A Low-Cost, Scalable Treatment Strategy for Improving Hypertension Control in Low and Middle-Income Settings: Formative Phase (Aim 1)

Short Title & Acronym: **A C**ombination **T**riple pill **I**mplementation strategy for blood pressure c**ON**trol (**ACTION**)



Therapeutic indication: Hypertension

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Principal Investigator: Professor Otavio Berwanger

Co-investigators: Professor Dike Ojji, Professor Asita de Silva

SPONSOR

Imperial College London is the Sponsor for this study. For further information regarding the sponsorship conditions, please contact the Head of Research Governance and Integrity.

This protocol describes the formative phase of A Low-Cost, Scalable Treatment Strategy for Improving Hypertension Control in Low and Middle-Income Settings study. Every care was taken in its drafting, but corrections or amendments may be necessary.

This study will adhere to the principles outlined in the UK Policy Frame Work for Health and Social Care Research. It will be conducted in compliance with the protocol, regulations to a standard equivalent to the UK Data Protection Act 2018, General Data Protection Regulations (Europe), the UK Human Tissue Act 2004, the UK Mental Capacity Act 2005 the Medicines for Human Use (Clinical Trials) Regulations 2004 (SI 2004/1031), amended regulations (SI 2006/1928) and any subsequent amendments of the clinical trial regulations, Good Clinical Practice (GCP) guidelines, and other regulatory requirements as appropriate.

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PROTOCOL VERSION HISTORY

Version No.	Version date	Main reason for change
V3.0	09 April 2026	1. Removed The George Institute for Global Health designation as a study Sponsor from the protocol. Reason: Imperial College London is the sole Sponsor for the study. 2. Deleted any statements that conflicted with or contradicted this designation.
V2.0	08 January 2026	1. Expansion of objective 1c to collect information about dietary interventions and salt substitution in preparation for a potential salt-substitution sub-study with the ACTION evaluative phase protocol. 2. Minor administrative changes and clarifications throughout.
V1.0	24 September 2025	Not applicable.

SIGNATURE PAGE

The undersigned confirm that the following protocol has been agreed and accepted and that the Investigator agrees to conduct the study in compliance with the approved protocol, all relevant local legislation, and regulations to a standard equivalent to the UK Human Tissue Act 2004; the UK Mental Capacity Act 2005 the Medicines for Human Use (Clinical Trials) Regulations 2004 (SI 2004/1031), amended regulations (SI 2006/1928) and any subsequent amendments of the clinical trial regulations, Good Clinical Practice (GCP) guidelines, the Sponsor's (and any other relevant) SOPs, and other regulatory requirements as amended.

I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the study without the prior written consent of the Sponsor.

I also confirm that I will make the findings of the study publicly available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the study will be given; and that any discrepancies and serious breaches of GCP from the study as planned in this protocol will be explained.

For and on behalf of the Study Sponsor:

Signature: Date:

..../...../.....

Name:

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Position:

.....

Investigator:

Signature: Date:

..../...../.....

Name:

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Position:

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KEY STUDY CONTACTS

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Collaborating Institutions	The George Institute for Global Health UK / Imperial College London University of Abuja, Nigeria RemediumOne/University of Kelaniya, Sri Lanka The George Institute for Global Health, India The George Institute for Global Health, Australia / University of New South Wales, Sydney	
Funder(s)	National Institute for Health and Care Research NIHR207002 (41379)	

ABBREVIATIONS

AE	Adverse Event
BFC	Budget and Finance Committee
BP	Blood Pressure
CEIC	Community Engagement & Involvement Committee
DBP	Diastolic Blood Pressure
DSMC	Data Safety Monitoring Committee
FCT	Federal Capital Territory
GCP	Good Clinical Practice
IRB	Institutional Review Board
IB	Investigator Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IMP	Investigational Medicinal Product
IMPD	Investigational Medicinal Product Dossier
LMIC	Low- and Middle-Income Countries
PCORI	Patient-Centred Outcomes Research Institute
PD	Protocol Deviation
PI	Principal Investigator
PISCF	Participant Information Sheet and Consent Form
PHC	Primary Healthcare Centre
RCT	Randomised Controlled Trial
REC	Research Ethics Committee
SB	Serious Breach
SBP	Systolic Blood Pressure
SC	Steering Committee
SMC	Study Management Committee
TCBC	Training and Capacity Building Committee

STUDY ROLES

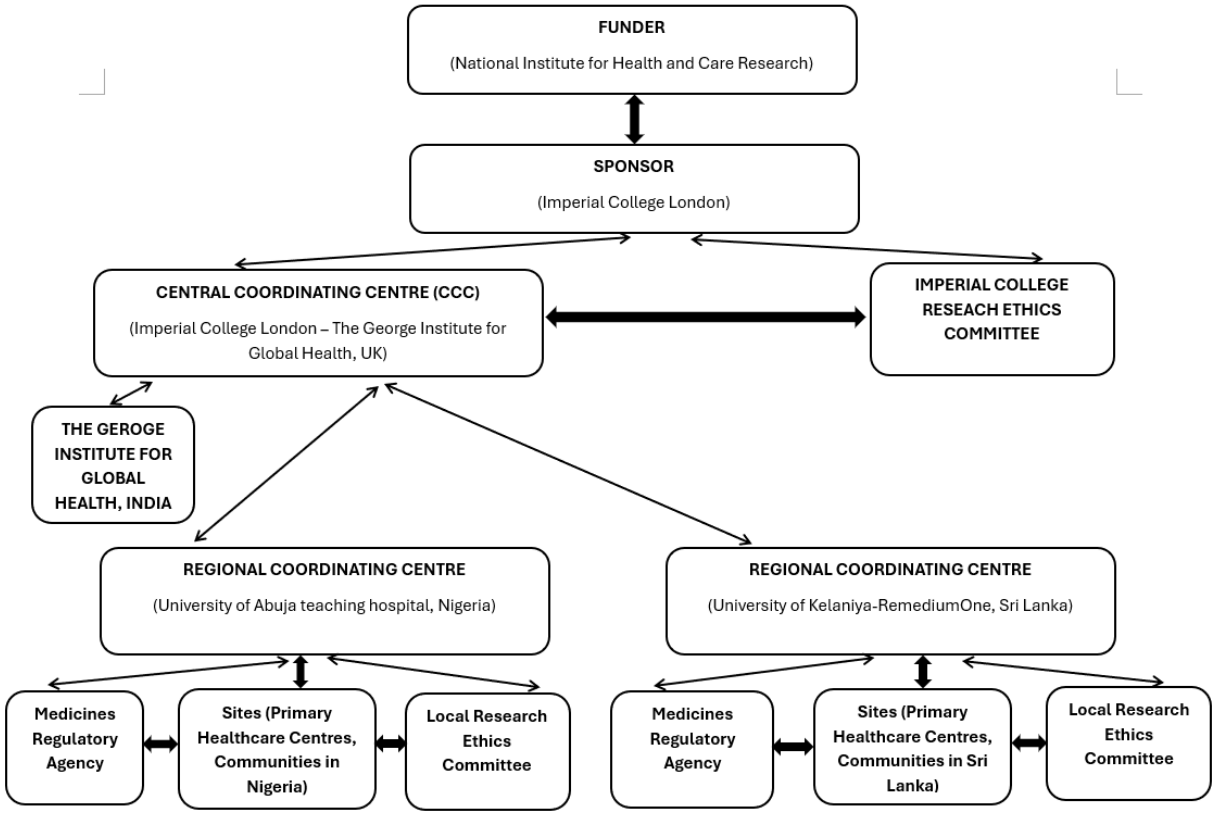


Figure 1: ACTION Study Roles hierarchy.

