THE GEORGE INSTITUTE
for Global Health

Pill Pilot study and SPACE Collaboration

Dr Ruth Webster

PILL Pilot

Programme to Improve Life and Longevity

Trial Design

- Randomised, controlled, double-blind trial, Red Heart Pill V2b - aspirin 75mg, simvastatin 20mg, lisinopril 10mg, hydrochlorothiazide 12.5mg
- (Polypill) vs. placebo
- N = 400
- Eligible if ≥ 7.5% CV risk and no indication or contraindication for treatment with RHP components
- 12 weeks follow-up plus 4 week post trial phone assessment

Regional Co-ordinating Centres

Country	PI	Project Manager	Other key staff
Australia	Anushka Patel	Bindu Patel	Oscar Donaldson, Evelyn Nangle
Brazil	Otavio Berwanger	Ligia Laranjeira	
India	Anushka Patel	Bindu Patel	Abdul Salam
New Zealand	Anthony Rodgers	Angela Wadham	Natasha Rafter, Vanessa Selak, Rina Prasad
The Netherlands	Rick Grobbee	Lizeth Vendrig	Michiel Bots, Lydeke Zwart, Ron Peters, Trees Groenveld
UK	Simon Thom & Neil Poulter	Thiagarajah Sasikaran (Sasi)	Rebecca James, Candida Coghlan, Hannah Lancon-Miller, Jill Bunker
USA	Richard Grimm	Rachel Moor	Jim Neaton, Alexa Camarena

