Study	**TRIUMPH - TRI**ple Pill vs. **U**sual care **M**anagement for **P**atients with mild-to-moderate **H**ypertension
Sponsor	The George Institute for Global Health
Study treatment	Triple blood pressure lowering Pill vs. Usual care
Development Phase	Phase III
Protocol	Version 1.0 – 30Oct2012
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Funder	National Health and Medical Research Council, Australia
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Triple Pill Manufacture and Distribution
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Study Funder
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LIST OF ABBREVIATIONS

ACE inhibitors	Angiotensin Converting Enzyme inhibitors
BP	Blood Pressure
CCDC	Centre for Chronic Disease Control
cm	Centimetres
CRF	Case Report Form (eCRF; electronic Case Report Form)
CV	Cardiovascular
CVD	Cardiovascular Disease
CKD	Chronic Kidney Disease
DBP	Diastolic Blood Pressure
DM	Diabetes Mellitus
eGFR/GFR	estimated Glomerular Filtration Rate/Glomerular Filtration Rate
EQ-5D	European Quality of life-5 Dimensions
F/U	Follow Up
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
HCTZ	Hydrochlorothiazide
HDL-cholesterol	High Density Lipoprotein cholesterol
HR	Heart Rate
IB	Investigator's Brochure
ICH	The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
INR	Indian Rupee
LFT	Liver Function Test
Kg	Kilogram
LDL-cholesterol	Low Density Lipoprotein cholesterol
mg	Milligram
mmHg	Millimetres of mercury
NHMRC	National Health and Medical Research Council
QALY	Quality Adjusted Life Year
REG	Registration
RAND	Randomisation
SAE	Serious Adverse Event
SBP	Systolic Blood Pressure
SUSAR	Suspected Unexpected Serious Adverse Reaction

PROTOCOL SYNOPSIS

Study design
The study is a prospective, open, randomised controlled clinical trial (n=700) of a combination blood pressure lowering pill ("Triple Pill")-based strategy compared to usual care among individuals with persistent mild-to-moderate hypertension on no or minimal drug therapy, augmented by a cost-effectiveness analysis and a formal process evaluation.

Aims
To assess whether provision of a Triple Pill compared to usual care improves blood pressure (BP) control at 6 months. Secondary outcomes include earlier BP control, mean change in BP, tolerability of treatment, self-reported adherence, quality of life, safety, acceptability, and healthcare resource consumption.

Patient recruitment
The study will be conducted within approximately 20 centres in India. The major inclusion criteria are patients with persistent hypertension for at least 6 weeks despite adequate lifestyle advice and/or lifestyle changes; and/or single drug therapy for BP lowering.

Randomisation and study medication
Eligible participants will be randomised to treatment with the Triple Pill or to continued usual care:

- *Triple Pill*:
  - strength 1 - *Telsartan Trio 20:* Telmisartan 20mg, Amlodipine 2.5mg, HCTZ 6.25mg
  - strength 2 - *Telsartan Trio:* Telmisartan 40mg, Amlodipine 5mg, HCTZ 12.5mg
- *Usual care*: separate BP lowering medication prescribed at the discretion of the responsible clinician.

For both groups any advice and /or other interventions relating to other BP lowering measures, including those relating to lifestyle modification, will continue at the discretion of the responsible clinician. Similarly all changes to medications in both groups will be at the discretion of the responsible clinician.

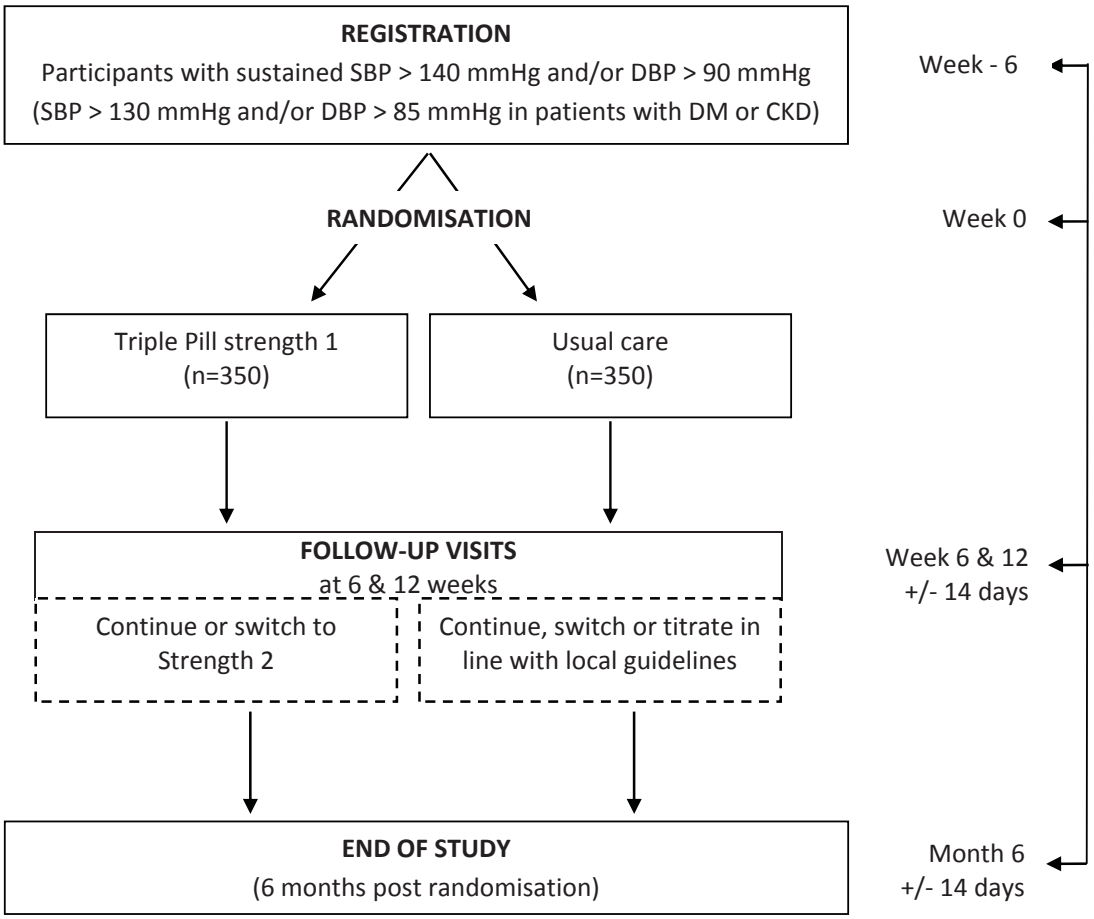
Data collection and follow-up
Participants will be followed up for 6 months. Blood pressure will be measured at baseline, 6 weeks, 12 weeks and the end of the study (6 month) visit. Information on safety and secondary outcomes will also be collected at these visits.

Outcomes
Primary outcome: Proportion of patients achieving target BP at the end of 6 months follow up: SBP < 140 mmHg and DBP < 85 mmHg (SBP < 130 mmHg and DBP < 85 mmHg for patients with diabetes and/or chronic kidney disease).

Secondary outcomes: Proportion of participants with BP control at 6 and 12 weeks; mean change in SBP and DBP; tolerance to treatment; use of health care services; self-reported BP lowering medication use; quality of life.

Statistical Power
A sample size of 700 patients will provide 90% power at 2p=0.05 (assuming 5% loss to follow-up with only 6 months of follow-up) to allow detection of at least a 12% absolute improvement in control rates from 50% to at least 62% (relative risk of 1.24).

STUDY SCHEMATIC



BACKGROUND

Hypertension and hypertension control in India

Hypertension has emerged as a significant public health problem for the developing world. WHO estimates indicate high blood pressure is the leading cause of premature death globally and the third leading cause of disease burden, with the majority of the burden falling in developing countries.[1] In India, the absolute number of hypertensive patients is predicted to rise from 118 million in 2000 to 200 million in 2025.[2] Increasing life expectancy, urbanization, increased per capita salt consumption, alcohol intake and overweight are some of the factors contributing to a higher prevalence of hypertension. It has been projected that Indians who are 35 years or older will constitute nearly 42% of the total Indian population by the year 2021, up from 28% in the year 1981.[3] Similarly, the number of Indians living in urbanized settlements by the year 2021 is expected to rise from 30% to nearly 43%. Given these changes in the demographic profile the likelihood of hypertension emerging as a major public health challenge is daunting.

The current prevalence of hypertension in India varies from 12-17% in rural areas to 30-40% in many urban districts.[4] However, even in some rural areas, a significantly higher prevalence has been reported due to local customs and practices – in the north eastern state of Assam, for instance, higher consumption of salt has led to a higher community burden of hypertension in tea garden workers. Hypertension in India is further characterized by a lack of awareness particularly among the less educated and rural populations. Based on several cross sectional surveys carried out at different times it is estimated that only 10-33% of affected individuals are aware of their condition.[5] In addition there is inadequate emphasis on evidence based management resulting in poor control even among those aware. For example in Chennai, where the prevalence of hypertension is estimated to be 22.8% in males and 19.7% in females, only a little more than a third of those with hypertension were aware of their blood pressure and only half were on any type of therapy. Only 40% of those on drug therapy had adequate control of their hypertension.[6]

Awareness and control of hypertension is relatively poor even amongst those who are well educated and have access to screening programs. In a large industrial populace from north India, with graduate or higher level of education, Prabhakaran et al reported hypertension awareness in only a third of those surveyed and optimal blood pressure control in another 38%.[7] Hypertension management strategies globally, such as those endorsed by most practice guidelines including the Indian Hypertension Guidelines (Indian Hypertension Guidelines-2007. Convenor: Siddharth Shah. Members: M Paul Anand, M Maiya, Sukumar Mukherjee, YP Munjal, GS Wander, S Kamath), have traditionally focussed on “tailored therapy” and “stepped-care” approaches. These tend to be costly and time consuming for doctor and patient, ignore the recognition that contemporary BP targets almost always necessitate additional medication and ignore the auto-regulatory mechanisms that limit responsiveness to a single drug administered alone.

Evidence on potential benefits of regimen simplification and use of 2-drug combination pills

Most patients with hypertension require BP lowering medication from 2 or more classes to achieve adequate control.[8] The need for titration of medication and addition of multiple classes of drug requires multiple physician visits and this in itself triggers poor adherence to prescribed medication and poor attendance at scheduled visits.[9] The requirement to take multiple medications in complex

regimes also results in poor adherence.[10] For physicians, the need for repeated up-titrating or adding extra medications can lead to inertia and complicit acceptance of inadequate BP control.[11-12]

Dual combination BP lowering medication has been shown to improve achieved BP reductions as well as cardiovascular event rates.[13] Initiating anti-hypertensive treatment with dual combination therapy not only accelerates the time taken to achieve control but also attains a lower final target.[14-15] For the patient, improved adherence has also been demonstrated without adversely affecting the side effect profile.[16] Further benefits in BP control are also available via simplifying up-titration regimes.[15]

Evidence on hypertension combination pills containing more than two medications

There are sound pharmacological principles to expect the maximum benefit to side effect ratio from low-dose triple combinations.[17-19] In short, benefits of each component are additive, and low doses typically avoid most side effects while achieving the large part of the potential blood pressure reduction to any given drug. Thus for example, three half-dose medications would typically lower blood pressure about as much as two full-dose medications, but with fewer side effects.[17]

However, a number of important questions remain to be answered. The triple BP lowering pills that have recently become available in high income countries, and the small number used in India at present, have focussed exclusively on severe hypertension that remains uncontrolled with full dose dual combination therapy. While an important group, this is a small fraction of people with hypertension. Furthermore, previous trials have been within the mode of traditional stepped care, and have not tested the integration of a low-dose triple combination within a simplified regimen. For example, the recent trial of Exforge[20] involved patients with moderate or severe hypertension with an average baseline BP of 170/107 mmHg. Patients were randomised to one of 4 arms to receive 8 weeks of treatment with either amlodipine /valsartan /HCTZ 10 /320 /25 mg or dual therapy with 2 of the previously mentioned three components. Perhaps unsurprisingly, this trial showed that patients on triple therapy achieved better BP reductions than patients on dual combination therapy.

To date no clinical trial has tested the benefits or cost-effectiveness of combination therapy with three, low dose BP lowering drugs in lower grades of hypertension. It is necessary to obtain direct evidence that the above strategies will be effective in each local context in which they are to be applied, (in this case, urban populations in India) as the impact of such a strategy will be affected by local health care systems and the population utilizing the strategy. It is particularly pertinent to test these questions in a setting with high prevalence of untreated and uncontrolled hypertension, and highly constrained resources.

AIM & OBJECTIVES

We aim to understand the effectiveness, cost-effectiveness and acceptability of a simplified strategy using a low-dose combination 3-in-1 antihypertensive pill ("Triple Pill") for the management of hypertension in India.

Specific objectives are

- To assess whether hypertension control is improved with a strategy of early use of a Triple Pill compared to usual care in India
- To determine the cost effectiveness of such a strategy
- To determine whether such a strategy is acceptable to clinicians and patients

RESEARCH PLAN

Study design

Randomised, open, controlled, parallel-group trial (N=700) of a simplified treatment initiation and titration strategy incorporating the use of a BP lowering 'Triple Pill' vs. usual care in patients with persistent mild-to-moderate hypertension. Prospective Randomised Open Blinded Evaluation [PROBE] design.[21]

Study participants

Inclusion criteria

- Adults ≥18 years of age.
- Sustained (≥6 weeks) SBP > 140 mmHg and/or DBP > 90 mmHg (or SBP > 130 mmHg and/or DBP > 85 mmHg in patients with diabetes* or chronic kidney disease**) despite diet and lifestyle advice and/or the use of single drug therapy.
- Trial Investigator is unsure as to whether a Triple Pill based therapy or usual care is better.

**Patients currently treated with oral antidiabetics and/or insulin, or have a fasting plasma glucose ≥ 126 mg/dL (7.0 mmol/L) or 2-h plasma glucose ≥200 mg/dL (11.1 mmol/L)*

***GFR/eGFR <60 mL/min/1.73m^2 or urinary albumin:creatinine ratio > 30 mg/g prior to the randomisation visit)*

Exclusion Criteria

- On two or more BP lowering drugs
- Severe or uncontrolled BP (SBP > 180 mmHg and/or DBP > 110 mmHg)
- Accelerated hypertension or hypertension at a level where the physician feels that slower up-titration of treatment is appropriate (e.g. elderly patients)
- Contraindication to any of the components of the Triple Pill
- Pregnancy, breast feeding, childbearing potential not on effective medically accepted method of child birth control.
- Unstable medical condition or known situation where medication regimen might be altered for a significant length of time, e.g. current acute cardiovascular event, planned coronary bypass graft operation, dialysis.
- Participants with clinically significant abnormal laboratory value judged to be unsuitable for trial participation by the investigator.

Randomisation

Randomisation will be conducted through a central, computer-based randomisation service, and will be stratified by study centre, and prescription of BP lowering therapy at baseline. The randomisation service will be built in the eCRF. Participants will be randomised 1:1 to either Triple Pill or Usual care.

Study treatments

Triple Pill arm

Treatment will commence at the lower strength of Triple Pill with the option to titrate upwards to strength 2 at subsequent follow-up visits. The dosage will be one Triple Pill once daily. Timing of the

dosage will be at the discretion of the responsible clinician. The two strengths of Triple Pill are as below.

Telsartan Trio 20: Telmisartan 20mg, Amlodipine 2.5mg, Hydrochlorothiazide 6.25mg
Telsartan Trio: Telmisartan 40mg, Amlodipine 5mg, Hydrochlorothiazide 12.5mg

Participants in intervention arm will be provided with the Triple Pill for free.

Triple Pill (for Triple Pill arm) will be dispensed from the trial centre/pharmacy at Randomisation, 6 week, and 12 week visits. Additional prescription can take place any time if the strength of the Triple Pill or the dose of usual care BP lowering drugs is required to be changed.

Usual care arm

Participants will continue to receive their usual BP management provided by the responsible clinician according to current guidelines. Participants will get their supply of prescribed drugs as per usual practice. Patients in the usual care arm will be reimbursed for the cost of their BP medications to a maximum of INR 8 per day (this being the cost of the generic components of the higher dose strength of the Triple pill) upon presentation of receipts to the trial centre.

Concomitant treatments

Prescription of additional medications on top of Triple Pill (if BP remains uncontrolled on the higher strength of the Triple Pill) will be unrestricted and at the discretion of the responsible clinician. For prescription of concomitant treatments, contraindications for components of Triple Pill and drug-drug interactions should be taken to consideration as per the monographs of drugs prescribed.

Withdrawal of Triple Pill

Post randomisation, Triple Pill can be withdrawn anytime if significant intolerance or contraindication develops. Further treatment should commence at the discretion of the responsible clinician in line with local guidelines. Such participants will still be followed-up and all trial assessments will be performed as per the protocol until the end of study unless the participant withdraws consent or the investigator withdraws the participant from the study.

Outcomes

Primary outcome

Proportion of patients achieving target BP at the end of 6 months follow up: SBP < 140 mmHg and DBP < 90 mmHg (SBP < 130 mmHg and DBP < 85 mmHg for patients with diabetes and/or chronic kidney disease).

Secondary outcomes

- Proportion of participants with BP control at 6 and 12 weeks
- Mean change in SBP and DBP
- Tolerance to treatment
- Use of health care services (hospitalizations, medical consultations, tests)

- Self-reported BP lowering medication use (7-day recall) – adherence defined as the patient taking the drug for at least 4 out of the last 7 days
- Quality of life

Visit schedule and assessments

Timing	**Week -6*** **(REG)**	**Week 0 (RAND)**	**Week 6 (W6)**	**Week 12 (W12)**	**Month 06 (M6)**
Visit window (days)			**+/- 7**	**+/- 14**	**+/- 14**
Informed consent	X				
Eligibility (inclusion/exclusion) criteria	X	X			
Participant demographics & medical history	X				
Height		X			
Weight		X			X
Blood pressure & heart rate		X	X	X	X
Fasting blood glucose & lipids	X**	X			X
Creatinine, uric acid, electrolytes and LFTs	X**	X			X
Urine protein (albumin) test	X**				X
Review of medications adherence		X	X	X	X
Reason for stopping medication (if any)			X	X	X
CV Lifestyle interventions		X	X	X	X
Health care visits		X	X	X	X
Serious Adverse Events		X	X	X	X
Quality of life (EQ-5D)		X			X
Dispensation of Triple Pill (Triple Pill arm only)		X	X	X	
Triple Pill accountability			X	X	X
Participant acceptability					X

*There must be at least 6 weeks between registration and randomisation in the case of a new diagnosis of hypertension being made at the registration visit. For patients diagnosed more than 6 weeks previously, there is no minimum time frame between registration and randomisation.

** *Either at REG or RAND or between these visits*

Patients will attend clinic visits at screening, randomisation, 6 weeks post randomisation, 12 weeks post-randomisation and 6 months post-randomisation. For newly diagnosed hypertensive patients, there must be a 6 week window between registration and randomisation to allow time for patients to apply diet and lifestyle advice. For patients who have been diagnosed more than 6 weeks prior to registration, or who are already taking one BP lowering medication, registration and randomisation may take place on the same day. Patients' demographic information and medical history will be collected at the baseline visit. Clinical biochemistry testing including electrolytes, creatinine, e-GFR and urinary protein will be conducted between the screening and randomisation visits or at the randomisation visit, but subsequently at the discretion of the responsible clinician. Diet and lifestyle advice will be given at the baseline visit along with prescription of medication. Physical examination at baseline will include standardised BP measurement, weight measurement and recording of heart rate. At 6 weeks follow-up, BP measurements will be repeated. At the final 6 month follow-up visit, in addition to BP measurement, detailed information on medication prescription and self-reported adherence, healthcare utilisation and quality of life will be obtained. Data on serious adverse events will be collected at each visit.

Registration

- Discuss participant information sheet with potentially eligible patients and obtain written consent for trial participation.
- Assess the potential participant's interest and eligibility for the trial.
- Collect demographic information (sex, date of birth).
- If eligible, arrange for baseline laboratory investigations.
- If eligible arrange randomisation visit.

Note: Baseline laboratory assessments can be performed between screening and randomisation visit or at the randomisation visit. Screening and Randomisation visit can occur on the same day.

Randomisation

- Assess eligibility according to the trial inclusion and exclusion criteria.
- Record all medication currently being taken by the participant.
- Measure blood pressure, heart rate, height, weight.
- Record baseline laboratory results.
- Record current lifestyle interventions and habits.
- Assess health-related quality of life.
- Confirm that participant is suitable to be randomised.
- Randomise participant.
- Trial Investigator reviews and prescribes drug and lifestyle treatment according to group allocation.
- Record any SAEs that have occurred since written informed consent obtained.
- Prescribe/dispense Triple Pill (Triple Pill arm only).

Week 6 & 12

- Record SAEs since previous trial visit.
- Review all medications being taken by the participant since previous trial visit and update medications summary if required.
- Review medication adherence.
- Record current lifestyle interventions and habits.
- Record number of Health care visits since previous trial visit.
- Collect and perform accountability of returned study drugs.
- Prescribe/dispense Triple Pill (Triple Pill arm only).
- Reimburse patients in the usual care arm for their medication costs to a maximum of INR 8 per day, upon presentation of receipts.

