



UNIVERSITY OF  
OXFORD

Oxford University Hospitals **NHS**  
NHS Trust

The word 'OVIVA' in a bold, black, sans-serif font. Above the second 'V' is a small, stylized illustration of a bone structure, possibly a vertebra or a joint, rendered in a light brown/gold color.

*M Scarborough, HK Li, R Zambellas, I Rombach and NOC BIU*



**NHS**  
**National Institute for  
Health Research**

Bone + Joint infx: Oral Vs Iv antibiotics



Oral Vs. IV Antibiotics for BJI

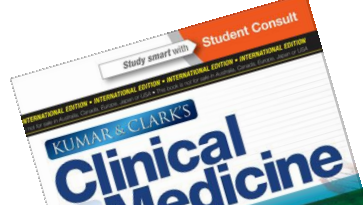
OVIVA

# Background

- Within NHS per year
  - 180,000 joints & fracture procedures / yr
  - ~3000 post-operative infections
  - ~5000 diabetic foot osteomyelitis
  - ~2000 other OM
  - Cost £20,000 – £40,000 per patient
- Current Practice
  - Prolonged, high dose, IV antibiotics
    - Associated patient inconvenience, risks, costs
    - OPAT not universally available
- Antibiotic treatment costs
  - 6/52 IV ~£2000
  - 6/52 PO ~£200

# What's the evidence for IV therapy?

- **Expert opinion**
- Trial evidence



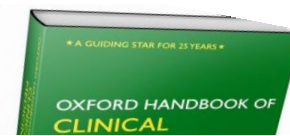
THE NEW ENGLAND JOURNAL OF MEDICINE

Jan. 22, 1970

## MEDICAL PROGRESS

### OSTEOMYELITIS: A REVIEW OF CLINICAL FEATURES, THERAPEUTIC CONSIDERATIONS AND UNUSUAL ASPECTS (First of Three Parts)\*

FRANCIS A. WALDVOGEL, M.D., GERALD MEDOFF, M.D., AND MORTON N. SWARTZ, M.D.



In our experience, clinically recurrent osteomyelitis is rarely controlled without the combination of careful, complete surgical debridement and prolonged (four to six weeks) parenteral antibiotic therapy at high dosage.