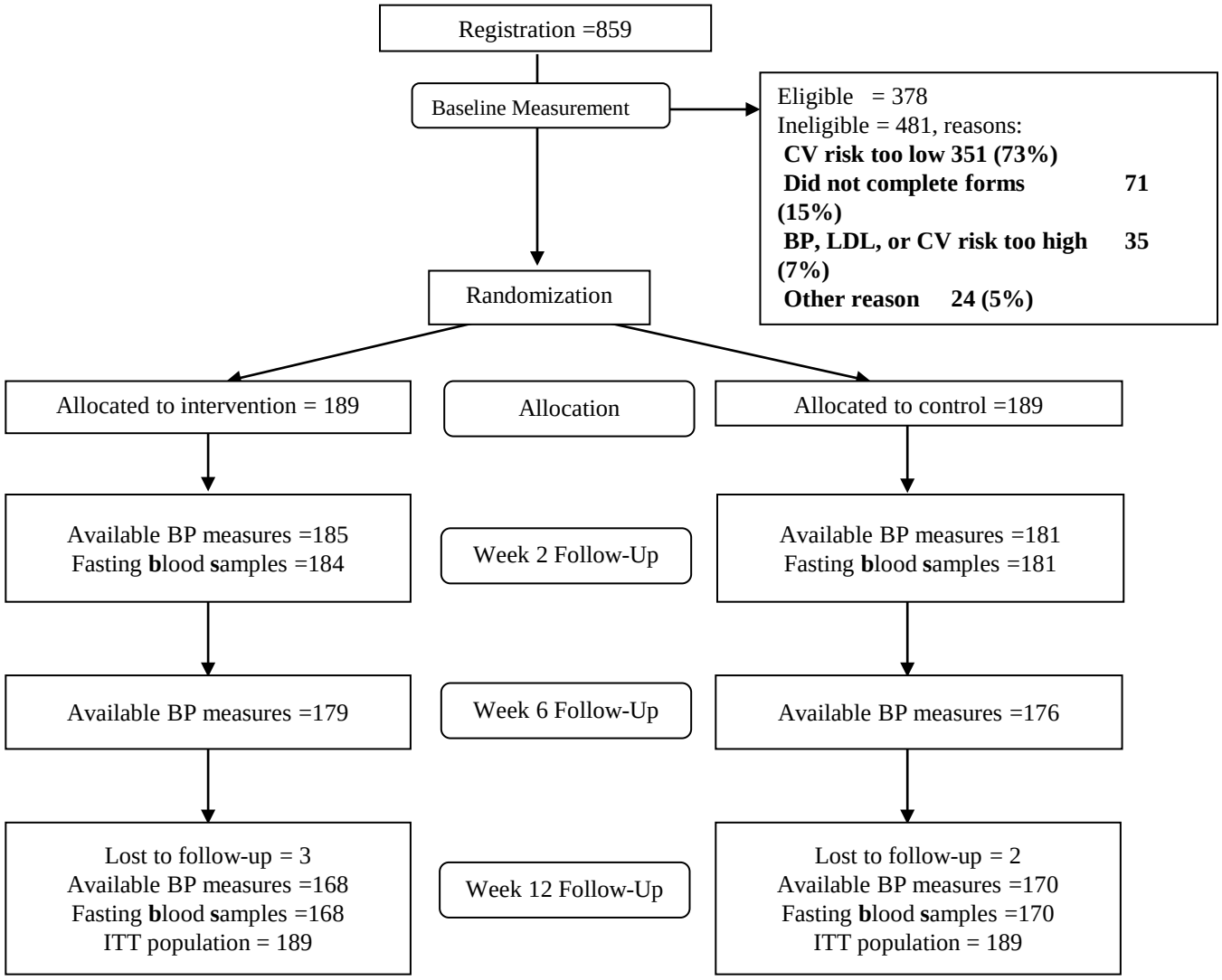