Month 06

- Record SAEs since previous trial visit.
- Review all medications being taken by the participant since previous trial visit and update medications summary if required.
- Review medication adherence.
- Record current lifestyle interventions and habits.
- Record number of Health care visits since previous trial visit.

- Collect and perform accountability of returned study drugs.
- Measure blood pressure, heart rate and weight.
- Arrange and record end of study laboratory results.
- Assess health-related quality of life.
- Trial Investigator reviews and either continues patient on marketed Triple pill or prescribes alternate BP lowering medication in line with local guidelines.
- Ask participant to report any SAEs during 30 days after the end of study visit.
- Reimburse patients in the usual care arm for their medication costs to a maximum of INR 8 per day, upon presentation of receipts.

Measurements

Blood pressure and heart rate (RAND, W6, W12 & M6) will be measured following the standardised protocol. Trial centres will be provided with calibrated electronic blood pressure monitors (OMRON) and printers for printed records of blood pressure and heart rate. *Height* (RAND) and *weight* (RAND & M6) will be measured in centimetres (cm) and kilograms (kg) respectively. Protocol required laboratory investigations; fasting blood glucose & lipids, creatinine, uric acid, electrolytes and LFT and urine protein (REG/RAND & M6) will be performed at local laboratories linked to the trial centres. Self-reported Medication adherence (RAND, W6, W12 & M6) will be measured by 7-day recall assessment. *Quality of life* (RAND and M6) will be assessed using E-Q5D.

Sample size and power calculation

Sample size calculations: Clinical trials investigating the effect of triple BP lowering vs. dual combination therapy (EXFORGE)[20] and simplification of treatment protocols including usage of dual combination BP lowering therapy (STITCH)[15] have shown absolute improvements of around 12% in BP control. Based on published data[6], we expect current usual care BP control rates in this population to be 30%-40%. A sample size of 700 patients will provide 90% power at 2=0.05, (assuming 5% loss to follow-up with only 6 months of follow-up) to allow detection of at least a 12% absolute improvement in control rates from 50% to at least 62% (relative risk of 1.24). This allows for some improvement in the usual care group's control rates that may occur because of trial participation. An extremely low rate of loss to follow-up is anticipated because of the short duration of follow-up and as per our experience in the UMPIRE trial (~3% in 15 months).

Safety Reporting

Severe adverse event (SAE)

Any untoward medical occurrence that at any dose:
- results in death,
- is life-threatening,
- requires inpatient hospitalization or prolongation of existing hospitalization,
- results in persistent or significant disability/incapacity,
or
- is a congenital anomaly/birth defect

Trial investigator responsibilities

Regardless of the suspected causality, every SAE occurring after the informed consent is signed by the participant and until 30 days after the participant has stopped study participation/stopped study

medication must be reported to the TRIUMPH coordinating centre within 24 hours. All SAEs should be reported by completing the paper and eCRF SAE form. The reports should identify participants by unique identification numbers assigned to the trial subjects rather than by the subjects' names and/or addresses. All SAEs should be promptly followed up until resolution. Worsening of conditions, recurrent episodes, and further complications if any are to be reported as follow-up of original event and these reports should be again submitted to the TRIUMPH coordinating centre within 24 hours. Investigator should assess and report the causal relationship between the study drug and the event indicating as unrelated, unlikely, possible, probable, and definite for each SAE reported. The Investigator should supply additional information (e.g. laboratory results, specialist/hospital letters, and autopsy results etc) if required by the coordinating centre. The investigator should report SAEs to their local ethics committees as per requirement of the ethics committee standard operating procedures.

TRIUMPH *coordinating centre responsibility*

The TRIUMPH coordinating centre will report SAEs to the regulatory authorities and trial centres as per the requirements of local regulation and ICH-GCP. A SUSAR is any adverse reaction that is classed as serious and is suspected to be caused by the Study drug that is NOT consistent with the information about the study drug in the IB. The Investigator Brochures will include a list of known side-effects for each drug in the trial. This should be checked with each SAE that occurs in terms of expectedness. The responsibility for SUSAR determination will be undertaken by the Triumph co-ordinating office. The TRIUMPH co-ordinating office will assess all Serious Adverse Drug Reactions (SADRs) in order to determine if the criteria for SUSAR classification are met. If an SADR is determined to be a SUSAR, the TRIUMPH Coordinating Office will report to the regulatory authorities within the required timelines. Reports will also be provided to overseeing ethics committees and Investigators as per country requirements.

STATISTICAL ANALYSES

All analyses will be performed on an intention-to-treat basis. Baseline characteristics by group will be compared using descriptive analyses. The primary analysis comparing the proportion of patients achieving target BP control at the end of follow-up will be compared using an unadjusted chi-square test. Analysis of secondary outcomes will be conducted using standard statistical procedures applicable to categorical or continuous data as appropriate. Longitudinal analyses of BP over time will be performed using generalised linear models with appropriate correlation adjustments. The frequency and nature of changes (additions, withdrawal, dose adjustments) to the BP lowering regimen in both groups will be described for both treatment groups. The number of participants discontinuing their BP lowering medication prematurely for any reason will be summarized by treatment group and by reasons for discontinuation. The incidence of all suspected serious adverse drug reactions will be summarized by treatment group.

ECONOMIC EVALUATION

A cost-effectiveness analysis, taking a health system perspective, will compare the Triple Pill strategy with usual care. This will entail a trial-based economic evaluation and a modelled economic evaluation of long-term costs and outcomes. In the trial based economic evaluation, the costs of

medications, based on actual market prices for each item including the Triple Pill, will be compared between the two groups (including follow-up of patients who fail to adhere to allocated treatment). Hospitalisations, medications, tests and medical consultations will be recorded at baseline and 6 months and costed at prevailing rates. In addition, the measures of self-reported health based on the EQ5D administered at each visit enable estimates of quality of life.[22] The trial-based economic evaluation will estimate the incremental cost effectiveness per responder (as defined by achievement of BP control at follow-up as per primary outcome) and the incremental cost per Quality Adjusted Life Year (QALY) gained. A modelled economic evaluation will be done, using a state transition or Markov model, to capture costs and outcomes which occur beyond the period of the trial. This will enable quality of life and survival to be examined beyond the 6-month follow-up. Using the Markov model, patients in usual care and the Triple Pill based strategy would be hypothetically tracked over an extended period to capture their progress over various health states. Given very low clinical event rates expected in the trial, the model will rely mainly on literature review to set parameters such as probabilities of transition from good health to major morbidity (for example, stroke), mortality rates, medication safety, costs and quality of life. With appropriate discounting, estimates of long-term costs and outcomes will be derived from the model. Sensitivity analyses will be conducted on the discount rate, uncertainty in outcome estimates and assumptions made in the costings.

PROCESS EVALUATION

A process evaluation will explore the barriers and enablers to implementing a Triple Pill-based strategy to enhance prescriber and consumer adherence to the indicated therapies.[23] This will inform the interpretation of the key findings of the trial, considerations regarding transferability of the results to other settings, and will assist in translating findings into policy and practice.[24] Semi-structured interviews (audio-recorded) will be conducted with key informants and staff in participating centres. The evaluation will aim to explore their views on the advantages, disadvantages, acceptability and applicability of the Triple Pill strategy along with accounts of how participation in the study itself changed their prescribing behaviour. At the end of follow-up, selected study participants will be interviewed (audio-recorded) to explore their views on the benefits, disadvantages and acceptability of the Triple Pill. Recruitment of staff and participants for interviews will be purposive, to maximise variation according to criteria including location, service size, role and degree of participation (for staff); and location, sex, age and outcomes (for patients). Analysis of the interview data will be primarily thematic[25] and will be informed by the realistic evaluation model of Pawson and Tilley[26], which seeks to understand human choices, actions and attitudes, within the context of the systems in which these players operate.

A multi-disciplinary team will undertake the analysis to ensure that its interpretation is sensitive to different perspectives. Using the constant comparative method [27], analyses will occur concurrently with interviews and themes will be continually modified by the team in the light of additional data. NVivo (QSR International, Melbourne, Victoria) will be used to assist with data management. This software is particularly useful when there are multiple coders across several sites, allowing us to bring local, context-rich analyses to interpretation of the findings.

DATA REVIEW AND MANAGEMENT

Study monitoring

At an investigator meeting and during site initiations the TRIUMPH representative will review the study protocol and procedures with the investigators and site staff. Adequate training will be given to RCC and trial centre staff before the study initiation and on ongoing basis, as and when required. TRIUMPH monitors will do interim site monitoring visits (as per the monitoring manual) and communication by telephone, mail and e-mail will be used as needed to supplement site visits when appropriate to oversee the conduct of the study and to check the completeness and accuracy of records in adherence to protocol, manual of procedures and ICH-GCP. The investigator should allow the monitors, the persons responsible for the audit, the representatives of the Ethics Committee, and of the Regulatory Authorities to have direct access to source data / documents.

Data collection

TRIUMPH will use an eCRF for data collection. Trial centre staff will be trained by TRIUMPH representative on eCRF. Delegated site staff will enter data in eCRF on a regular basis and any data queries will be resolved in a timely manner. The investigator will sign the eCRF confirming and certifying that the data entered is accurate and complete.

Quality control

The data management team at the George Institute for Global Health will be responsible for all data processing and will perform quality checks.

ETHICS AND REGULATORY COMPLIANCE

This study will be designed, conducted, analysed and reported in compliance with ICH-GCP and local regulatory requirements. Study approval/no objection certificate from the office of Drug Controller General of India (DCGI), Health Ministry Screening Committee (HMSC) and ethics committees at the participating trial centres and the funds administering institution (The University of Sydney) will be gained before study initiation.

Informed consent

Participants will be given adequate explanation about the study and will be given ample time to consider their trial participation. They will be given the opportunity to ask questions about the trial and what their participation involves and will receive full answers from the investigator. Prior to a subject's participation in the trial, a written informed consent form (using appropriately translated versions where appropriate) should be signed and personally dated by the subject or by the subject's legally acceptable representative, and by the person who conducted the informed consent discussion. If a subject is unable to read or if a legally acceptable representative is unable to read, an impartial witness should be present during the entire informed consent discussion.

Confidentiality

All documents and data relating to this study are strictly confidential. Documents given to the investigators and trial centres by the coordinating centres should not be disclosed to other parties without the written approval of the sponsor. The investigator and his team should maintain confidentiality of the identification of all study participants and assure security and confidentiality of study data and documents.

ADMINISTRATIVE SECTION

Steering Committee

Steering committee will be the decision making body. It will provide scientific direction to the study; approve protocol, monitor study progress and plan dissemination. The steering committee will meet on a regular basis through teleconference or other modes of communication at regular intervals to discuss study progress.

Operations Committee

The Operations Committee will include representatives from the coordinating centres (The George Institute and Centre for Chronic Disease Control-Delhi) and will be responsible for the management of the study including study start-up activities, trial centre selection, conducting investigator's meeting, trial centre initiation, interim monitoring, and study close out. The Project Management Team will provide day to day schedule management support and will be responsible for initiating the production and collection of interim reports necessary to produce the periodic and final project reports to the NHMRC.

Insurance

Dr Reddy's Laboratories and The George Institute for Global health shall at all times indemnify the study investigators and their staff from claims that may be made against them for any injury sustained by a study participant as a consequence of effects of the 'Triple Pill' used in the study in accordance with this protocol. This indemnity will be outlined in detail in the agreement between The George Institute and each participating centre.

Quality Control and Quality Assurance

Quality Control will be performed according to The George Institute for Global Health procedures. The trial can be audited by a quality assurance representative of The George Institute for Global Health or by an external service provider.

Record retention

All essential trial documents (including but not limited to those documents defined by ICH-GCP as essential documents) will be archived and retained at the trial centre for at least 15 years after the completion of the study. At the end of such period, the investigator shall notify in writing the project management team of its intent to destroy all such study material.

Ownership, Disclosure of Data and Publication

The steering committee will have full ownership of the study data, its storage, and dissemination. All publications will be reviewed and approved by the steering committee which will be named on all reports. The research teams, collaborating doctors and their respective centres will be named and trial participants acknowledged in the final report and in publications arising from the trial.

Funding

This study is funded by a National Health and Medical Research Council (NHMRC) and Global Alliance for Chronic Disease Implementation Research on Hypertension in Low & Middle Income Countries grant (ID 1040152). The Triple Pill will be supplied free of charge by Dr Reddy's Laboratories Limited.

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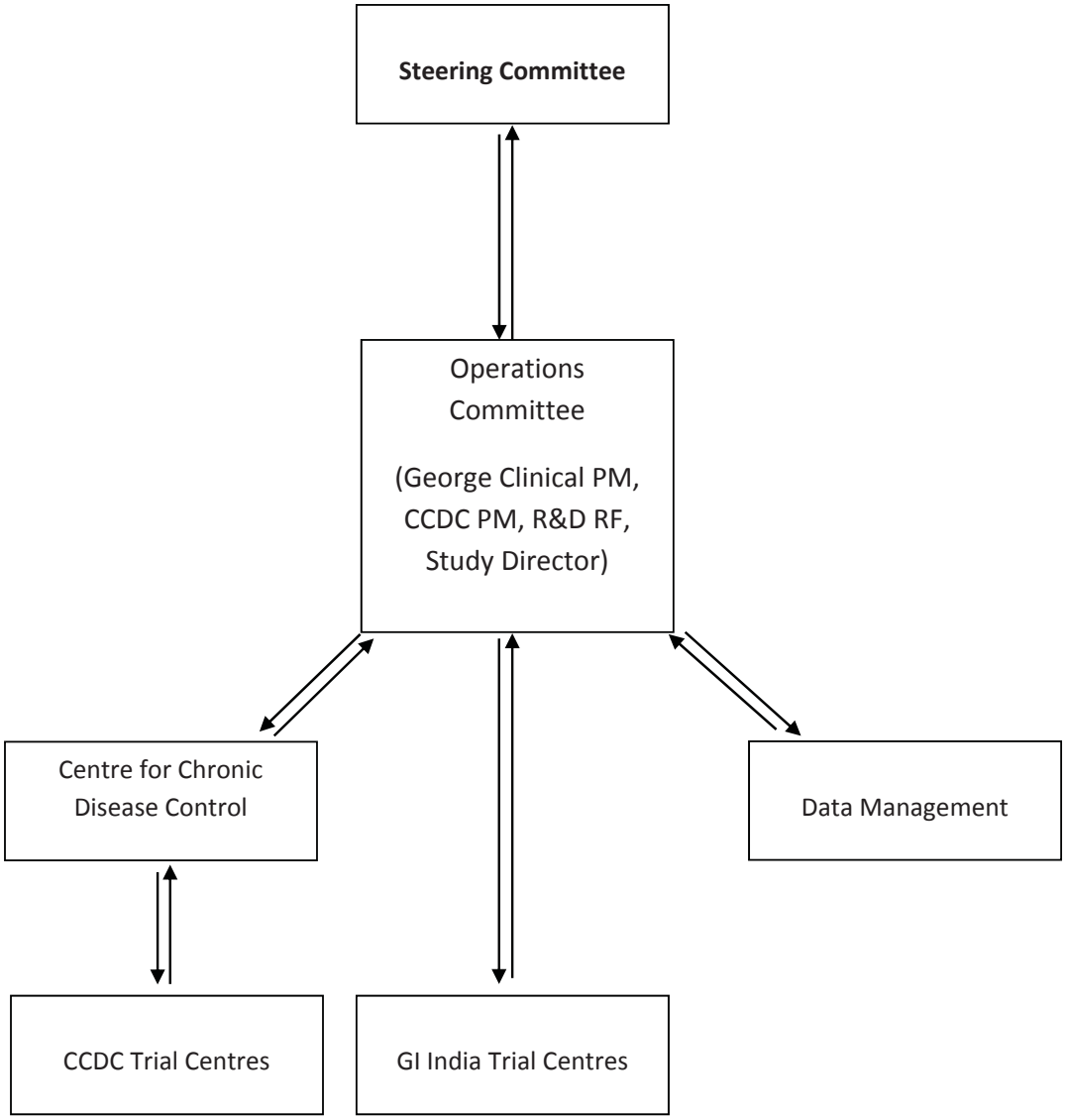
APPENDIX 1

STUDY ORGANIZATION



APPENDIX 2
PROTOCOL SIGNATURE PAGE

The signatures below constitute approval of this protocol by the signatories and provide the assurances that this study will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, regulatory requirement and ICH-GCP.

SPONSOR

The George Institute for Global Health

Signature _____

Date 14 November 2012

Name TIMOTHY REGAN

CHIEF INVESTIGATOR

Prof Anushka Patel
The George Institute for Global Health

Signature _____

Date 14th NOVEMBER, 2012

INVESTIGATOR

Trial centre _____

_____

_____

Signature _____

Date _____

Name _____

Title _____

Study	**TRIUMPH - TRI**ple Pill vs. **U**sual care **M**anagement for **P**atients with mild-to-moderate **H**ypertension
Study Number	1041052
Study treatment	Triple blood pressure lowering Pill vs. Usual care
Protocol	Version 5.0 – 23rd February, 2016
Trial registration	Clinical Trials Registry – India number: CTRI/2013/02/003388 Australian New Zealand Clinical Trials Registry number: ACTRN12612001120864 Sri Lankan Clinical Trial Registry number: SLCTR/2015/020
Funder	National Health and Medical Research Council, Australia
Sponsor	The George Institute for Global Health Level 3, 50 Bridge St, Sydney NSW 2000 Australia Postal Address: PO Box M201, Missenden Rd, NSW 2050 Australia T +61 2 9993 4557, F +61 2 9993 4502 E: rwebster@georgeinstitute.org.au

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Study Funder
National Health and Medical Research Council
Application Number 1040152

2. LIST OF ABBREVIATIONS

ACE inhibitors	Angiotensin Converting Enzyme inhibitors
BP	Blood Pressure
cm	Centimetres
CIOMS	Council for International Organizations of Medical Sciences
CRF	Case Report Form (eCRF; electronic Case Report Form)
CV	Cardiovascular
CVD	Cardiovascular Disease
CKD	Chronic Kidney Disease
DBP	Diastolic Blood Pressure
DM	Diabetes Mellitus
eGFR/GFR	estimated Glomerular Filtration Rate/Glomerular Filtration Rate
EoS	End of Study
EQ-5D	European Quality of life-5 Dimensions
F/U	Follow up
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
HDL-	High Density Lipoprotein cholesterol
HR	Heart Rate
IB	Investigator's Brochure
ICH	The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for
INR	Indian Rupee
LFT	Liver Function Test
kg	Kilogram
LDL-	Low Density Lipoprotein cholesterol
mg	Milligram
mmHg	Millimetres of mercury
NHMRC	National Health and Medical Research Council
QALY	Quality Adjusted Life Year
REG	Registration
RAND	Randomisation
SAE	Serious Adverse Event
SBP	Systolic Blood Pressure
SUSAR	Suspected Unexpected Serious Adverse Reaction

3. PROTOCOL SYNOPSIS

Study design
The study is a prospective, open, randomised controlled clinical trial (n=700) of a fixed dose combination blood pressure lowering pill ("Triple Pill")-based strategy compared to usual care among individuals with persistent mild-to-moderate hypertension on no or minimal drug therapy, augmented by a cost-effectiveness analysis and a formal process evaluation.

Aims
To assess whether provision of a Triple Pill compared to usual care improves blood pressure (BP) control at 6 months. Secondary outcomes include earlier BP control, mean change in BP, tolerability of treatment, self-reported adherence, quality of life, safety, acceptability, and healthcare resource consumption.

Participant recruitment
The study will be conducted within at least 11 trial centres in Sri Lanka. The major inclusion criteria are participants with persistent hypertension that the investigator feels requires initiation of drug therapy (for treatment naïve patients) or up-titration of drug therapy (for patients on single drug therapy).

Randomisation and study medication
Eligible participants will be randomised to treatment with the Triple Pill or to continued usual care:

- *Triple Pill*:
  - Strength 1: Low dose: Telmisartan 20mg, Amlodipine 2.5mg, Chlorthalidone 12.5 mg
  - Strength 2: High dose: Telmisartan 40mg, Amlodipine 5mg, Chlorthalidone 25 mg
- *Usual care*: Usual BP lowering medications prescribed at the discretion of the responsible clinician.

For both groups any advice and /or other interventions relating to other BP lowering measures, including those relating to lifestyle modification, will continue at the discretion of the responsible clinician. Similarly, all changes to medications in both groups will be at the discretion of the responsible clinician.

