

Table 1: Baseline characteristics

	FDC	Usual care
	(N = 1002)	(N = 1002)
Age	62.1 (10.4)	61.6 (10.8)
Male	817 (81.5%)	825 (82.3%)
SBP (mmHg)	137.0 (21.3)	137.7 (21.1)
DBP (mmHg)	77.4 (12.0)	78.1 (11.5)
Heart rate (beats/ min)	71.0 (15.1)	70.8 (14.6)
Total cholesterol (mmol/L)	4.2 (1.0)	4.2 (1.1)
HDL cholesterol (mmol/L)	1.1 (0.3)	1.1 (0.3)
LDL cholesterol (mmol/L)	2.3 (0.8)	2.4 (0.9)
Triglycerides (mmol/L)	1.5 (0.9)	1.5 (0.9)
Glucose (mmol/L)	6.3 (2.4)	6.3 (2.3)
Creatinine (umol/L)	89.0 (22.10)	89.7 (22.2)
Current smokers	131 (13.1%)	144 (14.4%)
Ever smoked cigarettes	541 (54.0%)	504 (50.3%)
<i>Medical history</i>		
Coronary heart disease	769 (76.7%)	759 (75.7%)
Cerebrovascular disease	154 (15.4%)	157 (15.7%)
Peripheral vascular disease	56 (5.6%)	43 (4.3%)
Diabetes mellitus	283 (28.2%)	281 (28.0%)
<i>Current drug treatment</i>		
Antihypertensive treatment		
None	76 (7.6%)	66 (6.6%)
1 BP drug	266 (26.5%)	225 (22.5%)
≥2 BP drugs	660 (65.9%)	711 (71.0%)
Statin	882 (88.0%)	878 (87.6%)
Anti-platelet drug	920 (91.8%)	912 (91.0%)
Indicated medications ¹	598 (59.7%)	635 (63.4%)

Data not shown as n (%) are mean (SD).

1 Indicated medications = statin + anti-platelet + ≥2 anti-hypertensive drugs.

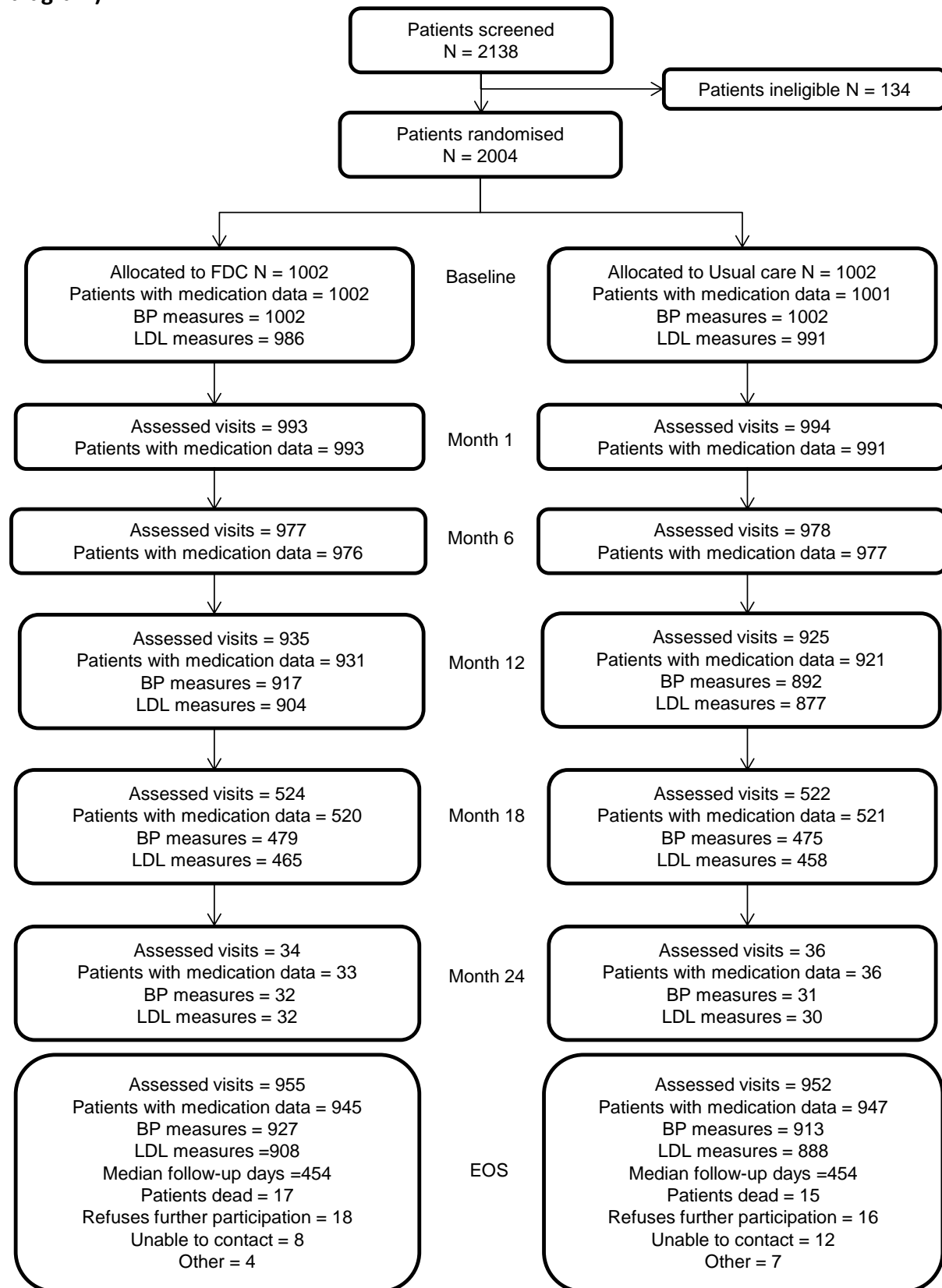
FDC = fixed dose combination.

Table 2: Effects of treatment on adherence to indicated medications, systolic blood pressure, LDL-cholesterol at end of study (primary endpoints) and on adherence at 12 months, diastolic blood pressure, cholesterol fractions and creatinine (secondary endpoints).

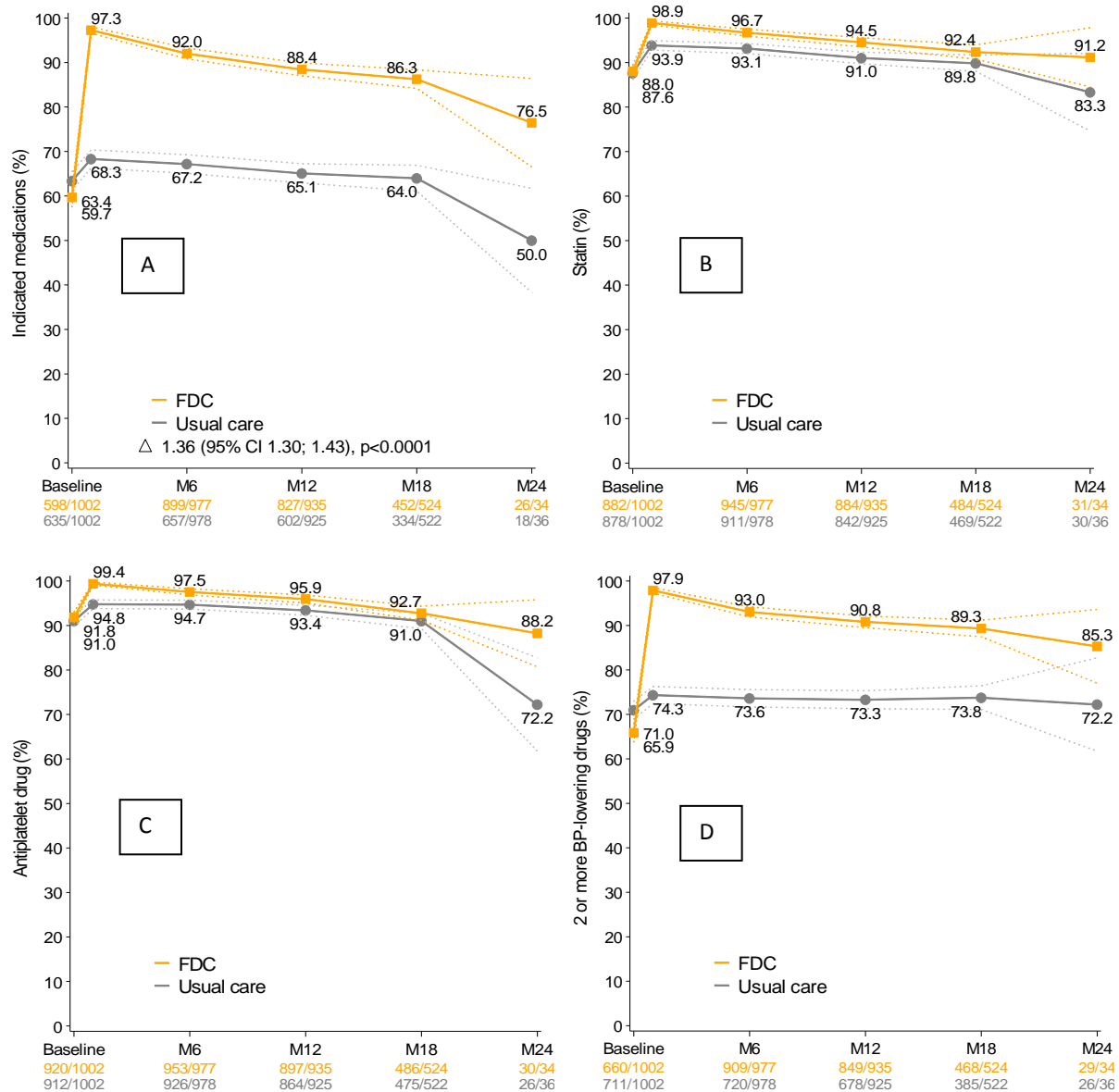
Outcome	FDC (N = 1002)	Usual care (N = 1002)	Treatment Effect ¹ (95% CI)	P-value
<i>Primary outcomes</i>				
Adherence ² (%)	829/961 (86%)	621/960 (65%)	1.33 (1.26; 1.41)	<.0001
Systolic blood pressure (mmHg)	129.2 (0.5)	131.7 (0.5)	-2.6 (-4.0; -1.1)	0.0005
LDL cholesterol (mmol/L)	2.18 (0.02)	2.29 (0.02)	-0.11 (-0.17; -0.05)	0.0005
<i>Secondary outcomes</i>				
Adherence at 12 months (%)	827/935 (88%)	602/925 (65%)	1.36 (1.29; 1.43)	<.0001
Diastolic blood pressure (mmHg)	72.8 (0.3)	75.2 (0.3)	-2.5 (-3.3; -1.6)	<.0001
Total cholesterol (mmol/L)	4.06 (0.03)	4.12 (0.03)	-0.07 (-0.14; 0.01)	0.0765
HDL cholesterol (mmol/L)	1.14 (0.01)	1.13 (0.01)	0.01 (0.00; 0.03)	0.1237
Triglycerides (mmol/L)	1.61 (0.03)	1.57 (0.03)	0.04 (-0.03; 0.11)	0.2806
Plasma creatinine (μmol/L)	94.6 (0.6)	91.9 (0.6)	2.7 (1.0; 4.4)	0.0017

1. Treatment effect: relative risk for adherence and mean difference for blood pressure, cholesterol fractions and creatinine

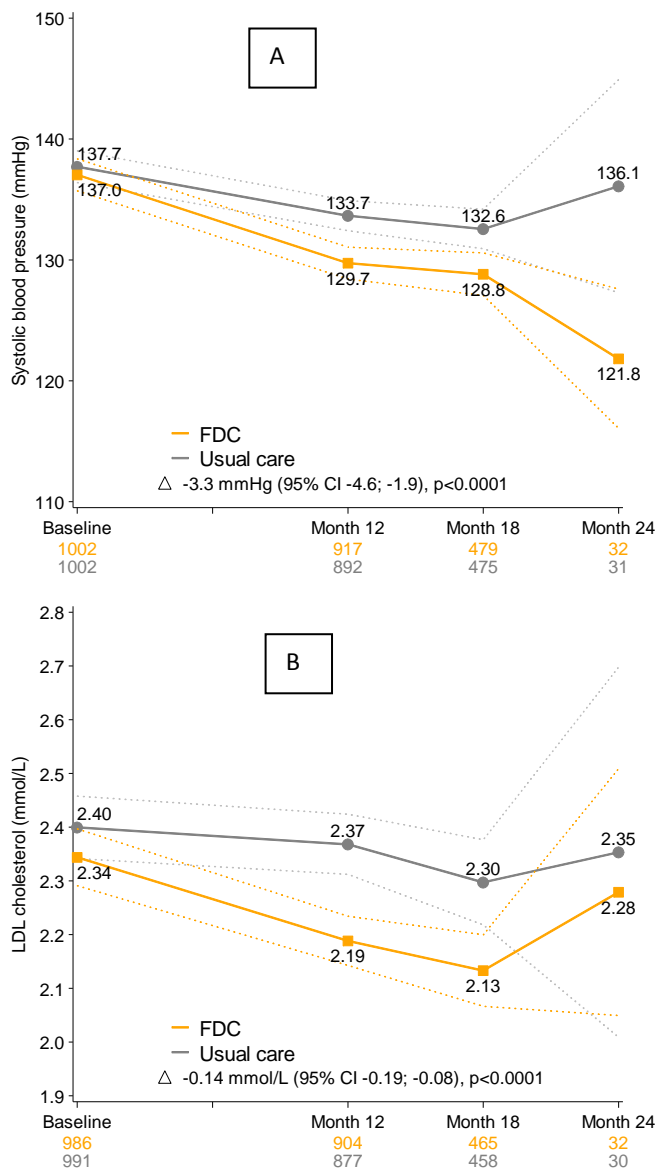
2. Self-reported use of antiplatelet, statin and combination (≥2) blood pressure lowering therapy

Figure 1: Registration, randomisation and follow-up of study participants (CONSORT diagram)

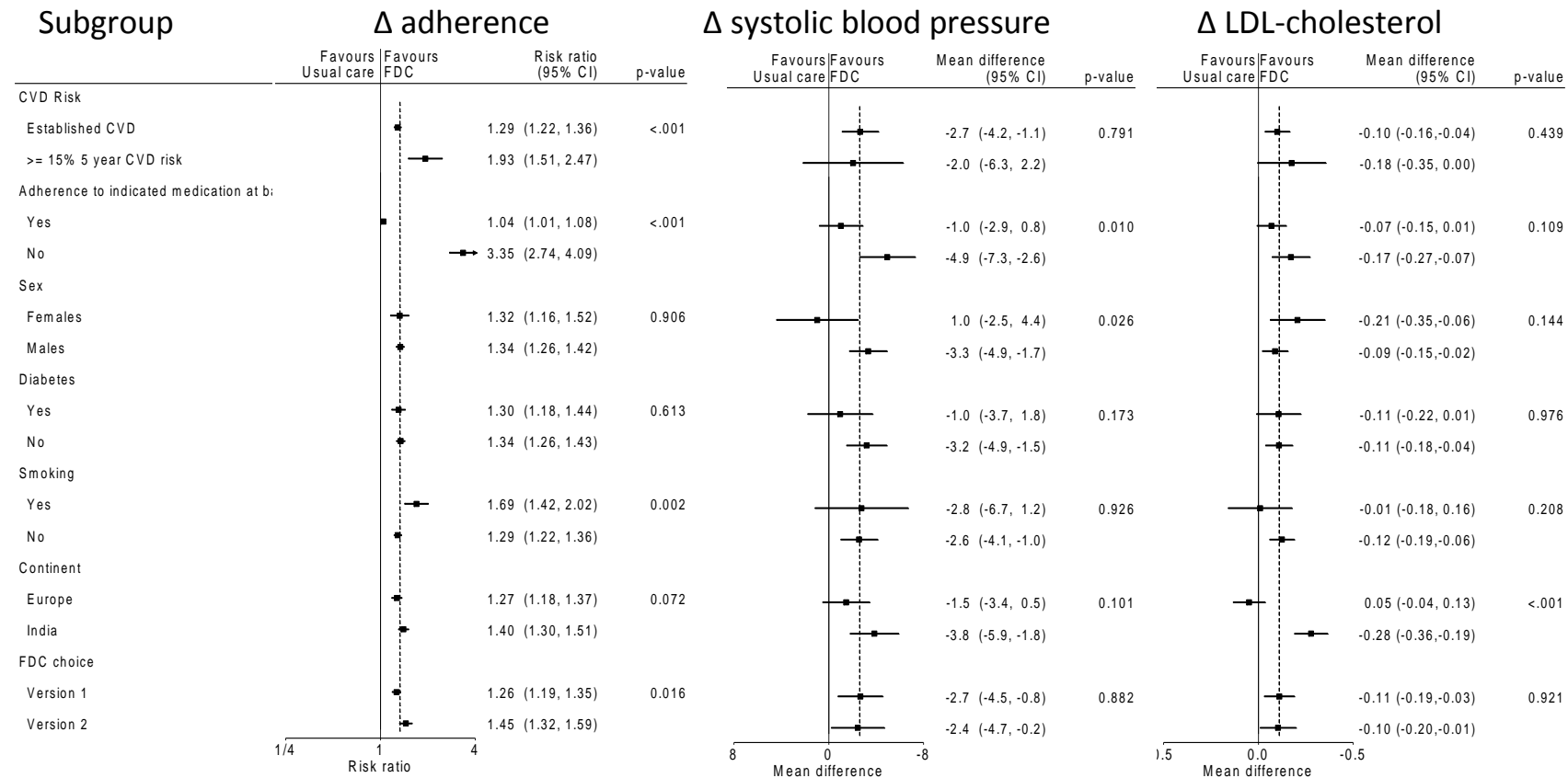
FDC = fixed dose combination; BP = blood pressure; LDL = low density lipoprotein cholesterol; EOS = end of study.

Figure 2: Adherence to indicated medications by treatment group over follow-up

Legend: Figure shows overall adherence (panel A), statin (panel B), antiplatelet drug (panel C), and ≥ 2 BP lowering drugs (panel D) by follow-up time in the FDC and usual care groups. M6-M24 are visits at months 6 to 24 and EOS is End of Study Visit (median time 15 months). Overall relative risk obtained via repeated log-binomial regression using a covariance matrix with a compound-symmetry structure (panel a. only). Estimates combine all non-missing values collected at months 1, 6, 12, 18 and 24. Model terms include treatment, month and treatment-by-month interaction. The numbers of participants at each visit are indicated along the x-axis. NB. 1st axis is at 30%, others begin at 60%

Figure 3: Systolic blood pressure and LDL-cholesterol by treatment group over follow-up

Legend: Systolic blood pressure (panel A) and LDL-cholesterol (panel B) values shown at baseline, during follow-up and at end of study (EOS) in the FDC and usual care groups. The numbers of participants at each visit are indicated along the x-axis. Overall mean differences obtained via repeated linear regression using a covariance matrix with a compound-symmetry structure. Estimates combine all non-missing values collected at months 12, 18 and 24. Model terms include treatment, month, treatment-by-month interaction and baseline SBP or LDL-cholesterol.

Figure 4: Primary outcomes by pre-specified subgroups

Legend: The three primary outcomes of adherence (defined as taking statin, aspirin and two or more blood pressure lowering drugs at end of study), systolic blood pressure, and LDL-cholesterol are shown by pre-specified baseline subgroups. Horizontal lines are proportional to the 95% confidence intervals, boxes are placed at the relative risk for and sized proportional to the amount of information per subgroup, and vertical dashed lines show the overall effect for each outcome. P-values are for the test of homogeneity for each subgroup.

Appendices

Appendix 1: Impact of covariate adjustment on treatment effect for adherence, SBP and LDL-cholesterol

Covariate(s)	Adherence		Systolic blood pressure		LDL-cholesterol	
	Relative Risk (95%CI)		Difference (95% CI)		Difference (95% CI)	
None	<i>1.33</i>	<i>(1.26;1.41)</i>	-3.1	(-4.8;-1.3)	-0.14	(-0.21;-0.07)
Baseline value *	1.13	(1.08;1.18)	-2.6	(-4.0;-1.1)	-0.11	(-0.17;-0.05)
Sex	1.33	(1.27;1.41)	-3.1	(-4.8;-1.3)	-0.14	(-0.21;-0.07)
Age	1.34	(1.27;1.41)	-3.3	(-5.0;-1.6)	-0.14	(-0.21;-0.07)
Site/country **	1.34	(1.27;1.41)	-3.1	(-4.7;-1.5)	-0.14	(-0.21;-0.07)
Risk stratum	1.32	(1.25;1.39)	-3.1	(-4.8;-1.4)	-0.14	(-0.21;-0.07)
Follow-up duration	1.33	(1.26;1.41)	-3.1	(-4.8;-1.3)	-0.14	(-0.21;-0.07)
All	1.13	(1.08;1.18)	-2.7	(-4.1;-1.3)	-0.11	(-0.17;-0.05)

Pre-specified primary analyses are in italics

* Baseline value: adjustment was conducted for the baseline value of the outcome measure for each of adherence, SBP or LDL-cholesterol separately.

** Indian sites were grouped; European sites were not grouped.

Appendix 2: Reported use of FDC and other cardiovascular medications in the FDC group, by study visit

	Month 1		Month 6		Month 12		Month 18		Month 24	
	n	%	n	%	n	%	n	%	n	%
Number of patients assessed (denominator)	993		977		935		524		34	
Adherent to FDC	940	94.7%	833	85.3%	757	81.0%	398	76.0%	22	64.7%
Not adherent to FDC	53	5.3%	144	14.7%	178	19.0%	126	24.0%	12	35.3%
Of those not taking FDC, no. taking other meds										
Not on statin, antiplatelet or BP lowering drugs	4	7.5%	17	11.8%	23	12.9%	26	20.6%	2	16.7%
On BP-lowering drug	49	92.5%	121	84.0%	146	82.0%	99	78.6%	11	91.7%
On statin	42	79.2%	112	77.8%	127	71.3%	86	68.3%	9	75.0%
On antiplatelet	47	88.7%	120	83.3%	140	78.7%	88	69.8%	8	66.7%
On combination of 1+1+1 *	39	73.6%	101	70.1%	111	62.4%	73	57.9%	7	58.3%
On combination of 1+1+2 **	26	49.1%	66	45.8%	70	39.3%	54	42.9%	4	33.3%

* 1+1+1 combination = 1 statin + 1 antiplatelet + 1 BP-lowering drug

** 1+1+2 combination = 1 statin + 1 antiplatelet + 2 BP-lowering drugs

Adherence defined as taking a drug at least 4 days in the week preceeding the visit

Appendix 3: Serious adverse events in FDC and usual care groups

Event type	FDC (N = 1002)	Usual care (N = 1002)
Total number of serious adverse events	154	142
Patients with at least one SAE	118 (11.8%)	102 (10.2%)
Cardiac disorders	42 (4.2%)	27 (2.7%)
Infections and infestations	16 (1.6%)	10 (1.0%)
Neoplasms benign and malignant	13 (1.3%)	11 (1.1%)
Vascular disorders	11 (1.1%)	12 (1.2%)
Nervous system disorders	9 (0.9%)	13 (1.3%)
Gastrointestinal disorders	10 (1.0%)	11 (1.1%)
General disorders and administration site conditions	8 (0.8%)	8 (0.8%)
Injury, poisoning and procedural complications	7 (0.7%)	5 (0.5%)
Musculoskeletal and connective tissue disorders	3 (0.3%)	6 (0.6%)
Metabolism and nutrition disorders	3 (0.3%)	5 (0.5%)
Renal and urinary disorders	5 (0.5%)	3 (0.3%)
Respiratory, thoracic and mediastinal disorders	5 (0.5%)	3 (0.3%)
Reproductive system and breast disorders	1 (0.1%)	6 (0.6%)
Surgical and medical procedures	3 (0.3%)	2 (0.2%)
Psychiatric disorders	1 (0.1%)	2 (0.2%)
Hepatobiliary disorders	1 (0.1%)	1 (0.1%)
Blood and lymphatic system disorders	1 (0.1%)	0
Congenital, familial and genetic disorders	0	1 (0.1%)
Immune system disorders	0	1 (0.1%)
Investigations	1 (0.1%)	0
Skin and subcutaneous tissue disorders	0	1 (0.1%)

Numerators are patients who experience an adverse event at least once

Denominators are all patients randomised

Serious adverse events (SAE) (defined as any untoward medical occurrence that results in death, is life-threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, is a congenital anomaly/birth defect, or requires intervention to prevent permanent impairment or damage) categorised by major system order class (SOC, MedDRA coding). FDC = fixed dose combination.

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BMJ Masterclasses

Innovative approaches to prevention of
CVD

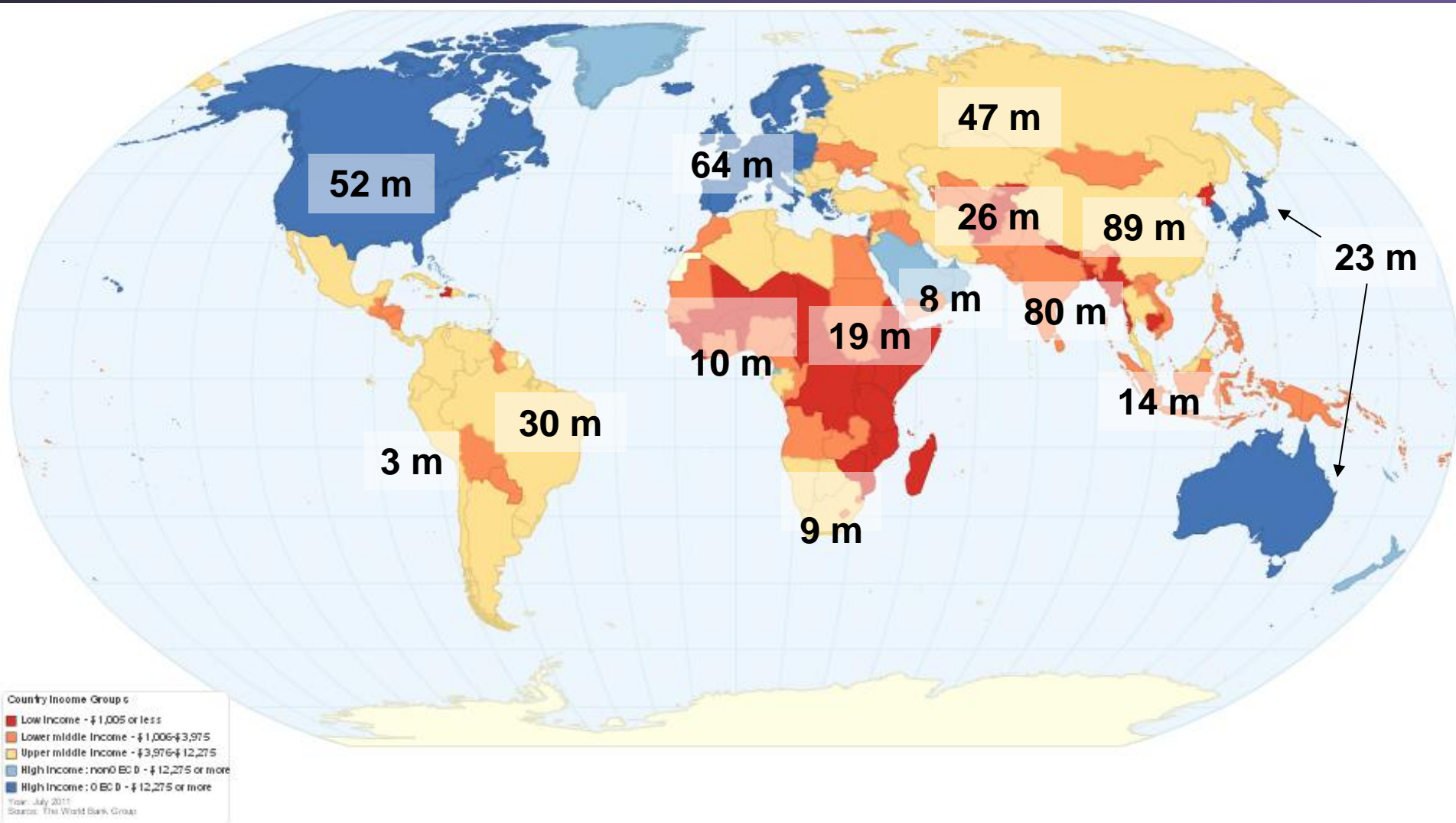
Delhi: December 7th 2012

Professor Simon Thom

Declaration of interests

- I have received funding for travel related to the UMPIRE Trial from Dr Reddy's Laboratories.
- Dr Reddy's supplied the fixed-dose combination (the polypill) used in the UMPIRE Trial.