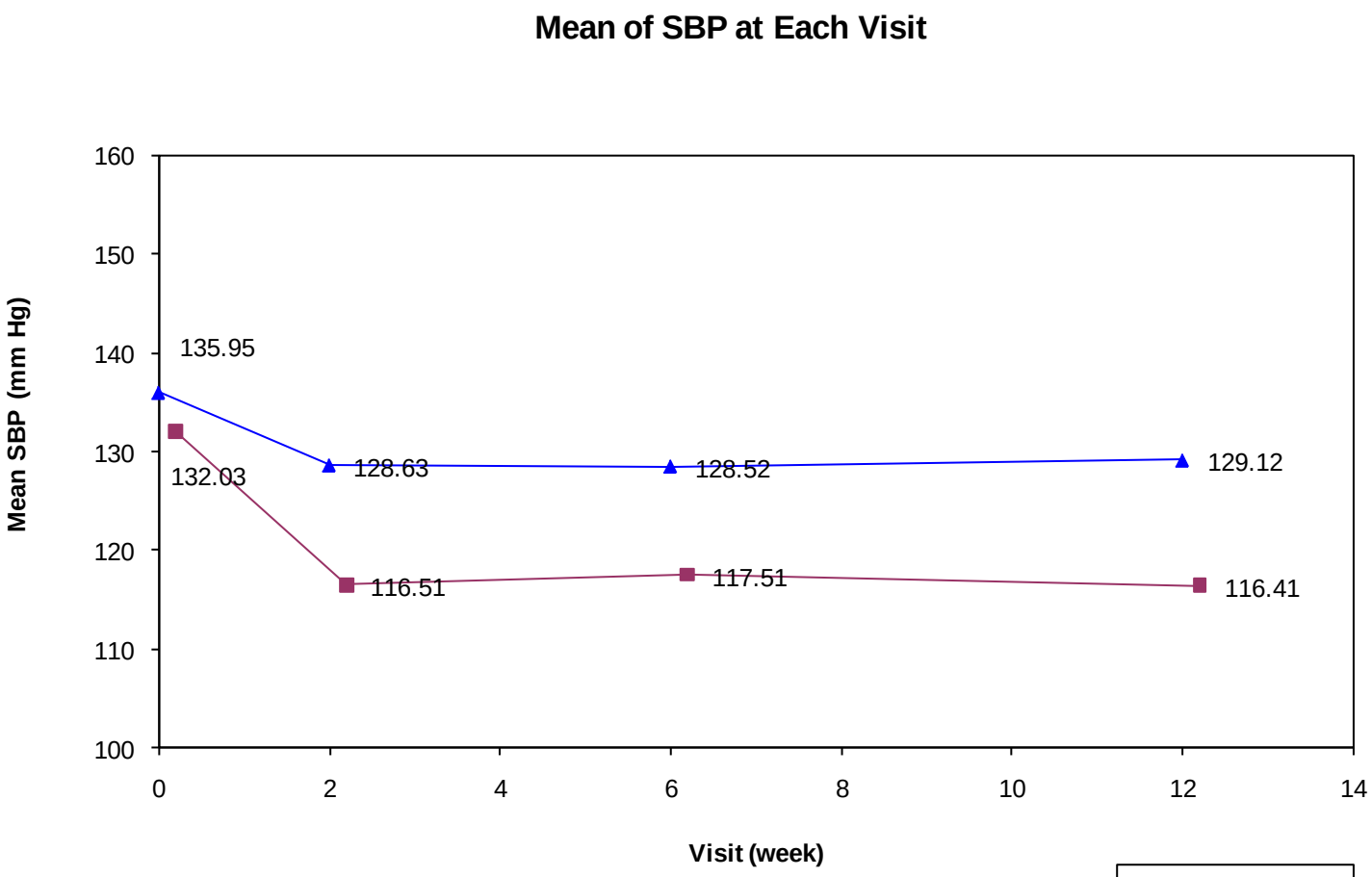


