

Update on Clinical Practice Guidelines for the UHMS

Enoch Huang, MD, MPH&TM

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Disclosures

- Dr. Huang has no financial relationships to disclose
- Dr. Mansouri is a paid scientific writer hired to coordinate and draft the Clinical Practice Guidelines for the UHMS

Goals and Objectives

- By the end of this lecture, attendees should be able to:
 - Develop an understanding of how to use GRADE methodology to evaluate the existing HBOT literature
 - Evaluate the preliminary recommendations from the DFU CPG Review Committee
 - Understand where future research needs to be directed

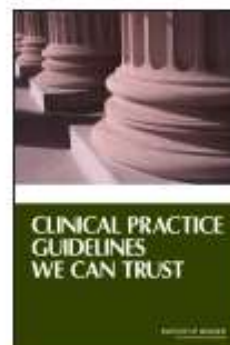
Overview

- The UHMS is creating a set of Clinical Practice Guidelines
- GRADE methodology is being used to conduct the meta-analysis
- UHMS plans on creating CPGs for multiple indications to publish on www.guidelines.gov

How UHMS is creating CPGs

- CPG Oversight Committee
 - Enoch Huang, MD (Chair, Publications)
 - John Feldmeier, DO (BOD)
 - Ken LeDez, MD (International)
 - Jeannie Le, MD (QUARC)
 - Richard Moon, MD (Oxygen Therapy Committee)
 - Hassan Murad, MD (GRADE Working Group)
 - Jaleh Mansouri, MD (Contracted Scientific Writer)

Clinical Practice Guidelines We Can Trust



Standards for Developing Trustworthy Clinical Practice Guidelines (CPGs)

STANDARD 1 Establishing transparency

- 1.1 The processes by which a CPG is developed and funded should be detailed explicitly and publicly accessible.

STANDARD 2 Management of conflict of interest (COI)

- 2.1 Prior to selection of the Guideline Development Group (GDG), individuals being considered for membership should declare all interests and activities potentially resulting in COI with development group activity, by written disclosure to those convening the GDG.
- Disclosure should reflect all current and planned commercial (including services from which a clinician derives a substantial proportion of income), non-commercial, intellectual, institutional, and patient/public activities pertinent to the potential scope of the CPG.
- 2.2 Disclosure of COIs within GDG
- All COI of each GDG member should be reported and discussed by the prospective development group prior to the onset of their work.
 - Each panel member should explain how their COI could influence the CPG development process or specific recommendations.
- 2.3 Divestment
- Members of the GDG should divest themselves of financial investments they or their family members have in, and not participate in marketing activities or advisory boards of, entities whose interests could be affected by CPG recommendations.

2.4 Exclusions

- Whenever possible GDG members should not have COI.
- In some circumstances, a GDG may not be able to perform its work without members who have COIs, such as relevant clinical specialists who receive a substantial portion of their incomes from services pertinent to the CPG.
- Members with COIs should represent not more than a minority of the GDG.
- The chair or co-chairs should not be a person(s) with COI.
- Funders should have no role in CPG development.

STANDARD 3 Guideline development group composition

- 3.1 The GDG should be multidisciplinary and balanced, comprising a variety of methodological experts and clinicians, and populations expected to be affected by the CPG.
- 3.2 Patient and public involvement should be facilitated by including (at least at the time of clinical question formulation and draft CPG review) a current or former patient and a patient advocate or patient/consumer organization representative in the GDG.
- 3.3 Strategies to increase effective participation of patient and consumer representatives, including training in appraisal of evidence, should be adopted by GDGs.