Estimated number of people with previous cardiovascular disease or at over 7.5% risk in next 5 years



CVD prevention

- Lifestyle modification

- Medication:

- ✓ BP lowering
- ✓ Cholesterol lowering (statins)
- ✓ Antiplatelet drug

**No contention
about the use of
this package in
patients with
established CVD**

JBS 2 Guidelines on CVD prevention Heart 2005; 91(s5): 1-52
<http://health.bih.nic.in/Docs/Guidelines-NPCDCS.pdf>

Innovations in reorienting health systems

- Changes in medical education & medical curricula
- Task shifting
- Harnessing the developments in IT & m-health
- Innovative methods in modifying risk factors

CME Activity for Thursday, November 29, 2012

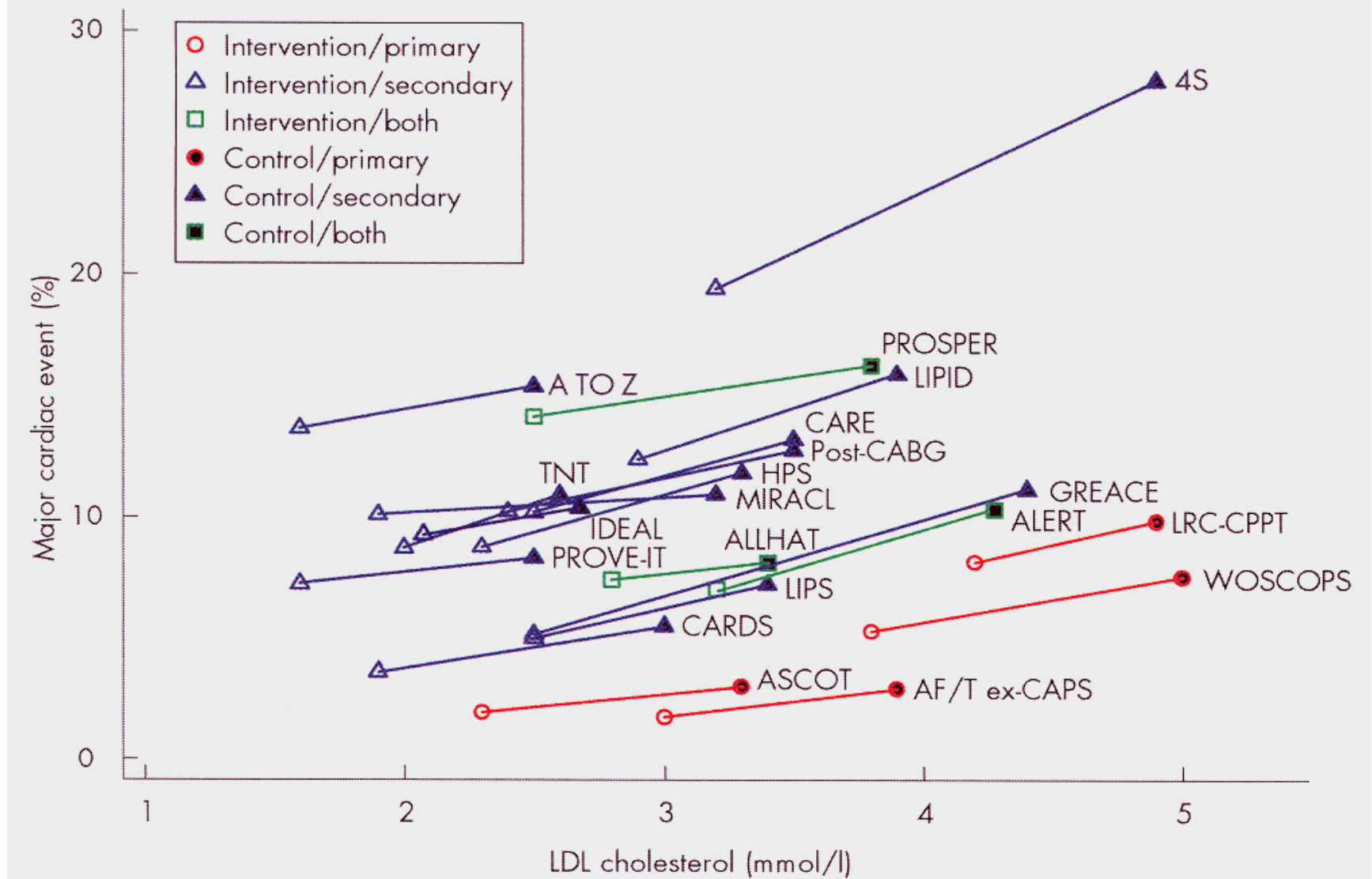
Will PCSK₉ Inhibition Close the Gap in Optimal LDL-C Reduction? CME

Evaluate the need for additional LDL-C-lowering therapies beyond current optimal medical therapy as a strategy for addressing lipid-related CV risk.

Earn CME Credit »

- PCSK₉ inhibitors lower LDL-cholesterol by 70+% on top of statins
but the excitement ignores
- The adherence gap
- Blockbuster drugs generally bust one risk factor at a time

Absolute reduction in LDL cholesterol & absolute reduction in risk of major cardiac event



Accessibility, Affordability



Medecins Sans Frontieres

- 15% of the world's population consumes over 90% of the world's pharmaceuticals.
- In many developing countries a month's treatment for hypertension or diabetes costs about a month's wages

World Health Organisation. The World Medicines Situation;
World pharmaceutical sales and consumption 2004;
<http://apps.who.int/medicinedocs/en/d/Js6160e/6.html>.

Choice?

- Better, more powerful drugs
- Bigger doses
- “how low should we go?”
- Better delivery of what we know works
- Implementation of proven strategies
- Implementation of novel strategies

.... or both?

The 20 most frequently dispensed drugs (2009), UK

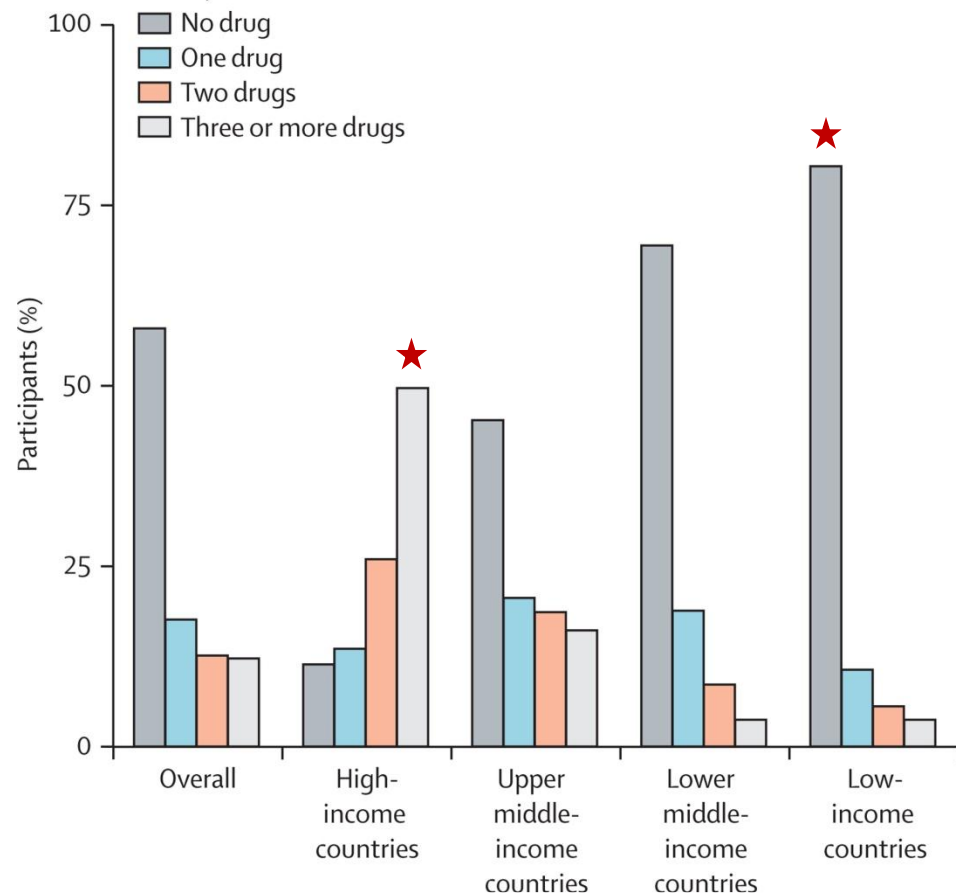
BNF Chemical name	Number of items dispensed (millions)
Simvastatin	37.3
Aspirin	33.9
Levothyroxine Sodium	21.9
Ramipril	19.3
Bendroflumethiazide	18.9
Paracetamol	18.7
Salbutamol	18.3
Omeprazole	18.3
Amlodipine	16.5
Lansoprazole	14.9
Co-Codamol	14.6
Atenolol	13.5
Metformin Hydrochloride	12.8
Aspirin	12.8
Paracetamol	11.6
Atorvastatin	10.9
Citalopram Hydrobromide	10.4
Ergocalciferol	10.2
Influenza Vaccines	10.0
Lisinopril	9.6

These drug classes – all on WHO essential medicines list

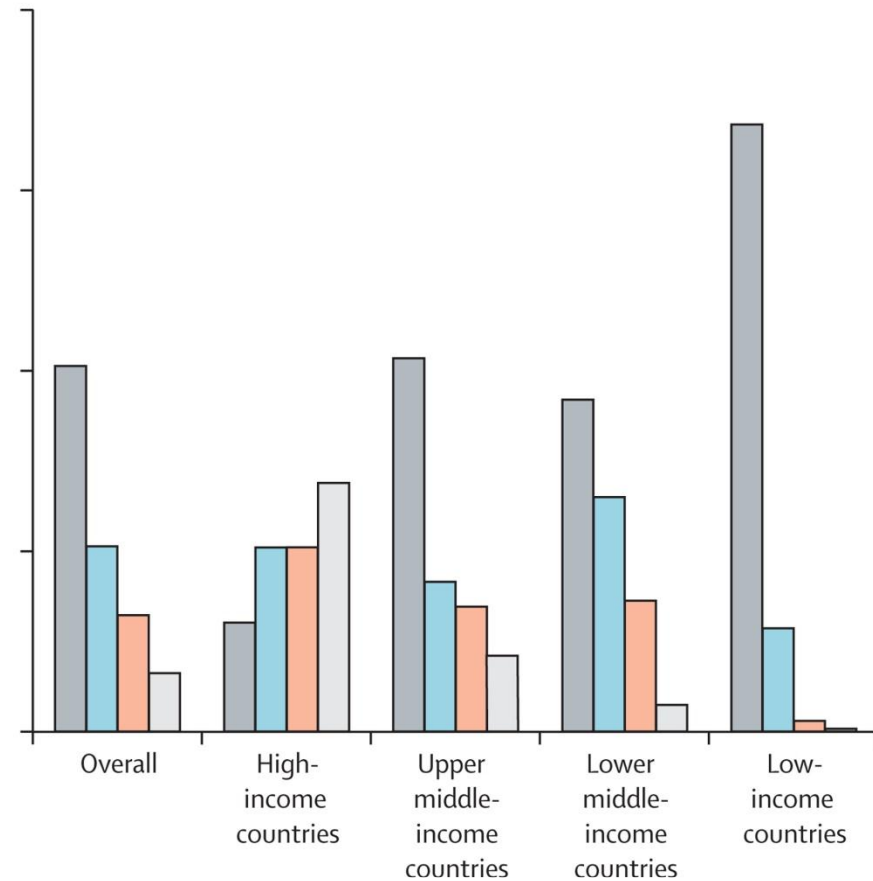
≡ RHP polypill component

Use of secondary prevention drugs for CVD in the community in high-income, middle-income, & low-income countries (the PURE Study)

A Coronary heart disease



B Stroke



The UMPIRE trial

Use of a Multidrug Pill In Reducing cardiovascular Events



In 2009 the European Commission called for research testing a treatment strategy that

combines existing safe and effective drugs for treating chronic diseases in a single daily pill

stipulating that

this fixed-dose-combination pill should be low-cost and suitable for production and widespread use in resource-poor countries

and that

the work should address two major challenges of effective secondary prevention and treatment of chronic diseases:

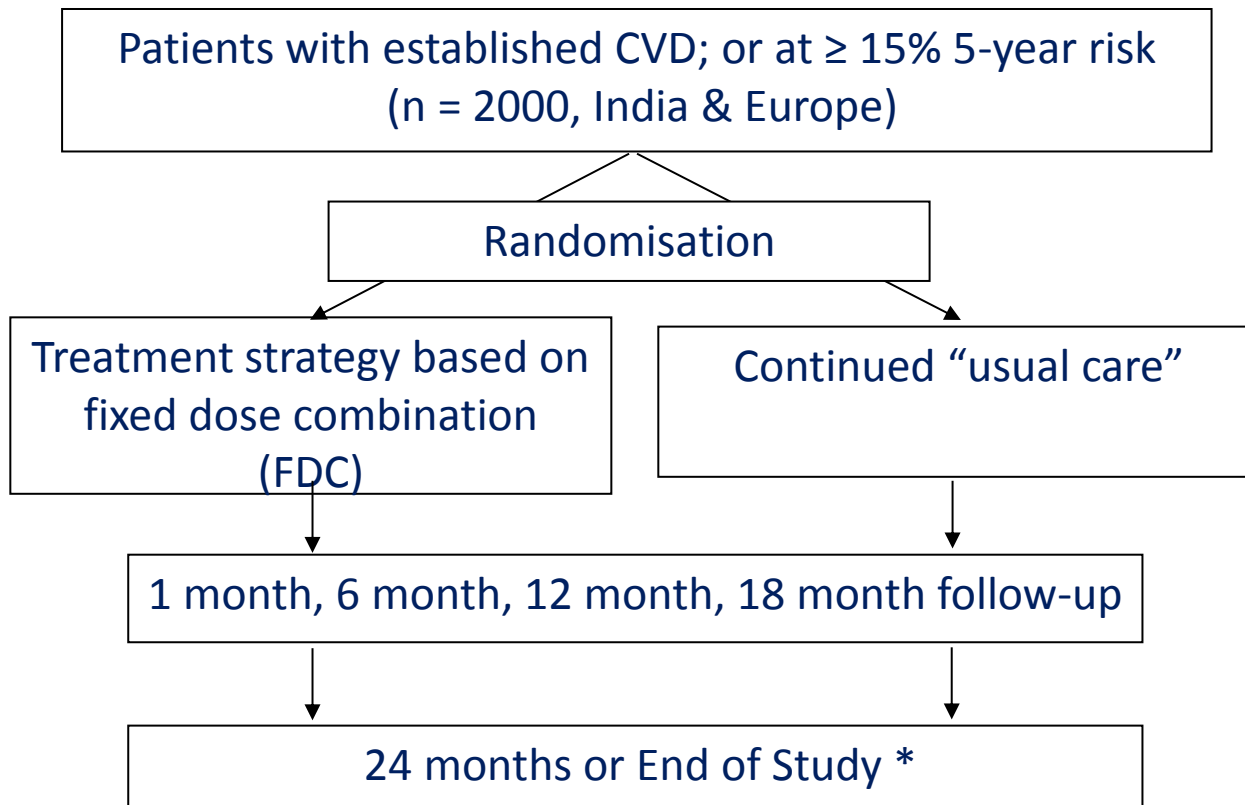
adherence and access to treatment in developing countries.

Primary objectives

UMPIRE trial

- To test the hypothesis that a fixed dose combination-based strategy (a “polypill”) for delivery of preventive medications (aspirin, statin and two blood pressure lowering agents) compared with usual care might improve:
 - Adherence to indicated therapy
 - Systolic BP
 - LDL-cholesterol,
at end of study,
in people with (or at high risk of) cardiovascular disease.

PROBE design



← inclusion

exclusion:
contraindications or
known intolerance of
FDC components

* 12 months after
last randomisation
(range 12 – 24)

Methods

- Adherence: self-reported use of [antiplatelet, statin and ≥ 2 BP lowering therapy]
- BP: electronic device (Omron 705CP II) + printer
- Cholesterol & all blood tests: local laboratories

Randomisation

- FDC : usual care, 1 : 1 (web-based)
- Stratified by presence or absence of established CVD

Trial sites

- 28 in India
- 3 in Europe (Dublin, London, Utrecht)

Recruitment

- June 2010 – July 2011

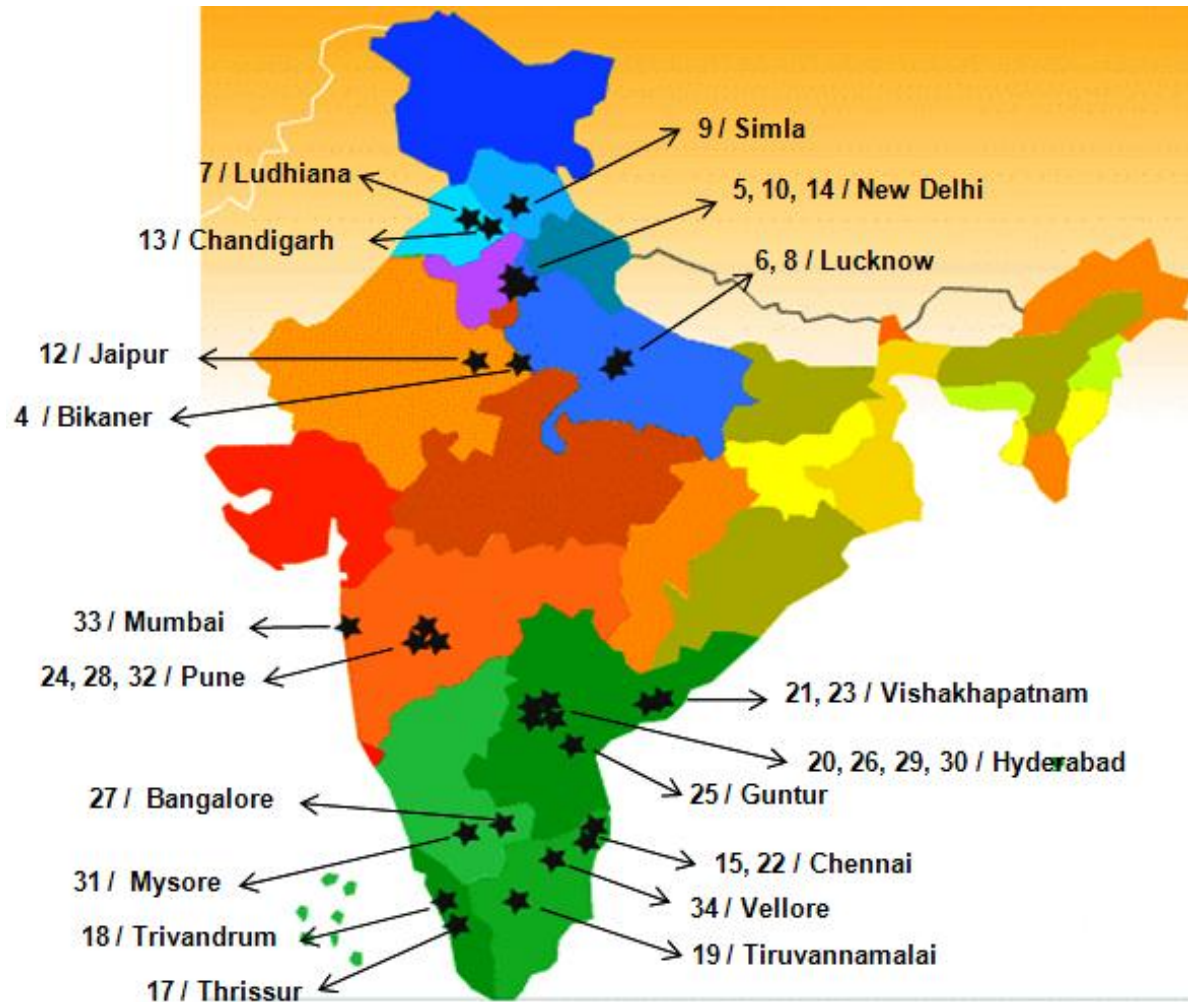
UMPIRE Trial sites

India

- 28 sites
- 2 coordinating centers:
Centre for Chronic Disease Control, New Delhi
George Institute for International Health, Hyderabad
- Policy: PHFI

Europe

- London, Utrecht, Dublin



Study treatments

Fixed doses combinations, x2

Version 1	Version 2
aspirin 75mg	aspirin 75mg
simvastatin 40mg	simvastatin 40mg
lisinopril 10mg	lisinopril 10mg
atenolol 50mg	hydrochlorothiazide 12.5mg

Physicians could add additional medications, stop the FDC & begin treatment with separate medications, or switch FDC version.

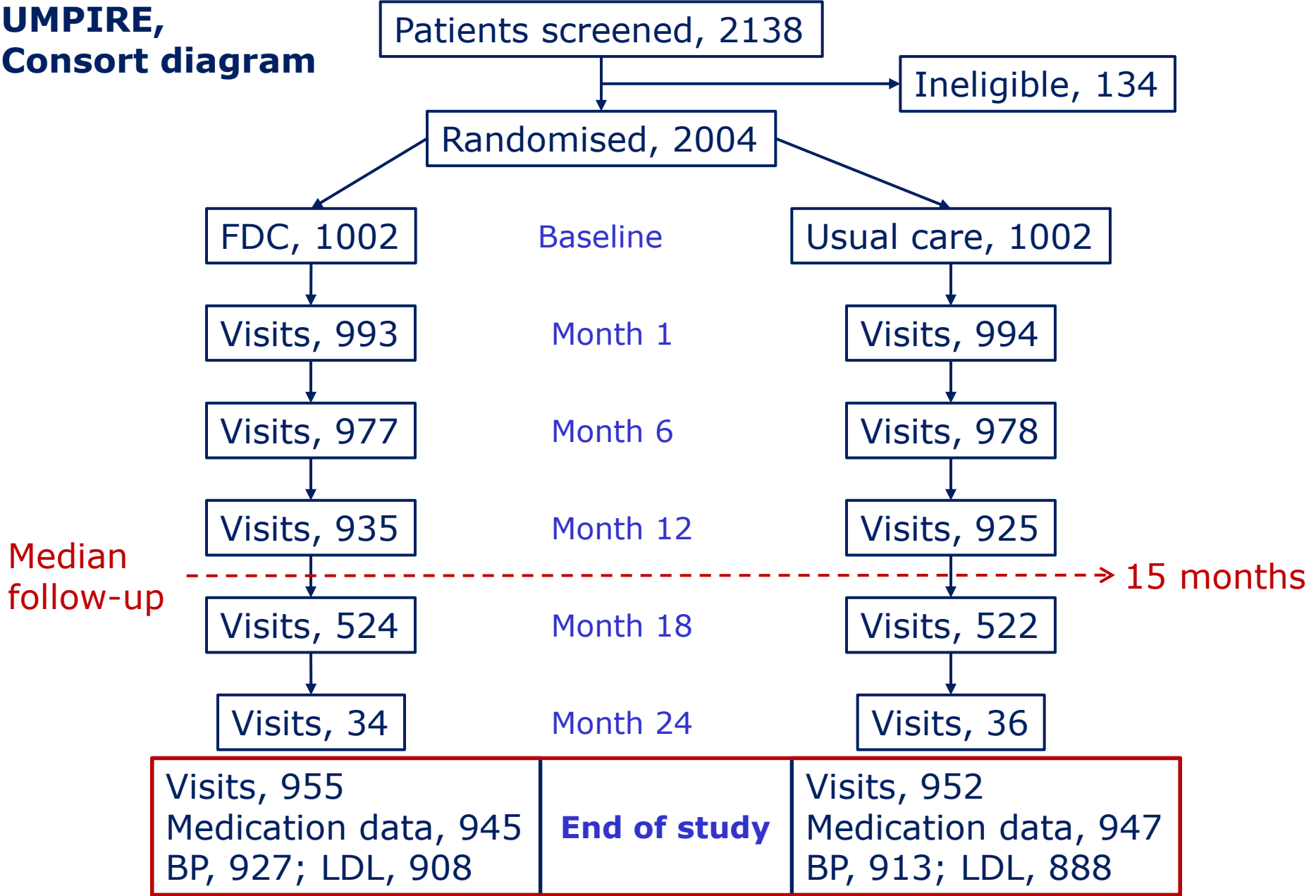
Usual care

As per local clinical guidelines.

Participants in the FDC group were dispensed study FDC free of charge from their trial centre.

Participants in the usual care group acquired their medications subject to local payments or exemptions.