Figure 1: **Consort flowchart**

Table 1: Baseline characteristics

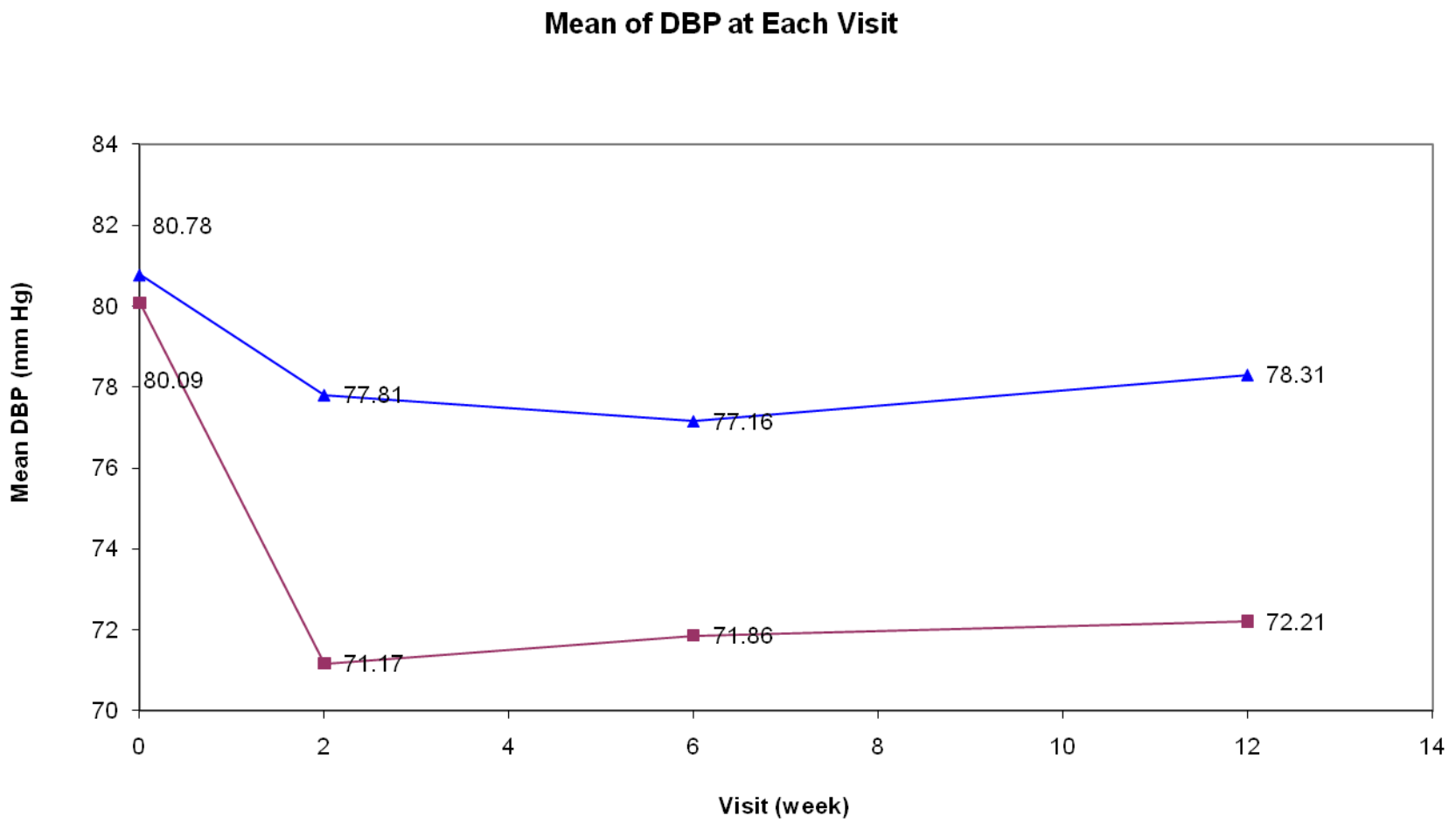
	Red Heart Pill n =189		**Placebo n =189**	
Cardiovascular risk factors in Framingham score				
Age (yrs)	61.2	(7.2)	61.6	(7.2)
Male	153	(81%)	152	(80%)
Blood pressure (mmHg)	132/80	(13/9)	136/81	(14/9)
LDL-cholesterol (mmol/L)	3.7	(0.9)	3.6	(0.9)
Total cholesterol (mmol/L)	5.6	(1.1)	5.4	(1.0)
HDL (mmol/L)	1.2	(0.3)	1.3	(0.4)
Smoker (or quit within the last year)	79	(42%)	74	(39%)
Cardiovascular risk				
5-year cardiovascular risk - Framingham function	10%	(4.1%)	11%	(4.5%)

