PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	UDAY: Protocol of a Comprehensive Diabetes and Hypertension Prevention and Management Program in India
AUTHORS	Mohan, Sailesh; Jarhyan, Prashant; Ghosh, Shreeparna; Srinivasapura Venkateshmurthy, Nikhil; Gupta, Ruby; Rana, Ritu; Malhotra, Cheena; Rao, Bhaskara; Kalra, Sanjay; Tandon, Nikhil; Reddy, KS; Prabhakaran, Dorairaj

VERSION 1 – REVIEW

REVIEWER	Anna Haste Newcastle University, England, UK
REVIEW RETURNED	16-Mar-2017

GENERAL COMMENTS	An important and relevant area of research. The protocol covers a substantial amount of work and methods to be conducted. However, several considerations are not addressed within the protocol: 1. The abstract has no mention that body measurements or bio-samples will be obtained in the study. 2. No justification is provided as to why a pre-post evaluation design was chosen and used over other research designs. 3. What is the multistage random sampling technique deployed to obtain a representative sample? How was it performed? 4. Questionnaires are described in the methods as developed for UDAY, have these undergone any piloting to check their validity, feasibility and acceptability? 5. No justification is used as to why any of the other questionnaires are being used in the surveys? 6. No description is included on how cost effectiveness is to be assessed even though it is one of the objectives of the study. 7. A large variety of methods and interventions are described in the protocol but no mention is included of how they are going to assess which intervention components are effective? i.e. how will they know if a diagnosis which has been identified is due to self-referral because of the marketing campaign or because of education provided to the health professionals? 8. I believe the protocol may benefit from description of the intervention first. At the moment the protocol is heavily focussed on the 5 surveys, which I understand need description, but the intervention programme, which is the key change in practice, is not described until page 29. 9. How were those with a diagnosis of diabetes and/or hypertension approached to take part in the study? It is stated within the healthcare facilities but how did they actually gain access to see the patient?

	10. There is no mention of trial registration. 11. No limitations of the study are discussed. 12. No references/comparison to other studies are used to support statements within the discussion. A large part of the discussion could be better fitted to the introduction to support the rationale for the study. This would then allow space for limitations to be discussed and possibly key findings from the baseline data. 13. Use of the collected baseline data to develop the intervention is described but no mention of how this actually informed the development of the intervention is included in the protocol. 14. The standard of English could be improved. At the moment the text is often hard to follow, which is possibly due to the substantial amount of data outcomes to be collected. Elongated sentences and descriptions are used, which could be simplified to make the method section as clear as possible.

REVIEWER	Richard Cooper Loyola Univ Chicago, US
REVIEW RETURNED	31-Mar-2017

GENERAL COMMENTS	The authors have undertaken a major intervention project in India which should provide important new information on the campaign to control chronic diseases. As written, however, the MS has important short-comings. I fully agree that baseline papers for major studies are essential but this MS appears to straddle two potential versions of a baseline description. From the perspective of most readers the details of data collection and sampling are likely to be of less interest, given that baseline data have actually been collected and are not reported here. My suggestion would be to divide the tasks into 2 parts. First, a description of the rationale and scientific base for this project could be addressed. There is an extensive literature on population based interventions to reduce NCD risk, most of it concluding that targeted experiments have little "real world" effect. I think this area of prevention science deserves much more careful justification. Why, for example, in the face of mostly negative prior studies do the investigators think they will succeed? Have they taken account of prior research and attempted to add novel - hopefully more effective - components to their design? Is it logical to transfer methods used in high income countries to an LMIC? For example, it is probably likely that the health care system is already very over burdened in India - is it realistic to expect them to take on these new tasks - unless substantial new resources are made available? We know that professional education alone does not bring change - what structural improvement in the system are possible? Finally, the outcomes to be measured are not adequately described, and assessment has always been a fundamental challenge for community based interventions. More thought should be invested in the topic. (For example, a sample size calculation is presented but it is unclear what is to be measured? Incidence of T2D?) As a complementary paper the baseline methods could be presented, and if data were available they should be included. Overall this project is potentially very significant. However a positive outcome will require more attention to the basic challenges of prevention science, especially as adapted to this social context. A discussion of those issues could be very worthwhile, both for the reader and most likely the investigators themselves.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

Comment 1: The abstract has no mention that body measurements or bio-samples will be obtained in the study.
Response: Thanks, we have added this information in the abstract on page 2 of the revised manuscript.

