BASIL TRIALS

Investigators' Meeting, VSGBI, Manchester, 23 November 2017

The Vascular Societies' Annual Scientific Meeting 2017

In conjunction with the Vascular Society of Great Britain and Ireland, the Society of Vascular Nurses, and the Society for Vascular technology of Great Britain and Ireland.

22nd–24th November 2017 Manchester Central

NHS National Institute for Health Research

Heart of England NHS Foundation Trust

Birmingham Clinical Trials Unit

University of Birmingham

Introduction

Professor Andrew Bradbury

BASIL-2 and 3 Chief Investigator

Birmingham Clinical Trials Unit

National Institute for Health Research

Heart of England NHS Foundation Trust

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BASIL-1 Trial

- Still the only RCT!
- NIHR HTA funding 1998
- Between 1999 and 2003
- 452 SLI patients randomised :
  - Bypass *first* (25% prosthetic)
  - PBA *first* (6 stents)
- 75% femoro-popliteal
- After 2 years – (vein) bypass better than PBA in terms of:
  - Amputation free survival
  - Overall survival
  - Quality of revascularisation

BASIL- 1: the usual interpretation

Patient with SLI due to femoro-popliteal (FP) disease

↓

Anticipated life expectancy?

< 2 years? → Angioplasty

> 2 years? → Vein?

Vein? → No → Angioplasty

Vein? → Yes → Bypass

NICE Research Recommendations

NHS
National Institute for
Health and Clinical Excellence

Home

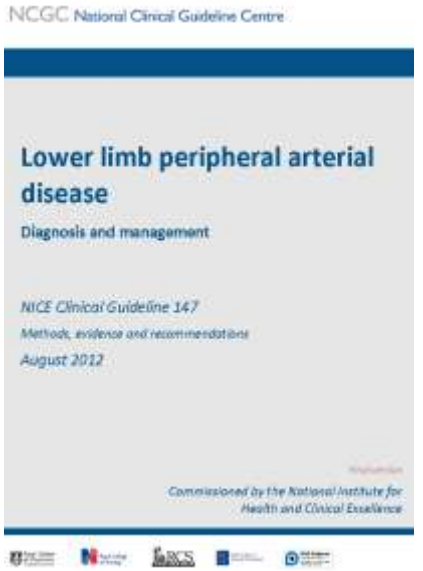
Find guidance | NICE Pathways | Quality standards | Into practice | QOF

Home > About NICE guidance > Guidance by type > Clinical guidelines > Lower limb peripheral arterial disease

CG147 Lower limb peripheral arterial disease (CG147)

Lower limb peripheral arterial disease pathway
Fast, easy summary view of NICE guidance on 'lower limb peripheral arterial disease'

CLTI recommendations based on BASIL-1, but…



What about infra-popliteal disease?

What about drug coated balloons and eluting stents?

NHS
National Institute for
Health and Clinical Excellence

BASIL 2/3 Co-applicants

Southampton (Professor Shearman, Dr Odurny)

St George's (Mr Hinchliffe and Professor Belli)

Imperial (Professor Davies, Dr Burfitt)

Oxford (Mr Perkins, Dr Uberoi)

Birmingham / WM (Mr Claridge, Dr Ganeshan)

Leicester (Professor Naylor, Dr Adair)

Hull (Professor Chetter, Professor Ettles)

Leeds (Professor Scott, Dr Patel)

Sheffield (Professor Beard, Dr Cleveland)

Newcastle (Professor Stansby, Dr Jackson)

Scotland (Professor Brittenden, Mr Stuart)

VSGBI

BSIR

ESVS

CF

Diabetes-UK

NHS National Institute for Health Research

Heart of England NHS Foundation Trust

THE UNIVERSITY OF BIRMINGHAM Centenary 2000

Research programmes

Funding opportunities

Project portfolio

Browse projects

Resources for researchers

Become a reviewer

HTA - 12/35/45: Multicentre randomised controlled trial to compare the clinical and cost-effectiveness of a vein bypass first with an endovascular first revascularisation strategy for severe limb ischaemia due to infrageniculate arterial disease (Bypass v Angioplasty in Severe Ischaemia of the Leg, BASIL-2)

Notify me when this item is published

£2.02m

BASIL-2

http://www.nets.nihr.ac.uk/projects/hta/123545

Research programmes

Funding opportunities

Project portfolio

Browse projects

Resources for researchers

Become a reviewer

HTA - 13/81/02: RCT of clinical and cost-effectiveness of drug coated balloons, drug eluting stents and balloon angioplasty with bail-out bare metal stent revascularisation strategies for severe limb ischaemia due to femoro-popliteal disease: BASIL-3 (Balloon vs Stenting in Severe Ischaemia of the Leg)

Notify me when this item is published

£2.54m

BASIL-3

http://www.nets.nihr.ac.uk/projects/hta/138102

NHS National Institute for Health Research

NHS National Institute for Health and Clinical Excellence

BASIL-2 – infra-popliteal (IP) SLI

Vein Bypass *first*
(n = 300?)

Best Endovascular Treatment *first* (n = 300?)

BASIL-3 – femoro-popliteal (FP) SLI

PBA
+/- BMS
(n = 282)

DCB
+/- BMS
(n = 282)

DES
(n = 282)

Follow-up 24-60 months
Amputation free survival
Overall Survival
Clinical end-points

Quality of revascularisation
Quality of life
Functional status
Health economic

The academic case for

Mr Matthew Popplewell

University of Birmingham

BASIL-2 Research Fellow

NHS National Institute for Health Research

Heart of England NHS Foundation Trust

UNIVERSITY OF BIRMINGHAM

Why BASIL-2?

“Why do we need BASIL-2 when it is *obvious* that endovascular revascularisation is the best strategy for almost all patients requiring infra-popliteal intervention for SLI?”

Current best evidence

Plain Balloon Angioplasty

Immediate technical success of IP angioplasty of 89% (pooled estimate)

Outcomes **suboptimal** at 12-months

Mortality ***15.1%***

Major Amputation ***14.9%***

Primary patency ***63.1%***

Re-intervention rate ***18.2%***

Peripheral Vascular Disease

Percutaneous Transluminal Angioplasty in Patients With Infrapopliteal Arterial Disease

Systematic Review and Meta-Analysis

J.A. Mustapha, MD; Sara M. Finton, BSN; Larry J. Diaz-Sandoval, MD; Fadi A. Saab, MD; Larry E. Miller, PhD

BASIL-1 IP Subgroup Analysis

ARTICLE IN PRESS

Eur J Vasc Endovasc Surg (2017) ■, 1–7

A Comparison of Outcomes in Patients with Infrapopliteal Disease Randomised to Vein Bypass or Plain Balloon Angioplasty in the Bypass vs. Angioplasty in Severe Ischaemia of the Leg (BASIL) Trial

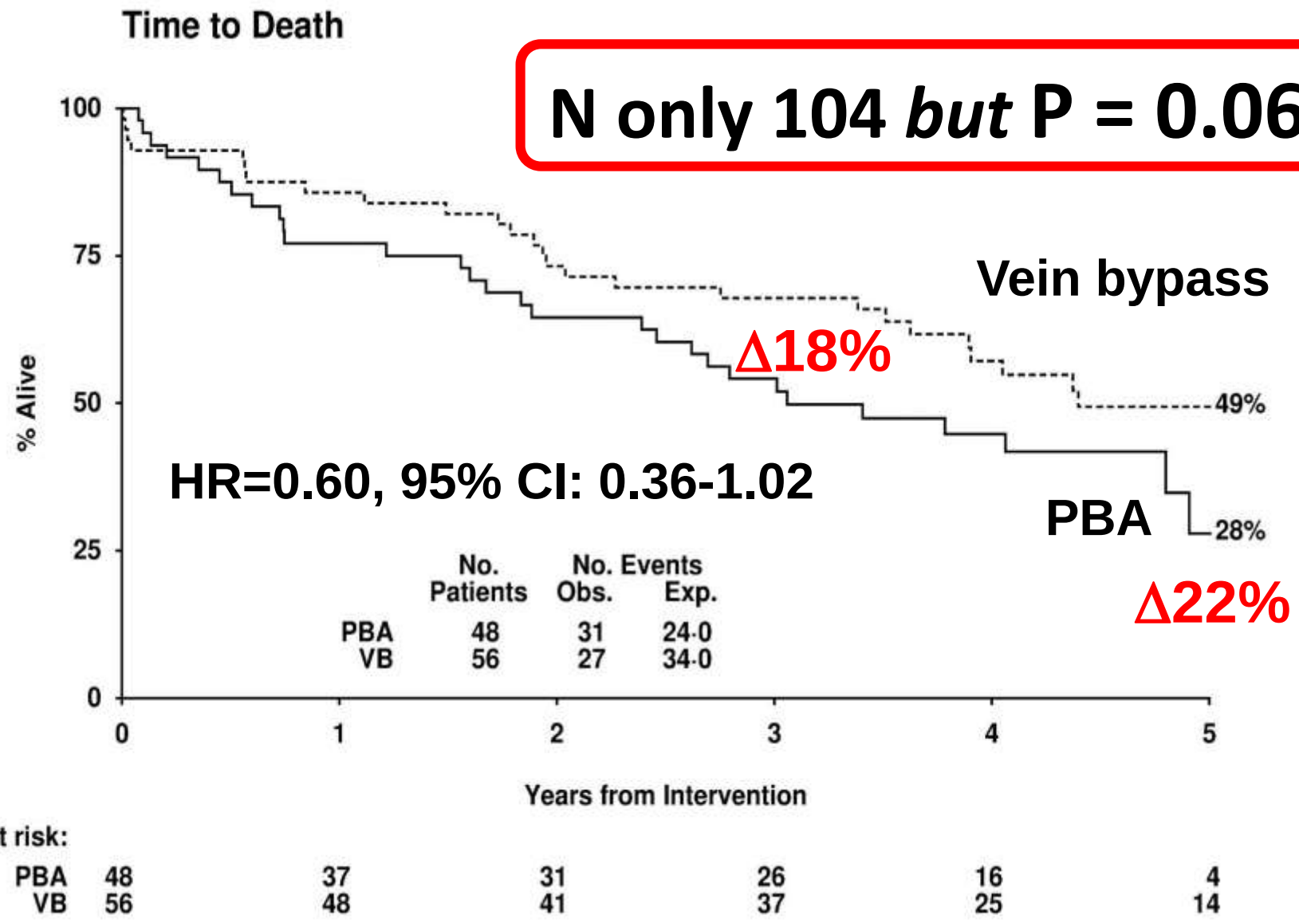
M.A. Popplewell [a,*], H.O.B. Davies [a], J. Narayanswami [a], M. Renton [b], A. Sharp [b], G. Bate [a], S. Patel [c], J. Deeks [c], A.W. Bradbury [a]

[a] Department of Vascular Surgery, University of Birmingham, Birmingham, UK
[b] Heart of England Foundation Trust, Birmingham, UK
[c] Birmingham Clinical Trials Unit, University of Birmingham, Birmingham, UK

