



**INterpreting the Processes of the UMPIRE Trial (INPUT):  
the design of a process evaluation of a fixed dose  
combination (FDC) strategy to improve adherence to  
cardiovascular medications**

Journal:	<i>BMJ Open</i>
Manuscript ID:	bmjopen-2012-002313
Article Type:	Protocol
Date Submitted by the Author:	05-Nov-2012
Complete List of Authors:	Salam, Abdul; The George Institute for Global Health, Stewart, Frances; Imperial College Healthcare NHS Trust, International Centre for Circulatory Health Singh, Kavita; Centre for Chronic Disease Control, Thom, Simon; Imperial College London, International Centre for Circulatory Health Williams, Hilarie; Imperial College London, International Centre for Circulatory Health Patel, Anushka; The George Institute for Global Health, Jan, Stephen; The George Institute for Global Health, Prabhakaran, Dorairaj; The George Institute for Global Health, Maulik, Pallab; The George Institute for Global Health, Day, Sophie; Imperial College London, School of Public Health Ward, Helen; Imperial College London, School of Public Health
<b>Primary Subject Heading</b>:	Cardiovascular medicine
Secondary Subject Heading:	Global health
Keywords:	Cardiovascular Disease, Fixed Dose Combination, Medication Adherence, Polypill, Prevention, Process Evaluation

SCHOLARONE™  
Manuscripts

**Title**

**Interpreting the Processes of the UMPIRE Trial (INPUT): the design of a process evaluation of a fixed dose combination (FDC) strategy to improve adherence to cardiovascular medications**

**Authors**

Abdul Salam<sup>1</sup>, Frances Stewart<sup>2\*</sup>, Kavita Singh<sup>3</sup>, Simon Thom<sup>2</sup>, Hilarie Jane Williams<sup>2</sup>, Anushka Patel<sup>4</sup>, Stephen Jan<sup>4</sup>, Tracey Laba<sup>4</sup>, Dorairaj Prabhakaran<sup>3</sup>, Pallab Maulik<sup>1</sup>, Sophie Day<sup>5</sup>, Helen Ward<sup>5</sup>

\*Corresponding Author: frances.stewart@imperial.nhs.uk

**Author institutions**

<sup>1</sup>The George Institute for Global Health, 839C, Road No. 44A, Jubilee Hills, Hyderabad – 500 033, Andhra Pradesh, India

<sup>2</sup>International Centre for Circulatory Health, Imperial College London and Imperial Healthcare NHS Trust, 59-61, North Wharf Road, London, W2 1LA, United Kingdom. Telephone number: 0207 594 1057, fax number: 0207 594 1148.

<sup>3</sup>Centre for Chronic Disease Control, Tower 4, Commercial Complex, C 9, Vasant Kunj, New Delhi - 110070, India

<sup>4</sup>The George Institute for Global Health, Level 10, King George V Building, 83-117 Missenden Road, Camperdown, NSW 2050, Australia

<sup>5</sup>School of Public Health, Imperial College London, Praed Street, London, W2 1NY, United Kingdom.

**Keywords**

Cardiovascular Disease, Fixed Dose Combination, Medication Adherence, Polypill, Prevention

**Word Count: 2318**

**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 semi-structured, in-depth interviews with local health professionals and UMPIRE trial participants in India and the United Kingdom 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-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] 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 risk. The primary objective of this study is to investigate whether provision of a once daily cardiovascular FDC (containing aspirin, statin and two blood pressure lowering agents) in comparison to usual care (the usual separate and multiple cardiovascular (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 European Commission Framework Program 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 (1,000 in India and 1,004 in Europe) and will identify patterns of adherence in the two treatment groups (FDC

1  
2  
3  
4 and usual care). Interpreting the Processes of UMPIRE Trial (INPUT) study will involve a  
5  
6 selected sub-set of participants in the UK and India. This study will provide a qualitative  
7  
8 exploration of factors associated with different medication adherence patterns observed  
9  
10 within the trial.  
11

12  
13  
14 Process evaluations complement the findings from randomised controlled trial (RCT)  
15  
16 investigations. Whilst RCTs test the effect of intervention(s) on pre-determined outcomes,  
17  
18 process evaluations, provide insight into the execution of investigation, the delivery and  
19  
20 receipt of the intervention, and the impact of the setting in which the intervention was  
21  
22 delivered[7]. In addition, process evaluations may provide an opportunity to formulate  
23  
24 hypotheses leading to further analysis of the trial data.  
25  
26  
27  
28

## 29 30 **METHOD**

31  
32  
33 This study will use an inductive approach to explore the processes underlying medication  
34  
35 adherence to both FDC and usual care. The method of grounded theory[8], will be adopted  
36  
37 because of its iterative approach to the testing of hypotheses emerging from the data,  
38  
39 underpinned by theoretical literature addressing the recursive process of reviewing existing  
40  
41 literature, sampling, data collection and analysis.  
42  
43  
44  
45

## 46 **Literature Reviews**

47  
48  
49 Current literature on medication adherence in multiple disease categories will inform the  
50  
51 data collection, with the analysis itself guiding further in-depth reviews of the literature.  
52  
53  
54  
55

## Interviews

Interviews will be undertaken in the UK and India using a sub-sample 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 the 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 cardiovascular disease (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 health care staff can influence patient decisions, and the feasibility of implementing a 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 number of participants recruited per site, hospital size, hospital setting (public/private) and site location (geographic and local language).

1  
2  
3  
4 Interviews will be semi-structured ensuring that the same general topics are explored whilst  
5  
6 allowing participants to lead the direction of discussion and explore in their own words their  
7  
8 views and experiences. Interviewers will follow a topic guide for both the key informant and  
9  
10 UMPIRE participant interviews in order to ensure consistency in the topics explored during  
11  
12 each interview.  
13  
14

15  
16  
17 The UMPIRE participant interviews will elicit views on the research process and their  
18  
19 individual lifestyle and routine including:  
20

- 21  
22 • Their views on the benefits, disadvantages and acceptability of their current  
23  
24 treatment (FDC or usual care).  
25  
26
- 27  
28 • Reports on specific instances where changes occurred to their usual adherence  
29  
30 behaviour and the circumstances surrounding these changes.  
31  
32
- 33  
34 • The factors that hinder or facilitate their attitude toward adherence to therapy  
35  
36 within the trial.  
37  
38
- 39  
40 • The factors that would be likely to make patients' adherence behaviour outside the  
41  
42 trial situation differ from that exhibited in the trial.  
43

44 Probing questions will be developed and refined to explore responses to these broad topics.  
45  
46 Key informant interviews will further contribute to the development of the topic guide for  
47  
48 the UMPIRE participant interviews. Interviews will be audio recorded, transcribed and  
49  
50 anonymised. At the end of each interview, the interviewer will reflect on the content and  
51  
52 note the main themes arising and any relevant remarks about the context of the interview.  
53  
54  
55  
56  
57  
58  
59  
60

