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Review of the Joint Global Health Trials funding scheme

Final Report – Summary Report

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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 late-stage 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 LMICs[1]). 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 findings[2] (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 NIH[3] (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 co-investigators 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 Summary report

This is a summary report of the Review of the Joint Global Health Trials scheme final report. For full details, please refer to the full report, as well as documents containing the 16 impact case studies and the appendices.

2.1 Overview of the Joint Global Health Trials scheme (JGHT)

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 scheme includes two strands of funding: *Full trial awards*, which support late-stage and health intervention trials (Phase III /IV) evaluating efficacy and effectiveness, and – starting from Call 5 - *Development awards*, which enable studies to carry out formative work in preparation for a trial.

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. There is no set limit for neither the size of the full trial awards, nor the duration of the grant. The scope of the scheme is broad and includes behavioural interventions, complex interventions, disease management, drugs, vaccines and hygiene and diagnostic strategies. 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.

2.2 Aim of the study and review methodology

The funders of the JGHT 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 conducted by Technopolis from October 2018 to October 2019. It four main objectives 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 value gained from this type of research programme can be increased
4) to provide guidance on future monitoring of the scheme

To address these questions, the review examined the outputs, outcomes, and impacts achieved by awards funded the 96 awards funded in Calls 1 – 7 of the scheme. At the time of the review, 28 full trial and 22 development awards had closed, and 35 full trial awards and 11 development awards were open.

Following a review of evaluation frameworks, the study team developed an impact logic model, a set of evaluation questions and indicators, and data collection methods to inform the JGHT review. To inform the study, evidence was gathered through a programme of interviews with 29 Principal Investigators (PIs) and 19 experts in global health research and funders ('key opinion leaders'); three surveys (PIs of active full trial awards; PIs of development awards; co-investigators); database analysis (MRC grants database, ResearchFish® database, clinical trial registries, bibliometric analysis); targeted online searches and literature review; and the development of 16 impact case studies.

2.3 Outcomes and impacts of the JGHT

The review examined whether policy influence has been achieved and/or interventions implemented, focussing on the 24 full trial awards which have published the main findings to date.

2.3.1 Policy influence

Eight full trials have informed policy and are cited in policy documents, e.g. guidelines, with evidence from a further three trials incorporated into policies to be released in the new few months. This includes:

- Direct influence on World Health Organisation (WHO) guidelines (4 trials, with one further in final draft stage) (see Case study summary 1)
- Addition of products to the WHO Essential Medicines list (2 trials, one of which also influenced guidelines)
- Influence on WHO policies in other ways, e.g. lending confidence to a guideline under scrutiny, uptake into a best practice strategy paper (4 trials)
- Influence on national policies (1 trial, with two further trials having influenced policies that are not yet published). Two of the three trial teams are currently involved with efforts to scale up influence beyond the country where the trial was conducted.
- Influence on strategy of international donors and shifted funding priorities (1 trial)

Three trials provided important evidence by informing decisions to *not* change a policy or implement an intervention (see Case study summary 1).

Case study summary 1: The REALITY trial (Gibb)

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

Funding period: Oct 2012 - Mar 2018	Funding amount: £3,986,746
Lead PI: Prof Diana Gibb	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 HIV-infected individuals with a low level of immunity start antiretroviral therapy (ART). The trial tested three different approaches, using a 2x2x2 factorial trial design, at trial centres in Zimbabwe, Uganda, Malawi, and Kenya.

The trial showed that taking a package of antimicrobial drugs at the same time as starting ART reduced the rate of death from 12.2% to 8.9%, saving 3 lives for every 1000 patients treated.

The antimicrobial prophylaxis package was taken up into WHO guidelines as a treatment option. Samples from the trial are currently being analysed to address concerns about antimicrobial resistance (funded by the MRC), and findings are expected to inform the next WHO guideline update.

The trial also showed that the two other approaches - 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. The latter finding however alleviated concerns over the safety of integrase inhibitors for treatment of HIV-infected individuals with very low immunity, and lent confidence to the current WHO guidelines recommending integrase inhibitors as the preferred treatment.

2.3.2 Implementation of health interventions

Nine full trials and one development award have led to the implementation of a health intervention:

- Four interventions were recommended by WHO guidelines, the cost of which is hence covered by donor organisations. The level of uptake is difficult to assess for these interventions, but at least two have been purchased by governments via the Global Fund (e.g. novel insecticidal bed nets).
- Four interventions are implemented (or at least piloted with a view to further roll-out) through national governments, as part of public health programmes
- One intervention is implemented by an NGO, with support from the national government (see Case study summary 2)

Case study summary 2: The GoLBeT trial (Davey)

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 a severe consequence of podoconiosis, an acute inflammation of skin, tissue, lymphatics, and lymph nodes (ADLA). 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 a 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 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 40 health professionals where trained.

2.3.3 Health impacts

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[4] were published in 2018 and 2019 (13 of 26), with just under one quarter published in 2019.

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 the potential to impact on the prevalence of infection and associated morbidity at a national level and, if scaled up as a result of a current larger trial, in multiple countries (see Case study summary 3). 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 summary 2).

