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INterpreting the Processes of the UMPIRE Trial (INPUT): protocol for a qualitative process evaluation study of a fixed-dose combination (FDC) strategy to improve adherence to cardiovascular medications

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To cite: Salam A, Stewart F, Singh K, *et al*. INterpreting the Processes of the UMPIRE Trial (INPUT): protocol for a qualitative process evaluation study of a fixed-dose combination (FDC) strategy to improve adherence to cardiovascular medications. *BMJ Open* 2013;**3**:e002313. doi:10.1136/bmjopen-2012-002313

▸ Prepublication history for this paper are available online. To view these files please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2012-002313).

Received 5 November 2012
Revised 25 March 2013
Accepted 2 April 2013

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ABSTRACT

Introduction: This paper describes a planned process evaluation of the Use of a Multidrug Pill In Reducing Cardiovascular Events (UMPIRE) trial, one of several randomised clinical trials taking place globally to assess the potential of cardiovascular drugs as a fixed-dose combination (polypill) in cardiovascular disease prevention. A fixed-dose combination may be a promising strategy for promoting adherence to medication; alleviating pill burden through simplifying regimens and reducing cost. This process evaluation will complement the UMPIRE trial by using qualitative research methods to inform understanding of the complex interplay of factors that underpin trial outcomes.

Methods: A series of semistructured, in-depth interviews with local health professionals and UMPIRE trial participants in India and the UK will be undertaken. The aim is to understand their views and experiences of the trial context and of day-to-day use of medications more generally. The grounded theory approach will be used to analyse data and help inform the processes of the UMPIRE trial.

Ethics and dissemination: The study has received ethical approval for all sites in the UK and India where trial participant interviews will be undertaken. The process evaluation will help inform and enhance the understanding of the UMPIRE trial results and its applicability to clinical practice as well as shaping policy regarding strategies for improving cardiovascular medication adherence.

INTRODUCTION

Cardiovascular disease (CVD) is the leading cause of death across the globe.[1] There is an enormous evidence base of proven effective pharmacotherapeutic agents in secondary prevention of CVD.[2 3] However, worldwide utilisation and persistence with such proven drugs is low, especially in low-income and middle-income countries (LMIC). The Single Pill to Avert Cardiovascular Events (SPACE) collaboration is coordinating CVD fixed-dose combination (FDC) trials in several countries.[4] The Use of a Multidrug Pill In Reducing cardiovascular Events (UMPIRE)[5] trial is a prospective, randomised, open-label, blinded endpoint (PROBE)[6] clinical trial of a FDC-based treatment strategy compared with usual care in participants at high cardiovascular (CV) risk. The primary objective of this study is to investigate whether provision of a once daily CV FDC (containing aspirin, statin and two blood pressure lowering agents) in comparison to usual care (the usual separate and multiple CV medications prescribed by the treating doctor) improves adherence to CVD medications and hence improves the clinical outcomes of blood pressure and cholesterol. Secondary objectives include assessment of barriers to medication adherence, quality of life and comparison of results between Europe and India. The UMPIRE trial is funded by the European Commission Framework Programme 7 and is led by researchers at Imperial College London with co-investigators in the Netherlands, Ireland, India and Australia. The low cost and simplicity of the FDC strategy is an important consideration in all economies but particularly so in India where it has the potential to transform the outlook for CVD prevention. The UMPIRE trial has recruited 2004 participants (1000 in India and 1004 in Europe) and will identify patterns of adherence in the two treatment groups (FDC and usual care).

Interpreting the Processes of UMPIRE Trial (INPUT) will involve a selected subset of participants in the UK and India. It will provide a qualitative exploration of factors associated with different medication adherence patterns observed within the trial.

Complexity[7] and cost[8] of regimens are among the major obstacles for effective management of CVD; these factors are particularly important in resource-poor LMIC. A FDC containing CV medications could be a cost-effective solution to address medication underutilisation or non-adherence. A process evaluation will help to identify any disparities between research and practice by allowing a detailed examination of the context and clarifying characteristics of the trial participants and the local circumstances under which the intervention was implemented. This insight will identify the moderating factors that could limit or enhance applicability to different contexts. The detailed descriptions about implementation provided by the narratives shared in semistructured interviews will inform future replication of the trial and its wider implication by understanding the scope and limits of generalisability.

Process evaluations complement the findings from randomised controlled trial (RCT) investigations. While RCTs test the effect of intervention(s) on predetermined outcomes, process evaluations provide insight into the execution of investigation, the delivery and receipt of the intervention and the impact of the setting in which the intervention was delivered.[9] In addition, process evaluations may provide an opportunity to formulate hypotheses leading to further analysis of the trial data.

