address local health needs, but many lacked experience with the JGHT application process and had poor English language skills. To level the playing field and enable full participation of LMIC researchers, the JGHT could:

• Support the proposal writing process by:

¹²¹ Technopolis Group (2018) Final evaluation of the Netherlands Global Health Policy and Health Systems Research (GHPHSR) programme

- Offering **online resources to assist with proposals**, such as a sample proposal (to show the type of information and level of detail required), and a webinar (to explain requirements for the various forms to be completed)
- Offering a **proof-reading service** at the full application stage to correct grammar and choice of vocabulary
- Providing **detailed feedback to unsuccessful applicants from LMICs** to improve grant writing skills as relevant to UK-funded projects
- **Promote JGHT calls in LMICs** by sending an email to LMIC contacts (or all contacts) in the grants database. This will enable researchers involved in JGHT-funded research to alert LMIC colleagues and share their experience. The option of disseminating calls via the medical/scientific literature could also be explored.
- Offer **small grants for 'partnership workshops**' for those invited to submit full trial proposals (stage 2) to facilitate full LMIC participation in UK-led trials, similar to the NIHR's Proposal and Partnership Development Awards (see also recommendation 2 / section 8.2.2).
- Consider "**match-making**" **activities** in research areas where LMIC researchers submitted interesting ideas, but where the proposed team lacked the knowledge and infrastructure to conduct a trial. This could take the form of workshops or meetings centred on priority health areas, bringing together LMIC researchers and local / UK trials expertise.

8.2.4 Agree on key criteria for project selection (wider strategic discussion)

The partnership of funders was viewed as very positive across the board. However, it is clear that the different remits of the four organisations creates a certain level of tension, and the funders have not (yet) reached a consensus on future strategy.

The current stated aim of the JGHT is "to support the best proposals to generate new knowledge about interventions that promise to contribute to the improvement of health in LMICs, addressing a major cause of mortality or morbidity". In the review process, this aim is currently operationalised by taking into consideration (Table 1):

- 1. The *scientific quality of the proposal*: Scoring criteria 'Track record of applicant' and 'Study design and feasibility'
- 2. The *size of the health need:* Scoring criterion 'Importance of the question/need for the trial' "Is there a need for such a trial now for this condition or group of patients in the proposed location(s), How important is the problem being addressed?"
- 3. The *potential level of impact on the individual*: Scoring criterion 'Impact' "How important an advance would this be? [...] Is it likely to lead to significant improvements in health?" [here, interpreted as relating to the level of improvement seen by the individual; 'cure' vs 'incremental improvement']
- 4. The *potential level of impact on the population*: Scoring criterion 'Impact' "Will the findings be generalizable?"
- **5**. The *likelihood of impact*: Scoring criterion 'Impact' "What is the likelihood that the findings will be taken up and implemented? Can the intervention be scaled up; is it cost effective?

As a programme focussed on research, rather than capacity building, the first of these factors – scientific quality – is a pre-requisite for the success of the scheme. The development award scheme is available to applicants (increases track record score) or for projects in research areas with a lower level of knowledge (improves study design and confidence in feasibility).

Factors 2-5 – size of the health need, potential level of impact of the research on the individual and at population level (i.e. 'cure' vs 'some improvement'), and likelihood of impact – vary in degree between awards funded. Figure 46 presents a simplified model of these factors, and the types of JGHT-funded trials within each category.

Figure 46 Model of characteristics of funded trials

Category 1 Issue widespread, intervention 'simple' e.g. infectious diseases such as malaria	Category 2 Issue widespread, intervention 'complex' e.g. non-communicable diseases such as CVD
• Widespread issues that can cured/much improved with a single intervention/change	• Widespread, complex issues that cannot be 'cured' with a single, simple intervention
• Interventions focussed on drugs / products; low(er) context-dependency (i.e. generalisable)	 Interventions focussed on behaviour/lifestyle, education and care; strongly context-dependent (i.e. not generalisable)
• Research focusses on effectiveness; delivery within existing health programmes can help to test implementation	 Research focusses on local implementation in local context(s) (in addition to effectiveness)
• A large body of research evidence already exists; trial needs to be of sufficient scale to 'compete' with ovicting recearch evidence	• A large body of evidence already exists (from HICs but not LMICs)
 Research is lower risk as the problem and tested 	 Research is high risk, as outcomes are subject to many external factors
intervention are strongly linked	• Includes issues where the full extent of effects is not yet understood, often in community settings (e.g. menstrual health management, clean stoves)
• A single trial can result in policy influence and health impact, as long as it is definitive	• Large need, but requires multiple trials, embedded in local contexts, to achieve policy and health
 For global policy change, trials need to be large (and hence costly) to provide definitive answers across countries 	 impact Benefits from high level of involvement of local researchers and stakeholders
• Opportunity to partner with other funders	• Funders need to accept higher risk of 'failure'
Category 3 Issue less common, intervention 'simple' e.g. endemic diseases such as podoconiosis	Category 4 Issue less common, intervention 'complex' [e.g. CVD in patients with rare predisposing genetic variant ¹²²]
• Issues with limited range (endemic) and of low public awareness, can be improved with a single intervention	• Complex issues, affecting a smaller number of individuals, that cannot be 'cured' with a single, simple intervention
• Low level of research activity to date, baseline data may not be available	• Issues and interventions strongly context-dependent (i.e. <u>not</u> generalisable)
• Standard of care may not have been established	• Research is high risk, as outcomes are subject to
• Research focusses on effectiveness; smaller trials	many external factors
• Research is generally lower cost and risk, as any findings will substantially increase the body of evidence on which to base policy decisions	
 A single trial can result in policy influence and health impact 	Compared to categories 1,2 and 3:
 Policy makers need to be engaged and interested in addressing the issue; awareness raising and stakeholder engagement are crucial 	Hign risk, limited potential for impact

Research in categories 1 and 3 drive the programme success metrics, as a single trial can result in policy influence and implementation of an intervention. And while category 3 research does not reach the same number of individuals as category 1, its research findings have a high likelihood of influencing policy in affected regions – as long as key decision makers have been engaged and are interested in addressing the underlying health need.