1  
2  
3  
4 In order to ensure consistency in procedures whilst allowing for emergent differences to  
5  
6 arise from the two data sets (UK and India), INPUT standard operating procedures for  
7  
8 conducting the interviews and data analysis will be followed. The researchers will undertake  
9  
10 regular joint supervision with experts in the fields of public health, epidemiology,  
11  
12 anthropology and cardiovascular disease.  
13  
14

### 15 16 17 **Study Procedure** 18

19  
20 At the end of the final UMPIRE trial visit the research team will invite participants to  
21  
22 consider taking part in the INPUT study and provide a written information sheet. Those who  
23  
24 agree to participate will be asked to give signed informed consent. Based on participant's  
25  
26 preference, interviews will either take place on the same day as the final UMPIRE trial visit  
27  
28 or at a later date, either at the trial centre or the participant's home. In India, participant  
29  
30 interviews will be conducted by interviewers either in English or in local languages. The  
31  
32 interviews conducted in local languages will be translated to English and will be then  
33  
34 checked for accuracy and anonymised.  
35  
36  
37  
38

39  
40 After each interview and based on its content, permission may be sought to take  
41  
42 photographs of the participant's medications and if the interview is done at their home the  
43  
44 photograph could include the location they usually keep their medications, to gain further  
45  
46 insights into their daily routines. These photographs will be included as visual sources of  
47  
48 qualitative data to contribute to the development and assessment of themes in the analysis.  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60



## ANALYSIS

The initial data analysis will be carried out independently for the UK and India. NVivo 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 occur for compound meaning. 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 more likely 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 analytic framework; thematic saturation of the emerging framework will be reached as the researcher compares more incidents and finds fewer differences in patterns arising. Existing literature will be used to delimit the framework and to determine whether the emerging patterns are well described or novel.

### Theoretical Sampling

1  
2  
3  
4 The researchers will seek to establish the conditions under which the patterns emerging in  
5  
6 the analysis lead to particular outcomes. During INPUT consent procedures, participants will  
7  
8 be asked to agree to possible follow-up discussion, should particular concepts need to be  
9  
10 explored in more detail or areas clarified. Additional participants may also be recruited, to  
11  
12 further explore topics deemed to be pertinent.  
13  
14

### 15 16 17 **International Comparison**

18  
19  
20 After separate analyses have been undertaken for both the UK and India data, the arising  
21  
22 themes will be examined to identify both common and divergent processes underlying  
23  
24 adherence to the FDC strategy in both data sets. This comparison will facilitate  
25  
26 understanding of how different contexts underpin the relevant trial processes. The process  
27  
28 evaluation will assist interpretation of results from the trial by examining how far variation  
29  
30 might relate to differences between health care systems and the national context and how  
31  
32 these factors impact trial outcomes.  
33  
34  
35  
36  
37  
38  
39  
40

## 41 42 **ETHICS AND DISSEMINATION**

### 43 44 45 **Ethics**

46  
47  
48 In the UK and India the INPUT protocol was approved by the ethics committees relevant to  
49  
50 the participating UMPIRE trial centres.  
51  
52

53  
54 Ethical considerations are relevant in all research methodologies including qualitative  
55  
56 designs where areas of potential harm to participants may be less apparent. Richard's and  
57  
58

1  
2  
3  
4 Schwarz's[9] outline four risks to participant's well-being during qualitative research  
5  
6 involvement; anxiety and distress, exploitation, misrepresentation, and identification of the  
7  
8 participant in published reports.  
9

10  
11  
12 The interviews to be undertaken for INPUT aim to gain disclosure of personal experience  
13  
14 and so the probing nature of the interviews has the potential to provoke unforeseen anxiety  
15  
16 and distress, especially as topics that could trigger distress cannot always be predicted.  
17  
18 There is also a risk of exploitation, when a participant is allowed to speak in their own terms,  
19  
20 the interview can take on the semblance of a therapeutic encounter for the participant and  
21  
22 lead them to disclose more information than they initially intended. Further, the  
23  
24 interpretation of the participants views such as their behaviour and beliefs may be at odds  
25  
26 with the participant's own perspective and reading the published results could itself have a  
27  
28 negative impact on the participant's sense of self.  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

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 to the participant the potential risk of distress 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

1  
2  
3  
4 experienced qualitative researchers in order to avoid participant's views being  
5  
6 misrepresented and to uphold anonymity of data by considering the multiple clues to  
7  
8 identity present in individual narratives.  
9

## 10 11 12 **Dissemination**

13  
14  
15 As INPUT will use an exploratory method, a plan of publication will be based on the trial  
16  
17 results and the poignant themes arising from interviews and their subsequent analysis.  
18  
19 There are several key areas that dissemination will likely focus including medication  
20  
21 adherence which is a complex health behaviour, influenced by social, psychological,  
22  
23 cognitive, economic, disease condition, and therapy-related factors as well as health-  
24  
25 systems and patient-provider relationship[10]. The process evaluation will also help to  
26  
27 enrich the trial results by exploring and identifying the key components of the intervention,  
28  
29 identifying when and under what circumstances the intervention is of benefit, or why the  
30  
31 intervention may not have been favourable. The results of a process evaluation of the  
32  
33 UMPIRE trial will also lead to a better understanding of the mechanisms involved in  
34  
35 adherence to cardiovascular medications in the trial context. Such information will provide  
36  
37 insights into the relevance of a cardiovascular FDC strategy in a clinical context, and may  
38  
39 prove useful for designing effective public health policy with regard to adopting or rejecting  
40  
41 such a strategy. We anticipate that the process evaluation will explore pertinent factors  
42  
43 underlying any variations in the UMPIRE results between India and the UK. It will also  
44  
45 consider data emerging from parallel studies within the SPACE collaboration (such as the  
46  
47 process evaluation planned[11] for the Kanyini Gap Trial in Australia), and comment on  
48  
49 variations between the different settings.  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

1  
2  
3  
4 Complexity[12] and cost[13] of regimens are amongst the major obstacles for effective  
5 management of CVD; these factors are particularly important in resource-poor LMIC. A FDC  
6 containing cardiovascular (CV) medications could be a cost-effective solution to address  
7 medication under-utilization or non-adherence. A process evaluation will help to identify  
8 any disparities between research and practice by allowing a detailed examination of the  
9 context and clarifying characteristics of the trial participants and the local circumstances  
10 under which the intervention was implemented. This insight will identify the moderating  
11 factors that could limit or enhance applicability to different contexts. The detailed  
12 descriptions about implementation provided by the narratives shared in semi-structured  
13 interviews will inform future replication of the trial and its wider implication by  
14 understanding the scope and limits of generalisability.  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30

31 As highlighted, across disease groups treatment success is often dependent on successful  
32 adherence to prescribed medications[10,14]. Poor adherence is a complex interplay of  
33 several factors[12]. Therefore, understanding more about the implementation of a FDC  
34 strategy on medicine taking behaviour will also provide important insight into the  
35 determinants of medication adherence.  
36  
37  
38  
39  
40  
41  
42  
43

#### 44 **FUNDING STATEMENT**

45  
46  
47 The INPUT study is funded by a research fellowship from Imperial Healthcare Charity, grant  
48 number 7021/R25D and the George Institute for Global Health.  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

## COMPETING INTEREST STATEMENT

The author(s) declare that they have no competing interests.