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 Africa[5], 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. The final impact will depend on many additional factors, including effective distribution and appropriate use of nets.

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

[5] WHO. World malaria report 2016. Geneva: World Health Organization, 2016.

Case study summary 3: The TUMIKIA trial (Pullan)

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 (from JGHT)
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 LSHTM in collaboration with investigators from the Kenya Medical Research Institute (KEMRI).

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 'Breaking Transmission Strategy' of the Kenyan government for 2019-2023, which targets STH 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.

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 TUMIKIA results. Its findings are likely to guide BMGF strategy and inform WHO and other international organisations.

2.3.4 Enablers and barriers

Factors supporting these trials to achieve policy and health ('**enablers**') outcomes fell into four categories. All trials that influenced policy were underpinned by at least two of these enablers.

1) The topic of the trial is currently under debate in the policy arena, key policy makers have strong interest in the research evidence (6 trials)
2) The trial addresses a little researched health issue; hence, little evidence was available before the trial (e.g. talaromycosis, podoconiosis, treatment of cryptococcal meningitis), and there was no established standard of care. JGHT trials substantially increased the level of robust evidence on which to base policy decisions (3 trials)
3) Active engagement, or collaboration, with policy makers during research planning and implementation (3 trials), e.g. embedding the trial within local health programmes (see Case study summary 3)
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)

The main challenges PIs encountered during the implementation of trials ('**barriers**'), as reported in surveys and interviews, were:

- Prolonged and complex administrative processes (65% of full trials, 31 of 48 and 60% of development awards, 12 of 20), particularly in relation to regulatory and ethical approval and contracts/financial transfers (35%, 17 and 15%, 7 of full trials, respectively)
- Difficulties with trial participant recruitment (48%, 23 of 48 full trials)
- Capacity issues: Hiring and retaining staff with the required skills at trial sites (35%, 17 full trials; 45%, 9 development awards)

All of these caused delays and, for some projects, required additional budget. Accordingly, of co-investigators who in hindsight would make changes to the project design, 42% would change the study timeline (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. Two PIs specifically called out the important role of 'joint units' (programmes or institutes funded by organisations from high-income countries (HICs) located in LMICs[6]) in providing trial management capacity.

The key enablers and barriers to policy influence and implementation identified are summarised in a model (Figure 1), centred around two main aspects:

- The utility of data and external conditions, dictating whether research evidence '**can**' (in principle) be used and implemented (or not)
- 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 (or not)

Figure 1 Model of conditions enabling policy and health outcomes

	Policy	**Implementation**	**Scale-up**
Utility of research evidence	***"Can use"***	***"Can implement"***	***"Can scale up"***
	Research evidence: • Demonstrates conclusive option for uptake into policy • Is not in conflict with existing evidence (no or 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)
Stakeholder knowledge and buy-in	***"Want to use"***	***"Want to implement/adopt"***	***"Want to scale up"***
	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

Source: Technopolis analysis

6 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.

2.3.5 *Future potential for policy and health impact*

The majority of JGHT-funded trials have not yet concluded or published results (38 of 62), or only published their main findings within the last year (e.g. eight trials published their main results in 2019); additional policy and health outcomes can hence be expected.

Based on the enablers and barriers reported by trials with achieved outcomes, the potential for policy influence for all closed trials and active trials that have published their main findings was assessed[7]. This assessment classified ten trials as 'high potential', given the nature of their findings (utility) and the level of policy engagement reported (stakeholder knowledge and buy-in).

Hence, taking 'policy influence' as a key performance indicator, the following estimate of the 'success rate' of the JGHT full trial award scheme can be made:

- 32% of JGHT-funded closed full trials (9 of 28) have resulted in success
- 36% of JGHT-funded closed full trials (10 of 28) have high potential for success

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

2.4 Research funded by the JGHT

Across calls 1-7, the JGHT has funded a portfolio of 63 full trial and 33 development awards in calls 1-7, representing an investment of £138.8m. The scheme is highly competitive, with a success rate of approx. 10% from outline stage to full trial award, and 20% for development awards. Full trial awards were on average £2.1m, with the five largest awards between £4m and £5m.

JGHT awards addressed a broad range of health issues (Figure 2). Across all awards, the largest share addressed the area of 'Infection' (44%)[8], followed by 'Reproductive Health and Childbirth' (15%). The share of 'Infection' decreased steadily, from 70% in Call 1 to 29% in Call 7, while the share of awards addressing 'Mental Health' increased from Call 5 and reached 36% in Call 7. Development awards addressed a broader range of areas, with an average of 8 health codes per call, compared to full trial awards, which covered an average of 4.4 health codes.

