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ORIGINAL ARTICLE

CURATE.AI-assisted dose titration for anti-hypertensive personalized therapy: study protocol for a multi-arm, randomized, pilot feasibility trial using CURATE.AI (CURATE.AI ADAPT trial)

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Aims Artificial intelligence–driven small data platforms such as CURATE.AI hold potential for personalized hypertension care by assisting physicians in identifying personalized anti-hypertensive doses for titration. This trial aims to assess the feasibility of a larger randomized controlled trial (RCT), evaluating the efficacy of CURATE.AI-assisted dose titration intervention. We will also collect preliminary efficacy and safety data and explore stakeholder feedback in the early design process.

Methods and results In this open-label, randomized, pilot feasibility trial, we aim to recruit 45 participants with primary hypertension. Participants will be randomized in 1:1:1 ratio into control (no intervention), home blood pressure monitoring (active control; HBPM), or CURATE.AI arms (intervention; HBPM and CURATE.AI-assisted dose titration). The home treatments include 1 month of two-drug anti-hypertensive regimens. Primary endpoints assess the logistical (e.g. dose adherence) and scientific (e.g. percentage of participants for which CURATE.AI profiles can be generated) feasibility, and define the progression criteria for the RCT in a 'traffic light system'. Secondary endpoints assess preliminary efficacy [e.g. mean change in office blood pressures (BPs)] and safety (e.g. hospitalization events) associated with each treatment protocol. Participants with both baseline and post-treatment BP measurements will form the intent-to-treat analysis. Following their involvement with the CURATE.AI intervention, feedback from CURATE.AI participants and healthcare providers will be collected via exit survey and interviews.

Conclusion Findings from this study will inform about potential refinements of the current treatment protocols before proceeding with a larger RCT, or potential expansion to collect additional information. Positive results may suggest the potential efficacy of CURATE.AI to improve BP control.

Trial registration number NCT05376683

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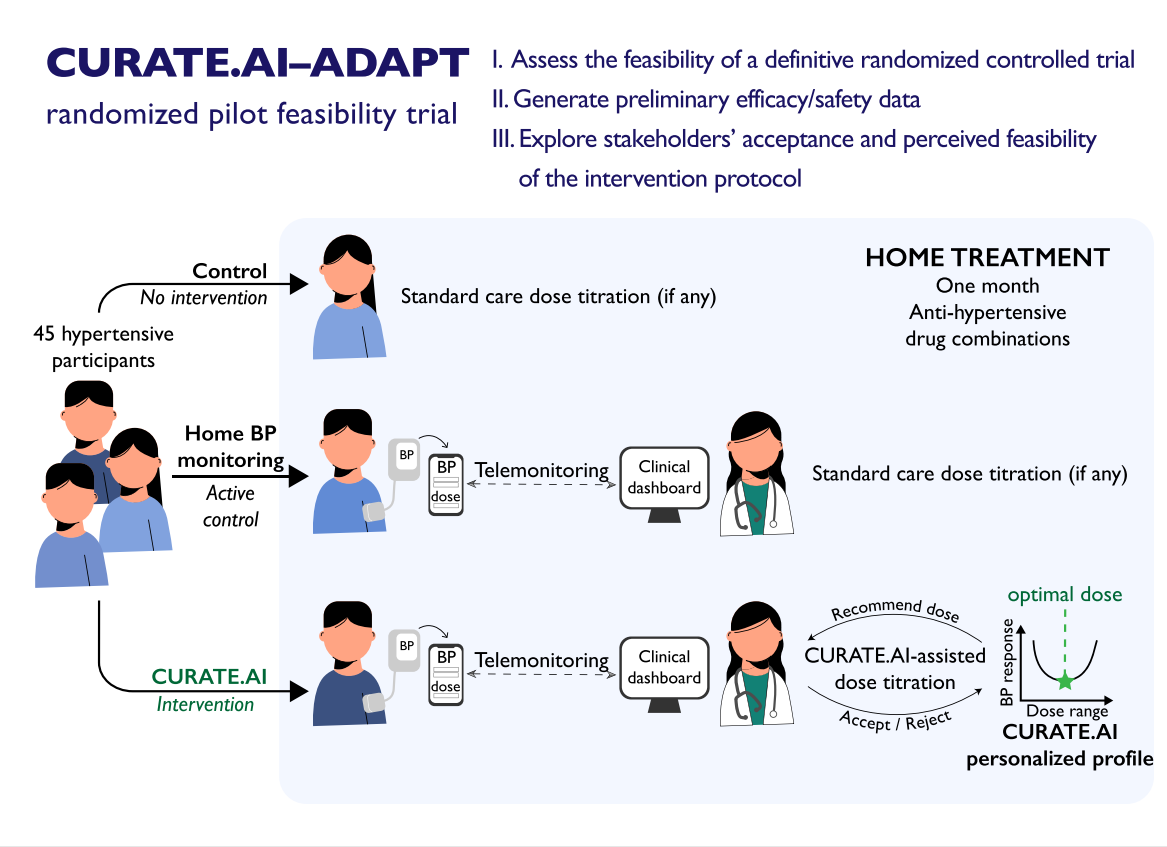
Graphical Abstract



Keywords Personalized dose titration • Hypertension • Artificial intelligence • CURATE.AI • Clinical decision support