Funder

This study is funded by the Research and Innovation for Global Health Transformation (RIGHT) Programme of the National Institute for Health and Care Research (NIHR). The funder has no role in the design, conduct, analysis, or reporting of the study.

Sponsor

Imperial College London (ICL) is the sponsor and will assume overall responsibility of the study.

Collaborating Institutions

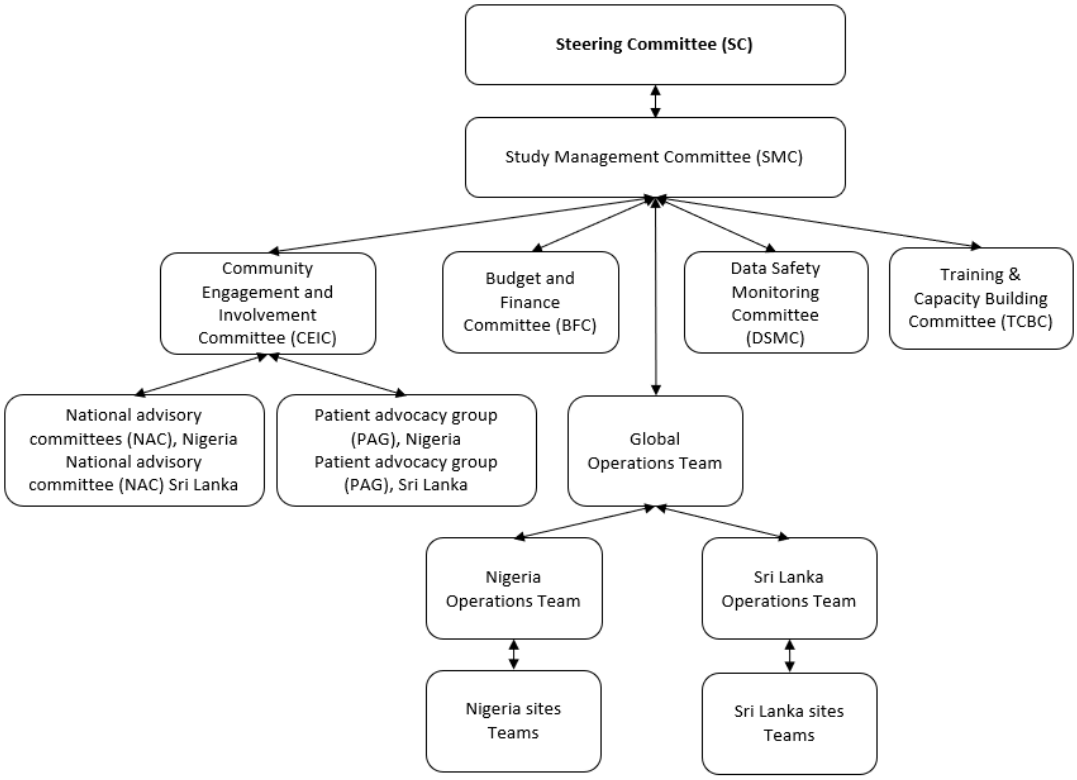
ICL - The George Institute for Global Health (TGI) UK (TGI@Imperial), in collaboration with the institutions listed below, will oversee the overall design, conduct, analysis, and reporting of the study, guided by the Steering Committee and the Study Management Committee.

RemediumOne-University of Kelaniya, Sri Lanka will provide oversight and input into study conduct in Sri Lanka.

University of Abuja, Nigeria will provide oversight and input into study conduct in Nigeria.

Data Management responsibilities will be undertaken by George Institute Services (GIS), India. Many of the staff at GIS have a dual appointment with The George Institute for Global Health, India.

COMMITTEES



Steering Committee

The Steering Committee (SC) will serve an advisory role in the design, conduct, analysis, and reporting of the study. The majority of SC members, including the Chair, will be independent. Members will bring diverse expertise relevant to the study's objectives and methodology.

Data Safety Monitoring Committee

The Data Safety Monitoring Committee (DSMC) is an independent committee that makes recommendations to the steering committee. The primary role of the DSMC will be to protect the safety of the study participants by:

- reviewing the protocol, informed consent documents and plans for data and safety monitoring prior to study commencement.

- reviewing DSMC reports describing the progress of the study, adherence to the protocol, participant recruitment, outcome reporting, data quality, and other issues related to participant safety.
- monitoring the assumptions underlying sample size calculations for the study and alerting the steering committee if they see substantial departures as the data accumulates; and
- ensuring the confidentiality of the study data until the conclusion of the study.

The DSMC will review the data on an ongoing basis and will recommend that the ACTION Steering Committee either continue, stop or amend the study based on the review after each DSMC meeting. The DSMC will also respond to specific ad hoc requests made by the Steering Committee or SMC as required and agreed with the DSMC Chair.

Community Engagement & Involvement Committee

The Community Engagement & Involvement Committee (CEIC) will plan, oversee and refine all community-engagement activities in Nigeria and Sri Lanka, supplying early and continuous input to shape research questions, surface patient and carer concerns and other stakeholder concerns, and ensure these inform protocol amendments and study conduct.

Budget and Finance Committee

The Budget and Finance Committee (BFC) will be responsible for ensuring the study is adherent to contract, budget disbursement, maintenance of due diligence by all institutions involved and ensuring all financial and timeline reporting is done in accordance with funding requirements.

Training and Capacity Building Committee

The Training and Capacity Building Committee (TCBC) will be responsible for planning and conducting training and capacity building activities in accordance with TCBC plan.

Management Committee

The Study Management Committee (SMC) will oversee the day-to-day conduct of the study. The SMC will discuss and implement any amendments to the study as advised by the SC. The committee will be made up of the Principal Investigator, Co-Principal Investigators from Sri Lanka and Nigeria and Co-Investigator from India as well as Project Managers from ICL/TGI, University of Abuja, Nigeria, and RemediumOne/University of Kelaniya, Sri Lanka. They will meet regularly to discuss the progress of the study, any country specific issues and any arising matters from the ACTION SC, DSMC or CEIC, BFC, and TCBC.