**UMPIRE,
Consort diagram**



Results

Baseline characteristics

	FDC (N = 1002)	Usual care (N = 1002)
Age	62.1 (10.4)	61.6 (10.8)
Male	81 %	82 %
SBP (mmHg)	137.0 (21.3)	137.7 (21.1)
LDL-cholesterol (mmol/L)	2.3 (0.8)	2.4 (0.9)
<i>Medical history</i>		
Established CVD	88 %	88 %
Diabetes mellitus	28 %	28 %
<i>Current drug treatment</i>		
<i>Antihypertensive treatment</i>		
None	7.6 %	6.6 %
1 BP drug	26.5 %	22.5 %
≥2 BP drugs	65.9 %	71.0 %
Statin	88.0 %	87.6 %
Antiplatelet drug	91.8 %	91.0 %
All indicated medications	59.7 %	63.4 %

Indicated medications =
statin +
antiplatelet +
≥2 antihypertensive drugs

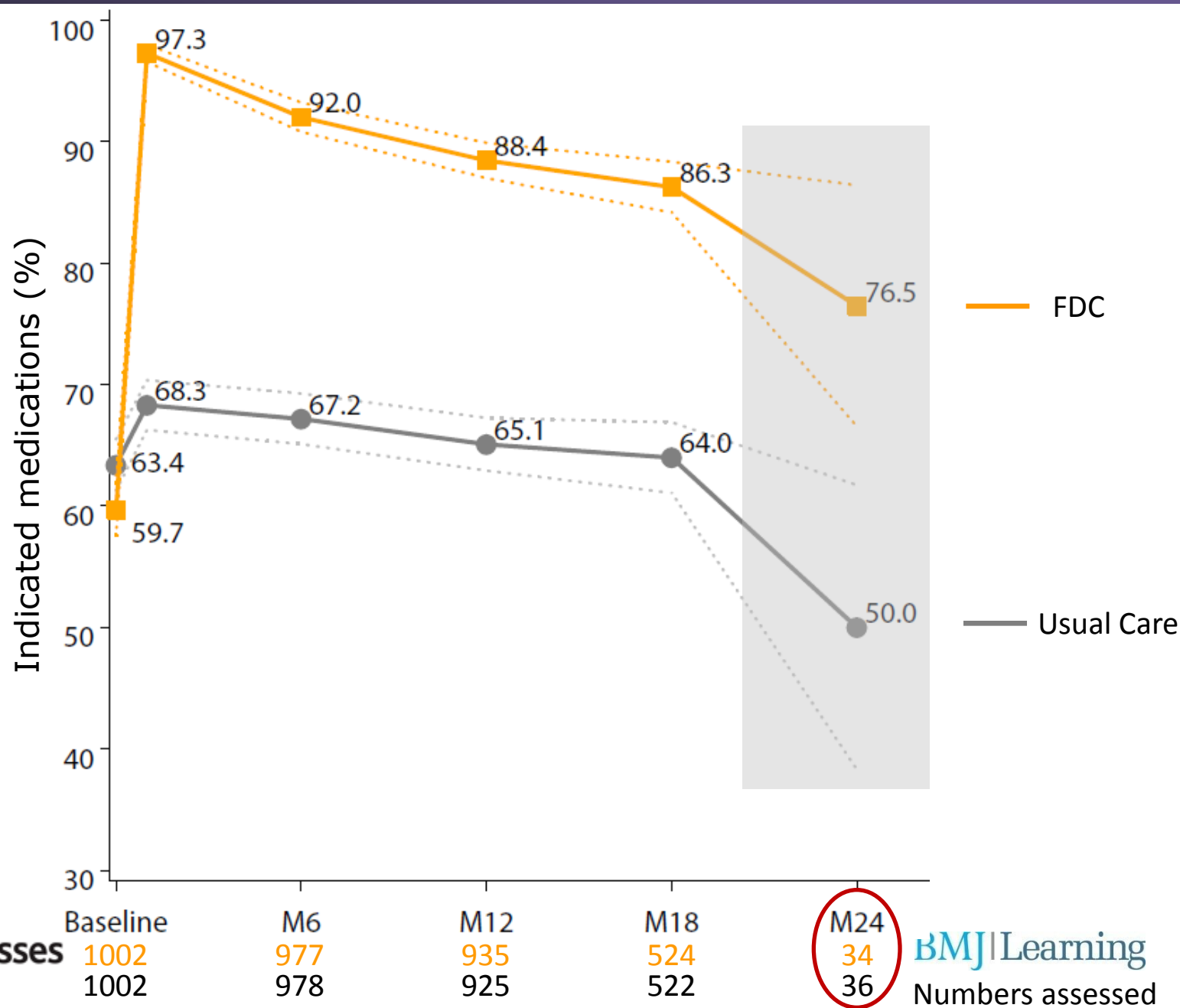
Effects on primary outcomes

- at end of study

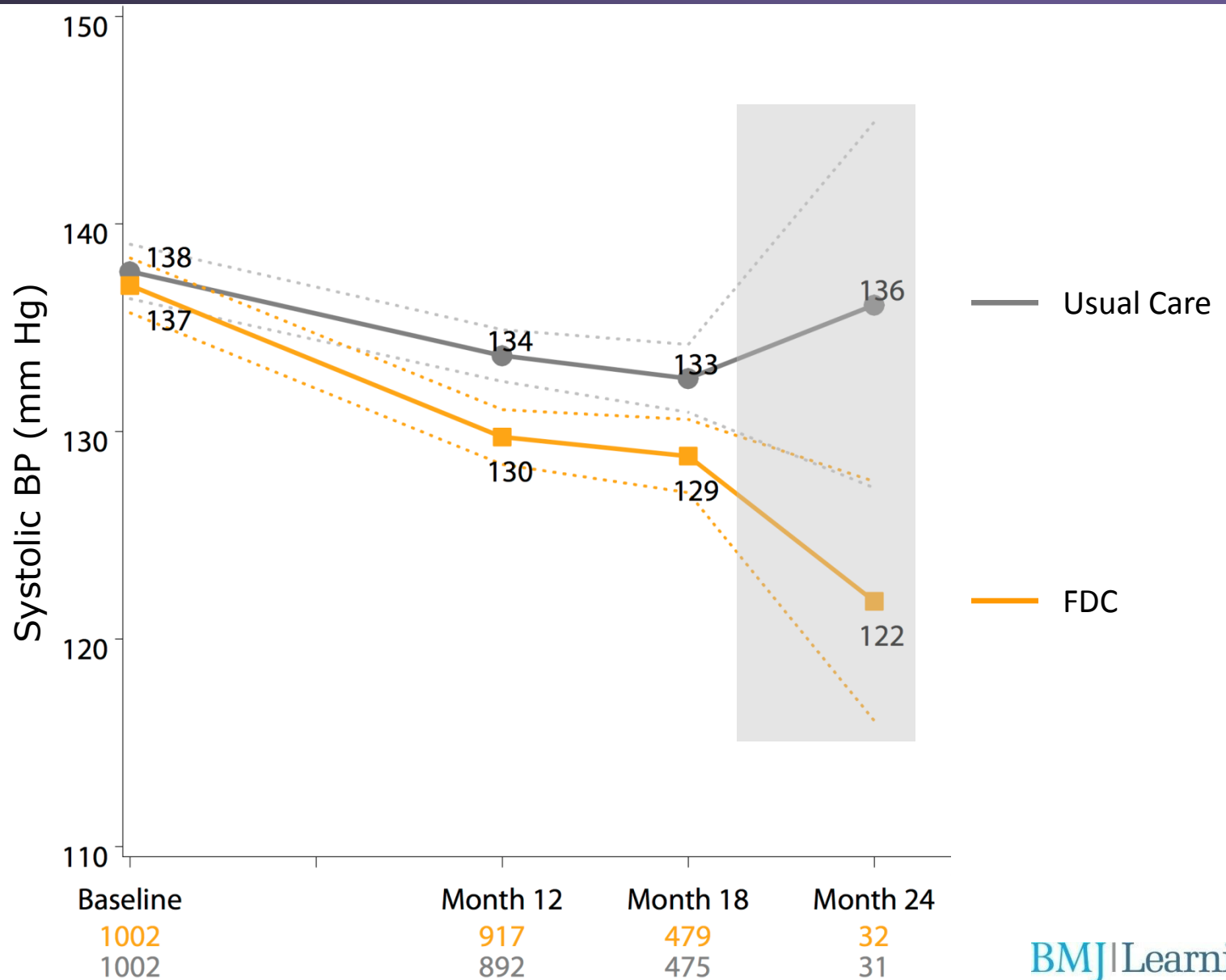
	FDC	Usual care	Treatment	
Outcome	(N = 1002)	(N = 1002)	Effect (95% CI)	P-value
Adherence (%)	86% (1%)	65% (2%)	1.33 (1.26; 1.41)	<.0001
Systolic BP (mmHg)	129.2 (0.5)	131.7 (0.5)	-2.6 (-4.0; -1.1)	0.0005
LDL-cholesterol (mmol/L)	2.18 (0.02)	2.29 (0.02)	-0.11 (-0.17; -0.05)	0.0005

1 mmol/L = 38.67 mg/dl cholesterol

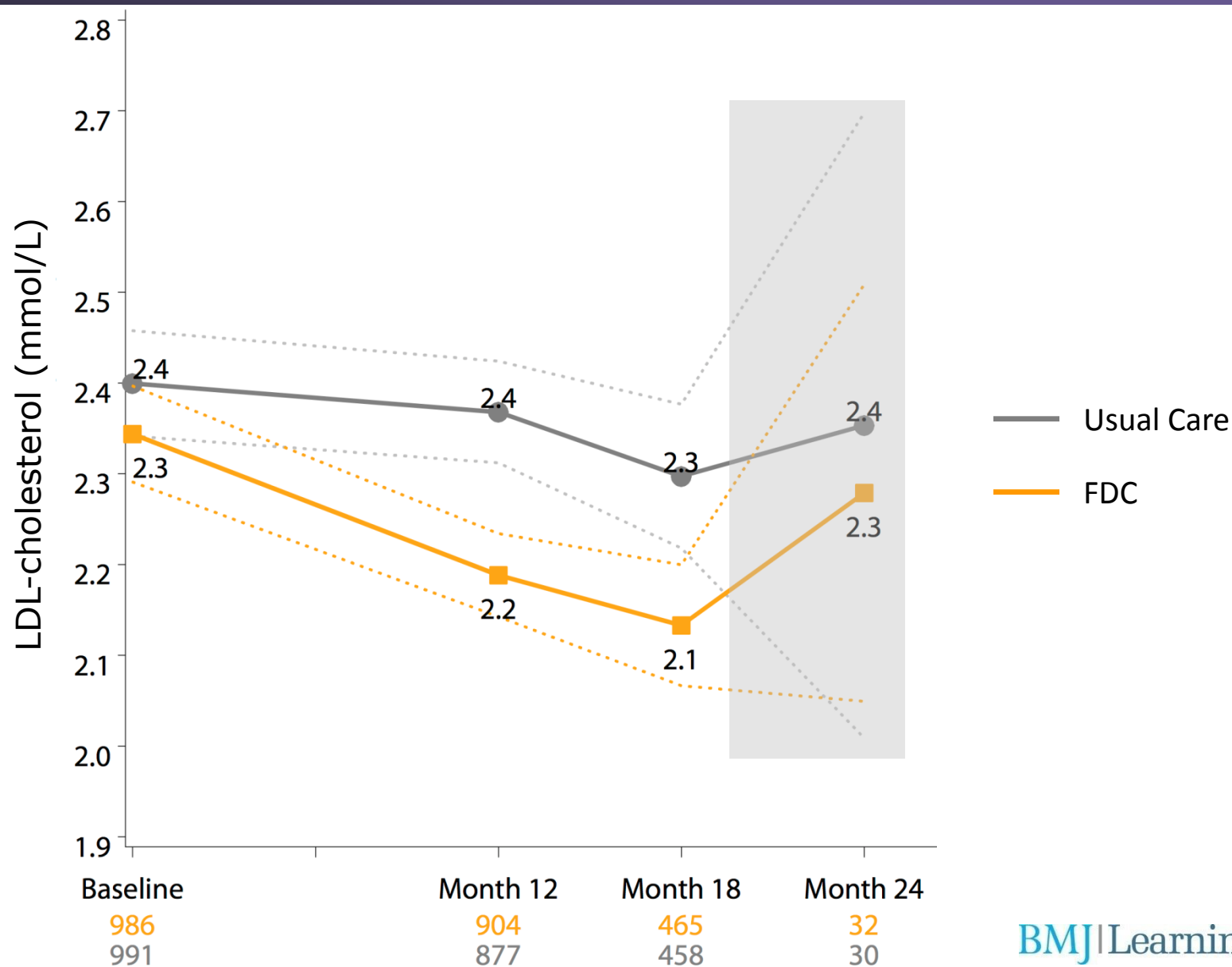
Adherence to indicated medications by treatment group



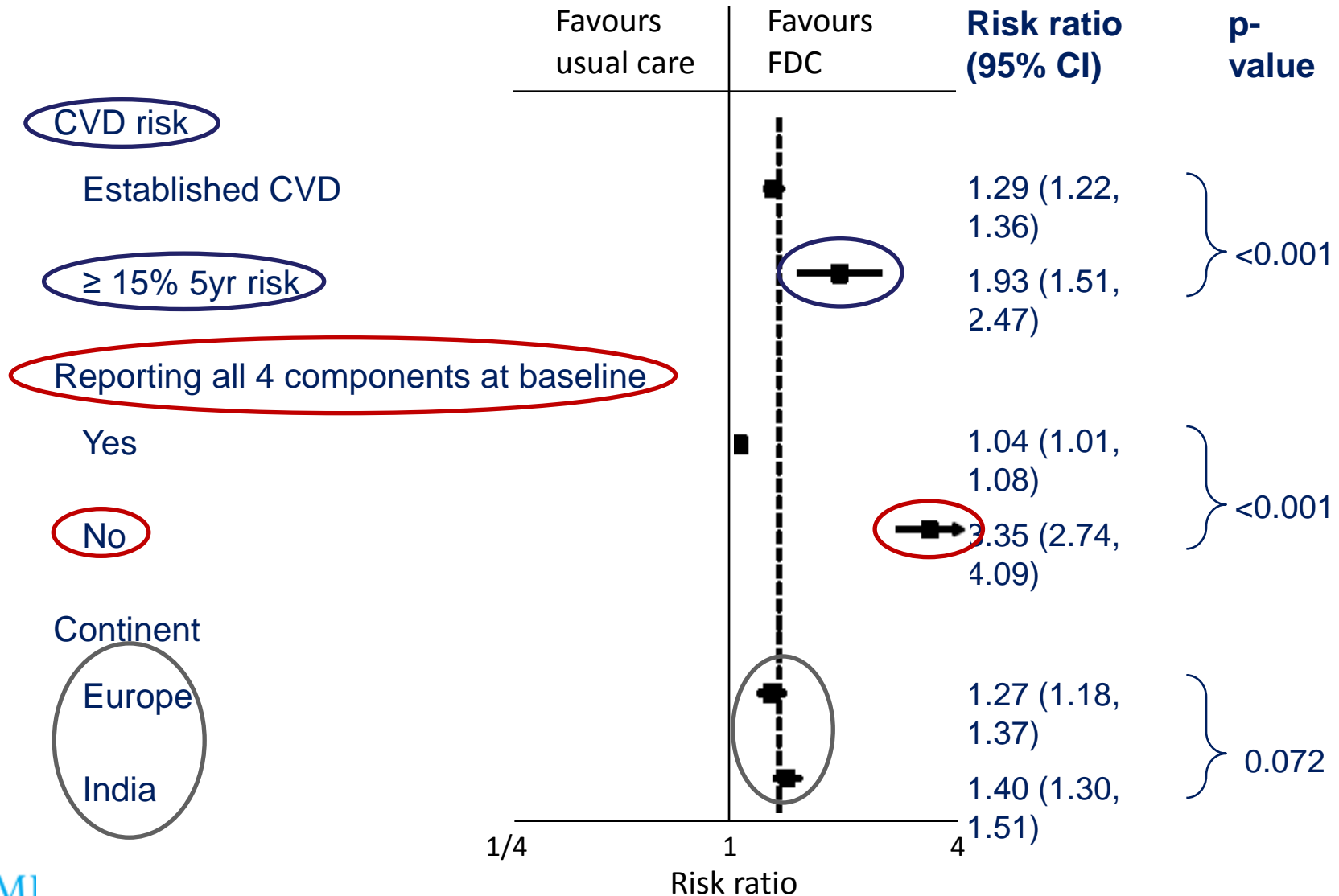
Systolic blood pressure by treatment group



LDL-cholesterol by treatment group



Adherence by pre-specified subgroups



Secondary outcomes

Outcome	FDC (N = 1002)	Usual care (N = 1002)	Treatment Effect (95% CI)	P-value
Adherence at 12 months (%)	88% (1%)	65% (2%)	1.36 (1.29; 1.43)	<.0001
Diastolic BP (mmHg)	72.8 (0.3)	75.2 (0.3)	-2.5 (-3.3; -1.6)	<.0001
Total cholesterol (mmol/L)	4.06 (0.03)	4.12 (0.03)	-0.07 (-0.14; 0.01)	0.08
HDL-cholesterol (mmol/L)	1.14 (0.01)	1.13 (0.01)	0.01 (0.00; 0.03)	0.1
Triglycerides (mmol/L)	1.61 (0.03)	1.57 (0.03)	0.04 (-0.03; 0.11)	0.3
Creatinine (μmol/L)	94.6 (0.6)	91.9 (0.6)	2.7 (1.0; 4.4)	0.002
Quality of life (EQ5D; VAS)	76.1 (0.56)	73.7 (0.57)	2.43 (0.87; 3.99)	0.002
Cardiovascular events (n)	50 (5%)	35 (3.5%)	1.45 (0.94; 2.24)	0.09

Cholesterol 1 mmol/L = 38.67 mg/dl; Triglyceride 1 mmol/L = 88.6 mg/dl; Creatinine 1 μmol/L = 0.0113 mg/dl.

Serious adverse events

SAE category	FDC (N = 1002)	Usual care (N = 1002)
Total	154	142
Patients with at least one SAE	118 (11.8%)	102 (10.2%)
Cardiac disorders	42 (4.2%)	27 (2.7%)
Infections & infestations	16 (1.6%)	10 (1.0%)
Neoplasms benign & malignant	13 (1.3%)	11 (1.1%)
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Other	36 (3.6%)	40 (4%)

Conclusions

- A fixed dose combination strategy including aspirin, statin & 2 BP lowering drugs improves adherence, blood pressure and cholesterol in patients with established cardiovascular disease and those at high risk.
- The effect, a 33% increase in adherence over a median interval of 15 months, was evident in a trial population with an unusually high reported use of indicated medication at the outset.

Polypill formulations

Version 1 (post MI)	Version 2 (post stroke, or high risk)
aspirin 75mg	aspirin 75mg
simvastatin 40mg	simvastatin 40mg
lisinopril 10mg	lisinopril 10mg
atenolol 50mg	hydrochlorothiazide 12.5mg



Cost ~ \$ 20 (1,000 INR) / person / year in developing countries; & international differential prices

Kanyini Guidelines Adherence with the Polypill - Kanyini-GAP



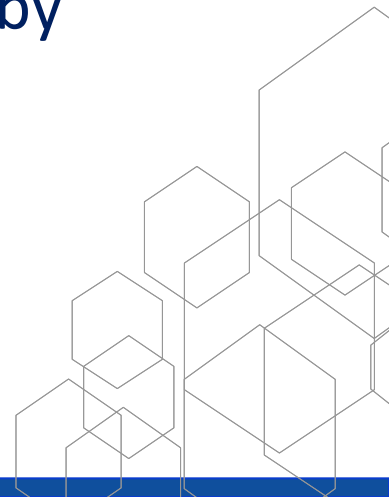
KANYINI GAP STUDY
Guidelines Adherence with the Polypill

- RCT of Red Heart Pill vs. Usual care
- Recruitment through GPs and Aboriginal Medical Centres in urban & remote Australia
- 623 patients randomised
- 50% Indigenous (Aboriginal/Torres Strait Islander)
- Primary outcomes: Adherence to statin, anti-platelet and combination BP lowering therapy; change in SBP; change in total cholesterol
- Current Status:

Datalock completed, results expected early 2013

IMPACT (NZ) - overview

- Randomised, controlled, open-label trial
- Primary care setting, Auckland & Waikato
 - N=513 (including 257 Māori, 50%)
- N=500 (including 250 indigenous Māori)
 - Recruitment completed July 2012
- Polypill-based care vs. usual care
 - Currently in follow-up phase
- 1^o outcomes: adherence, Δ SBP & LDL-cholesterol
 - End of trial planned July 2013
- Results to be presented end of 2013
- Polypill prescribed by usual GP & dispensed by community pharmacist



FOCUS – Phase 2

Fixed Dose Combination Drug for Secondary cardiovascular prevention

- RCT
- 1340 post-MI patients, 9 months follow-up
- FDC [aspirin 100, ramipril 2.5/5/10, simvastatin 40] vs. same drugs separately
- Outcomes: adherence, BP, LDL-cholesterol
- South America, Spain, Italy
- European Commission – FP7; reporting ? 2014

Lifestyle interventions

- Stop smoking
- Weight reduction
- Reduce salt intake
- Physical exercise
- Increased fruit & vegetable consumption
- Reduced total fat & saturated fat intake
- Replace saturated with poly- & mono-unsaturated fats
- Reduce total fat intake
- Increase oily fish consumption
- Limit of alcohol consumption

Global non-communicable diseases; lessons from the HIV–AIDS experience.

As in HIV–AIDS, although behaviors (such as eating an unhealthy diet and being physically inactive) are potent risk factors for cardiovascular disease and type 2 diabetes, the best available lifestyle interventions are insufficient on their own and mainly affect the most motivated adopters, leaving large groups of people at risk who can benefit from proven biomedical interventions (e.g. generic statins, antihypertensive and antidiabetic medications, or aspirin).

Therefore, although the rigorous pursuit of evidence-based behavioral interventions and societal policies that facilitate healthier lifestyles must continue, it is critical to welcome and integrate the use of low-cost biomedical interventions into prevention efforts for non-communicable diseases, viewing them as complementary and part of a holistic approach.

An examiner from Mars visits earth to grade our achievements with CV medications:

- Discovery, innovation, potential effectiveness ?
 - 8 out of 10
- Delivery to those in need ?
 - 1 out of 10

Thanks for your attention



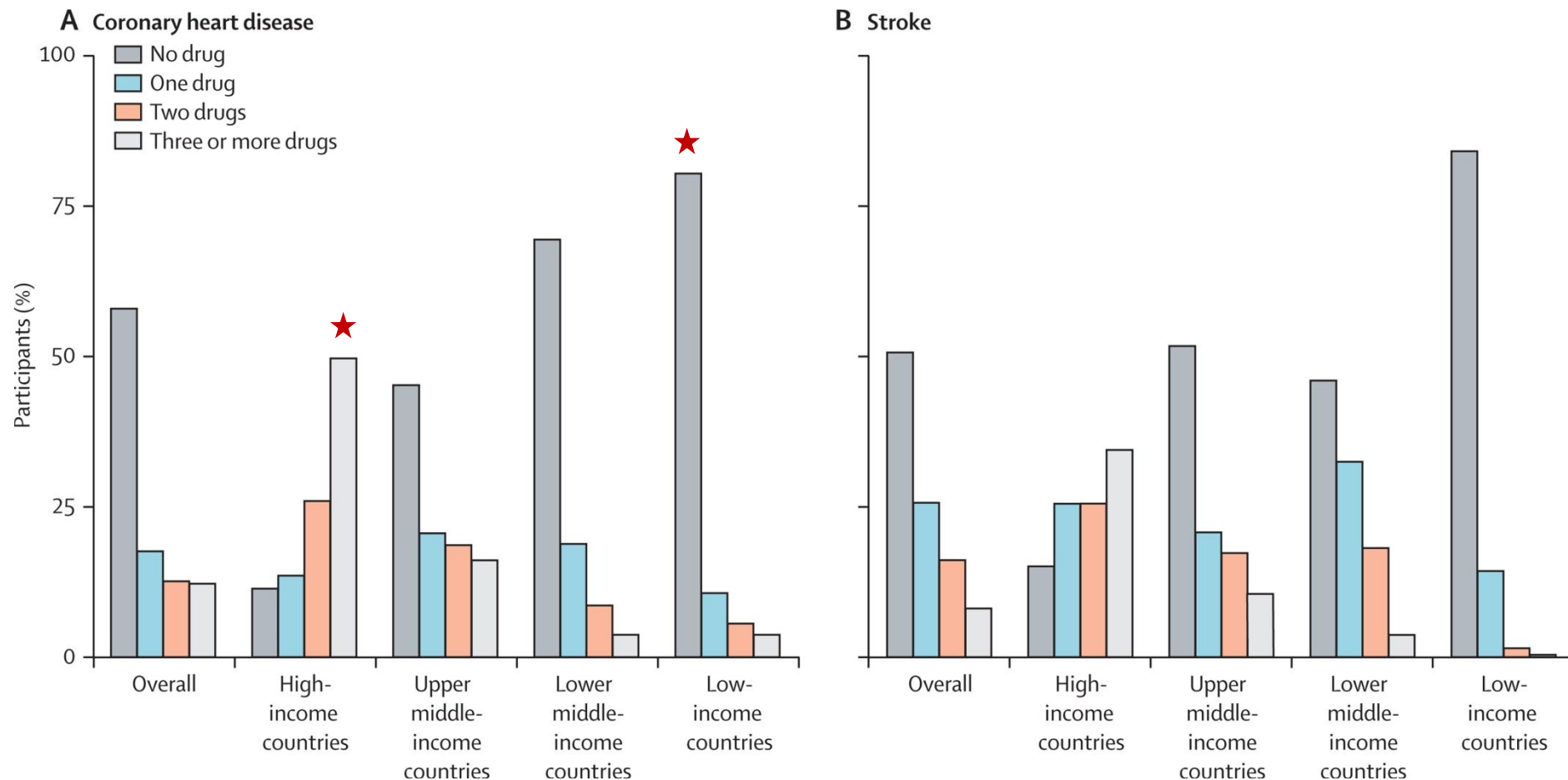
UMPIRE trial

Use of a Multidrug Pill In Reducing cardiovascular Events

Simon Thom; UMPIRE Collaborative group

Background

Use of secondary prevention drugs for CVD in the community in high-income, middle-income, & low-income countries (the PURE Study)

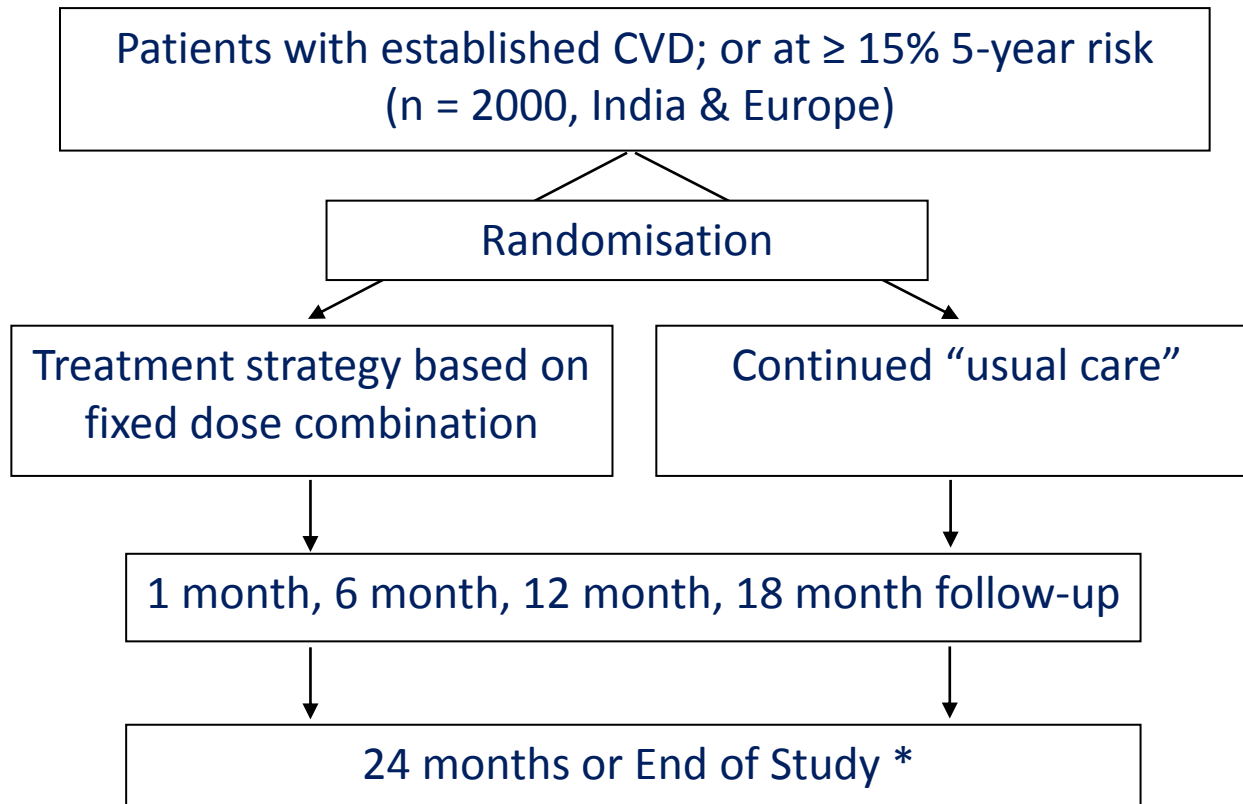


UMPIRE trial

Primary objectives

- To test the hypothesis that a fixed dose combination-based strategy (a “polypill”) for delivery of preventive medications (aspirin, statin and two blood pressure lowering agents) compared with usual care might improve:
 - Adherence to indicated therapy
 - Systolic BP
 - LDL-cholesterol,
at end of study,
in people with (or at high risk of) cardiovascular disease.