Introduction

Hypertension is a serious public health concern and the leading attributable risk factor for death and disability worldwide.[1] Despite a wide array of effective medications, there remains significant challenges to utilizing these proven drugs to their highest potential. First, physicians frequently adopt a stepped-care approach in conventional drug selection and dose escalation strategies.[2] Specifically, treatment drugs—in monotherapies, or two-drug combinations—are typically initiated at low doses and subsequently up-titrated. However, if limited efficacy or poor tolerance is observed, patients will be switched to other drugs, and this process repeats until the patients respond.[2] Currently, the control rates among known hypertensive patients [defined as blood pressure (BP) below 140/90 mmHg] remain low: averaging ~21% worldwide, and ranging from 10 to 50% across countries.[3,4] This suboptimal outcome is often attributed to the intra- and inter-patient variability that causes patients to respond differently to the same treatment at different time points.[5] This problem is further exacerbated in multi-drug therapy as drug–drug interactions are dose, time, and patient dependent, and therefore, highly unpredictable. Patients can be perceived as non-responders to therapy that may otherwise work when given at the correct doses and time points.[6] Secondly, current treatment decisions are guided by office BP measurements at a single time point or every 3–12 months, which may not be sufficient.[2,7,8] Alternatively, out-of-office BP measurements (e.g. home BP) have been recommended as important adjuncts for hypertension diagnosis and prognosis.[7,8] However, their frequent use for longitudinal monitoring and treatment guidance is still limited.[8]

With rapid technological advancements, digital health innovations (DHIs) hold potential to overcome these issues. In particular, wearable sensors and telemonitoring platforms present an opportunity for reliable treatment monitoring as physicians gain access to out-of-office BP data.[9] Mobile health (mHealth) apps incorporating strategies such as education, drug adherence reminder, and behavioural counselling could complement the pharmaceutical interventions towards improving BP control.[10] While these existing BP devices and digital management systems have yet to be widely adopted in standard clinical practice, many of them have already been undergoing rigorous clinical trials.[11] Furthermore, emerging DHIs have bolstered the enthusiasm for 'big data' approaches that require a vast amount of population and patient-specific data to predict treatment responses and guide drug and dose selection.[12,13] Although using big data for personalized care is promising, there remains persistent concerns over their practical implementation and true personalization outcomes in clinics.[14,15]

For these reasons, there has been growing appreciation for 'small data' or N-of-1 approaches with promising potential for implementation and accurate outcomes.[14,15] CURATE.AI is an artificial intelligence–driven

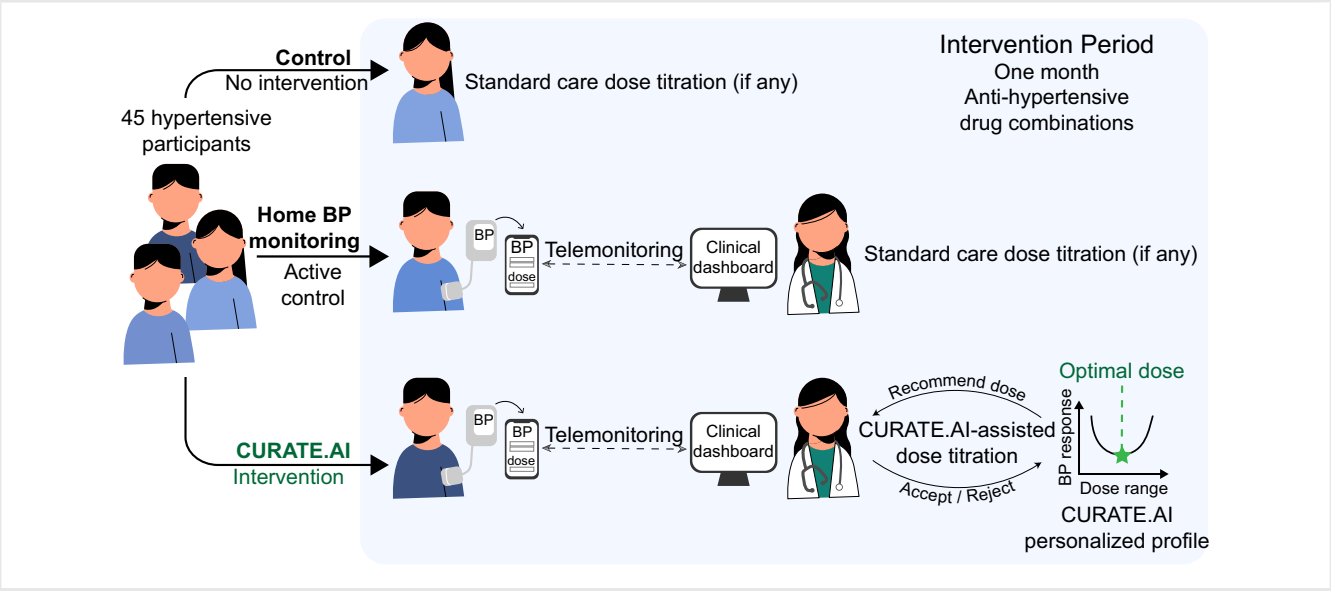


Figure 1 Study design overview.