1 BACKGROUND

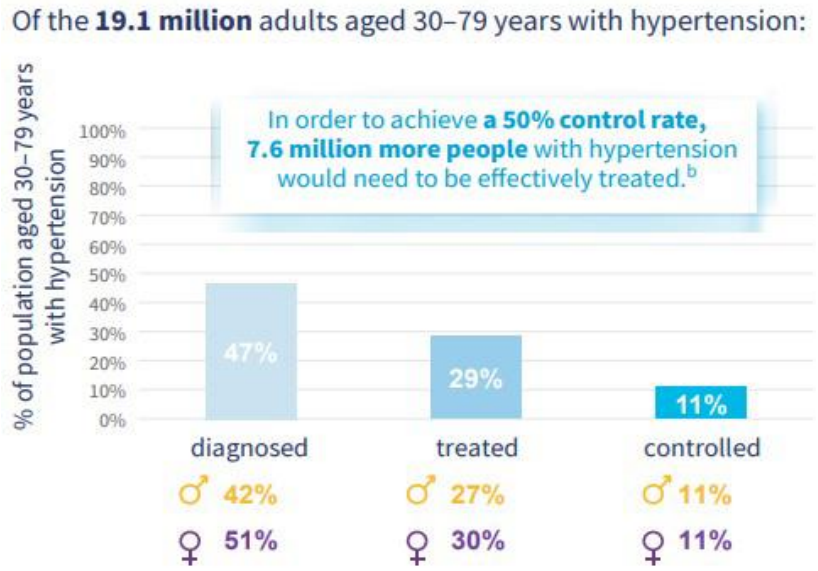
1.1 The global burden of hypertension

High Blood Pressure (BP) is the leading cause of death globally. In 2019 alone, high BP caused about 11 million deaths (19.2% of all deaths) and about 9% of all disability-adjusted life-years lost globally. [1, 2] In 2019, about 1.3 billion adults aged 30–79 years worldwide had hypertension, defined as Systolic Blood Pressure (SBP) ≥140 mmHg or Diastolic Blood Pressure (DBP) ≥90 mmHg or taking medication for hypertension. [3] Hypertension prevalence is increasing, largely due to population growth, unhealthy diets, physical inactivity, excessive alcohol consumption, obesity, and stress.[4] Hypertension is a major independent risk factor for stroke, coronary artery disease, heart failure, dementia, and chronic kidney disease, which impose a substantial burden on individuals, healthcare systems, and economies. Consequently, the economic impact of hypertension is significant, including direct healthcare costs for management, as well as indirect costs related to lost productivity and disability.[5]

1.2 The burden on hypertension in low- and middle-income countries

Over the past three decades, hypertension has transitioned from a significant burden in high-income countries (HICs) to one that is now highly prominent in low- and middle-income countries (LMICs) including South Asia and Sub-Saharan Africa. Besides the high prevalence and increased risk of mortality and of cardiovascular and renal events, there is a substantial burden of untreated and uncontrolled hypertension in LMICs. Sub-Saharan Africa and South Asia regions including countries like Nigeria and Sri Lanka are among those that bear the highest burdens.[4] In 2019, the prevalence of hypertension among adults aged 30–79 years in Nigeria was 36%, which is already higher than the global average of 33% (Figure 1). Of the estimated 19 million Nigerian adults (age 30-79 years) with hypertension, 47% were previously diagnosed, 27% treated, and only 11% were controlled (SBP <140 mm Hg and DBP <90 mmHg). These numbers are far below global averages (54% diagnosed, 42% treated, 21% controlled). Unpublished recent data from the 2023 STEPS demographic health survey in Nigeria (n=19,523; 55% female) show a similar pattern of the hypertension cascade (26% unadjusted prevalence, 45% diagnosed, 34% treated, 17% controlled).[6]

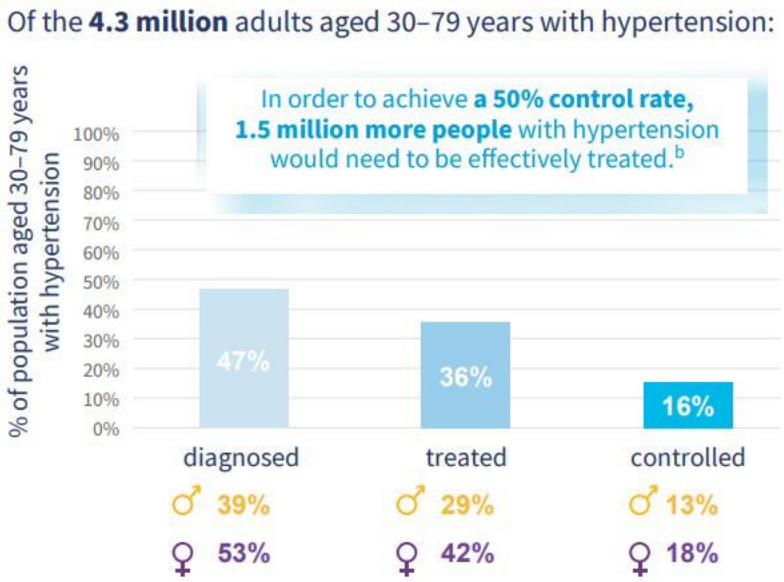
Figure 1: Hypertension Cascade in Nigeria, overall and by sex (2019)



The burden of hypertension in Sri Lanka among adults (aged 30–79 years) is also high, and similar to that in Nigeria – with a prevalence of 36% (Figure 2). Among 4 million Sri Lankan adults (age 30-79 years) with hypertension, 47% were previously diagnosed, 36% were treated, and only 16% were controlled, and again

these numbers are far below the global averages (54% diagnosed, 42% treated, 21% controlled respectively). [7]

Figure 2: Hypertension cascade in Sri Lanka, overall and by sex (2019)



The large and rising burden of hypertension in LMICs imposes economic hardships on patients and caregivers, and adds to the financial strains on health systems already facing challenges such as low physician-to-patient ratios and limited access to essential medicines.[4] Moreover, high rates of uncontrolled hypertension not only have several implications for the health of affected individuals and resource-constrained health systems in LMICs (e.g., Nigeria and Sri Lanka) but also entail substantial societal, developmental, and economic costs. [4] Therefore, it is crucial that new hypertension management strategies not only aim to improve BP control, reduce deaths and hospitalisations, but also reduce health care costs, particularly in LMICs. In LMICs, it is estimated that about half of all costs are from care delivery during clinic visits (personnel, site, and laboratory costs), with the remainder attributed to medication costs (ref).[4] For patients, out-of-pocket medication costs vary considerably but are often high and the lost work time from clinic visits also incurs costs.[4] Therefore, improved hypertension control through safe and effective, affordable, cost-effective, and scalable management strategies represents an urgent priority and a major unmet need in LMICs.

1.3 Study location justification

Nigeria, the most populous country in Africa, represents Black Sub-Saharan Africa (which constitutes ~15% of world's population) has a high prevalence of hypertension (higher than the global average), with very low BP control rates. Hypertension treatment and control are national priorities outlined in the National Multisectoral Action Plan for the Prevention and Control of NCDs. Nigeria has the national task shifting and sharing policy, which allows community health workers to prescribe BP-lowering medications according to a standardized protocol. Sri Lanka, represents South Asia (which constitutes 25% of world's population), also has high prevalence of hypertension, exceeding the global average, with very low BP control rates. Hypertension control is a national health priority. Sri Lanka's Ministry of Health has adopted the WHO HEARTS technical package for hypertension control and implemented quality improvement interventions, including standardized treatment protocols. While both countries share similarities in terms of hypertension burden, there are differences that provide a strong rationale for our research. Notably, there are major racial differences, and it is established that BP reduction is more difficult to achieve among Black Africans compared to other races. The hypertension standard treatment protocols in Nigeria and Sri Lanka are based on first-line monotherapy and first-line combination therapy, respectively. Thus, through the evaluative part of the study, we will compare our new treatment strategy with two different contextual comparator interventions. Nigeria

has poorer healthcare resources and hence poorer health and social indicators compared to Sri Lanka. The findings will have implications for the larger African region and South Asia.

2 RATIONALE

2.1 Current ineffective approaches and barriers to hypertension management in LMICs

Many national hypertension guidelines [8-10] continue to recommend a single BP-lowering drug as first-line therapy, and combination therapy only for "grade 2 hypertension" (BP >160/90 mmHg), despite most international/major guidelines [11-13], recommending two-drug combination as first-line for most patients. Many national standardised treatment protocols for hypertension recommend initial monotherapy, (which achieves on average only a 9/5 mmHg reduction in BP,[14] with higher dose monotherapy as the second step, which achieves only 1-2 mmHg additional BP reduction and can increase adverse effects. [14]

Additionally, most national standardized treatment protocols have 5 or more treatment steps, which could result in increase in cost and time.[15] Consequently, in most clinical practice settings, patients are started on monotherapy at a low dose, and remain on it long term [16] due to therapeutic inertia [17, 18] and the lack of available, affordable combination therapy options.[19] For example, studies in Nigeria, Ghana, and South Africa found that treatment was not up-titrated in up to 90% of the patients with uncontrolled BP.[20] Patient's adherence to BP-lowering drugs is also a major barrier [21-23].