PROBE design



← inclusion

exclusion:
contraindications or
known intolerance of
FDC components

* 12 months after
last randomisation
(range 12 – 24)

Methods

- Adherence: self-reported use of [antiplatelet, statin and ≥ 2 BP lowering therapy]
- BP: electronic device (Omron 705CP II) + printer
- Cholesterol & all blood tests: local laboratories

Randomisation

- FDC : usual care, 1 : 1 (web-based)
- Stratified by presence or absence of established CVD

Trial sites

- 28 in India
- 3 in Europe (Dublin, London, Utrecht)

Recruitment

- June 2010 – July 2011

Study treatments

Fixed dose combinations, x 2

Version 1	Version 2
aspirin 75mg	aspirin 75mg
simvastatin 40mg	simvastatin 40mg
lisinopril 10mg	lisinopril 10mg
atenolol 50mg	hydrochlorothiazide 12.5mg

Physicians could add additional medications, stop the FDC & begin treatment with separate medications, or switch FDC version.

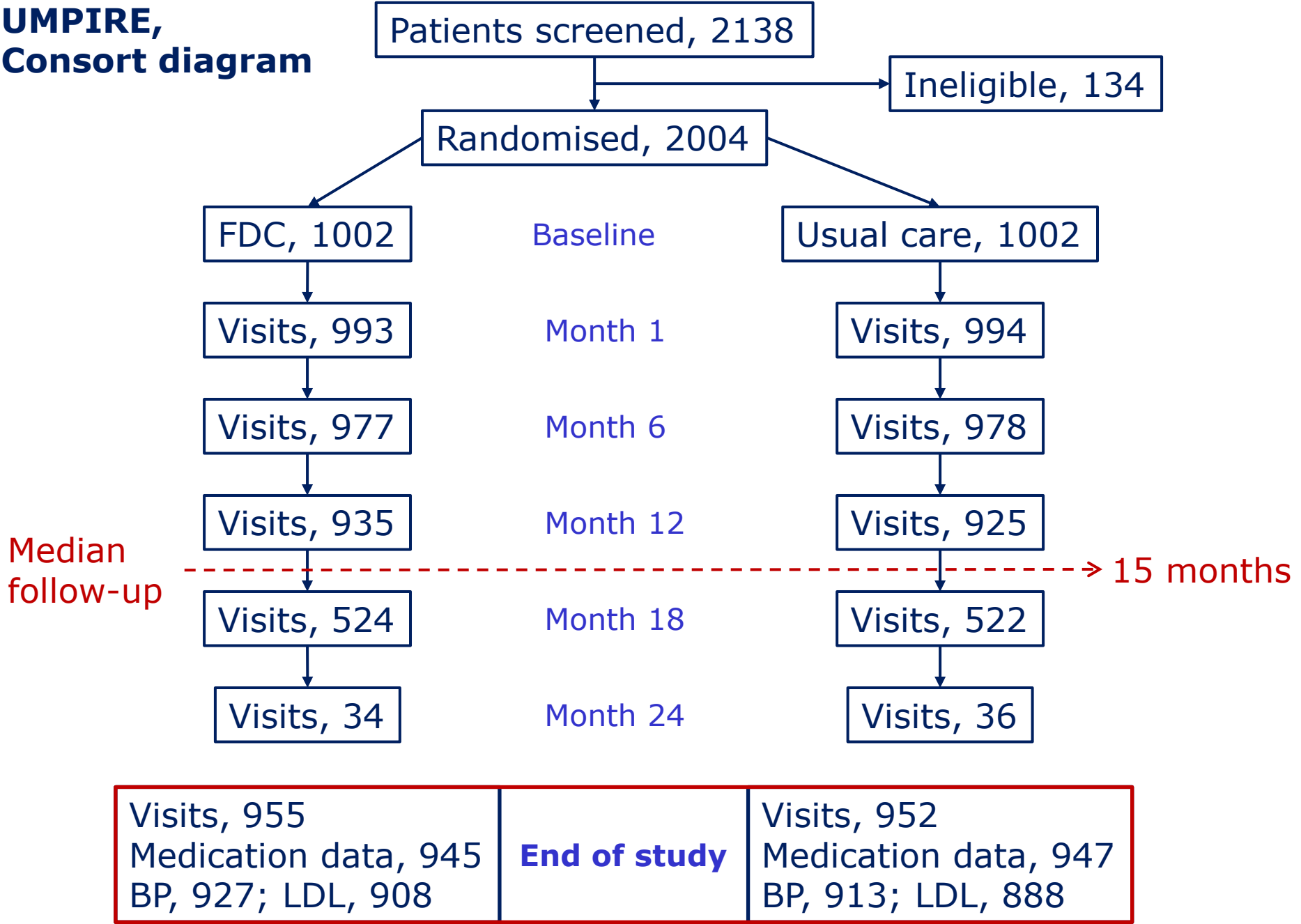
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**UMPIRE,
Consort diagram**



Results

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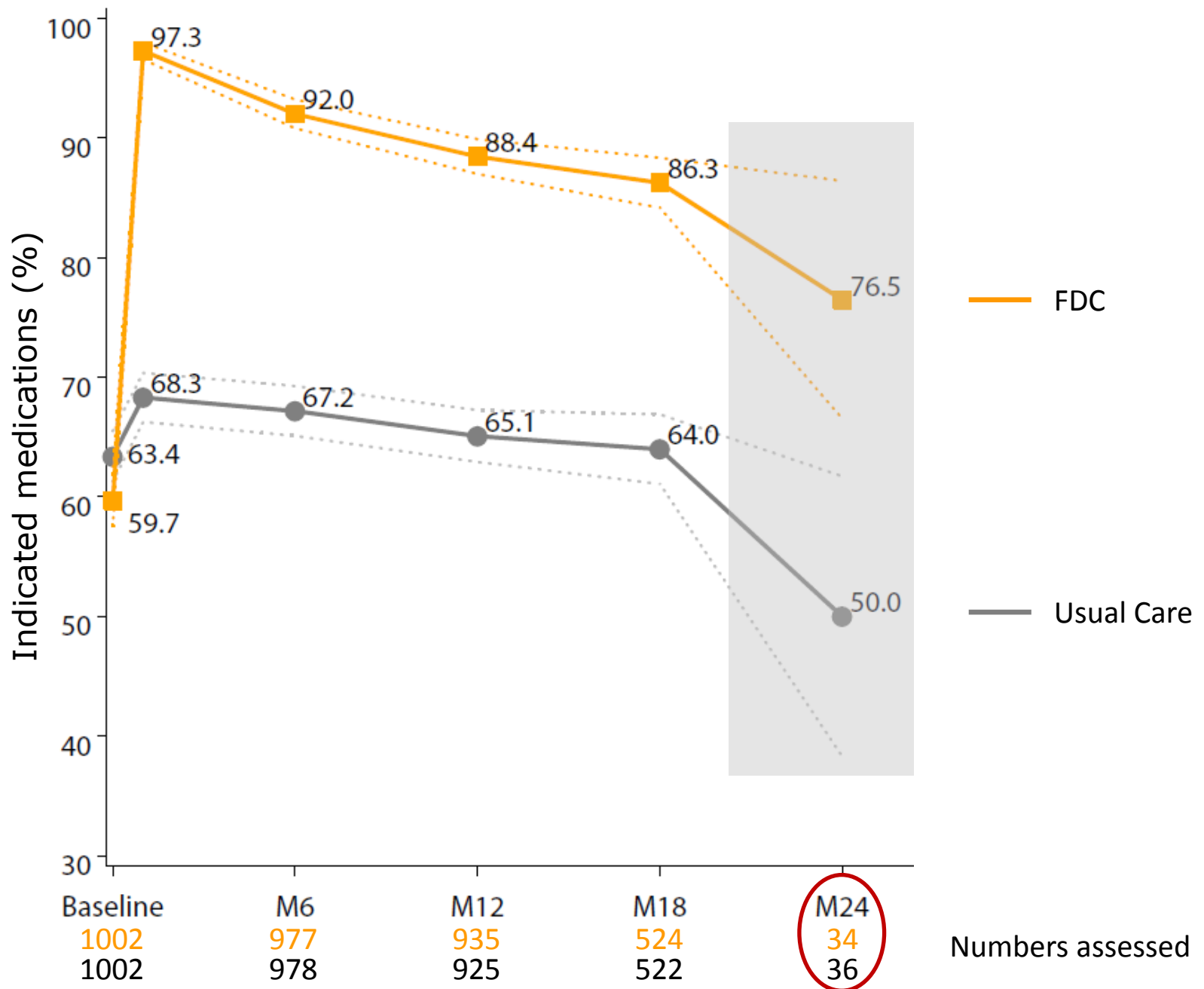
Effects on primary outcomes

- at end of study

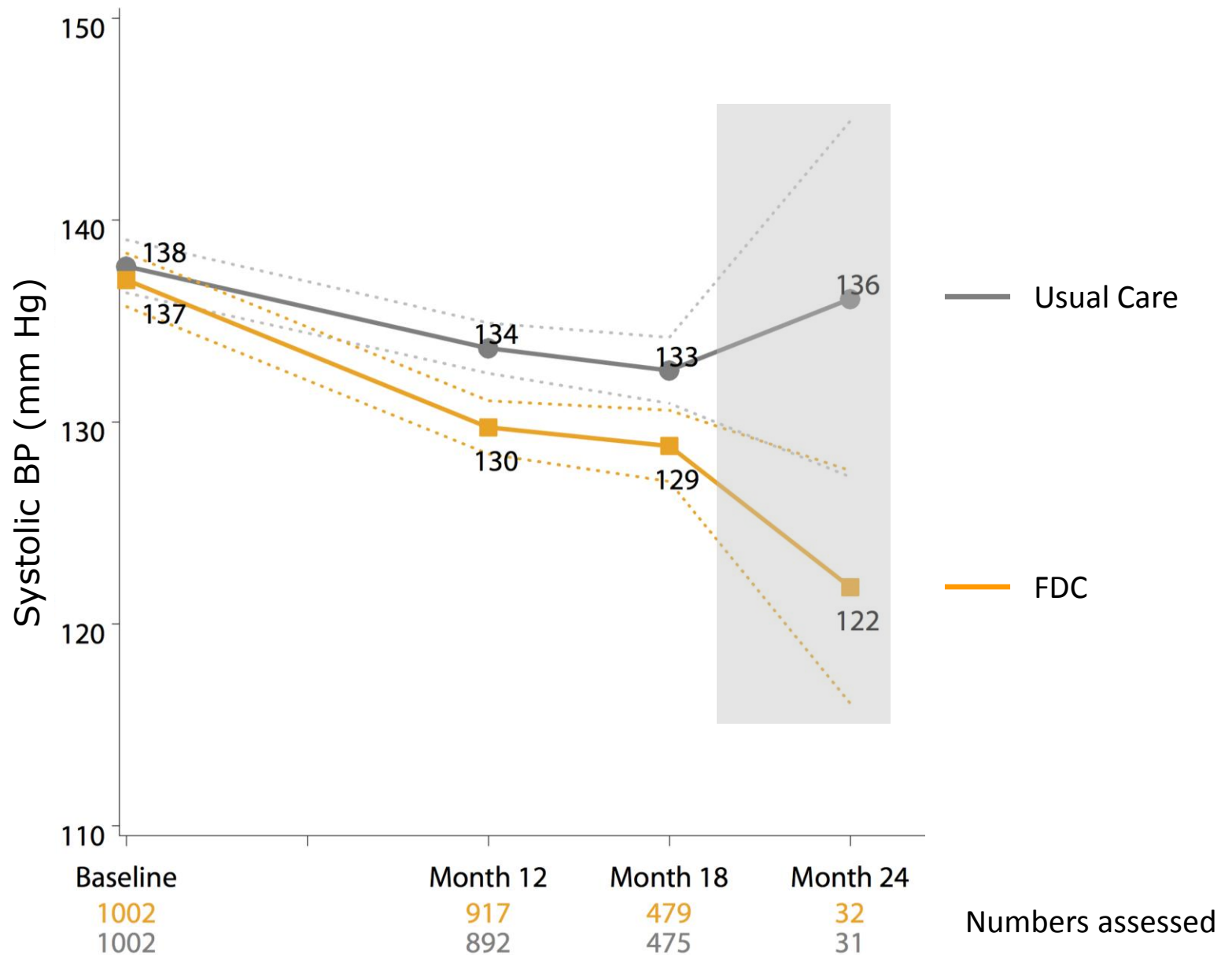
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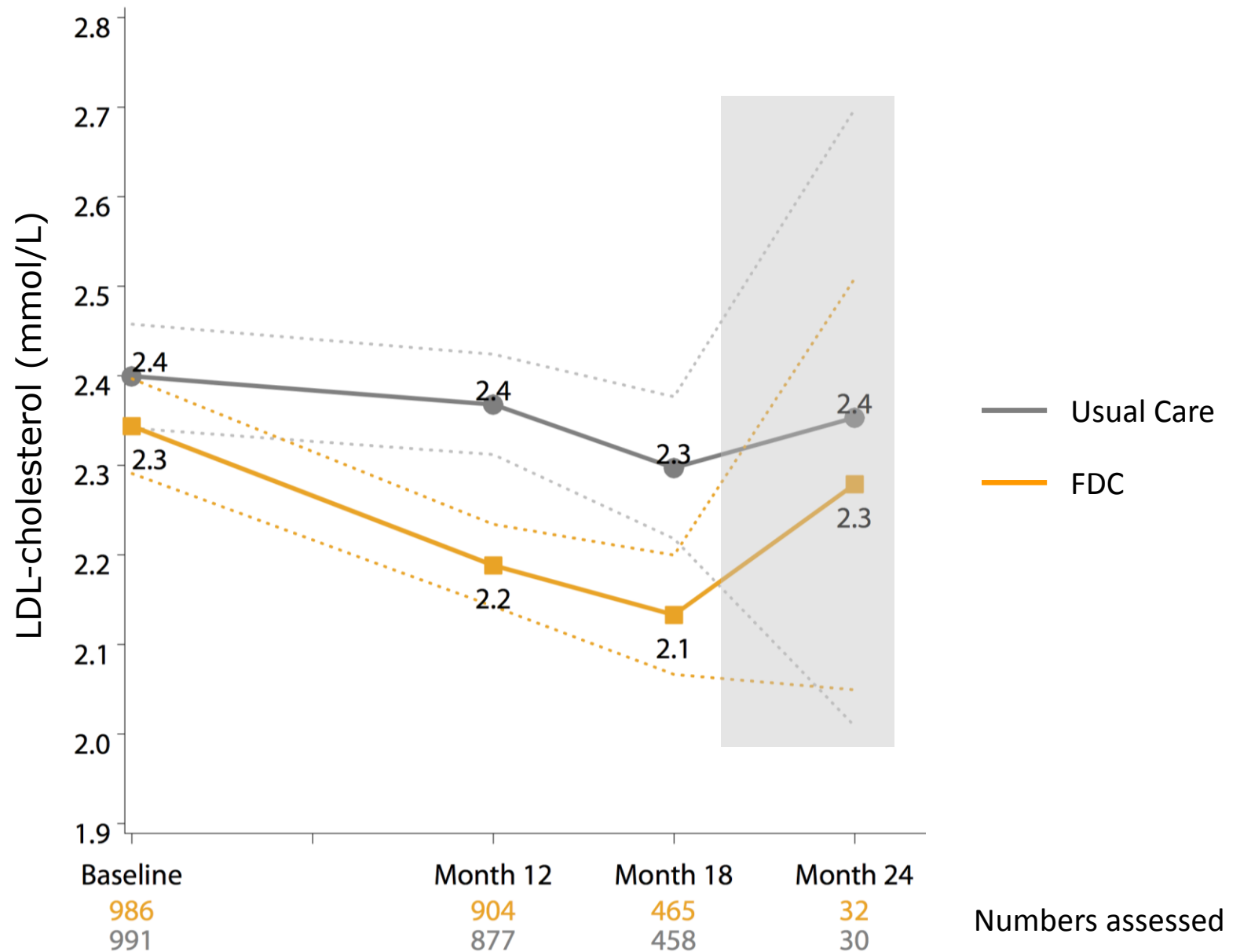
Adherence to indicated medications by treatment group



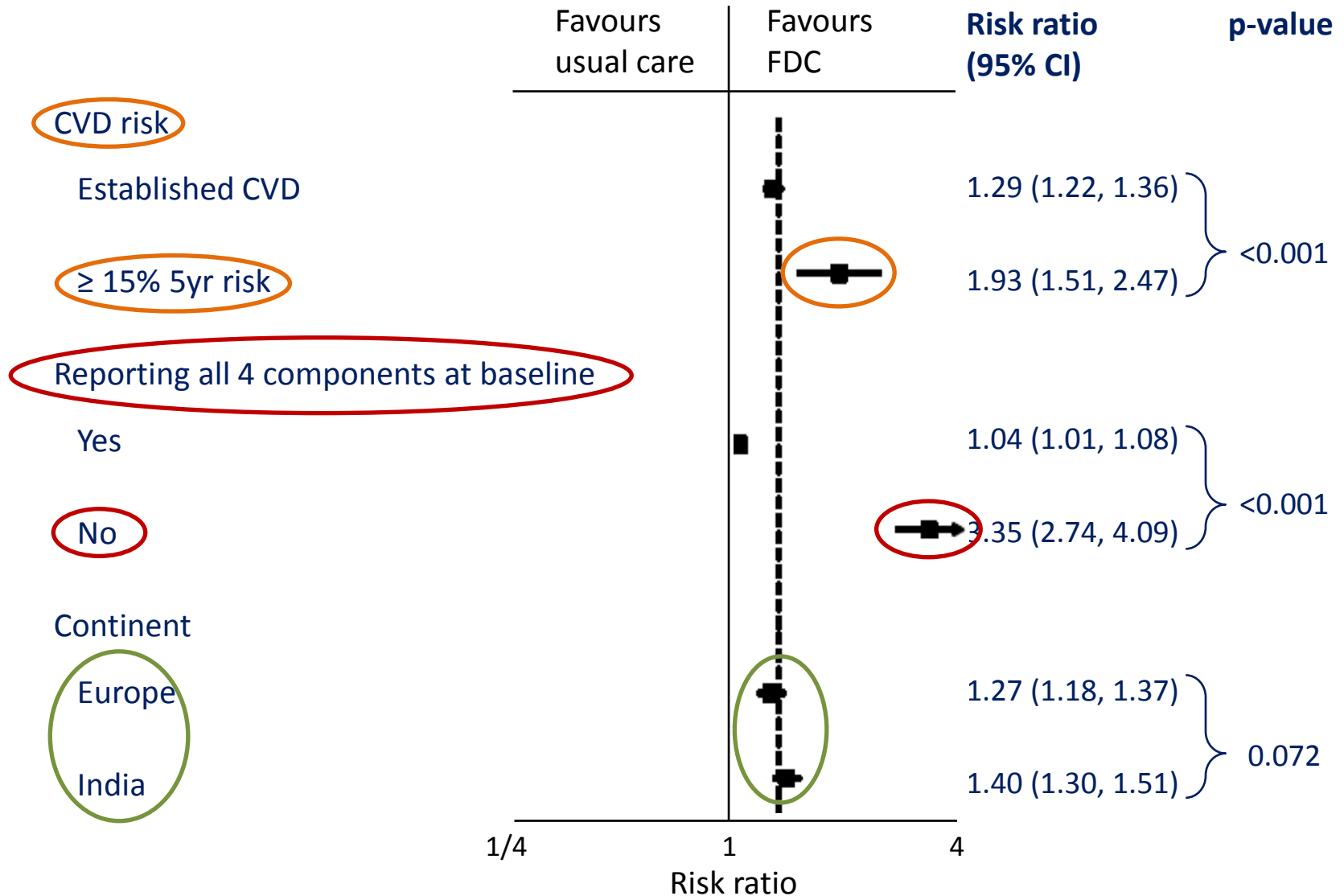
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LDL-cholesterol by treatment group



Adherence by pre-specified subgroups



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**Thanks for
your attention**

Investigators

Michiel Bots (UMCU, Utrecht)

Raghu Cidambi (Dr Reddy's, Hyderabad)

Jane Field (Imperial College London)

Rick Grobbee (UMCU, Utrecht)

Anushka Patel (George Inst. Hyderabad)

Neil Poulter (Imperial College London)

D. Prabhakaran (CCDC, Delhi)

K. Srinath Reddy (PHFI, Delhi)

Anthony Rodgers (George Inst. Sydney)

Alice Stanton (RCSI, Dublin)

Simon Thom (Imperial College London)

Statisticians

Laurent Billot (George Inst. Sydney)

Severine Bompont (George Inst. Sydney)

<http://www.spacecollaboration.org>

SPACE (Single Pill Against Cardiovascular Events)

<http://clinicaltrials.gov/ct2/show/NCT01057537?term=umpire&rank=1>

<http://www.ctri.in/Clinicaltrials/index.jsp>



1st International UMPIRE Newsletter – AUGUST 2010

Welcome to the first international UMPIRE newsletter! The official start date was 1st February 2010 and we are now 6 months into the trial. We have achieved a significant number of milestones in this short time and there has been a great deal of hard work and many important meetings, discussions and submissions to get us to this stage. Congratulations all round.

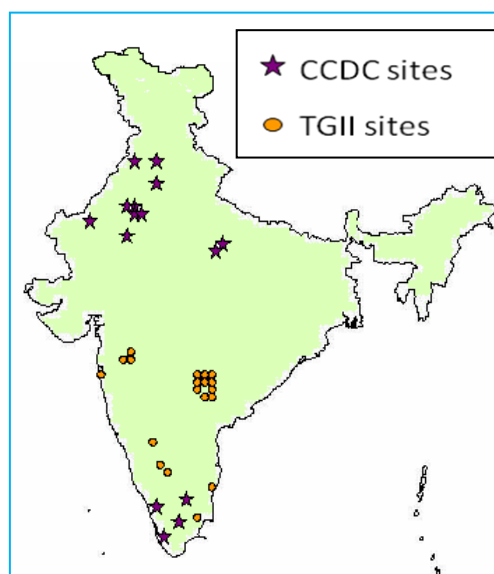
This newsletter will be circulated quarterly to keep everyone informed of the trial progress, important issues that have arisen, and emerging plans. There will also be a monthly newsletter circulated to the investigator sites with specific trial-related information on the protocol, procedures and documents. Please let us know if you have any comments or suggestions for topics / news to include in the next issue.

WHERE WE ARE NOW:



The first UMPIRE recruit was randomised on 22nd June by the team in Ireland (Dublin 002) under Prof Alice Stanton (champagne on the way), followed by the London team (London 001) on 13th July led by Dr Filomena Paciello. The Utrecht team (Utrecht 003) led by Profs Rick Grobbee and Michiel Bots started recruitment this week, and site 010 lead by PI Dr Ambuj Roy were the first Indian site to be initiated on 6AUG10 and to successfully randomise their first patient on 9AUG10. It is likely that a number of the Indian investigators (site numbers 004 – 034) will also start recruiting shortly.

The current recruitment status (as of 13AUG10) is 60 registered (2 screen failures) and 47 randomised (8 randomisation failures due to CV risk too low). Amongst the 25 patients randomised to the polypill, 7 (28%) have been prescribed RHP1c and 18 (72%) have been prescribed RHP2c. This is a great 'on schedule' start to recruitment, but we have a long way to go to reach the target of 2000 participants (1000 in Europe and 1000 in India) within a very tight 12 month recruitment period (now actually 10.5 months). We are having monthly teleconferences with the European research nurses to discuss recruitment and trial progress, and hope to be able to share 'best practice' to enhance recruitment through teleconferences and newsletters.



Dr Reddy's have accomplished the manufacturing, packaging, export and shipping process so that the Red Heart Pills were available at the European sites by 21st June. Red Heart Pill shipments are now in progress for the Indian investigator sites.

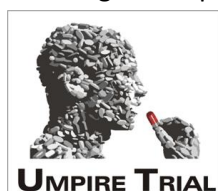
All contracts and financial agreements with the European Commission (EC) were finalised between the EC and Consortium partners in May, and we are now in the process of amendments to recognise the Centre for Chronic Disease Control (CCDC), New Delhi, as a consortium partner. This recognition reflects the parallel roles of the CCDC and The George Institute for International Health (GIH), Hyderabad in managing the clinical trial in India and recruiting 500 patients each between 30 trials sites. The Public Health Foundation of India (PHFI) will take the lead for dissemination of the results particularly in developing countries.

Membership has been finalised for the 3 trial Committees - Data Safety and Monitoring Board (DSMB), Clinical Endpoint Adjudication Committee (CEAC), and Expert Advisory Board (EAB), each with completed confidentiality agreements and Terms of Reference. Initial meetings of the Trial Steering Committee, DSMB and CEAC have taken place and will follow shortly for the EAB.

UMPIRE COMMITTEE MEMBERSHIP	
DSMB	Prof Jane Armitage (Chair - London) Prof Yolanda van der Graaf (Utrecht) Prof Ravindra Pandey (New Delhi)
EAB	Prof Kay-Tee Khaw (Chair - Cambridge) Dr Emer Shelley (Dublin) Dr Jonathan Morrell (Hastings) Prof Stephan Laurent (Paris) Prof Andrew Tonkin (Melbourne) Dr B Soma Raju (Hyderabad) Prof Raj Tandon (New Delhi) Prof Tom Gaziano (Boston)
CEAC	Dr Clara Chow (Sydney) Dr Michele McGrady (Sydney) Dr Neil Chapman (Chair - London) Dr Ajay Gupta (London) Dr S Harikrishnan (Trivandrum) Jenny Hibbard (Endpoint Coordinator – Sydney)

START-UP MEETINGS

We held the first international Principal Investigator meeting for UMPIRE in London on 11th and 12th March 2010. This was combined with a presentation of the results from the PILL-pilot trial and the inception of the SPACE collaborating group (**S**ingle **P**ill **A**gainst **C**ardiovascular **E**vents – no prizes for the acronym!). The SPACE group includes investigators from New Zealand, Australia, India, Brazil, Canada, Ireland, South Africa, the Netherlands, UK, China and USA. Representatives of all the UMPIRE consortium partners attended as well as representatives from the European Commission (Dr Jan Paehler), the DSMB (Prof Jane Armitage) and the EAB (Dr Jonathan Morrell). It was a very successful meeting and a fantastic opportunity for all polypill collaborators to met face to face, to learn the complex ground rules of EC projects and to discuss ‘past, present and future’ trials. The UMPIRE logo was chosen via a design completion and a remarkably democratic ballot – some of the imaginative contenders are shown below. Dr Reddy’s kindly covered travel & accommodation costs and stood us to dinner. During the meeting Raghu Cidambi talked about the fascinating development of the RHP over the past 10 years.