Efficacy - SBP



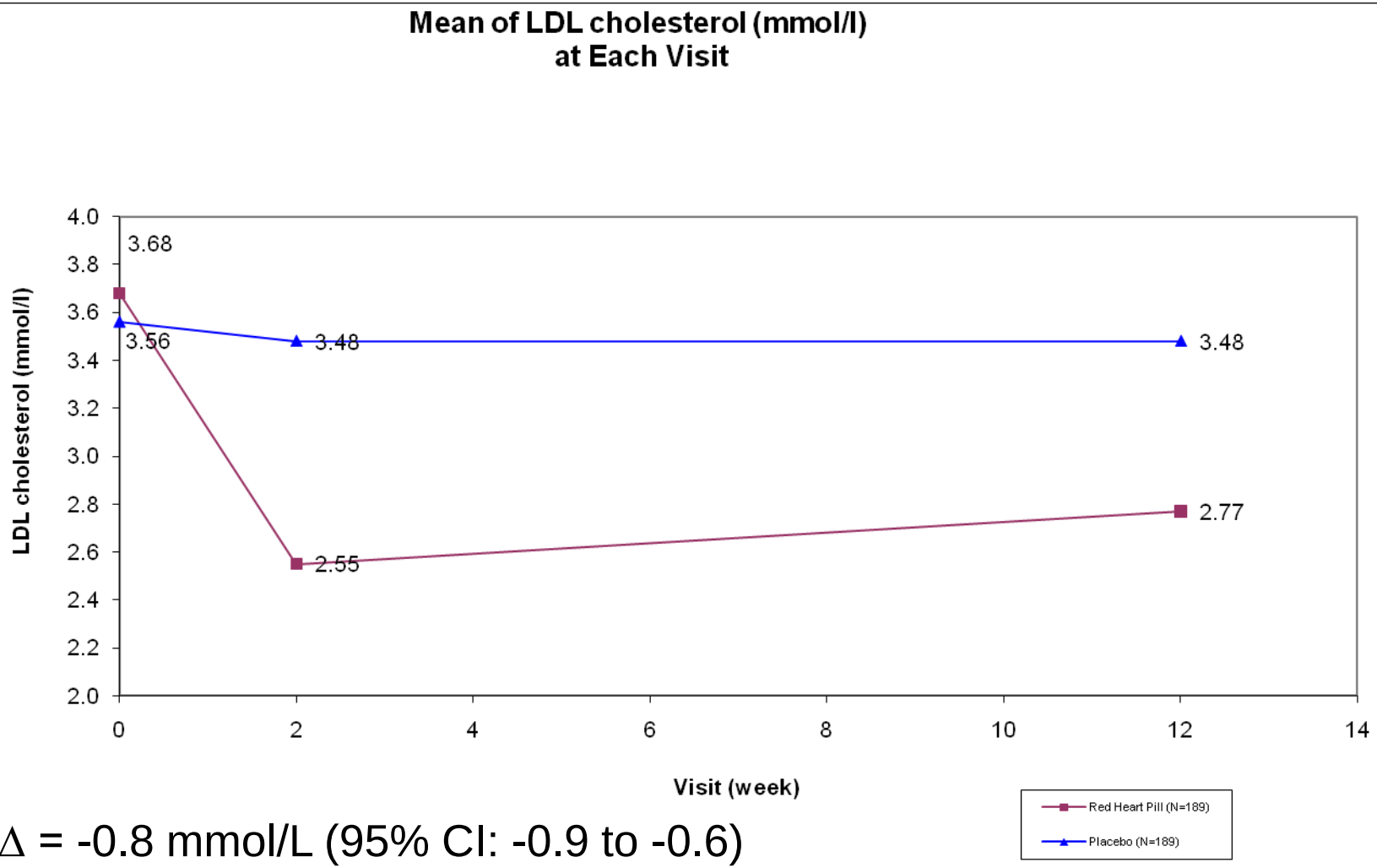
Δ = -9.9 mmHg (95% C.I. -12.1 to -7.7)