2.2 Potential role for new paradigm for using low dose single pill combinations

The potential of single pill combinations (SPCs) to improve efficacy, reduce inertia, increase efficiency by simplifying treatment choices and optimise drug procurement [11, 13, 24] has led to their inclusion in World Health Organization (WHO) model list of essential medicines [25] and recent standardised treatment protocols from WHO, Pan American Health Organization, Resolve To Save Lives and others.[15] In recent years, there has been increasing interest in low-dose SPCs with three or more drugs to extend the potential benefits of SPC-based care. Evidence from randomised clinical trials (RCTs) indicates that low-dose combinations of multiple drug classes may achieve greater hypertension control without increasing adverse effects [14].

Much of the BP-lowering efficacy of any monotherapy is achieved at low doses and efficacy dose-response curves are typically shallow above one-quarter of the standard dose at low doses, there are few or no adverse effects, but for most classes, adverse effects increase with increase in dose.[14, 26] The incidence of idiosyncratic reactions (e.g., anaphylaxis) to individual BP-lowering drugs is sufficiently low that the risks for a patient simultaneously taking three drugs is acceptably low.[14]. There is additivity of effects across drug classes that target different pathophysiological pathways, and there is clear evidence of greater reduction in cardiovascular events with greater BP reduction. [27]

2.3 Previous and ongoing research relevant to this proposal

Large and tolerable reductions in BP have been demonstrated in short-term (4-12 weeks) RCTs of triple and quadruple low-dose SPC therapy compared to placebo or monotherapy, conducted by our group and others.[26] These RCTs were sufficiently promising to lead to larger long-term evaluations of this new paradigm compared to usual care conducted by our group, three of which have now been completed (Table 1).

The Quadruple Ultra Low dose treatment for Hypertension (QUARTET) trial among 591 adults with hypertension, who were either untreated or on monotherapy, compared an ultra-low-dose combination to guideline-recommended treatment starting with standard dose monotherapy. Initial therapy was blinded, with other treatment open label, and the only recommendation about other therapy was that the first up-

titration step was amlodipine 5 mg. This trial demonstrated large reduction in 24-hour BP at 12 weeks and improvements in BP control. These benefits were maintained in a 52-week extension cohort. While there was an increase in symptoms due to hypotension, there was no increase in withdrawals from treatment due to adverse events.

A small sample size RCT among US patients with hypertension who receive care in federally qualified health sites compared quadruple quarter-dose combination vs. usual care demonstrated a similar direction and magnitude of results. [28]

The TRIple pill vs Usual care Management for Patients with mild-to-moderate Hypertension (TRIUMPH) [29] was a six-month open-label RCT conducted in tertiary care hospital in Sri Lanka that compared initial or early low-dose triple single SPC with usual care in 728 adults with uncontrolled hypertension. [29] In this RCT, use of SPC resulted in 80% hypertension control (BP <140/90 mmHg) vs. 65% with usual care (Figure 3).

Table 1: Summary of design and outcomes of previous trials of low-dose combination therapy vs usual care

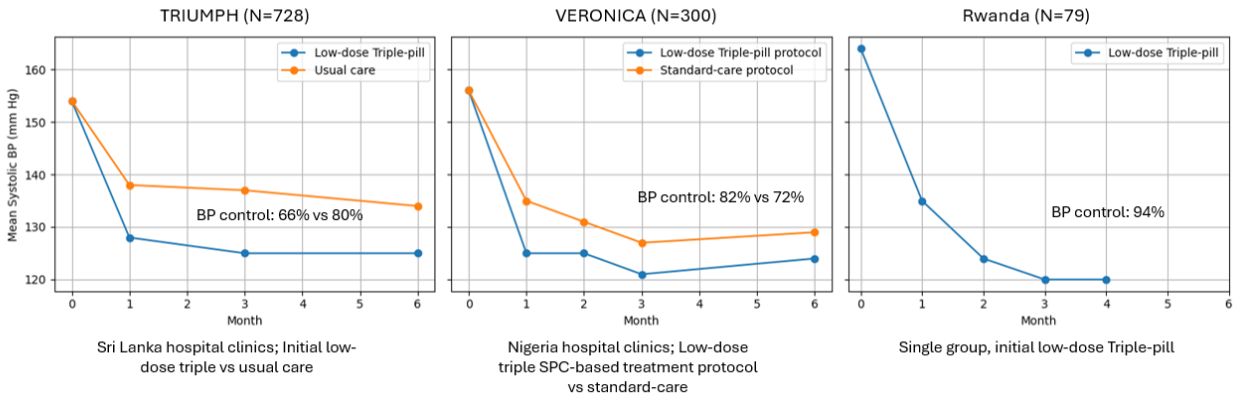
Study	Participants	Comparison	Outcomes
QUARTET AUS, 2019	591 patients with hypertension, untreated or on monotherapy	Quadruple quarter-dose (Irbesartan 37.5 mg, amlodipine 1.25 mg, indapamide 0.625 mg, bisoprolol 2.5 mg) vs Initial monotherapy (Irbesartan 150 mg) with optional open-label uptitration of 5 mg amlodipine	At 12 weeks, SBP reduction 6.9 mmHg (95% CI 4.9 to 8.9). At 12 months, SBP reduction: 7.7 mmHg, hypertension control: 81% vs 62%. Treatment withdrawal due to adverse events: 12 (4%) vs 7 (2%), NS
QUARTET USA, 2024	62 hypertensive patients with uncontrolled BP, untreated or on monotherapy	Quadruple quarter-dose (bisoprolol 2.5 mg, candesartan 2 mg, amlodipine 1.25 mg, indapamide 0.625 mg) vs Monotherapy (candesartan 8 mg) with open-label addition of 5 mg amlodipine	At 12 weeks, SBP reduction 4.8 mmHg (95% CI, -1.3 to 10.8). Treatment withdrawal due to adverse events: 1 (3%) vs 3 (10%), NS
VERONICA, Nigeria 2024	300 hypertensive patients with uncontrolled BP, untreated or on monotherapy	Triple SPC (¼, ½, and standard dose, containing telmisartan / amlodipine / indapamide [10/1.25/0.625 mg, 20/2.5/1.25 mg, and 40/5/2.5 mg]-based treatment protocol vs Standard care	At 6 months, home SBP reduction 5.8 mmHg (95%CI, 3.6 to 8); clinic BP control (<140/90mmHg) was 82%vs 72% (risk difference, 10% [95%CI, −2%to 20%]). No participants discontinued trial treatment due to adverse events.
TRIUMPH, Sri Lanka 2018	700 patients with hypertension, untreated or on monotherapy	Triple half-dose (telmisartan 20 mg, amlodipine 2.5 mg, chlorthalidone 12.5 mg), with option to be uptitrated to single pill with double these doses vs Usual care	At 6 months, hypertension control: 80% vs 60%. SBP reduction: 9.8 mmHg (95% CI, 7.9 to 11.6). Treatment withdrawal due to adverse events: 23 (7%) vs 24 (7%), NS