## AUTHORS CONTRIBUTION

HW and ST wrote the first draft of the protocol and all other authors contributed to the critical revision of the protocol.

## REFERENCES

1. World Health Organisation. Cardiovascular Diseases (CVDs). Fact Sheet No 317. 2012.  
<http://www.who.int./mediacentre/factsheets/fs317/en/index.html> (accessed 1 November 2012).
2. Smith SC, Benjamin EJ, Bonow RO, et al. AHA/ACCF Secondary Prevention and Risk Reduction Therapy for Patients with Coronary and other Atherosclerotic Vascular Disease: 2011 update: a guideline from the American Heart Association and American College of Cardiology Foundation. *Circulation*. 2011;**124**:2458-73.
3. Furie KL, Kasner SE, Adams RJ, et al. Guidelines for the prevention of stroke in patients with stroke or transient ischemic attack: a guideline for healthcare professionals from the american heart association/american stroke association. *Stroke*. 2011;**42**:227-76.
4. Health TGIfG. SPACE collaboration: Single Pill to Avert Cardiovascular Events.  
<http://www.spacecollaboration.org/> (accessed 28 Aug 2012).

- 1  
2  
3  
4 5. Thom S, Field J, Poulter N, et al. Use of a Multidrug Pill In Reducing cardiovascular  
5  
6 Events (UMPIRE): rationale and design of a randomised controlled trial of a  
7  
8 cardiovascular preventive polypill-based strategy in India and Europe. 2012. *Eur J*  
9  
10 *Prev Cardiol*.  
11  
12 <http://cpr.sagepub.com/search/results?fulltext=umpire&x=0&y=0&submit=yes&jour>  
13  
14 [nal\\_set=spcpr&src=selected&andorexactfulltext=and](http://cpr.sagepub.com/search/results?fulltext=umpire&x=0&y=0&submit=yes&jour) (accessed 1 Nov 2012).  
15  
16
- 17  
18 6. Hansson L, Hedner T, Dahlof B. Prospective randomized open blinded end-point  
19  
20 (PROBE) study. A novel design for intervention trials. Prospective Randomized Open  
21  
22 Blinded End-Point. *Blood Press*. 1992 Aug;**1**:113-9.  
23  
24
- 25 7. Oakley A, Strange V, Bonell C, et al. Process evaluation in randomised controlled  
26  
27 trials of complex interventions. *BMJ*. 2006;**332**:413-416.  
28  
29
- 30 8. Glaser BGS, Anselm L. The Discovery of Grounded Theory: Strategies for Qualitative  
31  
32 Research. Chicago: Aldine Publishing Company 1967.  
33  
34
- 35 9. Richards HM, Schwartz LJ. Ethics of qualitative research: are there special issues for  
36  
37 health services research? *Family Practice*. 2002; **19**:135-139.  
38  
39
- 40 10. World Health Organisation. Adherence for long-term therapies: Evidence for action.  
41  
42 2003. <http://whqlibdoc.who.int/publications/2003/9241545992.pdf> (accessed 1 Nov  
43  
44 2012).  
45  
46
- 47 11. Jan S, Usherwood T, Brien JA, et al. What determines adherence to treatment in  
48  
49 cardiovascular disease prevention? Protocol for a mixed methods preference study.  
50  
51 *BMJ Open*. 2011;**1**. <http://bmjopen.bmj.com/content/1/2/e000372.full.pdf>  
52  
53 (accessed 1 Nov 2012).  
54  
55  
56  
57  
58  
59  
60

- 1  
2  
3  
4 12. Donovan JL, Blake DR. Patient non-compliance: deviance or reasoned decision-  
5 making? *Soc Sci Med*. 1992;**34**:507-513.  
6  
7  
8  
9 13. Heisler M, Langa KM, Eby EL, Fendrick AM, Kabeto MU, Piette JD. The health effects  
10 of restricting prescription medication use because of cost. *Med Care*. 2004;**42**:626-  
11 634.  
12  
13  
14  
15  
16 14. DiMatteo MR, Haskard KB, Williams SL. Health beliefs, disease severity, and patient  
17 adherence: a meta-analysis. *Med Care*. 2007;**45**:521-528.  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60





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

Journal:	<i>BMJ Open</i>
Manuscript ID:	bmjopen-2012-002313.R1
Article Type:	Protocol
Date Submitted by the Author:	25-Mar-2013
Complete List of Authors:	Salam, Abdul; The George Institute for Global Health, Stewart, Frances; Imperial College Healthcare NHS Trust, International Centre for Circulatory Health Singh, Kavita; Centre for Chronic Disease Control, Thom, Simon; Imperial College London, International Centre for Circulatory Health Williams, Hilarie; Imperial College London, International Centre for Circulatory Health Patel, Anushka; The George Institute for Global Health, Jan, Stephen; The George Institute for Global Health, Prabhakaran, Dorairaj; The George Institute for Global Health, Maulik, Pallab; The George Institute for Global Health, Day, Sophie; Imperial College London, School of Public Health Ward, Helen; Imperial College London, School of Public Health
<b>Primary Subject Heading</b>:	Cardiovascular medicine
Secondary Subject Heading:	Global health, Qualitative research
Keywords:	Cardiovascular Disease, Fixed Dose Combination, Medication Adherence, Polypill, Prevention, Process Evaluation

SCHOLARONE™  
Manuscripts

**Title**

**Interpreting the Processes of the UMPIRE Trial (INPUT): the design of a process evaluation of a fixed dose combination (FDC) strategy to improve adherence to cardiovascular medications – a qualitative study**

**Authors**

Abdul Salam<sup>1</sup>, Frances Stewart<sup>2\*</sup>, Kavita Singh<sup>3</sup>, Simon Thom<sup>2</sup>, Hilarie Jane Williams<sup>2</sup>, Anushka Patel<sup>4</sup>, Stephen Jan<sup>4</sup>, Tracey Laba<sup>4</sup>, Dorairaj Prabhakaran<sup>3</sup>, Pallab Maulik<sup>1</sup>, Sophie Day<sup>5</sup>, Helen Ward<sup>5</sup>

\*Corresponding Author: frances.stewart@imperial.nhs.uk

**Author institutions**

<sup>1</sup>The George Institute for Global Health, 839C, Road No. 44A, Jubilee Hills, Hyderabad – 500 033, Andhra Pradesh, India

<sup>2</sup>International Centre for Circulatory Health, Imperial College London and Imperial Healthcare NHS Trust, 59-61, North Wharf Road, London, W2 1LA, United Kingdom. Telephone number: 0207 594 1057, fax number: 0207 594 1148.