Comment 2: No justification is provided as to why a pre-post evaluation design was chosen and used over other research designs.

Response: We selected this primarily due to the following reasons. In this study we wanted to evaluate if multi-component interventions delivered at multiple levels in a comprehensive manner can improve outcomes. Further, we also wanted to understand and examine the operational part of the program implementation to gain insights into underpinning factors behind success or failure that can inform possible replication and scale up in the future. The options for an implementation study of this nature with process outcomes are either a pre-post design or quasi-experimental design or step wedge design. We deemed a step wedge to be too complicated for this evaluation and given that quasi experimental design would not have enough power to decipher real differences, we chose a pre-post design. This was also aimed at cutting down costs. This has been added on pages 4-5 of the revised manuscript.

Comment 3: What is the multistage random sampling technique deployed to obtain a representative sample? How was it performed?

Response: We first selected clusters according to probability proportional to size, then from each of the selected clusters we randomly selected households. Census enumeration blocks (CEBs) were considered as the primary sampling unit in urban areas and villages in the rural areas respectively. In each sub-site, 85 clusters were randomly selected (urban Sonipat: 85/200 CEBs, urban Vizag: 85/207 CEBs and rural Sonipat: 85/168 clusters, rural Vizag: 85/147 clusters) according to probability proportional to size. From each cluster in the urban and rural sub-sites, 18 to 25 households were randomly selected and 1 eligible male and female were selected randomly within each household using Kish table. This is already indicated on page 14-16 as well as in Fig 4.

Comment 4: Questionnaires are described in the methods as developed for UDAY, have these undergone any piloting to check their validity, feasibility and acceptability?

Response: Most of the questionnaires that we have used have been previously validated and used in other large population studies in India. However, for assessing certain domains such as social well-being, awareness and knowledge of diabetes and hypertension we had to develop the questions. In addition, for the provider survey we had to develop afresh due to non-availability of a similar one in Indian settings. However, all the questionnaires were pretested for their feasibility and acceptability before being deployed for the surveys. We tested for face validity of the provider survey and given the higher educational level of providers we did not carry a detailed validity assessment due to resource constraints.

Comment 5: No justification is used as to why any of the other questionnaires are being used in the surveys?

Response: As indicated above, we used them as most of the questionnaires have been previously validated and extensively used in other large studies in the Indian population and were suitable for assessing the information we needed to meet the study objectives.

Comment 6: No description is included on how cost-effectiveness is to be assessed even though it is one of the objectives of the study.

Response: This will be evaluated by assessing the costs and benefits of the multi-component, multi-level comprehensive interventions in improving diabetes related health outcomes. Data on healthcare utilization and costs, as well as that of out of pocket expenditure will be collected in the baseline and end line surveys. In addition, data on direct costs including the cost of personnel, provider training, medications, lab tests and supplies, screening, outpatient visits, and costs related to the social marketing campaign will be obtained during the implementation process. The total costs entailed to identify a person with diabetes as well as to appropriately treat that person to recommended targets based on guidelines will be measured. In addition, we will model the costs accrued from the use of drugs and other related interventions, based on results of other such comprehensive programs and do a comparison to assess effectiveness. Based on the aforesaid indicators, we will develop a comprehensive cost-effectiveness model to assess the overall program effectiveness. This has been added on pages 28-29 of the revised manuscript.

Comment 7: A large variety of methods and interventions are described in the protocol but no mention is included of how they are going to assess which intervention components are effective? i.e. how will they know if a diagnosis which has been identified is due to self-referral because of the marketing campaign or because of education provided to the health professionals?