While the TRIUMPH results were promising, several improvements were required to enable this strategy to be more scalable as well as more effective. First, a product was developed for market, so that it was available for prescribers outside of a trial setting. A decision was made to use indapamide instead of chlorthalidone, given it has more extensive international regulatory approval status. Second, three dose versions were created and a simple standardised treatment protocol (STP) developed, since in TRIUMPH 30% of participants remained uncontrolled in the triple SPC arm, due to very limited up titration. The treatment strategy provides accelerated and simplified treatment, with an initial step that is considerably more efficacious than monotherapy, followed by uptitration steps that provide clinically meaningful improvements in efficacy. Furthermore, initial clinic follow-up visits are recommended at 2-weekly intervals to up-titrate therapy if BP ≥135/85 mmHg, after which visit frequency is reduced to monthly and 3 monthly, which is supported by:

- evidence that >80% of efficacy is achieved in 2 weeks with little additional BP reduction after 2 weeks, [30]
- the statistical certainty that to achieve sustained long-term BP control at <140/90mmHg (ie. >80% of measures over time) requires a mean SBP <130 mmHg, given intra-individual SBP variation, has an SD of about 7%. [31-33]. Considered in a different way, if the mean SBP for an individual is only just under 140 mmHg, then clearly only around 50% control at <140/90 mmHg will be observed for that person over the long-term – hence an evidence-based uptitration strategy should aim to achieve a BP level that assures high levels of long-term control <140/90mmHg

This adapted low-dose triple SPC-based standardised treatment protocol (STP) (henceforth triple SPC strategy) was evaluated against standard-care in 300 patients with uncontrolled BP on zero or one BP-lowering drug in VERONICA study [34,56] in three hospital-based family medicine clinics in Nigeria. At the end of 6 months treatment period, mean home SBP was −5.8 mm Hg (95% CI, −8.0 to −3.6) lower in the triple SPC-based standardised treatment protocol arm, and clinic BP control to <140/90 mmHg was 82% vs 72%. No participants discontinued trial treatment due to an adverse event. These results are consistent with a single arm before and after trial recently completed in rural Rwanda,[35] in which 79 patients with hypertension were treated with low-dose triple SPC as initial therapy resulting in 94% BP control at 4 months. As shown in Figure 3, all trials showed large improvement in hypertension control achieved quickly and sustained over 4-12 months.

Figure 3: Low-dose triple therapy in the treatment of hypertension in LMICs



As can be seen In the TRIUMPH RCT the usual care arm did not 'catch up' despite considerably higher rates of add-on BP treatment and monthly visits to tertiary care specialists for hypertension management.

Furthermore, the control arm had superior levels of care, with lower treatment inertia rates and higher hypertension control than are generally seen in normal clinical practice.

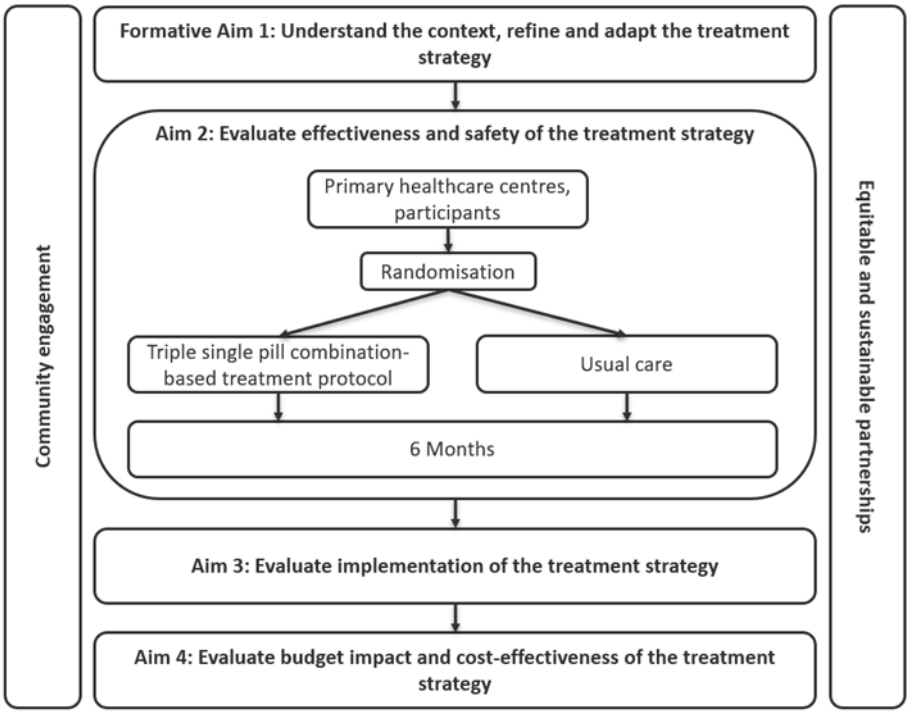
Our rationale to expand the evidence regarding hypertension management in LMICs, particularly in primary care settings in Nigeria and Sri Lanka is as follows:

- None of the previous studies of low-dose SPCs have been conducted with products available for clinical use – all have been with 'bespoke' formulations, which are only possible to use in a clinical study setting. Hence, a major novelty of the proposed study is the evaluation of a strategy that can potentially be scaled.
    - Currently available triple SPCs are only available at higher doses and only indicated for substitution among patients already taking all three-component drugs or as an add-on or substitution therapy among patients not adequately controlled on two of the component drugs.
    - None of the available triple SPCs are available in low-dose strengths, nor are they indicated for initial treatment. There are also no existing SPC products on the market with low-doses of an angiotensin receptor blocker (ARB), a calcium channel blocker (CCB) and a thiazide-like diuretic.
    - Finally, and perhaps most importantly, triple combinations are neither widely available nor affordable in LMICs. To address this unmet need, we propose to use a new triple SPC containing telmisartan, amlodipine, and indapamide developed by George Medicines for the treatment of hypertension, including as first-line therapy. George Medicines has completed pivotal efficacy and safety studies for this new triple SPC and recently received regulatory approval from the US Food and Drug Administration (FDA). Recently, triple SPCs have been included in the WHO Model List of Essential Medicines – 24th List (2025). This is will likely lead to their wider availability and increased affordability.
- While the treatment strategies being tested in our studies in tertiary care looks highly promising, uncertainty remains if they will be effective, safe, and feasible to implement in primary care settings in LMICs (in both urban and rural areas), where most patients in primary care settings with hypertension are diagnosed and treated.
- Of the numerous previous implementation studies of strategies to improve hypertension control in LMIC primary care settings, only one achieved over 80% hypertension control (from a baseline hypertension control of 61%), and this was achieved with a resource-intensive multicomponent treatment strategy.[36] Our simple and low-cost treatment strategies have the potential to achieve over 80% BP control in a short period of time and at scale.

3 OBJECTIVES

We aim to evaluate, among adults with uncontrolled hypertension, new treatment strategies (involving a low-dose triple SPC based standardised treatment protocol with or without a potassium-enriched salt substitute intervention) compared to usual care for effectiveness, implementation, budget impact and cost effectiveness for the treatment and control of hypertension in primary care settings in Nigeria and Sri Lanka (Figure 4).

Figure 4: Study overview (overall and specific objectives)



The aims of the study are as following:

Formative phase:

Aim 1: Understand the context and refine and adapt the new treatment strategies.