IOM Standards

1. Transparency
2. Management of Conflict of Interest
3. Guideline Development Group Composition
4. CPG – Systematic Review Intersection
5. Establishing Evidence Foundations for and Rating Strength of Recommendations
6. Articulation of Recommendations
7. External Review
8. Updating

CPG Review Committees

- Diabetic Foot Ulcers
 - Eugene Worth, MD* (HBOT, Anesthesiology)
 - Bill Tettelbach, MD* (HBOT, Infectious Disease)
 - Enoch Huang, MD (HBOT, EM)
 - Michael Strauss, MD (HBOT, Orthopedics)
 - Warren Joseph, DPM (Podiatry, Infectious Disease)

CPG Review Committees

- Chronic Radiation Tissue Injury
 - John Feldmeier, DO*
 - James Holm, MD
 - Laurie Gesell, MD

CPG Review Committees

- Compromised Flaps/Grafts
 - Richard Baynosa, MD*
 - George Pedrizet, MD
 - Lisa Gould, MD
 - Bruce Derrick, MD

CPG Review Committees

- Carbon Monoxide Poisoning
 - Jeannie Le, MD
 - Neil Hampson, MD
 - Stephen Thom, MD

Formulate question

Select outcomes

Rate importance

Outcomes across studies

Create evidence profile with GRADEpro

Rate quality of evidence for each outcome

RCT start high, obs. data start low

P
I
C
O

Outcome Critical

Outcome Critical

Outcome Important

Outcome Less important

important



Summary of findings & estimate of effect for each outcome

High
Moderate
Low
Very low

Grade down

1. Risk of bias
2. Inconsistency
3. Indirectness
4. Imprecision
5. Publication bias

Grade up

1. Large effect
2. Dose response
3. Confounders

Systematic review



Guideline development

Formulate recommendations:

- For or against (direction)
- Strong or weak (strength)

By considering:

- ☐ Quality of evidence
- ☐ Balance benefits/harms
- ☐ Values and preferences



Revise if necessary by considering:

- ☐ Resource use (cost)



Rate overall quality of evidence across outcomes based on lowest quality of **critical** outcomes

- "We recommend using..."
- "We suggest using..."
- "We recommend against using..."
- "We suggest against using..."

Courtesy of Dr. Yngve Falck-Ytter

Status of CPGs

[illegible]

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Formulating the Question

- PICO Format
 - Population
 - Intervention
 - Comparison
 - Outcomes

Question 1 of 7

- For a patient with a Diabetic Foot Ulcer, is HBOT with Standard Wound Care more effective than Standard Wound Care alone for the outcomes below?

Question 2 of 7

- For a patient with a moderate - severe (IDSA)
clinically infected Diabetic Foot Ulcer, is
HBOT with Standard Wound Care more
effective than Standard Wound Care alone for
the outcomes below?

Question 3 of 7

- For a patient with a non-infected or mildly infected (IDSA) Diabetic Foot Ulcer, is HBOT with Standard Wound Care more effective than Standard Wound Care alone for the outcomes below?

Question 4 of 7

- For a patient with a moderate - severe (IDSA)
clinically infected Diabetic Foot Ulcer, is
immediate use of HBOT more effective than
delayed (30 days) use of HBOT for the
outcomes below?

Question 5 of 7

- For a patient with a Diabetic Foot Ulcer and
TCOM < 30 mmHg, is HBOT plus Standard
Wound Care more effective than Standard
Wound Care alone for the outcomes below?

Question 6 of 7

- For a patient with a Diabetic Foot Ulcer and
TCOM > 30 mmHg, is HBOT plus Standard
Wound Care more effective than Standard
Wound Care alone for the outcomes below?

Question 7 of 7

- For a patient with a healing Diabetic Foot Ulcer, is a set number of treatments as effective as an indefinite number of treatments for the outcomes below?