clinical decision support system (AI-driven CDSS) that relies on this approach, and is designed to assist clinicians in identifying personalized doses for titration along the individual patient's treatment course. CURATE.AI requires only patient-specific data such as doses (input) and BP responses (phenotypic output) to systematically investigate the patient's response to a drug and dose range, and dynamically identify personalized doses along the treatment course.[6] Because of its 'N-of-1' or patient-specific workflow, CURATE.AI does not require population data to train AI models to subsequently dose individual patients. Instead, it uses only a patient's own data to prospectively calibrate their unique response to treatment. This patient-specific small data set is then used to guide only the patient's own care. This is a critical differentiator of CURATE.AI from traditional AI models and approaches. Therefore, due to its relatively modest resource requirements compared with conventional big data AI as well as prior validation, CURATE.AI holds promise to improve patient outcomes, while avoiding the high-burden information pitfall of complex AI models.[15]

In this protocol, we describe the CURATE.AI-assisted dose titration intervention that comprises two components—daily home BP monitoring (HBPM) via a telemonitoring platform; and personalized continuous dose titration with CURATE.AI recommending doses to physicians to assist them in dose titration. The primary objective of this pilot feasibility trial is to assess the logistical and scientific feasibility of a larger randomized controlled trial (RCT) that will evaluate the efficacy of the intervention. The secondary objective is to generate pilot efficacy and safety data instrumental for the power analysis and sample size calculation for an RCT. Additionally, we aim to explore the stakeholders'—both patients and healthcare providers—perspectives of the CURATE.AI-assisted dose titration protocol as part of an early-stage development of CURATE.AI.

Methods

Study design

CURATE.AI-ADAPT is an open-label, multi-arm, randomized, pilot feasibility trial of 45 hypertensive participants who will receive a 2-drug combination of a dihydropyridine calcium channel blocker (CCB) and either an angiotensin II receptor blocker (ARB) or an angiotensin-converting enzyme inhibitor (ACE-i) as per local guidelines.[2] The study was approved by the National Healthcare Group Domain-Specific Review Board (NHG DSRB; reference number 2022/00115; protocol version 7 approved on 4 April 2023) and registered at ClinicalTrials.gov (NCT05376683). This protocol aligns with the Standard Protocol Items: Recommendations for Interventional Trials—AI (SPIRIT-AI)[16] and the Developmental and Exploratory Clinical Investigations of DEcision support systems driven by Artificial Intelligence (DECIDE-AI)[17] (see Supplementary material online, *Appendix S1*).

Eligible participants will be randomized (1:1:1 ratio) into either the control arm (no intervention), HBPM arm (active control), or CURATE.AI arm (HBPM and CURATE.AI dose recommendation; intervention; *Figure 1*). A SPIRIT diagram of the schedule of enrolment, interventions, and assessments is outlined in Supplementary material online, *Table S1*. A follow-up interval of 1 month—more frequent than the recommended frequency by Singapore hypertension guideline[2]—is selected as an intensive standard of care (SOC) for the control arm. Additionally, the inclusion of the active control arm serves to delineate any potential effect of telemonitoring on the endpoints. Furthermore, to understand the stakeholders' (participants and healthcare providers) acceptance and their perceived feasibility of the CURATE.AI intervention, we will conduct an exit survey and interview for the CURATE.AI arm and an interview for the healthcare providers that engaged with CURATE.AI.

Participants

The investigators will identify potential participants during routine clinic visits at Alexandra Hospital (AH), Singapore. Diagnosis of hypertension was based on established guideline recommendation.[2] For patients on pre-existing anti-hypertensive therapy, this is confirmed by checking the electronic prescription records as well as the hypertension diagnosis code on the electronic medical records. For patients who are treatment-naïve, hypertension diagnosis may be confirmed with the following scenarios: in-office BP measurements of two elevated BP levels on separate visits; or 24 h ambulatory BP monitoring diagnosis of hypertension; or patient history and diagnosis code on the hospital's electronic medical records.

All eligible participants will be required to sign an informed consent form before undergoing any trial-related procedures (see Supplementary material). Withdrawal of the participants from the study is allowed at any time, and they will not be replaced. As this is a pilot feasibility trial, no formal sample size calculation was performed. The recruitment target is 45 (1:1:1), which is considered sufficient to inform about the feasibility of the

