How to critically assess the high risk foot literature

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Why would you want to?

	Estimated annual cost
Primary, community and outpatient care, ulceration	£629,161,354 – £786,451,692
Inpatient care, amputation	£43,797,632
Inpatient care, ulceration	£278,452,386
Post-amputation care	£20,813,777
Total	£972,225,149 – £1,129,515,487

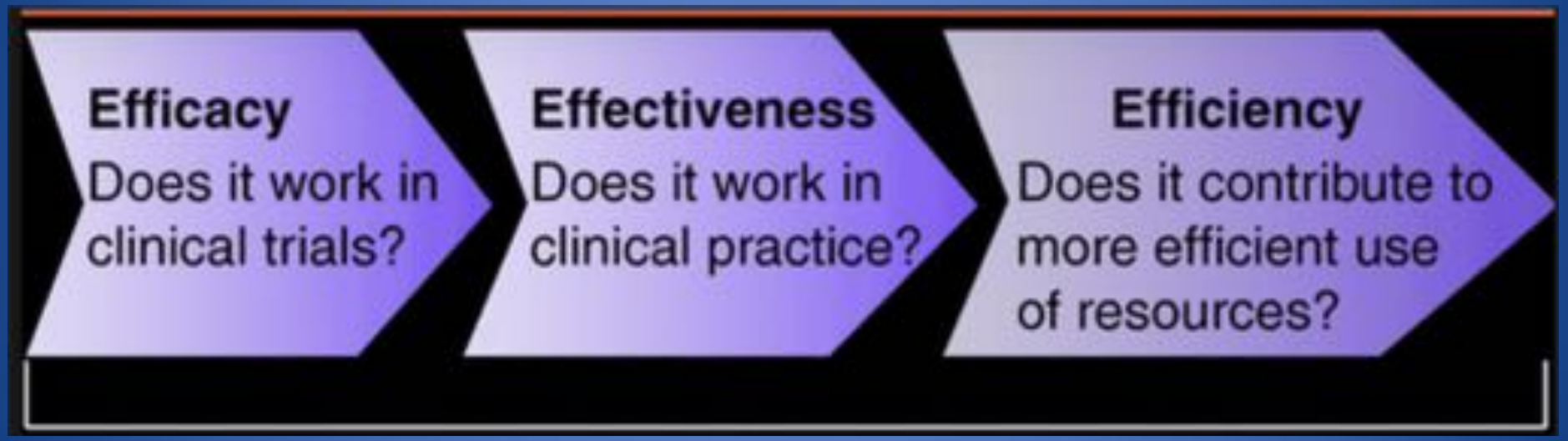
Table 1: Total estimated expenditure on diabetic foot disease, England, 2014–2015

DIABETES UK

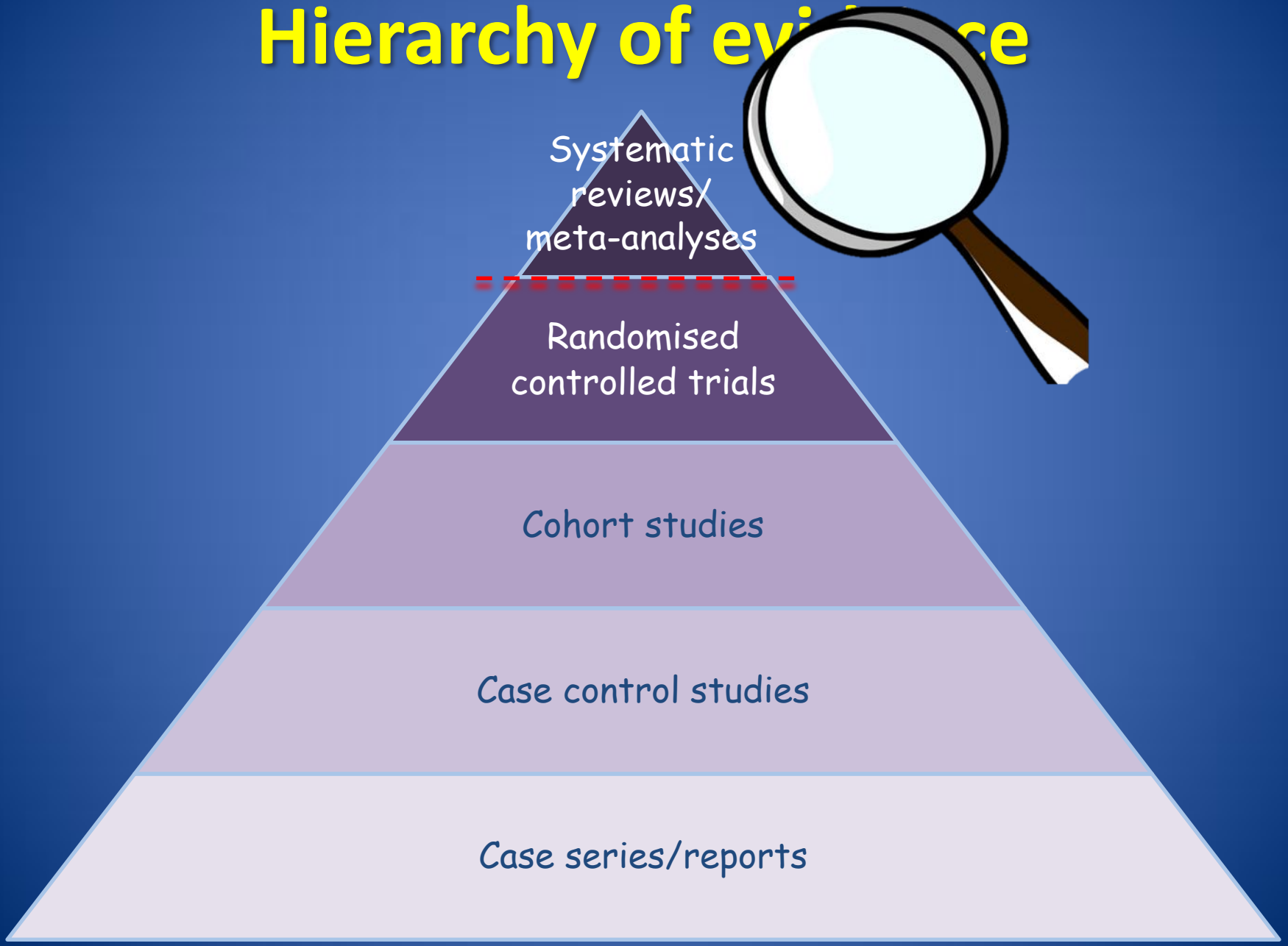
Improving footcare for people with diabetes and saving money: an economic study in England