<sup>3</sup>Centre for Chronic Disease Control, Tower 4, Commercial Complex, C 9, Vasant Kunj, New Delhi - 110070, India

<sup>4</sup>The George Institute for Global Health, Level 10, King George V Building, 83-117 Missenden Road, Camperdown, NSW 2050, Australia

<sup>5</sup>School of Public Health, Imperial College London, Praed Street, London, W2 1NY, United Kingdom.

**Keywords**

Cardiovascular Disease, Fixed Dose Combination, Medication Adherence, Polypill, Prevention

**Word Count:** 2300

**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 semi-structured, in-depth interviews with local health professionals and UMPIRE trial participants in India and the United Kingdom 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-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] 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 risk. The primary objective of this study is to investigate whether provision of a once daily cardiovascular FDC (containing aspirin, statin and two blood pressure lowering agents) in comparison to usual care (the usual separate and multiple cardiovascular (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 European Commission Framework Program 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 (1,000 in India and 1,004 in Europe) and will identify patterns of adherence in the two treatment groups (FDC

1  
2  
3  
4 and usual care). Interpreting the Processes of UMPIRE Trial (INPUT) study will involve a  
5  
6 selected sub-set of participants in the UK and India. This study will provide a qualitative  
7  
8 exploration of factors associated with different medication adherence patterns observed  
9  
10 within the trial.  
11

12  
13  
14 Complexity[7] and cost[8] of regimens are amongst the major obstacles for effective  
15  
16 management of CVD; these factors are particularly important in resource-poor LMIC. A FDC  
17  
18 containing cardiovascular (CV) medications could be a cost-effective solution to address  
19  
20 medication under-utilization or non-adherence. A process evaluation will help to identify  
21  
22 any disparities between research and practice by allowing a detailed examination of the  
23  
24 context and clarifying characteristics of the trial participants and the local circumstances  
25  
26 under which the intervention was implemented. This insight will identify the moderating  
27  
28 factors that could limit or enhance applicability to different contexts. The detailed  
29  
30 descriptions about implementation provided by the narratives shared in semi-structured  
31  
32 interviews will inform future replication of the trial and its wider implication by  
33  
34 understanding the scope and limits of generalisability.  
35  
36  
37  
38  
39

40  
41  
42 Process evaluations complement the findings from randomised controlled trial (RCT)  
43  
44 investigations. Whilst RCTs test the effect of intervention(s) on pre-determined outcomes,  
45  
46 process evaluations, provide insight into the execution of investigation, the delivery and  
47  
48 receipt of the intervention, and the impact of the setting in which the intervention was  
49  
50 delivered[9]. In addition, process evaluations may provide an opportunity to formulate  
51  
52 hypotheses leading to further analysis of the trial data.  
53  
54  
55  
56  
57  
58  
59  
60

## 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 sub-sample 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 the FDC) and duration of trial participation. Recruitment will continue until no new themes arise from the interviews (thematic saturation).

1  
2  
3  
4 In addition, local health professionals with expertise in the field of cardiovascular disease  
5  
6 (some who have patients participating in the UMPIRE trial) will be recruited as key  
7  
8 informants. Key informants will include: general practitioners, practice nurses, cardiologists,  
9  
10 neurologists and pharmacists. Key informants will also be asked to identify any other  
11  
12 professionals they feel would be able to share their views on the topics under investigation.  
13  
14 The inclusion of key informants will provide further insight into the trial context, how health  
15  
16 care staff can influence patient decisions, and the feasibility of implementing a FDC strategy  
17  
18 for CVD prevention in routine clinical practice.  
19  
20  
21  
22  
23

24 In India, as UMPIRE trial visits have occurred across many different trial sites, a sample of  
25  
26 these sites (approximately 7-9) will be used to recruit participants and key informants.  
27  
28 These sites will be selected to reflect variation across sites in number of participants  
29  
30 recruited per site, hospital size, hospital setting (public/private) and site location  
31  
32 (geographic and local language).  
33  
34  
35  
36

37 Interviews will be semi-structured ensuring that the same general topics are explored whilst  
38  
39 allowing participants to lead the direction of discussion and explore in their own words their  
40  
41 views and experiences. Interviewers will follow a topic guide for both the key informant and  
42  
43 UMPIRE participant interviews in order to ensure consistency in the topics explored during  
44  
45 each interview.  
46  
47  
48

49 The UMPIRE participant interviews will elicit views on the research process and their  
50  
51 individual lifestyle and routine including:  
52  
53  
54  
55  
56  
57  
58  
59  
60

- 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 toward adherence to therapy within the trial.
- The factors that would be 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 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 cardiovascular disease.

### **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 participant's



1  
2  
3  
4 preference, interviews will either take place on the same day as the final UMPIRE trial visit  
5  
6 or at a later date, either at the trial centre or the participant's home. In India, participant  
7  
8 interviews will be conducted by interviewers either in English or in local languages. The  
9  
10 interviews conducted in local languages will be translated to English and will be then  
11  
12 checked for accuracy and anonymised.  
13  
14

15  
16  
17 After each interview and based on its content, permission may be sought to take  
18  
19 photographs of the participant's medications and if the interview is done at their home the  
20  
21 photograph could include the location they usually keep their medications, to gain further  
22  
23 insights into their daily routines. These photographs will be included as visual sources of  
24  
25 qualitative data to contribute to the development and assessment of themes in the analysis  
26  
27 and provide further information about the context of the trial [11, 12].  
28  
29  
30  
31  
32  
33  
34  
35

## 36 ANALYSIS

37  
38  
39 The initial data analysis will be carried out independently for the UK and India. NVivo 9  
40  
41 qualitative analysis software will be used to assist with the data management.  
42  
43  
44

### 45 Open-coding

46  
47  
48 Initially, line-by-line reading of every interview transcript will be undertaken, categorising  
49  
50 sections of the transcripts into emergent themes. Repeated reading of the interview  
51  
52 transcripts will assist the reader in viewing the transcript from different perspectives.  
53  
54  
55 Emerging categories will constantly be compared within and between transcripts in an  
56  
57  
58  
59  
60

1  
2  
3  
4 iterative process. Emergent categories or themes may then form recognisable patterns that  
5  
6 better predict where a situation or a condition will more likely occur. The direction and  
7  
8 quantity of data collection will be guided by these emerging patterns in the data. Analysis  
9  
10 will seek the repeated presence of specific content that is present across a transcript or  
11  
12 between participants.  
13  
14