Investigator meetings were held for the Indian teams both in Hyderabad on 20th June (led by Prof Anushka Patel), and in New Delhi on 4th July (led by Prof Prabhakar). Both meetings were hugely well supported by investigators from centres across the length and breadth of India (see map on page 1); Prof Simon Thom and Jane Field from the UMPIRE coordinating office also attended. The meetings were marked by eager

enthusiasm, incisive questioning and a real sense of commitment – there is no doubt that the polypill concept has really captured the imagination of Indian physicians.

Slide resources and reports from these “start-up” meetings are available on the Trial website.



Photos from the Hyderabad UMPIRE Investigator Meeting – 20th



Investigator Meeting, New Delhi – 4th July



Profs Pandey, Thom and Prabhakaran



The George Institute for International Health – India : Team outbound day

During their time in India, Simon Thom and Jane Field also spent a week at GIIH and a week CCDC, discussing the trial management, visiting some of the investigator sites in Hyderabad and New Delhi, and meeting some of the DSMB (Prof Ravindra Pandey) and EAB members (Prof Raj Tandon, Dr B Soma Raju). It was an important opportunity to learn about the clinical and social settings in which the Trial will run. Considerable emphasis was placed on the importance of the results dissemination phase by Prof. Raj Tandon.

Dr Reddy's Development team

Thom & Field also visited Dr Reddy's offices in Hyderabad for a meeting with Dr Anji Reddy (Chairman) – Anji Reddy has since discussed UMPIRE with David Cameron when the British political delegation was recently in India. There followed a visit the manufacturing plant with Raghu Cidambi, who has been instrumental in championing the Red Heart Pill. Thom & Field met the development team who have spent years working on the Red Heart Pill formulation, design, and stability testing.



PRESS RELEASE

On 17th May 2010, the Imperial College Press Office coordinated an international news release about the UMPIRE Trial and there was national and international coverage. The story ran in the Independent, the Telegraph, the Guardian, the Daily Mail, the Press Association, BBC World Service and the Times of India, as well as more specialist outlets such as Pulse and the Pharma Times. There was a BBC Radio 4 interview recorded with Prof Anushka Patel, Prof Anthony Rodgers and Raghu Cidambi at the time of the Start-Up meeting in London, and released on the BBC World Service (see podcast – UMPIRE interview starts at 6.17 minutes) and a number of potential volunteers who contacted the UMPIRE Coordinating Office in response to the release were put in touch with the investigator sites.

[Podcast \(double-click\)](#)



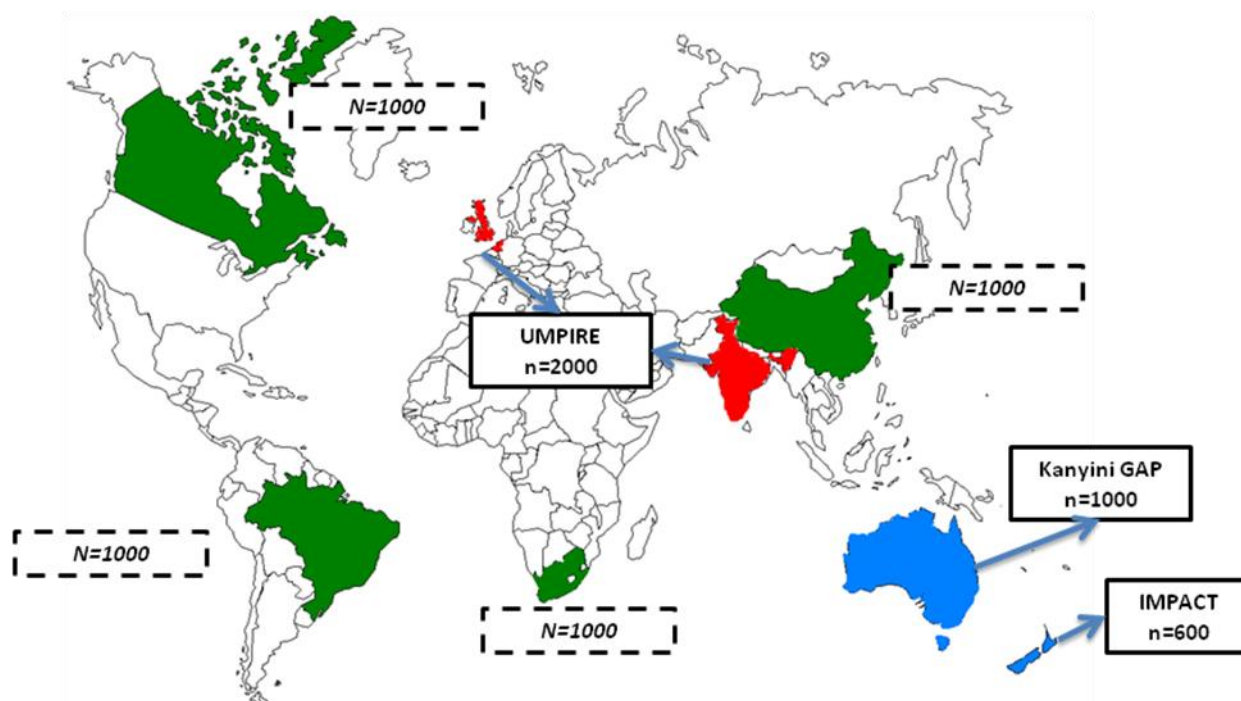
OTHER ACHIEVEMENTS SO FAR

- Completion of the European Commission Contracts – the partners were involved in a time-consuming process of completion of both Consortium and Grant Agreements with the EC, which involved numerous negotiations, reviews and signature of documents.
- Tutorials on financial reporting process completed: As the trial is funded by a European Commission 7th Framework Programme Grant, there are numerous rules and regulations to be met by the Consortium partners. Following an initial presentation on the EC financial and reporting requirements by the Imperial College finance and contracts teams at the Start-Up meeting in London in March, a number of teleconferences have taken place with the partner Finance and Administrative teams to ensure the responsibilities and requirements are fully understood and being followed. Reporting templates have also been circulated to the partner teams to ensure that the Management team have an overview of the trial work package progress and trial budget in preparation for the interim report to the EC at 18 months. Further trial funds are dependent on this interim report. Templates for the first 6 month period are being submitted by the consortium partners to Prof Thom by 14th August 2010.
- Site Initiation Visits (SIVs): SIVs have been completed at the 3 European sites in London, Dublin and Utrecht, and will soon take place at the ~30 sites India. There has been significant preparatory work by the coordinating centres to enable these visits to take place, including development of trial documents and manuals, training presentations, template monitoring documents, Investigator Site Field and communication with Dr Reddy's regarding RHP shipments supplies.

- E-CRF: The eCRF InForm system is up and running for trial electronic data capture. This process has involved significant work (templates, testing, and training) between the UMPIRE Coordinating office, London and Data Management at the George Institute for Global Health, Australia. All users involved in data entry or review need to have InForm training before user access and account activation.
- SPACE website: A polypill trials website has been set up for the SPACE collaboration. See: www.spacecollaboration.org This umbrella reflects the ambition to extend the series of parallel trials to additional countries thereby accumulating sufficient participants to power analysis of the polypill strategy on cardiovascular events. Dr Ruth Webster coordinates this activity (see below). This website has details on the UMPIRE, IMPACT and Kanyini GAP polypill Trials, and is a resource for each of the Trials to enable investigators to have access to relevant trial documents, slide resources and relevant publications. There is also a forum for investigators to discuss common trial issues, provide 'hints and tips', review FAQs or discuss other relevant CVD topics.
- FAQs for UMPIRE: A number of questions have been asked by the Dublin and London sites already participating in patient recruitment and related to specific trial aspects: the protocol, inclusion& exclusion criteria, RHP, and CV risk. This file will be updated and circulated as more questions are raised – as described above, it will be maintained on the SPACE website. If you have a trial related question, please check the current FAQ file, or contact your monitor or coordinating centre to check the appropriate response.

POLYPILL COLLABORATION

Dr Ruth Webster, based at the George Institute for Global Health, Australia, is coordinating the team of international collaborators planning polypill trials in other countries. Initial proposals have been put forward or are in progress for Brazil, Canada, China and South Africa. Concurrent polypill trials are already running in Australia (Kanyini-GAP – led by Prof Anushka Patel) and in New Zealand (IMPACT – led by Dr Raina Elley & Prof Anthony Rodgers). The global map below shows that if all current and planned trials are successful, the SPACE collaboration will include a total trial population of 7600 participants.



NEXT PRIORITIES

- Recruitment strategies
- Preferred titration strategies
- Monitoring tasks
- Partner finance reporting
- Publications

Next Newsletter

This will be sent out mid November. Please let us know of any exciting achievements, recognitions or stories to publish.



Congratulations to Dr Paciello and Research Nurse Benita Maguire who are both getting married this Autumn !

UMPIRE COORDINATING OFFICE (UCO):

Imperial Clinical Trials Unit, International Centre for Circulatory Health, Imperial College
London, 59 North Wharf Road, London W2 1LA, U.K.

Project Coordinator: Prof. Simon Thom, s.thom@imperial.ac.uk

Deputy Project Coordinator: Prof Neil Poulter, n.poulter@imperial.ac.uk

Project Manager: Jane Field, j.field@imperial.ac.uk



10th International UMPIRE Newsletter – DEC 2012

Welcome to the 10th and final edition of the UMPIRE International Newsletter.

CONGRATULATIONS AND THANK YOU !!

Many Thanks to everyone who has supported UMPIRE to achieve
all targets on schedule and successful completion of the trial.

It has resulted from hard work, commitment and collaboration and was an outstanding team effort!!

The trial results have been presented by Professor Thom at the American Heart Association (Los Angeles – 5th November 2012) and at the Cardiological Society of India (New Delhi – 7th December 2012). We are also in the process of journal submission and review for the final manuscript and we will ensure you are informed of the details once this is accepted for publication.

Thank you to all the Investigators and research team members who attended the CSI meeting and UMPIRE dinner on 7th December. It was a delight to be able to thank some of you in person and discuss the trial findings and future developments. A special “Thank you” also to the CCDC team for their organisation of the dinner and awards ceremony.

The remaining activity is the final reporting of the project to the European Commission, and all 8 UMPIRE partners will be involved in the completion of the final report to confirm all work packages were achieved, with supporting evidence for project deliverables and milestones, and financial accountability. The official end date of the project is 31st January 2013 with the EC final report submission made by 31st March 2013.

OTHER TRIAL UPDATES:

Close out Visits & RHP Destruction:

The UMPIRE trial monitors have completed all close out visits in India and these visits will also be conducted in Dublin and Utrecht early next year to ensure all UMPIRE investigator sites are closed. At this stage you will need to notify your local ethics committee that your site is closed, and prepare to archive the trial essential documents. Arrangements will be made for destruction of RHP (participant returns, unused stock, expired cartons) by Dr Reddy’s Laboratories.

If you have any questions about this, please let your monitor know.

Sub-study Updates:

The PESCA – Polypill Effects on Sub Clinical Atherosclerosis and INPUT (INterpreting the Processes of the UMPIRE Trial) sub-studies are under analysis and it is hoped that the results will be available for publication in early 2013.

Other Polypill trial Updates:

The Kanyini GAP trial completed their final visits in the last few months and the trial database has now been locked. Their team are in the process of analysing and reporting these data and are aiming for presentation next year.



The IMPACT trial has reached their target of 513 subjects randomised and will continue follow-up until early next year and database lock is planned for mid 2013.

CSI AND UMPIRE DINNER PHOTOS





Wishing everyone a Very Merry Christmas
and Very Best Wishes for 2013 !



UMPIRE COORDINATING OFFICE (UCO):

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9th International UMPIRE Newsletter – JUNE 2012

Welcome to the 9th edition of the UMPIRE International Newsletter.

CONGRATULATIONS AND THANK YOU !!

Many Thanks to everyone who has supported the trial to achieve
DATABASE LOCK on schedule today – Friday 7th September.

It has resulted from hard work, commitment and collaboration and was an outstanding team effort!!
This includes all the Principal Investigators and their research teams for their support with EOS patient




visits, data entry and cleaning and casebook signatures, the Europe and Indian coordinating teams for their support and management of the investigator sites and trial monitoring responsibilities, the George Institute Data Management and Statistical teams, the Clinical Endpoint Adjudication Committee members and



safety team at the George Institute, who coordinated and tracked the endpoints and adjudication. We would also like to take this opportunity to thank the following teams for their continuing support: Dr Reddy's and their Pharmacovigilance and Drug Management teams, the DSMB for their safety oversight, the Expert Advisory Board for their guidance on publication and dissemination plans, the SPACE Collaboration team, the European Research Office at Imperial, and the European Commission. We now look forward to the results and hope that this takes the story onwards.

Trial Timelines.

The next steps for the project are detailed below and we will keep everyone informed of progress.

UMPIRE TIMELINES		DUE DATE
Database Lock		7 SEP 2012 – Achieved
Final manuscript to Lancet		28 SEPT 2012
Publication		Early NOV 2012
Presentation at American Heart Association		5 NOV 12
BMJ Masterclass at Cardiological Society of India (Conference dates 6-9 th DEC12)		7 DEC 2012
EC Project end date		31 JAN 2013
Final Report to the European Commission		By 31 MAR 2013



OTHER TRIAL UPDATES:

Close out Visits & RHP Destruction:

Following database lock, the trial monitors will confirm dates for the close out visits, and during this visit final review and reconciliation of RHP accountability will be performed (if not complete already) and arrangements will be made for destruction of RHP (participant returns, unused stock, expired cartons) by Dr Reddy's Laboratories. Other close out visit activities will include:

- Review of ISF for completeness of essential documents and reconciliation with the TMF.
- Any outstanding documents required for the TMF will be collected.
- Ensure copies of final accountability logs, destruction records and trial duration temperature logs are filed in ISF.
- Ensure any outstanding follow-up actions from previous monitoring visits are resolved
- Arrangements for archiving site documents are in place, and that the Archiving Agreement document is completed and copies filed in ISF and TMF
- Site Principal Investigator meeting and discussion of his/her end of trial
- Notification to local and national ethics and regulatory bodies of end of trial.

If you have any questions about this, please let your monitor know.

Sub-study Updates:

The PESCA – Polypill Effects on Sub Clinical Atherosclerosis and INPUT (Interpreting the Processes of the UMPIRE Trial) sub-studies are progressing well and it is hoped that the results will be available for publication in early 2013.

Final Investigator Meeting

Following discussions with the BMJ and the Cardiological Society of India, it has now been confirmed that the CSI executive committee has approved inclusion of the BMJ Masterclass in this conference on 7DEC12 (CSI conference 6-9th DEC 2012, New Delhi). An agenda is being finalised but it is hoped that this will serve as an opportunity to hold an UMPIRE Investigator meeting and dinner with the opportunity to discuss the UMPIRE trial results. Further details about these arrangements will be circulated soon but please make a note of this date.

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8th International UMPIRE Newsletter – JUNE 2012

Welcome to the 8th edition of the UMPIRE International Newsletter. We have made significant progress with the trial and are reaching the final hurdle – just over **one month to go** before all final trial visits should be completed!

Following this, we will have other targets to achieve – clean data, signed casebooks and SAEs, and database lock!

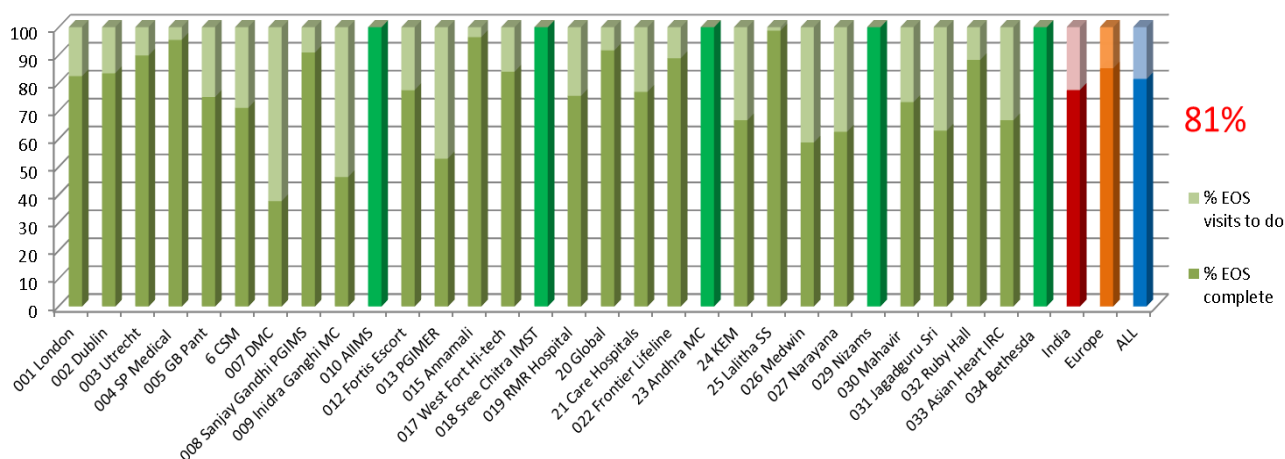


So we ask that you continue with your best efforts to achieve these targets and we thank all investigators and research teams, coordinating centres, committee members and partners for their continuing support with the UMPIRE trial.

FOLLOW-UP PHASE and End of Study Visits

As you can see from the graph below, we have completed **81%** of End of Study (EOS) visits to date. The follow-up phase was a minimum of 12 months and so we are aiming to complete EOS visits in India by the end of June (randomisation of 1000 patients by end of June 2011) and completion of EOS visits in Europe by the end of July (randomised 1004 patients by the 26 JUL 11). Our deadline for this is **31 JULY 2012**.

Progress with EOS visits - % actual vs expected completion (28JUN12)



Congratulations !!

.... to Sites 010 (AIIMS), 018 (Sree Chitra IMST), 023 (Andhra MC), 029 (Nizams) and 034 (Bethesda) for completion of all EOS visits, and there are several other sites who have nearly reached their target. Thank you for this great effort!

Well done also to the European sites who are all on target to achieve completion of their 330 + EOS visits by end of July!



The priorities for this final phase are:

- ❖ To ensure that **all randomized trial participants** have an **EOS visit entered in the eCRF** (This includes EOS completed by clinic visit, telephone contact, contact with relative or treating doctor; withdrawn consent; death or lost to follow-up patients)
- ❖ That EOS visits are conducted **in the clinic** wherever possible to obtain lipid results and blood pressures to validate medication adherence data.
- ❖ All EOS visits are completed and entered **in the eCRF by 31st July 2012** to allow sufficient time for data cleaning, database lock and analysis.
- ❖ **Please don't enter duplicate EOS data in the eCRF – if a 12M or 18M visit has been replaced by the EOS visit, only enter the data only in the EOS eCRF pages.**

The minimum data required for EOS is **subject vital status**; so please make sure that for any patient whom you have been unable to contact, every possible attempt is made to confirm their vital status by 31st July for the EOS visit (unless withdrawn consent). If you are notified of patient vital status before 31JUL12, please update this information in the eCRF. We currently have 18 patients indicated as lost to follow-up (LTF) and we need to reduce this number if possible over the next month. In addition (prior to database lock), all SAEs and eCRF casebooks will require Investigator signature.

In order to achieve these targets, Investigator sites should focus on the following activities:

1. **Prompt data entry** – please ensure EOS visit data is entered as soon as possible after the visit but within 5 days of the visit occurring.
2. **Open queries are addressed on a regular basis** - to ensure continuing review of data corrections and clarifications
3. **EOS visits schedules are adhered to** - ensuring complete final data for all randomised patients.
4. **Review of all previous trial visit CRFs** - Once the EOS is complete, this review should be conducted to ensure data is complete and clean (no queries, missing data). This includes the patient medications form and SAEs.
5. **Investigator signature of SAEs and casebooks** – this needs to be completed for all patients – screen failures, randomisation failures and randomised patients. To do this, ensure the answer is YES within the COMPLETE eCRF page at the EOS visit.

Data Cleaning

Data Management have completed a review of the baseline data and are now reviewing follow up visit data (1M, 6M, 12M and 18M) for any further data clarifications, and this may mean further queries are raised in InForm or requests are forwarded to the Investigator sites by the monitors. This process has indicated that the majority of this baseline data is complete and appropriate, and please can investigator sites respond promptly to these additional queries. The more data that can be reviewed and cleaned now, the easier the final data cleaning process will be. This will ensure that we can achieve database lock on schedule.

Trial Timelines

As a reminder to all teams, the table below confirms the projected timelines for UMPIRE, including final visits, database lock, final analysis and presentation and dissemination (still to be confirmed). We continue to plan for joint publication and presentation at the end of this year, in keeping with the European Commission project timelines and to achieve maximum impact of the trial results.



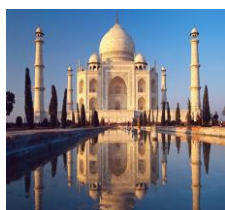
UMPIRE TIMELINES – DATA CLEANING and LOCK	DUE DATE
Last Patient Last Visit (LPLV)	31 JUL 2012
Last eCRF entered	7 AUG 2012
Last query answered and closed	15 AUG 2012
All SAEs entered (including 28 days follow-up)	28 AUG 2012
All SAEs and casebooks signed	28 AUG 2012
Data Management review – new queries issued	20 AUG 2012
Answer/close queries from final review	30 AUG 2012
All casebooks frozen	31 AUG 2012
Database Lock	7 SEP 2012
Final results	Late October 2012
Presentation at American Heart Association	3- 7 NOV 12

OTHER TRIAL UPDATES:

RHP Destruction:

In Europe, the trial monitor has been completing regular review of RHP accountability and auctioning the destruction of participant returns and expired stock. The Indian trial monitors will shortly start a final review and reconciliation of RHP accountability, and arrangements will be made for destruction of RHP (participant returns, unused stock, expired cartons) by Dr Reddy's Laboratories India.

INPUT Sub-study:



INPUT - Interpreting the Processes of the UMPIRE Trial - is a process evaluation sub-study coordinated by the London and Indian teams and involves qualitative interviews of a sample of health practitioners and trial participants at the end of the trial in London and India. Interviews are currently being conducted and exchange visits have been completed between the UK and Indian research fellows Frances Stewart and Abdul Salam.



Final Investigator Meeting

Plans are evolving for presentation of the UMPIRE results via a BMJ MasterClass, to be held in India towards the end of 2012. We will hope to settle a date and location shortly and will keep you informed.

Please let us know if you have any comments and suggestions for items or feedback for future editions.

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7th International UMPIRE Newsletter – MARCH 2012

WELCOME to the 7th edition of the UMPIRE International Newsletter! We hope that your research teams have started the End of Study (EOS) visits. We need to be on schedule for final patient visits in July 2012. This last phase of the trial will require timely data entry, prompt resolution of queries and review of any data issues, so we encourage both investigator site teams and monitoring teams to regularly check progress with the EOS visits. We understand that this will be a busy time but with the plans for publication and dissemination at the American Heart Association meeting in early November, we will need to be very organized to meet these tight timelines.

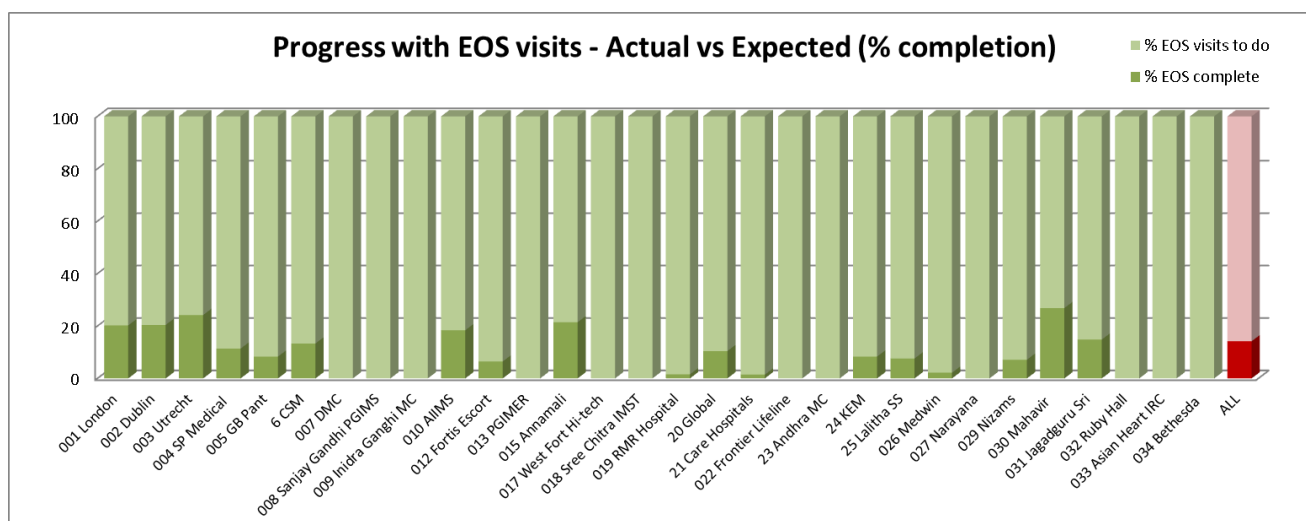


Cartoon above drawn by one of the London UMPIRE patients.

FOLLOW-UP PHASE and End of Study Visits

A priority for this final phase is to ensure that all trial participants have their final EOS **in the clinic** wherever possible. All EOS visits need to be completed by 31st July 2012 to allow sufficient time for data cleaning, database lock and analysis. Minimum data required for EOS is **subject vital status**; so please make sure that for any patient whom you have been unable to contact, every possible attempt is made to confirm their status by 31st July for the EOS visit (unless withdrawn consent) so that we can limit the number of lost to follow-up patients. Every trial participant needs to have an EOS visit completed in the eCRF to confirm status at the end of trial – this could be active patients for clinic or telephone visit, contact with relative or GP/treating doctor, withdrawn consent, deceased, lost to follow. In addition (prior to database lock), all SAEs and eCRF casebooks will require Investigator signature.

Correspondence has been circulated in this regard, including investigator newsletters, a formal letter from Prof Simon Thom and guidance from the monitoring teams. The graph below shows the actual and expected progress with EOS completion per site. Please contact your monitor if you have any questions or concerns about this process.



Data Capture and Cleaning

The priorities for this are:

- Completion of visit data in eCRF within 5 days of the visit occurring
- Any missing visits should be entered as soon as possible
- Complete all visit tabs – if data is missing or was not collected, please use the comment bubble
- Please review your “open queries” on a regular basis, so that these can be kept to a minimum
- Please complete an EOS visit in the eCRF for all patients to confirm final trial status.