Marion Kerr 2017

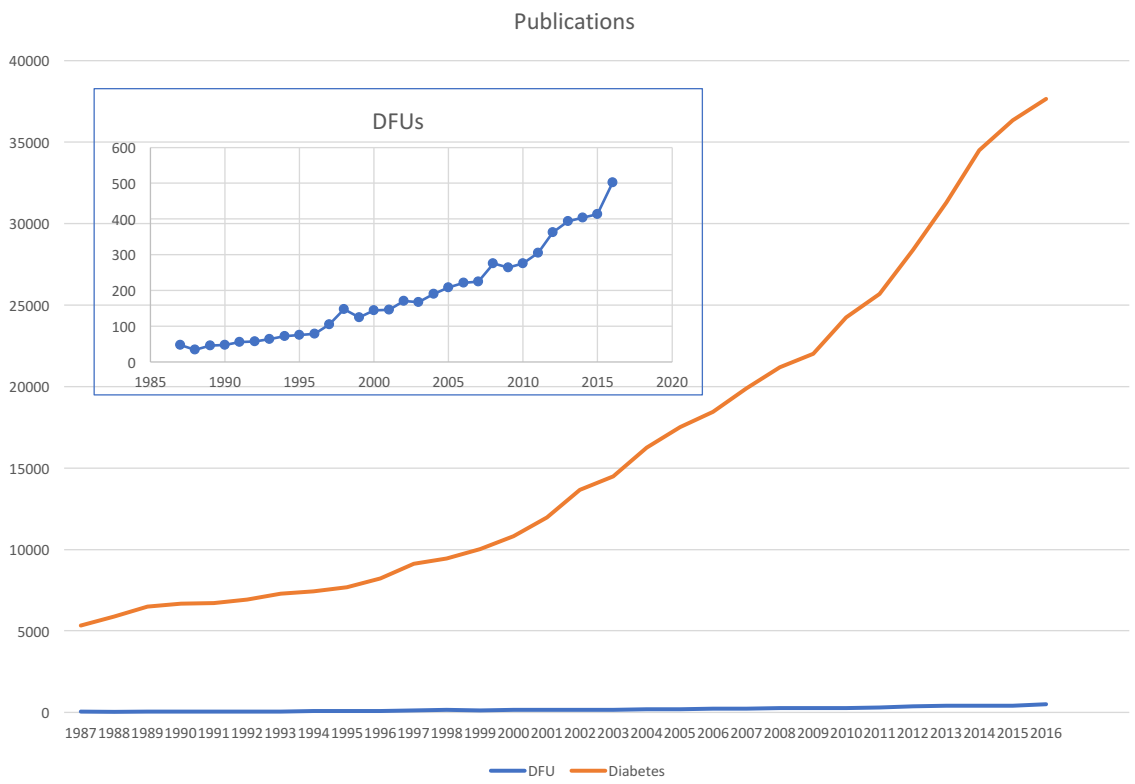
How do we know what works?



Hierarchy of evi ce



How much evidence is there?



What evidence exists for the management of diabetic foot disease?

Diab Metab Res Rev, 2016 Suppl 1

Effectiveness of interventions to enhance healing of chronic ulcers of the foot in diabetes: a systematic review

1. Debridement and wound bed preparation: sharp debridement, larvae

2. Wound bed preparation using antiseptics, applications and dressing products

3 Resection of the chronic wound

4. Oxygen and other gases

5. Compression or negative pressure wound therapy

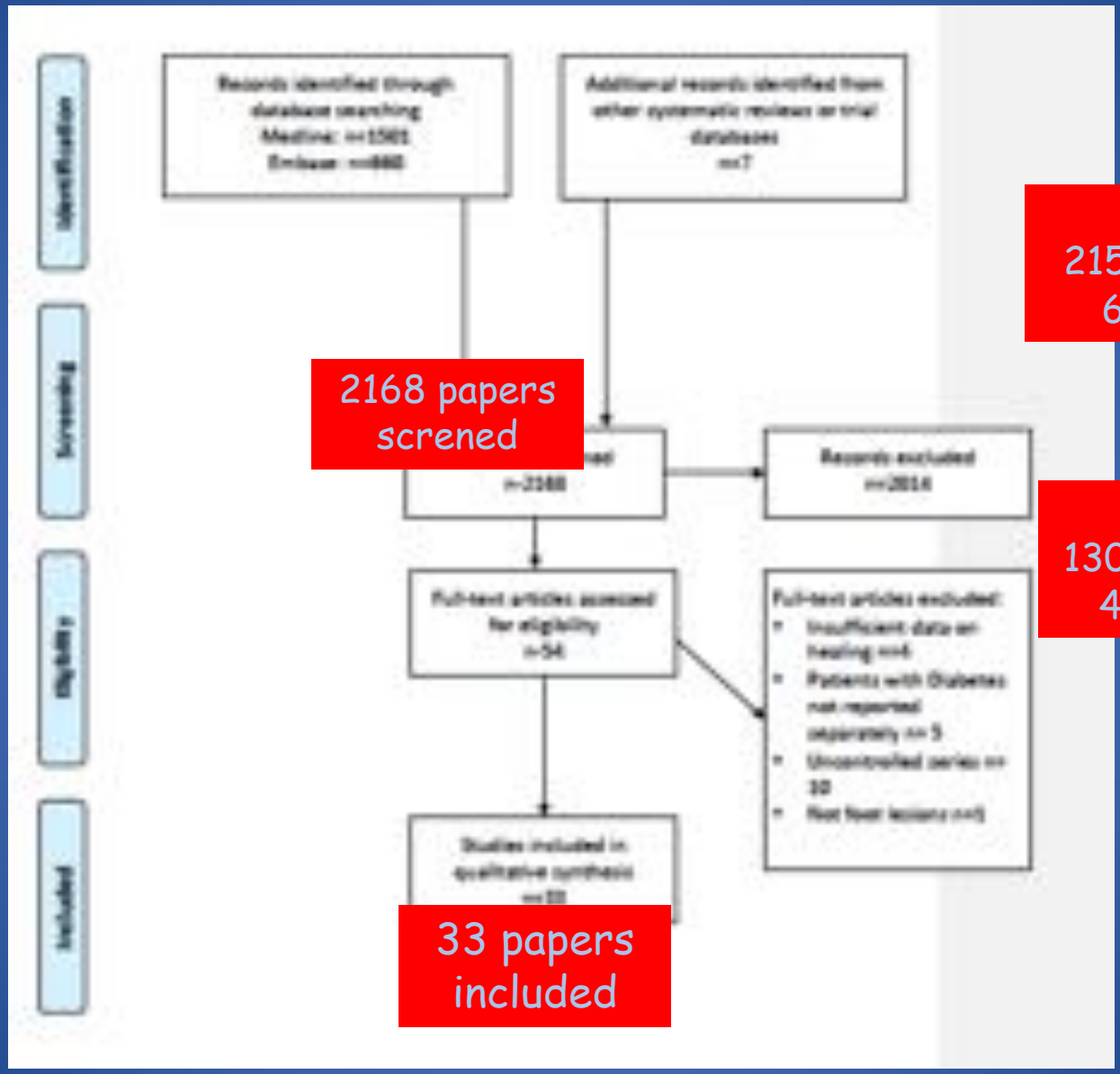
6. Products designed to correct aspects of wound biochemistry and cell biology associated with impaired wound healing