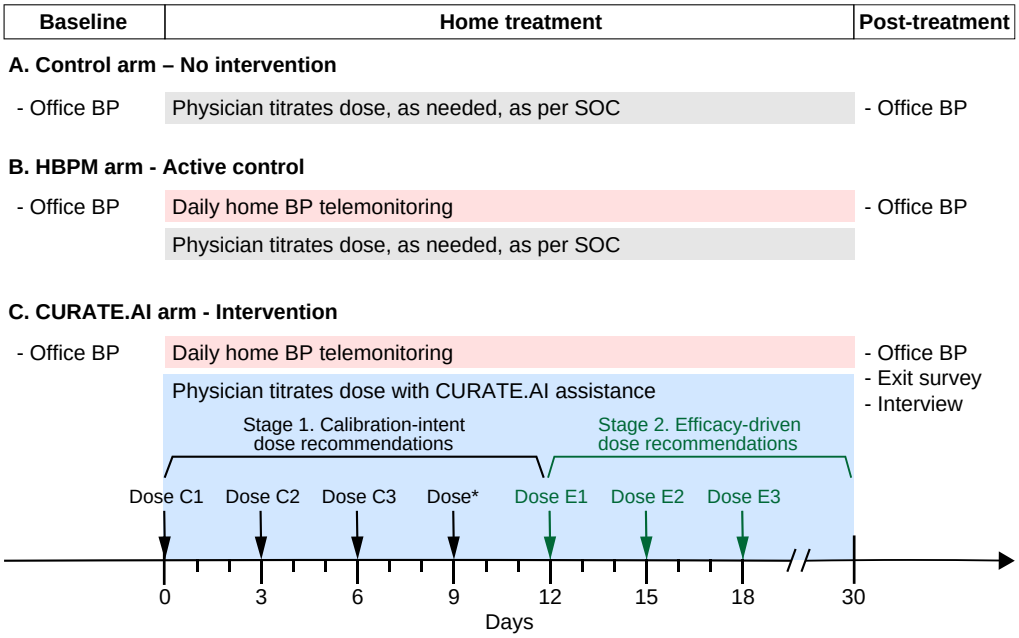


Figure 2 Overall trial schedule. All participants will attend two clinic visits, at baseline and after 1 month of treatment at home, for standard clinic assessment and endpoint evaluation. At baseline, all participants will be given drugs and doses based on the baseline office blood pressure measurements. (*A*) Control arm (no intervention): Participants will receive standard of care according to local best practice guidelines (Singapore hypertension guideline).[2] (*B*) Home blood pressure monitoring arm (active control): Participants will self-monitor and report home blood pressure measurements daily via a telemonitoring platform. Physicians may titrate dose based on home blood pressure measurements, as needed, as per standard of care. (*C*) CURATE.AI arm (intervention): Participants will self-monitor and report home blood pressure measurements daily via a telemonitoring platform. CURATE.AI will recommend doses to the physicians to assist them in selecting doses for titration. Participants will receive more frequent, personalized dose titration throughout the treatment period. Each dose cycle will last 3 ± 1 days, during which, the participants will take the prescribed dose as instructed. When participants and clinic encounter scheduling constraints, we may adjust the dosing cycle, and/or CURATE.AI may recommend a fixed dose for multiple cycles. CURATE.AI will be engaged in two stages. In Stage 1, a minimum of three CURATE.AI calibration-intent dose recommendations (Dose C1/2/3) will be provided to the physician at the start of the intervention protocol. The subsequent CURATE.AI dose recommendation(s) (Dose*) may serve either as a calibration-intent or as an efficacy-driven dose recommendation. After a profile is generated, the participants will enter Stage 2, wherein CURATE.AI will generate the recommendations of efficacy-driven doses (Dose E1/2) to the physicians. Throughout the trial, the physician will make the final decision whether to prescribe or reject the doses recommended by CURATE.AI based on their own judgement.

treatment protocols before initiating a bigger RCT with appropriate sample size calculation.

Eligibility criteria

Inclusion criteria include adults ≥30 years of age and ≤80 years; history of uncontrolled primary hypertension with a record of office systolic/diastolic BP (SBP/DBP) ≥ 140/90 mmHg; treatment-naïve or on single anti-hypertensive medication; not known to have complications of hypertension; eligible to undergo two-drug combinations of a dihydropyridine CCB and either ARB/ACE-i for ≥1 month; estimated glomerular filtration rate (eGFR) > 60 mL/min; sufficient fluency in English to be able to use the telemonitoring platform; able to give informed consent.

Exclusion criteria include suspected or known secondary hypertension; known postural hypotension or standing SBP <110 mmHg; malignant hypertension (BPs ≥180/110 mmHg) that requires emergency treatment; drug allergies to CCB, ARB, or ACE-i drug class or to other anti-hypertensive agents; regular medications that may affect or interact with ACE-i/ARB/CCB drugs; arm circumference not fitting BP cuff size which may affect the accuracy of HBPM; women who are pregnant, trying to become pregnant or of childbearing potential or not using birth control; history of cancer; liver cirrhosis or hepatic failure; chronic heart failure; chronic lung disease; chronic kidney disease (eGFR < 50 mL/min) or end-stage renal failure; diabetes mellitus on insulin and/or with microvascular/macrovascular complications; established cardiovascular disease such as stroke/transient ischaemic attack and ischaemic heart disease, even if the condition was stabilized; potential psychological factors or serious medical conditions limiting the ability to self-monitor their BP or limit adherence to intervention, such as dementia, active substance abuse, nursing home resident; participants without informed consent; participation in a concurrent clinical trial or investigation.

Randomization

Participants will be randomized in 1:1:1 allocation ratio using block randomization into the control, HBPM, or CURATE.AI arms. The randomization sequence will be generated online using GraphPads QuickCalcs and communicated via email to the trial coordinator. No blinding will be done in this open-label trial.

Study treatments

All participants will be prescribed 1 month of two-drug combination therapy (dihydropyridine CCB + ARB/ACE-i) and will subsequently follow treatment schedules of their respective arms (*Figure 2*). The study includes two clinic visits at AH, within 3 days before and 14 days after the 1 month intervention period for standard clinic assessment and endpoint evaluation. All trial-related and clinical procedures done during clinic visits are detailed in Supplementary material.