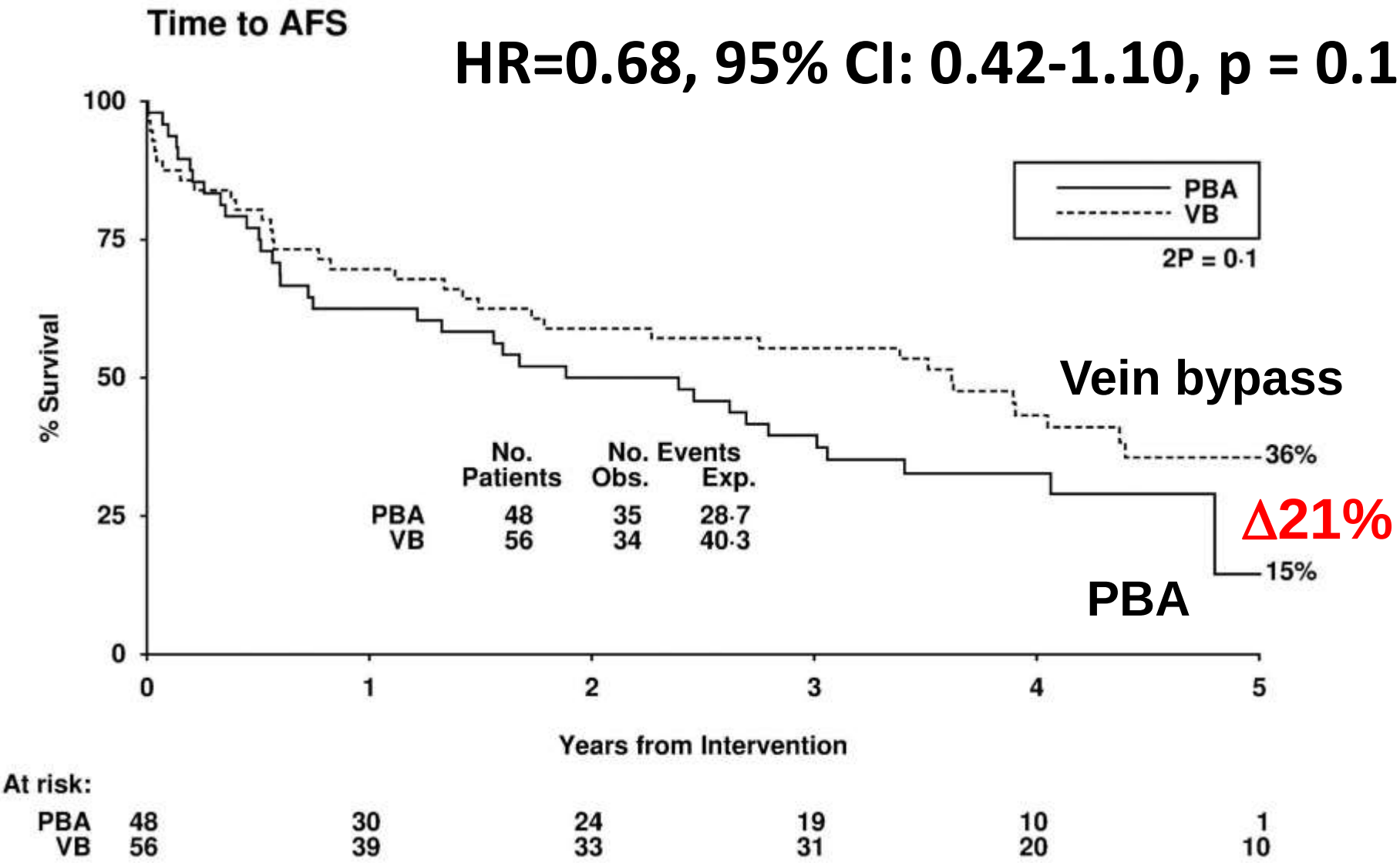
WHAT THIS PAPER ADDS

These data reconfirm the need for further publicly funded, unbiased, pragmatic randomised controlled trials, such as BASIL-2 and BEST-CLI, to compare the clinical and cost effectiveness of infra-popliteal vein bypass and best endovascular treatment in patients suitable for both interventions.