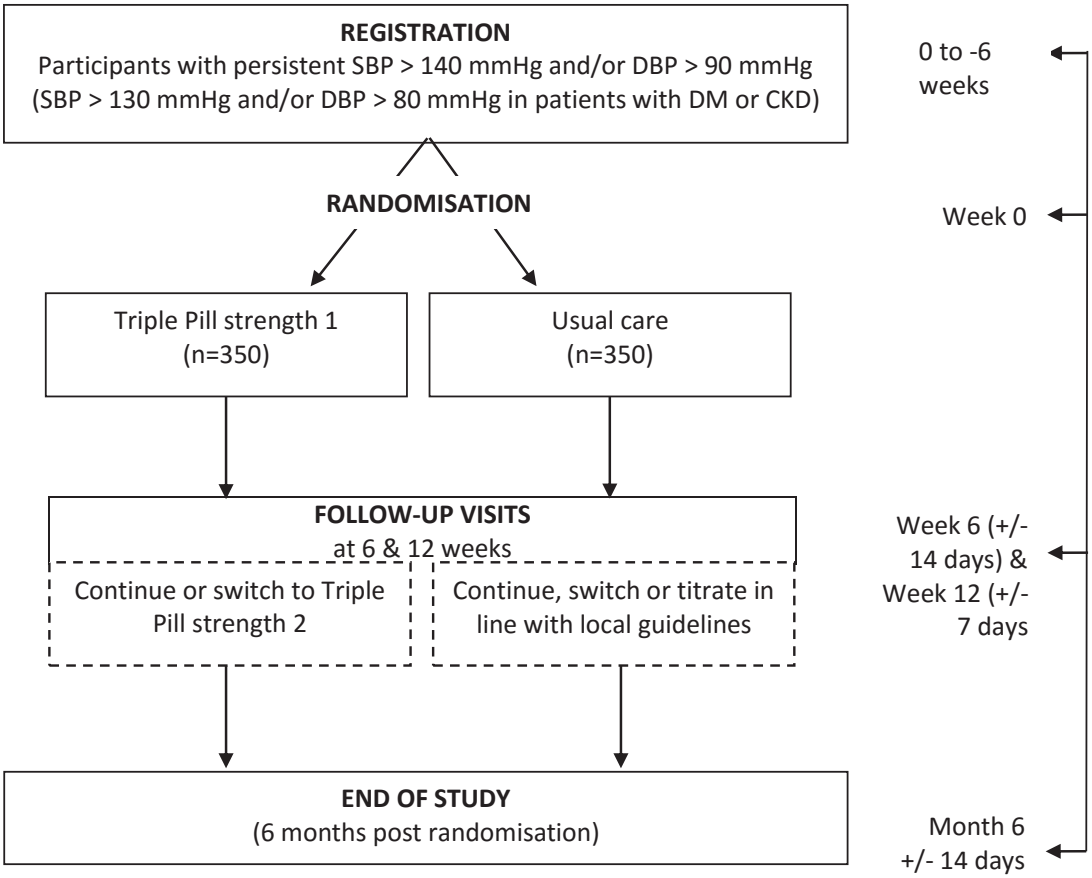
Data collection and follow-up
Participants will be followed up for 6 months. Blood pressure will be measured at baseline, 6 weeks, 12 weeks and the end of the study (6 month) visit. Information on safety and secondary outcomes will also be collected at these visits.

Outcomes
Primary outcome: Proportion of participants achieving target BP at the end of 6 months follow up: SBP < 140 mmHg and DBP < 90 mmHg (SBP < 130 mmHg and DBP < 80mmHg for participants with diabetes and/or chronic kidney disease).

Secondary outcomes: Proportion of participants with BP control at 6 and 12 weeks; mean change in SBP and DBP; tolerance to treatment; use of health care services; self-reported BP lowering medication use; quality of life.

Statistical Power
A sample size of 700 participants will provide 90% power at 2p=0.05 (assuming 5% loss to follow-up with only 6 months of follow-up) to allow detection of at least a 12% absolute improvement in control rates from 50% to at least 62% (relative risk of 1.24).

4. STUDY SCHEMATIC



5. BACKGROUND

a. Hypertension and hypertension control in India and Sri Lanka

Hypertension has emerged as a significant public health problem for the developing world. WHO estimates indicate high blood pressure is the leading cause of premature death globally and the third leading cause of disease burden, with the majority of the burden falling in developing countries.[1]

In Sri Lanka, high blood pressure is now the second highest risk factor for disease burden.[8] Ischemic heart disease and stroke (for which hypertension is a significant risk factor) rank as the first and third highest causes of premature death.[8] Data on hypertension prevalence in Sri Lanka is sparse, however estimates in published population based surveys range between 19 and 30% (both urban and rural populations included)[9-11] and up to 40% in a recent WHO South East Asian report.[12] Of those identified with hypertension in the population based surveys, between 30 and 50% were new diagnoses.[10,11] When combined with population size (approximately 22 million, of whom 60% are >25 years[13]), up to 5.3 million Sri Lankans currently have hypertension and about half of these cases are undiagnosed. Of those that are diagnosed, the Ceylon College of Physicians[14] estimates that about 1 in 5 are adequately controlled. These data indicate that hypertension is currently a major public health challenge in Sri Lanka.

Hypertension management strategies globally, such as those endorsed by most practice guidelines including in Sri Lanka, have traditionally focused on "tailored therapy" and "stepped-care" approaches. These tend to be costly and time consuming for doctor and patient, ignore the recognition that contemporary BP targets almost always necessitate additional medication and ignore the auto-regulatory mechanisms that limit responsiveness to a single drug administered alone.

b. Evidence on potential benefits of regimen simplification and use of 2-drug combination pills

Most patients with hypertension require BP lowering medication from two or more classes to achieve adequate control.[15] The need for titration of medication and addition of multiple classes of drug requires multiple physician visits and this in itself triggers poor adherence to prescribed medication and poor attendance at scheduled visits.[16] The requirement to take multiple medications in complex regimes also results in poor adherence.[17] For physicians, the need for repeated up-titrating or adding extra medications can lead to inertia and complicit acceptance of inadequate BP control.[18, 19]

Dual combination BP lowering medication has been shown to improve achieved BP reductions as well as cardiovascular event rates.[20] Initiating anti-hypertensive treatment with dual combination therapy not only accelerates the time taken to achieve control but also attains a lower final target.[21,22] For the patient, improved adherence has also been demonstrated without adversely affecting the side effect profile.[23] Further benefits in BP control are also available via simplifying up-titration regimes.[22]

c. Evidence on hypertension combination pills containing more than two medications

There are sound pharmacological principles to expect the maximum benefit to side effect ratio from

fixed dose triple combinations.[24-26] In short, benefits of each component are additive, and low doses typically avoid most side effects while achieving the large part of the potential blood pressure reduction to any given drug. Thus for example, three half-dose medications would typically lower blood pressure about as much as two full-dose medications, but with fewer side effects.[24]

However, a number of important questions remain unanswered. The triple BP lowering pills that have recently become available in high income countries, and the small number being used in South Asia at present, have focused exclusively on severe hypertension that remains uncontrolled with full dose dual combination therapy. While an important group, this is a small fraction of people with hypertension. Furthermore, previous trials have been within the mode of traditional stepped care, and have not tested the integration of a fixed dose triple combination within a simplified regimen. For example, the recent trial of Exforge[27] involved patients with moderate or severe hypertension with an average baseline BP of 170/107 mmHg. Patients were randomised to one of 4 arms to receive 8 weeks of treatment with either amlodipine /valsartan /HCTZ 10 /320 /25 mg or dual therapy with 2 of the previously mentioned three components. Perhaps unsurprisingly, this trial showed that patients on triple therapy achieved better BP reductions than patients on dual combination therapy.

To date no clinical trial has tested the benefits or cost-effectiveness of combination therapy with three, low dose BP lowering drugs in lower grades of hypertension. It is necessary to obtain direct evidence that the above strategies will be effective in each local context in which they are to be applied, (in this case, clinics in Sri Lanka) as the impact of such a strategy will be affected by local health care systems and the population utilizing the strategy. It is particularly pertinent to test these questions in a setting with high prevalence of untreated and uncontrolled hypertension, and highly constrained resources.

6. AIM & OBJECTIVES

We aim to understand the effectiveness, cost-effectiveness and acceptability of a simplified strategy using a fixed dose combination 3-in-1 blood pressure lowering pill ("Triple Pill") for the management of hypertension in Sri Lanka

Specific objectives are

- To assess whether hypertension control is improved with a strategy of early use of a Triple Pill compared to usual care
- To determine the cost effectiveness of such a strategy
- To determine whether such a strategy is acceptable to clinicians and patients

7. RESEARCH PLAN

a. Study design

Randomised, open, controlled, parallel-group trial (N=700) of a simplified treatment initiation and titration strategy incorporating the use of a BP lowering 'Triple Pill' vs. usual care in patients with persistent mild-to-moderate hypertension, augmented by cost-effectiveness analysis and process evaluation.

b. Participant recruitment

Participants will be recruited from at least 11 trial centers (general practice or cardiology clinics) located in urban/sub-urban areas of Sri Lanka. Recruitment using advertisements (e.g. study posters) may be used if required to meet the recruitment targets.

c. Study participants

Inclusion criteria

- Adults ≥18 years of age.
- The investigator is satisfied that the patient has persistent hypertension (SBP>140mmHg and/or DBP>90mmHg; or SBP>130mmHg and/or DBP>80mmHg in patients with diabetes mellitus or chronic kidney disease) requiring initiation of pharmacological treatment (in patients not taking drug therapy) or up-titration of pharmacological treatment (in patients taking single drug therapy)
- Trial Investigator is unsure as to whether a Triple Pill based therapy or usual care is better.

Exclusion Criteria

- On two or more BP lowering drugs
- Severe or uncontrolled BP (SBP > 180 mmHg and/or DBP > 110 mmHg)
- Accelerated hypertension or hypertension at a level where the physician feels that slower up-titration of treatment is appropriate (e.g. elderly patients)
- Contraindication to any of the components of the Triple Pill
- Pregnancy, breast feeding, childbearing potential and not on effective medically accepted method of child birth control.
- Unstable medical condition or known situation where medication regimen might be altered for a significant length of time, e.g. current acute cardiovascular event, planned coronary bypass graft operation, dialysis.
- Participants with clinically significant abnormal laboratory value judged to be unsuitable for trial participation by the investigator.

d. Randomisation

Randomisation will be conducted through a central, computer-based randomisation service, and will be stratified by study centre, and prescription of BP lowering therapy at baseline. The randomisation service will be built in the eCRF. Participants will be randomised 1:1 to either Triple Pill or usual care.

e. Study treatments

Triple Pill arm

For participants randomised to Triple Pill arm, their previous BP lowering medications will be withdrawn (if applicable) and treatment will commence at the lower strength of Triple Pill with the option to titrate upwards to strength 2 at subsequent follow-up visits. The dosage will be one Triple Pill once daily for the trial duration (i.e. 6 months). Timing of the dosage will be at the discretion of the responsible clinician. The two strengths of Triple Pill are as below.

Strength 1: Low dose*:* Telmisartan 20mg, Amlodipine 2.5mg, Chlorthalidone 12.5mg
Strength 2: High dose: Telmisartan 40mg, Amlodipine 5mg, Chlorthalidone 25mg

Triple Pill (for Triple Pill arm participants) will be dispensed free of charge from the trial centre/pharmacy at Randomisation, 6 week, and 12 week visits. Additional prescription during follow up can take place any time if the strength of the Triple Pill or the dose of usual care BP lowering drugs is required to be changed.

Usual care arm

Participants will continue to receive their usual BP management provided by the responsible clinician according to current guidelines. Participants will get their supply of prescribed drugs as per usual practice. In Sri Lanka, participants will receive their drugs free of cost, as per usual practice.

Concomitant treatments

Prescription of additional medications on top of Triple Pill (if BP remains uncontrolled on the higher strength of the Triple Pill) will be unrestricted and at the discretion of the responsible clinician. For prescription of concomitant treatments, contraindications for components of Triple Pill and drug-drug interactions should be taken i n to consideration as per the monographs of drugs prescribed. All other medical care will be delivered according to local standards by the responsible clinician.

Withdrawal of Triple Pill

Post randomisation, Triple Pill can be withdrawn anytime if significant intolerance or contraindication develops. Further treatment should commence at the discretion of the responsible clinician in line with local guidelines. Such participants will still be followed-up and all trial assessments will be performed as per the protocol until the end of study unless the participant withdraws consent or the investigator withdraws the participant from the study.

f. Blinding

Blinding of trial participants to study treatment allocation will not be possible because the comparator is usual care. Therefore this is an open-label trial. Bias that may arise from the unblinded measurement of blood pressure will be minimised by audited comparison of CRF entries with the printed values of automated blood pressure-measuring device by the trial monitor. During the review of the results within the trial team, all investigators will be blinded to treatment allocation.

g. **Outcomes**

Primary outcome

Proportion of participants achieving target BP at the end of 6 months follow up: SBP < 140 mmHg and DBP < 90 mmHg (SBP < 130 mmHg and DBP < 80 mmHg for patients with diabetes and/or chronic kidney disease).

Secondary outcomes

- Proportion of participants with BP control at 6 and 12 weeks
- Mean change in SBP and DBP at 6 months
- Tolerance to treatment at 6 months
- Use of health care services (hospitalizations, medical consultations, tests)
- Self-reported BP lowering medication use (7-day recall) at 6 months – adherence defined

as the participant taking the drug for at least 4 out of the last 7 days 6 months

- Quality of life at 6 months

h. Visit schedule and assessments

Timing	-6 to 0 weeks (REG)	Week 0 (RAND)	Week 6 (W6)	Week 12 (W12)	Month 06 (M6/EoS)
Visit window (days)			**+/- 14**	**+/- 7**	**+/- 14**
Informed consent	X				
Eligibility (inclusion/exclusion) criteria	X	X			
Participant demographics	X				
Medical history	X	X			
Height		X			
Weight		X			X
Blood pressure & heart rate	X	X †	X	X	X
Fasting blood glucose & lipids	X**	X			X
Creatinine, uric acid, electrolytes and LFTs	X**	X			X
Urine protein (albumin) test	X**				X
Socio-economic information		X			
Pregnancy status	X**				
Review of medications adherence		X	X	X	X
Reason for stopping BP lowering medications (if any)			X	X	X
CV Lifestyle interventions		X	X	X	X
Health care visits		X	X	X	X
Serious Adverse Events		X	X	X	X
Quality of life (EQ-5D)		X			X
Dispensation of Triple Pill (Triple Pill arm only)		X	X	X	
Triple Pill accountability			X	X	X
Participant acceptability					X
Investigators acceptability (Triple Pill arm only)					X

** *Either at REG or RAND or between these visits. Results from tests taken within the last 7 weeks prior to REG are also acceptable.*

† *Not required if REG and RAND occurs on the same day*

Participants will attend clinic visits at screening, randomisation, 6 weeks post randomisation, 12 weeks post-randomisation and 6 months post-randomisation. For all patients, registration and randomization visits may occur up to 6 weeks apart if the investigator feels that additional investigation is required prior to commencing drug treatment. However if patients satisfy all inclusion criteria, and the investigator believes immediate commencement of treatment is appropriate, registration and randomisation may take place on the same day. Participants' demographic information and medical history will be collected at the baseline visit. Clinical biochemistry testing including electrolytes, creatinine, and urinary protein will be conducted at baseline. If patient has had required bloods taken in the 7 weeks prior to registration these bloods are acceptable as baseline blood tests. Otherwise, sites should arrange bloods to be taken either between screening and randomisation visits, or at the randomisation visit. Blood tests should be repeated at EoS (at 6 months).Diet and lifestyle advice will be given at the baseline visit along with prescription of

medication. Physical examination at baseline will include standardised BP measurement, weight measurement and recording of heart rate. At 6 & 12 weeks follow-up, BP measurements will be repeated. At the final 6 month follow-up visit, in addition to BP measurement, detailed information on medication prescription and self-reported adherence, healthcare utilisation and quality of life will be obtained. Data on serious adverse events will be collected at each visit.

Registration

- Assess potential participant's interest and eligibility for the trial.
- Discuss participant information sheet and obtain written consent for trial participation.
- Collect demographic information (sex, date of birth).
- If eligible, arrange for baseline laboratory investigations.
- If eligible arrange randomisation visit.

Note: Baseline laboratory assessments can be performed between screening and randomisation visit or at the randomisation visit. Screening and Randomisation visit can occur on the same day.

Randomisation

- Assess eligibility according to the trial inclusion and exclusion criteria.
- Record all medication currently being taken by the participant.
- Measure blood pressure, heart rate, height, weight.
- Record baseline laboratory results.
- Record current lifestyle interventions and habits.
- Assess health-related quality of life.
- Confirm that participant is suitable to be randomised.
- Randomise participant.
- Trial Investigator reviews and prescribes drug and lifestyle treatment according to group allocation.
- Record any AEs that have occurred since written informed consent obtained.
- Prescribe/dispense Triple Pill (Triple Pill arm only)

Week 6 & 12

- Record AEs since previous trial visit.
- Review all medications being taken by the participant since previous trial visit and update medications summary if required.
- Review medication adherence.
- Record current lifestyle interventions and habits.
- Record number of health care visits since previous trial visit.
- Collect and perform accountability of returned study drugs.
- Prescribe/dispense Triple Pill (Triple Pill arm only).
- R

Month 06

- Record AEs since previous trial visit.
- Review all medications being taken by the participant since previous trial visit and update medications summary if required.
- Review medication adherence.

- Record current lifestyle interventions and habits.
- Record number of health care visits since previous trial visit.
- Collect and perform accountability of returned study drugs.
- Measure blood pressure, heart rate and weight.
- Arrange and record end of study laboratory results.
- Assess health-related quality of life.
- Participant acceptability assessment
- Investigator acceptability assessment (Triple Pill arm only)
- Trial Investigator reviews and either continues participants on marketed Triple pill (if available) or prescribes alternate BP lowering medication in line with local guidelines.
- Ask participant to report any AEs during 30 days after the end of study visit.
-
- Invitation to a sample of participants to participate in process evaluation interview

i. Measurements

Blood pressure and heart rate (at REG, RAND, W6, W12 & M6) will be measured following the standardised protocol. Trial centres will be provided with calibrated electronic blood pressure monitors (OMRON) and printers for printed records of blood pressure and heart rate. *Height* (at RAND) and *weight* (at RAND & M6) will be measured in centimetres (cm) and kilograms (kg) respectively. Protocol required laboratory investigations; fasting blood glucose & lipids, creatinine, uric acid, electrolytes and LFT and urine protein (at REG/RAND & M6) will be performed at a central laboratory (in Sri Lanka) following usual procedures of sample collection and analysis. Self-reported medication adherence (at RAND, W6, W12 & M6) will be measured by 7-day recall assessment. *Quality of life* (at RAND and M6) will be assessed using E-Q5D questionnaire.

j. Sample size and power calculation

Sample size calculations: Clinical trials investigating the effect of triple BP lowering vs. dual combination therapy (EXFORGE)[20] and simplification of treatment protocols including usage of dual combination BP lowering therapy (STITCH)[15] have shown absolute improvements of around 12% in BP control. Based on published data[6], we expect current usual care BP control rates in this population to be 30%-40%. A sample size of 700 participants will provide 90% power at 2=0.05, (assuming 5% loss to follow-up with only 6 months of follow-up) to allow detection of at least a 12% absolute improvement in control rates from 50% to at least 62% (relative risk of 1.24). This allows for some improvement in the usual care group's control rates that may occur because of trial participation. An extremely low rate of loss to follow-up is anticipated because of the short duration of follow-up and as per our experience in the UMPIRE trial (~3% in 15 months).

k. Safety Reporting

Adverse Event (AE)

Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An adverse event (AE) can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a

medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

Severe Adverse Event (SAE)
Any untoward medical occurrence that at any dose; results in death, is life-threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, or is a congenital anomaly/birth defect.

Trial site investigators, and sponsor (or representative) will adhere to local ethical and regulatory requirements of safety reporting.

Trial investigator responsibilities
Regardless of the suspected causality, every AE occurring after the informed consent is signed by the participant and until 30 days after the participant has stopped study participation/stopped study medication must be reported by the site investigators as per the local regulatory and ethical requirements. All SAEs should be reported by completing the paper (CIOMS or relevant form) and eCRF SAE form. The reports should identify participants by unique identification numbers assigned to the trial subjects rather than by the subjects' names, and/or addresses. All SAEs should be promptly followed up until resolution. Worsening of conditions, recurrent episodes, and further complications if any are to be reported as follow-up of original event. The Investigator should supply additional information (e.g. laboratory results, specialist/hospital letters, and autopsy results etc) if required by the Coordinating Centre.

TRIUMPH *Coordinating Centre responsibility*
The TRIUMPH Coordinating Centre will report SAEs occurring at the trial centers to the regulatory authorities, ethics committee and trial investigators as per the local ethical and regulatory requirements.

A SUSAR is any adverse reaction that is classed as serious and is suspected to be caused by the Study drug that is NOT consistent with the information about the study drug in the Investigator Brochure (IB). The IB will include a list of known side-effects for each drug in the trial. This should be checked with each SAE that occurs in terms of expectedness. The responsibility for SUSAR determination will be undertaken by the Triumph Coordinating centre. The TRIUMPH Coordinating Centre will assess all Serious Adverse Drug Reactions (SADRs) in order to determine if the criteria for SUSAR classification are met. If an SADR is determined to be a SUSAR, the TRIUMPH Coordinating Office will report to the regulatory authorities within the required timelines. Reports will also be provided to overseeing ethics committees and Investigators as per country requirements.

l. Data Safety & Monitoring Board (DSMB)
An Independent DSMB will evaluate interim safety and efficacy data at regular intervals and advise steering committee on continuing the trial.

m. Early Discontinuation of Individual Participants
In case of early discontinuation of trial medication by trial participant, reason for discontinuation will

be recorded in the case record form. A discontinuation occurs when an enrolled participant permanently ceases taking the trial medication, regardless of the circumstances, prior to completion of the trial. A discontinuation must be reported immediately to the TRIUMPH Coordinating Centre.