This aim has 2 objectives:

Objective 1:

a- Policy and evidence review: To review hypertension research, national and local policies, programs, clinical practice guidelines and treatment protocols in Nigeria and Sri Lanka to inform our research.
b- Health system assessment: To assess the availability and readiness of hypertension care in PHCs, and feasibility to conduct the RCT.
c- Understanding the characteristics of patients with hypertension, hypertension management and control, including use of pharmacological interventions and lifestyle management
d- Exploring experiences, practices, and views on hypertension care and the new treatment strategies

Objective 2:

Adapting and refining the new treatment strategies for evaluating effectiveness and implementation through RCT

Evaluative phase:

Aim 2: Evaluate the effectiveness and safety of the new treatment strategies.

Aim 3: Evaluate the implementation of the new treatment strategies.

Aim 4: Evaluate the budget impact and cost-effectiveness of the new treatment strategies

This protocol focuses solely on the formative phase of the study. Following the completion of the formative phase, the protocol will be amended to include details of the evaluative phase.

FORMATIVE PHASE AIM (WORK PACKAGE) 1: UNDERSTAND THE CONTEXT, AND REFINE AND ADAPT THE NEW TREATMENT STRATEGY

4 SPECIFIC OBJECTIVES AND METHODS

Objective 1a: Policy and evidence review: To review hypertension research, national and local policies, programs, clinical practice guidelines and treatment protocols in Nigeria and Sri Lanka to inform our research.

Design

Rapid literature review to build a clear picture of the current landscape of hypertension care.

Methods

Data sources:

We will systematically search major literature databases such as PubMed/MEDLINE, Google Scholar and regional sources to identify published studies. We will also search for grey literature, including reports, working papers, and documents produced by Ministries of Health, WHO, and other local and international organisations. We will also obtain national and local health policies, strategic plans, clinical guidelines, and treatment protocols from relevant websites or, if needed, request them from relevant organisations and stakeholders.

Search strategy:

We will use a structured search strategy that combines keywords related to hypertension, clinical guidelines, treatment protocols, policies, and programmes, alongside the country names Nigeria and Sri Lanka. In addition, we will check the reference lists of key documents to capture any sources we may have missed.

Eligibility criteria:

We will include documents published in English within the last ten years. If older documents are still foundational or remain in effect, we will include them too. The focus will be on sources that address the prevention, diagnosis, treatment, or control of hypertension in adults, particularly those relevant to primary healthcare.

Data extraction:

From included documents, key information will be extracted using a structured template. This will include the type of document, year of publication, issuing institution, and the recommendations it makes on diagnosis and treatment. We will also extract details of treatment protocols and drug regimens, and descriptions of programme approaches such as screening, referral, follow-up, task-shifting, and supply chain management and publications related to WHO's Service Availability and Readiness Assessment tool. Where possible, we will also note reported challenges, enabling factors, and monitoring or evaluation indicators.

Analysis:

We will use a content analysis approach with a focus on aspects most relevant to our study. Specifically, we will summarise recommendations on diagnosis, treatment thresholds, drug choices and sequencing, and models of care such as task-sharing, referral pathways, and follow-up mechanisms. Key findings will be organised in evidence tables to enable comparison across Nigeria and Sri Lanka, highlighting consistencies, gaps, and areas of divergence that may affect the feasibility and design of our study. Policies and guidelines will also be mapped against the components of our proposed treatment strategies to assess alignment, identify potential barriers, and highlight opportunities for adaptation. The synthesis will therefore provide targeted insights to refine the treatment strategies and ensure it is both policy-concordant and feasible within existing health system structures.

Objective 1b: Health system assessment: To assess the availability and readiness of hypertension care in PHCs, and feasibility to conduct the RCT.

Setting

In Nigeria, the study will be conducted in Federal Capital Territory (FCT) which includes both urban and rural areas and has a high burden of untreated and uncontrolled hypertension (15.3% as per unpublished data from a 2023 STEPS survey) [37]. FCT has the necessary primary healthcare infrastructure to support the proposed study. Primary healthcare in Nigeria is governed by the national primary care agency through the state primary care development boards, and the primary care provided is similar across Nigeria. We will conduct our study in family medicine clinics within Primary Healthcare Centres (PHCs) where most patients with hypertension are managed.

In Sri Lanka, the study will undertake in Gampaha district which also includes both urban and rural areas, and an estimated prevalence of hypertension of ≈25% [38] Within the district healthcare system, primary medical care units (PMCUs) play a vital role in providing primary curative, preventive, and health promotion activities, as well as outpatient care. As in Nigeria, primary healthcare provision in Sri Lanka is organised under a nationally standardised system, with PMCUs following uniform policies and service packages across.

Hypertension is primarily managed at PMCUs, with referrals to higher sites as needed. We will conduct our study in PMCUs.

We will make efforts to ensure representation of all population segments, including religious, racial, and socially disadvantaged groups in our study.

Design

Cross-sectional facility survey.

Methods

Sampling strategy:

PHCs in FCT in Nigeria and PMCUs in the Gampaha district in Sri Lanka will be surveyed.

Data collection:

At each PHC, a structured facility survey will be administered using and an adapted version of WHO's Service Availability and Readiness Assessment tool [39]. The focus will be to capture the contemporary availability of infrastructure and human and other resources (diagnostics, medicines etc.) for hypertension care. Data will also be collected on referral system and feasibility to conduct remaining components of the formative phase and subsequently the RCT of the new treatment strategy.

Data analysis

Descriptive statistics will be used to summarise facility characteristics. Frequencies and percentages will be reported for categorical variables and means with standard deviations or medians with interquartile ranges will be reported for continuous variables. Qualitative data will be summarized narratively. Data will be presented separately for Nigeria and Sri Lanka to enable comparisons across settings.

Objective 1c: Understanding the characteristics of patients with hypertension, hypertension management and control, including use of pharmacological interventions and lifestyle management

Setting

From the PHCs /PMCUs surveyed in Objective 1b, we will select sites that have at least two full-time staff (including at least one physician/doctor and one nurse), are accessible by road in all seasons, and are functional (defined as being open for at least five hours daily for a minimum of five days a week and offering the minimum PHC service package). Sites must also be willing to participate in the study. PHCs currently participating in the Hypertension Treatment in Nigeria 2.0 programme will be excluded.

Design

Cross-sectional survey.

Methods

Sampling strategy:

We will use a cluster sampling strategy and select & survey 40 PHCs/PMCUs (cluster)(20 in each country). At each PHC/PMCU, consecutive adult (age ≥18 years) patients with hypertension will be invited to participate until the target sample size approximately 30 per PHC/PMCU is achieved. Hypertension is defined as prior documented diagnosis of hypertension, or current use of BP-lowering drugs for hypertension, or SBP ≥140 mmHg, and/or DBP ≥90 mmHg measured on two separate occasions). Patients who are receiving BP-lowering drugs for conditions other than hypertension (e.g., benign prostate hyperplasia, migraine, etc) and without hypertension will not be included.

Data collection:

After obtaining written informed consent, participants will be asked to share their medical records for review and respond to questions posed by the research staff. Data will be collected using a structured interviewer administered questionnaire informed by the STEPS instrument [40] on various parameters including age, sex, height, weight, socio-economic status, medical history (current and past BP, medications), and health behaviours and lifestyle interventions (smoking, alcohol consumption, diet including consumption of salt and use of salt substitutes, and physical activity). BP will be measured on the day of enrolment. The collected data will be transcribed into a secure electronic data collection system (REDCap).

Mitigating risk of bias:

To minimise selection bias, sites will consecutively invite all eligible participants to ensure equal recruitment opportunity. Reasons for non-participation will be documented to identify patterns (e.g. demographic or health-related) and to inform analysis for non-response and generalisability. Interviewer bias will be reduced by training staff to follow standardised data collection procedures.