122 This is a hypothetical example; none of the trials funded by the JGHT and reviewed in this study fell into this category.

Category 2 includes areas of high need, to which there are no 'easy answers'; many of these issues are also present in HICs (e.g. cardiovascular disease). Multiple trials are required to make headway against these complex conditions, and each intervention is likely to only have an incremental benefit to the individual who receives it. In addition, areas that have been relatively 'under-researched', such as menstrual hygiene management, associated consequences may not be fully understood (e.g. transactional sex and STIs), and interventions tested have to be tailored as the cultural and social components of the issue are emerging.

The funders need to agree on a strategic direction of the JGHT, setting out whether categories 1, 2, and 3 are all, and equally, within the scope of the scheme. Specific types of research, or research specific health needs, can be encouraged by highlighting these as part of the call text. The 'research categories' can also be further supported by a number of measures:

- Research in category 1 could be supported by **funding very large 'definitive' trials**, answering key research questions to inform specific policies. This could also take the form of commissioned research, and/or coordination and partnership with other funders such as the EDCTP (e.g. co-funding for trial sites in Africa).
- Research in category 2 may influence policy in a specific location, but as these types of interventions can be highly dependent on individuals' behaviour and cultural context, solutions have to be tested in a wide range of settings. This is supported by **a high level of involvement of local researchers and stakeholders**, who are familiar with the context and health system. In recognition of the vast health need category 2 research addresses, funders have to be willing to **accept a higher risk of 'failure'** in terms of "generating new knowledge about interventions that promise to contribute to the improvement of health in LMICs" (as interventions tested may not be effective), and a **lower likelihood of health outcomes and impacts**. In addition, many NCD trials required **longer timeframes** to reach endpoint, e.g. compared to infectious diseases; the timeframe of the award needs to be able to accommodate this.
- Research in category 3 is most likely to arise from **response-mode proposals**, with researchers on the ground identifying local needs and potential solutions and delivery mechanisms. For these types of projects, **stakeholder engagement is crucial** to raise awareness of the issue addressed, and has to be an integral part of the trial. While impacts will be limited in scope by the smaller number of individuals affected, the research has a high likelihood of influencing policy (provided there is stakeholder buy-in) and practice (provided implementation can be financed).

8.2.5 Launch additional monitoring activities

ResearchFish® provides information on outputs and outcomes achieved, but does not enable an understanding of activities undertaken to achieve these and progress made. Additional monitoring of progress and outcomes is advisable, enabling the funders to identify opportunities where additional support for dissemination and policy engagement could lead to policy and health outcomes. The extent of monitoring will dependent on the level of resource the funders have available:

- At a minimum, the funders could actively monitor ResearchFish® for evidence of policy influence, and contact PIs to explore opportunities for supporting *scale-up* of influence and implementation, where appropriate. This approach requires little additional resource, but is also unlikely to identify trials with potential for policy influence that have *not* realised their potential.
- A single-contact measure would be to monitor via an end-of-grant report, requesting additional information as set out in Table 19. This will help funders to understand the policy implications of the trial findings and the research team's plans with regard to future engagement. Where trial findings have high potential for influence, the funders can support PIs in this.
- Valuable information could be gathered at multiple points, during the trial and after the award has closed, via a short annual survey or request for updates on policy/implementation activity. This could be in the form of additional questions during the annual ResearchFish® data collection (similar to NIHR beneficiaries provide additional data). This would also enable a deeper understanding of

the different approaches PIs and their teams take for engagement (and their levels of success), and flag any trials with limited engagement activity. For post-award surveys, trials with findings marked as 'no potential to influence policy' and 'not suitable for implementation' should provide a short summary of 'lessons learned', and can then be removed from the follow-up list.

A structured approach to collecting monitoring data from across awards would also help to assess the overall impact of the JGHT programme, and provide material for case studies to promote the scheme. Information to be collected is set out in Table 19.

	Suggested monitoring data
Full trial	Clinical trial registration number
awards	Trial hypothesis: confirmed/disproved/inconclusive
	Summary of key findings to date (with word limit)
	Publication of the main trial findings (actual, with reference/DOI; or expected timeline)
	Policy and/or implementation stakeholder engagement activity, during trial and post-trial (yes/no/continuing; brief description)
	Trial findings have potential to influence policy (yes/no/requires further research)
	Nature of achieved/expected policy influence (including reference if achieved), brief narrative of current status
	Trial findings suitable for implementation (yes/no/requires further research)
	Description of implementation (actual/expected)
	Description of barriers encountered
	Other key outcomes/impacts directly linked to JGHT-funded research (with word limit)
	Further funding to progress the same or related research question
	Skills and capacity development (separately in LMIC)
	Other
Development awards	Clinical trial registration number (if pilot study)
	Summary of key findings (with word limit)
	Publication of main findings (actual/expected)
	Intervention tested and conditions are suitable for full trial (yes/no/requires further research), with option to provide brief description
	Full trial application (planned/submitted/status – approved/rejected)
	Other key outcomes/impacts directly linked to JGHT-funded research

Table 19 Information requested from PIs