Typically, participants may discontinue trial medication for the following reasons:

a. At the request of the participant.
b. If the investigator considers that a participant's health will be compromised due a contraindication to one or more components of the Triple Pill, or due to adverse events or concomitant illness that develops after entering the trial.
c. The trial is terminated (e.g. if in the opinion of the DSMB interim data indicate that it might not be justifiable to continue the trial, the Steering Committee may terminate the trial).

For any participant who discontinues trial medication before the trial is completed, the investigator will:

a. Complete the case record form including any summary sheet, indicating the date of and explanation for the early discontinuation of trial medication.
b. If necessary, arrange for alternative cardiovascular medications to be prescribed for the discontinued participant
c. Follow the participant in the usual way to the end of the trial despite discontinuation of the trial medication**.**

Participants will be informed at the time of enrolment and consenting that, they are free to withdraw from the study at any time and for any reason without influencing any aspect of their usual medical care, their participation in this study may be terminated by the investigator if the study itself is terminated.

n. Post-trial access to Triple pill

Participants will be asked to stop and return any remaining Triple pill at the end of their participation in the study. The responsible clinician will switch participants to appropriate therapy in line with local standard of care.

8. STATISTICAL ANALYSES

All analyses will be performed on an intention-to-treat basis. Baseline characteristics by group will be compared using descriptive analyses. The primary analysis comparing the proportion of participants achieving target BP control at the end of follow-up will be compared using an unadjusted chi-square test. Analysis of secondary outcomes will be conducted using standard statistical procedures applicable to categorical or continuous data as appropriate. Longitudinal analyses of BP over time will be performed using generalised linear models with appropriate correlation adjustments. The frequency and nature of changes (additions, withdrawal, dose adjustments) to the BP lowering regimen in both groups will be described for both treatment groups. The number of participants discontinuing their BP lowering medication prematurely for any reason will be summarized by treatment group and by reasons for discontinuation. The incidence of all suspected serious adverse drug reactions will be summarized by treatment group.

9. ECONOMIC EVALUATION

A cost-effectiveness analysis, taking a health system perspective, will compare the Triple Pill strategy with usual care. This will entail a trial-based economic evaluation and a modelled economic evaluation of long-term costs and outcomes. In the trial based economic evaluation, the costs of medications, based on actual market prices for each item including the Triple Pill, will be compared between the two groups (including follow-up of participants who fail to adhere to allocated treatment). Hospitalisations, medications, tests and medical consultations will be recorded at baseline and 6 months and costed at prevailing rates. In addition, the measures of self-reported health based on the EQ5D administered at each visit enable estimates of quality of life.[28] The trial-based economic evaluation will estimate the incremental cost effectiveness per responder (as defined by achievement of BP control at follow-up as per primary outcome) and the incremental cost per Quality Adjusted Life Year (QALY) gained. A modelled economic evaluation will be done, using a state transition or Markov model, to capture costs and outcomes which occur beyond the period of the trial. This will enable quality of life and survival to be examined beyond the 6-month follow-up. Using the Markov model, participants in usual care and the Triple Pill based strategy would be hypothetically tracked over an extended period to capture their progress over various health states. Given very low clinical event rates expected in the trial, the model will rely mainly on literature review to set parameters such as probabilities of transition from good health to major morbidity (for example, stroke), mortality rates, medication safety, costs and quality of life. With appropriate discounting, estimates of long-term costs and outcomes will be derived from the model. Sensitivity analyses will be conducted on the discount rate, uncertainty in outcome estimates and assumptions made in the costings.

10. PROCESS EVALUATION

A process evaluation will explore the barriers and enablers to implementing a Triple Pill-based strategy to enhance prescriber and consumer adherence to the indicated therapies.[29] This will inform the interpretation of the key findings of the trial, considerations regarding the transferability of the results to other settings, and will assist in translating the findings into policy and practice.[30] Semi-structured interviews (audio-recorded) will be conducted with key informants and staff in participating centres. The evaluation will aim to explore their views on the advantages, disadvantages, acceptability and applicability of the Triple Pill strategy along with accounts of how participation in the study itself changed their prescribing behaviour. At the end of follow-up, selected study participants will be interviewed (audio-recorded) to explore their views on the benefits, disadvantages and acceptability of the Triple Pill. Recruitment of staff and participants for interviews will be purposive, to maximise variation according to criteria including location, service size, role and degree of participation (for staff); and location, sex, age and outcomes (for patients). Analysis of the interview data will be primarily thematic[31] and will be informed by the realistic evaluation model of Pawson and Tilley[32], which seeks to understand human choices, actions and attitudes, within the context of the systems in which these players operate.

A multi-disciplinary team will undertake the analysis to ensure that its interpretation is sensitive to different perspectives. Using the constant comparative method [33], analyses will occur concurrently with interviews and themes will be continually modified by the team in the light of additional data. NVivo (QSR International, Melbourne, Victoria) will be used to assist with data

management.

11. TRIPLE PILL MANAGEMENT

a. Manufacture, supply and storage

Pharmaceutical Packaging Professionals (PPP) Pty Ltd, a GMP and Therapeutic Goods Administration certified company in Australia will produce and distribute over-encapsulated Triple Pills for the purpose of this trial. To produce Triple pill, PPP will purchase commercial stock of component medications and place them into capsules (over-encapsulation). PPP will arrange export of the pills to the drug storage and distribution centre. The Coordinating Centres will keep accurate records of Triple Pill supplies to trial centres. At each trial centre the Investigator will be responsible to store and maintain accurate records of Triple Pill and report to Coordinating Centre. Trial centres will store Triple Pill as per the labelled instructions and will instruct the trial participants accordingly. At the end of the study all returned/unused Triple Pill supplies will be destroyed at the trial centres or at a vendor facility.

b. Packaging and labelling

The Triple Pill packaging and labelling will be as per the regulatory requirements. The low dose and high versions will be manufactured with different coloured capsules and different coloured labels to enable them to be easily distinguished from each other. Details of the packaging and labelling will be included within the Manual of Procedures.

12. DATA REVIEW AND MANAGEMENT

a. Study monitoring

At an investigator meeting and during trial centre initiation meetings the Coordinating Centre representative will review the study protocol and procedures with the investigators and site staff. Adequate training will be given to the trial centre staff before the study initiation and on an ongoing basis, as and when required. Coordinating Centre monitors will do interim site monitoring visits (as per the monitoring manual) and communication by telephone, mail and e-mail will be used as needed to supplement site visits when appropriate to oversee the conduct of the study and to check the completeness and accuracy of records in adherence to protocol, manual of procedures, ICH-GCP and regulatory requirements. The investigator should allow the monitors, the persons responsible for the audit, the representatives of the Ethics Committee, and of the Regulatory Authorities to have direct access to source data / documents.

b. Data collection

TRIUMPH will use an eCRF for data collection. Trial centre staff will be trained by a Coordinating Centre representative(s) on eCRF. Delegated site staff will enter data in eCRF on a regular basis according to the procedures documented in the eCRF manual and any data queries will be resolved in a timely manner. The investigator will sign the eCRF confirming and certifying that the data entered is accurate and complete. All data collected in the eCRF from the participating regions will be securely stored with access restricted to representatives authorized for data management, and data analysis at the end of study.

c. Quality control

The data management team at the George Institute for Global Health will be responsible for all data processing and will perform quality checks.

13. ETHICS AND REGULATORY COMPLIANCE

This study will be designed, conducted, analysed and reported in compliance with ICH-GCP and local regulatory requirements. In Sri Lanka approval from Ethics review committee (ECR), and (if necessary) Sub-Committee on Clinical Trials (SCOCT) will be gained before study initiation. In addition, approval of Royal Prince Alfred Hospital Ethics Committee, Sydney will be gained for the funds administering institution.

a. Informed consent

Participants willing to take part in the study will be consented by trial centres as per the local regulatory and ethical requirements. In brief, Participants will be given adequate explanation about the study and will be given ample time to consider their trial participation. They will be given the opportunity to ask questions about the trial and what their participation involves and will receive full answers from the Investigator. Prior to a subject's participation in the trial, a written informed consent form (using appropriately translated versions where appropriate) should be signed and personally dated by the subject or by the subject's legally acceptable representative, and by the person who conducted the informed consent discussion. If a subject is unable to read or if a legally acceptable representative is unable to read, an impartial witness should be present during the entire informed consent discussion and must attest informed consent form. A copy of the signed informed consent form to be given to the trial participant.

b. Confidentiality

All documents and data relating to this study are strictly confidential. Documents given to the investigators and trial centres by the Coordinating Centres should not be disclosed to other parties without the written approval of the sponsor. The investigator and his team should maintain confidentiality of the identification of all study participants and assure security and confidentiality of study data and documents.

14. ADMINISTRATIVE SECTION

a. **Steering Committee**

The Steering committee will be the decision making body. It will provide scientific direction to the study; approve protocol, monitor study progress and plan dissemination. The Steering Committee will meet on a regular basis through teleconference or other modes of communication at regular intervals to discuss study progress.

b. Operations Committee

The Operations Committee will include representatives from the Coordinating Centres (George Clinical, and RemediumOne) as well as the sponsor, The George Institute, and will be responsible for the management of the study including study start-up activities, trial centre selection, conducting investigator's meeting, trial centre initiation, interim monitoring, and study close out.

c. Insurance

In the event of a study related injury or death to a clinical trial participant, George Institute for Global Health and Pharmaceutical Packaging Professionals Pty Ltd holds insurance policies to cover medical expenses and/or pay compensation in compliance with local regulatory and ethical requirements.

d. Quality Control and Quality Assurance

Quality Control will be performed according to The George Institute for Global Health procedures. The trial can be audited by a quality assurance representative of The George Institute for Global Health or by an external service provider.

e. Record retention

All essential trial documents (including but not limited to those documents defined by ICH-GCP as essential documents) will be archived and retained at the trial centre and coordinating centers for at least 15 years after the completion of the study. At the end of such period, the investigator shall notify in writing the project management team of its intent to destroy all such study material.

f. Ownership, Disclosure of Data and Publication

The steering committee will have full ownership of the study data, its storage, and dissemination. All publications will be reviewed and approved by the steering committee which will be named on all reports. The research teams, collaborating investigators and their respective centres will be named, and trial participants acknowledged in the final report and in publications arising from the trial.

g. **Funding**

This study is funded by a National Health and Medical Research Council (NHMRC) and Global Alliance for Chronic Disease Implementation Research on Hypertension in Low & Middle Income Countries grant (ID 1040152).

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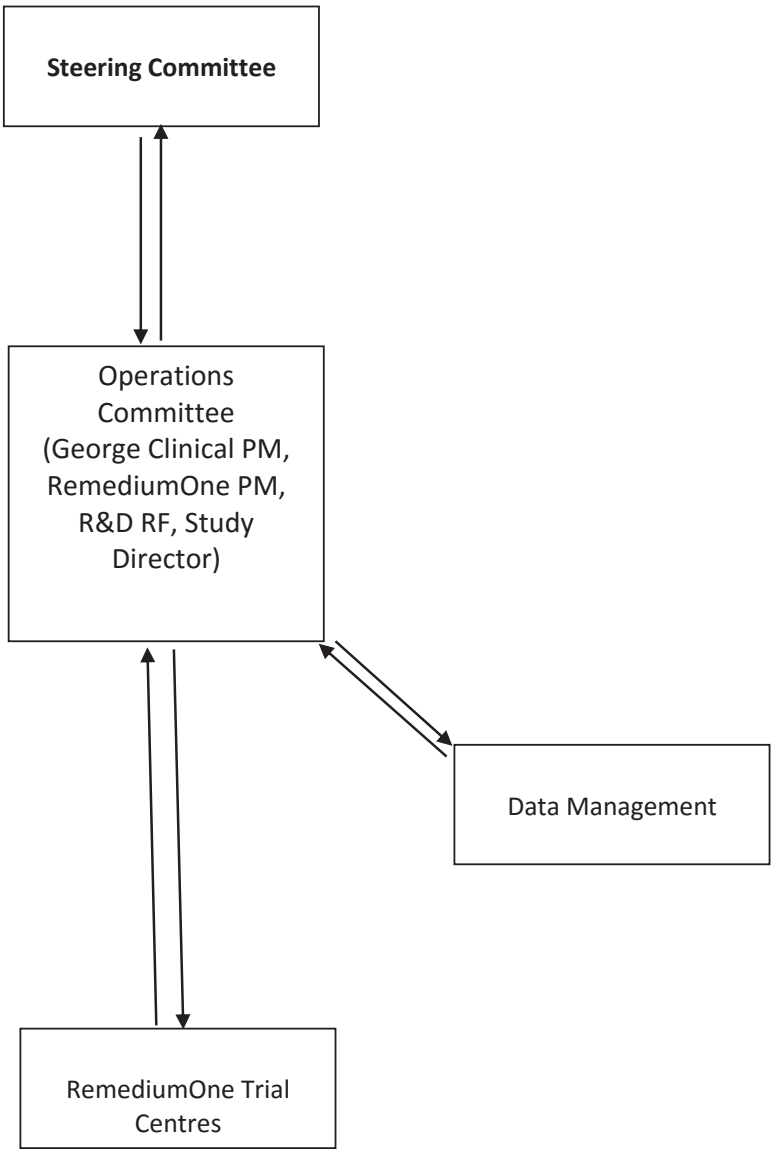
15. APPENDIX 1
STUDY ORGANIZATION



16. APPENDIX 2

PROTOCOL SIGNATURE PAGE

The signatures below constitute approval of this protocol by the signatories and provide the assurances that this study will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, regulatory requirement and ICH-GCP.

CHIEF INVESTIGATOR

Prof Anushka Patel
The George Institute for Global Health

Signature 

Date 23rd February, 2016

INVESTIGATOR

Trial centre _____

_____

_____

Signature _____

Date _____

Name _____

Title _____

Summary of changes - TRIUMPH protocol V1 to V1.1

Page Number	Old Text	New Text	Reason for change
1	Sponsor The George Institute for Global Health	Study Number **1041052**	Administrative
1	Development Phase Phase III	Text Deleted	Administrative
1	Protocol Version 1.0 – 30Oct2012	**Protocol** Version 1.1 – 10th December 2012	Administrative
Footer	TRIUMPH Protocol – Version 1.0 – 30Oct2012 Confidential Page 1 of 22	*TRIUMPH Protocol – Version 1.1 – 10Dec2012 Confidential Page 1 of 23*	Administrative
5	LIST OF ABBREVIATIONS	**LIST OF ABBREVIATIONS** Added: SmPC Summary of Product Characteristics	Administrative
6	…SBP < 140 mmHg and DBP < 85 mmHg (SBP < 130 mmHg and DBP < 85 mmHg for patients with diabetes and/or chronic kidney disease).	…SBP < 140 mmHg and DBP < 90 mmHg (SBP < 130 mmHg and DBP < 80mmHg for patients with diabetes and/or chronic kidney disease).	Clerical error corrected in goal BP for patients with diabetes and/or chronic kidney disease.
7	(in Study Schema)…(SBP > 130 mmHg and/or DBP > 85 mmHg in patients with DM or CKD)…	(In study Schema) (SBP > 130 mmHg and/or DBP > 80 mmHg in patients with DM or CKD)	Clerical error corrected in goal BP for patients with diabetes and/or chronic kidney disease.
9	… questions remain to be answered.	…questions remain unanswered.	Administrative
10	…patients with diabetes…	…patients with diabetes mellitus…	Administrative
10	Prospective Randomised Open Blinded Evaluation [PROBE] design.[21]	Deleted	Administrative
10	… use of single drug therapy…	…use of single BP-lowering drug therapy…	Administrative
10	*…urinary albumin:creatinine ratio…*	*…Albumin-to-Creatinine ratio…*	Administrative
10	…childbearing potential not…	… childbearing potential and not…	Administrative

10	Treatment will commence at the lower strength of Triple Pill with the option to titrate upwards to strength 2 at subsequent follow-up visits. The dosage will be one Triple Pill once daily. Timing of the…	For participants randomised to Triple Pill arm treatment will commence at the lower strength of Triple Pill with the option to titrate upwards to strength 2 at subsequent follow-up visits. The dosage will be one Triple Pill once daily for the trial duration (i.e. 6 months). Timing of the…	Administrative
11		…..free of charge….	Administrative
	…Additional prescription can take place…	… Additional prescription during follow up…	Administrative
11	No blinding	Blinding: Blinding of trial participants to study treatment allocation will not be possible because the comparator is usual care. Therefore this is an open-label trial. Bias from the unblinded measurement of blood pressure will be minimised by audited comparison of CRF entries with the memory values of automated blood pressure-measuring device by the trial monitor. During the review of the results within the trial team, all investigators will be blinded to treatment allocation	Administrative
11	…(SBP < 130 mmHg and DBP < 85 mmHg for patients with diabetes and/or chronic kidney disease)…	…(SBP < 130 mmHg and DBP < 80 mmHg for patients with diabetes and/or chronic kidney disease)…	Clerical error corrected in goal BP for patients with diabetes and/or chronic kidney disease.
11	Tolerance to treatment	…..at 6 months	Administrative
15	about the study drug in the IB	…Summary of Product Characteristics (SmPC). The SmPC will include…	Administrative
11	Mean change in SBP and DBP	Mean change in SBP and DBP at 6 months	Administrative
12	Tolerance to treatment	Tolerance to treatment at 6 months	Administrative
12	Quality of life	Quality of life at 6 months	Administrative
12	Self-reported BP lowering medication use (7-day recall) – adherence defined as the patient taking the drug for at least 4 out of the last 7 days	Self-reported BP lowering medication use (7-day recall) at 6 months – adherence defined as the patient taking the drug for at least 4 out of the last 7 days	

15-16 in V1.1		**Early Discontinuation of Individual Participants.** The reason for a participant discontinuing trial medication will be recorded in the case record form. A discontinuation occurs when an enrolled participant permanently ceases taking the trial medication, regardless of the circumstances, prior to completion of the trial. A discontinuation must be reported immediately to the TRIUMPH Coordinating Centre. Typically, participants may discontinue trial medication for the following reasons: a. At the request of the participant. b. If the investigator considers that a participant's health will be compromised due a contraindication to one or more components of the Triple Pill, or due to adverse events or concomitant illness that develops after entering the trial. c. The trial is terminated For any participant who discontinues trial medication before the trial is completed, the investigator will: a. Complete the case record form including any summary sheet, indicating the date of and explanation for the early discontinuation of trial medication. b. If necessary, arrange for alternative cardiovascular medications to be prescribed for the discontinued participant c. Follow the patient in the usual way to the end of the trial despite discontinuation of the trial medication**.** Participants will be informed at the time of enrolment and consenting that they are free to withdraw from the trial at any time and for any reason without influencing any aspect of their usual medical care.	To clarify when and how early discontinuation of trial participants could happen, and the actions to be taken
17 in V1.1		**TRIPLE PILL MANAGEMENT** **Manufacture, supply and storage** **Packaging and labelling.**	To provide information on manufacturing, supply, packaging,

		Dr Reddy's Laboratories Ltd will manufacture and distribute the Triple Pill to trial centres. Dr Reddy's Laboratories and the Coordinating Centres will keep accurate records of Triple Pill supplies to trial centres. At each trial centre the Investigator will be responsible to store and maintain accurate records of Triple Pill and report to Coordinating Centre. Trial centres will store Triple Pill as per the labelled instructions and will instruct the trial participants accordingly. At the end of the study all returned/unused Triple Pill supplies will either be returned to Dr Reddy's Laboratories or will be destroyed at the trial centres. **Packaging and labelling** The Triple Pill packaging and labelling will be as per the regulatory requirements. The low dose tablet (telmisartan 20 mg + amlodipine 2.5mg + hydrochlorothiazide 6.25 mg) is a white to off-white and light pink to orange pink specked, oval shaped two layer tablet debossed with the 'TAH' on one side and '20' on other side. The high dose tablet (telmisartan 40 mg + amlodipine 5mg + hydrochlorothiazide 12.5 mg) is a white to off-white and light pink to orange pink specked, oval shaped two layer tablet debossed with the 'TAH' on one side and '40' on other side.	labelling and physical properties of Triple pill.
17	…during site initiations the TRIUMPH representative will review…	…trial centre initiation meetings the Coordinating Centre representative…	Administrative
17	RCC and…	deleted	Administrative
17	TRIUMPH monitors…	…Coordinating Centre monitors…	Administrative
17	…by TRIUMPH representative…	…Coordinating Centre representative…	Administrative
17		according to the procedures documented in the eCRF manual	Administrative
18	…during site initiations the TRIUMPH representative will…	… during trial centre initiation meetings the Coordinating Centre representative…	Administrative
18	Dr Reddy's Laboratories and…	deleted	Administrative
19	Hansson L, Hedner T, Dahlof B.	deleted	Administrative

	Prospective randomized open blinded end-point (PROBE) study. A novel design for intervention trials. Prospective Randomized Open Blinded End-Point. Blood Press. 1992 Aug;1(2):113-9.		
22	APPENDIX 2 PROTOCOL SIGNATURE PAGE	deleted	Administrative