### 15 16 17 **Axial Coding** 18

19  
20 The resulting patterns identified in the analysis will form an analytic framework; thematic  
21  
22 saturation of the emerging framework will be reached as the researcher compares more  
23  
24 incidents and finds fewer differences in patterns arising. The framework will be considered  
25  
26 in terms of the existing literature, to determine whether the emerging patterns are well  
27  
28 described or novel.  
29  
30  
31

### 32 33 **Theoretical Sampling** 34

35  
36 The researchers will seek to establish the conditions under which the patterns emerging in  
37  
38 the analysis lead to particular outcomes. During INPUT consent procedures, participants will  
39  
40 be asked to agree to possible follow-up discussion, should particular concepts need to be  
41  
42 explored in more detail or areas clarified. Additional participants may also be recruited, to  
43  
44 further explore topics deemed to be pertinent.  
45  
46  
47

### 48 49 **International Comparison** 50

51  
52 After separate analyses have been undertaken for both the UK and India data, the arising  
53  
54 themes will be examined to identify both common and divergent processes underlying  
55  
56  
57

1  
2  
3  
4 adherence to the FDC strategy in both data sets. This comparison will facilitate  
5  
6 understanding of how different contexts underpin the relevant trial processes. The process  
7  
8 evaluation will assist interpretation of results from the trial by examining how far variation  
9  
10 might relate to differences between health care systems and the national context and how  
11  
12 these factors impact trial outcomes.  
13  
14

## 20 **ETHICS AND DISSEMINATION**

### 23 **Ethics**

24  
25  
26  
27 In the UK and India the INPUT protocol was approved by the ethics committees relevant to  
28  
29 the participating UMPIRE trial centres.  
30  
31

32  
33 Ethical considerations are relevant in all research methodologies including qualitative  
34  
35 designs where areas of potential harm to participants may be less apparent. Richard's and  
36  
37 Schwarz's[13] outline four risks to participant's well-being during qualitative research  
38  
39 involvement; anxiety and distress, exploitation, misrepresentation, and identification of the  
40  
41 participant in published reports.  
42  
43  
44

45  
46 The interviews to be undertaken for INPUT aim to gain disclosure of personal experience  
47  
48 and so the probing nature of the interviews has the potential to provoke unforeseen anxiety  
49  
50 and distress, especially as topics that could trigger distress cannot always be predicted.  
51  
52 There is also a risk of exploitation, when a participant is allowed to speak in their own terms,  
53  
54 the interview can take on the semblance of a therapeutic encounter for the participant and  
55  
56  
57

1  
2  
3  
4 lead them to disclose more information than they initially intended. Further, the  
5  
6 interpretation of the participants views such as their behaviour and beliefs may be at odds  
7  
8 with the participant's own perspective and reading the published results could itself have a  
9  
10 negative impact on the participant's sense of self.  
11  
12  
13

14  
15  
16  
17 During, the development of the INPUT protocol, ethical issues have been considered and  
18  
19 where relevant addressed. Although, the interviewers will be sensitive and avoid causing  
20  
21 distress to the interviewee as far as possible, the information sheet will also highlight to the  
22  
23 participant the potential risk of distress from participation and explicitly note that the  
24  
25 interview itself is for research purposes although it may also be profitable to discuss  
26  
27 experiences. Standard procedures have also been established for the management of any  
28  
29 participant who becomes distressed during the interview and this includes provision of  
30  
31 information and support should it be required. Further to this, rigorous analysis procedures  
32  
33 will be followed by the researchers including regular supervision of the analysis by  
34  
35 experienced qualitative researchers in order to avoid participant's views being  
36  
37 misrepresented and to uphold anonymity of data by considering the multiple clues to  
38  
39 identity present in individual narratives.  
40  
41  
42  
43  
44  
45

#### 46 47 **Dissemination**

48  
49  
50 As INPUT will use an exploratory method, a plan of publication will be based on the trial  
51  
52 results and the emerging themes arising from interviews and their subsequent analysis. The  
53  
54 process evaluation will also help to enrich the trial results by exploring and identifying the  
55  
56  
57

1  
2  
3  
4 key components of the intervention, identifying when and under what circumstances the  
5  
6 intervention is of benefit, or why the intervention may not have been favourable. The  
7  
8 results of a process evaluation of the UMPIRE trial will also lead to a better understanding of  
9  
10 the mechanisms involved in adherence to cardiovascular medications in the trial context.  
11  
12 Such information will provide insights into the relevance of a cardiovascular FDC strategy in  
13  
14 a clinical context, and may prove useful for designing effective public health policy with  
15  
16 regard to adopting or rejecting such a strategy. We anticipate that the process evaluation  
17  
18 will explore pertinent factors underlying any variations in the UMPIRE results between India  
19  
20 and the UK. It will also consider data emerging from parallel studies within the SPACE  
21  
22 collaboration (such as the process evaluation planned[14] for the Kanyini Gap Trial in  
23  
24 Australia), and comment on variations between the different settings.  
25  
26  
27  
28  
29  
30

31 As highlighted, across disease groups treatment success is often dependent on successful  
32  
33 adherence to prescribed medications[15,16]. Poor adherence is a complex interplay of  
34  
35 several factors[7]. Therefore, understanding more about the implementation of a FDC  
36  
37 strategy on medicine taking behaviour will also provide important insight into the  
38  
39 determinants of medication adherence.  
40  
41  
42

#### 43 44 **FUNDING STATEMENT**

45  
46  
47 The INPUT study is funded by a research fellowship from Imperial Healthcare Charity, grant  
48  
49 number 7021/R25D and the George Institute for Global Health.  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

## COMPETING INTEREST STATEMENT

The author(s) declare that they have no competing interests.

## AUTHORS CONTRIBUTION

HW and ST wrote the first draft of the protocol and all other authors contributed to the critical revision of the protocol.

## REFERENCES

1. World Health Organisation. Cardiovascular Diseases (CVDs). Fact Sheet No 317. 2012. <http://www.who.int./mediacentre/factsheets/fs317/en/index.html> (accessed 1 November 2012).
2. Smith SC, Benjamin EJ, Bonow RO, et al. AHA/ACCF Secondary Prevention and Risk Reduction Therapy for Patients with Coronary and other Atherosclerotic Vascular Disease: 2011 update: a guideline from the American Heart Association and American College of Cardiology Foundation. *Circulation*. 2011;**124**:2458-73.
3. Furie KL, Kasner SE, Adams RJ, et al. Guidelines for the prevention of stroke in patients with stroke or transient ischemic attack: a guideline for healthcare professionals from the american heart association/american stroke association. *Stroke*. 2011;**42**:227-76.
4. Health TGIfG. SPACE collaboration: Single Pill to Avert Cardiovascular Events. <http://www.spacecollaboration.org/> (accessed 28 Aug 2012).