PICO Questions

PICO #	Population	Intervention	Comparison
1	Diabetic Foot Ulcers (all)	HBOT + SC	SC
2	IDSA Mod-Severe DFU	HBOT + SC	SC
3	IDSA None-Mild DFU	HBOT + SC	SC
4	IDSA Mod-Severe DFU	Immediate Inpatient HBOT + SC	Delayed HBOT + SC
5	DFU + TCOM < 30 mmHg	HBOT + SC	SC
6	DFU + TCOM > 30 mmHg	HBOT + SC	SC
7	DFU (All)	Set #HBOT	Indefinite # HBOT

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Courtesy of Dr. Yngve Falck-Ytter

Selecting Outcomes

- CPG Review Committee debated the merits of different clinical outcomes and selected ten outcomes of interest
- GRADE recommends a maximum of 7 outcomes to focus on the most important ones

Outcomes of Interest

- Major Amp Rate
- Complete Healing @ 1 year
- Cost Effectiveness
- Resolution of Infection
- Healing Durability
- Mortality
- Quality of Life (Mobility/SF36)
- Time to Heal
- Minor Amp Rate
- Adverse Events

Rating Importance of Outcomes

- For each outcome, reviewers rate how critical that outcome is on a 1-9 scale
 - (7-9) Of Critical Importance
 - (4-6) Important
 - (1-3) Not important

Outcomes of Interest

- Major Amp Rate – 9 (Critical)
- Complete Healing @ 1 year – 8 (Critical)
- Cost Effectiveness – 8 (Critical)
- Resolution of Infection – 8 (Critical)
- Healing Durability – 7 (Critical)
- Mortality – 7 (Critical)
- Quality of Life (Mobility/SF36) – 7 (Critical)
- Time to Heal – 6 (Important)
- Minor Amp Rate – 5 (Important)
- Adverse Events – 4 (Important)

Outcomes of Interest – Patient Survey

- Major Amp Rate – 9 (Critical)
- Complete Healing @ 1 year – 9 (Critical)
- Cost Effectiveness – 9 (Critical)
- Resolution of Infection – 9 (Critical)
- Healing Durability – 9 (Critical)
- Mortality – 9 (Critical)
- Quality of Life (Mobility/SF36) – 9 (Critical)
- Time to Heal – 9 (Critical)
- Minor Amp Rate – 9 (Critical)
- Adverse Events – 9 (Critical)

All 9's

Outcomes of Interest

- How important is the outcome *with regard to making a recommendation for patients*
- Recommendations are made based on the lowest level of evidence for critical outcomes

Outcomes of Interest

- Major Amp Rate – (Critical)
- Complete Healing @ 1 year – (Critical)
- Healing Durability – (Important)
- Quality of Life (Mobility/SF36) – (Important)
- Time to Heal – (Important)
- Cost Effectiveness – (Important)
- Minor Amp Rate – (Important)
- Adverse Events – (Important)
- Resolution of Infection – (Important)
- Mortality – (Not Important)

Which Outcomes to Use?

- Take top 7?
- Take top 7 with evidence?

Cost Effectiveness

- Removed from outcomes of interest because it is not its own goal, but is a consideration only after Critical Outcomes are considered

Adverse Events

- Only one study reported Adverse Events that were not specific to HBOT, and that was because it was double-blinded
- Elected to use published papers on HBOT specific adverse events

Formulate question

Select outcomes

Rate importance

Outcomes
across studies

Create
evidence profile
with GRADEpro

Rate quality of
evidence for
each outcome

RCT start high,
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Systematic review



Guideline development

Formulate recommendations:

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Revise if necessary by considering:

- ☐ Resource use (cost)



Rate
overall quality of evidence
across outcomes based on
lowest quality
of **critical** outcomes