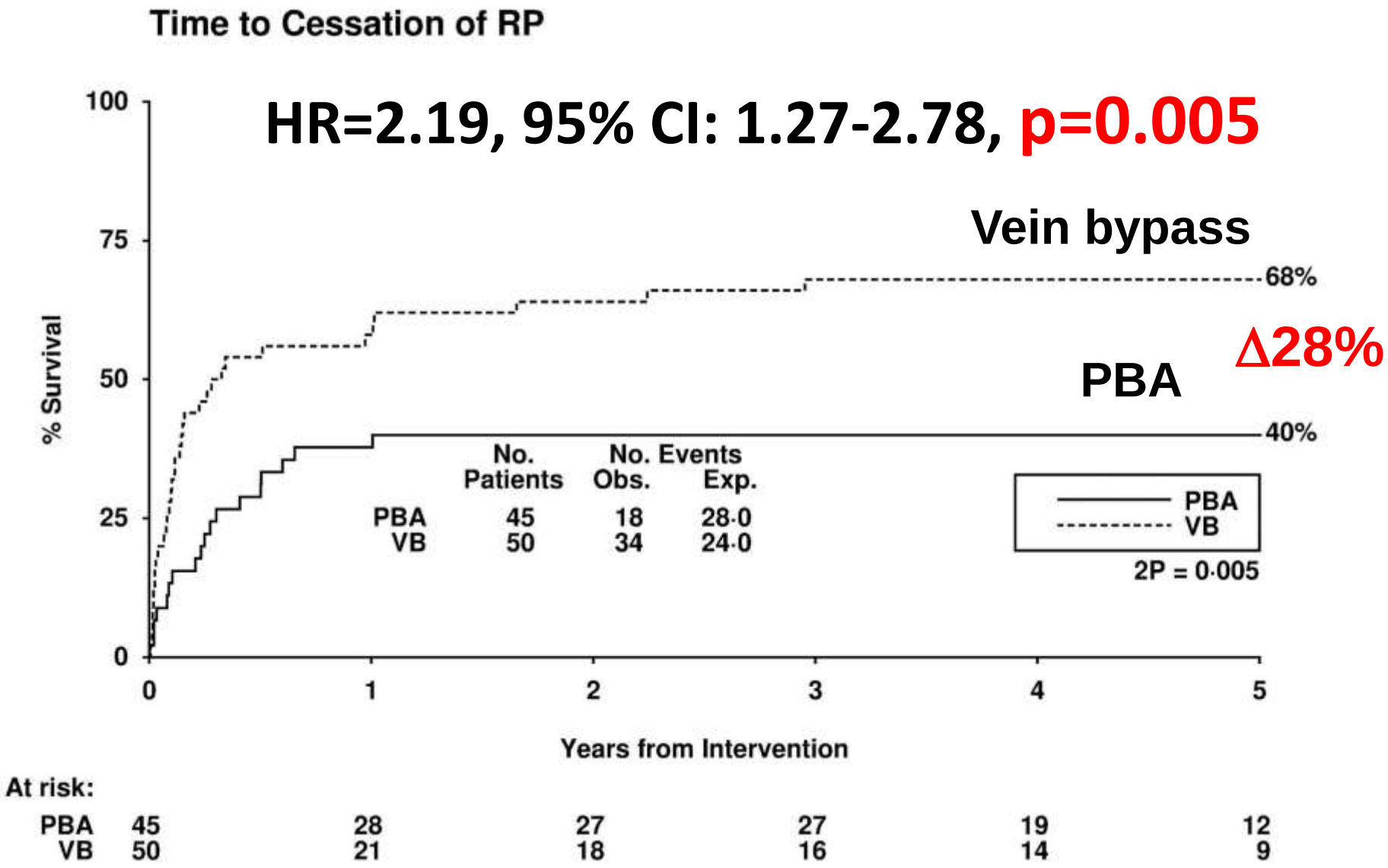
BASIL-1 IP: overall survival



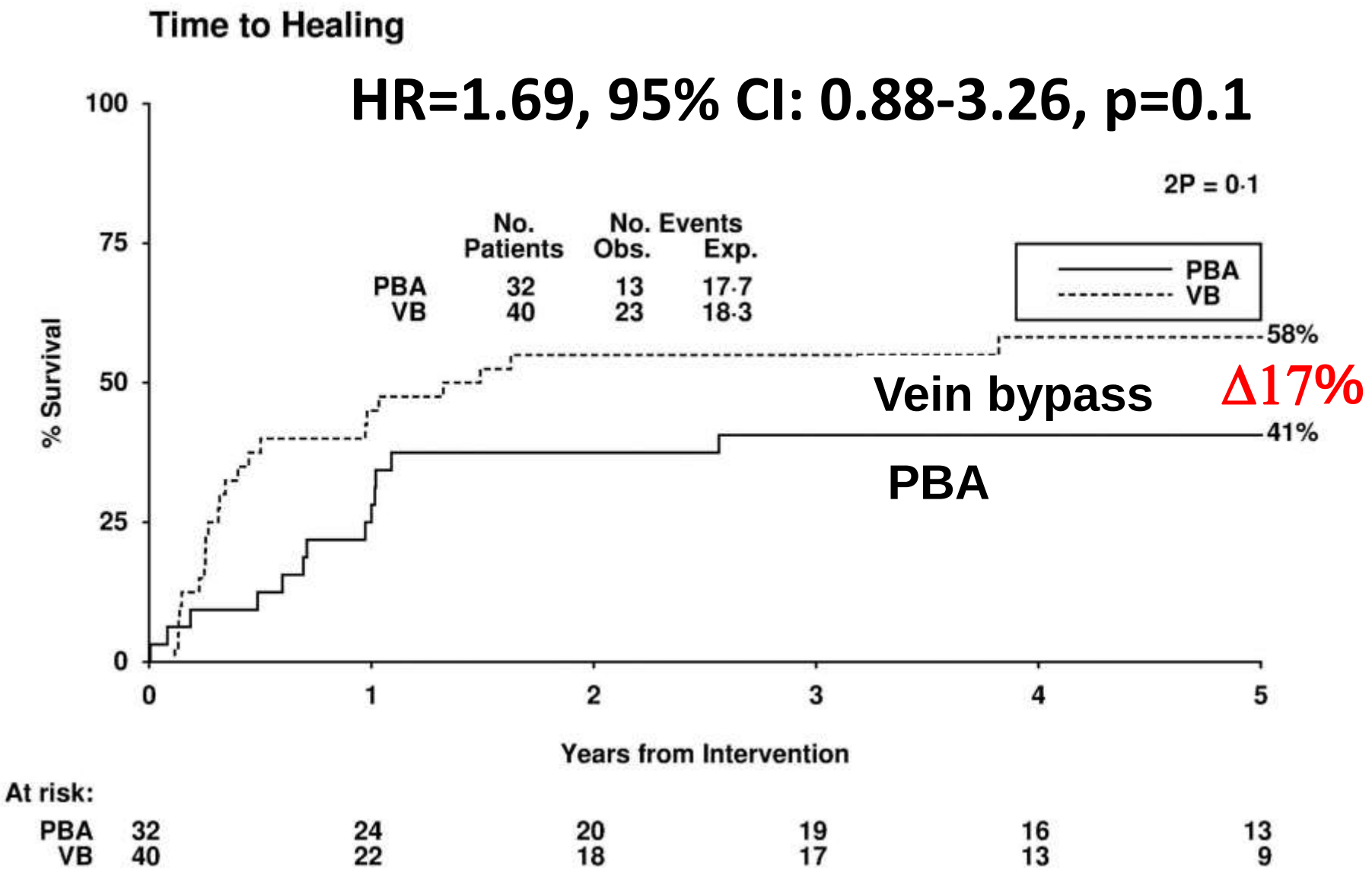
BASIL-1 IP: amputation free survival



BASIL-1 IP: relief of rest pain



BASIL-1 IP: time to wound healing



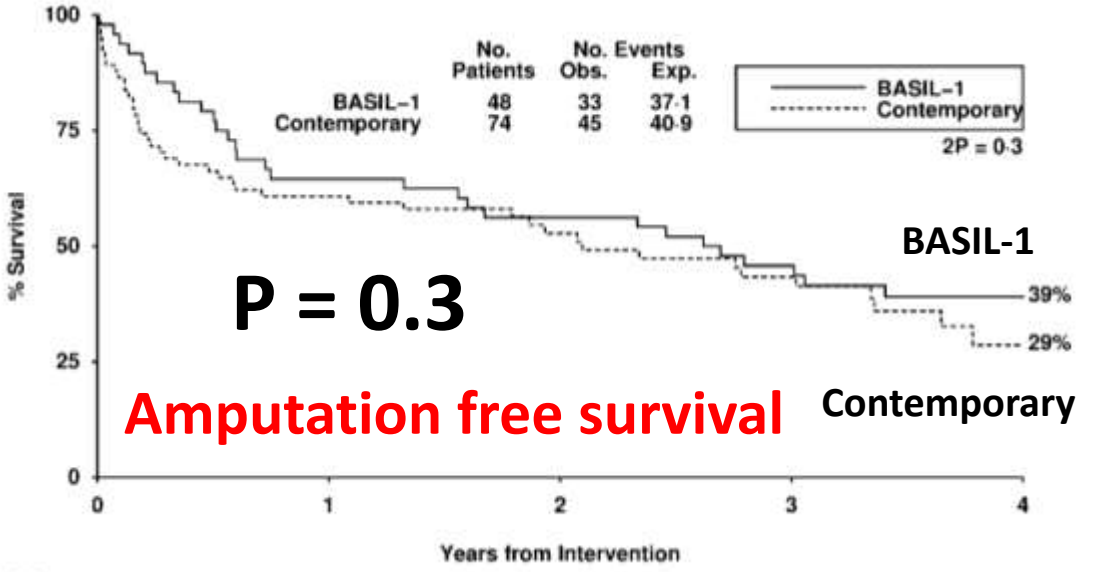
BASIL-1 IP: Statistical Interpretation

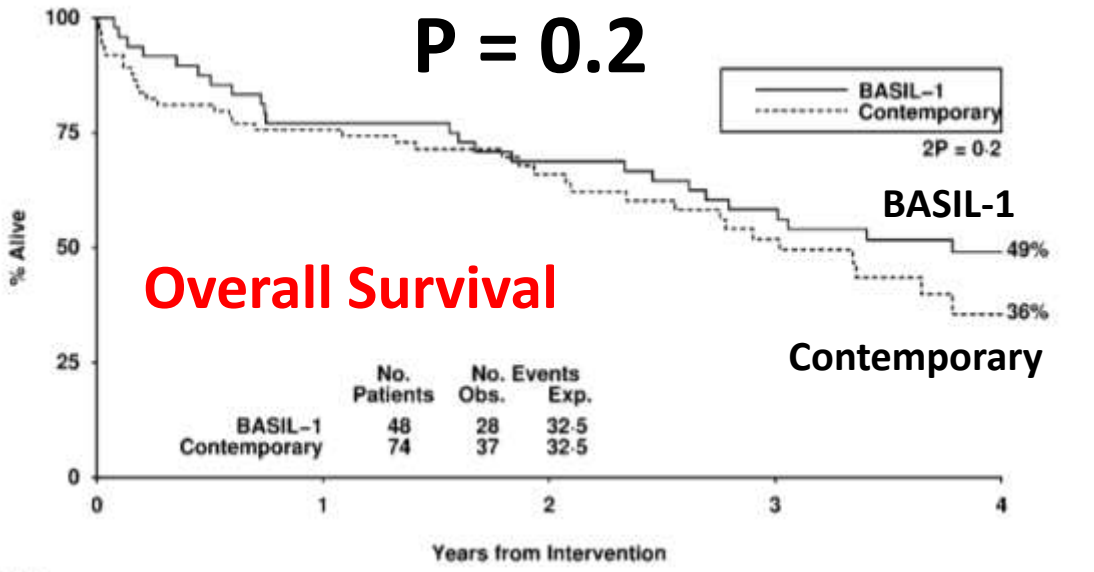
While the BASIL-1 results do not meet standard criteria for statistical significance, the direction of the effect *consistently favours bypass* and confidence intervals rule out the possibility of clinically important effects in favour of balloon angioplasty

Birmingham Clinical Trials Unit

BASIL-1 outcomes outdated?

NO, despite fewer technical failures, AFS and OS after IP endovascular intervention in our unit (HEFT) are currently (**2009-2014**) no better than those observed in BASIL-1 (**1999-2004**)





Heart of England NHS
NHS Foundation Trust

Why BASIL-2?

Because, there is **no** evidence to support endovascular intervention as the preferred treatment for SLI due to IP disease in patients who can have a vein bypass

Indeed, what data we have indicates that endovascular is **unlikely to be better** and **should usually be reserved for those who cannot have distal vein bypass**

BASIL - HEFT PCS (screening log)

01/07/2014 to 31/10/2017 - 388 new SLI patients

185/388 (48%) IP +/- INFLOW disease

Primary amputation
29 (16%)

Revascularisation attempted
115 (62%)

Conservative
39 (22%)

8 other surgery

Vein bypass (outside trial)
29 (25%)

Endovascular (outside trial)
62 (54%)

B3 randomising from 29/01/16 – 01/10/16

143 patients screened with CLTI

45/143 randomised to B3 (32%)