- 1  
2  
3  
4 5. Thom S, Field J, Poulter N, et al. Use of a Multidrug Pill In Reducing cardiovascular  
5  
6 Events (UMPIRE): rationale and design of a randomised controlled trial of a  
7  
8 cardiovascular preventive polypill-based strategy in India and Europe. 2012. *Eur J*  
9  
10 *Prev Cardiol*.  
11  
12 <http://cpr.sagepub.com/search/results?fulltext=umpire&x=0&y=0&submit=yes&jour>  
13  
14 [nal\\_set=spcpr&src=selected&andorexactfulltext=and](http://cpr.sagepub.com/search/results?fulltext=umpire&x=0&y=0&submit=yes&jour) (accessed 1 Nov 2012).  
15  
16
- 17  
18 6. Hansson L, Hedner T, Dahlof B. Prospective randomized open blinded end-point  
19  
20 (PROBE) study. A novel design for intervention trials. Prospective Randomized Open  
21  
22 Blinded End-Point. *Blood Press*. 1992 Aug;**1**:113-9.  
23  
24
- 25  
26 7. Donovan JL, Blake DR. Patient non-compliance: deviance or reasoned decision-  
27  
28 making? *Soc Sci Med*. 1992;**34**:507-513.  
29
- 30  
31 8. Heisler M, Langa KM, Eby EL, et al. The health effects of restricting prescription  
32  
33 medication use because of cost. *Med Care*. 2004;**42**:626-634.  
34
- 35  
36 9. Oakley A, Strange V, Bonell C, et al. Process evaluation in randomised controlled  
37  
38 trials of complex interventions. *BMJ*. 2006;**332**:413-416.  
39
- 40  
41 10. Glaser BGS, Anselm L. The Discovery of Grounded Theory: Strategies for Qualitative  
42  
43 Research. Chicago: Aldine Publishing Company; 1967.  
44
- 45  
46 11. Pink S. Doing visual ethnography: Images, media and representation in research.  
47  
48 *London: SAGE; 2000*.  
49
- 50  
51 12. Wiles R, Prosser J, Bagnoli A, et al. ESRC national Centre for Research Methods: ESRC  
52  
53 National Centre for Research Methods Review Paper: Visual Ethics: Ethical Issues in  
54  
55 Visual. 2008. <http://eprints.ncrm.ac.uk/421/1/MethodsReviewPaperNCRM-011.pdf>  
56  
57 (accessed 31 October 2011)  
58  
59  
60

- 1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60
13. Richards HM, Schwartz LJ. Ethics of qualitative research: are there special issues for health services research? *Family Practice*. 2002; **19**:135-139.
14. Jan S, Usherwood T, Brien JA, et al. What determines adherence to treatment in cardiovascular disease prevention? Protocol for a mixed methods preference study. *BMJ Open*. 2011;**1**. <http://bmjopen.bmj.com/content/1/2/e000372.full.pdf> (accessed 1 Nov 2012).
15. World Health Organisation. Adherence for long-term therapies: Evidence for action. 2003. <http://whqlibdoc.who.int/publications/2003/9241545992.pdf> (accessed 1 Nov 2012).
16. DiMatteo MR, Haskard KB, Williams SL. Health beliefs, disease severity, and patient adherence: a meta-analysis. *Med Care*. 2007;**45**:521-528.



**Title**

**Interpreting the Processes of the UMPIRE Trial (INPUT): the design of a process evaluation of a fixed dose combination (FDC) strategy to improve adherence to cardiovascular medications – a qualitative study**

**Authors**

Abdul Salam<sup>1</sup>, Frances Stewart<sup>2\*</sup>, Kavita Singh<sup>3</sup>, Simon Thom<sup>2</sup>, Hilarie Jane Williams<sup>2</sup>, Anushka Patel<sup>4</sup>, Stephen Jan<sup>4</sup>, Tracey Laba<sup>4</sup>, Dorairaj Prabhakaran<sup>3</sup>, Pallab Maulik<sup>1</sup>, Sophie Day<sup>5</sup>, Helen Ward<sup>5</sup>

\*Corresponding Author: frances.stewart@imperial.nhs.uk

**Author institutions**

<sup>1</sup>The George Institute for Global Health, 839C, Road No. 44A, Jubilee Hills, Hyderabad – 500 033, Andhra Pradesh, India

<sup>2</sup>International Centre for Circulatory Health, Imperial College London and Imperial Healthcare NHS Trust, 59-61, North Wharf Road, London, W2 1LA, United Kingdom. Telephone number: 0207 594 1057, fax number: 0207 594 1148.

<sup>3</sup>Centre for Chronic Disease Control, Tower 4, Commercial Complex, C 9, Vasant Kunj, New Delhi - 110070, India

<sup>4</sup>The George Institute for Global Health, Level 10, King George V Building, 83-117 Missenden Road, Camperdown, NSW 2050, Australia

<sup>5</sup>School of Public Health, Imperial College London, Praed Street, London, W2 1NY, United Kingdom.

**Keywords**

Cardiovascular Disease, Fixed Dose Combination, Medication Adherence, Polypill, Prevention

**Word Count:** ~~2318~~2300

**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 semi-structured, in-depth interviews with local health professionals and UMPIRE trial participants in India and the United Kingdom 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-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] 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 risk. The primary objective of this study is to investigate whether provision of a once daily cardiovascular FDC (containing aspirin, statin and two blood pressure lowering agents) in comparison to usual care (the usual separate and multiple cardiovascular (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 European Commission Framework Program 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 (1,000 in India and 1,004 in Europe) and will identify patterns of adherence in the two treatment groups (FDC

1  
2  
3  
4  
5  
6  
7  
8 and usual care). Interpreting the Processes of UMPIRE Trial (INPUT) study will involve a  
9  
10 selected sub-set of participants in the UK and India. This study will provide a qualitative  
11  
12 exploration of factors associated with different medication adherence patterns observed  
13  
14 within the trial.

15  
16  
17 Complexity[7] and cost[8] of regimens are amongst the major obstacles for effective  
18  
19 management of CVD; these factors are particularly important in resource-poor LMIC. A FDC  
20  
21 containing cardiovascular (CV) medications could be a cost-effective solution to address  
22  
23 medication under-utilization or non-adherence. A process evaluation will help to identify  
24  
25 any disparities between research and practice by allowing a detailed examination of the  
26  
27 context and clarifying characteristics of the trial participants and the local circumstances  
28  
29 under which the intervention was implemented. This insight will identify the moderating  
30  
31 factors that could limit or enhance applicability to different contexts. The detailed  
32  
33 descriptions about implementation provided by the narratives shared in semi-structured  
34  
35 interviews will inform future replication of the trial and its wider implication by  
36  
37 understanding the scope and limits of generalisability.  
38  
39

40  
41 Process evaluations complement the findings from randomised controlled trial (RCT)  
42  
43 investigations. Whilst RCTs test the effect of intervention(s) on pre-determined outcomes,  
44  
45 process evaluations, provide insight into the execution of investigation, the delivery and  
46  
47 receipt of the intervention, and the impact of the setting in which the intervention was  
48  
49 delivered[9]. In addition, process evaluations may provide an opportunity to formulate  
50  
51 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 itself guiding further in-depth reviews of the literature.