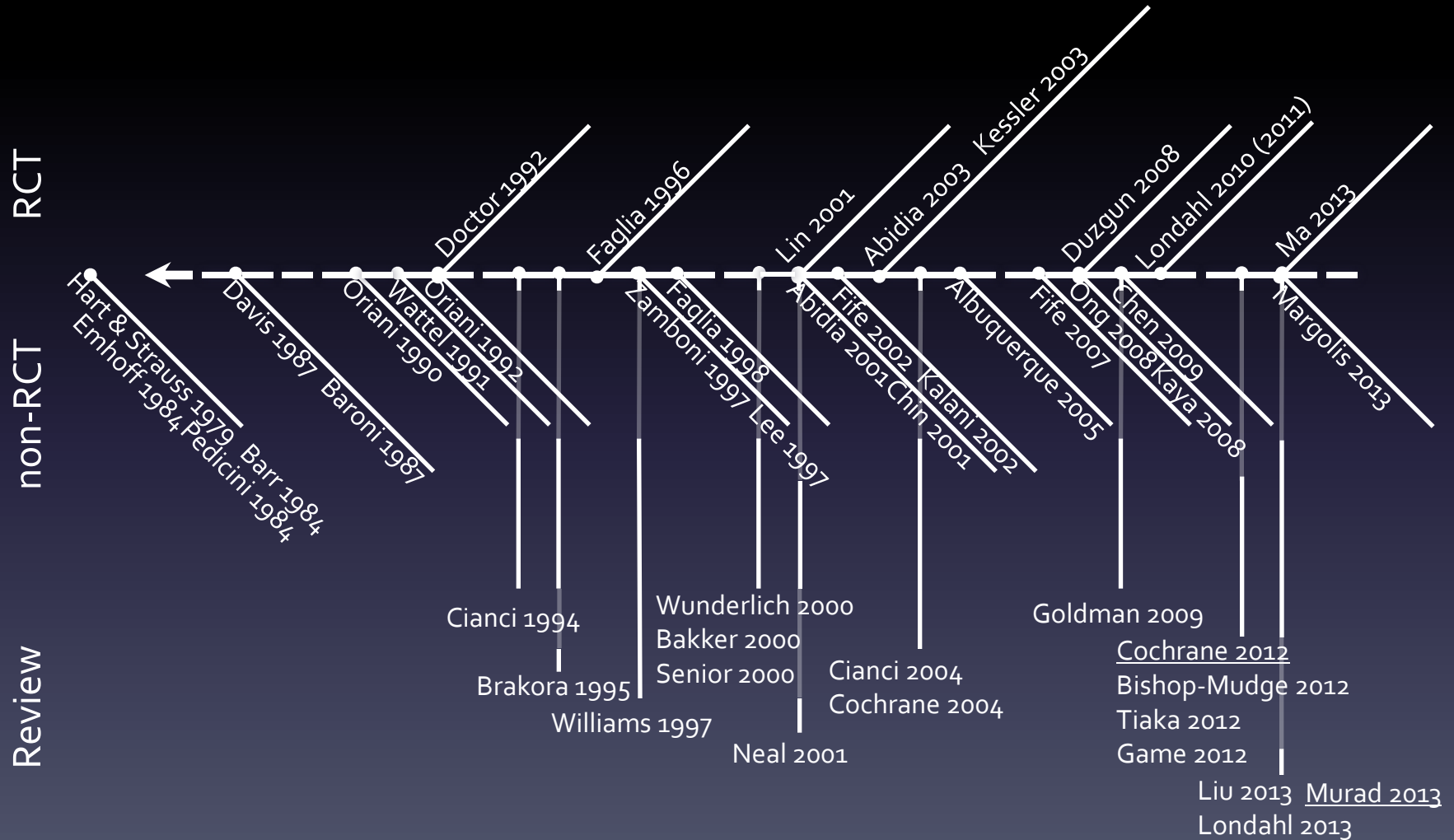
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Courtesy of Dr. Yngve Falck-Ytter

Outcomes Across Studies

- Literature Search
 - Randomized Controlled Trials
 - Observational Studies
 - Meta-Analyses
- Determination of whether paper included the outcome of interest or not
- Determination of whether paper included the PICO population or not

Timeline of Studies



Create Data Abstraction Matrix

[illegible]

Randomized Controlled Trials	Doctor 1992	Faglia 1996	Abidia 2003	Kessler 2003	Duzgan 2008	Löndahl 2010	Ma 2013
Outcomes							
Major Amputation Rate							
Complete Healing (1 year)							
Resolution of Infection							
Healing Durability							
Mortality							
Quality of Life (SF36)							
Time to Heal							
Minor Amputation Rate							