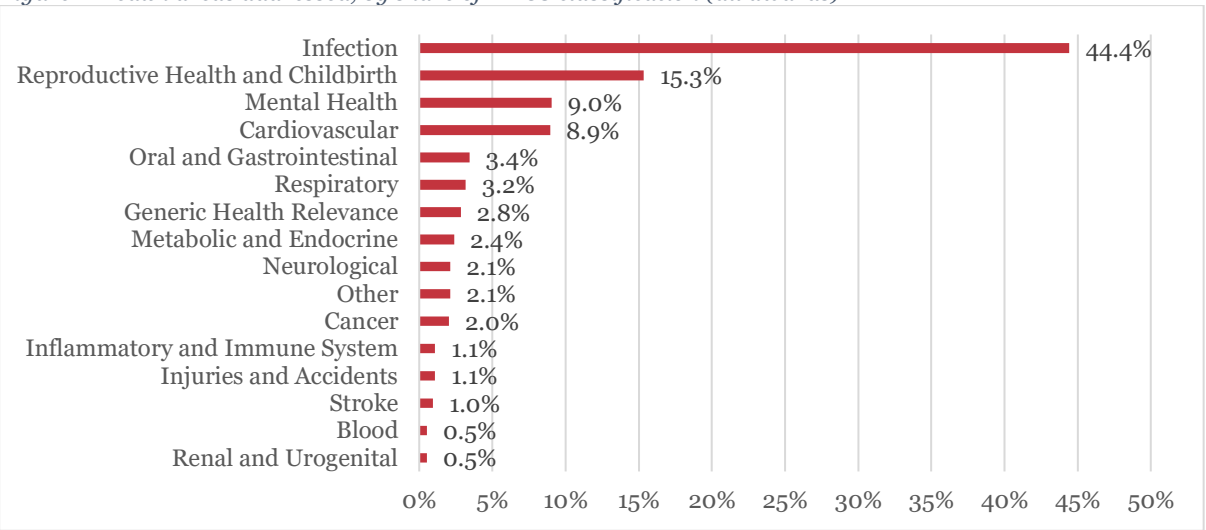
A quarter of all full trial awards were related to malaria and 14% addressed aspects of TB. The largest number of development awards addressed issues related to nutrition (15%) followed by interventions addressing cardiovascular disease, diabetes, and tobacco use (9%).

The largest share of research fell into the category 'Treatment evaluation' (46%), followed by 'Prevention' (34%), 'Health and social care services' (10%) and 'Management of diseases' (7%). This was broadly similar for full trial awards and development awards, with a stronger emphasis on 'Treatment evaluation' in full trial awards (50% of full trial awards vs. 39% of development awards), and a stronger emphasis on 'Prevention' in development awards (44% of development awards vs. 29% of full trial awards).

[7] It should be noted that this assessment is based on a limited level of information, in particular for trials where researchers no or very limited input into the review.

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

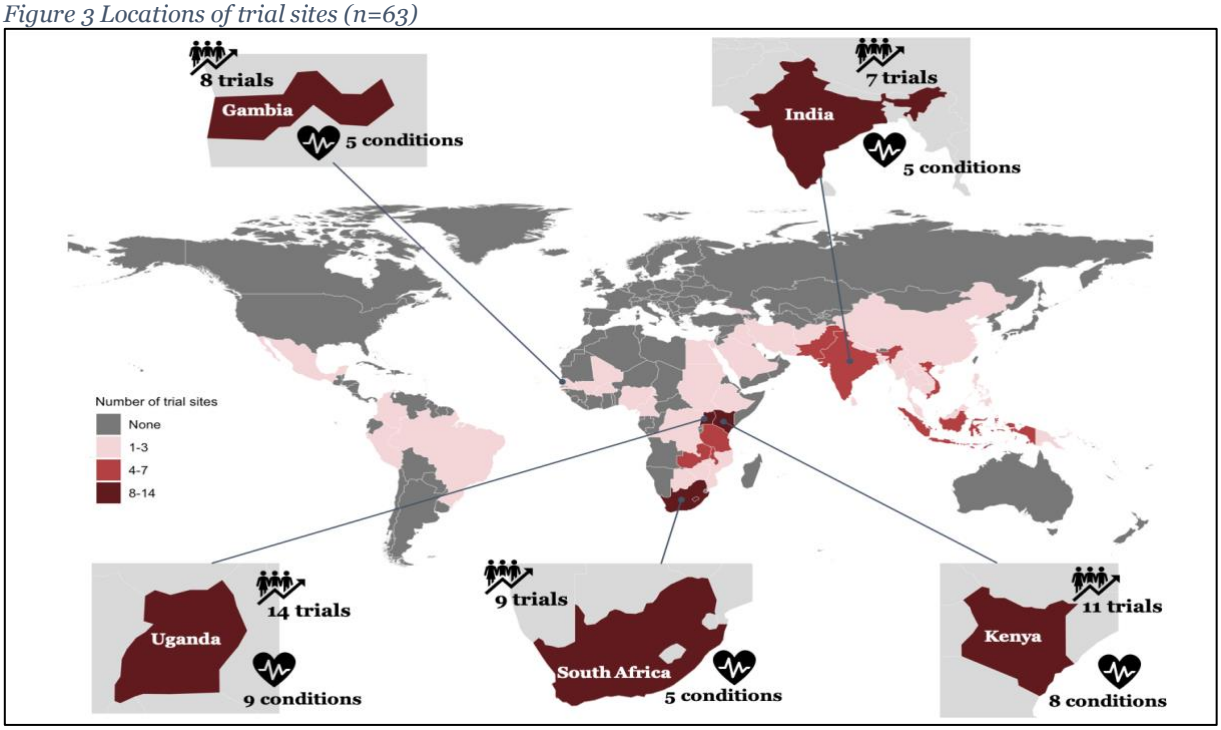
Figure 2 Health areas addressed, by share of HRCS classification (all awards)



Source of data: MRC grants database

The 63 full trials were implemented at trial sites located in 47 countries[9], with 75% of trials including sites in Africa, 30% of trials sites in Asia and 8% sites in Central and South America (Figure 3). Uganda hosted sites for the largest number of trials (14), followed by Kenya (11) and South Africa (9). One third of trials involve sites in more than one country, with 13% (8 trials) involving sites on more than one continent.