Participants in the control arm will receive treatment following the clinical best practice guidelines (SOC; *Figure 2A*). In addition, as an active control, participants in the HBPM arm will self-monitor their BP and report their BP values daily via the telemonitoring platform (*Figure 2B*). Participants will be given guided instructions to measure their morning home BPs based on the HOPE Asia network recommendations.[7] Two BP readings, 1 min apart, will be obtained with the provided standard home BP device. Measurements will be done in a seated position, after 2 min of rest and at least 30 min after smoking, consuming alcohol, and exercising, within 1 h of waking up, after urination, and before taking food and medication. Treating physicians may titrate participants' drug doses based on home BP according to SOC.[2]

For participants in the CURATE.AI arm, upon randomization, the physicians will select one of the two drugs given in combination to be titrated with CURATE.AI's assistance. Prior to the baseline visit, dose recommendations by CURATE.AI will be provided to the physicians for each participant for profile generation (*Figure 2C*, Stage 1). The physicians are free to accept and prescribe the CURATE.AI-recommended doses or reject them and instead prescribe according to SOC. During the home treatment period, CURATE.AI participants will undergo similar HBPM procedures as in the HBPM arm (*Figure 2C*). CURATE.AI will receive the data after their de-identification by the trial coordinator. The data set will include daily dose adherence (i.e. whether the participant reports taking or skipping the prescribed dose on the telemonitoring platform) and home BP readings. After a profile is generated, participants will move into Stage 2, during which dose recommendations by CURATE.AI will be provided to the physicians for each participant with efficacy-driven intent (*Figure 2C*, Stage 2). The physicians will make the final dose decision, as described above. All dose titrations will be communicated to the participants in-person or via a telemonitoring platform, text messages, or calls that are cybersecurity and patient-privacy compliant. Dose titration will be done up to once per cycle, during which participants will take the drug dose as prescribed. Other drug(s) in the combination regimen will be held at fixed dose(s) or given following SOC. At any point during the trial, the physicians may titrate doses, change regimen, or initiate additional clinic follow-ups according to clinical best practice guidelines at the discretion of the clinical team.

Outcomes

Primary outcome measures

The primary endpoints will assess the logistic and scientific feasibility of the trial protocol for a larger RCT to evaluate the efficacy of the CURATE.AI-assisted dose titration intervention. The feasibility criteria and progression criteria for the RCT are defined in *Table 1*. We adopted a 'traffic light system' based on the Consolidated Standard Of Reporting Trials (CONSORT) statement.[18]

Secondary outcome measures

The secondary endpoints include efficacy and safety endpoints, which will inform about the potential efficacy of the CURATE.AI-assisted dose titration intervention. The efficacy endpoints are listed in *Table 2*. The safety endpoints include the composite of hospitalization due to hypotension (SBP < 90 mmHg, with symptoms and signs of hypoperfusion), bradycardia (heart rate < 50 b.p.m., with symptoms and signs of hypoperfusion), hyperkalaemia (serum potassium > 6.0 mmol/L with the need for cessation of ACE-i/ARB/aldosterone blockers or potassium-lowering treatment), or acute kidney injury (serum creatinine increased > two times of baseline measurement or glomerular filtration rate decreased >50%).

Digital platforms

Telemonitoring platform

Bot MD Care—a telemonitoring platform for capturing participant treatment data (e.g. BP, heart rate, measurement time, dose adherence)—will be used in this study. Participants can access Bot MD Care via common chat platforms such as Whatsapp and will be provided with a secured link to report home monitoring data. Data will be securely transferred and compiled on a Bot MD Care Clinical Dashboard for physicians' access (*Figure 1B and C*). Bot MD Care is currently deployed at AH to manage clinically and technically suitable patients with hypertension, allowing patients to report their BPs, and physicians to monitor their patients' BPs remotely.[19]

Table 1 Primary endpoints for feasibility assessment based on 'the traffic light system'

	Green (%)	Yellow (%)	Red (%)
Logistical feasibility endpoints			
BP monitoring adherence[a]	>80	30–80	<30
Drug dose adherence[b]	>80	20–80	<20
Physician acceptability of CURATE.AI dose recommendations[c]	>70	10–70	<10
Scientific feasibility endpoints			
CURATE.AI applicability[d]	>70	10–70	<10
Percentage of dosing cycles that CURATE.AI recommends dose with calibration intent to physicians	<60	60–99	100
Percentage of dosing cycles that CURATE.AI recommends dose with efficacy-driven intent to physicians	>40	1–40	0
Clinically significant dose changes[e]	>20	1–20	0

Green status indicates that a future RCT is feasible. Yellow status indicates that a future RCT is possibly feasible with appropriate modifications of the study design. Red indicates that a future RCT is unfeasible.
[a]Percentage of BP entries by participants into the telemonitoring platform.
[b]Percentage of dosing events that participants report that they adhere to the prescribed doses.
[c]Percentage of doses recommended by CURATE.AI which was prescribed by the treating physician(s).
[d]Percentage of participants in whom CURATE.AI profiles are generated and applied.
[e]Percentage of participants from the CURATE.AI arm with CURATE.AI-assisted cumulative dose that is substantially (≥10%) different from the projected SOC cumulative dose, defined as the maximum daily dosage of the drug multiplied by the number of treatment days.

CURATE.AI dose titration platform

CURATE.AI software is classified as a Class B medical device (low-to-moderate risk) by the Health Sciences Authority in Singapore. It is developed as a CDSS with human oversight to assist physicians in identifying personalized doses for effective titration. CURATE.AI requires only an individual participant's data, including doses (inputs) and BP responses (phenotypic outputs), to generate a quadratic CURATE.AI personalized profile mapping a participant's response to a drug dose range.[6] Using the generated profiles, CURATE.AI recommends personalized doses for titration. CURATE.AI has been clinically validated for post-liver transplant immunosuppression,[20] metastatic prostate cancer,[21] and is currently being studied for the treatment of solid tumour,[22,23] Waldenström macroglobulinaemia (NCT04522284), and multiple myeloma (NCT03759093). This investigational use of CURATE.AI for anti-hypertensive dose titration is documented in the Clinical Research Materials notification to the HSA under the National University of Singapore.