Randomized Controlled Trials Outcomes	Doctor 1992	Faglia 1996	Abidia 2003	Kessler 2003	Duzgan 2008	Löndahl 2010	Ma 2013
Major Amputation Rate							
Complete Healing (1 year)							
Resolution of Infection							
Healing Durability							
Mortality							
Quality of Life (SF36)							
Time to Heal							
Minor Amputation Rate							

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Major Amputation Rate							
Complete Healing (1 year)							
Resolution of Infection							
Quality of Life (SF36)							
Minor Amputation Rate							

PICO Questions

PICO	Population	Intervention	Comparison	RCT	OBS
1	Diabetic Foot Ulcers (all)	HBOT + SC	SC	7	7
2	IDSA Mod-Severe DFU	HBOT + SC	SC	0	0
3	IDSA None-Mild DFU	HBOT + SC	SC	0	0
4	IDSA Mod-Severe DFU	Immediate HBOT + SC	Delayed HBOT + SC	0	0
5	DFU + TCOM < 30 mmHg	HBOT + SC	SC	0	0
6	DFU + TCOM > 30 mmHg	HBOT + SC	SC	0	0
7	DFU	Set # HBOT	Indefinite # HBOT	0	0

PICO Questions (Revised)

PICO	Population	Intervention	Comparison	RCT	OBS
1	All DFU	HBOT + SC	SC	6	7
2	DFU (≥ 30 days, Wagner ≥ 3)	HBOT + SC	SC	1 of 4	0
3	DFU (≥ 30 days, Wagner ≤ 2)	HBOT + SC	SC	3 of 6	5
4	DFU (immediate surgical intervention, Wagner ≥ 3)	Immediate HBOT + SC	SC	2	4
5	DFU + TCOM (SL) < 30 mmHg and TCOM (HBOT) ≥ 200 mmHg	HBOT + SC	SC	0	0
6	DFU + TCOM > 30 mmHg	HBOT + SC	SC	0	0
7	DFU	Set # HBOT	Indefinite # HBOT	0	0

PICO Questions (Revised)

PICO	Population	Intervention	Comparison	RCT	OBS
1	All DFU	HBOT + SC	SC	6	7
2	DFU (≥ 30 days, Wagner ≥ 3)	HBOT + SC	SC	1 of 4	0
3	DFU (≥ 30 days, Wagner ≤ 2)	HBOT + SC	SC	3 of 6	5
4	DFU (immediate surgical intervention, Wagner ≥ 3)	Immediate HBOT + SC	SC	2	4