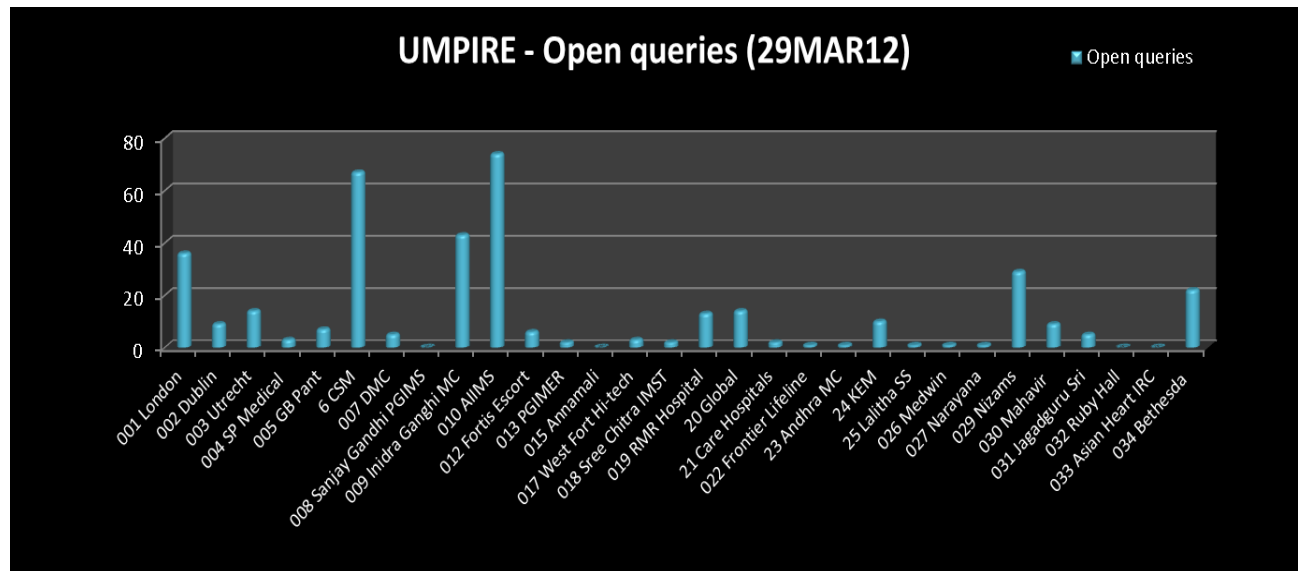
The table below confirms the projected timelines for the database lock, so that all investigators and coordinating teams are aware of the forthcoming schedule for data analysis and reporting. We have an ambitious target of joint publication and presentation at the end of this year, in keeping with the European Commission project timelines and to achieve maximum impact of the trial results. To successfully achieve this will require support and commitment from all involved parties.

UMPIRE TIMELINES – DATA CLEANING and LOCK	DUE DATE
Last Patient Last Visit (LPLV)	31 JUL 2012
Last eCRF entered	7 AUG 2012
Last query answered	10 AUG 2012
Last query closed	15 AUG 2012
All lab results entered	15 AUG 2012
All SAEs entered (including 28 days follow-up)	28 AUG 2012
All SAEs and casebooks signed	28 AUG 2012
Data Management review – new queries issued	20 AUG 2012
Answer/close queries from final review	28 AUG 2012
All casebooks frozen	31 AUG 2012
Database Lock	7 SEP 2012



QUERY STATUS

The graph below shows a great improvement in open queries for the trial since the last newsletter, with most sites having a count of 10 queries or less. Well done to all our Investigators and research teams, and please make sure you continue to keep a regular review of your open queries and answer them as soon as possible.




OTHER TRIAL UPDATES:

Safety reporting:

The DSMB held their third safety review meeting on 15th March and following discussion of the available primary outcome and safety data, they are happy for the trial to continue. A letter from the DSMB chair dated 21MAR12 confirming this was circulated to all investigators, and will need to be submitted to ethics committees as per local requirements. The Annual Safety report (Development Safety Update – DSUR - #2) has also been written and submitted to each of the participating country regulatory authorities and main ethics committees. Please remember to submit local progress updates to the IECs as required.

A reminder to investigators to use **Version 3, dated 13 OCT 11** of the Endpoint package cover sheet when reporting endpoints for the trial (see left). This cover sheet allows endpoint reporting for both UMPIRE and Kanyini GAP trials as adjudication of events is performed by a joint trial Clinical Endpoint Adjudication Committee (CEAC), and this form should be used from now on to assist the endpoint coordinating process. In addition, please provide the necessary endpoint document package as soon as you can after reporting the SAE, to assist with the timely adjudication of the events. Please also remember that any SAEs notified to the Investigator site notified within 28 days of the EOS visit will need to be reported to the UMPIRE coordinating office as an SAE (paper report, eCRF alert, DCGI SAE report) and also with an endpoint package if appropriate.

 **UMPIRE**
Use of a Multidrug Pill In Reducing Cardiovascular Events

Endpoint Documentation Package Cover Sheet

- One cover sheet to be completed per endpoint (includes events that are deaths and procedures)
- Patient Name, Medical Record Number and other patient identifiers to be removed from all pages of documentation provided
- All pages of documentation provided to be labeled with the Site Number, Patient Number, Patient Initials, and Date of Birth
- Mask any text that could unblind the adjudicators to the treatment allocation

Trial ID (tick one): Kanyini GAP (KG) ☐ UMPIRE ☐

Centre ID _____ Patient ID _____ Patient Initials _____

Reported Endpoint event/procedure as completed on SAE Form:

Event _____ Start Date _____

Endpoint category (tick the appropriate category):

☐ Death (please also state): Proximate cause of death: _____

Underlying cause of death: _____

☐ Stroke ☐ Transient Ischaemic Attack ☐ Subarachnoid Haemorrhage

☐ Coronary Bypass Graft ☐ Myocardial Infarction ☐ Percutaneous Coronary Intervention

☐ Heart Failure (death or hospitalisation) ☐ Hospitalisation for Unstable Angina ☐ Major bleeding event

☐ New symptomatic claudication ☐ Amputation due to ischaemia ☐ Peripheral arterial revascularisation

☐ Microalbuminuria (KG trial only) ☐ Macroalbuminuria (KG trial only) ☐ 50% loss of estimated GFR (KG trial only)

☐ Commencement of renal replacement therapy for end-stage renal disease (KG trial only)

Documentation provided (Tick all that apply. If there is more than one endpoint cover sheet completed, please indicate which documentation applies to which endpoint e.g. label 'A', 'B' etc):

☐ Discharge/Admission Summary

☐ Clinical Notes

☐ Imaging/Procedural/Analysis Reports

☐ Laboratory reports (separate to Discharge Summary)

☐ ECG

☐ CT scan

☐ Chest x-ray

☐ Autopsy Report

☐ Death Certificate

☐ Physician Narrative

☐ File Note

☐ Other, please specify: _____

Site Staff Name: _____

Site Staff Signature: _____ Date: _____

If additional information becomes available, please mark as appropriate (with initial and date) on the original cover sheet and re-send with the additional information.

V3.0, 13Oct2011 Page 1 of 1

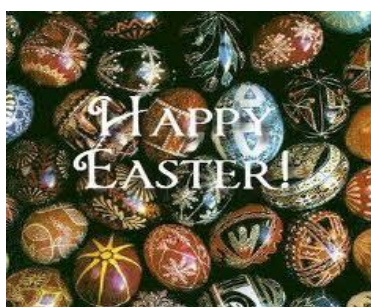


RHP Supply:

All trial sites should now have received a final supply of RHP and should therefore have adequate stocks to complete the trial. Remember at the EOS visits for the polypill patients, the RHP will need to be stopped and the patient changed back to separate cardiovascular medications. Please also remember to add the RHP “stop date” in the Patient Medication page, indicating reason as ‘EOS’.

Final Investigator Meeting

Plans are evolving for a final investigators meeting to be held in India towards the end of November 2012. We will hope to settle a date and location shortly and will keep you informed.



Wishing all our teams a very
Happy Easter !

Please let us know if you have any
comments and suggestions for items or
feedback for future editions.



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6th International UMPIRE Newsletter – DECEMBER 2011

WELCOME to the 6th edition of the UMPIRE International Newsletter! We hope that your research teams are conducting follow-up trial visits to schedule and everything is on track for final patient visits in July 2012. Thank you for your continuing support of the trial, and for your hard work in this follow-up phase to ensure the continuation of subject participation and data collection. The recent opportunity to visit a number of the Indian investigator sites and see the trial conduct and activities first hand was an invaluable experience, and it was also very encouraging to note the overall enthusiasm for the Red Heart Pill from both investigators and patients.



We'd also like to wish everyone
A very Merry Christmas and
all the best for a
Happy, Prosperous and Successful New Year in 2012 !



FOLLOW-UP PHASE

The follow-up phase of the UMPIRE trial requires that all participants attend their follow-up visits as per the schedule and within visit windows, that trial visit data is captured in the eCRF in a timely manner, and that data queries are reviewed promptly and answered. In addition any SAEs and endpoints should be reported following the reporting timelines, trial MOPs and any local ethical and regulatory requirements. Remember that the essential data for the trial primary outcome is medication adherence (as captured on the patient medication page in the eCRF – Q9. How many days in the last week have you taken this medication?). These data will be supported by change in results between baseline and 12m and EOS for BP measurements and blood lipids. For polypill patients, we also need to ensure that dispensing and accountability documentation is properly maintained. This documentation includes prescription forms, accountability logs with dispensing and returns information, temperature logs and data capture in the eCRF on the POLYPILL pages.

Polypill patient contact and possible bias

It is also extremely important that the subject contact – site clinic visits, telephone calls – is equally maintained for both the polypill and usual care groups. We need to avoid any bias by way of extra medical attention that might favour one or other group.

End of Study (EOS) visits

The End of Study (EOS) visit schedules have now been created for every patient at each site to provide all research teams with a specific final trial visit date. These schedules should ensure completion of all visits within our follow-up phase timelines. These EOS visits will be scheduled to take place between MARCH – JULY 2012 and will be dependent on when a subject was randomized into the UMPIRE trial – the minimum follow-up will be 12 months (for those patients randomized in June and July 2011) and maximum follow-up will be 21 months. The important points to note about the EOS visits are;

- All visits will need to be completed by **31 JUL 2012**.
- Some scheduled 12M or 18M visits will be **replaced** by an EOS visit
- The EOS visit window is **+/- 14 days**
- The EOS visit is like a 12M visit but also includes **patient and doctor questionnaires**
- Minimum data required for EOS is **subject vital status**



Please make sure that for any patient that you have been unable to contact for a follow-up visit, every possible attempt is made to confirm their status for the EOS visit (unless withdrawn consent) and limit the number of lost to follow-up patients.

Data Capture and Cleaning

In preparation for the database lock next year (August 2012), the baseline visits are being cleaned and frozen by the monitors and reviewed by data management. To help the monitors with this, please can investigators and research teams ensure that any open queries are addressed and any missing visits are completed as soon as possible. All 1M visits should now have been conducted and by the end of December, all 6M visits should have been completed in India and in Europe, the 6M visits will be complete by end of January 2012. In March 2012, certain sites will start their EOS visits, so we need to have complete data on schedule to ensure that we can achieve our tight database lock timelines.

UMPIRE TIMELINES - EVENT	DATE	WORK PACKAGE Month
Official Start Date	1 st February 2010	0
Trial authorisations and approvals	April – May 2010	3-4
First Patient First Visit (FPFV)	July 2010	6
Last Patient First Visits (LPFV) - 2004 patients randomised	July 2011	18
Last Patient Last Visit (LPLV) end of Follow-up	July 2012	30
Database Lock	August 2012	31
Clinical Report	September 2012	32
Dissemination and Publication	Oct – Nov 2012	33-34
Final Report to European Commission	January 2013	36

Data Cleaning Priorities

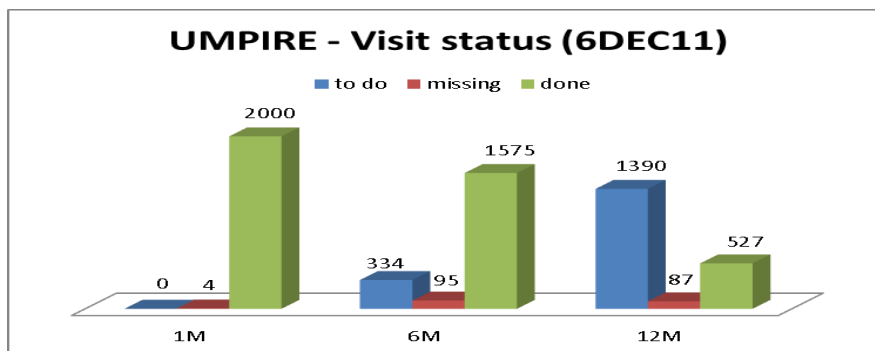
Over the last few months we have been focusing on the following data cleaning issues;

1. **Complete baseline data** – once all data are entered and clean (no queries), the Registration and Randomisation visits are being ‘frozen’ by the monitors so that any data collected and verified cannot be changed.
2. **Medication in eCRF** – Make sure the Patient Medication page is updated for any changes in ongoing medications e.g. stop dates, new lines if increased or reduced dose, adherence data are captured in Q9. reasons for medications being stopped are captured in Q10. The **adherence data** describe the number of days in the last 7 days that the patient took that medication i.e. if the trial visit takes place on a Tuesday, on which days in the last 7 days (Monday to previous Tuesday) was the medication taken. Adherence data only needs to be captured for those medications that are ongoing at the time of the trial visit e.g. if a treatment was stopped at randomization, adherence is not required for the follow-up visits. If a medication was started a month before month 6, adherence would be ‘0’ for RAND and 1M, and then captured for 6M going forward.
Trade name capture – we would also like to request that the **trade names** of all medications are added in brackets next to the generic names of the treatments, if not already captured on the Patient Medications page in the eCRF. This can be done when updating medication adherence data at follow-up visits and will enable a cost analysis to be performed on this data.
3. **Missing visits** – reports of visits which are not yet captured in the eCRF are circulated to the monitors every 2 weeks. Recently, the number of 6M and 12M visits has been increasing. Every investigator site should have



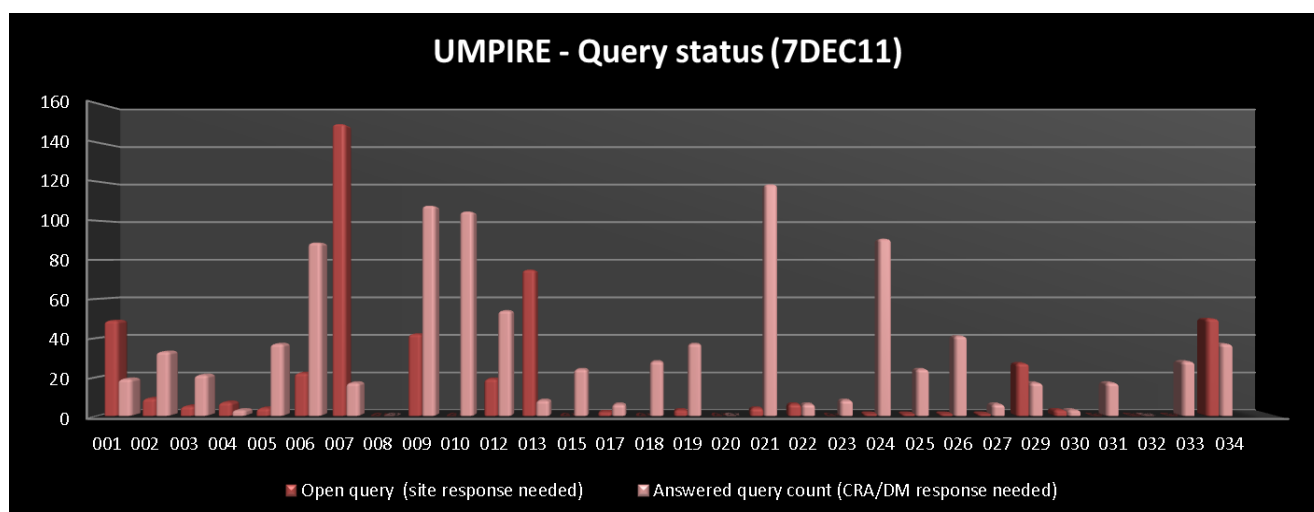
access to every randomised patient visit schedule, and each follow-up visit window is +/- 14 days so there should be few missing visits or reasons why patient have not attended.

There are still 4 patients with missing 1M visits in the eCRF – 006-1194 (expected 4APR11), 006-2011 (expected 29JUL11), 009-1548 (expected 30MAY11) and 034-1987 (expected 27JUL11). Please can these visits be entered with either “data obtained” or “Not Done” as the earliest opportunity.



4. **Open and answered data queries** – If any data need to be clarified, an automatic or manual query can be raised. The automatic queries result from unexpected data e.g. blood result out of range, visit outside scheduled window and the manual queries are raised by the monitors following source data verification (SDV) or by data management when reviewing medications or SAEs for coding. Please review and respond to these queries on a regular basis.

The total query status as of 7DEC11 showed 801 open queries, 956 answered queries, and over 30,000 closed queries ! Thank you and well done to Sites 008, 010, 015, 018, 020, 023, 031, 032 and 033 for currently having no open queries, and sites 002, 003, 004, 005, 017, 019, 021, 022, 024, 025, 026, 027 and 030 for having less than 1 page of open queries.



OTHER TRIAL UPDATES:

European Commission Periodic Report:

As the UMPIRE trial is funded by a Framework 7 Programme Grant, the UMPIRE Coordinating Office (UCO) was required to provide an interim (18 month) progress report to the European Commission in September. This described the activities of the 8 partner organisations involved in coordinating and managing the project; Imperial College London, Royal College of Surgeons Ireland, University Medical Centre Utrecht, The George Institute for Global Health – Australia and India, Public Health Foundation of India, Centre for Chronic Disease Control and Dr Reddy's Laboratories Ltd. The report summarised the trial progress and achievements so far, including documented evidence of meeting the deliverables and milestone targets and also provided financial summaries from each of the project partners on



how the project funding has been spent to date. We have recently received confirmation that this report has been accepted by our EC Project and Finance officers, which is a huge achievement and thank you to the partner teams for their support with this. It also means that the EC will now release the next payments to the partners and the ICL team will coordinate and distribute the funds shortly.

Safety reporting:

167 SAEs have now been reported, of which 29 events are from the Indian sites and 138 from the European sites and the endpoint count is 65 events, some of which still need supporting documents. The “Quick Reference Guide to UMPIRE Endpoints” which is included in the Site Safety and Endpoint MOP (V1, 11JUN10) details the supporting documents required for all endpoints and their adjudication. As a reminder, the categories of SAEs and endpoints are listed in the tables below.

Endpoints events are;

- All deaths
- Stroke and TIAs
- Subarachnoid Haemorrhage
- Myocardial Infarction
- Heart Failure leading to hospitalisation or death
- Hospitalisation for unstable angina
- Coronary Artery bypass graft and PCIs
- New symptomatic claudication
 - Amputation due to ischaemia
 - Peripheral Arterial Revascularisation
- Major bleeding events

SAEs are events that;

- Result in death
- Life-threatening
- Hospitalisation or prolongation of hospital admission
- Persistent or significant disability or incapacity
- Congenital abnormality or birth defect
- Medically important event e.g. malignancy

Trial Investigators - Please remember to ask patients at their follow-up visits about any hospitalisations or other medically important events that may have occurred, and report them to your coordinating centre **within 24 hours of notification**. This reporting should be done via both the eCRF and the paper SAE form (V3, 12OCT10). Any SAE follow-up information should also be provided within 24 hours of notification.

There was also a new endpoint document package cover sheet circulated (Version 3, 13OCT11) that allows endpoint reporting for both UMPIRE and Kanyini GAP trials as adjudication of events is performed by a joint trial Clinical Endpoint Adjudication Committee (CEAC), and this form should be used from now on to assist the endpoint coordinating process.

The next 6M line listing of SADRs and SUSARs (15JUN11 – 14DEC11) is expected in December from the Dr Reddy’s Pharmacovigilance team and this will be circulated to all investigators for their information and submission to ethics committees as per local requirements.

The last DSMB meeting was held for 22SEP11 and their recommendations were that they had no safety concerns and that the trial should continue. The next DSMB meeting is scheduled for March 2012. A copy of the DSMB letter has been circulated to all investigators for information and local EC submission.

RHP Supply:

A new batch of RHP 1c and RHP 2 c will be available in the New Year, but please inform your site monitor if you need further supplies. Please also ensure any RHP stocks with expiry FEB12 are removed from the current stock by the end of December and no longer dispensed to trial subjects.

Unfortunately, there will not be a marketing plan for the Red Heart Pill in either Europe or India by the time the EOS visits are conducted. This means all patients randomised to the polypill arm will need to be started on separate cardiovascular medications, which could be the doses of the individual components as in the Red Heart Pill or the prescription used prior to entry in the study. The prescription of suitable treatment will be the responsibility of the UMPIRE Newsletter No. 6 – DEC11



trial investigator or treating doctor (GP / cardiologist / physician). Following recent visits to a number of Indian investigator sites it is encouraging to report that the feedback from both investigators and patients with respect to the RHP was both very positive and enthusiastic. We await the results with interest. It is hoped that the UMPIRE results (if they favour a polypill CVD preventive strategy) will provide support regulatory approval of the Red Heart Pill.

Sub-Studies:

There are a number of on-going or planned sub-studies. The PESCA sub - study (Polypill Effects on Sub Clinical Atherosclerosis) is running in the European sites to assess whether the polypill reduces progression of atherosclerosis (carotid-IMT) and lowers central blood pressure.(Pulsecor); phase 1 data have been collected from 604 participants. A second sub-study (INPUT - Interpreting the Processes of the UMPIRE Trial) is a process evaluation involving qualitative interviews of a sample of health practitioners and trial participants at the end of the trial (summer 2012) in London and India. A health economic analysis (RUPEE – Researching the Use of the Polypill, an Economic Evaluation) will be conducted within the SPACE Trials, subject to additional funding.

The SPACE Collaboration

Links to UMPIRE information can be found at www.spacecollaboration.org. In addition, a slide presentation set prepared by Simon Thom (UMPIRE SUMMARY slide collection 9DEC11.pptx) with relevant information on UMPIRE and the polypill is available to UMPIRE investigators via the SPACE collaboration investigator website. The direct link to this site is <https://sharing.spacecollaboration.org/> the username and password for investigators to access the site is:

Username: pi Password: rhppi

Indian Site Visits – NOV 2011

Simon Thom and Jane Field would like to thank all of the Indian investigator sites and teams whom they visited between 21st November - 2nd December for their enthusiasm and interest in the trial, positive feedback and hospitality. The schedule was very busy and included 13 of the 27 Indian investigator sites. It was an ideal opportunity to see how each research site conducts the trial and completes protocol activities, and to meet with the monitoring teams from CCDC and TGI-India on-site to review monitoring progress. Some of the team photos are shown on the last page.

Please let us know if you have any comments and suggestions for items or feedback for future editions.

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Project Manager: Jane Field

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Site 024: KEM hospital, Pune



Site 026: Medwin Hospital, Hyderabad



Site 007: DMC and Hospital, Ludhiana



Site 018 Sree Chitra Tirunal IMST, Trivandrum



Site 009: Indira Gandhi Medical College, Shimla



Site 020: Global Hospital, Hyderabad



Site 025: Lalitha Super Specialities Hospital, Guntur



5th International UMPIRE Newsletter – AUGUST 2011



WELCOME to the 5th edition of the UMPIRE International Newsletter and the

fantastic news is that we've achieved our target !

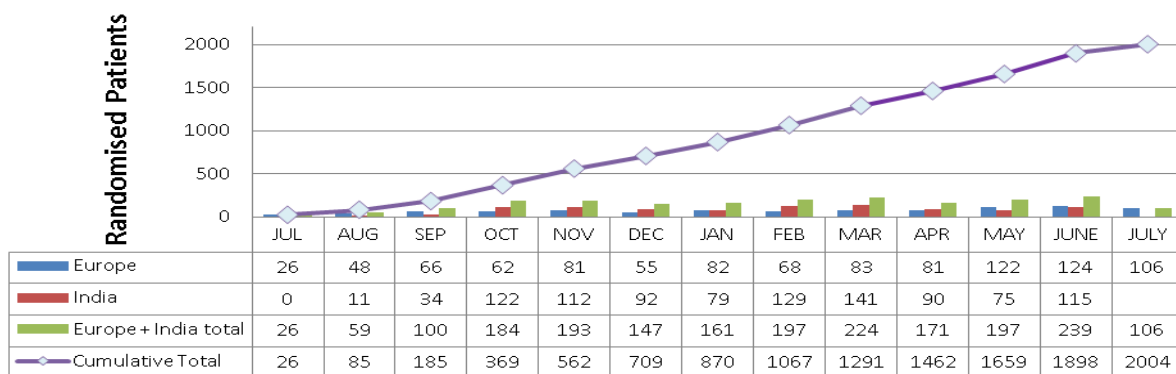
**2004 patients have been randomised
between 25JUN10 - 26JUL11 !!**

CONGRATULATIONS, WELL DONE AND THANK YOU ...

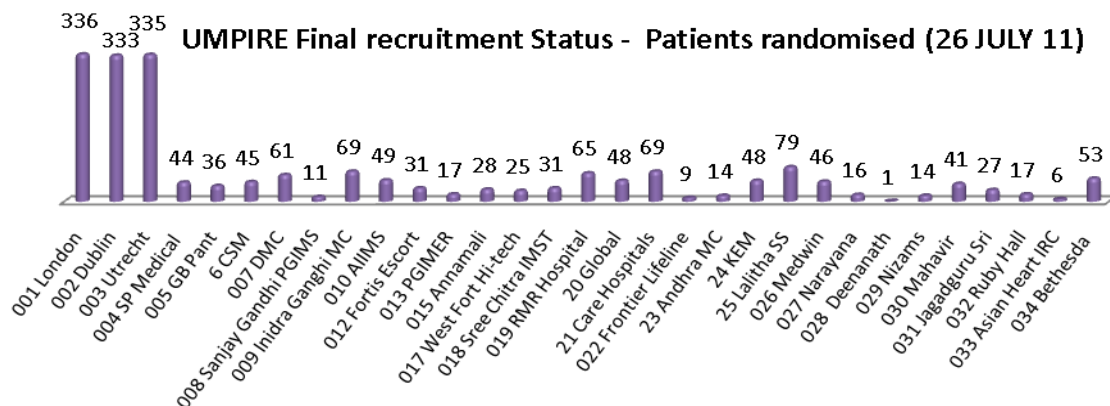


...to all participating investigator site teams (study investigators, research nurses, coordinators, administrators) for their timely and successful recruitment, and also to the coordinating centre staff, UMPIRE partners and other trial representatives who have all had roles in making this outstanding achievement possible. The final UMPIRE site participant totals are shown in the graph below, and the plot shows how successful this process was. The Indian investigators recruited their 1000 patient target by 30JUN11, which was an exceptional result considering that their first patient was randomised on 9AUG10. The George Institute India and Centre for Chronic Disease Control sites achieved their 500th patient on 29JUN11 and 30 JUN11 respectively. The Dublin team worked extremely hard to catch up by recruiting 51 and 52 patients in JUN11 and JUL11 respectively – this is an astounding effort and the highest monthly recruitment rates at any stage in the trial! Utrecht and London also did very well to consistently recruit and to meet and exceed their targets. The UMPIRE Coordinating Office and the Steering Committee recognise and appreciate the hard work, team efforts and commitment to the trial and we are delighted with this result !