Summary of changes - TRIUMPH protocol V1.1 to V2

Page No	**Current text (V 1.1 – 14 Dec 12)**	**Amended text (V 2 – 17 Apr 13)**	**Reason for change**
1	Version 1.1 - 10th December 2012	Version 2.0 - 17th April 2013	Revised version
1	Trial registration…	Clinical Trials Registry – India number: CTRI/2013/02/003388	Added - CTRI registration number
1	Contact	Sponsor	To clarify that the contact details are those of the sponsor
All pages	Version 1.1- 10 Dec 2010	Version 2.0 - 17th April 2013	Revised version

4	Dr Reddy's Laboratories, Pty Ltd	Dr Reddy's Laboratories, Pty Ltd Door No 8-2-337, Road No 3, Banjara Hills Hyderabad - 500034. Andhra Pradesh	Added - Dr Reddy's full address
5	After - eGFR/GFR	EoS End of Study	Added - abbreviation for End of Study visit
5	SmPc summary of product Characteristics	Deleted	SmPc will not be used for this study
7	…randomised controlled clinical trial (n=700) of a combination blood pressure lowering pill …	…randomised controlled clinical trial (n=700) of fixed dose combination blood pressure lowering pill…	The term "Fixed dose" added to the protocol as per the advice of HSMC expert reviewer.
7, 9, 12, 13, 14, 15, 17, & 18	Patient/s	Participant/s	For uniformity in the document the term "patient/s" is replaced with "participant/s" to represent trial participants.
7	... at least 6 weeks despite adequate lifestyle advice and/or lifestyle changes…	…at least 6 weeks despite diet and lifestyle advice…	Clerical error corrected

7	separate	Usual	Clerical error corrected
8	sustained	persistent	Preferred term to indicate continual high blood pressure
8	Continue or switch to strength 2	Continue or switch to Triple Pill strength 2	Addition of term “Triple pill” to add more clarity
10	…maximum benefit to side effect ratio from low-dose triple combinations…	…maximum benefit to side effect ratio from fixed dose triple combinations…	The term “fixed dose” added to the protocol as per the advice of HSMC review expert.
10	…and have not tested the integration of a low-dose triple combination…	…and have not tested the integration of a fixed dose triple combination…	The term “fixed dose” added to the protocol as per the advice of HSMC review expert.
10	…using a low-dose combination 3-in-1 antihypertensive pill…	…using a fixed dose combination 3-in-1 blood pressure lowering pill…	The term “fixed dose” added to the protocol as per the advice of HSMC review expert. The term “antihypertensive pill” replaced with “blood pressure lowering pill”
11	Sustained	Persistent	Preferred term to indicate continued high blood pressure

12	… (this being the cost of the generic components of the higher dose strength of the Triple pill)…	… (this being the approximate cost of the generic components of the higher dose strength of the Triple pill)…	To indicate INR 8 is the “approximate” cost of components of triple pill
13	Month 06 (M6)	Month 06 (M6/EoS)	Addition of abbreviation for end of study (EoS)
13	Participant demographic and medical history	Participant demographic	medical history deleted here and added a separate row added for it
13	After - participant demographics	Medical history	Added of a separate row for medical history
13	After- Urine protein (albumin) test	Socioeconomic information	Added - was inadvertently missed in the previous version
13	After - Socioeconomic information	Pregnancy status	Added - was missed in the previous version
13	Reason for stopping medication (if any)	Reason for stopping blood pressure lowering medications (if any)	Clarification that reasons for stopping medication will be limited to blood pressure lowering medications
13	After - Participant acceptability	Investigators acceptability (Triple pill arm only)	Added – was inadvertently missed in previous version

13	After - ** Either at REG or RAND or between these visits	† Not required if REG and RAND occurs on the same day	Added to clarify that protocol required BP & HR assessment needs to performed once only if both Registration and Randomisation visit occurs on the same day
14	At 6 weeks follow-up	At 6 & 12 weeks followup	Clerical error corrected
15	After - Assess healthrelated quality of life.	Participant acceptability assessment	Added – was inadvertently missed in previous version
15	After - Participant acceptability assessment	Investigator acceptability assessment (Triple Pill arm only)	Added – was inadvertently missed in previous version
15	Reimburse patients in the usual care arm for their medication costs to a maximum of INR 8 per day, upon presentation of receipts.	Cover the cost of participant's blood pressure lowering medications in the usual care arm to a maximum of INR 8 per day.	Reworded to clarify that only the cost of BP lowering medications will be reimbursed. The requirement to present receipts was deleted as it is perceived to be operationally difficult.
15	After - Cover the cost of participant's blood pressure lowering medications in the usual care arm to a maximum of INR 8 per day	Invitation to a sample of participants to participate in process evaluation interview	Added – was inadvertently missed in previous version
15	Quality of life (RAND and M6) will be assessed using E-Q5D.	Quality of life (RAND and M6) will be assessed using E-Q5D questionnaire	Clerical error corrected.

16	*Severe adverse event* Any untoward medical occurrence that at any dose: - results in death, - is life-threatening, - requires inpatient hospitalization or prolongation of existing hospitalization, - results in persistent or significant disability/incapacity, or - is a congenital anomaly/birth defect	*Severe adverse event (SAE)* Any untoward medical occurrence during a clinical trial that is associated with death, in patient hospitalisation (in case of study was being conducted on outpatient) prolongation of hospitalisation (in case the study was being conducted on in-patient), persistent or significant disability or incapacity, a congenital anomaly or birth defect or is otherwise life threatening.	Definition of SAE replaced with the new definition as per the recent amendment to Drugs and Cosmetic rule (GSR 53 E dated 30 Jan 2013)
16	…must be reported to the TRIUMPH Coordinating centre within 24 hours per site…	…must be reported as per the regulatory requirements, the requirements of the site ethics committee and the Safety Reporting Manual…	Reworded to indicate that SAEs must be reported as per the requirements of the regulatory authorities, the overseeing ethics committee and as per the safety reporting manual provided by the sponsors which will ensure compliance with the current regulatory requirements.
16	…event indicating as unrelated, unlikely, possible, probable, and definite for each SAE reported…	…event indicating as related/unrelated, for each SAE reported…	Reworded to be in line with the regulatory requirements

16	The investigator should report SAEs to their local ethics committees as per requirement of the ethics committee standard operating procedures.	deleted	Considered redundant after revision of the section.
16	…about the study drug in the Summary of Product Characteristics (SmPC). The SmPC …	…about the study drug in the Investigator Brochure (IB). The IB…	SmPC replaced with the IB
17	After - Reports will also be provided to overseeing ethics committees and Investigators as per country requirements.	In case of injury/death of a participant in a clinical trial the sponsor/sponsor representative is responsible for providing medical management to the participant and also provide financial compensation in case of clinical trial injury/death.	Added to be in compliance with the recent amendment to Drugs and Cosmetic rule
19	…manual of procedures, and ICH-GCP.	…manual of procedures, ICH-GCP and regulatory requirements.	Addition of term “regulatory requirements” to ensure compliance with regulatory requirements.
20	…participating trial centres and the funds administering institution (The University of Sydney) will be gained before study initiation.	…participating trial centres and the Ethics committee (The University of Sydney) responsible for the funds administering institution will be gained before study initiation.	Reworded to add more clarity

20	After - If a subject is unable to read or if a legally acceptable representative is unable to read, an impartial witness should be present during the entire informed consent discussion.	A copy of the signed informed consent form to be given to the trial participant. In case of any new information pertaining to the trial is available the same should be passed on to the participant.	Added – to ensure that participating trials centres provide a copy of signed ICF to the participants and communicate any new information pertaining to the trial
21	The George Institute for Global health shall at all times indemnify the study investigators and their staff from claims that may be made against them for any injury sustained by a study participant as a consequence of effects of the 'Triple Pill' used in the study in accordance with this protocol.	In the event of a study related injury or death, to clinical trial participant George Institute for Global Health and Dr. Reddy's laboratories holds insurance policies to pay compensation. The minimum quantum (amount) for trial related injuries and death will be as deemed appropriate by the expert committee of the licensing authority (DCGI).	Reworded as per the advice of the HMSC expert committee to add more clarity regarding trial insurance and to indicate that the amount of compensation will be as deemed appropriate by the expert committee of DCGI.

Summary of changes - TRIUMPH protocol V2 to V3

Page Number	Old Text	New Text	Reason for change
1	Version 2.0 – 17th April 2013	Version 3.0 – 26 March 2015	Administrative
1	TRIUMPH Protocol – Version 2.0 – 17th April 2013	TRIUMPH Protocol – Version 3.0 – 26 March 2015	Administrative

1	George Institute for Global Health India 839C, Road No. 44A, Jubilee Hills Hyderabad 500033, India T: +91 40 2355 8091, F: +91 40 2354 1980 E: triumphpm@georgeinstitute.org.in	The George Institute for Global Health India Unit No. 301, Second Floor, ANR Center Road No.1, Banjara Hills Hyderabad 500034, India T: +91 40 3099 4444, F: +91 40 3099 4400 E: triumphpm@georgeinstitute.org.in	Administrative
4		Prof Asita de Silva E: asita@remediumone.com T: +94112665266, F: +94112665300 Clinical Trials Unit at the Faculty of Medicine, University of Kelaniya	Addition of Co-Investigators from Sri Lanka
4		RemediumOne T: +94112665266, F: +94112665300 Post Code: 07000, No. 41/10, Guildford Crescent Colombo 07, Sri Lanka	Addition of collaborator from Sri Lanka
5		CIOMS Council for International Organizations of Medical Sciences	Administrative
	……..20 centres in India	…….20 trial centres in India and Sri Lanka	Including trial centres from Sri Lanka
6	strength 1 - *Telsartan Trio 20:*	strength 1 – *Optidoz:*	Administrative
7	Week 6 & 12 +/- 14 days	Week 6 & 12 +/- 7 days	Reduced window period from 14 to 7 days
8	Hypertension and hypertension control in India	a. Hypertension and hypertension control in India and Sri Lanka	Inclusion of trial centres from Sri Lanka
8		In Sri Lanka, high blood pressure is now the second highest risk factor for disease burden.8 Ischemic heart disease and stroke (for which hypertension is a significant risk factor) rank as	Addition of epidemiology of hypertension in Sri Lanka

		the first and third highest causes of premature death.8 Data on hypertension prevalence in Sri Lanka is sparse, however estimates in published population based surveys range between 19 and 30% (both urban and rural populations included)9-11 and up to 40% in a recent WHO South East Asian report.12 Of those identified with hypertension in the population based surveys, between 30 and 50% were new diagnoses.10,11 When combined with population size (approximately 22 million, of whom 60% are >25 years13), up to 5.3 million Sri Lankans currently have hypertension and about half of these cases are undiagnosed. Of those that are diagnosed, the Ceylon College of Physicians14 estimates that about 1 in 5 are adequately controlled. These data indicate that hypertension is currently a major public health challenge in Sri Lanka.	
8,9	…Indian Hypertension Guidelines (Indian Hypertension Guidelines-2007. Convenor: Siddharth Shah. Members: M Paul Anand, M Maiya, Sukumar Mukherjee, YP Munjal, GS Wander, S Kamath), have traditionally focussed on "tailored therapy" and "stepped-care" approaches…..	India and Sri Lanka, have traditionally focused on "tailored therapy" and "stepped-care" approaches.	Inclusion of Sri Lanka
9	in this case, urban populations in India	in this case, clinics in urban India and Sri Lanka	Inclusion of Sri Lanka

9	The management of hypertension in India	The management of hypertension in India and Sri Lanka	Inclusion of Sri Lanka
9, 10	...a strategy of early use of a Triple Pill compared to usual care in India	…… a strategy of early use of a Triple Pill compared to usual care	Administrative
10	patients with persistent mild-to-moderate hypertension.	persistent mild-to-moderate hypertension, augmented by cost-effectiveness analysis and process evaluation.	Administrative
10		**b. Participant recruitment** Participants will be recruited from about 20 trial centers (general practice or cardiology clinics) located in urban/sub-urban areas of India and Sri Lanka. Recruitment using advertisements (e.g. study posters) may be used if required to meet the recruitment targets.	Clarification from where and where trial participants will be recruited.
11		….their previous BP lowering medications will be withdrawn (if applicable)	Clarification on withdrawal of pre-randomisation BP lowering medications
11	*Telsartan Trio 20:*	Strength 1 (Optidoz):	Administrative
11	*Telsartan Trio*	Strength 2 (Telsartan Trio):	Administrative
	In the usual care… …receipts of the trial	In India, participants in the usual care… …to cover the out-of-pocket expense of buying BP lowering medications. In Sri Lanka, participants will receive their drugs free of cost, as per usual practice.	Clarification on how participants in the usual care arm will receive their BP lowering drugs in India and Sri Lanka.
12		All other medical care will be delivered according to local	Clarification on how trial participants general medical care.

		standards by the responsible clinician.	
12	Bias from the unblinded measurement	Bias that may arise from the unblinded measurement	Administrative
11,12	…with the memory values …	…with the printed values…	Administrative
13	Clinical biochemistry…	Clinical biochemistry testing (routine laboratory investigations recommended in the management of high blood pressure) …	Administrative
13	between the screening and randomisation visits or at the randomisation visit, but subsequently at the discretion of the responsible clinician…	…(between screening and randomisation visits or at the randomisation visit) and EoS (at 6 months)…	Trial required laboratory investigation to be done at baseline and end of study.
13		Assess potential participant's interest and eligibility for the trial.	Administrative
13	…….with potentially eligible patients.	Deleted	Administrative
13	Record any SAEs that…	Record any AEs that…	Reporting of not just SAEs but also AEs (including SAEs)
13	Record SAEs since previous trial visit.	Record AEs since previous trial visit.	Reporting of not just SAEs but also AEs (including SAEs)
13	Prescribe/dispense Triple Pill (Triple Pill arm only). Week 6 & 12)	Prescribe/dispense Triple Pill (Triple Pill arm only).	Clerical typo corrected
14	Record SAEs since previous trial visit.	Record AEs since previous trial visit.	Reporting of not just SAEs but also AEs (including SAEs)
14	Ask participant to report any AEs during 30 days after the end of study visit.	Ask participant to report any AEs during 30 days after the end of study visit.	Reporting of not just SAEs but also AEs (including SAEs)
14,15	Cover the cost of participant's blood pressure lowering medications in the	Reimburse cost of participant's blood pressure lowering medications in the usual care	Administrative, clarification that reimbursement is only applicable to India.

	usual care arm a maximum of INR 8 per day	arm (in India) to a maximum of INR 8 per day.	
14,15	….. local laboratories linked to the trial centres	….local laboratories linked to the trial centres (in India) or at a central laboratory (in Sri Lanka) following usual procedures of sample collection and analysis	Administrative
15		Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An adverse event (AE) can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.	Addition of definition of AE
15,16	Any untoward medical occurrence during a clinical trial that is associated with death, in patient hospitalisation (in case of study was being conducted on out-patient) prolongation of hospitalisation (in case the study was being conducted on in-patient), persistent or significant disability or incapacity, a congenital anomaly or birth defect or is otherwise life threatening.	Any untoward medical occurrence that at any dose; results in death, is life-threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, or is a congenital anomaly/birth defect.	Correction of definition of SAE as per ICH-GCP

16		Trial site investigators, and sponsor (or representative) will adhere to local ethical and regulatory requirements of safety reporting.	Clarification on reporting of safety events as per local requirement in India and Sri Lanka.
15	….. must be reported. as per the regulatory requirements, the requirements of the site ethics committee and the Safety Reporting Manual.	……must be reported by the site investigators as per the local regulatory and ethical requirements	Administrative
	……completing the paper and eCRF SAE form.	….. completing the paper (CIOMS or relevant form) eCRF SAE form.	Administrative
15,16	and these reports should be again submitted to the TRIUMPH Coordinating Centre within 24 hours. Investigator should assess and report the causal relationship between the study drug and the event indicating as related/unrelated, for each SAE reported.	Deleted	Administrative
15,16	The TRIUMPH Coordinating Centre will report SAEs to the regulatory authorities and trial centres as per the requirements of local regulation and ICH-GCP.	The TRIUMPH Coordinating Centre will report SAEs occurring at the trial centers to the regulatory authorities, ethics committee and trial investigators as per the local ethical and regulatory requirements	Administrative
15	In case of injury/death of a participant in a clinical trial the sponsor/sponsor representative is responsible for providing medical management to the	Deleted	Administrative

	participant and also provide financial compensation in case of clinical trial injury/death.		
16		l. Data Safety & Monitoring Board (DSMB) An Independent DSMB will evaluate interim safety and efficacy data at regular intervals and advise steering committee on continuing the trial.	Addition of information of DSMB
16,17	The reason for a participant discontinuing trial medication will be recorded in the case record form.	In case of early discontinuation of trial medication by trial participant, reason for discontinuation will be recorded in the case record form.	Administrative
16,17	The trial is terminated.	The trial is terminated (e.g. if in the opinion of the DSMB interim data indicate that it might not be justifiable to continue the trial, the Steering Committee may terminate the trial).	Administrative
16,17	…… usual medical care.	usual medical care, their participation in this study may be terminated by the investigator if the study itself is terminated	Administrative
17		n. Post-trial access to Triple pill Participants will be asked to stop and return any remaining Triple pill at the end of their participation in the study. The responsible clinician will switch participants to appropriate therapy in line with local standard of care. Results of this study will be made fully available to the manufacturer to support any marketing approval that they may seek.	Addition of information on post-trial access to Triple pill

	This software is particularly useful when there are multiple coders across several sites, allowing us to bring local, context-rich analyses to interpretation of the findings.	Deleted	Administrative
18,19	The low dose tablet (telmisartan 20 mg + amlodipine 2.5mg + hydrochlorothiazide 6.25 mg)…	The low dose tablet – strength 1 – Optidoz (telmisartan 20 mg + amlodipine 2.5mg + hydrochlorothiazide 6.25 mg)…	Administrative
18,19	The high dose tablet (telmisartan 40 mg + amlodipine 5mg + hydrochlorothiazide 12.5 mg)…	The high dose tablet – strength 2 – Telsartan trio (telmisartan 40 mg + amlodipine 5mg + hydrochlorothiazide 12.5 mg)…	Administrative
20		All data collected in the eCRF from the participating regions will be securely stored with access restricted to representatives authorized for data management, and data analysis at the end of study	Addition of information on data access.
18,20	Study approval/No Objection certificate from the office of Drug Controller General of India (DCGI), Health Ministry Screening Committee (HMSC) and ethics committees at the participating trial centres and the Ethics committee (The University of Sydney) responsible for the funds administering institution will be gained before study initiation	In India, study approval/No Objection certificate from the office of Drug Controller General of India (DCGI), Health Ministry Screening Committee (HMSC) and ethics committees at the participating trial centres; and in Sri Lanka approval from Ethics review committee (ECR), and (if necessary) Sub-Committee on Clinical Trials (SCOCT) will be gained before study initiation. In addition, approval of Royal Prince Alfred Hospital Ethics Committee, Sydney will be gained for the funds administering institution	Administrative

20		Participants willing to take part in the study will be consented by trial centres as per the local regulatory and ethical requirements. In brief,	Administrative
20		and must attest informed consent form.	Administrative
20	In case of any new information pertaining to the trial is available the same should be passed on to the participant	Deleted	Administrative
19,21	(The George Institute and Centre for Chronic Disease Control-Delhi)	(The George Institute, Centre for Chronic Disease Control-Delhi and RemediumOne)	Administrative
19	The Project Management Team will provide day to day schedule management support and will be responsible for initiating the production and collection of interim reports necessary to produce the periodic and final project reports to the NHMRC.	Deleted	Administrative
19,21	…insurance policies to pay compensation…	…insurance policies to cover medical expenses… and/or pay compensation in compliance with local regulatory and ethical requirements. In India,….	Administrative
19	This indemnity will be outlined in detail in the agreement between The George Institute and each participating trial centre.	Deleted	Administrative

19	…retained at the trial centres..	…retained at the trial centre and coordinating centers…	Administrative
19	…collaborating doctors and…	…collaborating Investigators and…	Administrative

Summary of changes - TRIUMPH protocol V3 to V4

Page/Section	**Old Text** (version 3.0 – 26 March 2015)	**New Text** (Version 4.0 – 23 November 2015)	**Reason for change**
All pages/footer	Version 3.0 – 26 March 2015	Version 4.0 – 23 November 2015	Administrative
1/title page	George Institute for Global Health India 839C, Road No. 44A, Jubilee Hills Hyderabad 500033, India T: +91 40 2355 8091, F: +91 40 2354 1980 E: triumphpm@georgeinstitute.org.in	--	Administrative
4/ Coordinating Centers	The George Institute for Global Health T: +91 40 2355 8091, F: +91 40 2354 1980 839C, Road No. 44A, Jubilee Hills Hyderabad-500 033, India	George Clinical India Private limited T: +91 80 2226 3647, F: +91 80 2226 3648, #333, Nova Miller, 4th Floor, Thimmaiah Road, Vasanth Nagar Bangalore- 560 052, India	Administrative
4/ Triple Pill Manufacture and Distribution	Triple Pill Manufacture and Distribution Dr Reddy's Laboratories, Pty Ltd Door No 8-2-337, Road No 3, Banjara Hills Hyderabad - 500034. Andhra Pradesh	Pharmaceutical Packaging Professionals Pty Ltd 3/31 Sabre Drive, Port Melbourne, Victoria, 3207, Australia	Change of the Triple pill manufacturer
5/ List Of Abbreviations	HCTZ - Hydrochlorothiazide	--	No longer necessary
6, 11/ Randomisation and study medication,	…… Optidoz Telmisartan 20mg, Amlodipine 2.5mg, HCTZ 6.25mg	……: Low dose: Telmisartan 20mg, Amlodipine 2.5mg, Chlorthalidone 12.5mg	Hydrochlorothiazide replaced with Chlorthalidone. Replaced brand name "optidoz" with "low dose"

Study treatments			
6, 11/ Randomisation and study medication, Study treatments	…… Telsartan Trio: Telmisartan 40mg, Amlodipine 5mg, HCTZ 12.5mg	…….: High dose: Telmisartan 40mg, Amlodipine 5mg, Chlorthalidone 25mg	Hydrochlorothiazide replaced with Chlorthalidone. Replaced brand name "Telsartan Trio" with "high dose"
19/Manufacture, supply and storage	Dr Reddy's Laboratories Ltd will manufacture and supply the Triple Pill for the purpose of this trial. Dr Reddy's Laboratories ….	Pharmaceutical Packaging Professionals (PPP) Pty Ltd, a GMP and Therapeutic Goods Administration certified company in Australia will produce and distribute over-encapsulated Triple Pills for the purpose of this trial. To produce Triple pill, PPP will purchase commercial stock of component medications and place them into capsules (over-encapsulation). PPP will arrange export of the pills to the drug storage and distribution centre. tThe Coordinating Centres will keep….	Change of manufacturer from Dr Reddy's, to Pharmaceutical Packaging Professionals.
	….At the end of the study all returned/unused Triple Pill supplies will either be returned to Dr Reddy's Laboratories or will be destroyed at the trial centres.	……At the end of the study all returned/unused Triple Pill supplies will be destroyed at the trial centres or at a vendor facility.	Dr. Reddy's will no longer be involved in this study
19/Packaging and labelling	The low dose tablet – strength 1 – Optidoz (telmisartan 20 mg + amlodipine 2.5mg + hydrochlorothiazide 6.25 mg) is a white to off-white and light pink to orange pink specked, oval shaped two layer tablet debossed with the 'TAH' on one side and '20' on other side.	The low dose and high versions will be manufactured with different coloured capsules and different coloured labels to enable them to be easily distinguished from each other. Details of the packaging and labelling will be included within the Manual of Procedures.	Change of packaging of product.