7. Application of cells, including platelets and stem cells, and growth factors

8. Bioengineered skin and skin grafts

9. Electrical, electromagnetic, lasers, shockwaves and ultrasound

10. Other systemic therapies

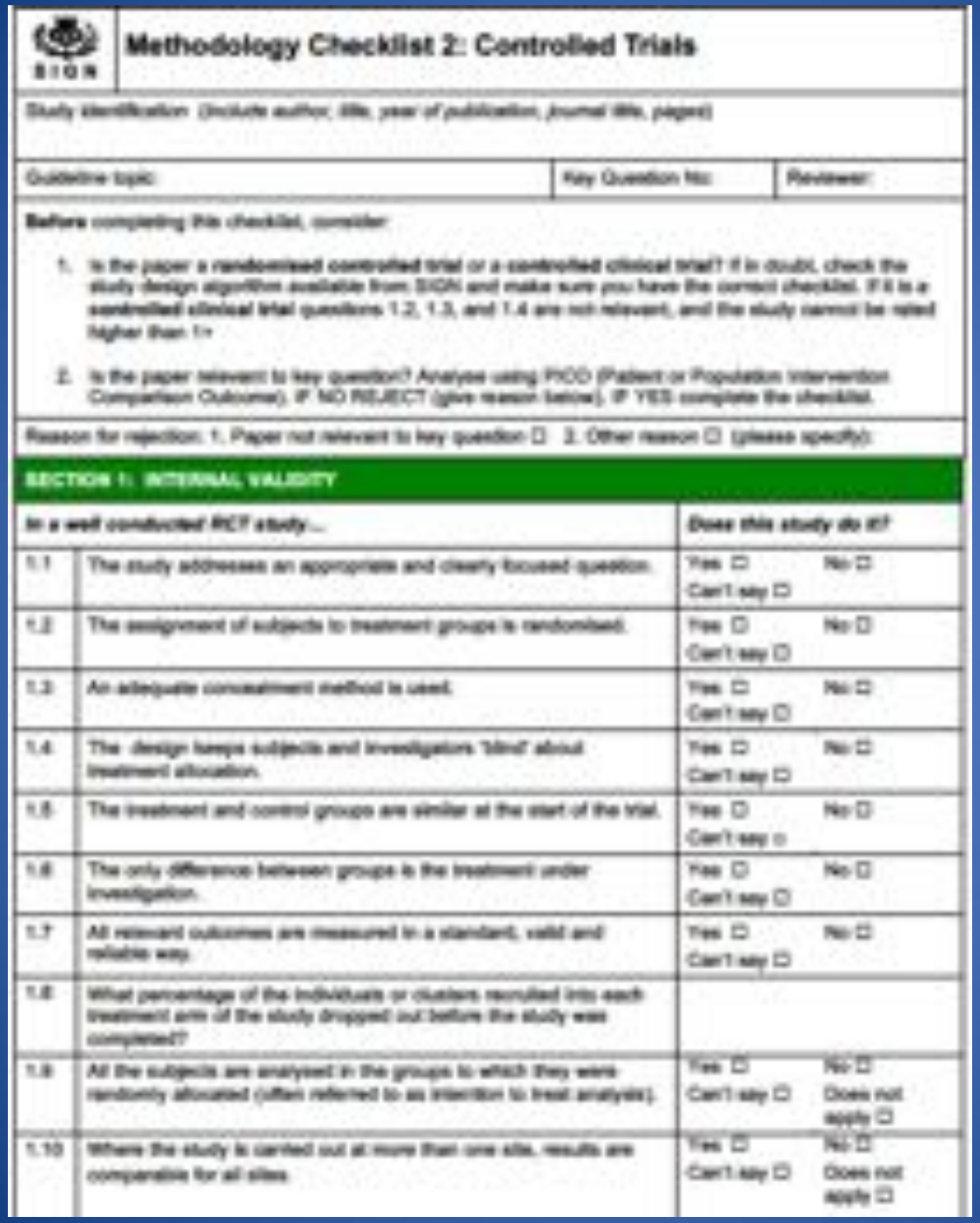


2008
2155 identified
61 included

2012
1309 identified
43 included

Quality of evidence

"Overall low evidence base for the assessment of interventions: poor trial design and reporting"



Methodology Checklist 2: Controlled Trials

Study identification (include author, title, year of publication, journal title, pages)

Guideline topic:	Key Question No:	Reviewer:

Before completing this checklist, consider:

1. Is the paper a **randomised controlled trial** or a **controlled clinical trial**? If in doubt, check the study design algorithm available from SIGN and make sure you have the correct checklist. If it is a **controlled clinical trial** questions 1.2, 1.3, and 1.4 are not relevant, and the study cannot be rated higher than 1+
2. Is the paper relevant to key question? Analyse using PICO (Patient or Population Intervention Comparison Outcome). IF NO REJECT (give reason below). IF YES complete the checklist.

Reason for rejection: 1. Paper not relevant to key question ☐ 2. Other reason ☐ (please specify)