Randomised to B2 =16

Angioplasty x 5

Vein Bypass x 11

14%

Randomised to B3 w/IP = 6

Recruitment update

Lucy Casley

University of Birmingham

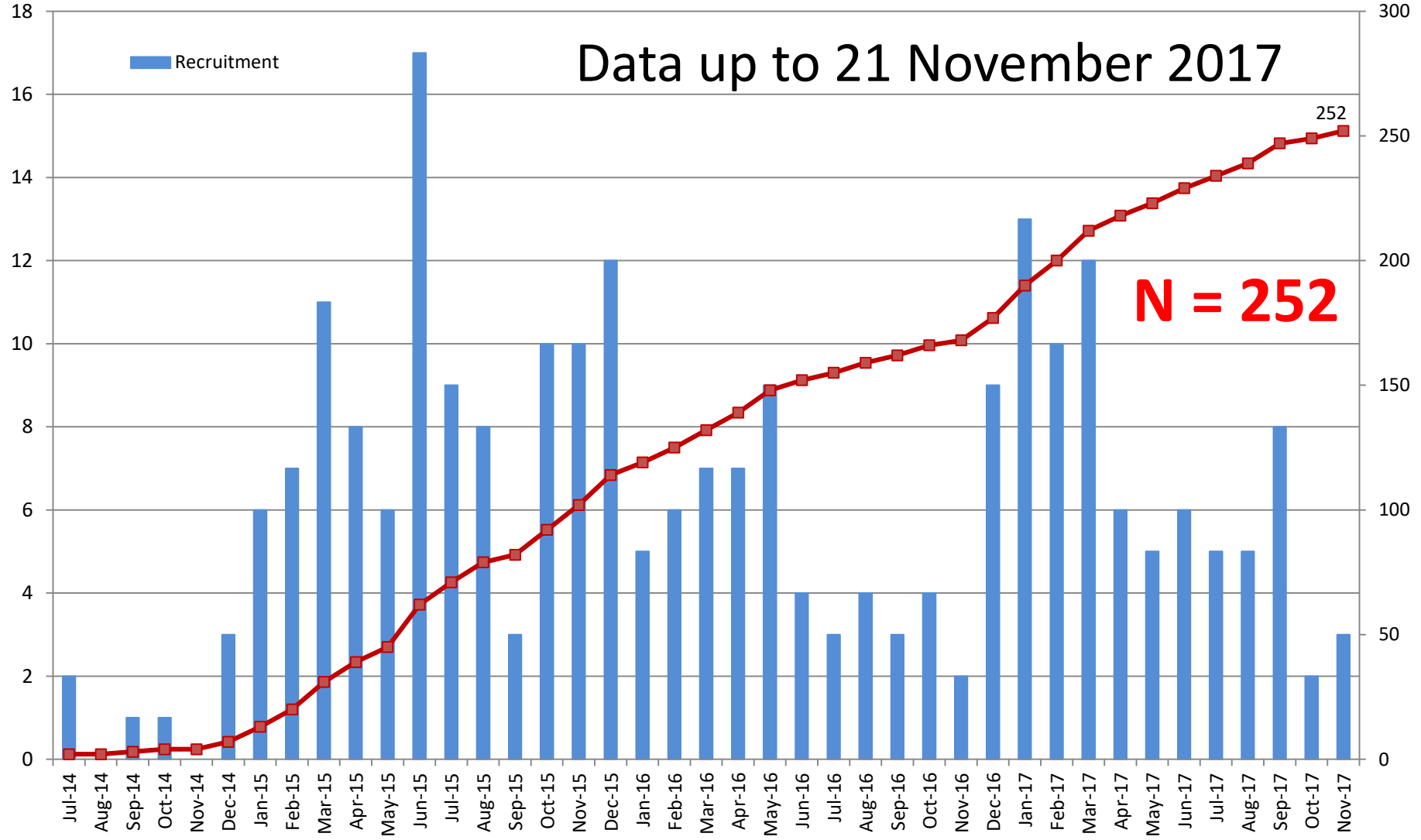
BASIL-2 Trial Co-ordinator

NHS National Institute for Health Research

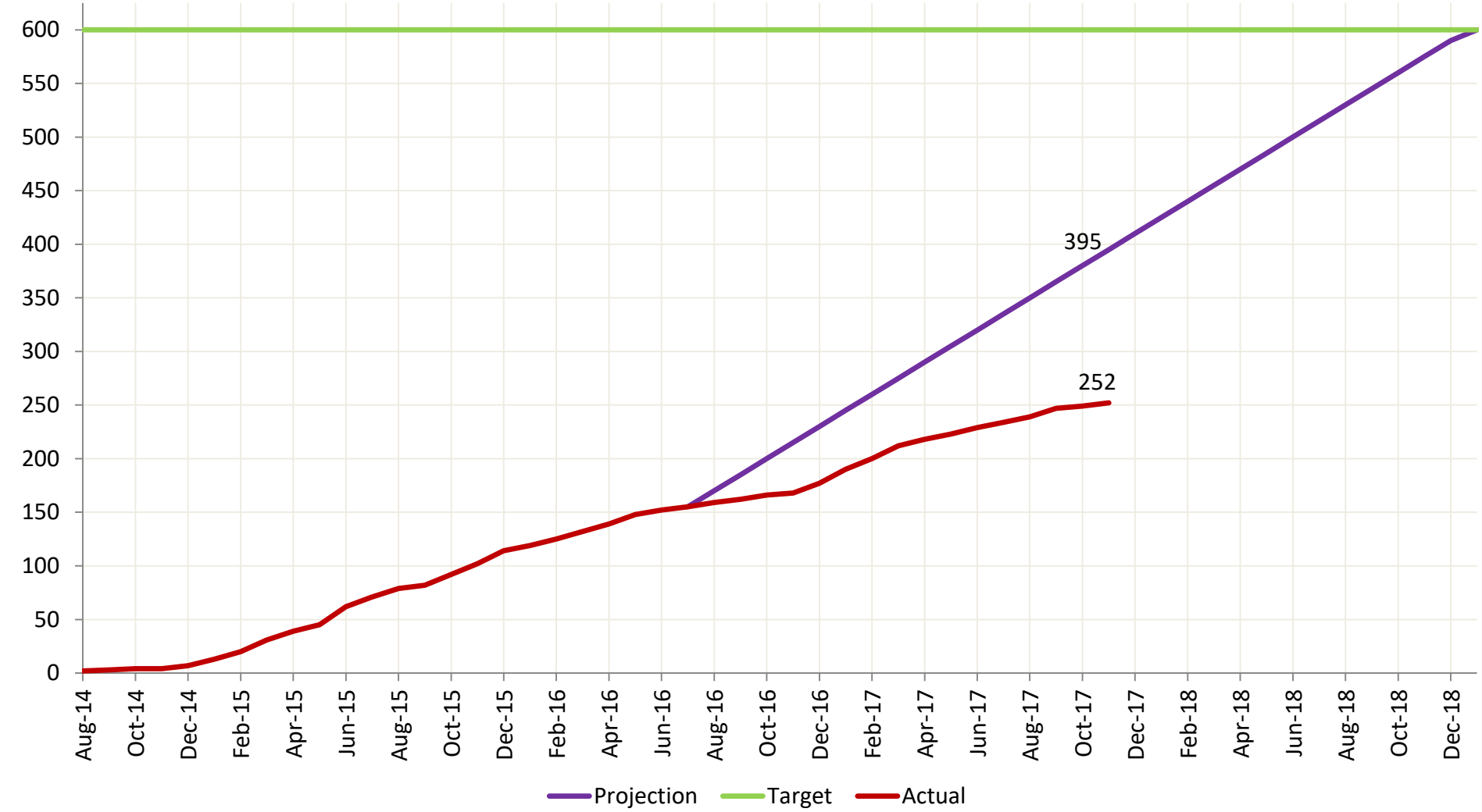
Heart of England NHS Foundation Trust

UNIVERSITY OF BIRMINGHAM

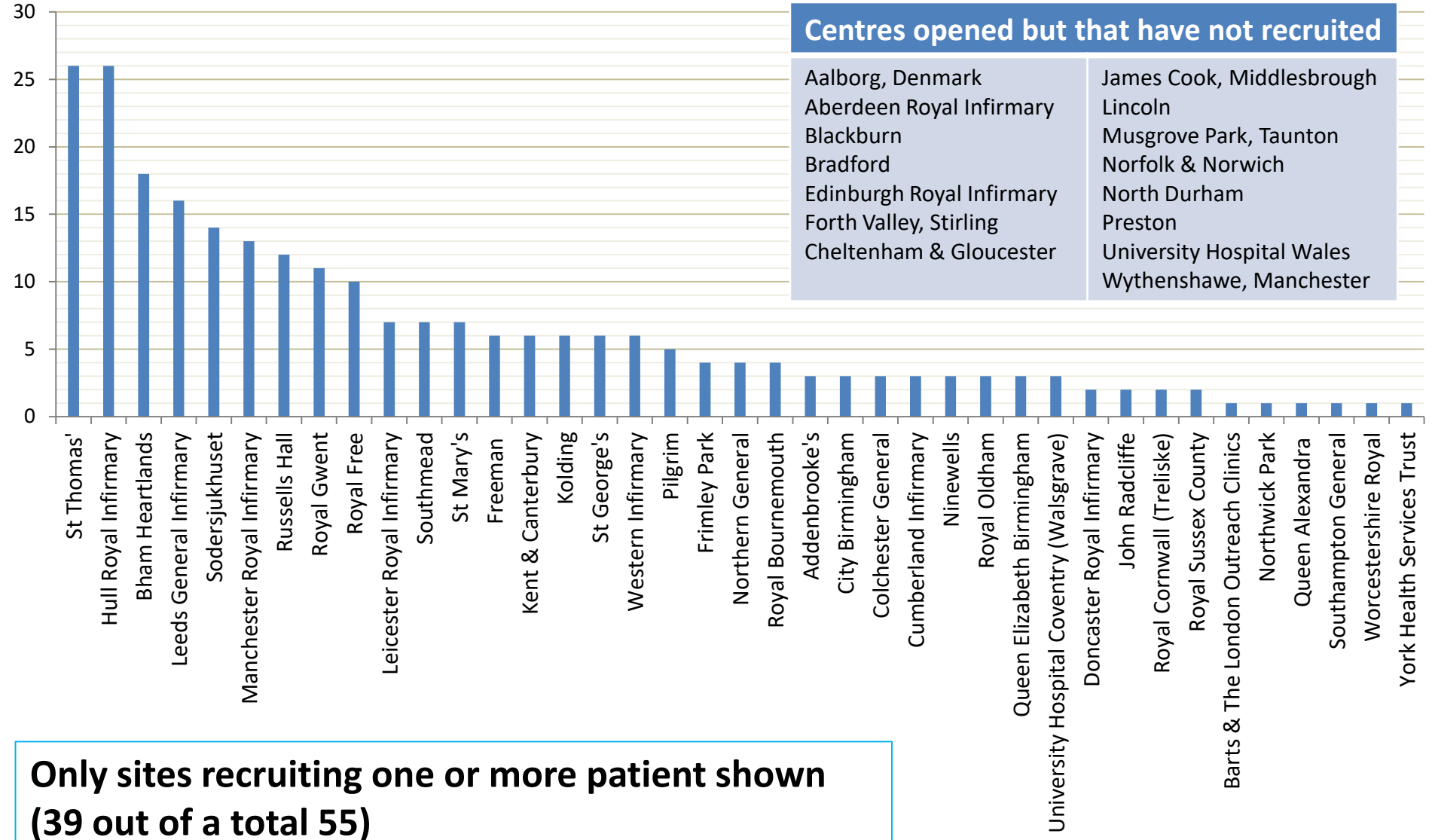
Current recruitment



Target recruitment



Recruitment by centre



Centres opened but that have not recruited

Aalborg, Denmark	James Cook, Middlesbrough
Aberdeen Royal Infirmary	Lincoln
Blackburn	Musgrove Park, Taunton
Bradford	Norfolk & Norwich
Edinburgh Royal Infirmary	North Durham
Forth Valley, Stirling	Preston
Cheltenham & Gloucester	University Hospital Wales
	Wythenshawe, Manchester

Only sites recruiting one or more patient shown (39 out of a total 55)

The academic case for

Mr Lewis Meecham

University of Birmingham

BASIL-3 Research Fellow

NHS National Institute for Health Research

Heart of England NHS Foundation Trust

UNIVERSITY OF BIRMINGHAM

Why do we need BASIL-3?

"There are already randomised controlled trials between drug eluting technology and plain balloon angioplasty and we 'know' the outcomes are better, why do we need a new trial?"

Drug coated balloon

Trial	Device	End Points	Patients
PACIFIER (2016)	IN.PACT pacific (Medtronic)	Radiological – DCB Clinical – No difference	N= 91 (1:1) Claud = 87
LEVANT 2 (2015)	Lutonix (Bard)	Radiological – DCB Clinical – No difference	N=476 (2:1) Claud = 438
BIOLUX P-1 (2015)	Passeo-18 LUX (Biotronik)	Radiological – DCB Clinical – No difference	N = 52 (1:1) Claud = 50
IN.PACT SFA (2015)	IN.PACT admiral (Medtronic)	Radiological – DCB Clinical – No difference	N=331 (2:1) Claud = 313
THUNDER (2014)	Standard Balloon coated with Paclitaxel	Radiological – DCB Clinical – No difference	N = 102 (1:1) Claud = 82
LEVANT 1 (2014)	Lutonix (Bard)	Radiological – DCB Clinical – No difference	N = 92 (1:1) Claud = 94
DEBELLUM (2012)	IN.PACT admiral (Medtronic)	Radiological – DCB Clinical – No difference	N = 50 (1:1) Claud = 45
FemPac (2008)	Coated PTA Balloon (Bavaria MT GmbH)	Radiological – DCB Clinical – No difference	N = 87 (1:1) Claud = 82

Drug eluting stent

Trial	Device	End Points	Patients
ZILVER PTX (2011)	ZILVER PTX (COOK)	1° Patency (12m) – 83.1% vs 32.8% FF TLR – 90.5% vs 82.5% Amputation – 0% vs 0% Overall survival 100% vs 100%	DES=241 PBA=238 R2/3 - 91% R4-6 – 9%

Some other stent trials comparing DES vs BMS in femoro-popliteal segment:

- Duda et al. 2002
- Duda et al. 2006 SIROCCO trial

Majority of DES trials in the infra-popliteal segment:

- Rastan et al. 2012
- Scheinert et al. 2012
- Tepe et al 2010 BELOW study
- Falkowski et al. 2009
- Siablis et al. 2014 IDEAS trial

Evidence for DCB/DES in CLTI

Most trials are industry sponsored

Most patients are claudicants

Most CLTI patients have rest pain only (Rutherford 4)

Highly selected (centres, patients, lesions)