Figure 3 Locations of trial sites (n=63)



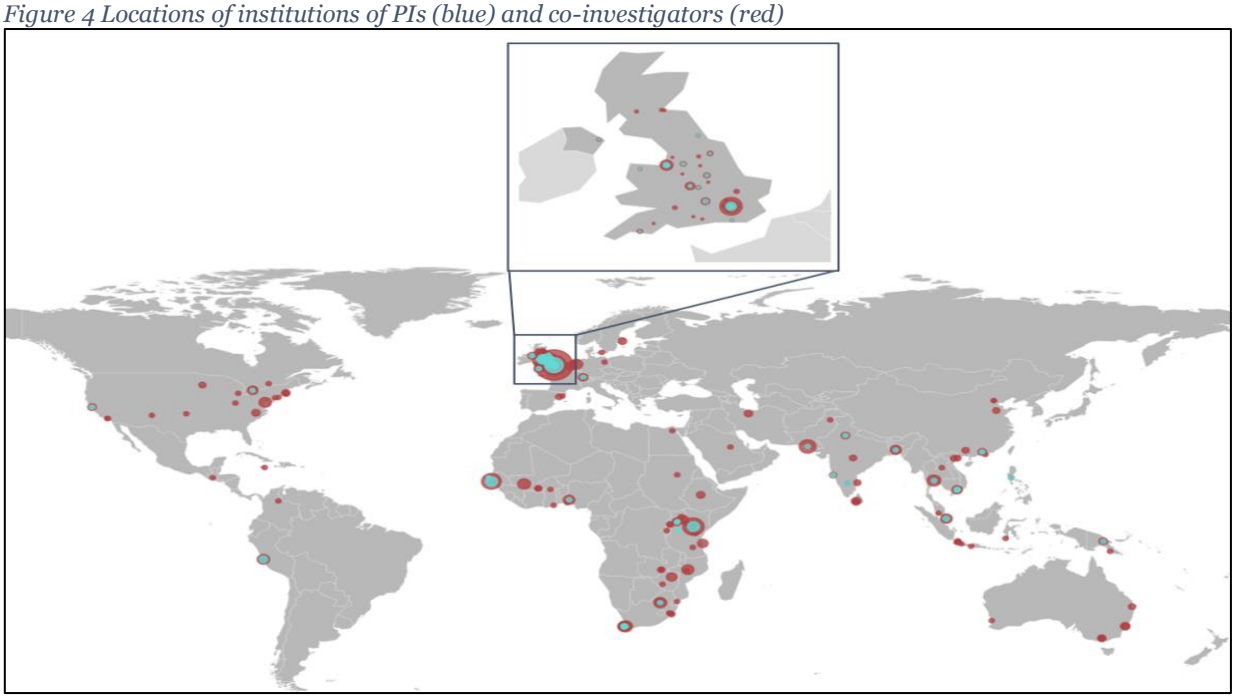
Source of data: Clinical trial databases: ISRCTN, ICTRP and clinicaltrials.gov. Two trials received co-funding to conduct parallel trials involving sites in HICs and LMICs (MR/M009211/1 and MR/N006127/1); HIC sites are not included in the map.

[9] Two trials (MR/M009211/1 and MR/N006127/1) included sites in HICs funded through alternative sources. These sites were excluded from this analysis.

The largest share of full trial awards (63%, 40 of 63) were led by PIs affiliated with institutions located in high-income countries (HICs), compared to 13% (8) led by researchers from LMIC institutions and 24% (15) led by researchers at joint units (Figure 4). PIs at the London School of Hygiene and Tropical Medicine alone led 19% of full trials (12) and 9% of development awards (3). Other institutions with PIs leading multiple trials include the Liverpool School of Tropical Medicine (5), University College London (4) and the University of Oxford (3).

Project plans submitted during the application process indicated that a total of 647 individuals were involved as PIs or co-investigators in JGHT-funded research. These individuals were affiliated with 212 organisations, half of which were located in LMICs (excluding joint units) (Figure 4). The largest number of institutions were located in South Africa, Uganda, and India (5-7%). Institutions in LMICs involved in the largest number of proposed teams were The Aga Kahn University, Pakistan, and the University of Malawi, Malawi (6 awards each). An analysis of author affiliation of the main trial findings of 22 closed full trial awards[10] showed a similar distribution.

Figure 4 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.