# What's the evidence for IV therapy?

- Expert opinion
- **Trial evidence**

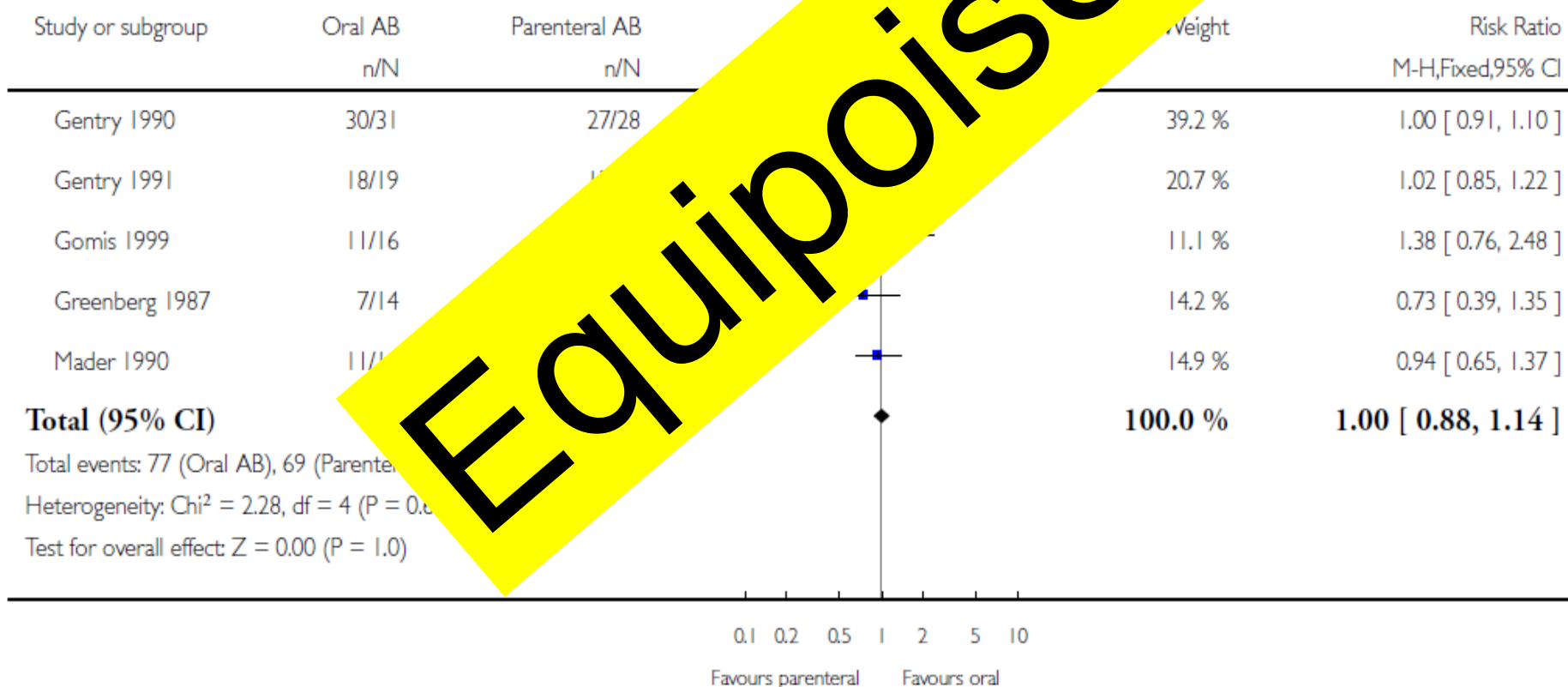
Study	PO / IV	N	PO (%)	IV (%)	p value
Endocarditis Heldman '96	Cip+Rif / Oxacillin	44	95	88	0.6
Spontaneous Bacterial Peritonitis Navasa '96	Oflox / Cefotaxime	123	84	85	1.0
Skin and Soft Tissue Infection (MRSA) Weigelt '05	Linezolid / Linezolid	592	91.2	93.5	0.34
Open hernia prophylaxis Kuzu '05	Augmentin / Augmentin	408	99.5	98.5	n/a
Community Acquired pneumonia (Paeds) Atkinson '07	Amox / Benpen	246	97	96	n/a
Perforated appendix Adibe '08	Co-T / Amp-sulbactam	149	96	86	0.08
Febrile neutropenia Gupta '09	Oflox+Amox / Ceftriax	123	90	93	0.74
S. aureus osteomyelitis Euba '09	Co-T + Rif / Cloxacillin	42	92	94	1.0
Osteomyelitis (Cochrane) Conterno '09	Various / Various	180	82	80	1.0

## Analysis 1.1. Comparison 1 Oral antibiotic versus parenteral antibiotic (AB) Outcome 1 Remission at the end of treatment.

Review: Antibiotics for treating chronic osteomyelitis in adults

Comparison: 1 Oral antibiotic versus parenteral antibiotic (AB)

Outcome: 1 Remission at the end of treatment



**“The main finding of this review is the lack of evidence to inform practice.”**



# So.....

- No evidence that IV antibiotic therapy is superior in several types of infection
- Variation in practice
- Insufficient evidence to state that oral therapy is non-inferior to IV therapy in BJI





# OVIVA Trial design

- Pragmatic — open label, **oral vs IV for first 6/52**, non-CTIMP
- No trial specific samples / investigations / clinics
- Wide data point margins (@ ~ 6/52, 4/12, 1 yr)
- Follow up - 1 year
- Hard end points

# End points

- Primary – definite treatment failure\*
  - Bacteriological, histological, clinical
- Secondary
  - SAEs
  - Line complications
  - Probable or possible treatment failure\*
  - Early termination of randomised route
  - Resource utilisation
  - Questionnaire results

\* All definite, probable and possible treatment failures are reviewed by the EPC using **redacted notes**

# Inclusion / Exclusion

- A clinical syndrome comprising any of the following; a) localized pain OR b) localized erythema OR c) temperature  $\geq 38.0^{\circ}\text{C}$  OR d) a discharging sinus or wound AND
- willing and able to give informed consent
- aged 18 years or above
- the patient has not received any systemic antimicrobial therapy for joint or joint space infection within 12 months prior to randomization