Exclusions and short (incomplete) follow-up

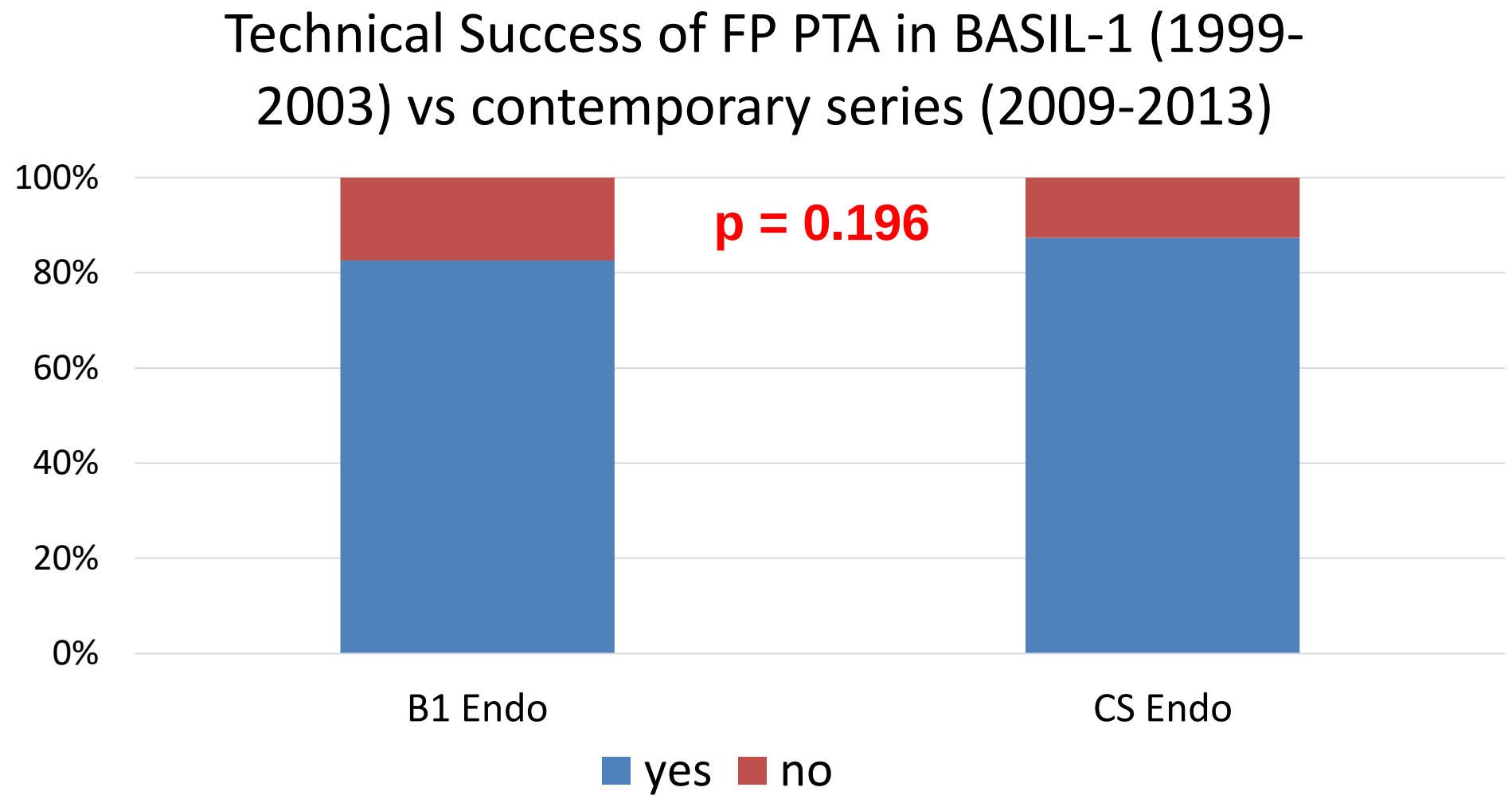
Few “head to head” comparisons

Anatomic, not clinical, end-points

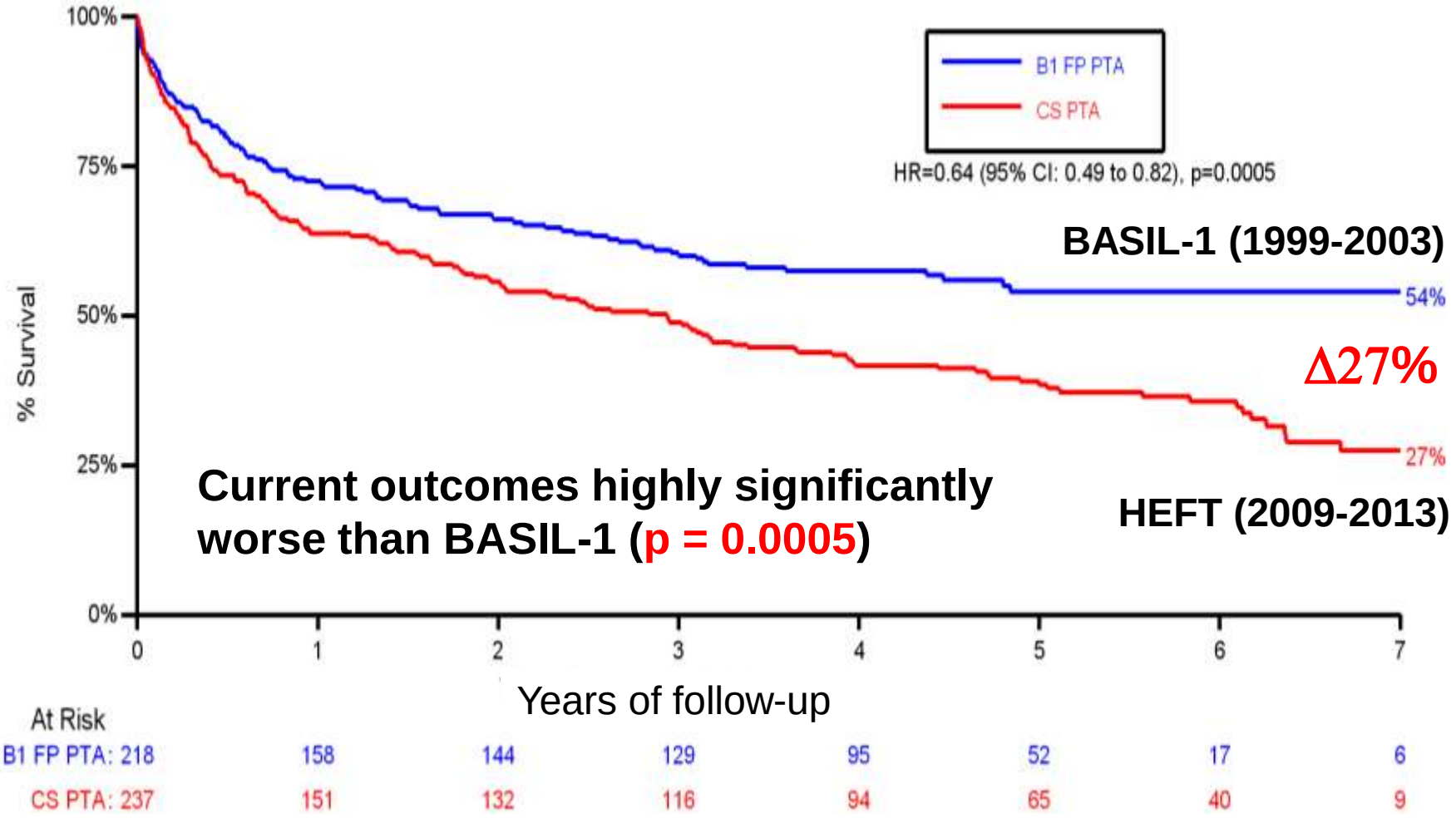
No cost-effectiveness analysis

UK NICE: no credible evidence of real world clinical benefit at current ‘willingness to pay’ thresholds; await BASIL-3 before recommending DCB/DES

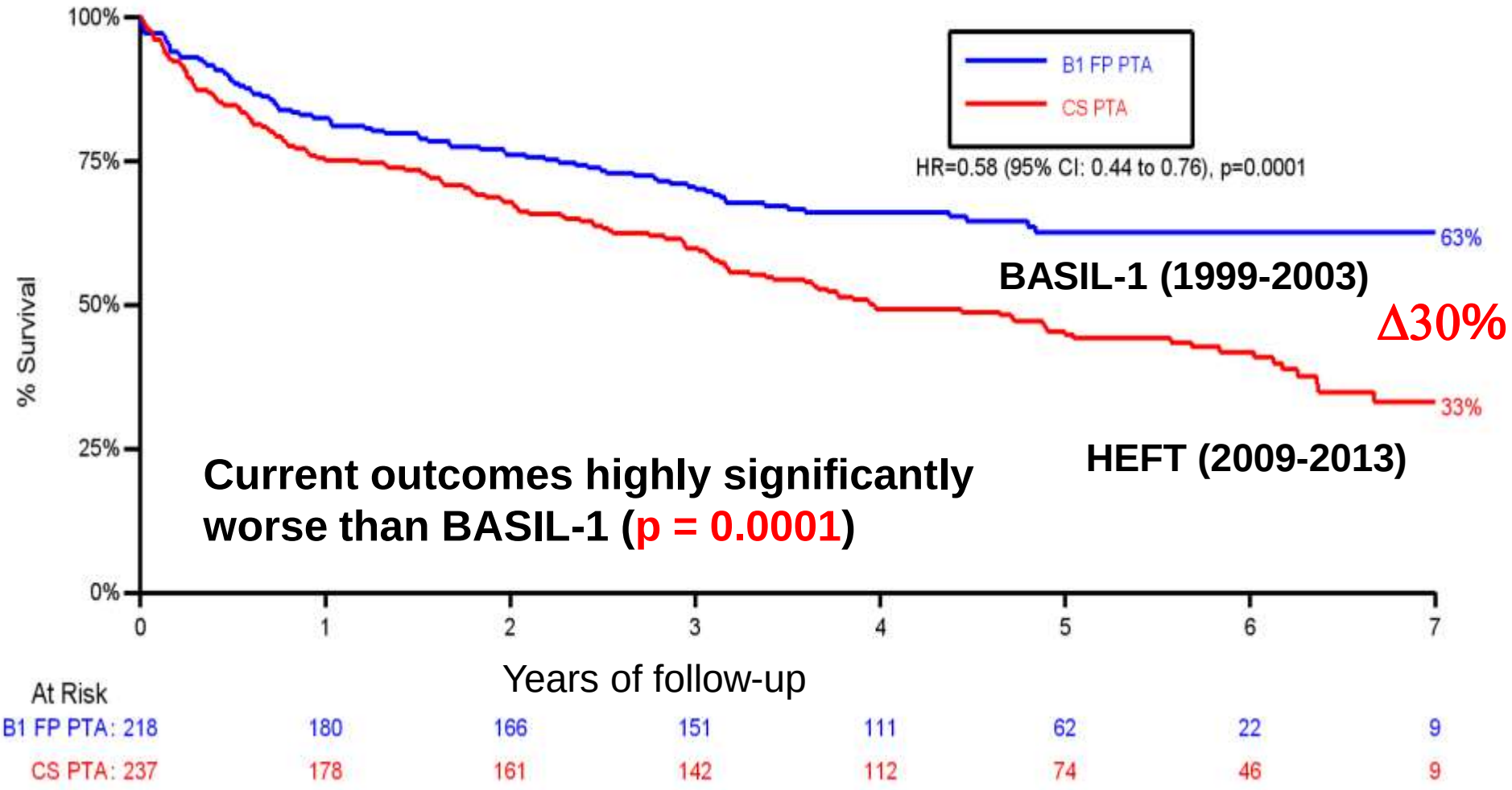
Has technical success improved?



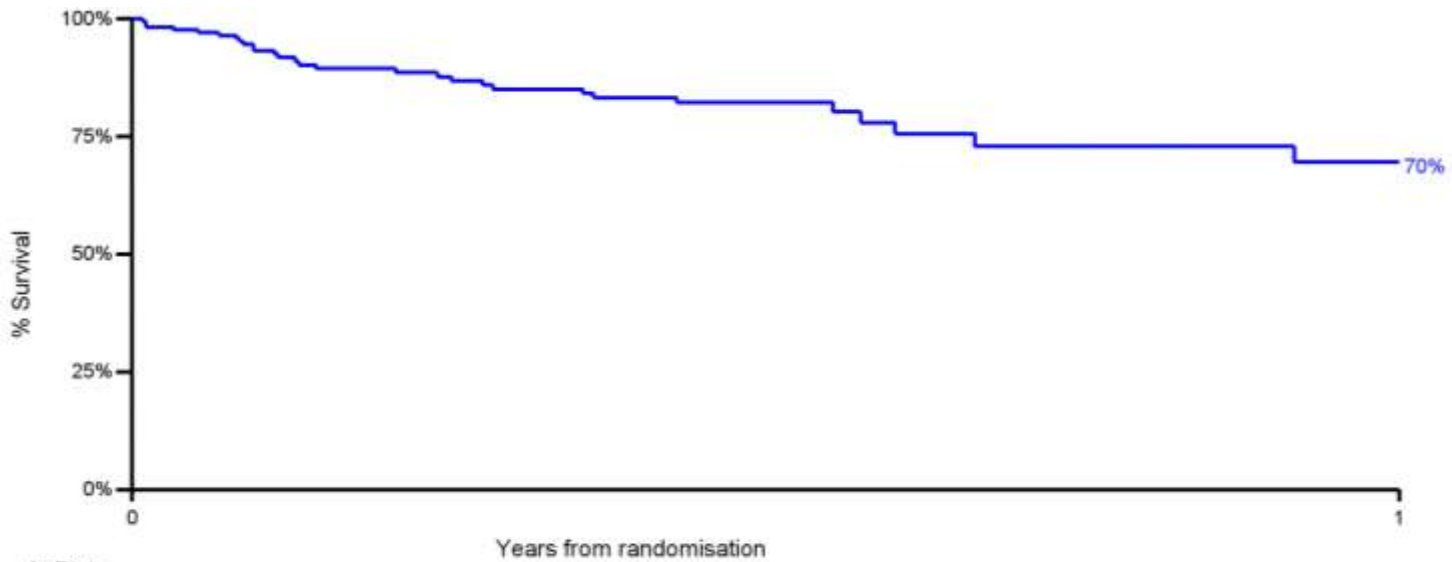
Amputation free survival after femoro-popliteal plain balloon angioplasty in BASIL-1 and in a contemporary series at HEFT