Applications led by PIs affiliated with joint units were highly successful and achieved a 75% success rate for full applications (i.e. at the second stage of the full trial application process. In comparison, the success rate for full trial applications led by PIs at HIC and LMIC institutions was 48% and 21%, respectively. This rate has not improved over time; in fact, there were no full trials led by PIs at LMIC institutions in Calls 6 and 7. For development awards, the success rates were 25% for PIs at HIC institutions and 15.5% for LMIC institution-led applications (while joint units rarely applied for these awards, accounting for only 3% of applications).

Three LMIC organisations led two awards: the University of Cape Town (two full trial awards), and the Peruvian University Cayetano Heredia and Sangath, India (two development awards each). Overall, PIs at LMIC institutions headed 8 full trials and 12 development awards.

[10] 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).

The share of awards led by female PIs was 37% for full trials and 30% for development awards, with significant variation between calls but no discernible trends over time. While 41% of PIs at institutions in HICs were female, this was the case for only 26% for PIs at institutions in LMICs.

2.4.1 Stakeholder engagement

The majority of JGHT-funded projects engaged with policy makers during the design and/or implementation of the research. PIs of 87% of full trials (41 of 47[11]) and all development awards (20) reported that they had engaged with policy makers. However, six PIs indicated that they had not engaged with policy makers[12], and only one of these had engaged with implementing organisations/NGOs. Of 28 the full trial PIs interviewed, 29% had engaged with international policy organisations, foremost WHO, and 61% with representatives from a national government. Two PIs were members of WHO guideline committees, and five were members of government committees or government employees. Several trials were embedded within national public health programmes; others kept relevant policy makers informed in regular targeted meetings or by setting up dedicated policy liaison groups. 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.

39% of PIs interviewed (11 of 28) reported that they 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. A number of 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 and how this had helped to avoid and overcome challenges during trial implementation. 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.

2.5 Research outputs and scientific outcomes

2.5.1 Completed trials and 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 published three papers describing the findings for each of the three interventions tested, bringing the total number of publications of main trial findings to 26.

Of the 28 closed full trial awards, the majority (82%, 23) have published or are in the process of publishing the main trial results, and two are in the final analysis phase, indicating a high completion rate[13]. PIs of nine development awards (82%, 9 of 11) reported that they had or were in the process of publishing their results. While the timeframe since publication is too short for a full citation analysis comparing citation rates of JGHT publications with those publications in the same research field, indications are that citation impact is high as shown by the five most highly-cited papers (Figure 5).

[11] The review team did not receive information on stakeholder engagement of the remaining 16 full trials.

[12] 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.

[13] Of the remaining three closed awards, one trial did not take place due to external circumstances, and the status of the other two is unknown.

Figure 5 JGHT main trial publications with the highest number of citations

- 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**
- 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 spray 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**

Data from ResearchFish® indicates that 58 awards had led to 434 publications, at a mean of around 9 publications for full trial awards and 4 for development awards.

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 included a full trial which was stopped as the intervention was found to cause harm to participants, a full trial comparing two interventions finding a significant difference between the two, and a feasibility and a pilot study funded in Call 1 (which led to a full trial award in Call 5).

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'.

2.5.2 Follow-on funding

60% of JGHT awards (50 of 84) reported on ResearchFish® that they had received substantial additional funding (co-funding and follow-on funding), mainly in the form of research grants, capturing a total of around £160m. The major funders in terms of amount provided were Wellcome, EDCTP, NIHR, BMGF and US NIH (in order). In interviews and surveys, nearly half of the PIs of full trials (48%, 24 of 50) and development awards (45%, 10 of 22) reported that they had secured additional funding for research related to the JGHT award, and a further 25% PI of both types of awards were developing or had submitted proposals (see also Case study summary 3). Co-investigators reported that the scientific knowledge they had acquired as part of the JGHT-funded research provided the basis on which they were able to secure additional funding (28%, 48 of 171).

2.5.3 Development awards leading to full trials

The aim of the development award scheme is to develop trial application ideas into robust and competitive proposals. Of 22 closed development awards funded so far, at least 23% (5) have led to full trials (one funded by the JGHT, four by other funders). In addition, a smaller award funded in Call 1 led to a full trial award in Call 5 (see Case study summary 4).

An increase in applications from development award holders (and potentially successes) can be expected in the future: 40% of PIs (6 of 15) who had not yet secured further funding 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.

Case study summary 4: Menstrual solutions feasibility study (Phillips-Howard)

Menstrual solutions in adolescent schoolgirls 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.

2.5.4 New collaborations

Most projects involved partners in LMICs who had not previously collaborated with the lead PI who submitted the proposal to the JGHT (77%, 16 of 21 open full trial awards; 65%, 15 of 20 development awards). Half of co-investigators surveyed felt that the JGHT project had provided them with 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). 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 third of LMIC researchers also indicated that they had established new collaborations with implementation partners (35%, 23), compared to 13% of researchers from HICs (10 of 76).

45% of active full trial PIs (9 of 20) and 35% development award PIs (7 of 20) had worked with new policy and implementation partners as part of the JGHT-funded research - mainly WHO, LMIC ministries of health (or equivalent), and NGOs.

2.5.5 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.

22 publications of full trial awards named investigators affiliated with 106 institutes; 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. 27% (7 of 26) of lead (first) authors of main trial publications were affiliated with LMIC institutions, comparable to the shares of lead authors affiliated with joint units (31%, 8), and institutions in HICs (27%, 7).