Response: The overall impact of the intervention program will be assessed by the conduct of the baseline and end line surveys and by examining the change in select indicators pertaining to the interventions targeted at the population, patients and providers from baseline to end line. Given that the study objective is to evaluate if multi-component interventions delivered at multiple levels to the population, patients and providers in a comprehensive manner can improve outcomes, we will not be able to assess the impact of individual interventions.

Comment 8: I believe the protocol may benefit from description of the intervention first. At the moment the protocol is heavily focused on the 5 surveys, which I understand need description, but the intervention programme, which is the key change in practice, is not described until page 29.

Response: Thanks for pointing this out, we have shifted the description of the intervention component of the program and placed it after the study sites on pages 7-13 of the revised manuscript. We have also added a section on intervention development and outcome assessment (table 2).

Table 2: Assessment of intervention outcomes

Indicator	Target Population	Metric	Evaluation Methodology
1. Patient outcomes	Diabetes and hypertension patients	% implementing lifestyle change (meet the recommended levels of physical activity, and intend to and/or implement dietary changes)	Baseline and endline surveys, diabetes registry
		% engaging in self-monitoring/testing	Baseline and endline surveys, diabetes registry
		% increase in correct self-management practices	Baseline and endline surveys, diabetes registry
		% increase in knowledge on diabetes and hypertension	Baseline and endline surveys, diabetes registry
		% of patients on treatment, whose diabetes, hypertension is successfully controlled, i.e., HbA1C≤ 7% / BP ≤130/80 mm Hg	Baseline and endline surveys, diabetes registry
2. Awareness and knowledge about diabetes and hypertension	General population	% increase in knowledge of diabetes, hypertension and their risk factors	Baseline and endline surveys
		% increase in detection rate and in seeking healthcare	Baseline and endline surveys, screening program
		% implementing lifestyle change (meet the recommended levels of physical activity, and intend to and/or implement dietary changes)	Baseline and endline surveys, screening program
		% exposed to health promotion campaign	Baseline and endline surveys, screening program
3. Provider knowledge and practices	Physicians, other health workers	# who participate in training programs	Training participation data
		% increase in knowledge related to diabetes and hypertension management	Baseline and endline surveys of providers, diabetes registry
		% increase in practices related to diabetes and hypertension management and providing lifestyle advice	Baseline and endline surveys of providers, diabetes registry
	Pharmacists	% of pharmacists who identify people at risk of and with diabetes, hypertension	Baseline and endline surveys of providers
		% increase in pharmacists dispensing and filling prescriptions correctly	Baseline and endline surveys of providers, diabetes registry
4. Program cost-effectiveness	Diabetes patients	Cost per diabetic patient treated to recommended target	Baseline and endline surveys of patients, program cost data, diabetes registry
		% reduction in out of pocket expenditure	Baseline and endline surveys of patients, diabetes registry
	General population	Cost per diabetes case identified	Surveys, screening program, program cost

			data
5. Access to treatment	Healthcare system	Improvements in access to and availability of medications	Baseline and endline surveys of patients, facility survey, diabetes registry
		% increase in the proportion patients who report that medicines are easily available	Baseline and endline surveys of patients, facility survey, diabetes registry
		% reduction in stock outs of medicines	Baseline and endline surveys of patients, facility survey, diabetes registry
		Adherence to IPHS guidelines on drugs, services	Facility survey, diabetes registry

Comment 9: How were those with a diagnosis of diabetes and/or hypertension approached to take part in the study? It is stated within the healthcare facilities but how did they actually gain access to see the patient?

Response: We approached patients attending outpatient section of health facilities and identified those with the diagnosis based on their prescription note and approached them for participating in the study. This has been clarified on page 21 of the revised manuscript.

Comment 10: There is no mention of trial registration.

Response: We did not register for trial registration as this study utilizes a pre-post design and is not a trial

Comment 11: No limitations of the study are discussed.

Response: We have added the study limitations in the discussion and revised this section. Firstly, we used a pre-post study design for evaluating the effect of our interventions. Though, a randomized controlled trial is a better design to evaluate the effectiveness of interventions, providing a higher level of evidence than a pre-post design, to study the effect of multi-component interventions delivered at multiple levels in a comprehensive manner in a large population over a vast geographic area, we considered the pre-post design as more appropriate for our study. Further, we also wanted to understand and examine the operational part of the program implementation to gain insights into underpinning factors behind success or failure that can inform possible replication and scale up in the future.