Sample size:

Previous research indicates hypertension control (SBP < 140 mmHg and DBP < 90 mmHg) in primary care settings among treated individuals in Nigeria and Sri Lanka varies and is up to 50%. [41, 42] Assuming a conservative prevalence of hypertension control at 50%, an average cluster size of 30 participants, and an intraclass correlation coefficient of 0.02 [42], a sample size of 608 participants per country is required. This will allow us to accurately estimate the country-specific prevalence of hypertension control to within ±5% error with 95% confidence level. Therefore, the total sample size to be recruited across both countries is 1216 participants.

Statistical analysis:

Descriptive statistics will be computed to determine the frequency and percentages for categorical variables and mean (standard deviation) or median (interquartile range) for continuous variables. To identify factors

associated with poor control of hypertension, we will use multilevel logistic regression with clustering by PHC (random intercept)). Covariate selection will be guided by a conceptual framework; core adjustments will include age, sex, treatment status, and comorbidity. We will report adjusted odds ratio with 95% CIs. Subgroup analysis will be explored by sex, age group and treatment status. All analysis will be stratified by country.

Objective 1d: Exploring experiences, practices, and views on hypertension care and the new treatment strategy

Setting

PHCs included in Objective 1c., and policymakers in each region e.g. Ministry of Health

Design

Qualitative study using focus groups discussions (FGDs) and in-depth interviews (IDIs), guided by the Implementation Research Logic Model (IRLM) [44] and the Consolidated Framework for Implementation Research (CFIR) [45].

Methods

Participants and sampling strategy:

Participants will include adults with hypertension and their carers; healthcare providers (community health workers, nurses, and doctors or physicians); clinic administrators; and policymakers. We will use purposive, maximum-variation sampling to capture diversity by country, site (urban/rural), and key characteristics of patients (sex, age, and BP-control status, treatment status, comorbidities etc); and providers (role, seniority, facility workload, site context [urban/rural] etc). Per country, we plan 9-12 focus group discussions (6–8 with patients/carers and approximately 3-4 with community health workers and nurses), each with 6–8 participants (≈54–96invited), and ~9–14 in-depth interviews (e.g., 6–8 physicians and 3–6 administrators/policymakers), with additional recruitment via snowballing if needed to achieve thematic saturation. The extent of FGDs, IDIs, and their combination will be determined by the local qualitative experts based on feasibility and the richness of the emerging data.

Data collection:

Participants will be identified via PHCs/PMCUs and nearby communities. After obtaining written informed consent, trained researcher will be conducted FGDs and IDIs in participants' preferred language with using guides appropriate for the role of interviewee. Interview guides will be developed based on domains in the Implementation Research Logic Model [43] and aligned with the Consolidated Framework for Implementation Research 2.0 (i.e., innovation, individuals, inner context, outer context, and implementation process [44]). The patient /carer and community health workers guides, and information sheets will be translated to Sinhala and Tamil languages in Sri Lanka.

Interview guides will cover experiences of current hypertension care; service availability, accessibility, and affordability; provider training and adherence to guidelines; barriers and facilitators to hypertension treatment and control; patient journey of people seeking hypertension care; and appropriateness and acceptability of the new treatment strategies in primary care. FGD/IDIs may last 30-90 minutes and will be audio recorded.

Data management and analysis:

Audio will be transcribed verbatim, and where needed, translated into English. Dedoose [45], or similar software will be used to assist with organising, coding, and analysing the qualitative data. Trained researchers

will read the transcripts several times to familiarise themselves with the text. Transcripts will be analysed using deductive and inductive content analysis simultaneously. Deductive content analysis begins by grouping participant quotes into codes that follow predefined topics from the interview guide based on the IRLM and CFIR. The research team will develop a codebook after independently reviewing the same set of transcripts. The resulting codebook will include codes reflecting topics from the interview guide, in addition to previously unexpected topics identified inductively.

The draft coding scheme will be reviewed by the study team and reconciled by consensus.

When the codebook is finalized, we will organise participants' responses by the corresponding codes. Senior researcher will also review 10% of the data and audit the findings, which will provide additional rigor, accuracy, and face validity of results. Common themes will also be developed inductively during video conferences, synthesising participants' responses across codes to reflect the themes. Data saturation will be assessed throughout the analysis process, whereby the research team will continually review newly collected data to determine if additional interviews or focus groups are necessary to capture new insights. Saturation will be considered reached when no new themes or information emerge from the data, indicating that the research has adequately captured the range and depth of perspectives on the topic. This iterative approach to analysis will allow for flexibility and responsiveness to emerging findings, ensuring that the research comprehensively explores the complexities of health system influences on hypertension care delivery.

Objective 2: Adapting and refining the new treatment strategy for evaluating effectiveness and implementation through RCT

Guided by the WHO's Tool for the development of a consensus protocol for the treatment of hypertension [46], we will adapt and refine the new treatment strategies in consultation with experts (in hypertension management and primary healthcare), the NAC, and the PAG. Meetings will be in-person, virtual or hybrid. Ahead of the meetings, the study team will prepare information packages on the new treatment strategies adapted from VERONICA pilot study, informed by its process evaluation, characteristics of patients with hypertension and current management of hypertension in the target setting, potential barriers and facilitators to implementation of the new treatment strategy, and any complementary implementation strategies identified based on the findings of the formative research. Based on the feedback we receive from our consultation; the study team will refine and further develop the new treatment strategies and complementary implementation strategies using FRAME-IS (FRAMEwork for documenting modifications to Implementation Strategies in healthcare) (Ref). The study team will finally convene a consensus meeting to discuss and agree upon the final treatment strategy to be evaluated in the interventional phase of the study.

5 DATA MANAGEMENT (FORMATIVE PHASE)

The formative phase data will be collected in both countries (Nigeria & Sri Lanka) and it will be pseudo anonymised/anonymised by the regional coordinating centres in-country. Quantitative data will be entered in the REDCap eCRF and the sever will be located at Imperial College London.

We will use REDCap as an electronic Data Capture System and the data captured will be analysed using statistical methods referenced in section 4 ensuring accurate interpretation of results. NVivo, Dedoose, or similar software will be used to assist with organising, coding, and analysing the qualitative data. More details will be available in the Data Management Plan (data collection, storage, and analysis).

6 COMMUNITY ENGAGEMENT AND INVOLVEMENT

Community Engagement and Involvement (CEI) is integral to this study. In both Nigeria and Sri Lanka, we have established multidisciplinary National Advisory Committees (NAC) and Patient Advocacy Groups (PAG) comprising patients, carers, opinion leaders, and other stakeholders. These groups contributed to the development of the proposal and will remain engaged throughout the study. Six to eight CEI meetings will be held over the study life cycle, conducted separately for NAC and PAG. To maximise impact, NAC and PAG will also co-host dissemination workshops after each aim/phase of the study, and we will work towards sustaining these partnerships beyond the study to support translation of findings into practice and deliver long-term community benefit.

7 MONITORING

7.1 Formative phase monitoring

Prior to commencement of the formative phase of the study at any participating site, all designated research staff including the PI, Co-investigator(s) and Research Nurse(s)/Coordinator(s) will be trained in the study procedures.

Data monitoring will take a risk-based approach and involve a combination of remote, online and on-site monitoring

Study monitoring will ensure that the study is being conducted in accordance with the protocol, ICH-GCP guidelines and meets relevant ethical and regulatory requirements. The monitor will verify patient consent and eligibility and review relevant source documents according to a monitoring plan available as a separate document.