82% of co-investigators felt that the JGHT-funded project had positively impacted their scientific knowledge (140 of 170). Of closed full trial PIs who discussed skills and knowledge in interviews, 65% (13 of 20) highlighted that the research had enhanced trial capacity at the trial site(s), 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.

Half of all co-investigators reported improved knowledge of local health needs (49% overall, 83 of 169), especially researchers from LMICs (60% vs 45% of investigators from HICs). 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).

2.5.6 Enhanced research environment

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

Co-investigators reported a range of effects of the JGHT awards at the research location, i.e. beyond the JGHT-funded study team, including that the research had[14]:

- convinced practitioners and decision makers of the value of global health trials and health research (35%, 54 of 161[15])
- increased LMIC researchers' leadership capabilities (35%, 54)
- reduced operational barriers to future health research (28%, 45)
- improved LMIC institutions' research governance structures (26% of LMIC co-investigators, 17)

2.5.7 Health benefits to trial participants

PIs described both direct and indirect benefits of JGHT-funded research for study participants and the wider community. 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, improving the standard of care at trial sites, 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.

Two (large) trials alone have led to direct health benefits as the result of the intervention itself for around 450,000 individuals. As part of the TUMIKIA trial, around 400,000 individuals benefitted from the reduced prevalence and transmission of helminths in clusters treated at a community-level, rather than through school-based deworming. In another trial, a total of 45,000 novel, more effective insecticidal bed nets were distributed, reducing the prevalence and transmission of malaria for those using the nets as well as more widely in the villages. The REALITY 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.

[14] 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 to lead to impacts as they progress to a later stage.

[15] 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.

2.6 Global health trial funding landscape

The JGHT fills a gap in the global health research funding landscape. It is considered to be 'unique', combining a focus on global health research with a) the opportunity to address any health need in any LMIC and b) the ability of LMIC researchers to apply.

The 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 diseases taking place in sub-Saharan Africa (while encompassing a broader funding remit, e.g. all clinical trial phases (I-IV), research investigating health services optimisation, and capacity strengthening and networking activities). Other funders such as the Bill and Melinda Gates Foundation (BMGF), the US National Institutes of Health (US 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. The JGHT complements these funders' activities by focussing on large-scale trials whilst covering areas such as NCDs, mental health and violence as well as funding trials for interventions other than drugs, vaccines and diagnostics.

Given the diversity of health needs addressed by the JGHT, the research funding landscape was determined for 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), with many other funders contributing to these research areas (e.g. BMGF, US NIH, EDCTP). The JGHT 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 these areas (33%).

Despite the numerous funders operating in the global health trial funding landscape and the diversity of programmes funded, researchers and key opinion leaders feel that funding gaps still remain. These were identified as lack of sufficient funding for implementation research, research on NCDs in LMICs, research capacity building in LMICs and smaller Phase II trials.

2.7 Design and management of the JGHT

Researchers and key opinion leaders were predominantly positive regarding the design of the JGHT. 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. 57% of PIs (21 of 37) and 79% of co-investigators (115 of 146) felt there were no aspects of the JGHT design or requirements that could be improved. Researchers and key opinion leaders were also overall positive about the development award scheme. Nearly all key opinion leaders who discussed this funding stream were complimentary, highlighting its importance in preparing the ground for full trials (13 of 14).

Conversely, 29% 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. Of PIs who described a weakness, 29% (8 of 28) 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). 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 and BMGF - were cited as offering much larger awards and (at least in the case of the EDCTP) over longer periods of time.

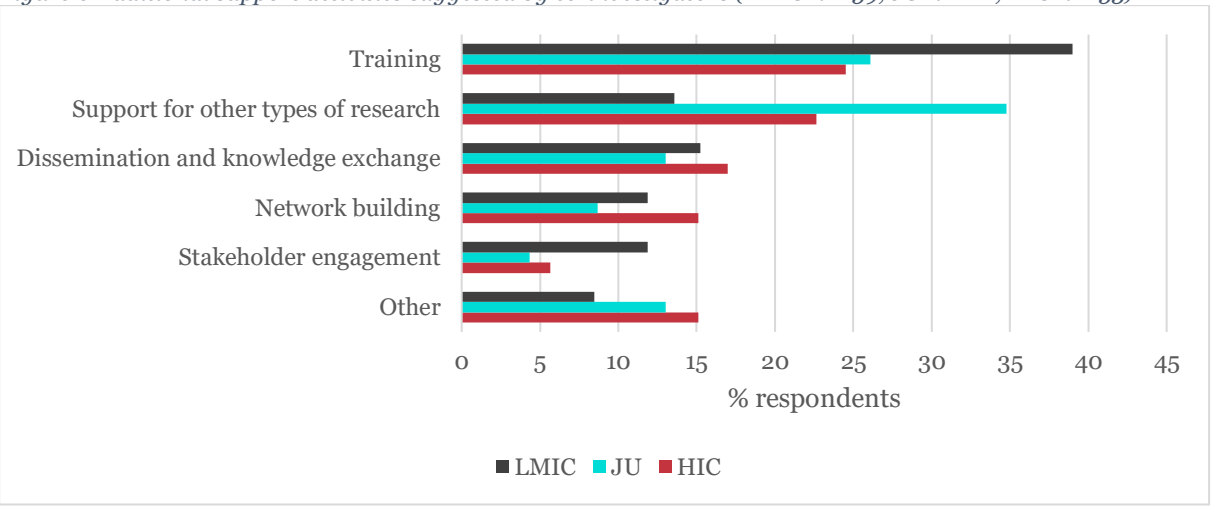
Among co-investigators, the most common weaknesses reported were related to award administration, such as lengthy processes and limited communication with funders (24%, 18 of 76). A higher share of co-investigators working at LMIC institutions (40%, 12 of 30) considered these problematic.