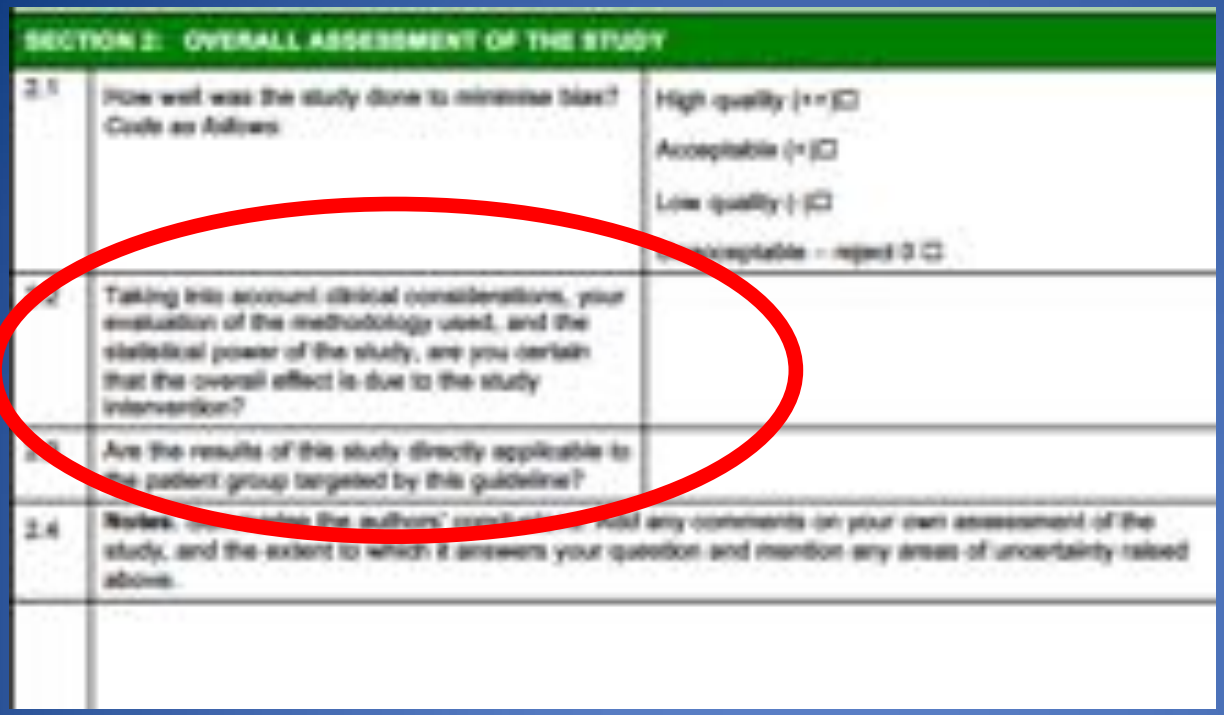
SECTION 1: INTERNAL VALIDITY

	In a well conducted RCT study...	***Does this study do it?***
1.1	The study addresses an appropriate and clearly focused question.	Yes ☐ No ☐ Can't say ☐
1.2	The assignment of subjects to treatment groups is randomised.	Yes ☐ No ☐ Can't say ☐
1.3	An adequate concealment method is used.	Yes ☐ No ☐ Can't say ☐
1.4	The design keeps subjects and investigators *'blind'* about treatment allocation.	Yes ☐ No ☐ Can't say ☐
1.5	The treatment and control groups are similar at the start of the trial.	Yes ☐ No ☐ Can't say ☐
1.6	The only difference between groups is the treatment under investigation.	Yes ☐ No ☐ Can't say ☐
1.7	All relevant outcomes are measured in a standard, valid and reliable way.	Yes ☐ No ☐ Can't say ☐
1.8	What percentage of the individuals or clusters recruited into each treatment arm of the study dropped out before the study was completed?	
1.9	All the subjects are analysed in the groups to which they were randomly allocated (often referred to as intention to treat analysis).	Yes ☐ No ☐ Can't say ☐ Does not apply ☐
1.10	Where the study is carried out at more than one site, results are comparable for all sites.	Yes ☐ No ☐ Can't say ☐ Does not apply ☐

- **Only 25 studies were randomised**
- **Only 5 studies scored 6 or more**

SECTION 2: OVERALL ASSESSMENT OF THE STUDY		
2.1	How well was the study done to minimise bias? Code as follows	High quality (++) ☐ Acceptable (+) ☐ Low quality (-) ☐ Unacceptable – reject 0 ☐
2.2	Taking into account clinical considerations, your evaluation of the methodology used, and the statistical power of the study, are you certain that the overall effect is due to the study intervention?	
2.3	Are the results of this study directly applicable to the patient group targeted by this guideline?	
2.4	**Notes.** Summarise the authors' conclusions. Add any comments on your own assessment of the study, and the extent to which it answers your question and mention any areas of uncertainty raised above.	