METHOD

This study will use an inductive approach to explore the processes underlying medication adherence to both FDC and usual care. The method of grounded theory[10] will be adopted because of its iterative approach to the testing of hypotheses emerging from the data, underpinned by theoretical literature addressing the recursive process of reviewing existing literature, sampling, data collection and analysis.

Literature reviews

Current literature on medication adherence in multiple disease categories will inform the data collection, with the analysis and the emerging themes guiding further in-depth reviews of the literature.

Interviews

Interviews will be undertaken in the UK and India using a subsample of the UMPIRE trial participants. The total number of recruits will depend on the consistency of findings in the interviews, but a minimum of 50 interviews will be carried out (approximately 25 in each trial arm) within each country to ensure variation across participants is in terms of age, gender, treatment arm (including those discontinuing FDC) and duration of trial participation. Recruitment will continue until no new themes arise from the interviews (thematic saturation).

In addition, local health professionals with expertise in the field of CVD (some who have patients participating in the UMPIRE trial) will be recruited as key informants. Key informants will include: general practitioners, practice nurses, cardiologists, neurologists and pharmacists. Key informants will also be asked to identify any other professionals they feel would be able to share their views on the topics under investigation. The inclusion of key informants will provide further insight into the trial context, how healthcare staff can influence patient decisions, and the feasibility of implementing an FDC strategy for CVD prevention in routine clinical practice.

In India, as UMPIRE trial visits have occurred across many different trial sites, a sample of these sites (approximately 7–9) will be used to recruit participants and key informants. These sites will be selected to reflect variation across sites in the number of participants recruited per site, hospital size, hospital setting (public/private) and site location (geographical and local language).

Interviews will be semistructured, ensuring that the same general topics are explored while allowing participants to lead the direction of discussion and explore in their own words their views and experiences. Interviewers will follow a topic guide for both the key informants and UMPIRE participant interviews in order to ensure consistency in the topics explored during each interview.

The UMPIRE participant interviews will elicit views on the research process and their individual lifestyle and routine including:

- Their views on the benefits, disadvantages and acceptability of their current treatment (FDC or usual care)
- Reports on specific instances where changes occurred to their usual adherence behaviour and the circumstances surrounding these changes
- The factors that hinder or facilitate their attitude towards adherence to therapy within the trial
- The factors that would be most likely to make patients' adherence behaviour outside the trial situation differ from that exhibited in the trial

Probing questions will be developed and refined to explore responses to these broad topics. Key informant interviews will further contribute to the development of the topic guide for the UMPIRE participant interviews. Interviews will be audio recorded, transcribed and anonymised. At the end of each interview, the interviewer will reflect on the content and note the main themes arising and any relevant remarks about the context of the interview.

To ensure that similar methods are followed for data collection and analysis in the UK and India, standard operating procedures have been written and will be followed throughout the study. The researchers will undertake regular joint supervision with experts in the fields of public health, epidemiology, anthropology and CVD.

Study procedure

At the end of the final UMPIRE trial visit, the research team will invite participants to consider taking part in the INPUT study and provide a written information sheet. Those who agree to participate will be asked to give signed informed consent. Based on the participant's preference, interviews will either take place on the same day as the final UMPIRE trial visit or at a later date, either at the trial centre or at the participant's home. In India, participant interviews will be conducted by interviewers either in English or in the local languages. The interviews conducted in the local languages will be translated into English and then checked for accuracy and anonymised.

After each interview and based on its content, permission may be sought to take photographs of the participant's medications; if the interview is held at their home, the photograph could include the location where they usually keep their medications, to gain further insights into their daily routines. These photographs will be included as visual sources of qualitative data to contribute to the development and assessment of themes in the analysis and provide further information about the context of the trial.[11 12]

ANALYSIS

The initial data analysis will be carried out independently for the UK and India. NVivo V.9 qualitative analysis software will be used to assist with the data management.

Open coding

Initially, line-by-line reading of every interview transcript will be undertaken, categorising sections of the transcripts into emergent themes. Repeated reading of the interview transcripts will assist the reader in viewing the transcript from different perspectives. Emerging categories will constantly be compared within and between transcripts in an iterative process. Emergent categories or themes may then form recognisable patterns that better predict where a situation or a condition will be more likely to occur. The direction and quantity of data collection will be guided by these emerging patterns in the data. Analysis will seek the repeated presence of specific content that is present across a transcript or between participants.