Other aspects of the JGHT's design and managements which researchers commented on include the following:

- Application process: Nearly all PIs surveyed held a positive view of the application process (97%, 29 of 30), with the majority (63%, 19) describing the JGHT as "simpler than other schemes" and "straightforward" (e.g. compared to the EDCTP and NIH). 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.
- 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, and monitoring requirements were considered 'light touch'. Researchers commented positively on the scheme's flexible approach to funding and openness to accommodating changes in case of a change in project circumstances.
- Promotion of scheme: 92% of PIs (35 of 38) and 73% of co-investigators (110 of 149) surveyed felt that information on the JGHT is communicated through the right channels and that information reaches the relevant research communities. 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.
- Additional activities to improve impact: When asked which additional activities the JGHT could support that would help it achieve its aims, researchers highlighted a number of areas (see also Figure 6).
  - Training: 21% of PIs (7 of 33) and 31% of co-investigators (43 of 139) surveyed highlighted this area, with a higher share of co-investigators from LMICs (39%, 23 of 59) than from HICs (25%, 13 of 53) holding this view. Key opinion leaders agreed that capacity building was important, but the majority thought it should not be funded through the JGHT.
  - Dissemination and knowledge exchange: 21% of PIs (7 of 33) and 22% of co-investigators (30 of 139) surveyed highlighted this area, and seven interviewed PIs specifically suggested 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.

    Key opinion leaders also had a positive view (86%, 6 of 7) when asked to comment on the option of disseminating research results through the funders' existing networks, i.e. funders taking an active role in dissemination and engagement.
  - Other types of research: 21% of PIs (7 of 33) and 22% of co-investigators (30 of 139) pointed to funding for additional types of research. Suggestions from researchers and key opinion leaders ranged from Phase II trials to implementation pilot studies and 'bolt on' laboratory-based work. There was no consensus on the additional type of research to be supported, and many key opinion leaders advised against shifting the focus of the JGHT from trials.
  - The majority of key opinion leaders (82%, 9 of 11) supported funding / offering additional support for LMIC applicants, but also cautioned against lowering the quality bar in the review process or awarding funding to LMIC institutions that do not have the necessary capacity and infrastructure to lead a full trial. Suggestions included a proofreading service for LMIC applicants, and making available examples of successful applications and webinars explaining how to fill in the various forms.

Figure 6 Additional support activities suggested by co-investigators (LMIC n = 59, JU n = 22, HIC n = 53)



Source of data: Survey of co-investigators

2.7.1 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, with indicators of health impact, e.g. changes in morbidity and mortality, considered too difficult to track and outside the knowledge of the PI.

Commenting on ResearchFish®, many key opinion leaders expressed the view that it 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, case studies, and regular contact with the PI.

2.8 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 funders in interviews:

- *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. Many held the view that restrictions would limit the flow of new ideas and lower the overall quality of funded projects; health needs in LMICs change and cannot be predicted, and researchers and public health experts on the ground have the best understanding of the issues to be addressed.

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

60% (6 of 10) of key opinion leaders and representatives of funding organisations were against, and 40% in favour of commissioning research projects, to enable focus on key questions. Those opposed disapproved of top-down approaches, or thought that commissioned research was more suitable to be funded by other schemes. Those in favour thought commissioned research would enable focus on key questions. One suggested to coordinate with NIHR-commissioned research.

- *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.*

62% (8 of 13) of key opinion leaders and representatives of JGHT funders were not in favour of increasing the scheme's focus on larger trials. 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. 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.

- *A small number of key opinion leaders expressed the view that the JGHT should enhance its 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.".

2.9 Added value of a partnership of funders

The four funders, committee members, and researchers had an overall positive view of the partnership. The benefits described were:

Pooling budgets and de-risking investment

- De-fragmentation of the funding landscape
- Closer cooperation between funders
- Sharing of expertise
- Broadening areas of research and the research community

The partnership was seen to have helped maintain the UK's reputation and international leadership in producing high quality research of relevance to LMICs. 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.

2.10 Value for Money

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

- Delivery of the JGHT through a partnership of funders has represented efficiency gains for both funders and applicants by:
  - Reducing duplication of effort, avoiding unnecessary time investment by researchers in submitting proposals to multiple schemes, and review panels reviewing the same proposal multiple times. Funders are able to draw on their respective expertise to inform the review process, ensuring a high quality of projects selected. Efficiencies are also achieved through centralised scheme management.
  - Enabling a strategic view of the scheme's direction and the global health trial portfolio funded. This ensures that gaps or duplications are identified (a risk if individual funders work in silos).