Secondly, our study does not include controls for the comparison. Given the size of the population covered by the interventions, we would have had to recruit control communities of similar size and numbers, which wasn't feasible from an implementation and resources availability point of view. However, our baseline and end line surveys that evaluate the impact are done on independent random samples of the population, which should provide robust data regarding potential changes over baseline in the levels of: public awareness and knowledge about diabetes and hypertension; those aware, diagnosed, treated and controlled to recommended targets; the use of guideline based management by providers leading to improved health outcomes and access to healthcare for people living with diabetes and hypertension in India. In addition, we will be comparing our results with ongoing national survey data on NCDs and their risk factors (National Family Health Survey, Annual Health Survey, District Level Household Survey) as well as a New National NCD survey which is being implemented currently. This will help assess secular trends and evaluate our findings in conjunction with such trends if any. Also we did not account for the regression to the mean as there would be at least some people both in the end line and baseline. We will do sensitivity analysis to explore this bias.

Thirdly, one of the major interventions of our program is to implement a community based screening, follow-up and educational program through health workers. We specifically hired and trained health workers to implement this interventional component, which might add to the cost of implementing a community based diabetes and hypertension prevention and management program. However, the additional cost of is likely to be minimal as indicated by previous modelling estimates of training and using health workers.

Fourthly, we are using multi-component interventions at multiple levels (health promotion campaigns, health workers led home based screening, follow-up and education, training of healthcare providers, registry for facility based improvement in quality of care, patient networks and advocacy to strengthen the health system) which makes it difficult to evaluate the individual contribution of each intervention. However, the purpose is to deliver it in a comprehensive manner to improve outcomes, which to our knowledge has hitherto not been implemented in similar settings, and not to tease out impact of individual interventions in a milieu where many individuals have elevations of multiple NCD risk factors and suffer often from co-morbid conditions that require to be addressed comprehensively.

Comment 12: No references/comparison to other studies are used to support statements within the discussion. A large part of the discussion could be better fitted to the introduction to support the rationale for the study. This would then allow space for limitations to be discussed and possibly key findings from the baseline data.

Response: We have shifted some of the statements that are relevant to support the rationale to the introduction section. We have also revised the discussion with incorporation of the limitations. We haven't added key findings from the baseline data as they will be reported in a separate manuscript.

Comment 13: Use of the collected baseline data to develop the intervention is described but no mention of how this actually informed the development of the intervention is included in the protocol.

Response: As indicated in response to comment 8 above, we have added a section on intervention development and outcome assessment on pages 7-13 of the revised manuscript. The results from the baseline surveys (population, patient, facility and providers) enabled us to develop and refine the interventions, which were subsequently piloted. For example, from population survey we found that there were differences in the awareness of risk factors for developing diabetes/hypertension across rural/urban areas and the two study sites in North and South India. Therefore, taking this into cognizance, we designed the tailored health promotion program and messages to be delivered by trained health workers ti increase awareness about the risk factors. Facility and providers' surveys helped us to design the training programs for training healthcare providers as well as to conduct advocacy to improve access to the health system. Similarly, findings from the patients' survey helped us to focus the training of health workers on building self-management skills of people with diabetes/hypertension and for developing patient networks.

Comment 14: The standard of English could be improved. At the moment the text is often hard to follow, which is possibly due to the substantial amount of data outcomes to be collected. Elongated sentences and descriptions are used, which could be simplified to make the method section as clear as possible.

Response: Where possible we have tried to incorporate this suggestion to the extent feasible.