19/Packaging and labelling	The high dose tablet – strength 2 – Telsartan trio (telmisartan 40 mg + amlodipine 5mg + hydrochlorothiazide 12.5 mg) is a white to off-white and light pink to orange pink specked, oval shaped two layer tablet debossed with the 'TAH' on one side and '40' on other side.	The low dose and high versions will be manufactured with different coloured capsules and different coloured labels to enable them to be easily distinguished from each other. Details of the packaging and labelling will be included within the Manual of Procedures.	Change of packaging of product.
21/Insurance	Dr. Reddy's laboratories	Pharmaceutical Packaging Professionals Pty Ltd	Change of study manufacturer
21/Funding	The Triple Pill will be supplied free of charge by Dr Reddy's Laboratories Limited.	--	Dr. Reddy's will no longer be involved in this study

List of changes - TRIUMPH protocol V4 to V5

Page Number	Old Text	New Text	Reason for change
1	Version 4.0 – 25 November 2015	Version 5.0 – 23rd February, 2016	New version
1		Sri Lankan Clinical Trial Registry number: SLCTR/2015/020	Addition of Sri Lankan Clinical Trial Registry number
1	Level 13, 321 Kent St, Sydney NSW 2000 Australia	Level 3, 50 Bridge St, Sydney NSW 2000 Australia	Administrative change due to change of office
Footer	TRIUMPH Protocol – Version 4.0 – 25 Nov 2015	TRIUMPH Protocol – Version 5.0 – 23rd February, 2016	Change of Protocol version
4	Centre for Chronic Disease Control T: +91 11 43421900, F: +91 11 43421975	Text deleted	The TRIUMPH study will now recruit all patients in Sri Lanka as this capacity exists, and resource and logistic considerations strongly favour completing the entire trial in one country.

	Tower 4, Commercial Complex C 9, Vasant Kunj, New Delhi-110070, India		
5	Various abbreviations	Deleted	Abbreviations removed as no longer included in text
6	20 trial centres in India and Sri Lanka	At least 11 trial centres in Sri Lanka	Removed reference to India
6 & 10	The major inclusion criteria are participants with persistent hypertension for at least 6 weeks despite diet and lifestyle advice; and/or single drug therapy for BP lowering. Persistent (≥6 weeks) SBP > 140 mmHg and/or DBP > 90 mmHg (or SBP > 130 mmHg and/or DBP > 80mmHg in patients with diabetes mellitus or chronic kidney disease) despite diet and lifestyle advice and/or the use of single BP-lowering drug therapy.	The major inclusion criteria are participants with persistent hypertension that the investigator feels requires initiation of drug therapy (for treatment naïve patients) or up-titration of drug therapy (for patients on single drug therapy). The investigator is satisfied that the patient has persistent hypertension (SBP>140mmHg and/or DBP>90mmHg; or SBP>130mmHg and/or DBP>80mmHg in patients with diabetes mellitus or chronic kidney disease) requiring initiation of pharmacological treatment (in patients not taking drug therapy) or up-titration of pharmacological treatment (in patients taking single drug therapy)	The TRIUMPH study is a pragmatic randomised controlled trial and the aim is to reflect 'real-world' practice as much as possible. The new wording of this inclusion criteria incorporates the previous inclusion criteria but also broadens the criteria to more accurately reflect 'real-world' decision making. Additionally verification of this inclusion criteria is problematic in the field and therefore has been modified.
7 – Study schema	Week -6	-6 to 0 weeks	The wording of the required length of time between registration and randomisation visits has been edited to provide clarity that clinician judgement should be used as to

13 – Study visit schedule			when blood pressure lowering therapy should be started. Randomisation can occur on the day of registration if all inclusion criteria are met, or patient can be registered and brought back up to 6 weeks later for randomisation.
7 – study Schema 13 – Study visit schedule	Week 6 (+/- 7 days)	Week 6 (+/- 14 days)	Visit window for first follow-up visit extended to allow usual practice of bringing the patient back after 1 month for follow-up.
8	In India, the absolute number of hypertensive participants……. A third of those surveyed and optimal blood pressure control in another 38%.	Deleted	Reflecting change to recruit solely in Sri Lanka.
9	India	South Asia	Reflecting change to recruit solely in Sri Lanka.
9	…urban India and ….	Deleted	Reflecting change to recruit solely in Sri Lanka.
10	20 trial centres	At least 11 trial centres	Reflecting change to recruit solely in Sri Lanka.
10	… India and ….	Deleted	Reflecting change to recruit solely in Sri Lanka.
10	**Patients currently treated with oral antidiabetics and/or insulin, or have a fasting plasma glucose ≥ 126 mg/dL (7.0 mmol/L) or 2-h plasma glucose ≥200 mg/dL (11.1 mmol/L)* ***GFR/eGFR <60 mL/min/1.73m2 or Urine Albumin-to-Creatinine ratio > 30 mg/g prior to the randomisation visit*	Deleted	Presence of Diabetes and Chronic Renal Failure to be confirmed and documented by investigator as per their usual clinical practice thereby reflecting locally relevant clinical definitions rather than a study defined requirement (which is consistent with TRIUMPH being a pragmatic RCT).
11	In India, participants in the usual care arm will be reimbursed for	Deleted	Reflecting change to recruit solely in Sri Lanka.

	the cost of their BP medications to a maximum …… of buying BP lowering medications.		
13	For newly diagnosed hypertensive patients, there must be a 6 week window between registration and randomisation to allow time to apply diet and lifestyle advice. For patients who have been diagnosed more than 6 weeks prior to registration, or who are already taking one BP lowering medication, registration and randomisation may take place on the same day.	For all patients, registration and randomization visits may occur up to 6 weeks apart if the investigator feels that additional investigation is required prior to commencing drug treatment. However if patients satisfy all inclusion criteria and the investigator believes immediate commencement of treatment is appropriate, registration and randomisation may take place on the same day.	The wording of the required length of time between registration and randomisation visits has been edited to provide clarity that clinician judgement should be used as to when blood pressure lowering therapy should be started (in line with the fact that this is a pragmatic randomised controlled trial). Randomisation can occur on the day of registration if all inclusion criteria are met, or patient can be registered and brought back up to 6 weeks later for randomisation.
14	Clinical biochemistry testing (routine laboratory investigations recommended in the management of high blood pressure) including electrolytes, creatinine, and urinary protein will be conducted at baseline (between screening and randomisation visits or at the randomisation visit)	Clinical biochemistry testing including electrolytes, creatinine, and urinary protein will be conducted at baseline. If patient has had required bloods taken in the 7 weeks prior to registration these bloods are acceptable as baseline blood tests. Otherwise, sites should arrange bloods to be taken either between screening and randomisation visits, or at the randomisation visit. Blood tests should be repeated at EoS (at 6 months).	Additional time frame inserted to provide clarity around when blood tests must be done and allow existing blood tests to be used for baseline data.
14, 15	Reimburse participants in the usual care arm (in India) for	Deleted	Reflecting change to recruit solely in Sri Lanka.

	their medication costs to a maximum of INR 8 per day, upon presentation of receipts.		
15	…..at local laboratories linked to the trial centres (in India)….	Deleted	Reflecting change to recruit solely in Sri Lanka.
17	Results of this study will be made fully available to the manufacturer to support any marketing approval that they may seek.	Deleted	Not applicable to current manufacturer of IP.
20, 21 & 25	Various admin passages	Deleted	Reflecting change to recruit solely in Sri Lanka.
26	25th November, 2015	23rd February, 2016	Change of version

STATISTICAL ANALYSIS PLAN

TRIUMPH

Triple pill vs. usual care management for patients with mild-to-moderate hypertension

Final version
15th November 2017

STATISTICAL ANALYSIS PLAN APPROVAL SHEET

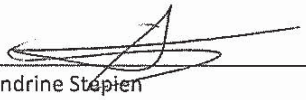
Study: TRIUMPH

Title:

A prospective, open, randomised controlled clinical trial of a fixed dose combination blood pressure lowering pill ("Triple Pill")-based strategy compared to usual care among individuals with persistent mild-to-moderate hypertension on no or minimal drug therapy, augmented by a cost-effectiveness analysis and a formal process evaluation.

Principal Author of Analysis Plan: Sandrine Stepien
QC reviewer:
Version: 4.0 (Final)
Version date: 15NOV2017

The undersigned have reviewed this plan and find it to be consistent with the requirements of the protocol as it applies to their respective areas. The principal author also finds this plan to be in compliance with ICH-E9 as well as The George Institute's SOP ST-SOP-04.



16 NOV 2017

Author: Sandrine Stepien — Date
Biostatistician

16th Nov 2017

Reviewer: Anushka Patel — Date
Chief Scientist

Table of contents

1. Modification history

Unique Identifier for this Version	Date of the Document Version	Author	Significant Changes from Previous Authorized Version
1.0	16MAY2017	Sandrine Stepien	N/A – First Version
2.0	12JUL2017	Sandrine Stepien	Integrate comments Create the table shells
3.0	18SEP2017	Sandrine Stepien	2nd round of comments Update covariate adjustement analysis
4.0	15NOV2017	Sandrine Stepien	Final version completed after blind review meeting: Added clarification on selection of blood pressure valid data for analysis Adding 1 table on pill burden and nature of change of BP lowering Updated section 6.3. Removed the condition of p<0.05 for primary endpoint to then investigate subgroup analysis

2. Introduction

This document describes the intended statistical analyses to be performed on data collected in the TRIUMPH trial. It describes, in detail, the data and variables to be summarized and analysed, including specifics of the statistical analyses to be performed. This document is based on the protocol version 5.0 – 23rd February, 2016.

It is intended to be stand-alone from the protocol and adhere to the main points in the analysis summary specified in the protocol. However the Statistical Analysis Plan can undergo revision outside of the protocol version 5.0 – 23rd February, 2016.

The analysis plan also outlines the proposed layout of tables and figures that will be presented.

3. Study objectives

This trial has been designed to understand the effectiveness, cost-effectiveness and acceptability of a simplified strategy using a fixed dose combination 3-in-1 blood pressure (BP) lowering pill ("Triple Pill") for the management of hypertension in Sri Lanka.

3.1. Primary objective

The primary objective of this study is to determine whether BP control is improved with a strategy of early use of a Triple Pill compared to usual care at end of follow-up visit.

3.2. Secondary objectives

Secondary objectives of this study are to assess the effectiveness of BP control at earlier time points, tolerability of treatment, self-reported BP lowering medication use, the cost effectiveness of such strategy and finally to investigate the acceptability to clinicians and patients.

3.3. Process Evaluation

The acceptability and feasibility of the process will be examined to understand the potential barriers and enablers to implementing a Triple Pill-based strategy to enhance prescriber and consumer adherence to the indicated therapies.

Those sections are not described in this statistical analysis plan (SAP). See separate analysis plan for the process evaluation analysis.

3.4. Economic evaluation

A cost-effectiveness analysis, taking a health system perspective, will compare the Triple Pill strategy with usual care. See separate analysis plan for the economic evaluation analysis.

4. Study design

4.1. General Description

TRIUMPH trial is a randomised, open, controlled trial with 24 weeks (6 months) of follow-up. The study is conducted in Sri Lanka, recruiting participants with persistent mild-to-moderate hypertension from urban tertiary level hospitals.

Intervention or standard care have been randomly allocated, in a 1:1 ratio, to 700 patients

who consented to participate to the trial and who have persistent hypertension requiring initiation or intensification of pharmacological treatment.

- The control group continue to receive their usual blood pressure management,
- The Triple Pill group commences intervention treatment at the lower strength of Triple Pill with the option to titrate upwards to strength 2 at subsequent follow-up visits.
    - ✓ Strength 1: Low dose: Telmisartan 20mg, Amlodipine 2.5mg, Chlorthalidone 12.5mg
    - ✓ Strength 2: High dose: Telmisartan 40mg, Amlodipine 5mg, Chlorthalidone 25mg

4.2. Control/Intervention Groups

4.2.1. Description

The usual care group for blood pressure management includes prescribed drugs as per usual practice.

Triple Pill group has a 2 strength option (low/high). For participants randomised to Triple Pill arm, their previous BP lowering medications is withdrawn (if applicable) and then they commence intervention treatment at the lower strength of Triple Pill with the option to titrate upwards to strength 2 at subsequent follow-up visits. Dosage is one Triple Pill once daily for the trial duration. Timing of dosage is at the discretion of the responsible clinician. Triple Pill is dispensed from the trial centre at randomisation, 6 week and 12 week visits.

4.2.2. Method of Assigning Patients to Control/Intervention Groups

Randomisation is accessible through a central, computer-based randomization service, and is stratified by study centre and prescription of BP lowering therapy at baseline. The random allocation sequence is 1:1 (control:intervention) allocation ratio.

4.2.3. Blinding

This study is open label. Blinding of trial participants to study treatment allocation is not possible because the comparator is usual care. Bias that may arise from the unblinded measurement of blood pressure will be minimised by audited comparison of CRF entries with the printed values of automated blood pressure-measuring device by the trial monitor. During the review of the results within the trial team, all investigators will be blinded to treatment allocation.

4.3. Determination of Sample Size

Clinical trials investigating the effect of triple BP lowering vs. dual combination therapy (EXFORGE)20 and simplification of treatment protocols including usage of dual combination BP lowering therapy (STITCH)15 have shown absolute improvements of around 12% in BP control. Based on published data6, we expect current usual care BP control rates in this population to be 30%-40%. A sample size of 700 participants will provide 90% power at alpha=0.05, (assuming 5% loss to follow-up with only 24 weeks of follow-up) to allow detection of at least a 12% absolute improvement in control rates from 50% to at least 62% (relative risk of 1.24). This allows for some improvement in the usual care group's control rates that may occur because of trial participation. An extremely low rate of loss to follow-up is anticipated because of the short duration of follow-up and as per our experience in the

UMPIRE trial (~3% in 15 months).

4.4. Changes in the Conduct of the Study or Planned Analyses

4.4.1. Changes in the Conduct of the Study

Not applicable.

4.4.2. Changes in Planned Analysis

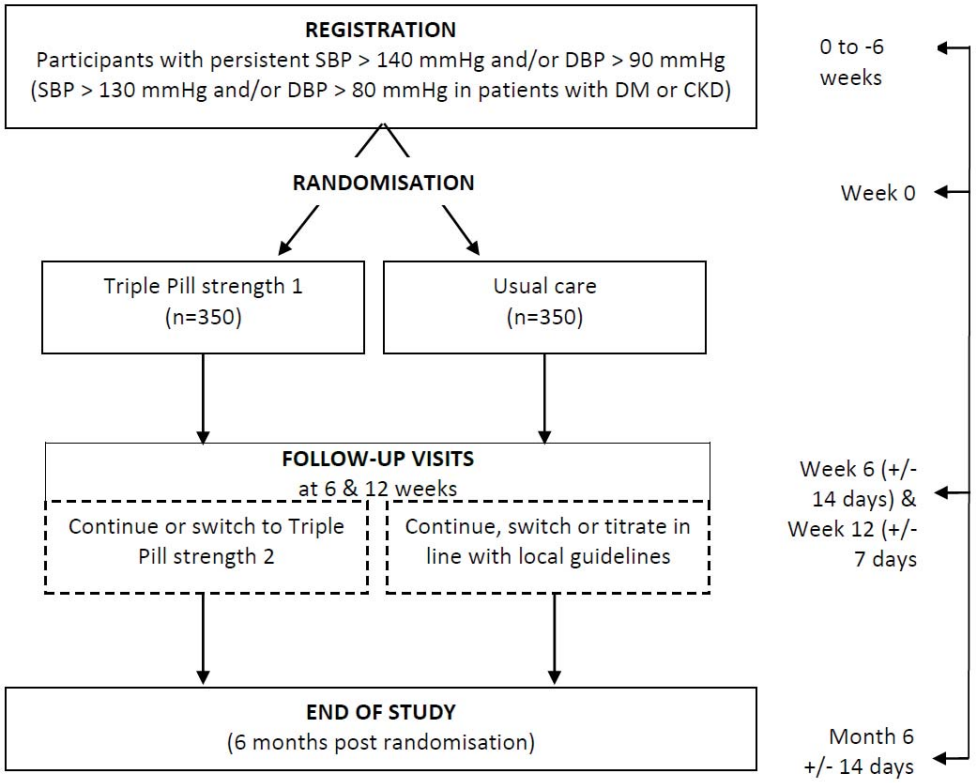
For the primary analysis the protocol suggests comparing the proportion of participants achieving target blood pressure control at the end of follow up by using an unadjusted chi-square test. However the following paper; *Kahan BC, Morris TP. Improper analysis of trials randomised using stratified blocks or minimisation. Stat Med 2012;31: 328-40;* has shown that the stratification variables need to be considered into the model for analysing the primary outcome.

Therefore, the primary analysis will be a log-binomial regression (i.e. a generalised linear model with a binomial distribution and a logarithmic link – see www.ats.ucla.edu/stat/sas/faq/relative_risk.htm) with treatment group, prescription of BP lowering therapy at baseline as fixed effects and center as random effect. Relative risks will be presented with related p-value.

During the blind review process it was decided that blood pressure values that have been collected during a phone visit will be considered missing in the analysis.

5. Efficacy and Safety Variables

5.1. Schedule of Evaluations



5.2. Schedule of Events

Evaluation	Screening	Week 0	Week 6 (+/- 14 days)	Week 12 (+/- 7 days)	Week 24 (6 Month) (+/- 14 days) /EOS
Demographics	X				
Medical history	X				
Height, weight		X			
Blood pressure, heart rate	X	X	X	X	X
Blood biochemistry ✓ Fasting blood glucose and lipids ✓ Creatinine, uric acid, electrolytes and LFTs	X	X			X
Urine protein (albumin) test	X				X
Medication adherence		X	X	X	X
Dispensation of Triple Pill		X	X	X	
Triple Pill accountability			X	X	X
Quality of life (EQ-5D)		X			X
Health care visits		X	X	X	X
Serious Adverse Events		X	X	X	X

5.3. Primary Efficacy Variable

Proportion of participants achieving target BP at end of follow up: SBP < 140 mmHg and DBP < 90 mmHg (SBP < 130 mmHg and DBP < 80 mmHg for patients with diabetes and/or chronic kidney disease).

5.4. Secondary Efficacy Variables

The secondary variables are:

- Proportion of participants with BP control (as defined in 5.3) at 6 and 12 weeks
- Mean change in SBP and DBP at end of follow up
- Tolerance to treatment at end of follow up
- Use of health care services (hospitalizations, medical consultations, tests)
- Self-reported BP lowering medication use (7-day recall) at end of follow up – adherence defined as the participant taking the drug for at least 4 out of the last 7 days
- Quality of life at end of follow up.