  In addition, working in partnership has enabled funding of large-scale global health trials from pooled resources, at the same time reducing the risk of investment for individual funders.

- The flexibility of the scheme's management is contributing to VfM 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. Flexibility of the JGHT has avoided 'wasted' research efforts by allowing for non-costed, as well as some costed extensions.

- The JGHT has funded high quality research projects. At least 89% of the 28 closed full trials awards have completed the research. This is in line with a recent analysis of Phase III and Phase IV trial completion rates, at 85% and 87%, respectively16.
- 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.
- 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). 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.
- 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, strengthening the wider research ecosystem. This has also helped to leverage additional funding. 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. 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 benefits17. 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 JGHT-funded 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
  - Potential cost savings for LMIC health systems. For example, the TUMIKIA trial 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 approaches involving a harmful intervention.

  However, most studies are still in the process of completing their full cost-effectiveness assessments, and the potential for cost savings through implementation of JGHT findings is not yet known.

2.11 Conclusions and recommendations

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

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

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

implementation of a health intervention. A further 10 trials - 36% of JGHT-funded closed full trials - have high potential for success. As more trials complete, further outcomes can be expected.

The review makes a number of recommendations to increase the value gained from JGHT-funded research, both in relation to both the type of research conducted, and support for stakeholder engagement prior to, during, and after the award, and monitoring arrangements to capture the outcomes and impacts of the scheme and identify projects that can benefit from further support:

1) Keep the overall design of the JGHT, but clearly set out the scheme's award parameters; communicate to potential applicants that time and budget are flexible and re-focus researchers on asking the right questions and proposing appropriately sized approaches to answer them

2) Provide additional support for stakeholder engagement, both:
   - pre-award, e.g. through small grants for 'partnership workshops' *and/or* 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
   - post-award, e.g. through opportunities for PIs or other members of the team to apply for additional funding to cover engagement activities after the award has closed. Funders should explore options for maximising opportunities for dissemination and engagement for trials with high potential for policy influence and health impact

3) Increase support for LMIC researchers, including:
   - offering online resources to assist with proposal and a proof-reading service at the full application stage to correct grammar and choice of vocabulary, and providing detailed feedback to unsuccessful applicants from LMICs
   - promoting JGHT calls in LMICs, offering small grants for 'partnership workshops' to facilitate full LMIC participation in UK-led trials
   - potential "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

4) Agree on key criteria for project selection among JGHT funders (wider strategic discussion), taking into consideration the balance between:
   - the size of the health need addressed
   - the risk of interventions not proving effective
   - the likelihood of policy influence.

   The model in Figure 7 can serve as a basis for discussion.

5) Launch additional project monitoring, enabling the funders to better track progress and outcomes and to identify opportunities where additional support for dissemination and policy engagement could lead to policy and health outcomes. This could include:
   - active monitoring of ResearchFish® for evidence of policy influence, and discussion with PIs to explore opportunities for supporting *scale-up* of influence and implementation
   - an end-of-grant report, requesting additional information such as the PIs assessment of the potential for policy influence, and the team's stakeholder engagement activity
   - a short survey or request for updates on policy/implementation activity at regular intervals, e.g. annually. This could be in the form of additional questions during the annual ResearchFish® data collection.

Figure 7 Model of characteristics of funded trials (key considerations for funders in italics)

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 • Interventions focussed on drugs / products; low(er) context-dependency (i.e. generalisable) • Research focusses on effectiveness; delivery within existing health programmes can help to test implementation • A large body of research evidence already exists; trial needs to be of sufficient scale to 'compete' with existing research evidence • Research is lower risk as the problem and tested intervention are strongly linked • *A single trial can result in policy influence and health impact, as long as it is definitive* • *For global policy change, trials need to be large (and hence costly) to provide definitive answers across countries* • *Opportunity to partner with other funders*	• Widespread, complex issues that cannot be 'cured' with a single, simple intervention • Interventions focussed on behaviour/lifestyle, education and care; strongly context-dependent (i.e. not generalisable) • Research focusses on local implementation in local context(s) (in addition to effectiveness) • A large body of evidence already exists (from HICs but not LMICs) • Research is high risk, as outcomes are subject to many external factors • Includes issues where the full extent of effects is not yet understood, often in community settings (e.g. menstrual health management, clean stoves) • *Large need, but requires multiple trials, embedded in local contexts, to achieve policy and health impact* • *Benefits from high level of involvement of local researchers and stakeholders* • *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[18]]
• Issues with limited range (endemic) and of low public awareness, can be improved with a single intervention • Low level of research activity to date, baseline data may not be available • Standard of care may not have been established • Research focusses on effectiveness; smaller trials • 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* • *Policy makers need to be engaged and interested in addressing the issue; awareness raising and stakeholder engagement are crucial*	• Complex issues, affecting a smaller number of individuals, that cannot be 'cured' with a single, simple intervention • Issues and interventions strongly context-dependent (i.e. not generalisable) • Research is high risk, as outcomes are subject to many external factors • *Compared to categories 1,2 and 3:* *High risk, limited potential for impact*

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