**UMPIRE Monthly recruitment rates in Europe and India -
(JULY10 - JULY11)**



UMPIRE Final recruitment Status - Patients randomised (26 JULY 11)





FOLLOW-UP PHASE

There will now be 12 months further follow-up from the point of the 1000th patient randomised in each region (in India patient 2031 on 30JUN11, and in Europe patient 2142 on 26JUL11) and all **End of Study (EOS) visits** will need to be completed by **31 JUL 2012**. The monitor teams will soon provide each site with a specific EOS visit schedule for all of their patients to be followed, and it may mean that some 12M or 18M visits are actually EOS visits.

Investigators sites should continue to complete the 1M, 6M, and 12M follow-up visits as scheduled, ensuring that the adherence data is collected for all current medications at each visit and as verification of adherence data, collection of fasting blood results and BP measurements at the 12M and EOS visits for the trial primary outcome analysis.

The trial monitors are now in the process of verification and cleaning of data related to the Registration and Randomisation visits, so that these data can be identified as complete, clean and then frozen in preparation for the database lock next year (August 2012). Following the latest data review, the majority of visits are now complete and minimal data are missing. This is a great effort but there are still a number of open queries to be answered (identified by red traffic lights and red text with a pink background in the eCRF pages). The investigators and site teams should ensure that any missing data are provided and all open queries have been answered. There should also have been a review of Patient Medications to ensure that adherence data are captured for all visits, start and stop dates are recorded for any medications changes, and any combination BP medications have been split – please refer to the Medications Guidance (V1, 21FEB11) document circulated. The deadline for ensuring these visits are complete is 01 SEP 11. Please discuss this with your monitor if you foresee any problems with this timeline.

A summary table of the UMPIRE trial timelines of shown below.

UMPIRE TIMELINES EVENT	DATE	WORK PACKAGE Month
Official Start Date	1 st February 2010	0
Trial authorisations and approvals	April – May 2010	3-4
First Patient First Visit (FPFV)	July 2010	6
Last Patient First Visits (LPFV) - 2000 patients randomised	July 2011	18
Last Patient Last Visit (LPLV) end of Follow-up	July 2012	30
Database Lock	August 2012	31
Clinical Report	September 2012	32
Dissemination and Publication	October – November 2012	33-34
Final Report to European Commission	January 2013	36

OTHER TRIAL UPDATES:

European Commission Periodic Report:

As the UMPIRE trial is funded by a Framework 7 Programme grant, the UMPIRE Coordinating Office (UCO) need to provide a progress report to the European Commission. The project has 2 reporting periods - 18 months and 36 months. The UCO will be making the 18 month periodic report submission to the European Commission by the end of September, as required in the Agreements and to ensure further trial funding is provided. This report will summarise the project's progress and achievements so far, including deliverables and milestone targets, and provide financial summaries from each of the project partners.



Safety reporting:

80 SAEs have now been reported, of which 12 are from the Indian sites and 68 from the European sites and the endpoint count is 32 events. The “Quick Reference Guide to UMPIRE Endpoints” which is included in the Site Safety and Endpoint MOP (V1, 11JUN10) details the supporting documents required for all endpoints and their adjudication. The next 6M line listing of SADRs and SUSARs (15DEC10 – 14JUN11) has been circulated to all investigators for their information and submission to ethics committees as per local requirements.

Trial Investigators - Please remember to ask patients at their follow-up visits about any hospitalizations or other medically important events that may have occurred, and report them to your coordinating centre within 24 hours of notification. This reporting should be done via both the eCRF and the paper SAE form (V3, 12OCT10). Any SAE follow-up information should also be provided within 24 hours of notification.

The Investigator’s Brochures for RHP 1c and RHP 2c have recently been updated to include the expected adverse drug reactions as listed in the Summary of Product Characteristics, and have been circulated to investigators with IB receipts. Please ensure the site investigators have received and reviewed this document, and that it has been submitted to local ethics committees.

The next DSMB meeting is planned for 22SEP11 and their recommendations will be circulated subsequently.

RHP Supply:

A new batch of RHP 1c is being manufacture specifically for UMPIRE. This should be available at the end of August for distribution to the investigator sites as needed.

This is the preferred RHP version in India (73% 1c vs. 27% 2c) while in Europe the prescribing is more even (44% 1c vs. 56% 2c) but with variations between the 3 European sites (London:-52% 1c vs. 48% 2c; Dublin: 21% 1c vs. 79% 2c; Utrecht: 60% 1c vs. 40% 2c). Further RHP batch production will be planned in the next 5 months to ensure there is sufficient stock to supply all current polypill trials.

Clinical Trial Registries:

The clinicaltrials.gov website (NCT01057537) has been updated to confirm that UMPIRE recruitment is completed, and the same information will be updated on the Indian Clinical Trials Registry (CTRI/2010/091/000250).

Sub-Studies:

There are a number of sub-studies ongoing or planned for the UMPIRE trial. The PESCA sub - study (Polypill Effects on Sub Clinical Atherosclerosis) is being conducted in the European sites to assess whether the polypill reduces progression of atherosclerosis as compared to usual cardiovascular medications in high risk patients, and will be assessed by measuring carotid intima-media thickness (IMT) and central blood pressure using the PulseCor device. A second sub-study (INPUT) is a process evaluation involving qualitative interviews of a sample of health practitioners and trial participants at the end of the trial (summer 2012) in London and India. A health economic analysis will be conducted, subject to additional funding.

The SPACE Collaboration

As mentioned n the last International Newsletter, the SPACE collaboration website has had an overhaul with a new designs and links to UMPIRE information, and can be found at www.spacecollaboration.org. The investigator website is also being updated and will provide a central location for all teams to find UMPIRE trial information and trial documents – information about access and accounts will be circulated soon.

Dr Ruth Webster is coordinating and reviewing the progress of all current polypill trials, and leads regular contacts between the team project managers and Chief Investigators.

The Brazil team is in the process of obtaining approvals with regulatory approval expected in the next 2 weeks, liaising with Dr Reddy’s regarding RHP supplies and developing their eCRF. The Trial is expected to start patient recruitment in Brazil in October 2011.



Kanyini GAP trial (Australia) – led by Prof Anushka Patel - has enrolled 514 patients and randomised 431 patients recruitment is until December 2011. More GP sites are being initiated and their RHP dispensing distribution is 40% RHP 1c and 60% RHP 2c. The trial has had 134 SAEs and 37 endpoints reported. Their focus is still on recruitment, making trial database changes, and raising additional funding to complete the study.

IMPACT trial (New Zealand) – led by Prof Raina Elley (now replaced by Prof Chris Bullen) – has current recruitment status of 372 randomised patients split between 230 non-Maori and 142 Maori patients, and their recruitment period will also finish in December 2011. They have 50:50 RHP dispensing and have reported 21 SAEs and 6 endpoints.

Goodbye & Welcome !

We would like to welcome **Ann Collins and Mags McGrath**, who joined the Dublin research team back in April and welcome to any new members at the Indian sites – good luck in your new UMPIRE role! We'd also like to congratulate Dominic Byrne (Clinical Data Management, TGI AUS) on his recent marriage and we wish the couple much love and happiness in the future.

Please let us know if you have any comments and suggestions for items or feedback for future editions.

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n.poulter@imperial.ac.uk

Project Manager: Jane Field

j.field@imperial.ac.uk





Safety reporting:

45 SAEs have now been reported and the endpoint count is 15 events, 10 of which have been adjudicated by the Clinical Endpoint Adjudication Committee. The next 6M line listing of SADR and SUSARs will be provided mid June. Of the 45 SAEs, 24 of these have occurred amongst polypill group patients and 5 of these were reported as having a relationship with the polypill (2 unexpected, 3 expected).

This also means that our second SUSAR has been reported in UMPIRE for 002-0253, (renal impairment, increased plasma creatinine) on 21APR11 and thought to be possibly related to the RHP 2c components Lisinopril and Hydrochlorothiazide. The clinical picture was compounded by recent left leg cellulitis, infection and dehydration, and although renal dysfunction is reported as an adverse drug reaction in the Summary of Product Characteristics (SmPC), it is not listed in the UMPIRE IB and is therefore 'unexpected'. Documentation related to this event has been submitted to the Irish regulatory and Ethics committee, and CIOMS and Investigator Notification letters have been circulated from the UMPIRE Coordinating Office to inform all investigators of the event and to submit to their local ethics committees.

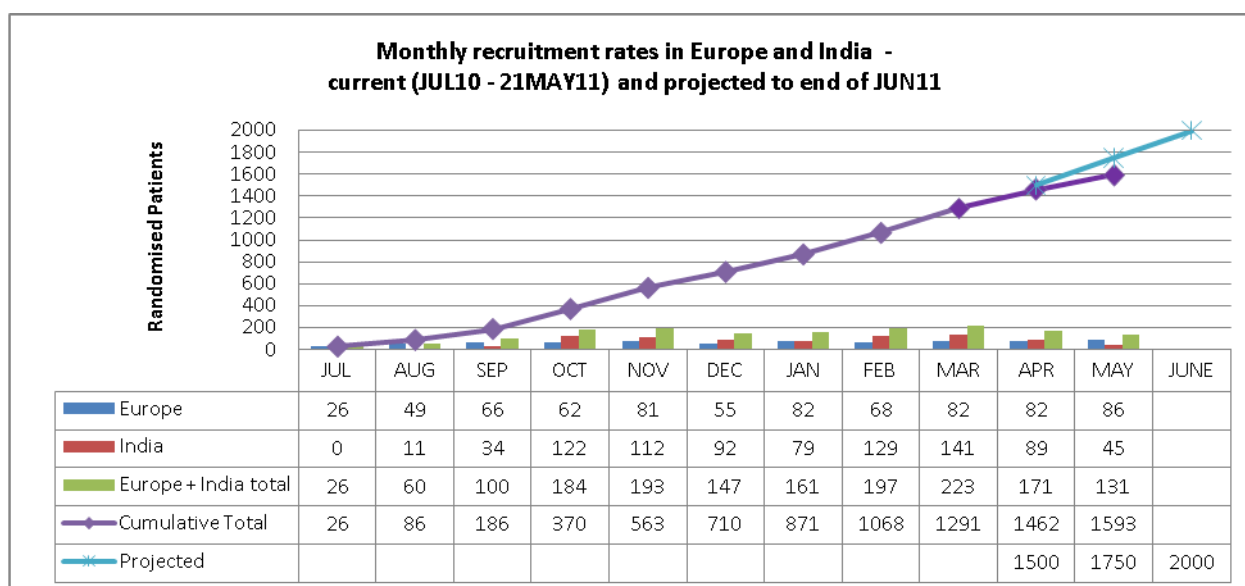


!! SUSAR ALERT !!

RHP supply is coordinated on a regular basis for the Indian investigator sites, and a shipment is expected to the European sites at the end of May. Monitoring and tracking of RHP dispensing, stock requirements and shipment requests comprise a busy process for all involved, and our thanks go to Haranath Robby for coordinating this trial activity, as well as overseeing new batch manufacture, packaging and analysis. Within the trial, the dispensing rate of the RHP versions seems to vary between countries, with India showing a preference for RHP 1c, Ireland for RHP 2c, and London and Utrecht almost 50:50. The results from the data captured on the INVCHOICE eCRF page indicate that for all randomised patients, there would be a 60:40 dispensing ratio for RHP 1c : RHP 2c, which may be valuable data for Dr Reddy's future marketing plans.

RECRUITMENT FOCUS:

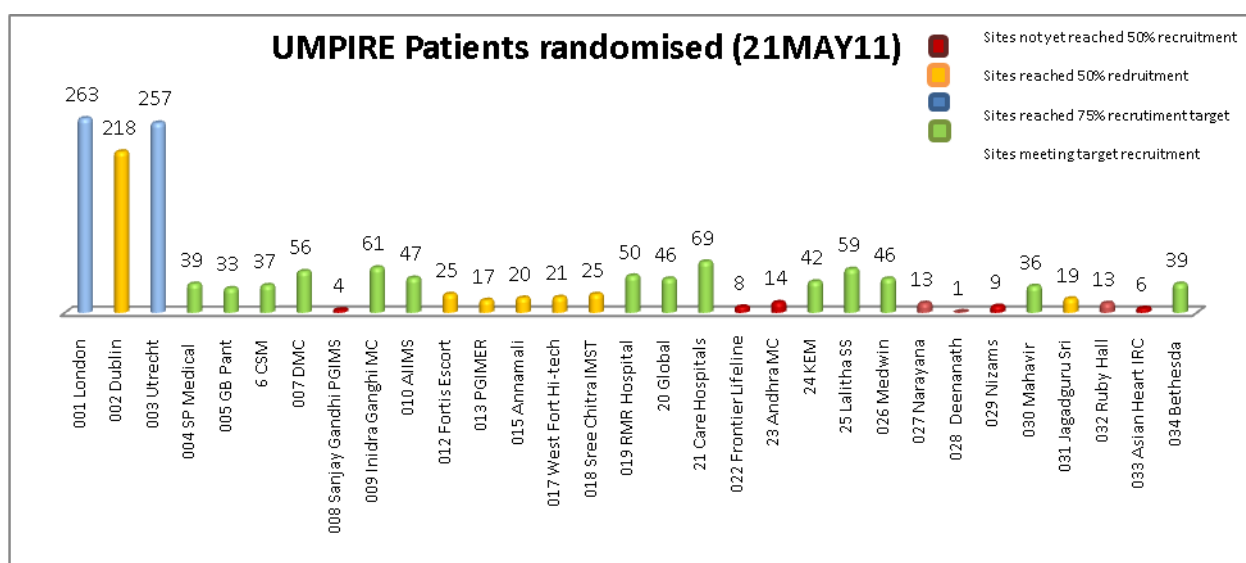
As of 24MAY11, 1726 patients have been registered and 1608 patients have been randomised. All 3 European sites have achieved 60 - 80% of their target of 333 patients, and all have randomised over 200 patients. The randomised patient split is 860 in India and 748 in Europe.





Recruitment should be bolstered in Dublin following very successful advertisements by Prof Stanton on local television and radio stations, so that the team has been inundated with willing volunteers with established CVD. The London and Utrecht teams are competing to see who stays in 'pole' position with only a few patients between them! As mentioned earlier, half of the Indian investigators have done extremely well to meet and exceed their target of 30 patients per site (see recruitment graph below), and 6 sites have achieved >50% of their target. The Indian Coordinating centres will now be looking at timelines for "last patient first visit (LPFV)" and notifying all sites to stop recruiting when the Indian total reaches 1000 randomised patients, which we expect to happen in early June.

Current recruitment status for active sites :



FOCUS ON EUROPE:

The three European research centres have significant experience with clinical trials, and have worked in collaboration with Profs Thom and Poulter on a number of projects, including ASCOT, ADVANCE, ADVANCE-ON, PREMIUM, PILL-pilot. The progress made so far would not have been possible without the support of these dedicated teams, and photos of some members of the investigator teams are below.



Site 001 - The London Team

From left to right : Prof Simon Thom (Project Coordinator and CI), Jill Bunker (Research Manager), Becky James (Research Nurse - RN), Hannah Lanzon-Miller (RN), Natesha Henry-Mitchell (CTA), Dr Filomena Paciello (PI), Candy Coghlan (RN), Wendy Callister (RN), Dr Judy MacKay (Study Physician)



Site 002 – Beaumont Hospital Dublin

Left : left to right - Dr Liam Kavanagh (Study Physician), Barbara Gallagher (CTA), Prof Alice Stanton (PI), Kathleen Shortall (RN).
Below : left to right – Mags McGrath (RN), Ann Collins (RN), Dr Ursula Quinn (Study Physician)



**Site 003 – The Julius Centre Team,
University Medical Centre Utrecht**

Left to right: Lydeke Zwart (Research Nurse), Gerry van Hemert (Research Nurse), Dr Melvin Lafaber (Study Physician), Lizeth Vendrig (Head Research Clinic), Aisha Anjum (European CRA)



eCRF UPDATE :

The monitoring teams continue to review data and queries in the eCRF data and particular points to note are highlighted below;

- **ADHERENCE** – please remember to record in the eCRF on the Patient Medications page (Q9.) the **number of days** prior to the trial visit the patient has taken each ongoing medication (minimum 0, maximum 7) for the 1M and 6M follow-up visits, as these data are essential for the primary outcome of self reported adherence to indicated therapies.
- **PATIENT MEDICATIONS** – please record all medications using the **GENERIC** name of the medication (**not** the trade name) and **combination BP medications** need to be split into singles line for the individual components
- **BP MEASUREMENT** - Remember to adhere to the BP measurement guidelines in the protocol (Appendix 4), in that the 3 BP measurements should be taken after 5 minutes rest and each reading should be 1-2 minutes apart. Remember to use the same arm and cuff for each trial visit where BP is measured e.g. RAND, 12M, EOS, and document this in the notes. This is to ensure consistency of BP measurements between all investigator sites.
- **1M and 6M visits** – Please refer to the individual visit SCHEDULE in the eCRF for when patient follow-up visits are due, as a number of 1M and 6M visits should be been completed but are not captured in the eCRF.
- **SAE sign off** – Remember to ask investigators to sign off the SAE forms once the event is resolved and the data complete in the eCRF using 'Signatures'
- **DATA QUERIES** - Remember that open queries should be resolved within 14 days, so check the eCRF regularly for red traffic lights !
- **DATA ENTRY TIMELINES** - Please ensure data are entered in the eCRF within 5 days of the trial visit.



POLYPILL COLLABORATION

The SPACE collaboration website has had an overhaul with a new front page design and links to UMPIRE information, and can be found at www.spacecollaboration.org There is also the investigator website – <https://studies.thegeorgeinstitute.org/redheart/> where you can find useful links to the UMPIRE trial information and trial documents – please ask your monitor if you’ve forgotten the access information. Dr Ruth Webster is coordinating and reviewing the progress of all current polypill trials, and leads regular contacts between the team project managers.

The Brazil team, as mentioned in the last International newsletter, are in the process of obtaining approvals, liaising with Dr Reddy’s regarding RHP supplies and developing their CRF, and are expecting to start patient recruitment in October 2011.

Kanyini GAP trial (Australia) – led by Prof Anushka Patel - has enrolled 483 patients and randomised 408 patients since starting recruitment in December 2009. They currently have 24 GP practices and are planning to recruit more sites to improve recruitment rates to meet their target of 1000 patients by September 2011.

IMPACT trial (New Zealand) – led by Prof Raina Elley – has current recruitment status of 558 patient registered and 280 patients randomised in 105 GP sites, and they plan to recruit their patient target of 600 randomised by the end of 2011.

PUBLICATIONS

We are delighted to circulate the published paper from PILL Pilot, and a copy of the official press release. Please note that there is a strict embargo until 2pm Pacific Standard Time, 10pm British Standard time (Weds 25 MAY), 7am AEST and 9am NZST (Thurs 26 MAY).

Angela Wadham and Anthony Rodgers have provided the following statement:

There will be a number of media items about these results, and you may well receive questions from patients in your trial. It is worth noting in this regard that The PILL study addressed a different question in a different patient group: PILL assessed likely benefits and side effects compared to no treatment – in contrast, the ongoing IMPACT, Kanyini/GAP and UMPIRE trials are assessing the value of polypill-based vs usual care. The relevance of the results generated is particularly topical, given the resurgence of interest in aspirin following The Lancet papers on cancer reduction, the fact that this the first trial to reliably assess side effects, and the first on a polypill that can be made available internationally, and affordably. Undoubtedly PILL further strengthens the rationale for our ongoing trials, and as such we hope it helps with recruitment. The initiative has also been a testament to the power of collaboration – congratulations all.

Well done and Congratulations to all involved!

Goodbye & Welcome !

We would like to say thank you and farewell to **Neha Khanna**, the CRA from CCDC and we wish her every success in the future. We would also like to welcome **Sanjay Singh**, who will be replacing Neha within the CCDC team – good luck in your new UMPIRE role!

Please let us know if you have any comments, suggestions for items or feedback for future editions.

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Project Manager: Jane Field

j.field@imperial.ac.uk



3rd International UMPIRE Newsletter – FEBRUARY 2011

Welcome to the 3rd edition of the UMPIRE international newsletter. This coincides with the February anniversary of the official project start date.

The big news is that we reached **1000 patients randomised !!** on 17 FEB 11.

Congratulations!! to site 027 (Narayana Hrudayala in Bangalore) and their patient 1085, and also to all participating investigator sites for making this happen and for achieving this important milestone!



We've had a very busy year with successful progress towards trial targets:

- 27 investigator sites are now active in India and 3 in Europe. Initiation of the trial sites has involved major efforts by the coordinating teams, by Dr Reddy's in the manufacture and distribution of the RHP, and by the investigator site teams in recruiting participants and performing the trial visits.
- Involvement of the 3 trial committees: Clinical Endpoint Adjudication Committee, Data Safety Monitoring Board and Expert Advisory Board.
- Significant data review by the monitoring and data management teams.
- Work Package milestones achieved: 25% total randomised patients by November 2010 and 50% total randomised patients by February 2011 - a great effort !!

We would like to extend our thanks to everyone involved – researchers, patients & supporters - for making UMPIRE work and keeping it on target.

WHERE WE ARE NOW:

At 13 months into the project schedule and with 7 recruitment months behind us, we are progressing well and we expect to achieve the target of 1000 patients randomised in both Europe and India (2000 patients in total) by the end of June 2011. There are still only a few SAEs and endpoints reported. The DSMB reviewed the trial data captured so far on 27JAN11 (registration, randomisation and 1M data). There are no concerns about patient safety and the Chair, Professor Jane Armitage, has written to the Steering Committee confirming continuation of the trial. All investigator sites should have received the UMPIRE Office covering letter with Professor Armitage's letter dated 27JAN11 attached. Receipt needs to be acknowledged and a copy submitted to local ethics committees. A 6 monthly line listing (15JUN10 – 14DEC10) for all SADR and SUSARs reported in UMPIRE was circulated in January for investigator information and IEC submission. Annual safety and progress reports will need to be submitted shortly to the relevant ethics committees and regulatory authorities.



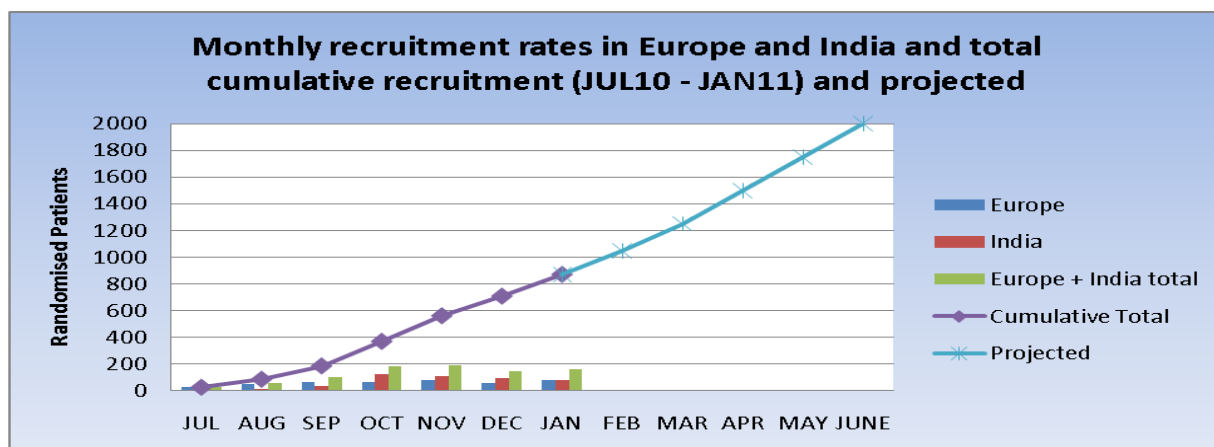
Severe winter weather, heavy snow and the Christmas break all conspired to drop the recruitment rate at the European sites - there were days when neither staff nor patients could get to their research sites. During a December RHP shipment to the European sites, the data loggers that are enclosed with the shipments picked up below freezing temperatures, which the Dr Reddy's team had to confirm was acceptable! New Delhi experienced surprisingly cold temperatures for December and January (and the CCDC team had to wear jumpers!) and it even snowed in Shimla, which was not expected at this time of year. Following the temporary downturn, recruitment picked up quickly in the New Year.



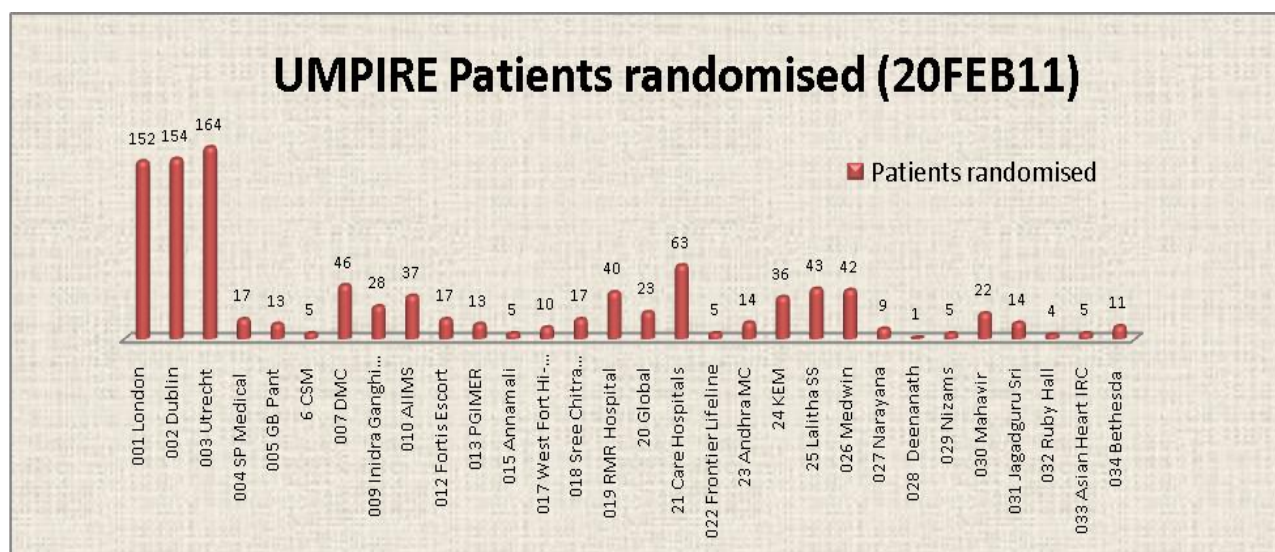


RECRUITMENT FOCUS:

As of 20FEB11, 1098 patients have been registered and 1015 patients have been randomised. All 3 European sites still have 50-60% of their participants to randomise to meet their targets of 333 patients each. They have continued to recruit steadily during the last 7 months and January was one of the best months for London and Dublin, with 31 and 30 patients randomised respectively. Utrecht continue to stay just ahead of the other 2 European sites, currently with 164 randomised patients as of 20FEB11. Dublin and London are close behind with 154 and 152 randomised patients respectively. Seven of the Indian sites have met or exceeded their targets of 30 randomised patients [007 DMC & Hospital, 010 AIIMS, 019 RMR Hospital, 021 Care Hospital, 024 KEM Hospital, 025 LSS Hospitals, 026 Medwin Hospital], and six Indian sites are over half way there [004, 009, 012, 018, 020, 030] but there are still a number who need to get up to speed. Concurrently the CCDC coordinating centre in New Delhi has had to drop 3 of their collaborating sites (due to delayed approval processes), so the 12 active sites will need to recruit an extra 90 patients between them. We must all keep working hard on recruitment over the next few months, needing 250 randomised patients a month in March, April, May and June to meet the 2000 patient target.