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Systematic review



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Data Abstraction

	B	C	D	E	F	G	H	I	J	K	L
1. What is the sample size of the RCT?		Inpatient 15 vs 15	Inpatient 33 vs 37	17 vs 12	9 vs 9	14 vs 13	50 vs 50	38 vs 37	38 vs 37	38 vs 37	18 vs 18
2. Is there blinding to the randomization process, treatment?		No blinding	No blinding	No blinding	Allocation concealed at enrollment	No blinding	No blinding	Blinded	Blinded	Blinded	No Blinding
3. Is the level of generalizability (for example is there sampling bias) high or low?		High - Wagner 3 and 4 patients	High - Wagner 2, 3 and 4	Low - Wagner 0, 1, and 2	Low - Wagner 1 and 2	Low - Wagner 1, 2, and 3	High - Wagner 2, 3, and 4	High - Wagner 2, 3, and 4	High - Wagner 2, 3, and 4	High - Wagner 2, 3, and 4	Low - Wagner 1, 2, and 3
4. What is the measure/estimate of effect and how large is it?											
Healing % (1 year)		11/12 (92%) HBO vs 8/11 (73%) Control	n/a		5/8 (5/9) vs 0/8 (0/9), p=0.026	n/a	66% vs. 0%, p<0.05		25/49 (52%) vs. 12/45 (29%), P=0.03		no ulcers healed in 2 weeks
Wagner 1							0 vs 0				
Wagner 2							6/6 vs 0/12				
Wagner 3							13/19 vs 0/18				
Wagner 4							18/25 vs. 0/20				
Wagner 5							0 vs 0				
Major Amputation Rate		2/15 (13%) vs. 7/15 (47%), p<0.5	3/35 (8.6%) vs. 11/33 (33.3%), p<0.016		1/8 (1/9) vs 1/8 (1/9)	n/a	0 vs 34%, p<0.05		3/49 vs 1/44, NS		n/a
Wagner 1			0 vs 0				0 vs 0				
Wagner 2			0/4 vs. 0/5		1/8 (1/9) vs 1/8 (1/9)		0/6 vs 0/12				
Wagner 3		2/15 (13%) vs. 7/15 (47%), p<0.5	1/4 vs. 0/8				0/19 vs 0/18				
Wagner 4			2/22 vs. 11/20				0/25 vs. 17/20				
Wagner 5			0 vs 0				0 vs 0				
Minor Amputation Rate		4/15 (27%) vs 2/15 (13%), p=NS	no difference if considering minor amp out of remaining patients, but if we look at all patients, 21/35 vs. 22/33, p=0.61		1/9 vs 0/9	n/a	8 vs 48%, p<0.05		4/49 and 4/45 with minor amputations, NS		n/a
Wagner 1							0 vs 0				
Wagner 2							0/6 vs 4/12				
Wagner 3							1/19 vs 17/18				
Wagner 4							3/12 vs 3/18				
Wagner 5							0 vs 0				
Healing Durability		n/a	n/a		More ulcers remained healed at 1 year in HBO group than in control group	n/a	mean duration of FU was 92±12 weeks		Reported healing at 1 year		n/a
Adverse Events		0 in HBO groups	2/35 HBO group had otic barotrauma		None	1/14 with otic barotrauma	n/a		1 fatality in HBOT group during Tx, Hypoglycemia in 2 and 4 patients in each group, 1 HBOT patient with otic barotrauma, 2 in each group with PETs, 1 pt with dizziness and 1 pt with cataract maturation in HBOT group, no O2 seizure or PTX seen		No serious complications such as death or amputation or other adverse reactions such as barotraumatic otitis, dizziness, seizures, or pneumothorax occurred
Mortality		n/a	n/a		n/a	n/a	n/a		1/49 vs 3/45, NS		n/a
Resolution of Infection		fewer positive cultures in HBO group (20% vs 80%, p<0.5)	Infection Recovery was 26/35 (74.2%) vs 17/33 (51.6%), p=0.08		n/a	n/a	n/a		n/a		n/a
Cost Effectiveness		n/a	n/a		reduced cost by 2960 pounds per pt for 1 year	n/a	n/a		n/a		n/a
Quality of Life		n/a	n/a		5/36 detected improved general health and vitality in HBO group but not overall	n/a	n/a		There was a significant difference between pre- and post-treatment responses to mental summary score and two of the eight SF-36 domains in the HBOT group, whereas no significant improvement in the QoL in the placebo group		n/a
Time to Heal		n/a	n/a		5/8 ulcers healed at 6 weeks in HBO vs 1/8 in control group	n/a	n/a		The greatest difference in healing was at 9 months		n/a
5. Is there a dose-response gradient?		No	No		No	no	no		no		no