CURATE.AI-assisted dose titration

CURATE.AI internal workflow

Stage 1: calibration-intent doses to generate personalized dose-response profile

At least three dose levels and corresponding BP responses (or their mathematical transformations) from each participant are required to generate a quadratic CURATE.AI personalized profile. Thus, participants will first undergo a data collection stage for the purpose of generating a CURATE.AI profile (*Figure 3*, Steps 1–6). CURATE.AI will recommend a set of three calibration-intent doses of the selected drug for consideration by the treating physician(s) (Steps 1 and 2; Supplementary material). Corresponding BP responses will be collected (Step 3). The CURATE.AI

Table 2 Efficacy endpoints for preliminary evaluation of efficacy of CURATE.AI-assisted dose titration

Efficacy endpoints	Control arm	HBPM arm	CURATE.AI arm
Mean change in office SBP or DBP[a]	X	X	X
Percentage of participants with ≥5 mmHg reduction in office SBP or DBP[a]	X	X	X
Percentage of participants who achieved target office SBP or DBP at 1 month clinic visit[a,b]	X	X	X
Average time to reach the target home SBP or DBP for the first time[a,c]		X	X
Time in therapeutic range for SBP or DBP[a]: percentage of home SBP or DBP recorded within the target home BP[c]		X	X

All participants will undergo office BP measurements, consisting of SBP and DBP measurements, at baseline and post-treatment clinic visits for the evaluation of efficacy endpoints. Participants in the HBPM arm and CURATE.AI arm will have additional efficacy endpoints relating to home BP measurements. 'X' indicates applicability of the endpoints to each study arm.
[a]SBP and DBP will be assessed separately.
[b]Target office BPs are defined as SBP and DBP <140 and <90 mmHg, respectively.[2]
[c]Target home BPs are defined as SBP and DBP <135 and <85 mmHg, respectively.[2]

team will analyse all collected data to determine whether a profile can be generated (Steps 4–6; Supplementary material). Steps 1–6 may be repeated to obtain an actionable CURATE.AI profile before proceeding to Stage 2.

Stage 2: efficacy-driven doses

Participants with actionable CURATE.AI profiles will enter Stage 2, where recommended doses will aim to achieve the target home BPs, defined as home SBP <135 mmHg and/or home DBP <85 mmHg (Step 7).[2] When the participants' BPs are outside the target range, CURATE.AI will recommend to the physicians an efficacy-driven dose based on the generated profile (Step 8). If the target BPs have already been achieved, CURATE.AI may not recommend any dose adjustment (Step 9). In both cases, the physicians have the final decision on the prescribed doses. Participants will continue with HBPM under careful telemonitoring by the physicians throughout the treatment duration (Step 10). All new data collected will be analysed to determine whether the CURATE.AI profiles are reliable to be used for efficacy-driven dose recommendation (Step 11). In the presence of systemic changes that may affect the BP responses across dose range, such as addition/removal of anti-hypertensive drugs and hospitalization events, a profile recalibration (i.e. creating a new profile or adjusting the existing profile) may be required (Step 11). In such case, the participant may need to re-enter Stage 1 (return to Steps 1–6).

CURATE.AI safety mechanism

The CURATE.AI operations include careful human oversight, including frequent interactions between engineering experts and physicians throughout the dose recommendation process (*Figure 3*). Dose recommendations generated by CURATE.AI will always fall within the pre-determined safety dose range set by the physicians. Additionally, CURATE.AI will only assist by recommending doses to the physicians, following which they are free to prescribe the recommended dose or follow the SOC guidelines. CURATE.AI will only recommend dose titration for the selected drug and will not recommend a change of drug. At any time, the physicians may titrate the dose, change drug regimen, or interrupt treatment if further BP management is necessary.

Exit survey and interview

We aim to explore the stakeholders' experience with the intervention protocol, including barriers to adoption, and potential improvements to the protocol. Participants in the CURATE.AI arm will be offered to undergo an exit survey (5 min) and a semi-structured interview (60 min). The healthcare providers engaged with CURATE.AI will be invited to a post-study semi-structured interview (60 min). The sample questionnaire and interview guides are described in Supplementary material.

Statistical analysis

An intent-to-treat analysis will be done for all randomized participants with both baseline and 1 month BP measurements. Participant baseline characteristics and drug combinations will be examined with descriptive statistics. We will perform descriptive statistical analyses of the feasibility endpoints of the CURATE.AI arm. We will analyse the within-group and between-group differences in the secondary endpoints in the relevant study arms (*Table 2*). Of note, this preliminary analysis serves to inform about potential intervention effects and is not intended to provide a statistically significant conclusion. Within-group analyses include descriptive statistics and a two-tailed *t*-test. Between-group analyses include analysis of covariance for multiple group comparison, *t*-test (continuous variables) or χ^2 test (categorical variables) for two-group comparison. All tests will be two-sided, with a significance level of 5%. Inductive thematic analysis will be used to identify recurring themes from the questionnaire and interviews (Supplementary material). A per-protocol analysis will be performed for participants with major protocol violation (e.g. missing baseline or post-treatment office BP measurements) and other protocol violations that will possibly be defined during data review. Additional analyses might be performed. The data management plan is outlined in Supplementary material.