Current recruitment status for active sites :





FOCUS ON INDIA:

The progress in India wouldn't have happened without the management, dedication and support of the teams at the two UMPIRE coordinating centres in New Delhi (Centre for Chronic Disease Control) and Hyderabad (The George Institute for Global Health – India). Below are photos of the respective teams who will be familiar to many of you.

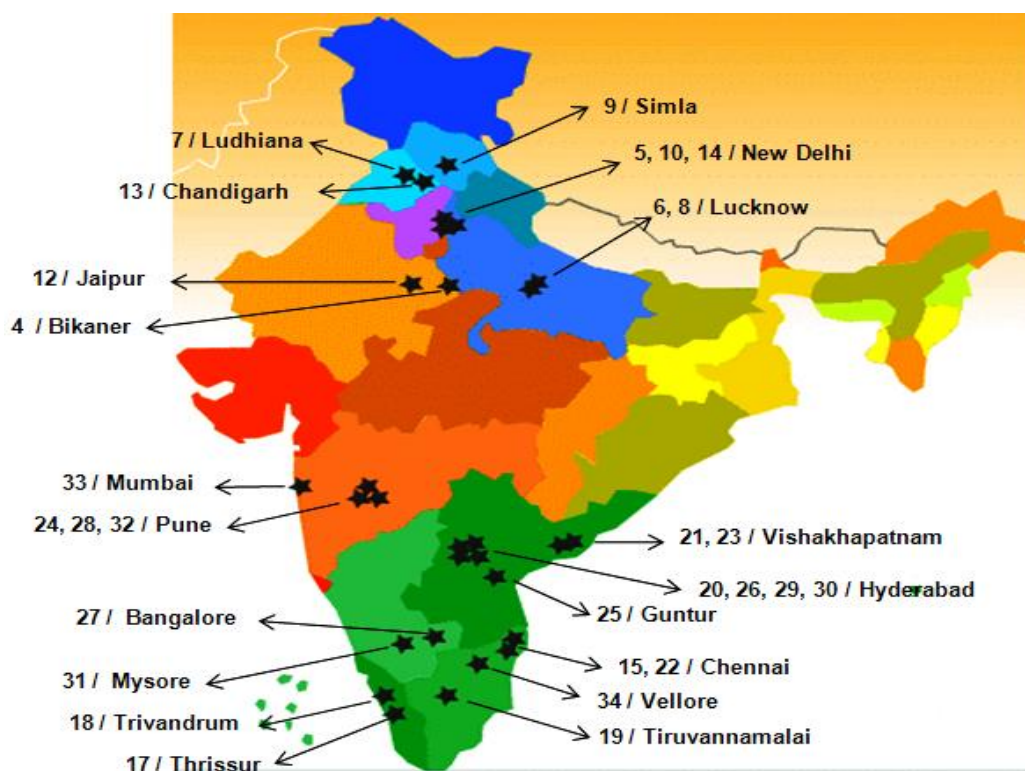


CCDC – Neha Khanna (CRA), Dr Roopa (Medical Advisor), Kavita Singh (PM)



The George Institute India – Sudha Kallakuri (CRA), G Sarath Punna Rao (Manual Randomisation Officer), Nitin Pathak (CTA), Abdul Salam (Lead CRA), Dr Rama Guggilla (Medical Advisor), Dr Vinod Patil (Head of Clinical Research)

However, the achievements made so far with patient recruitment would also not have been possible without the commitment and research activities of the Investigator sites. Photos of the investigator teams at some of the high recruiting Indian sites are below.



Thanks to Abdul Salam for this brilliant map of the Indian site locations !



Site 021 – Department of Cardiology, Care Hospital, Vishakhapatnam; PI – Dr M Baskhara Rao
56 patients randomised in 3 months (SEP – NOV10)
– 35 patients in October, total now 63 randomised patients



Site 025 – Department of Cardiology, Lalitha Super Specialities Hospital, Guntur; PI Dr P V Raghva Sarma
40 patients randomised between AUG-DEC10



Site 026 – Medwin Hospital, Hyderabad, PI - Dr B R Babu
42 patients randomised between OCT10 and FEB11



Site 010 – AIIMS, New Delhi, PI - Dr Ambuj Roy
37 patients randomised between AUG10 and FEB11



Site 007 – Department of Cardiology, Dayanand Medical College and Hospital
PI - Dr Bishav Mohan, 46 patients randomised between AUG10 and FEB11



Recent publications of interest are detailed below:

- **Capitalizing on the Demographic Transition: Tackling Non communicable Diseases in South Asia**
The World Bank rates heart diseases as the leading cause of death in adults aged 15-69, & South Asians suffer their first heart attack six years earlier than other groups worldwide. By 2030, cardiovascular diseases would emerge as the main cause of death (36 per cent) in India.
<http://blogs.worldbank.org/endpovertyinsouthasia/node/665>
- **Indian J Med Res 132, November 2010, pp 475-652 – Special Edition Cardiovascular Research**
- **A Polypill for primary prevention of cardiovascular disease: A feasibility study of the World Health Organization** Soliman et al. Trials 2011, 12:3; <http://www.trialsjournal.com/content/12/1/3C>
- **Drug and Therapeutics Bulletin – Polypill is a triumph of Hype over Experience**
<http://www.medicalnewstoday.com/articles/215945.php>
- **Chronic diseases and injuries in India.** Patel V, Chatterji S, Chisholm D, Ebrahim S, Gopalakrishna G, Mathers C, Mohan V, Prabhakaran D, Ravindran RD, Reddy KS Lancet 2011 (Jan 29th); 377: 413 - 428
(and ensuing Lancet series of articles)
- **Implementation of a simple age-based strategy in the prevention of cardiovascular disease: the Polypill approach.** David S. Wald MD FRCP1 and Nicholas J. Wald FRS FRCP2. Journal of Evaluation in Clinical Practice ISSN 1365-2753

DR REDDY'S UPDATE:



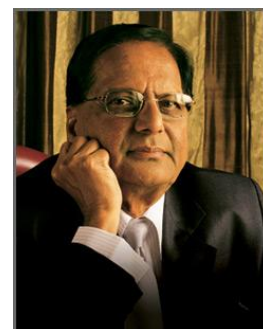
The Dr Reddy's team have been busy manufacturing more batches of the Red Heart Pill for the ongoing polypill trials, and we keep a careful eye on UMPIRE recruitment rates to ensure that current investigator site stocks of RHP are sufficient and resupplies are available.



Haranath Robby, from Dr Reddy's Laboratories India is a key contact for the Project Managers, and has played an essential role in the manufacturing, shipping and resupplies organisation and management. The entire Dr Reddy's team is strongly committed to all the RHP trials; this includes the Drug Development team, the Pharmacovigilance team, the QA teams, and the drug manufacturing teams busy making our capsules.

Dr Anji Reddy, Founder Chairman was recently awarded the Padma Bhushan - the third highest civilian award in India and a very notable honour. His acceptance statement on the Dr Reddy's website reads:

"I am honoured to receive this prestigious award. 10 years back I was awarded the Padma Shri for my contributions in providing affordable medicines to the people of India. Today this concept is so deeply entrenched in the pharma industry that it is not possible to resort to "Profiteering" at the expense of affordability. In the next decade, I will dedicate myself to providing and expanding this base to the poorest of the poor and also spread this to the nook and corner of the country – be it a hamlet, a village or a town. This recognition is a testimony of not only my personal efforts, but also of the thousands of Dr. Reddy's employees, both past and present, who have made a significant contribution to fulfilling a very important societal need".



eCRF UPDATE :

The monitoring teams have reviewed significant source and eCRF data in recent site visits, and there are a few items that we wish to highlight with the staff:



- **ADHERENCE** – please remember to record in the eCRF on the Patient Medications page (Q9.) the number of days prior to the trial visit the patient has taken each ongoing medication (minimum 0, maximum 7) as these data are essential for the primary outcome of self reported adherence to indicated therapies.
- **PATIENT MEDICATIONS** – please record all medications (excluding the RHP 1c or 2c) on the patient medications page using the **GENERIC** name of the medication (**not** the trade name)
- **POLYPILL** – If the patient is randomised to the polypill group, remember to capture the polypill and version on the Patient Medication page, and also the details regarding dispensing in the POLYPILL page – this assists to assess and monitor the RHP requirements for each sites
- **BP MEASUREMENT** - Remember to adhere to the BP measurement guidelines in the protocol (Appendix 4), in that the 3 BP measurements should be taken after 5 minutes rest and each reading should be 1-2 minutes apart. Remember to use the same arm and cuff for each trial visit where BP is measured e.g. RAND, 12M, EOS, and document this in the notes. This is to ensure consistency of BP measurements between all investigator sites.
- **SEX & PREG** - Remember to ensure that the SEX of the patient is completed on the demography page, and if female, the dynamic polypill PREG page is completed prior to randomisation
- **CMAE OPEN QUERIES** - Remember that most of open queries on the CMAE pages “Please ignore and do not answer ...” are for Data Management only – please do not answer these queries.
- **DATA ENTRY TIMELINES** - Please ensure data are entered in the eCRF within 5 days of the trial visit taking place.

SAE REPORTING :

There have been 14 SAEs reported so far in UMPIRE, 11 from the European sites and 3 from the Indian sites. Please don't forget to ask your trial patients if they have had any SAEs at follow-up visits, and report these in the eCRF and also on the paper SAE form (V3, dated 12OCT10). Remember that the protocol (V2, dated 21APR10) details SAE reporting in section 6 – Safety Reporting, and that there is also a reference to events which don't meet the SAE criteria;

A hospitalisation is to be considered an SAE only if it is an official admission (> 24hrs), and any elective hospital admissions planned, due to a pre-existing condition present prior to registration into the trial that has not worsened, does not constitute an SAE; e.g. elective hospitalisation for total knee replacement due to osteoarthritis of knee, that has not worsened during the trial.

Protocol section 6A SAEs (page 30)

If you are unsure if an event is an SAE, please complete the following checks;

1. Review the protocol
2. Review the Site Safety and Endpoint MOP (Version 1, dated 11JUN10) where on page 4 there is a table of events the considered SAEs
3. Discuss with your monitor
4. If still in doubt, report the event within 24 hours of notification

POLYPILL COLLABORATION

Dr Ruth Webster, based at the George Institute for Global Health – Australia, is currently on maternity leave after giving birth to baby daughter Emily Rose on 11 January (Congratulations Ruth from the UMPIRE teams!), but she will be 'back on the case' part time from March and will continue to develop the SPACE collaboration website, and oversee the liaison between the teams of international collaborators currently conducting or planning to start a RHP polypill trial.



Kanyini GAP trial (Australia) – led by Prof Anushka Patel - has enrolled 415 patients, with 343 patients randomised via 24 GP practices, and their current aim is to improve recruitment rates through more GP sites to meet their target of 1000 patients.

IMPACT trial (New Zealand) – led by Prof Raina Elley – has current recruitment status of 184 patients randomised in 73 sites, and their patient target is 600 randomised over 18 months i.e. by the end of 2011. The IMPACT team is currently working on increasing the number of participating GP practices and consequently their recruitment rate.

Brazil Update:

There is great news for Brazil - Dr Otavio Berwanger, who was involved in the PILL pilot trial, recently announced support for a cardiovascular polypill trial in Brazil. Otavio is part of the SPACE Collaboration and the trial will mirror the ongoing UMPIRE, KANYINI-GAP and IMPACT trials. Funding will be provided by the Ministry of Health within the Brazilian government, and they are very supportive of the efforts to establish a secondary prevention polypill trial in Brazil. The Trial will include 2000 participants and should start later this year, again with Dr Reddy's supporting the trial by providing the Red Heart Pill.



Management team (Left to right) : Otavio Berwanger, Anna Buehler, Ana Denise Zazula, Alexandre Biasi

PUBLICATIONS

- The PILL pilot results paper is under review with PLoS One.
- A paper entitled 'Where we are now with the polypill?' has been submitted to the BMJ, written and co-authored by representatives from the UMPIRE partner teams.
- An UMPIRE trial design paper is in draft.

HELLO & GOODBYE

With such a large international study, there will always be staff changes and we'd like to take this opportunity to welcome some new team members, and also say thank you, goodbye and good luck to those who are moving on:

Welcome to Aisha Anjum, who will be the new European CRA based at the UMPIRE Coordinating Office, London; Narvada Jugnee – Research Nurse (London 001)

Farewell to Lucy Gilmour – Research Nurse (London 001) and Benita Maguire, Kevin Barrett – Research Nurses (Dublin 002). Good Luck to Jo Dobson - ICCH Statistician who will go on maternity leave in March !

Please let us know if you have any comments, suggestions for items or feedback for future editions.

UMPIRE COORDINATING OFFICE (UCO):

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2nd International UMPIRE Newsletter – NOVEMBER 2010

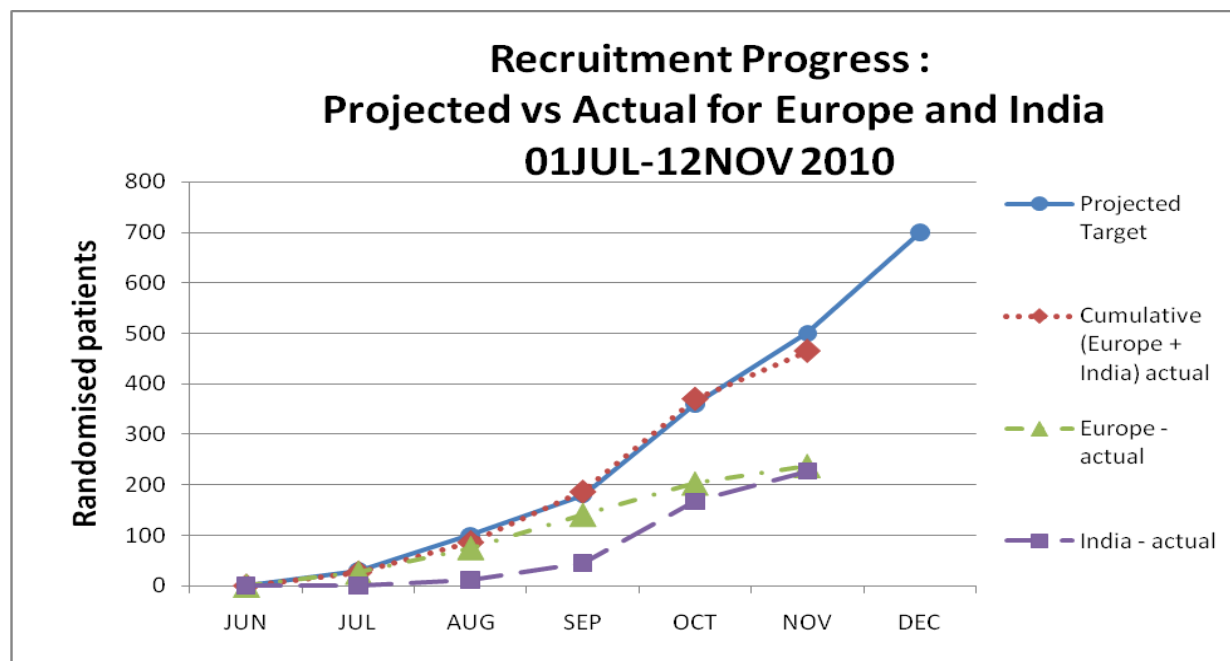
Welcome to the next edition of the UMPIRE international newsletter. We are meeting the milestones and this achievement reflects everyone's continued support and effort on the trial. Thanks to all involved.

WHERE WE ARE NOW:

We are now 10 months into the trial, with 5 months of active recruitment and things are progressing well. Dr Reddy's has manufactured the next batch of RHP (expiry June 2012) for UMPIRE. Supplies are also available for the other active polypills trials (Kanyini GAP and IMPACT) and forthcoming new projects. The amendment to the European Commission documents for inclusion of the Centre for Chronic Disease Control (CCDC) is in progress. This should be completed before Christmas. The trials committees have all had their first meetings, future meetings are scheduled, and the statistical analysis plan will be finalised shortly. A number of SAEs and endpoints have been reported; these are summarised below, but no surprises have emerged in relation to the Red Heart Pill. The trial site monitoring is in progress and the monitors are reporting good data quality and adherence to the protocol.

RECRUITMENT FOCUS:

Our current focus is patient recruitment and having now had 5 months, we have started the 'climb up the mountain' towards the goal of 2000 randomised participants. All 3 European sites – London 001, Dublin 002 and Utrecht 003 – have started well and continued to randomise patients on a steady basis. In India, the first sites started recruiting in August, and there are now 15 active sites. As of 12NOV10, there are 520 registered patients, and total randomised patients per region are 238 in Europe and 227 in India giving us a total of 465 randomised patients (23% of target). The figure below illustrates progress.



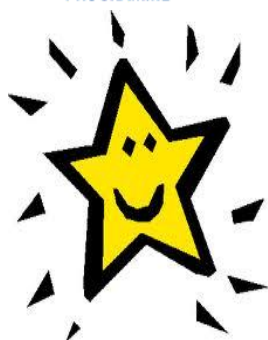
We anticipate that recruitment will accelerate as a further 10 Indian sites come on board and this needs to happen to reach the next targets within the coming 6 months. Several centres are awaiting local ethics approvals for the trial documents (specifically Protocol V2 [21APR10], Patient Information Sheet & Consent forms V2) or receipt of other essential documents, so it would be helpful if these documents were available at the Indian Coordinating Centres as soon as possible.

Our immediate plan is to have randomised 25% of the total (500 patients) by the end of November. As 40 patients were randomised in the first week of November, we are on track.

Current recruitment status for active sites :

Site No.	Site Name	Country	Recruitment Target	Date recruitment started	Patients registered	Patients randomised
001	London	UK	334	13-Jul-10	87	68
002	Dublin	IRE	333	23-Jun-10	107	76
003	Utrecht	NL	333	12-Aug-10	95	94
004	SP MC & AG Hospitals	INDIA	30	4-Oct-10	4	4
005	G.B. Pant Hospital	INDIA	30	28-Sep-10	3	3
007	DMC & Hospital	INDIA	30	26-Aug-10	28	28
009	Indira Gandhi MC	INDIA	30	9-Nov-10	4	4
010	AIIMS	INDIA	30	9-Aug-10	15	14
012	Fortis Escorts Hospital	INDIA	30	28-Aug-10	9	9
017	West Fort Hi-tech Hospital	INDIA	30	28-Aug-10	4	4
019	Ramana Maharishi-Rangammal H	INDIA	30	9-Nov-10	3	3
020	Global Hospitals	INDIA	30	3-Sep-10	5	5
021	Care Hospital	INDIA	30	28-Sep-10	53	53
022	Frontier Lifeline	INDIA	30	10-Nov-10	1	1
023	Andhra MC, King George H	INDIA	30	1-Nov-10	8	8
024	KEM Hospital	INDIA	30	29-Sep-10	23	23
025	Lalitha Super-Specialties Hospital	INDIA	30	28-Aug-10	35	33
026	Medwin Hospital	INDIA	30	30-Sep-10	30	30
029	Nizam's Inst Med Sci	INDIA	30	29-Oct-10	1	1
031	Jagadguru Sri-S MC & H	INDIA	30	5-Nov-10	1	1
032	Ruby Hall Clinic	INDIA	30	2-Nov-10	1	1
033	Asian Heart Inst & Res Centre	INDIA	30	6-Oct-10	2	2

MC = Medical College; H = Hospital



Congratulations !! to 021 Care Hospital, 025 Lalitha Super Specialities Hospital and 026 Medwin Hospital who have already exceeded their recruitment target of 30 patients. **Well done** also to sites 007 DMC and Hospital and 024 KEM Hospital who have also almost reached that 30 patient target. Remember that it is competitive recruitment, and we hope to see new sites below starting imminently and the others making good progress in the next few months! **Another target** will be achieved when 003 Utrecht reach their 100th patient randomised – almost 1/3 of the way there !!

Indian sites to start recruiting:

Site No.	Site Name	Site No.	Site Name
006	CSM College & Hospital	018	Sree Chitra Tirunal Inst Med Sci & Technology
008	Sanjay Gandhi PGIMS	027	Narayana Hrudayala
013	PGI Med Education & Research	028	Deenanath Mangeshkar Hospital & Research Centre
014	Dr RML Hospital	030	Mahavir Hospital & Research Centre
015	Annamali University	034	Bethesda Hospital

We have been informed that sites 008, 013 and 028 are expected to be high recruiters, so we look forward to monitoring progress of these sites in particular, but also would be delighted if there are others out there who excel at recruiting for UMPIRE ! We are also aware of the amazing conversion ratio of registered to randomised patients, and this is primarily due to the selection of patients with established CVD.

SAFETY UPDATE :

We have received reports for five SAEs, the details of which are summarised below.

Event	onset	resolved ?	Classification	Event also an endpoint	Randomised Group	Relationship with polypill	Action taken wrt polypill
Hemorrhage following PCI	18-Aug-10	19-Aug-10	SAE - hospitalisation	yes	RHP 1c	unrelated	no action
Collapse, secondary to bradycardia and hypotension	24-Sep-10	14-Oct-10	SUSAR - hospitalisation	no	RHP 2c	possible	permanently discontinued
MI	23-Sep-10	25-Sep-10	SAE - hospitalisation	yes	Usual care	not applicable	not applicable
Death due to stent thrombosis	11-Oct-10	11-Oct-10	SAE - fatal	yes	Usual care	not applicable	not applicable
MI after PCI	11-Oct-10	20-Oct-10	SAE - life threatening	yes	RHP 1c	unlikely	permanently discontinued

SUSAR REPORTING :

Those at the investigator sites will have received notification of a SUSAR for 002-0183, and copies of the safety reports from Dr Reddy's will have been provided to the investigators , and consequently should be provided to the investigator sites' local ethics committees. Please can the investigators ensure that they confirm receipt of the notification via the fax-back form, and submit letters of submission and acknowledgement as received to their monitors. Investigator sites should be using the latest version of the paper SAE template (Version 3, dated 12OCT10) when reporting SAEs to their coordinating centre.

In the **Kanyini Gap Trial**, there have been 2 SUSARs reported:

For patient 015-0086, an event of macroscopic haematuria was reported on 19AUG10. The event was classified as a SUSAR, having been related to the RHP 1c, specifically the aspirin and was classified as 'unexpected' due to the lack of a general reference to bleeding (apart from GI and intracranial) and more specifically haematuria, in the IB or in the Product Information (PI) for aspirin.

For patient 102-0007, an event of decreased glomerular filtration rate reported on 12JUL10 was initially classified as a SUSAR, having been assigned a possible relationship with the RHP 1c by the site investigator, but follow-up information and investigations confirmed that the event was linked to a myeloma, and so the SUSAR was downgraded to 'unrelated'.

POLYPILL COLLABORATION

Dr Ruth Webster, based at the George Institute for Global Health – Australia, oversees the teams of international collaborators including those planning to start a polypill RHP trial in other countries. The recruitment status for other concurrent polypill trials is that in Australia, the Kanyini GAP trial – led by Prof Anushka Patel - has enrolled 307 patients, with 246 patients randomised via GP practices, and their current aim is to improve recruitment rates to meet their target of 1000 patients randomised and initiate more GP sites. In New Zealand, the IMPACT trial – led by Prof Raina Elley – has current recruitment status of 187 registered and 82 patients randomised, and their patient target is 600 randomised over 18 months i.e. by the end of 2011. The IMPACT team is currently working on increasing the number of participating GP practices and consequently their recruitment rate.

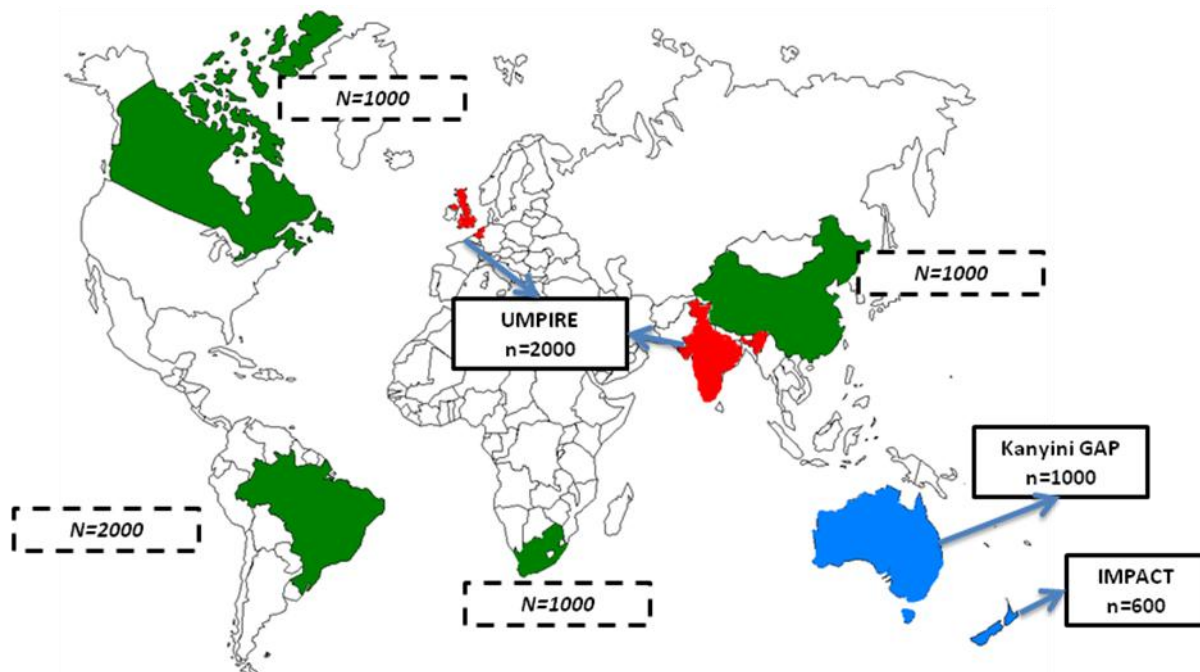
Countries applying for funding:

Brazil – Otavio Berwanger is extremely confident that the Ministry of Health will approve funding very soon, and their aim is to recruit 2000 patients with recruitment starting next year.

Canada – The Canadian collaborators have applied for funding to do a small pilot of around 100 patients to improve their chances of being fully funded for a complete trial. The pilot is unlikely to happen until July 2011 with application for full funding to be submitted in September.

South Africa – A preliminary application has been submitted from a group of Investigators led by Dr Andre Pascal Kengne in response to the recent Wellcome/MRC/DFid funding call. A decision should be made at the end of this year to determine whether the South Africa collaborative team can proceed to the full application stage.

As a reminder, the global map below shows location and recruitment targets of current and prospective polypill trials.



PUBLICATIONS

Prof Rogers and Ruth Webster are currently finalizing a draft rationale/protocol paper for the collaboration which will be distributed to all members of the collaboration once it's ready for comment.

The PILL pilot results paper is under review with the BMJ.

A paper entitled 'Where we are now with the polypill' will also be submitted to the BMJ. This is being written and co-authored by representatives from the UMPIRE partner teams.

An UMPIRE trial design paper is in draft.

Please let us know if you have any comments, suggestions for items or feedback for future editions.

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