Creating Evidence Profiles

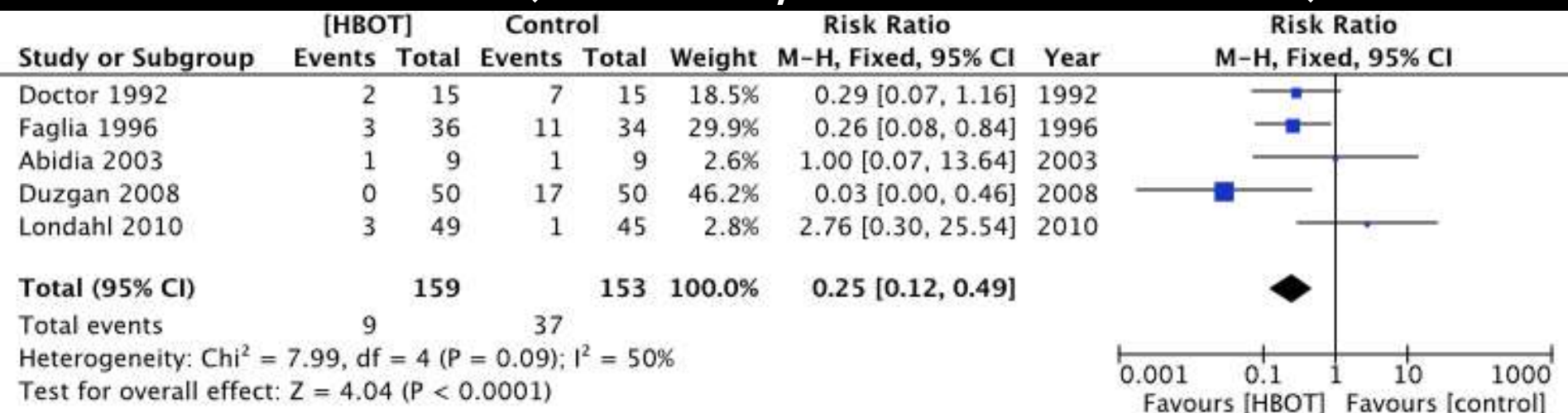
- Forest Plots
 - Generated for each PICO question *and* each Outcome
 - Graphical representation of data from multiple studies
 - Studies with higher “n” have more influence on results
 - Weighted Average generated based on individual studies
 - I^2 measures heterogeneity
 - higher number has increased heterogeneity (bad)
 - Lower number has increased homogeneity (good)

Risk of Bias

Randomized Controlled Trials Risk of Bias	Doctor 1992	Faglia 1996	Abidia 2003	Kessler 2003	Duzgan 2008	Löndahl 2010	Ma 2013
No Stopping Early for Benefit	Green	Green	Green	Green	Green	Green	Green
Strict Allocation Concealment	Yellow	Yellow	Yellow	Yellow	Green	Yellow	Yellow
None Lost to Follow-up	Yellow	Green	Yellow	Green	Green	Green	Green
Blinded Study	Red	Yellow	Green	Green	Yellow	Green	Green
Used Intention to Treat	Yellow	Red	Yellow	Yellow	Green	Green	Green

Major Amputation

PICO #1 (All DFU , HBOT +SC vs. SC)