Reviewer: 2

Comment: The authors have undertaken a major intervention project in India which should provide important new information on the campaign to control chronic diseases. As written, however, the MS has important short-comings. I fully agree that baseline papers for major studies are essential but this MS appears to straddle two potential versions of a baseline description. From the perspective of most readers the details of data collection and sampling are likely to be of less interest, given that baseline data have actually been collected and are not reported here. My suggestion would be to divide the tasks into 2 parts. First, a description of the rationale and scientific base for this project could be addressed. There is an extensive literature on population based interventions to reduce NCD risk, most of it concluding that targeted experiments have little "real world" effect. I think this area of prevention science deserves much more careful justification. Why, for example, in the face of mostly negative prior studies do the investigators think they will succeed? Have they taken account of prior research and attempted to add novel - hopefully more effective - components to their design? Is it logical to transfer methods used in high income countries to an LMIC? For example, it is probably likely that the health care system is already very over burdened in India - is it realistic to expect them to take on these new tasks - unless substantial new resources are made available? We know that professional education alone does not bring change - what structural improvement in the system are possible? Finally, the outcomes to be measured are not adequately described, and assessment has always been a fundamental challenge for community based interventions. More thought should be invested in the topic. (For example, a sample size calculation is presented but it is unclear what is to be measured? Incidence of T2D?)

As a complementary paper the baseline methods could be presented, and if data were available they should be included.

Overall this project is potentially very significant. However a positive outcome will require more attention to the basic challenges of prevention science, especially as adapted to this social context. A discussion of those issues could be very worthwhile, both for the reader and most likely the investigators themselves.

Response: Thanks very much to the reviewer for the useful suggestions. This paper is the study protocol describing the study in detail, its rationale, methods etc. with minimal data on the study setting (refer to table 3) including the some pertaining to the GIS mapping of important built environment features (refer to table 8), that will be analyzed in more detail in conjunction with the baseline surveys. We plan to report the findings from the baseline surveys as a separate paper. Thus, this is in essence purely a protocol paper with very minimal data required for the reader to understand the study setting, scale and scope.

Most of the evidence on community interventions are from developed countries. In the last 2 decades some evidence has emerged from developing countries as well but not quite in proportion to the disproportionate burden borne by them (80% NCD mortality).This is due to several reasons including resources to conduct such large projects as well as the technical capacity. However, available information indicates that results are likely better in developing countries (e.g. Isfahan Healthy Heart Program in Iran, diabetes prevention programs in China and India etc.). We have taken into account findings of such prior research and attempted to address the reported gaps by adding relevant elements to the design of our study. For instance, most such intervention programs have entailed community based interventions (largely targeting lifestyle modification) but have not had active healthcare system and advocacy interventions as proposed in our study. In addition, many of the diabetes prevention programs have targeted high risk groups and not the general free living population as envisaged in this program.

Further, we have used several innovations (refer to table 1) including task shifting/sharing of care to non-physician health workers by the extensively leveraging low-cost m-health technology to enable and empower them to screen and deliver interventions as well as physicians to treat patients as per evidence based algorithms. We have also used GIS mapping to characterize the sites, built environment, healthcare facilities and providers to examine the influence of built environment on diabetes/hypertension and their risks factors as well as care pathways that patients undertake, in order to deliver interventions in a more focused way. In addition, we have built in extensive stakeholder and community engagement in the study implementation which should aid in improving acceptability and buy in for the intervention program.

We agree with the reviewer that direct transfer of methods from HICs to LMICs may not be many feasible and have tailored all the interventions to suit the context where necessary. For example, unlike in HICs, most people with NCDs or elevated risk factors in LMICs have sub-optimal access to the healthcare system due to variety of reasons (health system related and individual related). And there are not many organized community based screening programs. Thus, early detection and appropriate linkage to the healthcare system is limited, with most with disease and risk factor elevation remaining undetected. We anticipate that health worker led screening and linkage to care as proposed in the study will address this critical gap. In addition, we have piloted all the interventions to assess the acceptability and feasibility vis-à-vis implementation before deploying them in the study. We also agree with the reviewer that the health system is overburdened to some extent. Of note, in recent years as NCD burden has increased in India, there have been numerous efforts to increase the capacity of the health system by implementing the National Health Mission and the National Programme for Prevention and Control of Cancer, Diabetes, Cardiovascular Disease and Stroke (NPCDCS). These new initiatives are aimed at addressing structural issues pertaining to health manpower, quality of care, drug and diagnostic availability.