## Adults

Bone, joint or metalware infx

Has had < 7 days IV therapy

Can consent

Likely to live for a year

- *Staphylococcus aureus* bacteraemia on previous treatment within last 1 month OR
- bacterial endocarditis on previous treatment within last 1 month OR
- there are no studies required to be included in the review
- Staph bacteraemia, endocarditis etc.
- Needs IVs for other reasons
- No oral option
- Wouldn't normally get 6/52 abx
- Unlikely to comply
- TB / fungal / parasitic infx
- Receiving an IMP
- The patient is receiving an investigational medical product as part of another clinical trial.



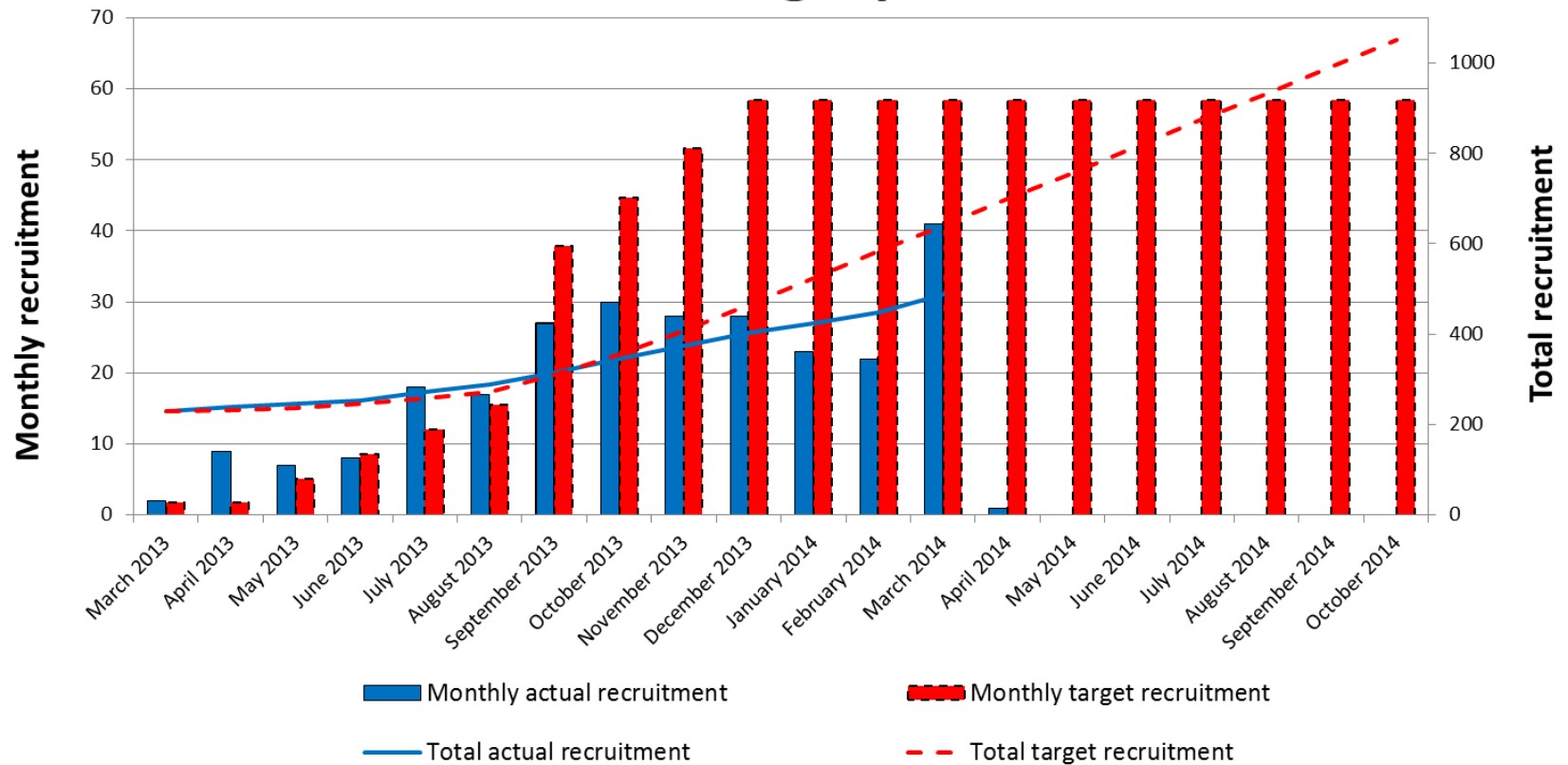
# Typical cases

- Single stage, 1<sup>st</sup> stage or DAIR for PJI
- Osteomyelitis treated surgically
- Infected metalware treated surgically
- Discitis/spondylitis
- Dialysis-related osteomyelitis

i.e. ~ any '6 weeker'

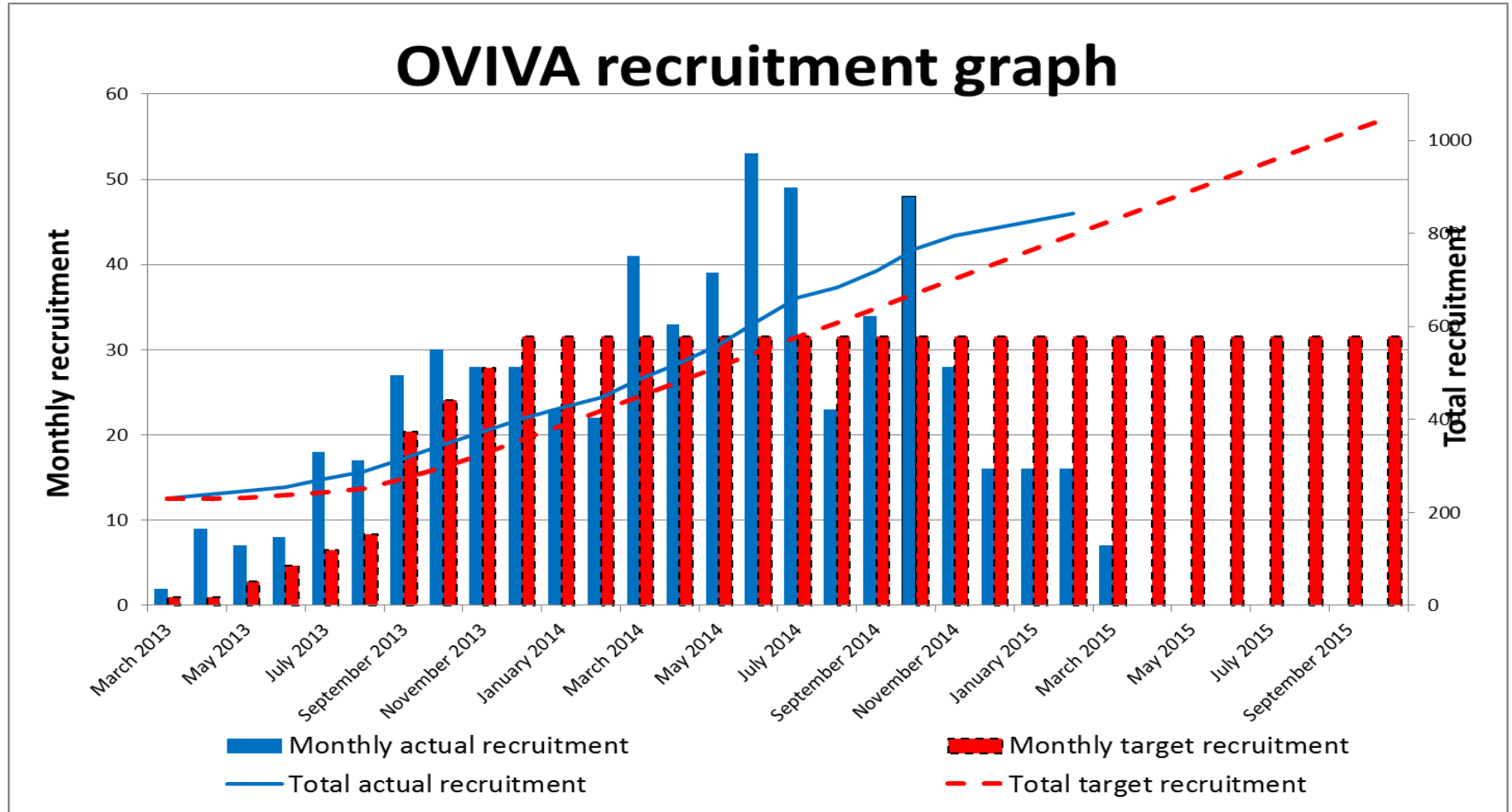
# This time last year.....