- **Only 6 studies were blinded**



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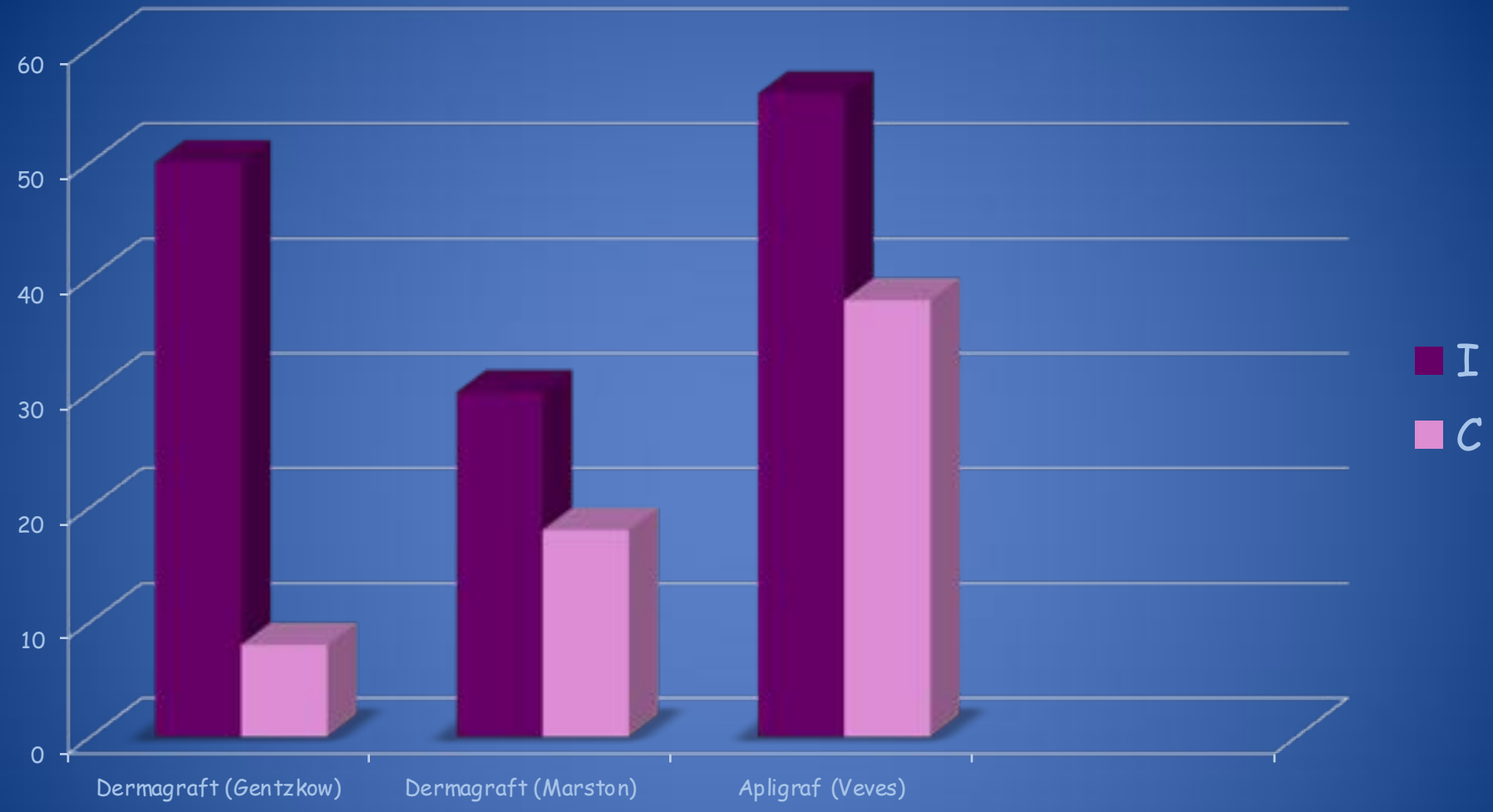
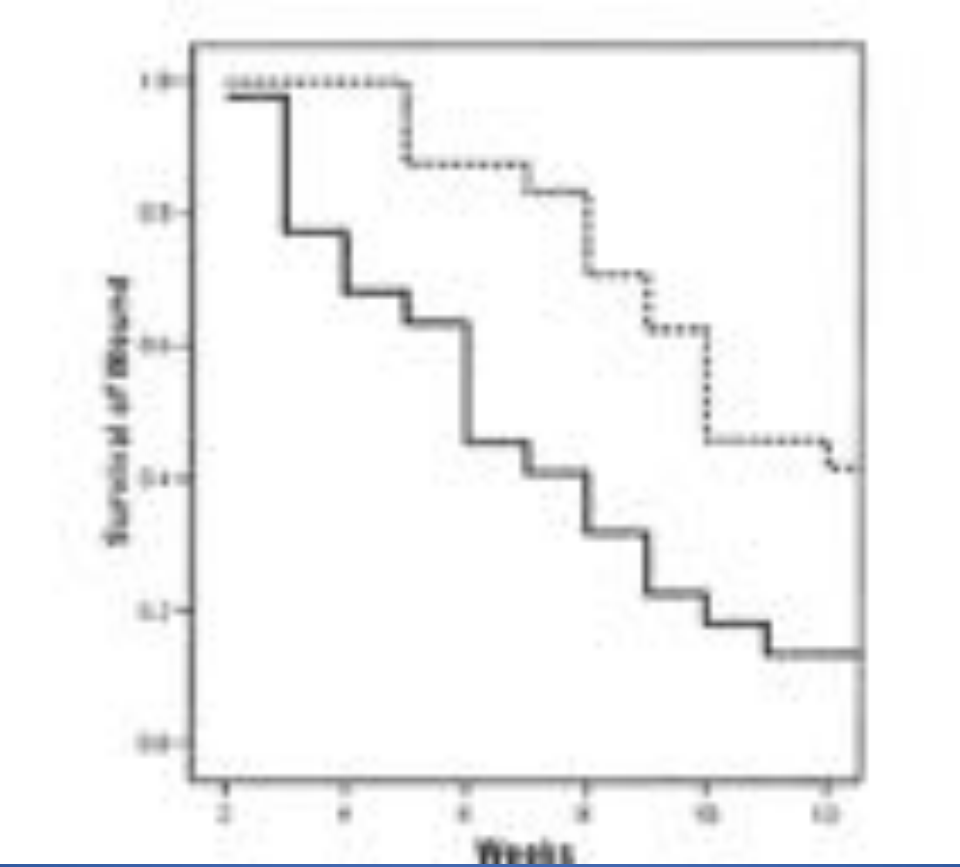
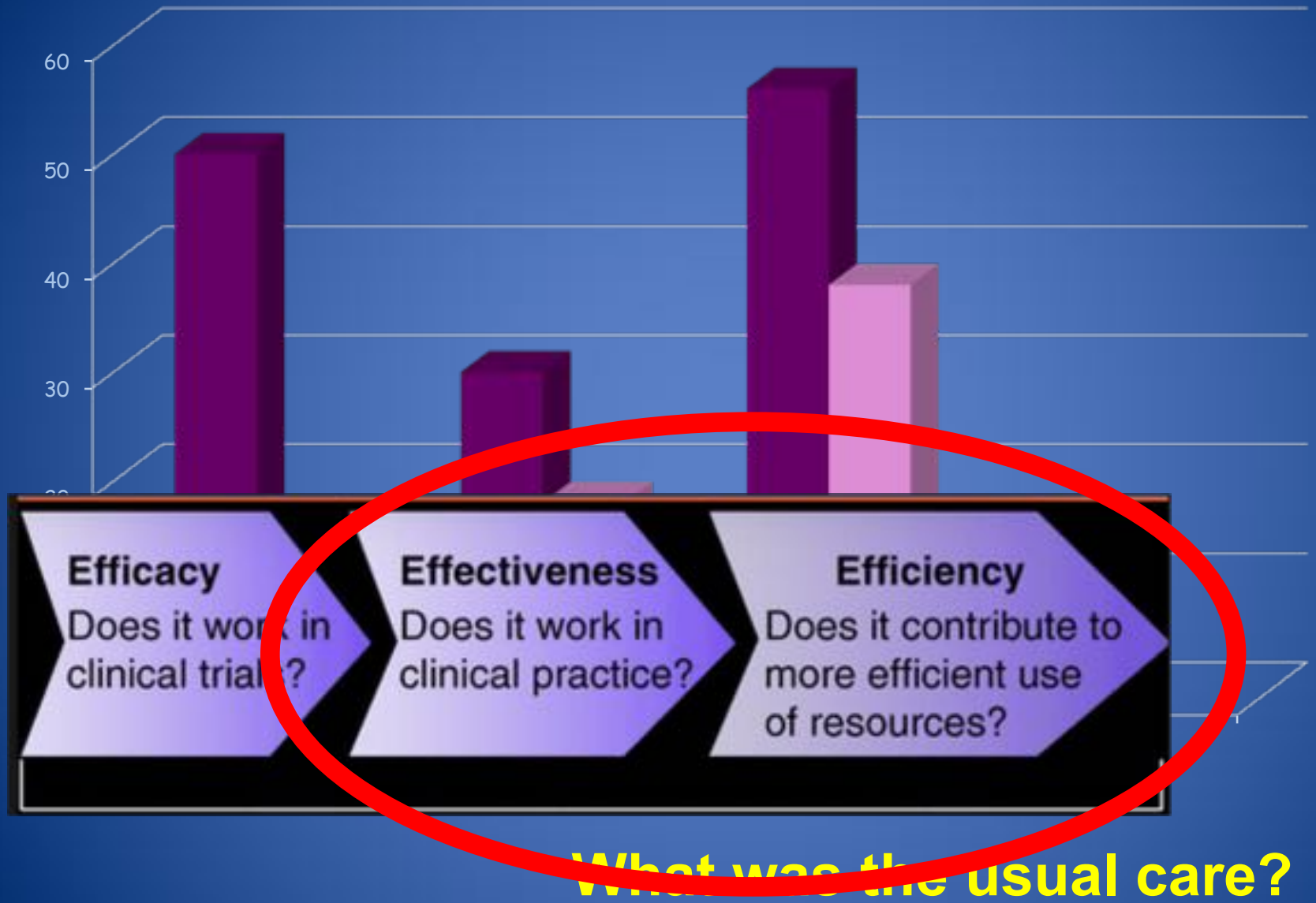

60
50
40
30
20
10
0
Dermagraft (Gentzkow)
Dermagraft (Marston)
Apligraf (Veves)
I
C