### Interviews

Interviews will be undertaken in the UK and India using a sub-sample 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 the FDC) and duration of trial participation. Recruitment will continue until no new themes arise from the interviews (thematic saturation).

1  
2  
3  
4  
5  
6  
7  
8 In addition, local health professionals with expertise in the field of cardiovascular disease  
9 (some who have patients participating in the UMPIRE trial) will be recruited as key  
10 informants. Key informants will include: general practitioners, practice nurses, cardiologists,  
11 neurologists and pharmacists. Key informants will also be asked to identify any other  
12 professionals they feel would be able to share their views on the topics under investigation.  
13  
14 The inclusion of key informants will provide further insight into the trial context, how health  
15 care staff can influence patient decisions, and the feasibility of implementing a FDC strategy  
16 for CVD prevention in routine clinical practice.  
17

18  
19  
20 In India, as UMPIRE trial visits have occurred across many different trial sites, a sample of  
21 these sites (approximately 7-9) will be used to recruit participants and key informants.  
22  
23 These sites will be selected to reflect variation across sites in number of participants  
24 recruited per site, hospital size, hospital setting (public/private) and site location  
25 (geographic and local language).  
26

27  
28 Interviews will be semi-structured ensuring that the same general topics are explored whilst  
29 allowing participants to lead the direction of discussion and explore in their own words their  
30 views and experiences. Interviewers will follow a topic guide for both the key informant and  
31 UMPIRE participant interviews in order to ensure consistency in the topics explored during  
32 each interview.  
33

34  
35  
36 The UMPIRE participant interviews will elicit views on the research process and their  
37 individual lifestyle and routine including:  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50

- 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 toward adherence to therapy within the trial.
- The factors that would be 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.

~~In order to ensure consistency in similar methods are followed for data collection and analysis in the UK and India whilst allowing for emergent differences to arise from the two data sets (UK and India), INPUT standard operating procedures for conducting the interviews and data analysis 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 cardiovascular disease.

#### Study Procedure

1  
2  
3  
4  
5  
6  
7  
8 At the end of the final UMPIRE trial visit the research team will invite participants to  
9 consider taking part in the INPUT study and provide a written information sheet. Those who  
10 agree to participate will be asked to give signed informed consent. Based on participant's  
11 preference, interviews will either take place on the same day as the final UMPIRE trial visit  
12 or at a later date, either at the trial centre or the participant's home. In India, participant  
13 interviews will be conducted by interviewers either in English or in local languages. The  
14 interviews conducted in local languages will be translated to English and will be then  
15 checked for accuracy and anonymised.  
16  
17  
18  
19  
20  
21  
22  
23  
24

25 After each interview and based on its content, permission may be sought to take  
26 photographs of the participant's medications and if the interview is done at their home the  
27 photograph could include the location they usually keep their medications, to gain further  
28 insights into their daily routines. These photographs will be included as visual sources of  
29 qualitative data to contribute to the development and assessment of themes in the analysis  
30 and provide further information about the context of the trial [11, 12].  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40

## 41 ANALYSIS

42  
43  
44 The initial data analysis will be carried out independently for the UK and India. NVivo 9  
45 qualitative analysis software will be used to assist with the data management.  
46  
47  
48

## 49 Open-coding



1  
2  
3  
4  
5  
6  
7  
8 Initially, line-by-line reading of every interview transcript will be undertaken, categorising  
9 sections of the transcripts into emergent themes. Repeated reading of the interview  
10 transcripts will ~~assist the reader in viewing the transcript from different perspectives occur~~  
11 ~~for compound meaning.~~ Emerging categories will constantly be compared within and  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

Formatted: Font: 12 pt, Not Bold

Formatted: Font: 12 pt, Not Bold

### Axial Coding

The resulting patterns identified in the analysis will form an analytic framework; thematic saturation of the emerging framework will be reached as the researcher compares more incidents and finds fewer differences in patterns arising. ~~The framework will be considered in terms of the e~~Existing literature, ~~will be used to determine~~limit the framework and 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 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 health care 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 harm to participants may be less apparent. Richard's and Schwarz's[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 so the probing nature of the interviews has the potential to provoke unforeseen anxiety

Page 10 of 16

1  
2  
3  
4  
5  
6  
7  
8 and distress, especially as topics that could trigger distress cannot always be predicted.  
9  
10 There is also a risk of exploitation, when a participant is allowed to speak in their own terms,  
11  
12 the interview can take on the semblance of a therapeutic encounter for the participant and  
13  
14 lead them to disclose more information than they initially intended. Further, the  
15  
16 interpretation of the participants views such as their behaviour and beliefs may be at odds  
17  
18 with the participant's own perspective and reading the published results could itself have a  
19  
20 negative impact on the participant's sense of self.  
21  
22  
23  
24

25  
26 During, the development of the INPUT protocol, ethical issues have been considered and  
27  
28 where relevant addressed. Although, the interviewers will be sensitive and avoid causing  
29  
30 distress to the interviewee as far as possible, the information sheet will also highlight to the  
31  
32 participant the potential risk of distress from participation and explicitly note that the  
33  
34 interview itself is for research purposes although it may also be profitable to discuss  
35  
36 experiences. Standard procedures have also been established for the management of any  
37  
38 participant who becomes distressed during the interview and this includes provision of  
39  
40 information and support should it be required. Further to this, rigorous analysis procedures  
41  
42 will be followed by the researchers including regular supervision of the analysis by  
43  
44 experienced qualitative researchers in order to avoid participant's views being  
45  
46 misrepresented and to uphold anonymity of data by considering the multiple clues to  
47  
48 identity present in individual narratives.  
49

#### 50 51 **Dissemination** 52 53 54

1  
2  
3  
4  
5  
6  
7  
8 As INPUT will use an exploratory method, a plan of publication will be based on the trial  
9  
10 results and the poignant-emerging themes arising from interviews and their subsequent  
11 analysis. ~~There are several key areas that dissemination will likely focus including~~  
12 ~~medication adherence which is a complex health behaviour, influenced by social,~~  
13 ~~psychological, cognitive, economic, disease condition, and therapy related factors as well as~~  
14 ~~health systems and patient-provider relationship[10].~~ The process evaluation will also help  
15  
16 to enrich the trial results by exploring and identifying the key components of the  
17  
18 intervention, identifying when and under what circumstances the intervention is of benefit,  
19  
20 or why the intervention may not have been favourable. The results of a process evaluation  
21  
22 of the UMPIRE trial will also lead to a better understanding of the mechanisms involved in  
23  
24 adherence to cardiovascular medications in the trial context. Such information will provide  
25  
26 insights into the relevance of a cardiovascular FDC strategy in a clinical context, and may  
27  
28 prove useful for designing effective public health policy with regard to adopting or rejecting  
29  
30 such a strategy. We anticipate that the process evaluation will explore pertinent factors  
31  
32 underlying any variations in the UMPIRE results between India and the UK. It will also  
33  
34 consider data emerging from parallel studies within the SPACE collaboration (such as the  
35  
36 process evaluation planned[14] for the Kanyini Gap Trial in Australia), and comment on  
37  
38 variations between the different settings.  
39  
40  
41  
42  
43  
44