Safety monitoring

Safety monitoring of all adverse events and serious adverse events will be done by the study team following the safety monitoring protocol set out in AH (Supplementary material). Serious adverse events will be notified to the principal investigator or delegate within 24 h of detection to determine expectedness and relatedness to the study procedure.

Discussion

Personalized precision dosing is increasingly appreciated as a viable alternative to the traditional dose escalation approach in hypertension management, to overcome the unpredictable inter- and intra-patient variabilities in treatment responses.[15] AI-driven big data platforms have shown promise as tools to tailor dosing to subpopulations.[14,15] However, small data approaches, such as CURATE.AI,[24] may further enable a dynamic personalization of therapies at the individual level, which may be more suitable for long-term chronic disease management.[14] CURATE.AI has been clinically validated across a wide range of disease indications[20–22] and has also shown promise in an earlier retrospective case series of its applicability for hypertension.[6] The wide-ranging applicability of this platform may be attributed to its indication-agnostic and mechanism-independent properties.[24] However, to better evaluate the CURATE.AI's feasibility of being integrated within the current hypertension clinical workflow, it is necessary to generate clinical evidence through this prospective randomized pilot trial.

Furthermore, this study will help to better understand potential challenges in adopting DHIs such as CURATE.AI within the current care pathway, from the perspectives of physicians, patients, and healthcare system at large. For physicians, the vast amount of data made available from telemonitoring may inadvertently lead to decisional overload, if

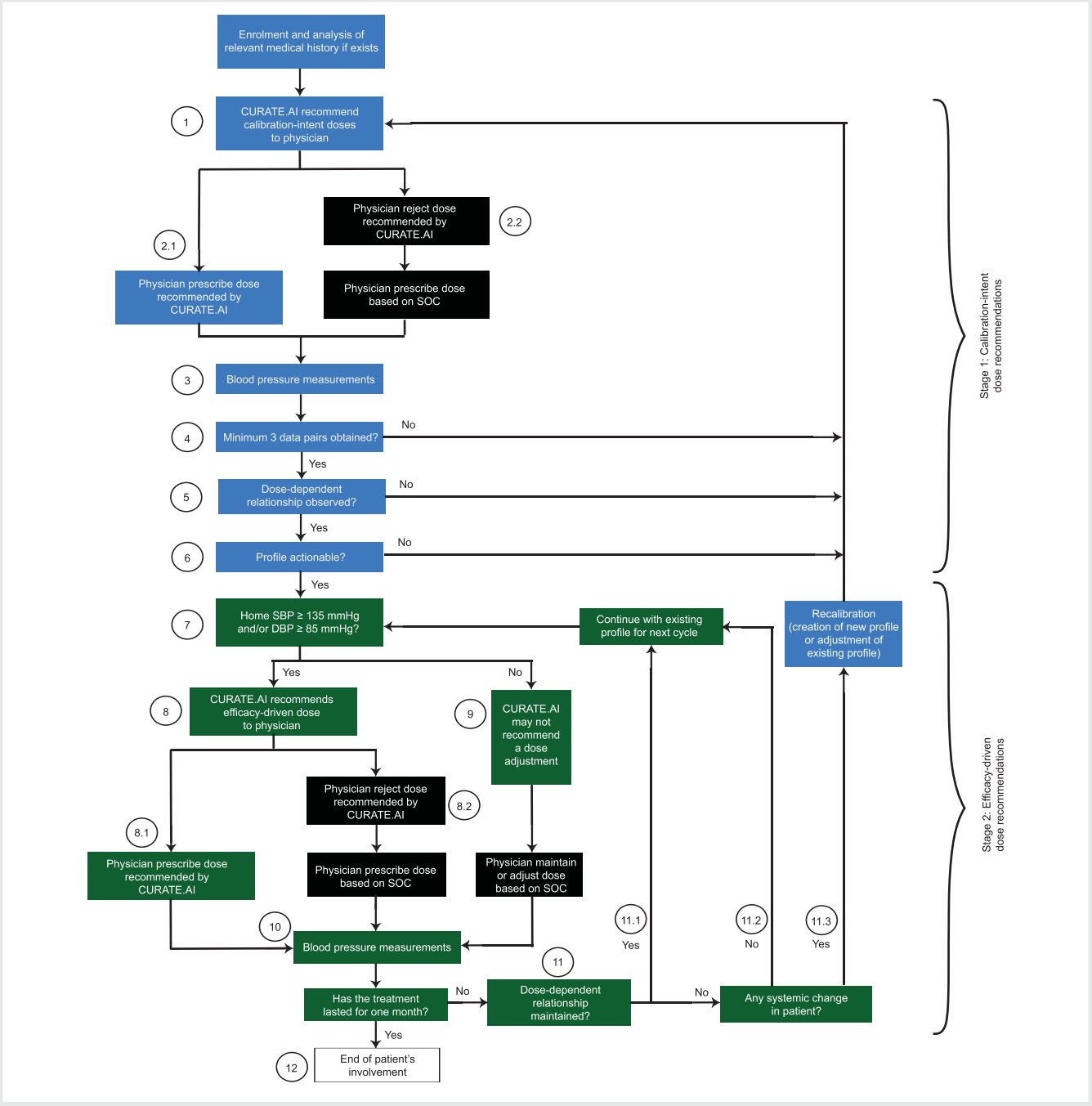


Figure 3 CURATE.AI-assisted dose titration internal workflow for the CURATE.AI arm. CURATE.AI operation includes two stages—Stage 1: personalized profile generation (Steps 1-6); and Stage 2: efficacy-driven dose recommendations (Steps 7-11). CURATE.AI will recommend doses to the physician to assist them in making dose decisions. At any time, the physician may reject the CURATE.AI dose recommendations and titrate dose based on standard of care guideline (Steps 2.2 and 8.2).