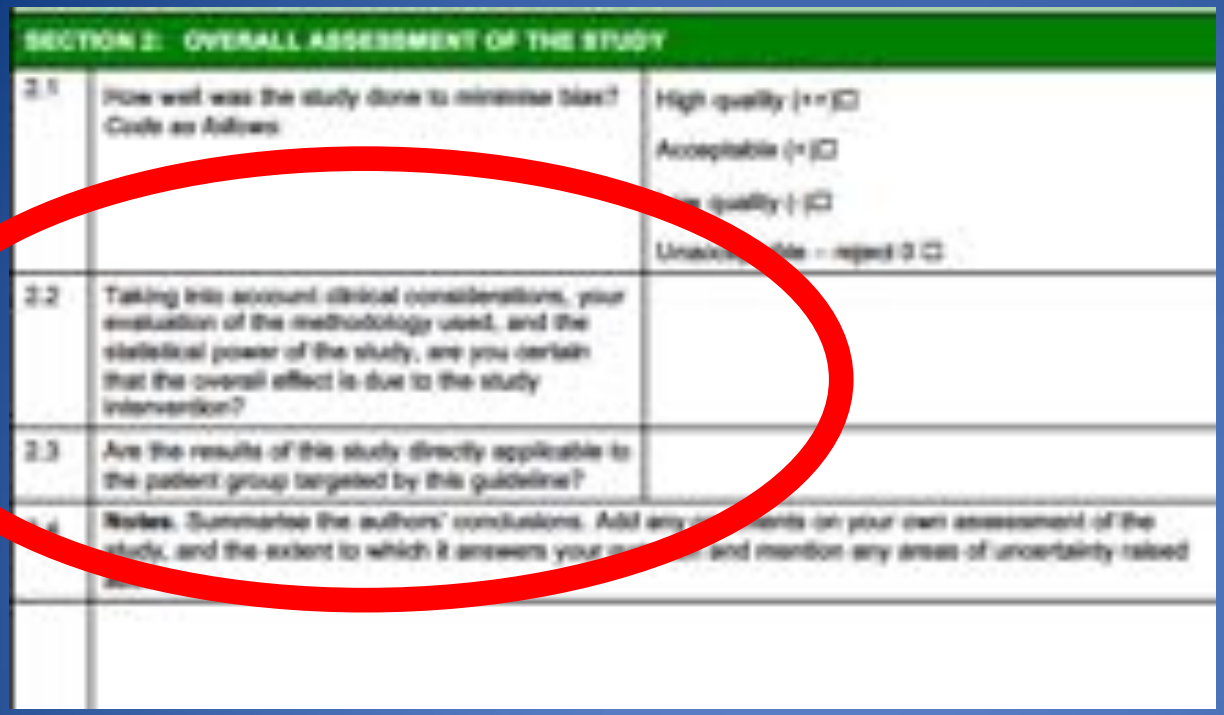
Offloading



Armstrong et al, D Care 2005



What was the usual care?



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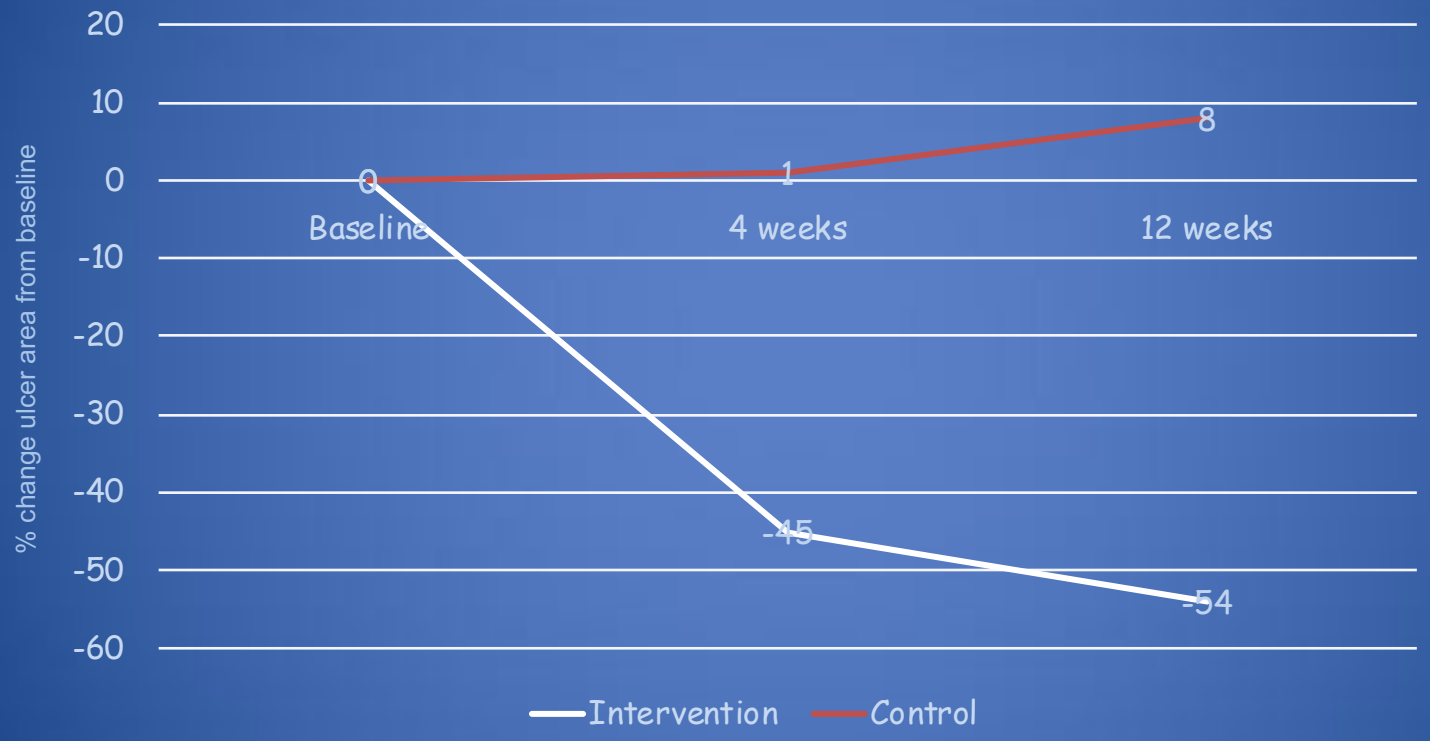
- Only 6 studies were blinded