## OVIVA recruitment graph





..... and now.



# Participating centres

- Birmingham Heartlands
- Brighton and Sussex
- Bristol Royal Infirmary
- Cambridge
- Gartnavel General
- Guys and St Thomas' Hospitals
- Hull Royal Infirmary
- Kings Lynn
- Leeds Teaching Hospitals
- Medway Maritime, Kent
- Newcastle
- Norfolk and Norwich
- Northampton
- Northumbria
- Oxford
- Royal Cornwall , Truro
- Edinburgh
- Royal Free + RNOH, London
- Royal Hallamshire, Sheffield
- Liverpool University Hospital
- University Hospital, North Staffs
- Tayside University Hospitals Trust
- Tunbridge Wells
- University College Hospital, London



## Enrolment

Assessed for eligibility (n=1485)

### Not randomised (n=249)

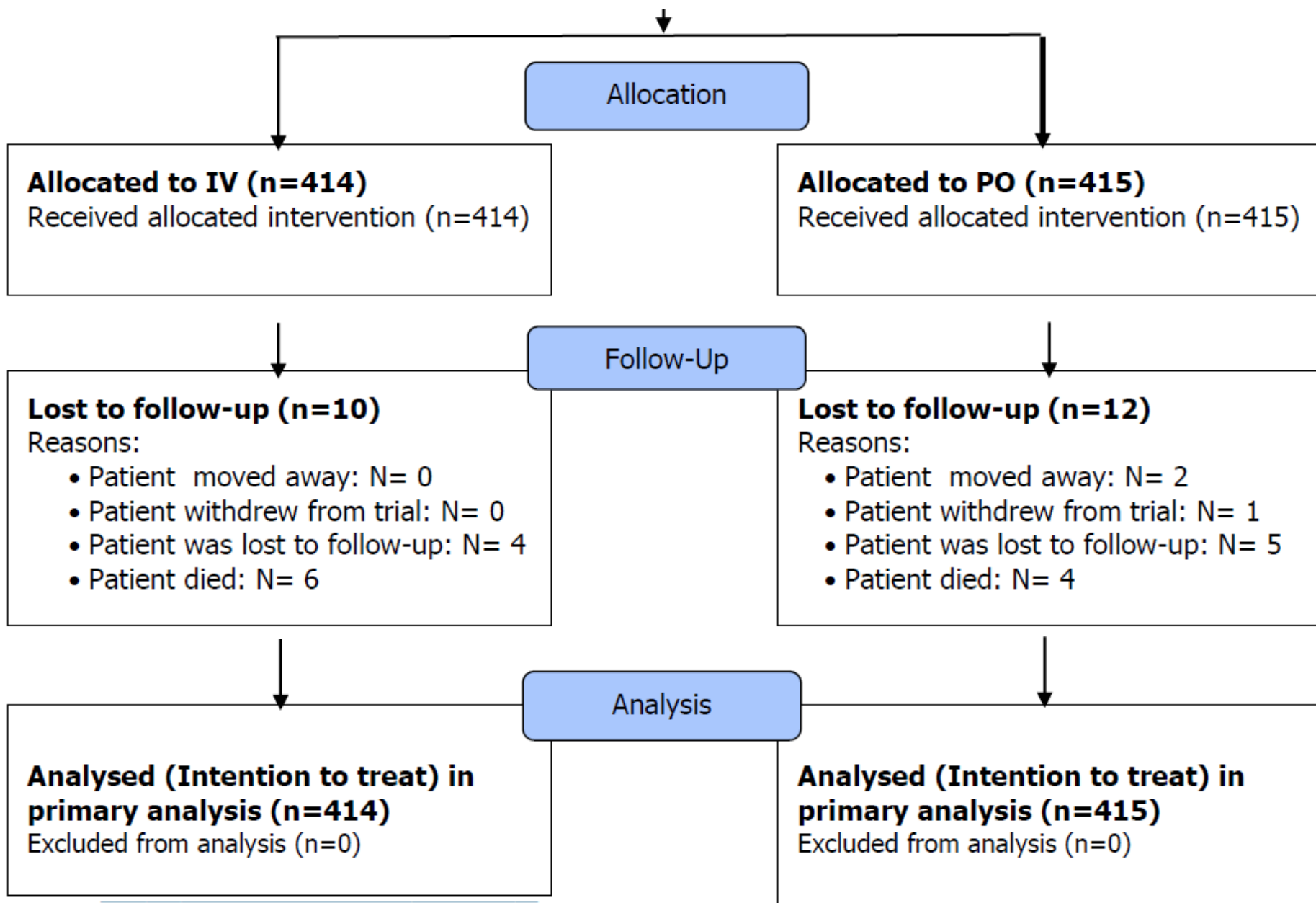
- Prefer IVs, N= 49
- Prefer POs, N=, N=29
- OPAT out of area, N=15
- Left to go abroad, N=9
- Doctors not in agreement, N= 4
- Discharged before randomisation, N=1
- Pre-planned Hickman line, N= 1
- Unable to read questionnaire, English not being the first language, N=1
- Declined without providing further reason, N= 107
- Reasons not reported, N=33