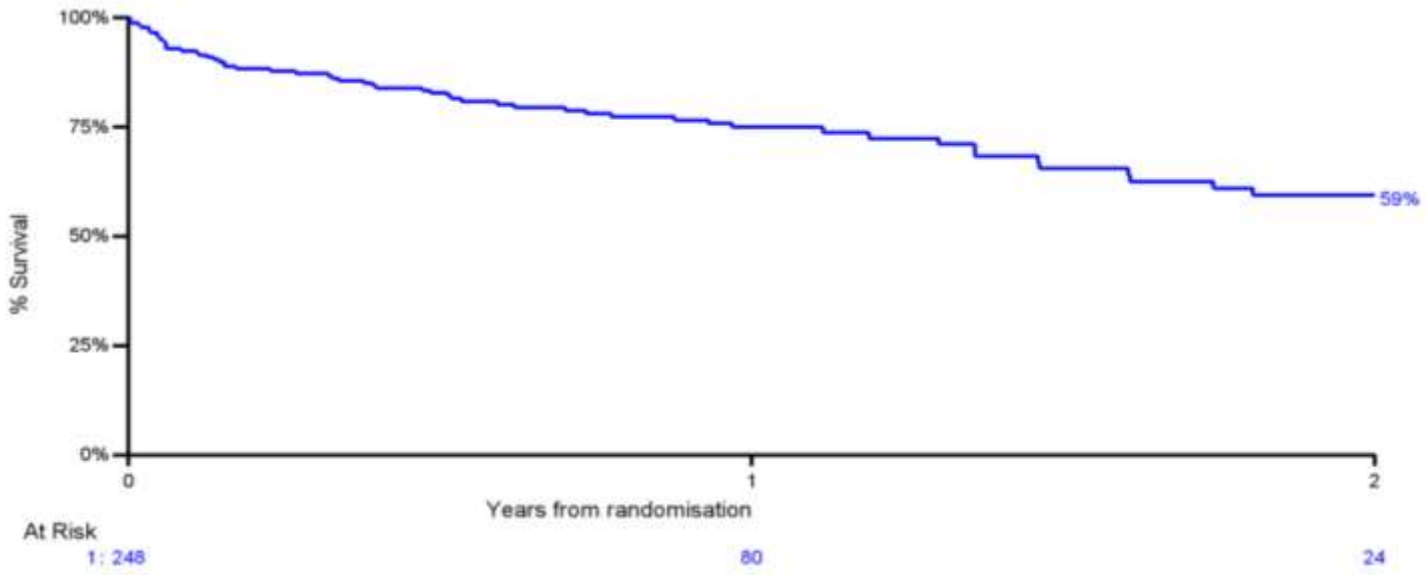


Overall survival after femoro-popliteal plain balloon angioplasty in BASIL-1 and in a contemporary series at HEFT



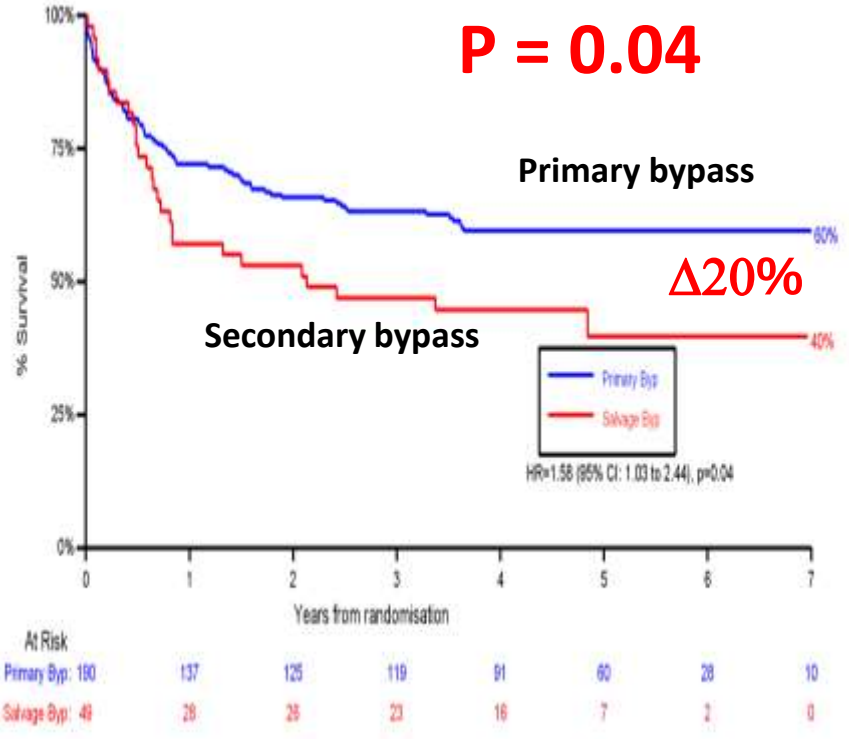
AFS in BASIL 2 and 3



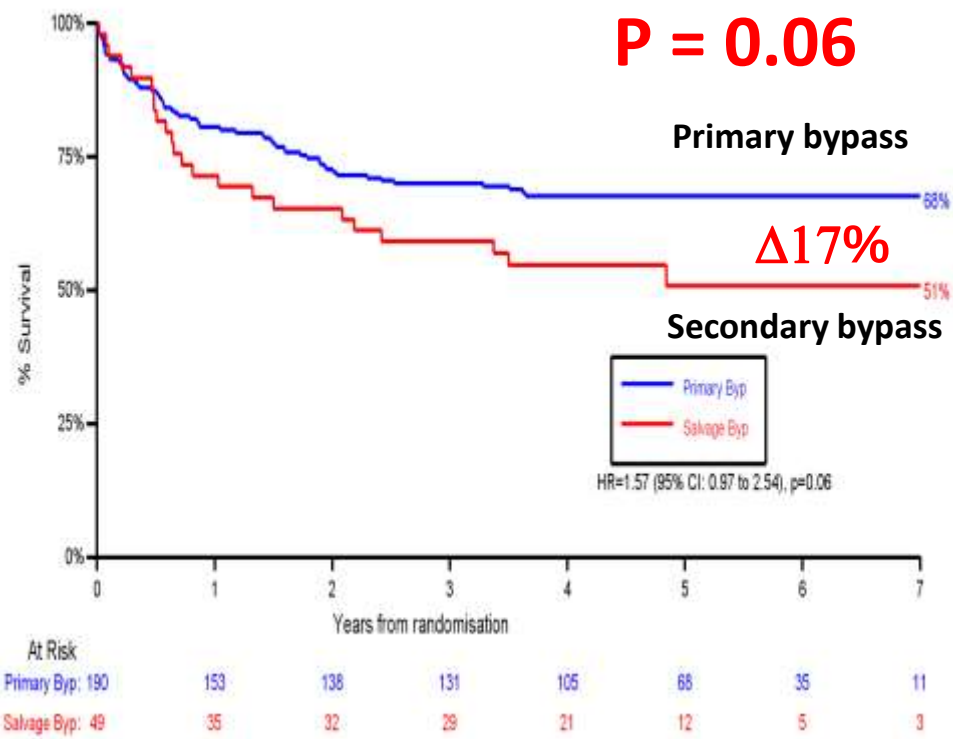


Outcomes following primary bypass and secondary bypass after failed PBA in BASIL-1

Amputation free survival



Overall survival



AFS and OS worse after secondary bypass for failed PBA

Recruitment update

Mr Hugh Jarrett

University of Birmingham

BASIL-3 Senior Trial Co-ordinator

Birmingham Clinical Trials Unit

National Institute for Health Research

Heart of England NHS Foundation Trust

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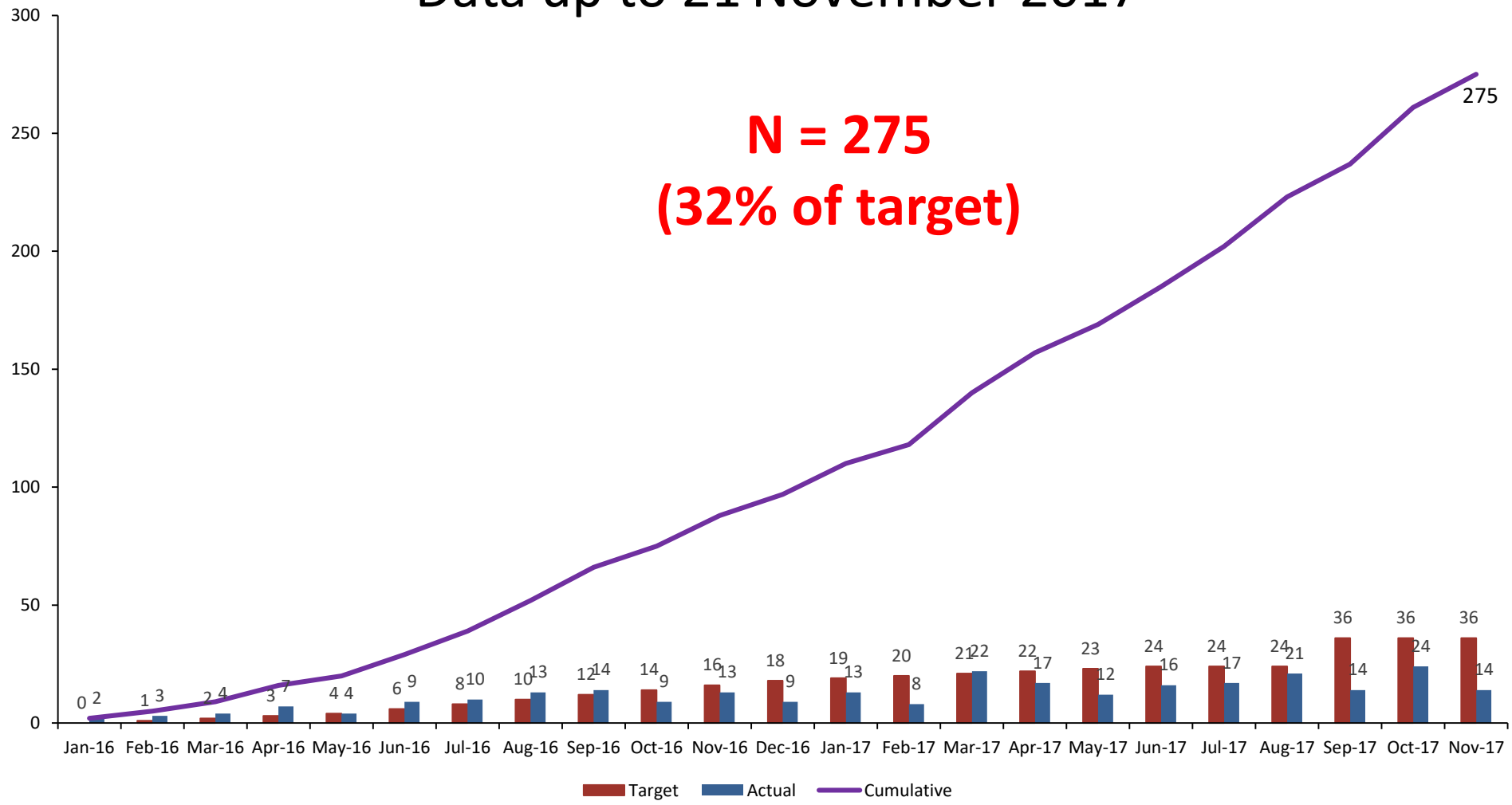
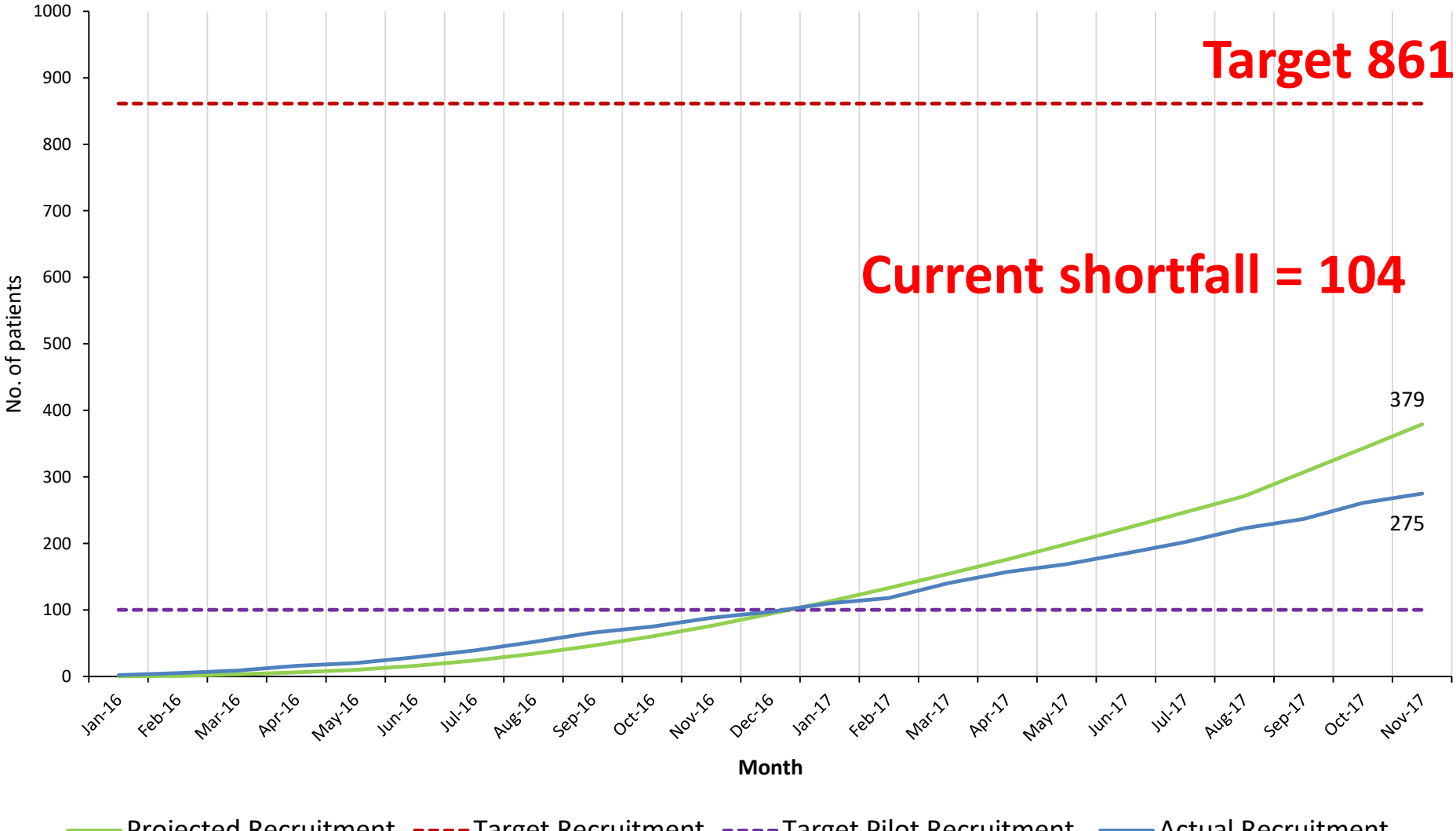
BASIL-3 recruitment