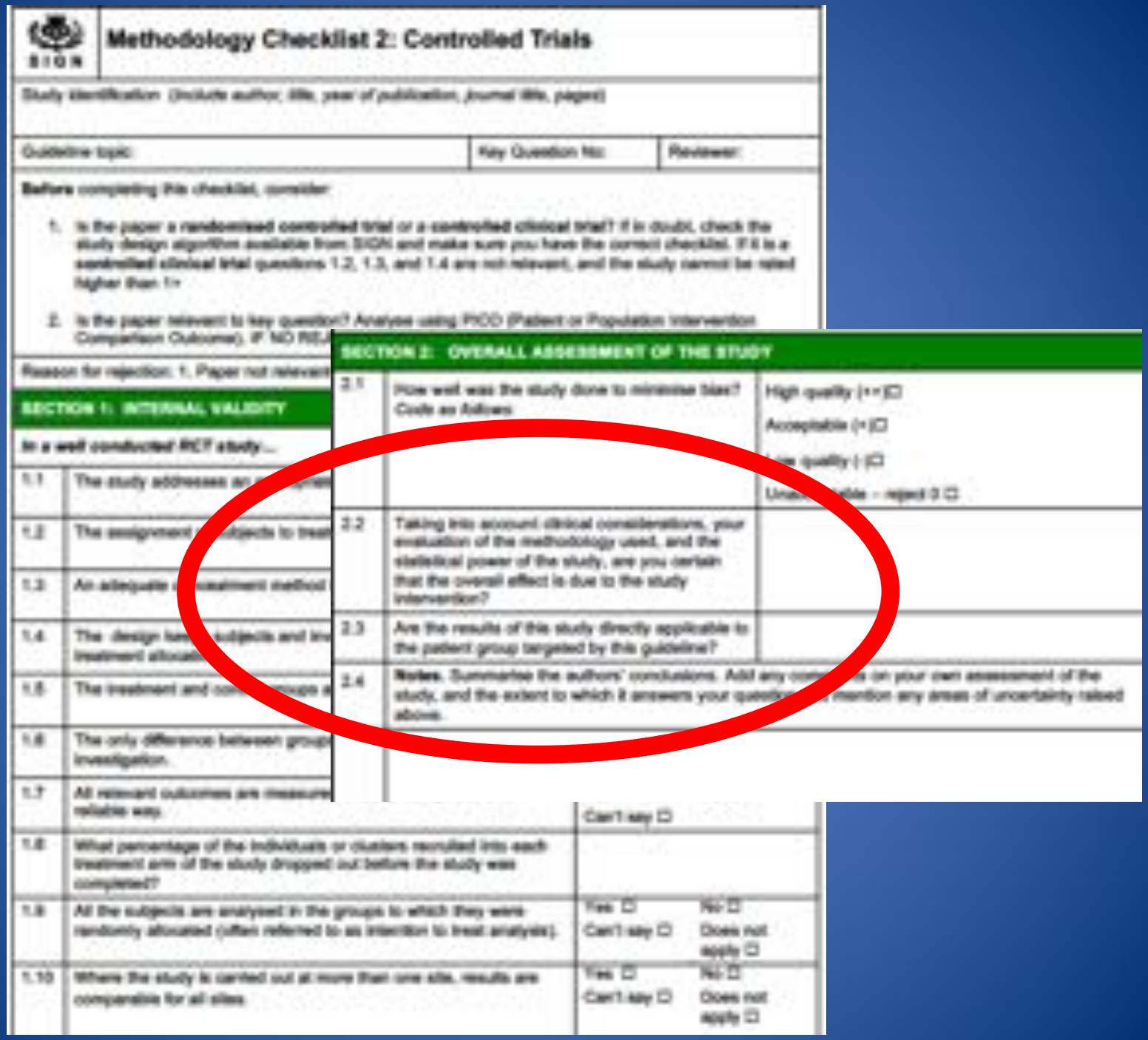
- Baseline characteristics:
- Ulcer area missing in 14 studies
- No mention of arterial status in 16 (unclear methodology even in those that did)

Description of standard care very poor.

- "Standard wound care"
- Offloading : 3 (bed rest 1, post-op shoe 1)

Clostridium collagenase ointment vs saline moistened gauze (n=48) (Tallis 2013)





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Reason for rejection: 1. Paper not relevant

SECTION 1: INTERNAL VALIDITY

In a well conducted RCT study...

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1.2	The assignment	subjects to treat
1.3	An adequate	treatment method
1.4	The design ke	subjects and inv treatment allocati
1.5	The treatment and co	groups a
1.6	The only difference between group investigation.	
1.7	All relevant outcomes are measure reliable way.	Can't say ☐
1.8	What percentage of the individuals or clusters recruited into each treatment arm of the study dropped out before the study was completed?	
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2.4	**Notes.** Summarise the authors' conclusions. Add any com s on your own assessment of the study, and the extent to which it answers your questi mention any areas of uncertainty raised above.	

Reporting standards of studies and papers on the prevention and management of foot ulcers in diabetes: required details and markers of good quality

William J Jeffcoate, Sicco A Bus, Frances L Game, Robert J Hinchliffe, Patricia E Price, Nicolaas C Schaper, on behalf of the International Working Group on the Diabetic Foot and the European Wound Management Association

The evidence base for many aspects of the management of foot ulcers in people with diabetes is weak, and good-quality research, especially relating to studies of direct relevance to routine clinical care, is needed. In this paper, we summarise the core details required in the planning and reporting of intervention studies in the prevention and management of diabetic foot ulcers, including studies that focus on off-loading, stimulation of wound healing, peripheral artery disease, and infection. We highlight aspects of trial design, conduct, and reporting that should be taken into account to minimise bias and improve quality. We also provide a 21-point checklist for researchers and for readers who assess the quality of published work.

Lancet Diabetes Endocrinol 2016; 4: 781–88

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Foot Ulcer Trials Unit, Department of Diabetes and Endocrinology, Nottingham University Hospitals Trust, Nottingham, UK (Prof W J Jeffcoate MRCP); **Academic Medical Centre, University of Amsterdam, Amsterdam, Netherlands** (S A Bus PhD); **Derby Teaching Hospitals, National Health Service Foundation Trust, Derby, UK** (Prof F L Game FRCP); **St George's Vascular Unit, St George's Hospital, London,**

Introduction

Foot ulcers pose an enormous problem for people with diabetes,[1] and their prevention and management are undermined by the scarcity of evidence on which to base treatment choices. Many systematic reviews[2–7] have repeatedly drawn attention to the urgent need for higher-quality studies in both prevention and management. Despite this call for action and the escalating size of the clinical problem, the number of reports of high-quality

conducted and submitted for publication. Finally, through doing repeated systematic reviews, we found that existing tools for assessing the literature do not fully meet the needs of research in this complex clinical area; therefore, we also include a checklist as both a guide to authors and a tool for readers to assess the quality of reported work.

This definition of standards for the design and reporting of research into disease of the foot in diabetes

Population*
Person
Limb
Ulcer
Interventions

	Prevention of foot ulcers in diabetes
Population*	
Person	• Age, sex, and ethnicity • Diabetes type, duration, and adequacy of glycaemic control • Comorbidities (eg, established renal failure, heart failure, immobility, impaired vision) • Ulcer risk classification: low, medium, or high • Ambulatory status • Educational status, socioeconomic status, and capacity for self-care (for studies on education)
Limb	• Peripheral artery disease: minimal assessment by palpation of pulses and ankle-brachial pressure index, or toe blood pressure, or both • Neuropathy: minimal assessment by determining loss of protective sensation (eg, with a 10 g monofilament or vibration perception) • Foot deformity (type or severity, or both) • History of previous foot ulceration and amputation
Ulcer	Not applicable
Interventions	• All interventions: details of interventions (including duration and frequency); person or team providing foot care; setting of the study • Footwear: details on design, customisation, and materials used; evidence of pressure-reducing efficacy if study relates to plantar ulceration • Education or behavioural change: whether aimed at patients, carers, or health-care professionals • Surgery: evidence of pressure-reducing efficacy if study relates to plantar ulceration