5.5. Other Efficacy Variables

Frequency and nature of changes (additions, withdrawal, dose adjustments) to the BP lowering regimen.

5.6. Safety Assessments

The safety variables are:

- The proportion of patients with adverse events and serious adverse events
- The blood biochemistry parameters
- Urine protein test.

6. Statistical Methods

6.1. General Methodology

SAS version 9.3 or any relevant recognized statistical software for academic studies will be used in the statistical analysis.

No visit window will be applied to determine the inclusion of the visit assessment in the analysis. Any visits outside the visit window range will be reported in the protocol deviation listing.

All statistical tests will be two-tailed and a 5% significance level maintained throughout the analyses. All intervention evaluations will be performed on the principle of 'intention to treat' unless otherwise specified.

Methods of handling missing data for the primary and secondary endpoints are described section 6.2 of this SAP. No adjustments for multiplicity are planned for the primary and secondary endpoints.

Summaries of continuous baseline variables will be presented as means and standard deviations together with medians and inter-quartile ranges. Categorical variables will be presented as frequencies and percentages.

Mock tabular are shown in the Appendix of this document.

6.2. Handling of Dropouts or Missing Data

Dropouts will not be replaced in this study.

The percentage of missing data and dropouts will be investigated in order to confirm the power of the analysis being 90% still.

If more than 10% of the blood pressure data (either diastolic or systolic blood pressure) are missing, a multiple imputation technique will be used to investigate the results and conclusions on the data analysis. This is will be implemented and discussed in further details at the time of data base lock (blind review) if the threshold of 10% of missing data is reached.

6.3. Adjustments for Covariates

At this stage no further adjustment than the ones planned for the primary analysis will be made. However in the case of unexpected important imbalances in baseline variables considered to be potential confounders, we will run an adjusted model by adding the unbalanced baseline variables in the model. Also while investigating the data, if it seems important to look at some additional adjustments, a post-hoc analysis will be described and run at a later stage.

6.4. Interim Analyses and Data Monitoring

6.4.1. Blind review

Between the first SAP sign-off and unblinding, a brief blind review will be performed to assess the amount of data that is missing or inconsistent. The blind review will :

- ✓ Investigate visit window deviations: flag any deviation for authorised time frame with visit windows.
- ✓ check the number of phone visits with blood pressure recordings
- ✓ describe how to handle missing data for missing blood pressure and self reported adherence at all visits
- ✓ looking at how many patients per sites and assessing if grouping of study sites are required for purpose of analysis.
- ✓ examine medications data for completeness and accuracy of reporting of combination medications.

If the number of deviations is high and may impact the final analysis, the SAP will be revised to account for additional sensitivity analysis in order to refine/confirm the methods described in this SAP.

6.5. Multicenter Studies

This study is stratified by centre and as a consequence the primary analysis will be revised and adjusted by center (as well as by other stratification variables). (see 4.4.2)

6.6. Multiple Comparisons/Multiplicity

No multiple comparison adjustments will be made.

6.7. Examination of Subgroups

The following pre-specified subgroup analyses will be conducted on the primary efficacy variable:

- Age (split by the median)
- Sex
- Diabetes
- Chronic renal disease (see section 7.5.1.1 for definition)
- Education (high/low)
- Economic strata
- Systolic blood pressure at baseline into tertiles
- Diastolic blood pressure at baseline into tertiles
- By BP lowering treatment at baseline (no treatment vs monotherapy)

For each subgroup analysis a model will include the subgroup variable along with its interaction with treatment. A test of whether the treatment effect differs across the levels of the subgroup will be constructed by assessing the significance of the interaction term. The results of these subgroup analyses will be treated with caution as this study was not powered for these analyses. Forest plots will be prepared for ease of presentation.

7. Statistical Analysis

7.1. Disposition of Subjects

All subjects screened and randomised will be accounted for. All post-randomisation discontinuations will be summarised overall and by time of discontinuation. Reason for discontinuation will also be summarised.

Subject disposition will be based on the screened set and tabulated for the following categories:

- Total number of subjects screened
- Total number of subjects randomised
- Number (percentage) of subjects completing the study
- Number (percentage) of subjects prematurely discontinuing from the study
- Primary reason for premature discontinuation
- Number of subjects in the Safety analysis set
- Number of subjects in the ITT analysis set

For each analysis set, reasons for exclusion from the analysis set will be carefully described. The flow of subjects will be presented using a consort

7.2. Selection of Subjects to be included in the Analyses

Safety

- Some post-randomisation data relating to safety are available.

Intent-to-treat (ITT)

- Received at least one dose of Triple Pill for the Intervention arm
- Some post-randomisation data of SBP and DBP are available

7.3. Baseline Characteristics

Baseline demographic variables such as:

- age,
- sex,
- body mass index (BMI),
- height,
- weight,
- systolic blood pressure,
- diastolic blood pressure,
- heart rate,
- lifestyle status: smoking habit and drinking habit,
- socio economics,
- medical History: CVD, diabetes,
- baseline medications : Blood pressure lowering, other cardiovascular medications, any alternative medicine for hypertension or CVD,
- pregnancy status

will be summarised per group (control/intervention) on the randomised population.

See the Appendix for a list of tables that will be used for presenting baseline characteristics.

Systolic and diastolic blood pressure as well as heart rate values summarised in the descriptive tables will be the mean value of the second and third measurements.

Smoking habit refers to cigarette/pipe current smokers, former smokers as well as current and former tobacco chewing habits.

7.4. Medications

7.4.1. Variable descriptions/derivations

Medications will be classified into the following categories: antiplatelet, cholesterol lowering, BP lowering, other.

Concomitant medications are all medications that started or were ongoing from randomisation (Week 0) to the end of study.

7.4.2. Analysis

Concomitant medications will be summarised descriptively and presented by treatment group and drug category.

7.5. Analysis of Efficacy

7.5.1. Primary Analysis

7.5.1.1. Variable descriptions/derivations

Systolic and Diastolic values used for this analysis, will be the average value of the second and third measurements done at end of follow up, then classified into BP control target Yes/No as follow:

- ✓ For subjects with no diabetes and no chronic kidney disease: SBP < 140 mmHg and DBP < 90 mmHg.
- ✓ For subjects with diabetes and/or chronic kidney disease: SBP < 130 mmHg and DBP < 80 mmHg.
- ✓ Diabetes and Chronic Kidney Disease status will be re-classified at Week 6 and Week 12 visits according to any new diagnoses recorded in trial documentation. A new diagnosis of diabetes will also be noted with any new prescription of a hypoglycemic drug.
    - o Incident DM/CKD patients will have the same blood pressure targets applied as prevalent patients i.e. SBP <130 mmHg and DBP < 80 mmHg.
- ✓ Diabetes and Chronic Kidney Disease status will be re-classified at end of follow up visit as per the following:
    - o New onset diabetes mellitus – defined as new diagnosis of diabetes mellitus as recorded in trial documentation, fasting plasma glucose $\geq$ 7.0 mmol/L at the end of follow up visit, or new prescription of hypoglycaemic drugs
    - o New Onset CKD- Defined as new diagnosis of CKD as recorded in trial documentation, GFR/eGFR <60 mL/min/1.73m^2 or Urine Albumin-to-Creatinine ratio > 30 mg/g at any visit.
    - o Incident DM/CKD patients will have the same blood pressure targets applied as prevalent patients i.e. SBP <130mmHg and DBP <80mmHg.

Blood pressure values recorded during a phone visit will be considered missing for the analysis.

7.5.1.2. Analysis

The proportion of participants achieving target blood pressure control at end of follow up visit will be summarized descriptively as well as analysed using log-binomial regression with treatment group and prescription of BP lowering therapy as fixed effects and center entered as random effect. Proportions by treatment groups with 95% Confidence Intervals (CI) will be presented along with the associated estimated relative risk and its corresponding p-value.

7.5.2. Secondary Analyses

7.5.2.1. Variable descriptions/derivations

- The proportion of participants achieving target blood pressure control at 6 and 12 weeks:

  The derivation of patient meeting the target BP is described in section 7.3.1.2.

- Tolerance to treatment:

  Reported Adverse Events (AE), serious AEs and reason for withdrawal.

- Self-reported BP lowering medication use (7-day recall) at end of follow up visit:

  Adherence is defined as the participant taking the drug for at least 4 out of the last 7 days. This information is self-reported.

- Quality of life (EQ-5D-3L) at end of follow up visit

  EQ-5D with 3 levels will be used for this study. EQSL scores will be derived as shown in appendix 1 with description of coefficients and computation of the global score.

7.5.2.2. Analysis

The proportion of participants achieving BP control target at 6 and 12 weeks will be descriptively summarised and similarly analysed as the primary endpoint (see section 7.3.1.2).

Change from baseline for blood pressure values will be summarised descriptively by treatment group and visits. An analysis of covariance on change from baseline at end of follow up visit will also be presented.

A longitudinal analysis of change from baseline BP over time will include the following terms: treatment group, visit as a categorical variable, a treatment-by-visit interaction, the baseline value (i.e. baseline SBP or baseline DBP), prescription of BP lowering therapy at baseline, as well as center.

```
class   TREATMENT_GROUP_ID VISIT PATIENT_ID CENTER BL_PRESCRIPTION;
model   BP = BASELINE_BP BL_PRESCRIPTION VISIT TREATMENT_GROUP_ID
                  VISIT*TREATMENT_GROUP_ID;
random   INTERCEPT / sub=CENTER ;
repeated VISIT / type=un subject=PATIENT_ID;
lsmeans VISIT*TREATMENT_GROUP_ID / diff=all slice=VISIT cl;
estimate "Overall difference"     VISIT       0   0   0
                     TREATMENT_GROUP_ID      42   -42
               VISIT*TREATMENT_GROUP_ID      6  12  24   -6  -12  -24/ divisor=42 cl;
```

Mean difference between intervention and control and corresponding 95% CI for each post

baseline visit will be estimated with the above model by using the appropriate coefficients and contrasts.

Self reported adherence (Yes/No) at end of follow up visit will be analysed using the descriptive statistics and analysed as per primary analysis model described in section 7.3.1.2. This will be repeated for week 6 and 12.

A longitudinal analysis of adherence over time will include the following terms: treatment group, visit as a categorical variable, a treatment-by-visit interaction, prescription of BP lowering therapy at baseline, as well as center.

EQ-5D-3L EQSL score (health state score) will be analysed using an analysis of covariance using the following terms: treatment group, the baseline EQSL score, prescription of BP lowering therapy at baseline as fixed effects and center as random effect. The estimated means by treatment group and the mean difference at end of follow up visit will be presented along with 95% CI and corresponding p-value.

7.5.3. Other efficacy Analysis

The frequency and nature of changes (additions, withdrawal, dose adjustments) to the BP lowering regimen will be investigated. Proportion of patients in both arms on 0, 1, 2, 3 or 4+ BP lowering medications will be described as will the pill burden (number of pills taken) for BP lowering medications and overall.

7.5.4. Subset Analyses

There is no planned subset analysis for this trial.

7.6. Analysis of Safety

All safety analysis will be run on the safety population as described paragraph 6.3.

7.6.1. Adverse Events and Serious Adverse Events

7.6.1.1. Variable descriptions/derivations

A treatment emergent is defined as an AE occurring on or after the first intake date.

Drug related AEs are AEs with a causality to drug being possibly, probably, definitely related or with a missing causality.

A Serious Adverse Event (SAE) is any AE that meets 1 or more of the following criteria:

- Results in death;
- Is life-threatening;
- Requires in-patient hospitalisation or prolongation of existing hospitalisation;
- Results in persistent or significant disability/incapacity;
- Results in a congenital anomaly/birth defect.

7.6.1.2. Analysis

Number of events and numbers and proportions of subjects experiencing AEs will be tabulated by treatment group received and overall. AEs and SAEs will be classified according to the MeDRA v18.1 (Medical Dictionary for Regulatory Activities) system and summarized by system organ class and preferred term. SAEs and drug related AEs will also be tabulated separately by treatment group.

No inferential statistics will be used to compare proportions between treatment groups.

Mock tables 17 to 19 show how AEs should be summarized and displayed in each outputs.

7.6.2. Blood Biochemistry and Urine

Blood biochemistry and urine parameters will be collected according to the schedule of events (screening/week 0 and end of follow up visit). Actual values and changes from baseline will be descriptively summarized by treatment group and overall.

7.7. Other analysis

Not applicable.

8. References

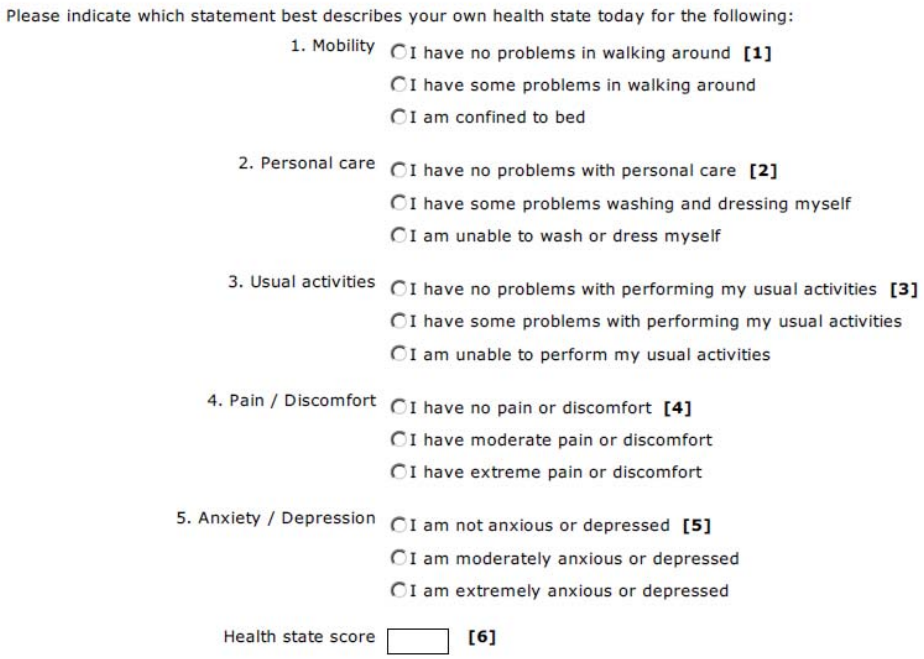
Altman DG. Practical Statistics for Medical Research. London: Chapman and Hall, 1991.

Kahan BC, Morris TP. Improper analysis of trials randomised using stratified blocks or minimisation. Stat Med 2012;31: 328-40

9. List of tables

10. List of listings

11. Appendix 1 – EQ-5D 3Lcomponents derivation


Please indicate which statement best describes your own health state today for the following:

1. Mobility
- I have no problems in walking around **[1]**
- I have some problems in walking around
- I am confined to bed

2. Personal care
- I have no problems with personal care **[2]**
- I have some problems washing and dressing myself
- I am unable to wash or dress myself

3. Usual activities
- I have no problems with performing my usual activities **[3]**
- I have some problems with performing my usual activities
- I am unable to perform my usual activities

4. Pain / Discomfort
- I have no pain or discomfort **[4]**
- I have moderate pain or discomfort
- I have extreme pain or discomfort

5. Anxiety / Depression
- I am not anxious or depressed **[5]**
- I am moderately anxious or depressed
- I am extremely anxious or depressed

Health state score [ ] **[6]**

coefficients to apply to health state scores

EQ-5D-3L value set for Sri Lanka		Example: the value health state of 12133
constant	1	Constant = 1
Mobility=2	-0.166	
Mobility=3	-1.071	
Self care=2	-0.119	- 0.119
Self care=3	-0.337	
Usual activities=2	-0.071	
Usual activities=3	-0.419	
Pain/discomfort=2	-0.057	
Pain/discomfort=3	-0.300	-0.300
Anxiety/depression=2	-0.044	
Anxiety/depression=3	-0.194	-0.194
		State 12133 = 0.387

12. Appendix 2 – Table shells

Table 1: Disposition of patients at End of Study

Number of patients	Intervention	Control	Total
Screened			xxx
Randomised	xxx (100%)	xxx (100%)	xxx (100%)
Completed	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Discontinued	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Reason for discontinuation			
Death	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
SAE	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Participant withdrew consent	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Lost to follow-up	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Other	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)

Note:
Percentages for randomised, completed and discontinued are based on the number of randomised patients
Percentages of the different reasons for discontinuation are based on the number of patients who discontinued from the study

Table 2: Data available for primary endpoint analysis – Intent to treat population

Visit Parameters	Intervention (N = xxx)	Control (N = xxx)	Total (N = xxx)
Baseline			
Systolic BP (mmHg)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Diastolic BP (mmHg)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
End of Follow-up			
Systolic BP (mmHg)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Diastolic BP (mmHg)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Both assessments and both Parameters	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)

Note:
Percentages are based on the number of patients in the intent to treat population

Table 3: Baseline characteristics – Randomised population

Characteristics	Intervention (N = xxx)	Control (N = xxx)	Total (N = xxx)
Age (years)			
n	xxx	xxx	xxx
Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
Median (IQR)	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)
Sex			
Male	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Female	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
BMI (kg/m^2)			
n	xxx	xxx	xxx
Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
Median (IQR)	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)
BMI > 25 kg/m^2	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Weight (kg)			
n	xxx	xxx	xxx
Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
Median (IQR)	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)
Height (cm)			
n	xxx	xxx	xxx
Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
Median (IQR)	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)
Systolic blood pressure (mmHg) (1)			
n	xxx	xxx	xxx

Characteristics	Intervention (N = xxx)	Control (N = xxx)	Total (N = xxx)
Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
Median (IQR)	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)
SBP > 140 mmHg (2)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Diastolic blood pressure (mmHg) (1)			
n	xxx	xxx	xxx
Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
Median (IQR)	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)
DBP > 90 mmHg (3)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Heart rate (bpm) (1)			
n	xxx	xxx	xxx
Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
Median (IQR)	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)
Received one blood pressure lowering medication (4)			
Yes	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
No	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)

Note (1) average of the 2 last recordings for that visit. Done at resting, sitting position at week 0.
Note (2) if diabetic and/or has CKD then SBP > 130 mmHg
Note (3) if diabetic and/or has CKD then DBP > 80 mmHg
Note (4) stratification factor

Table 4: Baseline lifestyle characteristics – Randomised Population

Parameter	Intervention (N = xxx)	Control (N = xxx)	Total (N = xxx)
Current smoker (1)	xx (xx.x%)	xx (xx.x%)	xxx (xx.x%)
Cigarettes smoked per day			
n	xxx	xxx	xxx
Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
Median (IQR)	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)
Pipes smoked per day			
n	xxx	xxx	xxx
Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
Median (IQR)	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)
Number of years being a smoker			
n	xxx	xxx	xxx
Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
Median (IQR)	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)
Former smoker	xx (xx.x%)	xx (xx.x%)	xxx (xx.x%)
Cigarettes smoked per day			
n	xxx	xxx	xxx
Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
Median (IQR)	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)
Pipes smoked per day			
n	xxx	xxx	xxx
Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
Median (IQR)	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)

Parameter	Intervention (N = xxx)	Control (N = xxx)	Total (N = xxx)
Number of years being a smoker			
n	xxx	xxx	xxx
Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
Median (IQR)	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)
Number of years since stopped smoking			
n	xxx	xxx	xxx
Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
Median (IQR)	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)
Current tobacco chewer	xx (xx.x%)	xx (xx.x%)	xxx (xx.x%)
Times per day			
n	xxx	xxx	xxx
Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
Median (IQR)	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)
Number of years being a chewer			
n	xxx	xxx	xxx
Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
Median (IQR)	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)
Former tobacco chewer	xx (xx.x%)	xx (xx.x%)	xxx (xx.x%)
Times per day			
n	xxx	xxx	xxx
Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
Median (IQR)	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)
Number of years being a chewer			
n	xxx	xxx	xxx

Parameter	Intervention (N = xxx)	Control (N = xxx)	Total (N = xxx)
Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
Median (IQR)	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)
Number of years since stopped chewing			
n	xxx	xxx	xxx
Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
Median (IQR)	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)
Tobacco user (2)	xx (xx.x%)	xx (xx.x%)	xxx (xx.x%)
Current drinker	xx (xx.x%)	xx (xx.x%)	xxx (xx.x%)
Number of standard drinks per week			
n	xxx	xxx	xxx
Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
Median (IQR)	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)

Note: (1) current smokers include cigarettes and pipes smokers.
Note: (2) tobacco users includes patients smoking cigarettes or pipes as well as tobacco chewers.