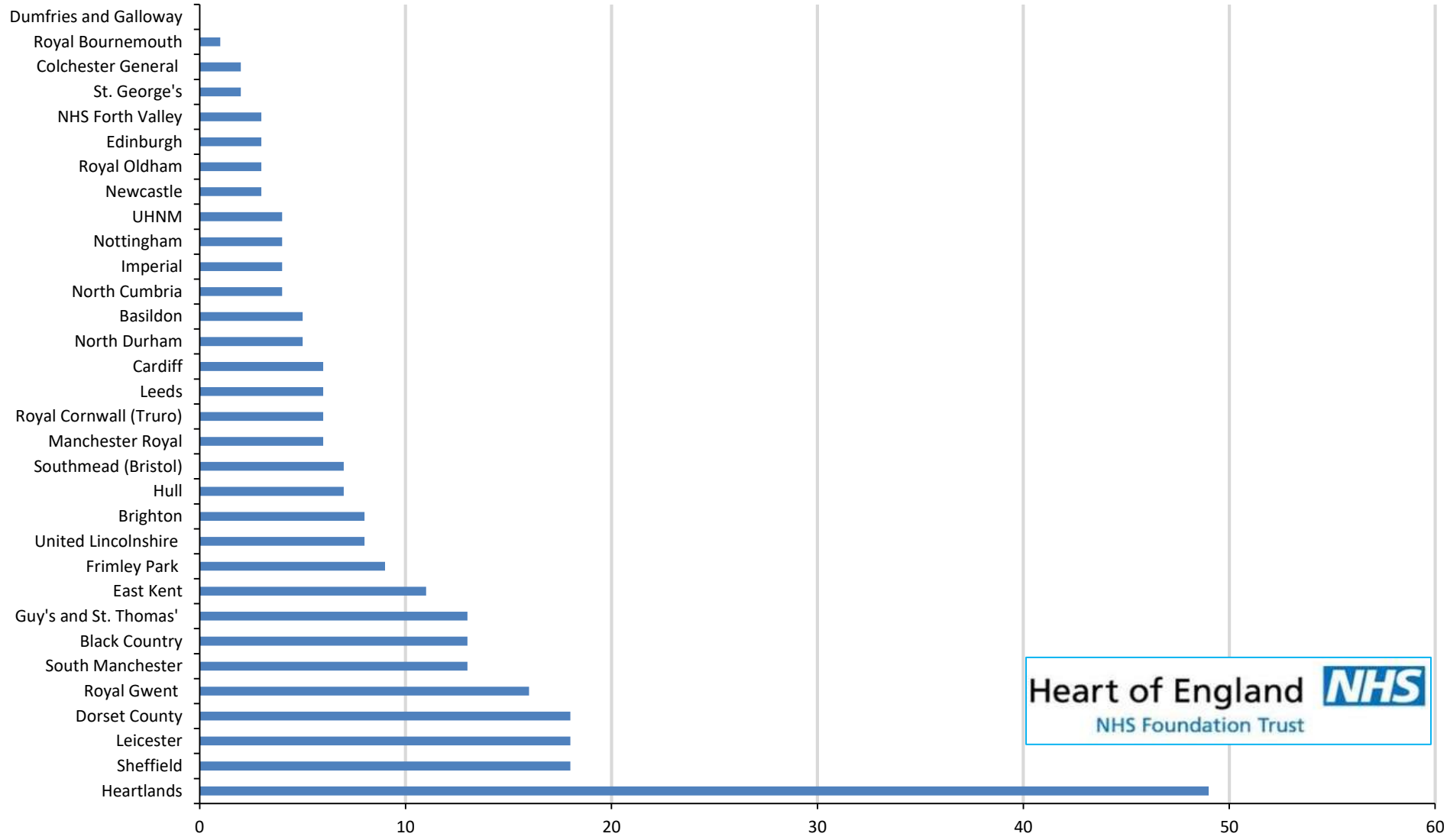
Data up to 21 November 2017



BASIL-3 recruitment



Recruitment by centre



Summary

Professor Andrew Bradbury

BASIL 2 and 3 Chief Investigator

Birmingham Clinical Trials Unit

UNIVERSITY OF BIRMINGHAM

NHS National Institute for Health Research

Heart of England NHS Foundation Trust

BASIL-3 Summary

- Should be a much easier than B-2 as three endovascular arms
- Recruitment is due to complete Q1 2019
- End of study Q3 2021
- Pilot phase recruited ahead of schedule
- But, monthly recruitment has reduced in proportion to the number of centres now open and we are now increasingly falling behind target – **why?**

Follow-up Issues

Mr Gareth Bate

University of Birmingham

BASIL Senior Research Nurse

BASIL Follow-up

PROM/HRQL data are arguably the most important data and are **time sensitive**; can be completed

- Face to face (clinic or home)
- Telephone
- Post (local or Trial Office administration)

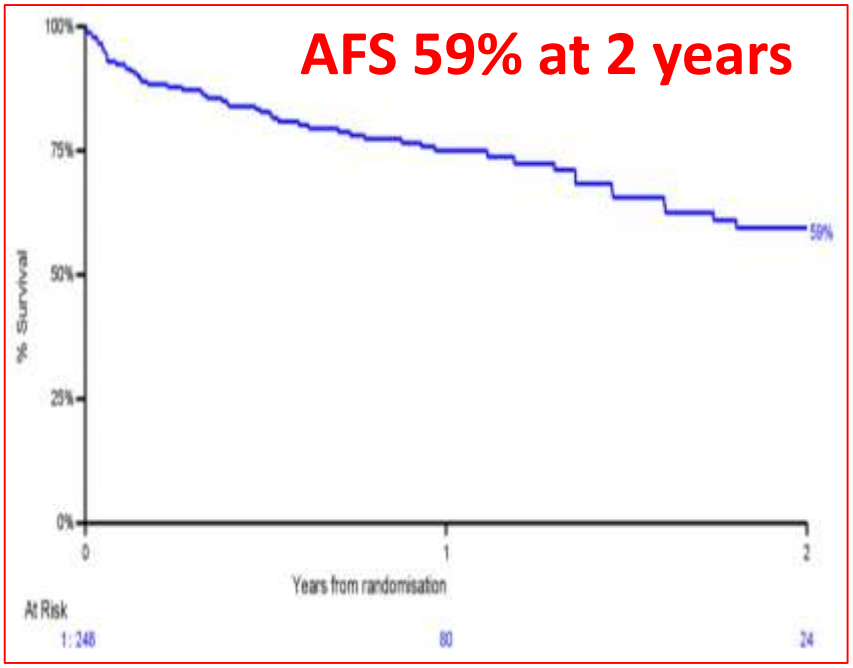
Can collect many clinical outcomes from routine hospital data and central data-bases (+ telephone interviews)

Flexible – will work pragmatically with local PI's to overcome barriers to follow-up (travel expenses)


ORIGINAL MOTION PICTURE SCORES
All Music Composed And Conducted By MIKLÓS RÓZSA
QUO VADIS
BASIL-2
incl. Madame Bovary · Ivanhoe · Plymouth Adventure
TSUNAMI

B2 HTA 13 November 2017

- Recruitment difficult: intellectual vs. logistical equipoise
- 600 by end 2018 unrealistic
- Significantly underspent
- Event rate (AFS) as anticipated
- Longer recruitment and follow-up
- Events ↑ = statistical power ↑
- Important secondary end-points
- HE analysis (time sensitive data)
- Patient journey (quality of revascularisation)
- More overseas centres?
- Meta-analysis with BEST-CLI in the US