They have also brought in additional resources. However, the aim of the proposed interventions in the study is to strengthen the health system with innovative approaches such as task sharing/shifting and use of technology to ease work flow and enhance care. For instance, the registry and quality improvement program we are implementing in select facilities will streamline data collection as well as improve ability of physicians to deliver evidence based care. Further, through advocacy efforts we are working with the health system stakeholders to improve availability of drugs and diagnostics, manpower and lab services. To improve capacity in evidence based management, we have also enrolled physicians in the study areas into an innovative nationally popular capacity enhancing medical education program (Bhalla S et al. Innovation in capacity building of primary-care physicians in diabetes management in India: a new slant in medical education. Lancet Diabetes and Endocrinology, Volume 4, No. 3, p200–202, March 2016). We believe that these measures will facilitate strengthening of the healthcare system in the study areas to address NCDs effectively. More description on the outcomes to be measured are described in the section on interventions on pages 10-12 (including table 2). With regard to sample size, we plan to measure diabetes prevalence (change from baseline to end line) rather than incidence.

VERSION 2 – REVIEW

REVIEWER	Richard Cooper Loyola Medical School Chicago IL USA
REVIEW RETURNED	15-Aug-2017

GENERAL COMMENTS	The authors have made extensive revisions in response to the prior review, most of which add value. However I still have concerns about the design and feasibility of this project. I accept the assertion that an intervention of this sort might work better in a LIC than a HIC, and will leave the issue at that. I am a little puzzled by the use of prevalence data as the primary outcome. Presumably there will be cases at baseline, and some "loss of cases" (ie, death) and incidence of new cases. If the prevalence remained unchanged, is that a "positive" outcome? Or if a net negative change in prevalence is expected, how much of a change is required? This statistical issue should definitely be addressed before acceptance.

VERSION 2 – AUTHOR RESPONSE

Comment:
I am a little puzzled by the use of prevalence data as the primary outcome. Presumably there will be cases at baseline, and some "loss of cases" (ie, death) and incidence of new cases. If the prevalence remained unchanged, is that a "positive" outcome? Or if a net negative change in prevalence is expected, how much of a change is required? This statistical issue should definitely be addressed before acceptance.

Response:
Thanks for the comment. As mentioned in the previous response to reviewers' comments, the overall impact of the intervention program will be assessed by the conduct of the baseline and end line surveys (in 2 independent cross-sectional samples) and by examining the change in select indicators pertaining to the interventions targeted at the population, patients and providers, from baseline to end line,. We have not indicated that prevalence data will be used as the primary outcome. We had added a section (including table 2) on the outcome assessment in the previous response , which illustrated the range of indices we will use to measure the outcome. We hope that this clarifies the issue.

VERSION 3 – REVIEW

REVIEWER	Richard Cooper Loyola University Chicago USA
REVIEW RETURNED	15-Oct-2017

GENERAL COMMENTS	In this response the authors appear to have clarified the framework for this intervention - or perhaps I just wasn't perceptive enough before and it was clear all along . . . So this is really implementation science - the outcomes are primarily rate of uptake of the prescribed interventions. That framework is appropriate when the interventions can be said to have been of "proven value" - ie, actually work in settings similar to the one they are using them for. *Unfortunately that does not appear to be the case here - we don't yet know how effective these interventions* are in a normal medical setting - prior evidence in fact suggests they may be rather weak. Having said that, I agree it is time to move forward with the version in hand. My own suggestion is that there really needs to be some prioritization of the outcome measures - you cannot really test so a long list without suffering a severe multiple comparisons penalty. It would be much preferable to create a list of some sort - most important first. Otherwise a "pos" outcome for just one cannot be called a positive outcome for the intervention, and one might even conclude that the effort has come to naught, unless you have a convincing result. But, oh this work is difficult! And I heartily agree - we need much much more of these efforts. The "epidemiologic transition" into higher rates of T2D will be a terrifying nightmare of LMIC's. The authors might refer to the NEJM paper on Mexico City Nov 17 2016