Axial coding

The resulting patterns identified in the analysis will form an analytical framework; thematic saturation of the emerging framework will be reached as the researcher compares more incidents and finds fewer differences arising in patterns. The framework will be considered in terms of the existing literature, to determine whether the emerging patterns are well described or novel.

Theoretical sampling

The researchers will seek to establish the conditions under which the patterns emerging in the analysis lead to particular outcomes. During INPUT consent procedures, participants will be asked to agree to possible follow-up discussion, should particular concepts need to be explored in more detail or areas clarified. Additional participants may also be recruited to further explore topics deemed to be pertinent.

International comparison

After separate analyses have been undertaken for both the UK and India data, the arising themes will be examined to identify both common and divergent processes underlying adherence to the FDC strategy in both data sets. This comparison will facilitate an understanding of how different contexts underpin the relevant trial processes. The process evaluation will assist interpretation of results from the trial by examining how far variation might relate to differences between healthcare systems and the national context and how these factors impact trial outcomes.

ETHICS AND DISSEMINATION

Ethics

In the UK and India, the INPUT protocol was approved by the ethics committees relevant to the participating UMPIRE trial centres.

Ethical considerations are relevant in all research methodologies, including qualitative designs where areas of potential harmful to participants may be less apparent. Richards and Schwartz[13] outline four risks to participant's well-being during qualitative research involvement—anxiety and distress, exploitation, misrepresentation and identification of the participant in published reports.

The interviews to be undertaken for INPUT aim to gain disclosure of personal experience, and therefore the probing nature of the interviews has the potential to provoke unforeseen anxiety and distress, especially as topics that could trigger distress cannot always be predicted. There is also a risk of exploitation; when a participant is allowed to speak in their own terms, the interview can take on the semblance of a therapeutic encounter for the participant and lead them to disclose more information than they initially intended. Further, the interpretation of the participant's views, such as their behaviour and beliefs, may be at odds with the participant's own perspective, and reading the published results could itself have a negative impact on the participant's sense of self.

During the development of the INPUT protocol, ethical issues have been considered and, where relevant, addressed. Although the interviewers will be sensitive and avoid causing distress to the interviewee as far as possible, the information sheet will also highlight the potential risk of distress to the participant from participation and explicitly note that the interview itself is for research purposes, although it may also be profitable to discuss experiences. Standard procedures have also been established for the management of any participant who becomes distressed during the interview, and this includes provision of information and support should it

be required. Further to this, rigorous analysis procedures will be followed by the researchers including regular supervision of the analysis by experienced qualitative researchers in order to avoid the participant's views being misrepresented and to uphold anonymity of data by considering the multiple clues to identity present in individual narratives.

Dissemination

As INPUT will use an exploratory method, a plan of publication will be based on the trial results and the emerging themes arising from interviews and their subsequent analysis. The process evaluation will also help to enrich the trial results by exploring and identifying the key components of the intervention, identifying when and under what circumstances the intervention is of benefit, or why the intervention may not have been favourable. The results of a process evaluation of the UMPIRE trial will also lead to a better understanding of the mechanisms involved in adherence to CV medications in the trial context. Such information will provide insights into the relevance of a CV FDC strategy in a clinical context, and may prove useful for designing effective public health policy with regard to adopting or rejecting such a strategy. We anticipate that the process evaluation will explore pertinent factors underlying any variations in the UMPIRE results between India and the UK. It will also consider data emerging from parallel studies within the SPACE collaboration (such as the process evaluation planned[14] for the Kanyini-Gap Trial in Australia), and comment on variations between the different settings.

As highlighted, across disease groups, treatment success is often dependent on successful adherence to prescribed medications.[15 16] Poor adherence is a complex interplay of several factors.[7] Therefore, understanding more about the implementation of an FDC strategy on medicine taking behaviour will also provide important insight into the determinants of medication adherence.

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Funding INterpreting the Processes of UMPIRE (Use of a Multidrug Pill in Reducing Cardiovascular Events) Trial (INPUT) study is funded by a research fellowship from Imperial Healthcare Charity, grant number 7021/R25D and the George Institute for Global Health.

Competing interests The authors AS, KS, ST, AP and DP have received funding for travel to investigator meetings related to the UMPIRE trial from Dr Reddy's Laboratories. The George Institute for Global Health recently secured an exclusive global license for the fixed-dose combinations used in this trial following a decision by Dr Reddy's Laboratories not to proceed with taking the products to market because of existing regulatory requirements.

Ethics approval National Health Service (NHS) Research Ethics Committee and Local Indian Ethics Committees at all sites.

Provenance and peer review Not commissioned; externally peer reviewed.

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