Efficacy - DBP



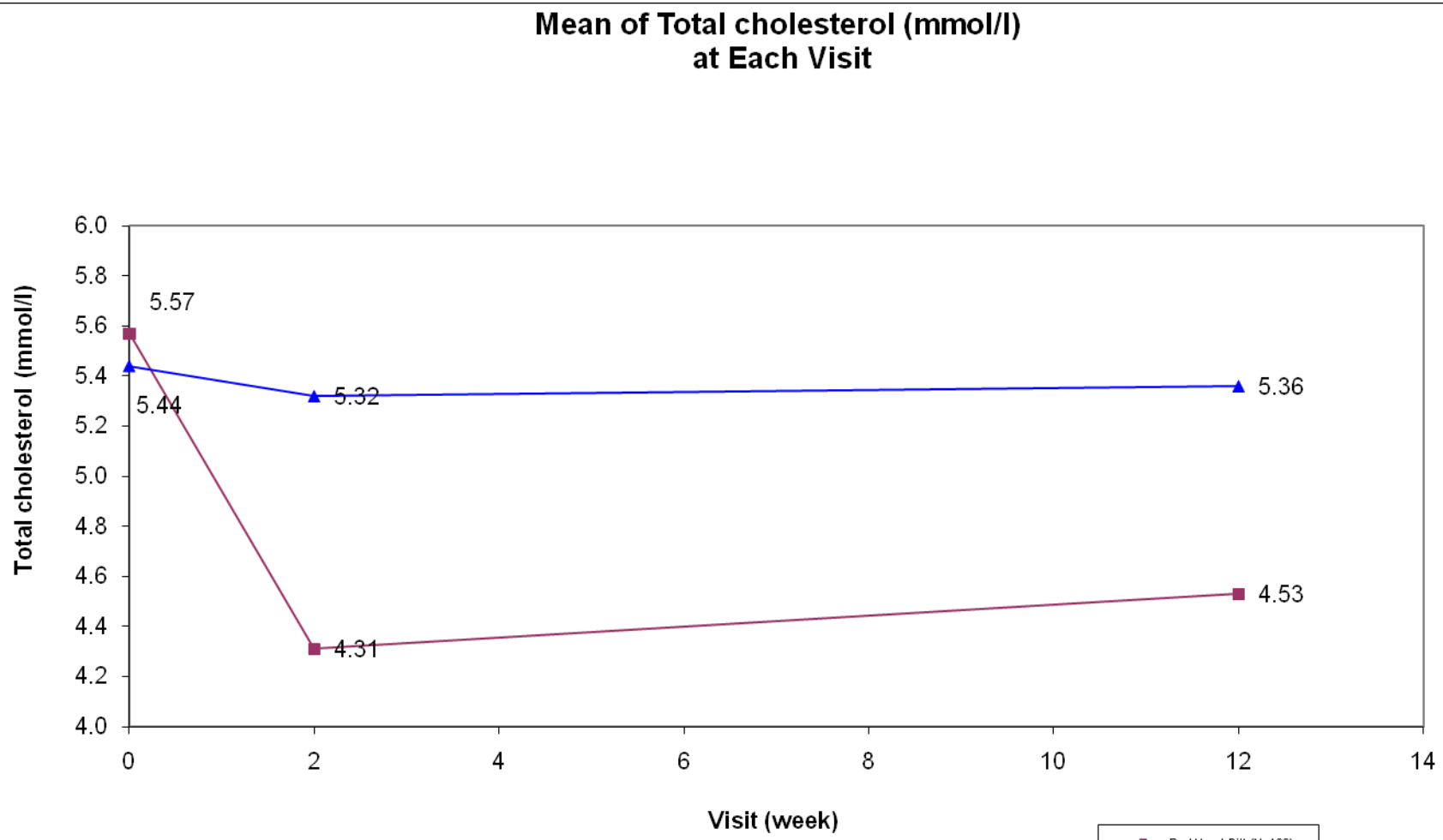
Δ = -5.3 mmHg (95% C.I. -6.7 to -3.9)

Efficacy – LDL cholesterol



Δ = -0.8 mmol/L (95% CI: -0.9 to -0.6)

Efficacy – Total cholesterol



Δ = -0.8 mmol/L (95% CI: -1.0 to -0.7)

Table 2: Reported side effects of sufficient severity to discontinue study treatment*

	Red Heart Pill		Placebo		P-value
	n	%	n	%	
Gastric irritation	6	3%	1	1%	0.06
Increased bleeding tendency	0	0%	0	0%	
Cough	3	2%	2	1%	0.7
Light headed/dizziness/hypotension	7	4%	2	1%	0.09
Muscle pain or weakness	1	1%	2	1%	0.6
Headache	1	0%	0	0%	
Diarrhoea	0	0%	0	0%	
Fatigue	3	2%	2	1%	0.7
Other side effect	13	6%	12	6%	0.8
Patient choice	0	0%	3	2%	0.08
Total**	34	18%	24	13%	0.2

Table 2 cont'd: Reported side effects not necessitating discontinuation of study treatment

	Red Heart Pill		Placebo		P-value
	n	%	n	%	
Gastric irritation	23	12%	6	3%	0.0005
Increased bleeding tendency	4	2%	1	1%	0.2
Cough	19	10%	3	2%	0.0002
Light headed/dizziness/hypotension	28	15%	8	4%	0.0002
Muscle pain or weakness	13	7%	14	7%	0.9
Headache	4	2%	3	2%	0.6
Diarrhoea	4	2%	5	3%	0.8
Fatigue	13	7%	10	5%	0.4
Abdominal pain	4	2%	1	1%	0.2
Constipation	10	5%	4	2%	0.08
Flatulence	6	3%	5	3%	0.7
Other side effect	39	21%	28	15%	0.07
Total**	81	43%	59	31%	0.003