Eligible (n=1078)

Randomised (n=829)

### Not eligible (n=407)

- Staph aureus bacteraemia, N=19
- Bacterial endocarditis, N= 25
- Concomitant infection mandating IV therapy, N=19
- Mild disease requiring <6/52 antibiotics, N=62
- No suitable PO regimen available, N=60
- Previous enrolment in the trial, N=8
- Shock or other features mandating long IV therapy, N=4
- Unlikely to comply with trial requirements, N=43
- Mycobacterial, fungal, parasitic or viral aetiology, N= 7
- Receiving an investigational product in another trial, N=2
- Reasons not reported, N=158



# NB

- Treated, for analysis purposes, as a blinded trial  
(NO RESULTS REPORTED HERE)
- Oral follow-on allowed in either arm (~2/3)
- Adjunctive rifampicin allowed in either arm

# Baseline diagnoses

Diagnosis	Total (n=818 (%))
Chronic osteomyelitis	268 (32)
Chronic OM (not debrided)	38 (4)
Removal of metalware	271 (33)
DAIR	196 (23)
Single stage revision	78 (9)
Vertebral infx debrided	18 (2)
Vertebral infx not debrided	20 (2)

Histology	Total (n=753 (%))
Infected	425 (57)
Equivocal	24 (3)
Uninfected	44 (6)
Not done	257 (34)
Microbiology	
Staph aureus	286 (38)
CONS	143 (19)
Streptococci	20 (2)
GNR	106 (14)
Pseudomonas	36 (5)

# Antibiotics

IV treatment	% planned	% received
Glycopeptides	42	45
Penicillins	4.8	11.2
Cephalosporins	36.4	29.3
Carbapenems	8.9	10.4
Other or combination	7.9	4.8