the data are not collected in a structured and reliable manner, or if there are no reliable data analysis tools to support their decision-making process.[8] For patients, an extensive data collection process may create undue burdens, making them less receptive to adopting new technologies. Finally, from the point of view of the healthcare system, resource requirements for intensive intervention schedules may also hinder the adoption of DHIs. Although the current protocol is designed to minimize these challenges as far as possible, this study offers the opportunity to glean additional insights on the feasibility of implementing CURATE.AI in clinical practice, through the lens of relevant stakeholders.

First, to offload the decisional burden from physicians, this protocol provides a clear action plan—from supporting reliable telemonitoring to assisting physicians in dose decision-making with an AI-assisted analysis. The CURATE.AI intervention was designed to enable *meaningful* data generation and usage. This entails collecting quality data over time, via the systematic monitoring and reporting of both physiological (e.g. BP) and behavioural (e.g. adherence) data. In this way, CURATE.AI can

subsequently tailor dose recommendations to accommodate patients' treatment responses, preferences, and habits without imposing undue decisional burdens on physicians. Findings from the post-treatment interview will reveal the healthcare providers' perception of CURATE.AI's true potential to improve the decision-making process.

In minimizing patients' burden, only participant-specific data collected once a day will be required for CURATE.AI's 'small data' analysis of each participant. Findings from this study will inform about their perceived burden and acceptability towards the CURATE.AI treatment protocol. Moreover, this study may further shed light on ways to make data collection more acceptable to patients (e.g. less frequent monitoring, using automated BP devices) without compromising on CURATE.AI's scientific rigour.

The resource burden on the healthcare system may also be minimized as the frequent dose titration follow-ups will be done remotely. This may have further long-term benefits: the resulting frequent patient engagement may improve their treatment adherence and BP control, thereby reducing the need for the most resource-intensive in-person clinic visits in the long run.[25] Future studies with longer follow-ups will be necessary to verify this benefit of CURATE.AI. Additionally, the high frequency of touchpoints may be further reduced over time once CURATE.AI profiles are established. As such, this study will help identify avenues for reducing resource burden to the minimum required to sustain the intervention's effectiveness.

Early feedback from stakeholders during the pilot stage may allow for refinements of the intervention to respond to their needs and is therefore important as a way to give them actual power to shape clinical practice and improve patient outcomes.[26,27] In fact, the concept of stakeholder co-design has been recently emphasized in newer reporting guidelines, especially for early-stage clinical evaluation of an AI-driven CDSS.[17] The participatory design process outlined in this protocol provides a foundation for acceptability,[28] thereby increasing CURATE.AI's potential for adoption into routine use.

Conclusions

Learning from this study will inform about the next steps and enable the decision whether to potentially refine the current protocols before proceeding to a fully powered comparative RCT or to expand the study to collect additional information. As this is an early feasibility study, the participant's enrolment is limited to those receiving two-drug combination of CCB and ARB/ACE-i—the most common regimen in Singapore.[29] Future RCTs expanding to other treatments—more drug classes, in monotherapy, and three-drug combinations—will be necessary to improve the generalizability of the results.

Lead author biography

Dr Laureen Y.T. Wang is a practising clinician in cardiology and internal medicine at the Alexandra Hospital and National Heart Centre, Singapore. She graduated from the National University of Singapore, Yong Loo Lin School of Medicine in 2012. She completed her residency in Internal Medicine and her cardiology training at the National University Hospital, Singapore. Dr Laureen Y.T. Wang is active in preventive medicine for chronic diseases and women's health issues. She currently heads the preventive programme at Alexandra Hospital.

Supplementary material

Supplementary material is available at *European Heart Journal – Digital Health*.

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Author contribution

A.T.L.T., M.Y.C., A.B., L.Y.T.W., and D.H.: study conception. A.T.L.T., S.-B.T., G.Z.W., A.W.J.Y., M.E., V.V.L., M.Y.C., K.S.K., L.W.J.T., S.V., A.B., L.Y.T.W., and D.H.: study design. A.T.L.T., S.-B.T., M.E., and A.B.: writing—early draft. All authors: writing—review and editing. A.T.L.T., W.Y., A.B., and L.Y.T.W.: ethics applications. L.Y.T.W.: principal investigator.

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Conflict of interest: M.E. is an employee of Roche Diagnostics and a shareholder in F. Hoffmann-La Roche AG. A.T.L.T, S.-B.T., K.S.K., L.W.J.T., A.B., and D.H. are co-inventors of previously filed pending patents on AI-based therapy development. D.H. is a co-founder and shareholder of KYAN Therapeutics, which has licensed intellectual property pertaining to AI-based oncology drug development. All other authors have no conflict of interests to disclose.

Data availability

There are no new data associated with this article.

Ethics and dissemination

This study was approved by the NHG DSRB (reference number 2022/00115). The study results will be presented at scientific conferences and/or published in peer-reviewed journals.

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