Summary

- Excellent risk factor reductions achieved 10/5 mmHg and 0.8 mmol/L LDL
  - sustained
  - consistent across major subgroups
- Appreciable side effect rate, absolute excess of 16% reporting side effects and 6% stopping treatment:
  - mostly due to cough and GI symptoms
  - mostly apparent in first few weeks
- Predicted more than halving in CV risk

SPACE Collaboration

(Single Pill to Avert Cardiovascular Events)

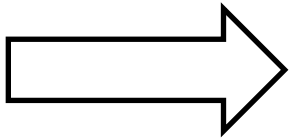
What is it?

An international academic collaboration for the clinical evaluation of combination pills containing statin, aspirin and blood pressure lowering medications in patients with established indications for treatment

Low Hanging fruit

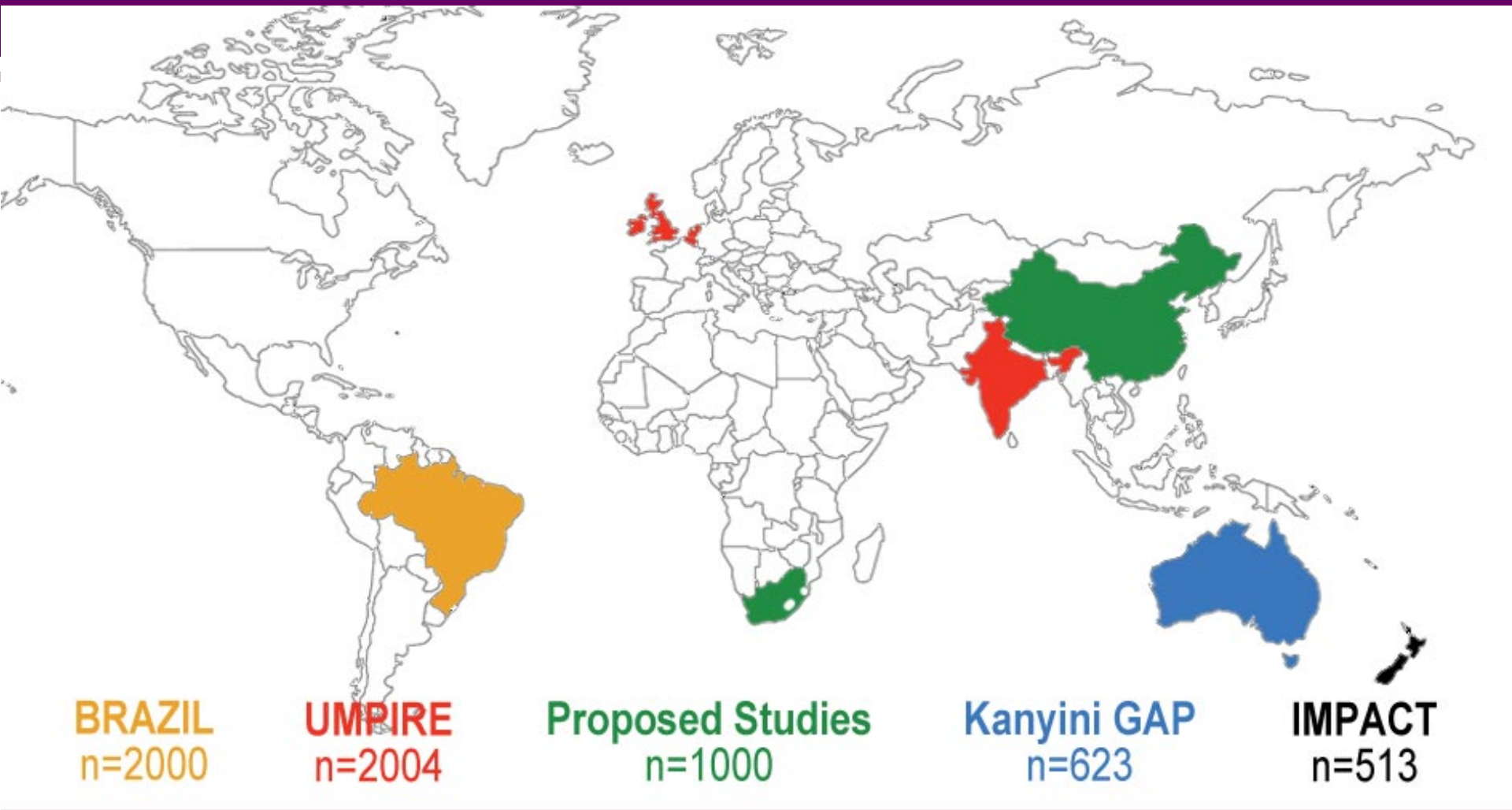
- **Secondary prevention/high risk primary prevention is the optimal first target group**
  - Highest risk
  - Maximum impact
  - All medications recommended