	Management of existing diabetic foot ulcers
Population*	
Person	• Age, sex, and ethnicity • Diabetes type, duration, and adequacy of glycaemic control • Comorbidities (eg, established renal failure, heart failure, immobility, impaired vision)
Limb	• Peripheral artery disease: minimal assessment by palpation of pulses and ankle-brachial pressure index • Neuropathy: minimal assessment by loss of protective sensation (eg, with a 10 g monofilament or vibration perception) • Foot deformity (type or severity, or both) • History of previous foot ulceration and amputation
Ulcer	• Number of active ulcers • Site of index ulcer • Duration of index ulcer • Type or classification of index ulcer (where appropriate) • Area and depth of index ulcer • Presence or absence of infection
Interventions	Many potential interventions are possible, and these can be administered systemically, regionally, or topically. For each intervention, sufficient information should be provided to define • its nature (including source) • route, frequency, and duration of delivery • person administering the delivery: professional, non-professional carer, the patient • place of delivery: home, community clinic, surgery, hospital, specialist centre

Outcomes
Foot and limb
Person
Surrogate

Outcomes	
Foot and limb	• Ulcer (defined according to existing guidelines) incidence expressed as a proportion of a population by a fixed time, or time to ulceration, or both • First ever ulcer • Recurrent ulcer (specified as being at the same site as a previous ulcer) or ulcer at a different site • Adherence to the intervention (eg, wearing footwear, self-care, or education, preferably measured objectively) • Foot pressure reduction (following provision of footwear or surgical interventions, or both) • Ambulatory activity level (for footwear studies), expressed as quantitatively as possible • False-positive and false-negative outcomes (in diagnostic self-care studies) • Amputation (major or minor, defined according to existing guidelines)
Person	• Survival • Ulcer-free survival (days) • Health-related quality of life • Adverse events or adverse device effects, or both
Surrogate	• Potential surrogate outcome measures for studies in which ulcer incidence is not the primary outcome • Incidence of pre-ulcerative lesions (eg, hyperkeratotic tissue, haemorrhage, blister, inflammation, each of which require definition) • Change in plantar foot pressures • Change in adherence • Knowledge and behaviour (patient, carer, health-care professional) • Foot examination skill (patient, carer, health-care professional) • Patient satisfaction and wellbeing

Outcomes	
Foot and limb	• Ulcer healing (defined according to existing guidelines—eg, IWGDF)—the number or percentage of index ulcers healed by a fixed time, or time to healing • Healing following local surgery, including operative debridement • Amputation (major or minor, defined according to existing guidelines) • Failure to heal by a fixed time
Person	• Survival • Being ulcer free or amputation free, or both, at a fixed time after presentation • Ulcer-free survival (days) • Adverse events or adverse device effects, or both • Health-related quality of life
Surrogate	• Change in ulcer area over a given period of time • Change in ulcer appearance, biochemistry, histology, or other laboratory measure of wound bed status

	Off-loading	Peripheral artery disease	Infections
Population	No additional details	• Smoking status • Ambulatory status • Previous interventions for peripheral artery disease • History of related disease (eg, coronary artery disease, heart failure, cerebrovascular disease) • Other relevant comorbidities (eg, renal disease, depression) • Relevant cardiovascular drugs • Limb symptoms: none, atypical (weakness or limping), intermittent claudication, and rest pain • Toe systolic pressure, toe-brachial pressure index, or $tcpO_2$ • Arterial pulse waveform • Anatomical distribution of the vascular disease in the leg • Number of active ulcers • Site of index ulcer	• Preceding antimicrobial use (type, route, duration, and time before presentation) • Immunosuppression • Infection type (using IDSA or PEDIS grading): none, mild, moderate, or severe • Involvement of bone or joint • Description of how samples were obtained for microbiological examination • Type of and results of microbiological examination (Gram stain and susceptibility)
Interventions	• Details on non-surgical device, application method, material use, and frequency of replacement • Specific design details of the foot-device interface • Person applying the device: the patient, a non-professional carer, or a health-care professional • Details of surgical intervention • Evidence of pressure-reducing efficacy if study is on plantar ulceration	No additional details	• Surgery undertaken before or in association with antimicrobial administration • Any other relevant intervention (including wound debridement, cleansing, and antiseptic use) undertaken before or in association with antimicrobial administration • Antimicrobial regimen: route of delivery, agents, and duration
Outcomes	• Ulcer healing • Adherence to the use of non-surgical removable interventions • Foot pressure (for footwear and surgical interventions) • Ambulatory activity level	• Number of participants alive with an intact foot • Description of outflow in the foot (in case of surgical or endovascular interventions) • Ulcer healing • Measures of the effectiveness of the vascular intervention (eg, toe pressures and $tcpO_2$) • Number of patients with minor and with major amputations	• Resolution of infection (which should be defined) at a prespecified time after stopping antimicrobial treatment • Clinical or laboratory signs of persistent infection at the end of antimicrobial treatment • Number and type of surgical procedures, including amputation (with level of amputation defined according to existing guidelines) • Days of antimicrobial use, antimicrobial-free days, and days of hospital admission • Prevalence of antimicrobial resistance after treatment

IDSA=Infectious Disease Society of America. PEDIS=perfusion, extent, depth, infection, and sensation. $tcpO_2$=transcutaneous partial pressure of oxygen.

Table 2: Additional core details for the reporting of intervention studies in the management of existing diabetic foot ulcers

21 point checklist

Study design

1. Are appropriate definitions included for the terms "ulcer", "healing", and all other required aspects of the population and the outcomes?
2. Was the choice of study population appropriate for the chosen intervention and the stated conclusions?
3. Was there a control population that was managed at the same time as those in the intervention group or groups?
4. Is the intervention sufficiently well described to enable another researcher to replicate the study?
5. Are the components of other aspects of care described for the intervention and comparator groups?
6. Were the participants randomised into intervention and comparator groups?
7. Were the participants randomised by an independent person or agency?
8. Was the number of participants studied in the trial based on an appropriate sample size calculation?
9. Was the chosen primary outcome of direct clinical relevance?
10. Was the person who assessed the primary outcome or outcomes blinded to group allocation?
11. Were either the clinical researcher who cared for the wound at research visits or the participants blinded to group allocation?

21 point checklist

Study conduct

12 Did the study complete recruitment?
13 Was it possible to document the primary outcome in 75% or more of those recruited?
14 Were the results analysed primarily by intention-to-treat analysis?
15 Were appropriate statistical methods used throughout?

Outcomes

16 Was the performance in the control group of the order that would be expected in routine clinical practice?
17 Are the results from all participating centres comparable? Answer "yes" if the study was done in only one centre.

Study reporting

18 Is the report free from errors of reporting—eg, discrepancies between data reported in different parts of the report?
19 Are the important strengths and weaknesses of the study discussed in a balanced way?
20 Are the conclusions supported by the findings?
21 Is the report free from any suggestion that the analysis or the conclusions could have been substantially influenced by people with commercial or other personal interests in the findings?

Quality of evidence : 2016

"Overall low evidence base for the assessment of interventions: poor trial design and reporting"

Quality of evidence : 2020

"Overall **good** evidence base for the assessment of interventions: poor trial design and reporting"

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