Table 5: Socio economic characteristics – Randomised Population

Parameter	Intervention (N = xxx)	Control (N = xxx)	Total (N = xxx)
Education			
None	xx (xx.x%)	xx (xx.x%)	xxx (xx.x%)
Primary school	xx (xx.x%)	xx (xx.x%)	xxx (xx.x%)
Secondary school	xx (xx.x%)	xx (xx.x%)	xxx (xx.x%)
Undergraduate degree	xx (xx.x%)	xx (xx.x%)	xxx (xx.x%)
Postgraduate degree or diploma	xx (xx.x%)	xx (xx.x%)	xxx (xx.x%)
Technical/vocational qualification	xx (xx.x%)	xx (xx.x%)	xxx (xx.x%)
Employment type			
Full-time paid	xx (xx.x%)	xx (xx.x%)	xxx (xx.x%)
Part-time paid	xx (xx.x%)	xx (xx.x%)	xxx (xx.x%)
Unpaid	xx (xx.x%)	xx (xx.x%)	xxx (xx.x%)
Main lifetime occupation			
Manager	xx (xx.x%)	xx (xx.x%)	xxx (xx.x%)
Professional	xx (xx.x%)	xx (xx.x%)	xxx (xx.x%)
Technicians / trade	xx (xx.x%)	xx (xx.x%)	xxx (xx.x%)
Community / Personal services	xx (xx.x%)	xx (xx.x%)	xxx (xx.x%)
Sales	xx (xx.x%)	xx (xx.x%)	xxx (xx.x%)
Machine operators / driver	xx (xx.x%)	xx (xx.x%)	xxx (xx.x%)
Labourer	xx (xx.x%)	xx (xx.x%)	xxx (xx.x%)
Home duties	xx (xx.x%)	xx (xx.x%)	xxx (xx.x%)
Clerical / admin worker	xx (xx.x%)	xx (xx.x%)	xxx (xx.x%)
Income (per month) (1)			
<5000	xx (xx.x%)	xx (xx.x%)	xxx (xx.x%)
5000 -< 20 000	xx (xx.x%)	xx (xx.x%)	xxx (xx.x%)
20 000 -< 50 000	xx (xx.x%)	xx (xx.x%)	xxx (xx.x%)
50 000 -< 75 000	xx (xx.x%)	xx (xx.x%)	xxx (xx.x%)

Parameter	Intervention (N = xxx)	Control (N = xxx)	Total (N = xxx)
75 000 - 150 000	xx (xx.x%)	xx (xx.x%)	xxx (xx.x%)
> 150 000	xx (xx.x%)	xx (xx.x%)	xxx (xx.x%)
Unknown	xx (xx.x%)	xx (xx.x%)	xxx (xx.x%)
Routine medications covered by			
Provided by a government scheme	xx (xx.x%)	xx (xx.x%)	xxx (xx.x%)
Paid by the participant	xx (xx.x%)	xx (xx.x%)	xxx (xx.x%)
Covered by health insurance	xx (xx.x%)	xx (xx.x%)	xxx (xx.x%)
Provided free by hospital	xx (xx.x%)	xx (xx.x%)	xxx (xx.x%)
Other	xx (xx.x%)	xx (xx.x%)	xxx (xx.x%)

Note (1) total gross monthly income of the participant's household.

Table 6: Medical History – Randomised population

Risk factors	Intervention (N = xxx)	Control (N = xxx)	Total (N = xxx)
Coronary artery disease	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Heart failure	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Atrial fibrillation	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Cerebrovascular disease	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Peripheral vascular disease	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Gout	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Chronic Kidney Disease	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Diabetes	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Years with diagnosed diabetes			
n	xxx	xxx	xxx
Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
Median (IQR)	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)
Type of diabetes (1)			
Type 1	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Type 2	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
HbA1c result >8% in past 12 months			
Yes	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
No	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Unknown	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)

Risk factors	Intervention (N = xxx)	Control (N = xxx)	Total (N = xxx)
Family history of heart disease or ischaemic stroke	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)

Note: (1) percentages are computed using the number of patients with diabetes as the denominator.

Table 7: Baseline medications – Randomised population

Medication	Intervention (N = xxx)	Control (N = xxx)	Total (N = xxx)
Blood pressure lowering medications	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Any other cardiovascular medications	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Any alternative medicine for hypertension or CVD	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Other	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)

Table 8: Concomitant medications – Safety population

Medication	Intervention (N = xxx)	Control (N = xxx)	Total (N = xxx)
antiplatelets	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
BP lowering	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Cholesterol lowering	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Other	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)

Table 9: Frequency and nature of changes to the BP lowering regimen - Intent to treat population

Parameter	Visit		Intervention (N = xxx)	Control (N = xxx)	Total (N = xxx)
BP lowering medications	Baseline	0	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)
		1	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)
		2	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)
		3	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)
		4+	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)
	Week 6	0	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)
		1	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)
		2	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)
		3	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)
		4+	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)
	Repeat for week 12 and End of Follow-up				
Number of pills taken for BP lowering medications	Baseline	0	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)
		1	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)
		2	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)
		3	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)
		4+	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)
	Repeat for week 6, 12 and End of Follow-up				
Number of pills taken for all medications	Repeat as above				

Parameter	Visit		Intervention (N = xxx)	Control (N = xxx)	Total (N = xxx)
Dose adjustment	Week 6	Yes	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)
		No	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)
	Week 12	Yes	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)
		No	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)
Stopping BP lowering medication	Week 0 to Week 6	Yes	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)
		No	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)
	Repeat for Week 6 to Week 12, Week 12 to Week 24				
Main Reason for stopping BP lowering medication	Week 6	Dizziness	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)
		Hypotension	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)
		Headache	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)
		Fatigue	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)
		Cough	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)
		Edema	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)
		Somnolence	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)
		Stomach upset or stomach pain	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)
		Nausea or Vomiting	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)
		Diarrhea	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)
		Constipation	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)
		Electrolyte imbalance	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)

Parameter	Visit		Intervention (N = xxx)	Control (N = xxx)	Total (N = xxx)
		Hyperglycemia	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)
		Elevated liver enzymes	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)
		Hypersensitivity reaction	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)
		Other side effect	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)
		Change in regimen to reduce amount of BP lowering	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)
		Change in regimen to increase amount of BP lowering	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)
		doctor decision	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)
		participant decision	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)
		Other	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)
	Repeat for week 12 and End of Follow-up				

Table 10: Vital signs – Descriptive statistics – Actual values - Intent to treat population

Parameter Visit	Intervention (N = xxx)	Control (N = xxx)	Total (N = xxx)
Systolic blood pressure (mmHg)			
Baseline			
n	xxx	xxx	xxx
Mean (SD)	xxx.x (xxx.xx)	xxx.x (xxx.xx)	xxx.x (xxx.xx)
Median (IQR)	xxx.x (xxx.x, xxx.x)	xxx.x (xxx.x, xxx.x)	xxx.x (xxx.x, xxx.x)
Week 6			
n	xxx	xxx	xxx
Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
Median (IQR)	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)
Week 12			
n	xxx	xxx	xxx
Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
Median (IQR)	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)
End of Follow-up			
n	xxx	xxx	xxx
Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
Median (IQR)	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)
Diastolic blood pressure (mmHg)			
Baseline			
n	xxx	xxx	xxx
Mean (SD)	xxx.x (xxx.xx)	xxx.x (xxx.xx)	xxx.x (xxx.xx)
Median (IQR)	xxx.x (xxx.x, xxx.x)	xxx.x (xxx.x, xxx.x)	xxx.x (xxx.x, xxx.x)
Week 6			
n	xxx	xxx	xxx
Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
Median (IQR)	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)
Week 12			
n	xxx	xxx	xxx

Parameter Visit	Intervention (N = xxx)	Control (N = xxx)	Total (N = xxx)
Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
Median (IQR)	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)
End of Follow-up			
n	xxx	xxx	xxx
Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
Median (IQR)	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)
Heart rate (bpm)			
Baseline			
n	xxx	xxx	xxx
Mean (SD)	xxx.x (xxx.xx)	xxx.x (xxx.xx)	xxx.x (xxx.xx)
Median (IQR)	xxx.x (xxx.x, xxx.x)	xxx.x (xxx.x, xxx.x)	xxx.x (xxx.x, xxx.x)
Week 6			
n	xxx	xxx	xxx
Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
Median (IQR)	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)
Week 12			
n	xxx	xxx	xxx
Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
Median (IQR)	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)
End of Follow-up			
n	xxx	xxx	xxx
Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
Median (IQR)	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)

Note: average of the last 2 recordings for that visit. Done at resting, sitting position.

Figure 1: Vital signs– Mean plot over time – Actual values - Intent to treat population

Present mean plots over time for SBP, DBP by treatment group on the same graph.

Another graph will present HR by treatment group

Table 11: Vital signs – Descriptive statistics – Change from baseline - Intent to treat population

Parameter Visit	Intervention (N = xxx)	Control (N = xxx)	Total (N = xxx)
Systolic blood pressure (mmHg)			
Week 6			
n	xxx	xxx	xxx
Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
Median (IQR)	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)
Week 12			
n	xxx	xxx	xxx
Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
Median (IQR)	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)
End of Follow-up			
n	xxx	xxx	xxx
Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
Median (IQR)	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)
Diastolic blood pressure (mmHg)			
Week 6			
n	xxx	xxx	xxx
Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
Median (IQR)	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)
Week 12			
n	xxx	xxx	xxx
Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
Median (IQR)	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)
End of Follow-up			
n	xxx	xxx	xxx
Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
Median (IQR)	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)
Heart rate (bpm)			

Parameter Visit	Intervention (N = xxx)	Control (N = xxx)	Total (N = xxx)
Week 6			
n	xxx	xxx	xxx
Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
Median (IQR)	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)
Week 12			
n	xxx	xxx	xxx
Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
Median (IQR)	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)
End of Follow-up			
n	xxx	xxx	xxx
Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
Median (IQR)	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)

Note: average of the last 2 recordings for that visit. Done at resting, sitting position.

Figure 2: Vital signs - Mean plot over time – Change from baseline - Intent to treat population

Present mean plots over time for SBP, DBP by treatment group on the same graph.

Another graph will present HR by treatment group

Table 12: Achieving blood pressure target – Intent to treat population

Visit	Intervention (N = xxx)	Control (N = xxx)	RR (95% CI)	P for the difference
Achieving BP target (1) (2)				
Week 6	xxx (xx.x%)	xxx (xx.x%)	x.xxx (x.xxx ;x.xxx%)	0.xxxx
Week 12	xxx (xx.x%)	xxx (xx.x%)	x.xxx (x.xxx ;x.xxx%)	0.xxxx
End of Follow-up (3)	xxx (xx.x%)	xxx (xx.x%)	x.xxx (x.xxx ;x.xxx%)	0.xxxx

Note (1) For subjects with no diabetes and no chronic kidney disease: SBP < 140 mmHg and DBP < 90 mmHg.
For subjects with diabetes and/or chronic kidney disease: SBP < 130 mmHg and DBP < 80 mmHg.

Note (2) log-binomial regression with treatment group and prescription of BP lowering therapy at baseline (Yes/No) as fixed effects and center entered as random effect

Note (3) Primary endpoint.

Table 13: Longitudinal analysis of blood pressure on change from baseline values – Intent to treat population

Parameter Timepoint	Intervention (N = xxx) Mean (95% CI)	Control (N = xxx) Mean (95% CI)	Mean difference (95% CI)	P for the difference
Systolic BP (mmHg)				
Week 6	x.xx (x.xx; x.xx)	x.xx (x.xx; x.xx)	x.xx (x.xx ;x.xx)	0.xxxx
Week 12	x.xx (x.xx; x.xx)	x.xx (x.xx; x.xx)	x.xx (x.xx ;x.xx)	0.xxxx
Week 24	x.xx (x.xx; x.xx)	x.xx (x.xx; x.xx)	x.xx (x.xx ;x.xx)	0.xxxx
Overall				0.xxxx
Diastolic BP (mmHg)				
Week 6	x.xx (x.xx; x.xx)	x.xx (x.xx; x.xx)	x.xx (x.xx ;x.xx)	0.xxxx
Week 12	x.xx (x.xx; x.xx)	x.xx (x.xx; x.xx)	x.xx (x.xx ;x.xx)	0.xxxx
Week 24	x.xx (x.xx; x.xx)	x.xx (x.xx; x.xx)	x.xx (x.xx ;x.xx)	0.xxxx
Overall				0.xxxx

Note: A longitudinal analysis of change from baseline BP over time including the following terms: treatment group, visit as a categorical variable, a treatment-by-visit interaction, the baseline value (i.e. baseline SBP, baseline DBP), prescription of BP lowering therapy at baseline, as well as center. All results presented in this table come from the model.

Table 14: Self reported adherence – Intent to treat population

Visit	Intervention (N = xxx)	Control (N = xxx)	RR (95% CI)	P for the difference
Week 6	xxx (xx.x%)	xxx (xx.x%)	x.xxx (x.xxx ;x.xxx%)	0.xxxx
Week 12	xxx (xx.x%)	xxx (xx.x%)	x.xxx (x.xxx ;x.xxx%)	0.xxxx
End of Follow-up	xxx (xx.x%)	xxx (xx.x%)	x.xxx (x.xxx ;x.xxx%)	0.xxxx

Note (2) log-binomial regression with treatment group and prescription of BP lowering therapy at baseline as fixed effects and center entered as random effect

Table 15: Longitudinal analysis of self-reported adherence – Intent to treat population

Timepoint	Intervention (N = xxx) Mean (95% CI)	Control (N = xxx) Mean (95% CI)	Mean difference (95% CI)	P for the difference
Week 6	x.xx (x.xx; x.xx)	x.xx (x.xx; x.xx)	x.xx (x.xx ;x.xx)	0.xxxx
Week 12	x.xx (x.xx; x.xx)	x.xx (x.xx; x.xx)	x.xx (x.xx ;x.xx)	0.xxxx
Week 24	x.xx (x.xx; x.xx)	x.xx (x.xx; x.xx)	x.xx (x.xx ;x.xx)	0.xxxx
Overall				0.xxxx

Note: A longitudinal analysis of self reported adherence over time including the following terms: treatment group, visit as a categorical variable, a treatment-by-visit interaction, prescription of BP lowering therapy at baseline, as well as center. All results presented in this table come from this pre-specified model.

Table 16: Quality of life - EQ-5D-3L – Descriptive statistics - Intent to treat population

Visit	EQ 5D items	Statistics	Intervention (N = xxx)	Control (N = xxx)	Total (N = xxx)
Baseline	Mobility				
	I have no problems in walking	n/N (%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)
	I have some problems in walking	n/N (%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)
	I am confined to bed	n/N (%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)
	Personal care				
	I have no problems with personal care	n/N (%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)
	I have some problems washing and dressing myself	n/N (%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)
	I am unable to wash and dress myself	n/N (%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)
	Usual activities				
	I have no problems with performing my usual activities	n/N (%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)
	I have some problems with performing my usual activities	n/N (%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)
	I am unable to perform my usual activities	n/N (%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)
	Pain / Discomfort				
	I have no pain or discomfort	n/N (%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)
	I have moderate pain or discomfort	n/N (%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)
	I have extreme pain or discomfort	n/N (%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)
	Anxiety / Depression				
	I am not anxious or depressed	n/N (%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)
	I am moderately anxious or depressed	n/N (%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)
	I am extremely anxious or depressed	n/N (%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)
	Health state score	n	xxx	xxx	xxx
		Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
		Median (IQR)	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)

Visit	EQ 5D items	Statistics	Intervention (N = xxx)	Control (N = xxx)	Total (N = xxx)
End of Follow-up	Mobility				
	I have no problems in walking	n/N (%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)
	I have some problems in walking	n/N (%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)
	I am confined to bed	n/N (%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)
	Personal care				
	I have no problems with personal care	n/N (%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)
	I have some problems washing and dressing myself	n/N (%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)
	I am unable to wash and dress myself	n/N (%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)
	Usual activities				
	I have no problems with performing my usual activities	n/N (%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)
	I have some problems with performing my usual activities	n/N (%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)
	I am unable to perform my usual activities	n/N (%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)
	Pain / Discomfort				
	I have no pain or discomfort	n/N (%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)
	I have moderate pain or discomfort	n/N (%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)
	I have extreme pain or discomfort	n/N (%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)
	Anxiety / Depression				
	I am not anxious or depressed	n/N (%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)
	I am moderately anxious or depressed	n/N (%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)
	I am extremely anxious or depressed	n/N (%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)
	Health state score	n	xxx	xxx	xxx
		Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
		Median (IQR)	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)

Table 17: Quality of life - EQ-5D-3L – Analysis of covariance - Intent to treat population

EQ 5D items	Intervention (N = xxx)	Control (N = xxx)	Mean difference (95% CI)	P-value
Health state score at End of Follow-up	xxx	xxx	xxx	
Mean (95% CI)	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)	0.xxxx

Note EQ-5D-3L EQSL score is analysed using an analysis of covariance with treatment group, the baseline EQSL score, prescription of BP lowering therapy at baseline as fixed effects and center as random effect

Table 18: Laboratory parameters – Safety population

Parameter Visit	Intervention (N = xxx)	Control (N = xxx)	Total (N = xxx)
Total cholesterol (mg/dL)			
Baseline			
n	xxx	xxx	xxx
Mean (SD)	xx.xx (xx.xxx)	xx.xx (xx.xxx)	xx.xx (xx.xxx)
Median (IQR)	xx.xx (xx.xx, xx.xx)	xx.xx (xx.xx, xx.xx)	xx.xx (xx.xx, xx.xx)
End of Follow-up			
n	xxx	xxx	xxx
Mean (SD)	xx.xx (xx.xxx)	xx.xx (xx.xxx)	xx.xx (xx.xxx)
Median (IQR)	xx.xx (xx.xx, xx.xx)	xx.xx (xx.xx, xx.xx)	xx.xx (xx.xx, xx.xx)
Change from baseline			
n	xxx	xxx	xxx
Mean (SD)	xx.xx (xx.xxx)	xx.xx (xx.xxx)	xx.xx (xx.xxx)
Median (IQR)	xx.xx (xx.xx, xx.xx)	xx.xx (xx.xx, xx.xx)	xx.xx (xx.xx, xx.xx)
HDL cholesterol (mg/dL)			
Baseline			
n	xxx	xxx	xxx
Mean (SD)	xx.xx (xx.xxx)	xx.xx (xx.xxx)	xx.xx (xx.xxx)
Median (IQR)	xx.xx (xx.xx, xx.xx)	xx.xx (xx.xx, xx.xx)	xx.xx (xx.xx, xx.xx)
End of Follow-up			
n	xxx	xxx	xxx
Mean (SD)	xx.xx (xx.xxx)	xx.xx (xx.xxx)	xx.xx (xx.xxx)
Median (IQR)	xx.xx (xx.xx, xx.xx)	xx.xx (xx.xx, xx.xx)	xx.xx (xx.xx, xx.xx)

Parameter Visit	Intervention (N = xxx)	Control (N = xxx)	Total (N = xxx)
Change from baseline			
n	xxx	xxx	xxx
Mean (SD)	xx.xx (xx.xxx)	xx.xx (xx.xxx)	xx.xx (xx.xxx)
Median (IQR)	xx.xx (xx.xx, xx.xx)	xx.xx (xx.xx, xx.xx)	xx.xx (xx.xx, xx.xx)
LDL cholesterol (mg/dL)			
etc..			
Repeat for:			
Triglycerides (mg/dL)			
Creatinine (mg/dL)			
Uric acid (mg/dL)			
Sodium (mmol/L)			
Potassium (mmol/L)			
ALT (IU/L)			
AST (IU/L)			
Glucose (mg/dL)			
UAC ratio (mg/dL)			

Table 19: Summary of adverse events – Safety population

Category	Statistics	Intervention (N = xxx)	Control (N = xxx)	Total (N = xxx)
Adverse Events (AEs)	ne / n (%)	xxx / xxx (xx.x%)	xxx / xxx (xx.x%)	xxx / xxx (xx.x%)
Treatment Emergent AEs (TEAEs)	ne / n (%)	xxx / xxx (xx.x%)	xxx / xxx (xx.x%)	xxx / xxx (xx.x%)
Serious TEAEs	ne / n (%)	xxx / xxx (xx.x%)	xxx / xxx (xx.x%)	xxx / xxx (xx.x%)
Related to Triple Pill	ne / n (%)	xxx / xxx (xx.x%)	xxx / xxx (xx.x%)	xxx / xxx (xx.x%)
AE leading to hospitalisation	ne / n (%)	xxx / xxx (xx.x%)	xxx / xxx (xx.x%)	xxx / xxx (xx.x%)
AE leading to death	ne / n (%)	xxx / xxx (xx.x%)	xxx / xxx (xx.x%)	xxx / xxx (xx.x%)

Note : ne is the number of events; n is the number of patients with an event.

Table 20: Treatment emergent adverse events – Safety analysis set

System Organ Class/ Preferred term	Intervention (N = xxx)	Control (N = xxx)	Total (N = xxx)
Total No. of events	xxx	xxx	xxx
Subjects reporting at least one event	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
SOC1	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
PT1	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
PT2	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Etc.			
SOC2	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
PT1	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
PT2	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Etc.			
Etc.			

Note: A TEAE is defined as an AE occurring on or after the first study drug administration. For each SOC or PT, the number and percentage represents subjects with at least one event (one subject is counted at most once within a SOC or PT). The denominator is the number of patients in the safety population.

Table 21: Serious treatment emergent adverse events – Safety analysis set

System Organ Class/ Preferred term	Intervention (N = xxx)	Control (N = xxx)	Total (N = xxx)
Total No. of events	xxx	xxx	xxx
Subjects reporting at least one event	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
SOC1	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
PT1	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
PT2	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Etc.			
SOC2	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
PT1	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
PT2	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Etc.			
Etc.			

Note: A TEAE is defined as an AE occurring on or after the first study drug administration. For each SOC or PT, the number and percentage represents subjects with at least one event (one subject is counted at most once within a SOC or PT). The denominator is the number of patients in the safety population.