- Opportunity to collaborate, share information and combine results for eventual meta-analysis



SPACE Collaboration

Collaboration trials



Global Trials Collaboration

Progress

- **UMPIRE (Europe and India – 2000 patients) has data-locked, results presented at AHA meeting in December**
- **Kanyini-GAP (Australia – 623 patients) final patient visits to be completed by September 30th, results available early 2013**
- **IMPACT (New Zealand – 513 patients) finishing mid 2013**
- **Meta-analysis mid- late 2013**

Meta-analysis

- **Primary endpoints:**
  - Self-reported current use of antiplatelet, statin and combination blood pressure lowering therapy at 12 months
  - Change in systolic blood pressure from baseline to 12 months (surrogate endpoint for adherence)
  - Change in Total Cholesterol from baseline to 12 months (surrogate endpoint for adherence)
  - Non-inferiority margins: 3mmHg SBP, 0.3 mmol/L Total cholesterol
- **Secondary endpoints:**
  - Change in LDL and other lipid fractions at 12 months
  - Change in Diastolic BP at 12 months
  - Self-reported current use of antiplatelet, statin and at least 1 BP lowering therapy at 12 months

- QOL (EQ5D)
- Mortality – CV, non-CV and all cause
- New onset DM
- CV events (composite endpoint)
- Each component of composite endpoint
- Calculation of RRR for CV events

    Unlikely to have power to determine this via meta-analysis of events

    Will be done by multiplying the RR for SBP and LDL proportional to the size of the reduction and the RRR for aspirin adjusted for adherence.

SPACE Collaboration Members

- **Co-ordinator:** Dr Ruth Webster
  The George Institute for Global Health, Sydney
- **Chair:** Professor Anthony Rodgers
  The George Institute for Global Health, Sydney
- **Deputy Chair:** Associate Professor Anushka Patel
  The George Institute for Global Health, Sydney/Hyderabad (UMPIRE, Kanyini-GAP)
- Prof Alan Cass, Ms Carol Burch
  The George Institute for Global Health, Sydney (Kanyini-GAP)
- Prof Chris Bullen, Ms Angela Wadham, Dr Vanessa Selak
  National Institute for Health Innovation, University of Auckland (IMPACT)
- Prof Simon Thom, Prof Neil Poulter, Ms Jane Field
  Imperial College, London (UMPIRE)
- Prof D Prabhakaran
  Centre for Chronic Disease Control, New Delhi
- Prof K Srinath Reddy
  Public Health Foundation of India, New Delhi (UMPIRE)
- Prof Alice Stanton
  Royal College of Surgeons in Ireland (UMPIRE)
- Prof Rick Grobbee, Prof Michiel Bots
  University Medical Centre Utrecht (UMPIRE)
- Prof Wu Yangfeng
  The George Institute for Global Health, China
- Dr Otavio Berwanger
  Hospital do Coração (Cardiac Hospital) , Sao Paulo, Brazil
- Dr Andre Pascal Kengne
  Medical Research Council of South Africa
- Mr Raghu Cidambi
  Dr Reddy's Laboratories India