At completion of the study, the monitor will ensure that there are plans in place for the long-term storage of all the relevant data and source documentation (for a minimum of 10 years or a longer period if required by applicable regulatory requirements).

8 AUDITING

The study may be subject to inspection and audit by Imperial College London under their remit as sponsor. The study may be audited by third parties and inspected by government regulatory authorities. CRFs, source documents and other study files must be accessible at all study sites at the time of auditing and inspection during the course of the study and after completion of the study.

9 PROTOCOL COMPLIANCE AND SERIOUS BREACHES

Protocol deviations (PDs) and serious breaches (SBs) will be reported in accordance with local ethical and regulatory requirements. If any sites amass an excessive number of PDs or SBs, additional action may be taken; i.e., an additional monitoring visit to be conducted. The number of deviations or breaches required to warrant such actions will be determined by the sponsor on a site-by-site basis.

All SBs and PDs that pertain to a specific participant, will be reported in the study database. These forms can be printed for reporting to the IRBs/RECs/sponsor as needed or a line listing report can be generated. SBs and PDs that are not participant-specific and that relate generally to the site will be collected via a separate study web-based database.

All PDs and SBs must be taken seriously, and corrective action implemented as soon as possible, to prevent recurrence. Persistent deviations or violations may trigger additional monitoring visits.

A 'Serious Breach' is a breach which is likely to effect to a significant degree the safety or physical or mental integrity of the participants of the study; or the scientific value of the study.

10 ETHICAL AND REGULATORY CONSIDERATIONS

10.1 Research Ethics Committee (REC) review & reports

This study will be carried out according to ICH-GCP Guidelines, and with the ethical principles laid down in the World Medical Associations Declaration of Helsinki. The protocol, information sheets and consent forms, any material to be given to prospective participants, and any subsequent modifications will be reviewed and approved by the REC or Institutional Review Board (IRB) responsible for oversight of the study before participants are enrolled. Prior to commencement of the study, investigators are required to sign a protocol signature page confirming their agreement to conduct the study in accordance with these documents and all the instructions and procedures contained in this protocol, and to give access to all relevant data and records to monitors, auditors, IRB/RECs, and regulatory authorities as required. If an inspection of the site is requested by a regulatory authority, the investigator must inform the sponsor immediately.

11 PROTOCOL AMENDMENTS

An amendment is defined as a written description of change(s) to or formal clarification of a study protocol which may impact the conduct of the study, potential benefit of the study, or may affect participant safety, including changes of study objectives, study design, subject population, sample size, study procedures, or significant administrative aspects. An administrative change is defined as a minor correction or clarification that has no significant impact on the way the study is conducted and no effect on subject safety. Protocol amendments must be approved by the Steering Committee, Regulatory Authorities where required, and the REC/IRB. In cases where the amendment is required in order to protect the participant safety, the amendment can be implemented prior the REC/IRB approval. Notwithstanding the need for formal approval of a protocol amendment, the investigator is expected to take any immediate action required for the safety of any participant included in the study, even if this action represents a deviation from the protocol. In such cases, the sponsor should be notified of this action and the relevant REC/IRB informed within 72 hours.

12 CONSENT

12.1 Informed consent

Potential participants for the formative phase may only be included in the study after providing written consent. Country-specific participant information sheet and informed consent forms (PISCFs) have been adapted from a global template which will be reviewed and approved by Imperial College Research Ethics Committee, UK. Only current participant information sheets (PIS) which have been reviewed and approved by both the global and local REC will be provided to participants. This review and approval will be documented and stored with other study documents.

The responsible study team member must fully inform the participant of all relevant aspects of the study. The participant must be allowed ample time to ask about the details of the study and to make an informed decision as to whether or not to participate in the study. The participant must sign the consent form indicating their agreement to participate in the study, and before any study-related procedures are conducted, including screening procedures.

The person authorised by the investigator to conduct the consent process must also sign and date the consent form. The original signed consent form must be retained within the study documents at the site. A copy of the signed PISCF should also be filed in the participant's medical record so that other health professionals are aware of their involvement in the study.

13 WITHDRAWAL CRITERIA

Each participant has the right to withdraw from the study at any time (formative phase), for any reason, and without obligation to give a reason for withdrawing prematurely.

The reason for withdrawal will be recorded in the participant records. All patient data collected up to the point of withdrawal will be used in the analysis unless the participant requests that it be destroyed.

14 CONFIDENTIALITY

Every precaution will be taken to respect the privacy of participants in the conduct of the study. Only de-identifiable data will be stored in either of the secure web-based data management systems to maintain participant confidentiality. All individual and site information will be de-identified in reporting data and resulting publications or presentations to protect the confidentiality of participants.

The Principal Investigator will preserve the confidentiality of participants taking part in the study and fulfil transparency requirements under the General Data Protection Regulation for health and care research. Data and all appropriate documentation will be stored for a minimum of 10 years, but more if needed as per local ethical and regulatory requirements, after the completion of the study, including the follow-up period.

15 DECLARATION OF INTERESTS

The investigators named on the protocol have no financial or other competing interests that impact on their responsibilities towards the scientific value or potential publishing activities associated with the study.

Anthony Rodgers is employed by The George Institute for Global Health (TGI) and Imperial College London. He is seconded parttime to George Medicines Pty Ltd (GM), which is partly owned by George Health Enterprises Pty Ltd (GHE), the social enterprise arm of TGI. TGI holds and have filed applications for method of treatment and composition patents in relation to low and ultra-lowdose fixed-dose combination products for the treatment of hypertension and diabetes, and AR is listed as an inventor (Granted: US 10,369,15; US 10,799,487; US 10,322,117; US 11,033,544; US 11,478,462; Pending: US 17/932,982; US 18/446,268; US 17/598,122; US 17/317,614; US 17/527,084; US 17/527,085; US 17/527,087). GHE and GM have received investment to support the development, assessment and regulatory approval of cardiovascular combination products. AR does not have a financial interest in these patent applications or investments.

Mark Huffman received travel support from the American Heart Association and World Heart Federation, consulting fees from PwC Switzerland. MH has pending patents for heart failure polypills.

Aletta E Schutte has received speaker fees from Omron, Medtronic, Aktiia, Servier, Sanofi, Novartis and is advisory board member for Skylabs and Abbott.

Otavio Berwanger, Stephen Jan, Helena Legido-Quigley, Altta Schutte, Mohammad Abdul Salam and Mark Huffman are employed fully or partly by TGI or are affiliated to TGI. None have personal financial interests in any patent applications or investments of TGI, GM or GHE.

Neil Poulter has received financial support from several pharmaceutical companies manufacturing BP-lowering agents, for consultancy fees (Servier, Aktiia), research projects and staff (Servier, Pfizer) and for arranging and speaking at educational meetings (AstraZeneca, Lri Therapharma, Napi, Servier, Sanofi, Eva Pharma, Pfizer, Emcure India, Dr Reddy's Laboratories and Zydus). NP holds no stocks/shares in any such companies.

There are no other conflicts of interest to declare.

16 INDEMNITY

Imperial College London holds negligent harm insurance policies which apply to this study.

17 ACCESS TO DATA

After completion of the study, requests for access to study data will be considered, and approved in writing where appropriate, after formal application to the Study Management Committee.

18 DISSEMINATION

A comprehensive dissemination plan will be outlined in the ACTION evaluative phase protocol.

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