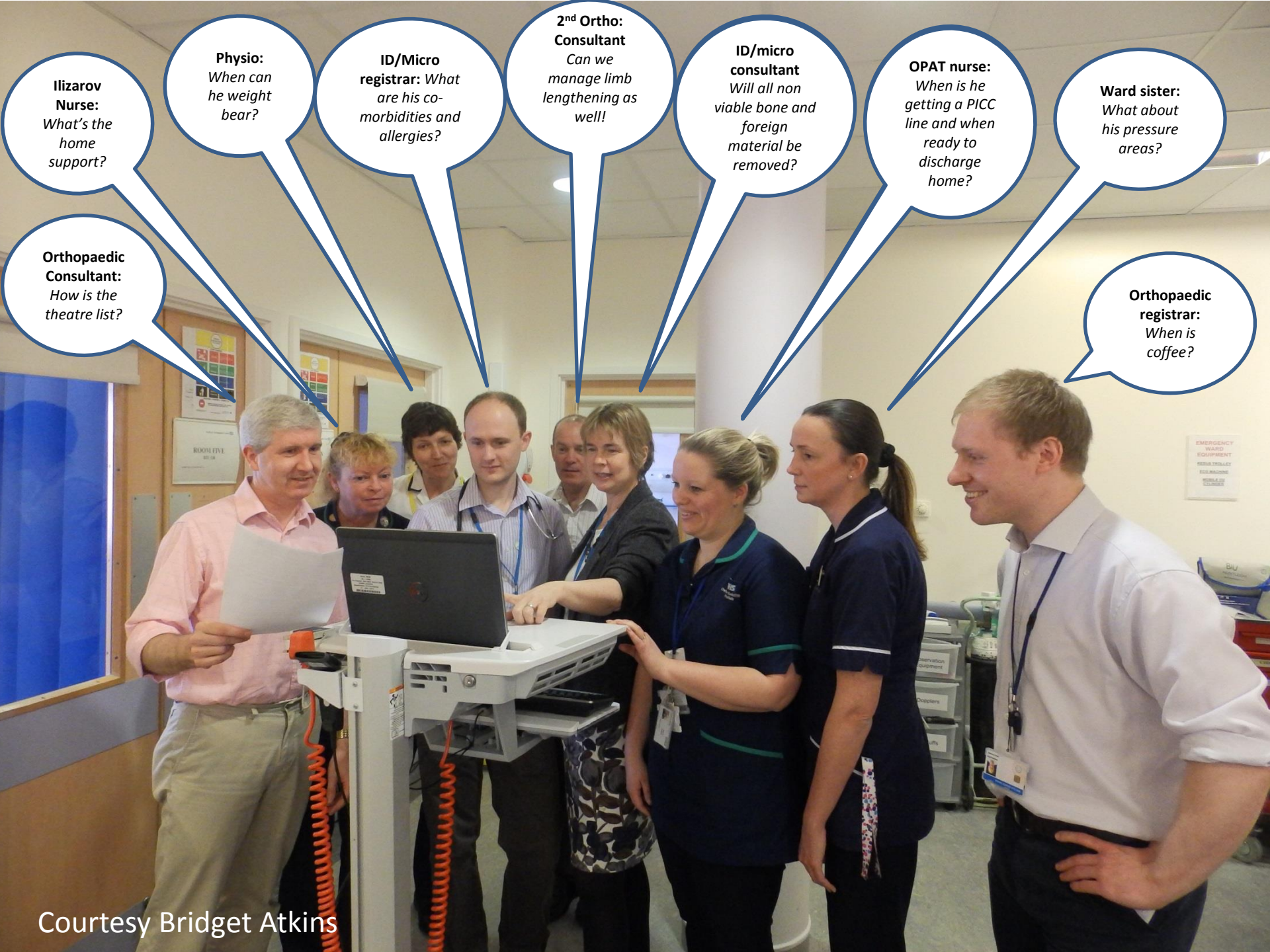
PO treatment	% planned	% received
Penicillins	15.0	15.2
Quinolones	45.1	37.6
Tetracyclines	9.4	12
Macrol/Lincosamide	11.6	16
Other or combination	18.9	20.8

Rifampicin included	%
IV randomisation	12.4
PO randomisation	50.7



# Secondary endpoints and SAEs

	% of cases
SAE reported	9.4
C. diff	0.9
Line complications	5.2 (*)
Early termination of allocated strategy	15.2
(* denominator includes all pts randomised)	



**Ilizarov Nurse:**  
*What's the home support?*

**Physio:**  
*When can he weight bear?*

**ID/Micro registrar:** *What are his co-morbidities and allergies?*

**2nd Ortho: Consultant**  
*Can we manage limb lengthening as well!*

**ID/micro consultant**  
*Will all non viable bone and foreign material be removed?*

**OPAT nurse:**  
*When is he getting a PICC line and when ready to discharge home?*

**Ward sister:**  
*What about his pressure areas?*

**Orthopaedic Consultant:**  
*How is the theatre list?*

**Orthopaedic registrar:**  
*When is coffee?*

# Conclusion

- Pragmatic
- Nearly there
- Built by surgeons, RNs and OPAT teams.
- Potentially important implications for patients, the NHS and maybe for OPAT

Thanks to all sites, staff, OPAT teams and the NIHR



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