45 ~~Complexity[12] and cost[13] of regimens are amongst the major obstacles for effective~~  
46 ~~management of CVD; these factors are particularly important in resource-poor LMIC. A FDC~~  
47 ~~containing cardiovascular (CV) medications could be a cost-effective solution to address~~  
48 ~~medication under-utilization or non-adherence. A process evaluation will help to identify~~  
49  
50  
51  
52  
53

~~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 semi-structured interviews will inform future replication of the trial and its wider implication by understanding the scope and limits of generalisability.~~

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 a FDC strategy on medicine taking behaviour will also provide important insight into the determinants of medication adherence.

#### **FUNDING STATEMENT**

The INPUT study is funded by a research fellowship from Imperial Healthcare Charity, grant number 7021/R25D and the George Institute for Global Health.

#### **COMPETING INTEREST STATEMENT**

The author(s) declare that they have no competing interests.

#### **AUTHORS CONTRIBUTION**

1  
2  
3  
4  
5  
6  
7  
8 HW and ST wrote the first draft of the protocol and all other authors contributed to the  
9  
10 critical revision of the protocol.

#### 11 12 13 14 REFERENCES

- 15  
16  
17 1. World Health Organisation. Cardiovascular Diseases (CVDs). Fact Sheet No 317. 2012.  
18  
19 <http://www.who.int./mediacentre/factsheets/fs317/en/index.html> (accessed 1  
20  
21 November 2012).
- 22  
23 2. Smith SC, Benjamin EJ, Bonow RO, et al. AHA/ACCF Secondary Prevention and Risk  
24  
25 Reduction Therapy for Patients with Coronary and other Atherosclerotic Vascular  
26  
27 Disease: 2011 update: a guideline from the American Heart Association and  
28  
29 American College of Cardiology Foundation. *Circulation*. 2011;**124**:2458-73.
- 30  
31 3. Furie KL, Kasner SE, Adams RJ, et al. Guidelines for the prevention of stroke in  
32  
33 patients with stroke or transient ischemic attack: a guideline for healthcare  
34  
35 professionals from the american heart association/american stroke association.  
36  
37 *Stroke*. 2011;**42**:227-76.
- 38  
39 4. Health TGifG. SPACE colloboration: Single Pill to Avert Cardiovascular Events.  
40  
41 <http://www.spacecollaboration.org/> (accessed 28 Aug 2012).
- 42  
43 5. Thom S, Field J, Poulter N, et al. Use of a Multidrug Pill In Reducing cardiovascular  
44  
45 Events (UMPIRE): rationale and design of a randomised controlled trial of a  
46  
47 cardiovascular preventive polypill-based strategy in India and Europe. 2012. *Eur J*  
48  
49 *Prev Cardiol*.
- 50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

1  
2  
3  
4  
5  
6  
7  
8 [http://cpr.sagepub.com/search/results?fulltext=umpire&x=0&y=0&submit=yes&journal\\_set=spcpr&src=selected&andorexactfulltext=and](http://cpr.sagepub.com/search/results?fulltext=umpire&x=0&y=0&submit=yes&journal_set=spcpr&src=selected&andorexactfulltext=and) (accessed 1 Nov 2012).

- 11 6. Hansson L, Hedner T, Dahlof B. Prospective randomized open blinded end-point  
12 (PROBE) study. A novel design for intervention trials. Prospective Randomized Open  
13 Blinded End-Point. *Blood Press*. 1992 Aug;**1**:113-9.

17 ~~12-7.~~ Donovan JL, Blake DR. Patient non-compliance: deviance or reasoned decision-  
18 making? *Soc Sci Med*. 1992;**34**:507-513.

- 21 8. Heisler M, Langa KM, Eby EL, Fendrick AM, Kabeto MU, Piette JD. The health effects  
22 of restricting prescription medication use because of cost. *Med Care*. 2004;**42**:626-  
23 634.

- 27 9. Oakley A, Strange V, Bonell C, et al. Process evaluation in randomised controlled  
28 trials of complex interventions. *BMJ*. 2006;**332**:413-416.

32 ~~8-10.~~ Glaser BGS, Anselm L. The Discovery of Grounded Theory: Strategies for Qualitative  
33 Research. Chicago: Aldine Publishing Company; 1967.

36 ~~11.~~ [Pink S. Doing visual ethnography: Images, media and representation in research.](#)  
37 [London: SAGE; 2000.](#)

40 ~~11-12.~~ [Wiles R, Prosser J, Bagnoli A, Clark A, Davies K, Holland S, Renold E. ESRC national](#)  
41 [Centre for Research Methods: ESRC National Centre for Research Methods Review](#)  
42 [Paper: Visual Ethics: Ethical Issues in Visual. 2008.](#)  
43 <http://eprints.ncrm.ac.uk/421/1/MethodsReviewPaperNCRM-011.pdf> (accessed 31  
44 [October 2011\)](#)

50 ~~12-13.~~ Richards HM, Schwartz LJ. Ethics of qualitative research: are there special issues for  
51 health services research? *Family Practice*. 2002; **19**:135-139.

Formatted: Bullets and Numbering

Formatted: Bullets and Numbering

1  
2  
3  
4  
5  
6  
7  
8 | ~~13-14.~~ Jan S, Usherwood T, Brien JA, et al. What determines adherence to treatment in  
9  
10 | cardiovascular disease prevention? Protocol for a mixed methods preference study.  
11 | *BMJ Open*. 2011;**1**. <http://bmjopen.bmj.com/content/1/2/e000372.full.pdf>  
12 | (accessed 1 Nov 2012).  
13

14  
15  
16 | ~~10-15.~~ World Health Organisation. Adherence for long-term therapies: Evidence for action. ←  
17 | 2003. <http://whqlibdoc.who.int/publications/2003/9241545992.pdf> (accessed 1 Nov  
18 | 2012).  
19  
20

21  
22 | ~~14-16.~~ DiMatteo MR, Haskard KB, Williams SL. Health beliefs, disease severity, and patient  
23 | adherence: a meta-analysis. *Med Care*. 2007;**45**:521-528.  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

Formatted: Bullets and Numbering