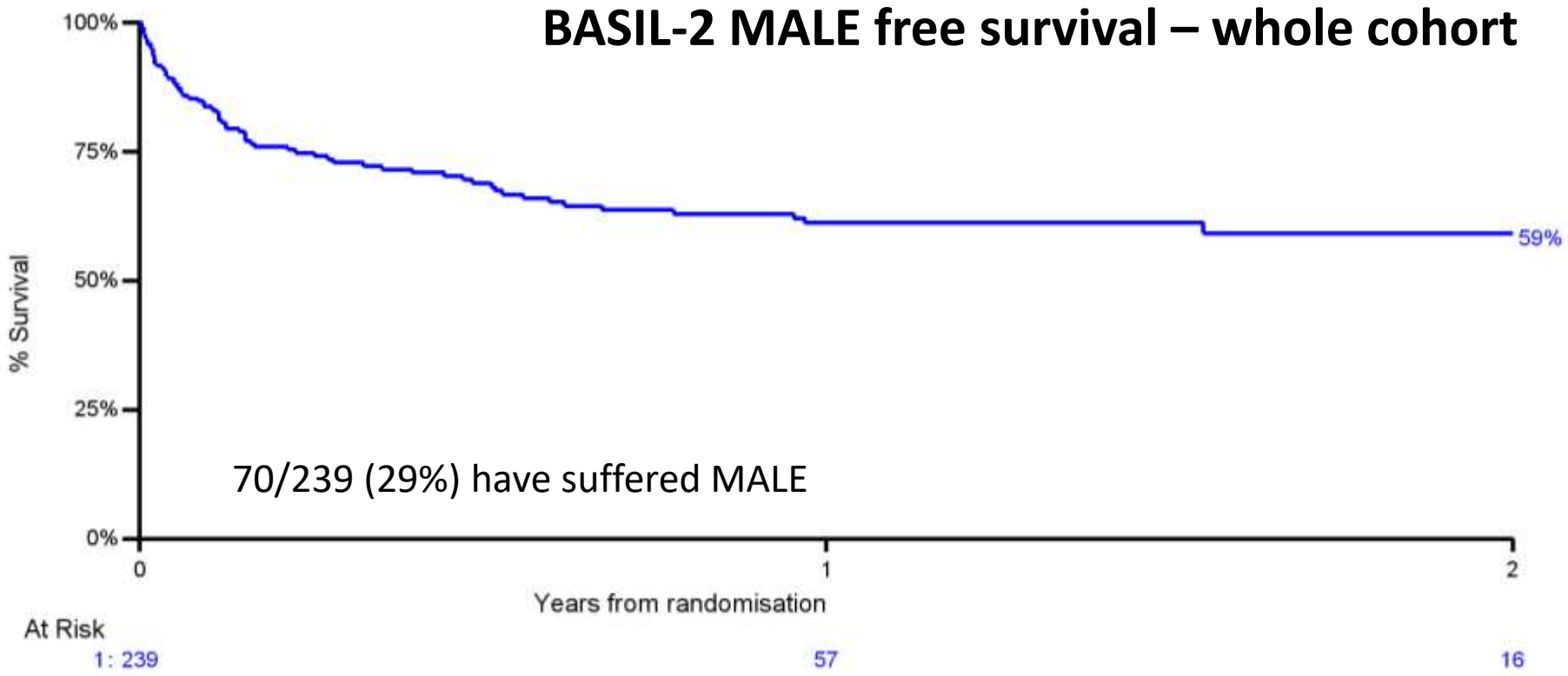


BEST-CLI
Best Endovascular versus Best Surgical Therapy in Patients with Critical Limb Ischemia

Major adverse limb event (MALE)

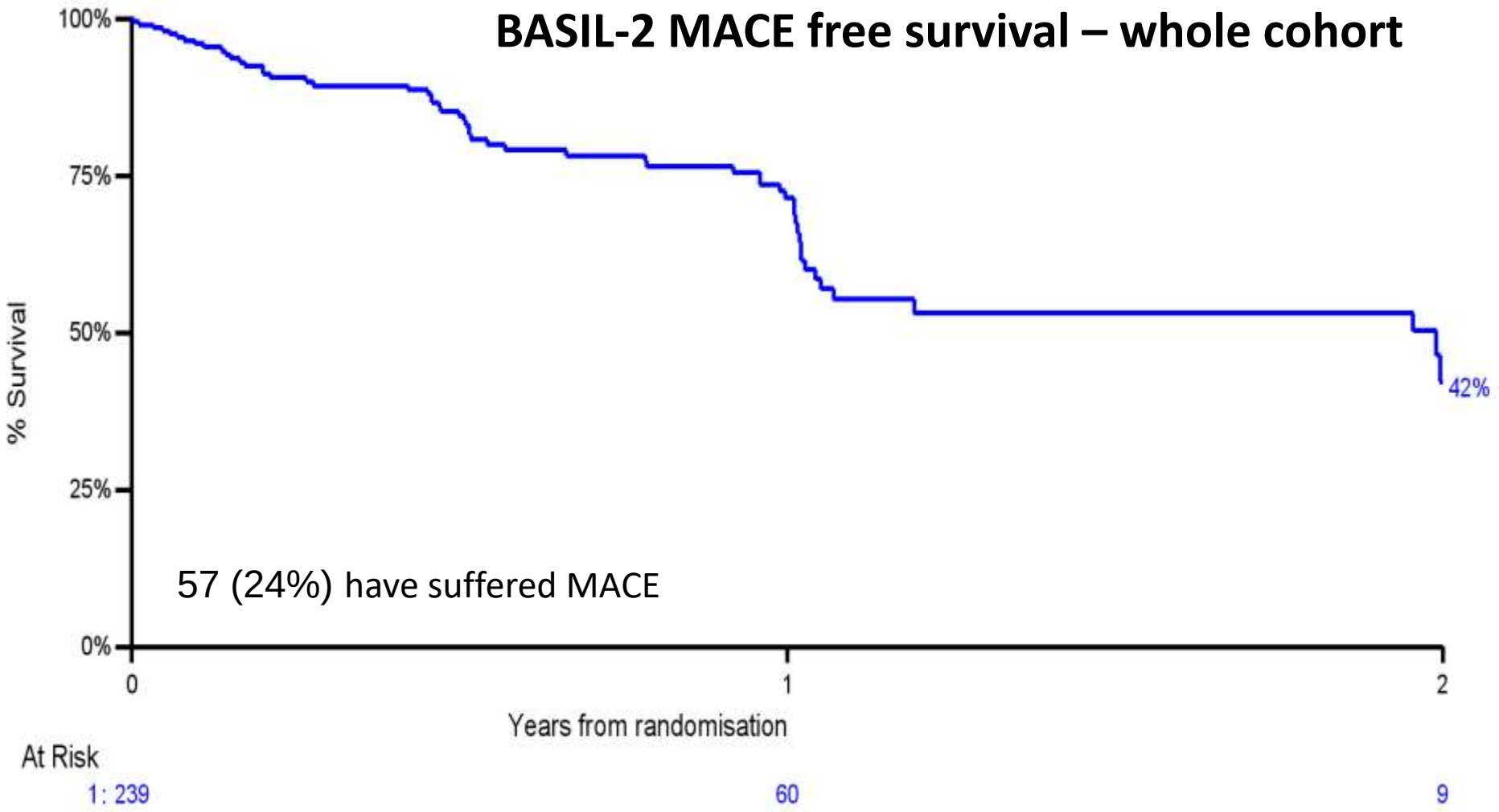
MALE is defined as defined as one or more of the following:

- Amputation (trans-tibial or above)
- Major vascular intervention (thrombectomy, thrombolysis, endarterectomy, patch angioplasty)
- Balloon angioplasty or stenting (re-intervention or cross-over)
- Bypass surgery (re-intervention or cross-over)



Major adverse cardiovascular event (MALE)

MACE is defined as defined as one or more of the following: amputation (trans-metatarsal or above) to the non-trial leg, MI, stroke, TIA. CLTI in non-trial leg



B2 HTA 13 November 2017

Option 1 - Follow the current contract timeline (stop recruitment now, request a 3-month cost-free extension to permit a minimum of 2 years follow-up, power 56%)

Option 2 - Continue recruitment until the original target of 600 patients is reached (which we predict would require a 59-month costed extension, overpowered)

Option 3

- Continue recruitment until existing funding is exhausted
- If we recruit at long term average then with current funding we can recruit 400-450 patients by Q2 2020
- 2-7 year follow (**expected > 80% power**)

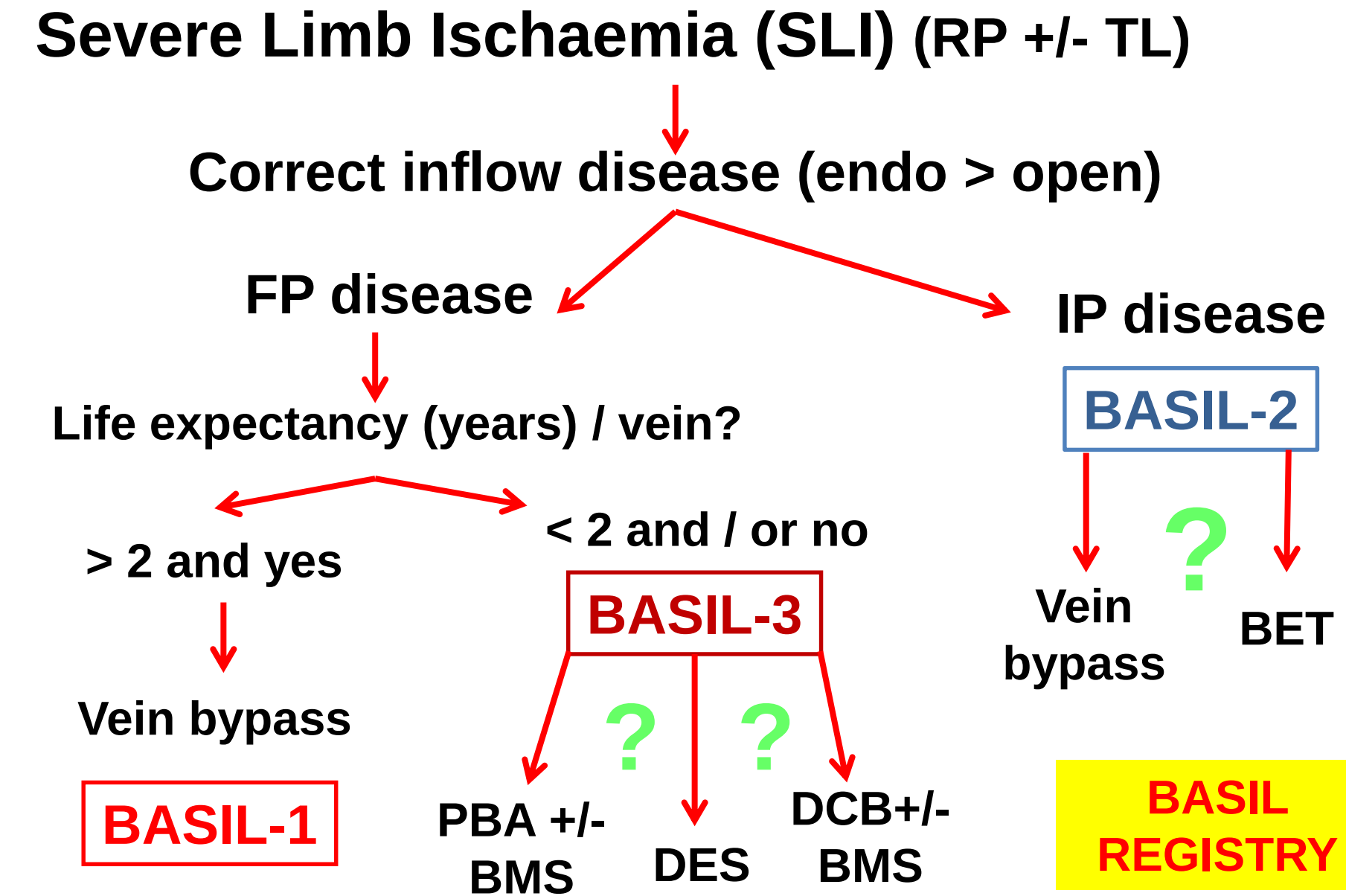
BASIL-2 Option 3

Assume 255 by end November 2017

29 months to end April 2020

- 6 per month (174) = 429
- 7 per month (203) = 458
- 8 per month (232) = 487

BASIL Trials Overview



Thank you – Questions?

http://www.birmingham.ac.uk/research/activity/mds/trials/bctu/trials/portfolio-v/Basil-2/index.aspx

http://www.birmingham.ac.uk/research/activity/mds/trials/bctu/trials/portfolio-v/Basil-3/index.aspx