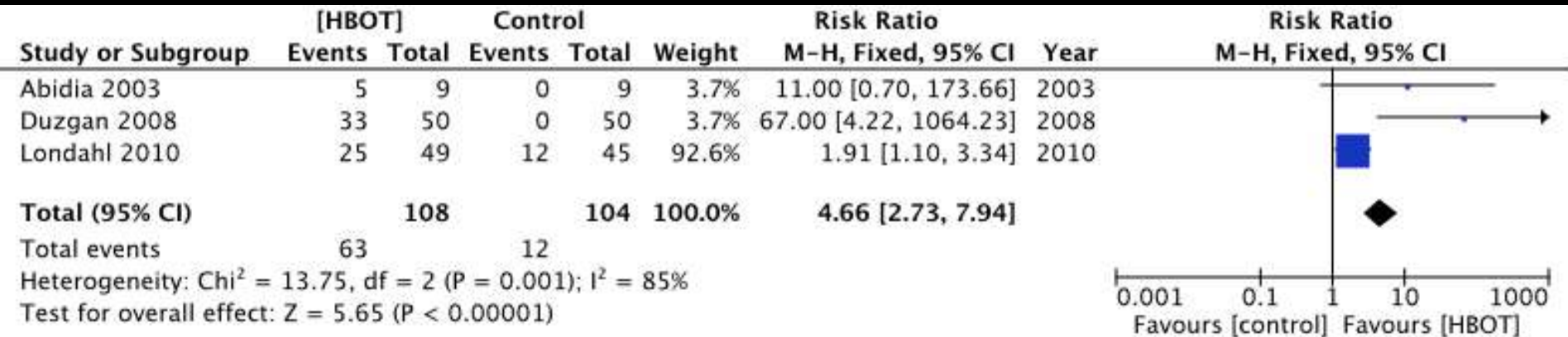


Randomized Controlled Trials	Doctor 1992	Faglia 1996	Abidia 2003	Vocler 2000	Duzgan 2008	Londahl 2010	M-H 2010
Risk of Bias							
No Stopping Early for Benefit							
Strict Allocation Concealment							
None Lost to Follow-up							
Blinded Study							
Used Intention to Treat							

START	4
Risk of Bias	-1
Inconsistency	-1
Indirectness	0
Imprecision	0
Publication Bias	0
Large Effect	1
Dose Response	0
Confounders	0
FINAL	3

Complete Healing at 1 Year

PICO #1 (All DFU, HBOT +SC vs. SC)



Randomized Controlled Trials	Abidia 2003	Duzgan 2008	Londahl 2010	Total
Risk of Bias				
No Stopping Early for Benefit				
Strict Allocation Concealment				
None Lost to Follow-up				
Blinded Study				
Used Intention to Treat				

START	4
Risk of Bias	-1
Inconsistency	-1
Indirectness	0
Imprecision	0
Publication Bias	0
Large Effect	1
Dose Response	0
Confounders	0
FINAL	3

Resolution of Infection

PICO #1 (All DFU, HBOT +SC vs. SC)



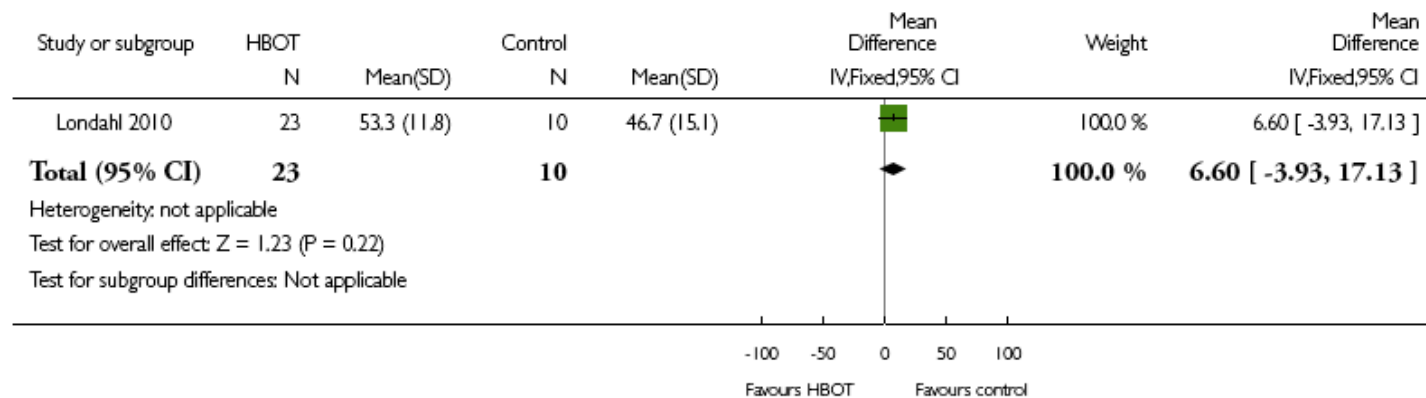
Randomized Controlled Trials	Doctor 1992	Faglia 1996	Albidin 2000	Vaccaro 2000	Durkin 2000	Lindahl 2000	Mazzoni
Risk of Bias							
No Stopping Early for Benefit							
Strict Allocation Concealment							
None Lost to Follow-up							
Blinded Study							
Used Intention to Treat							

START	4
Risk of Bias	-1
Inconsistency	-2
Indirectness	0
Imprecision	0
Publication Bias	0
Large Effect	0
Dose Response	0
Confounders	0
FINAL	1

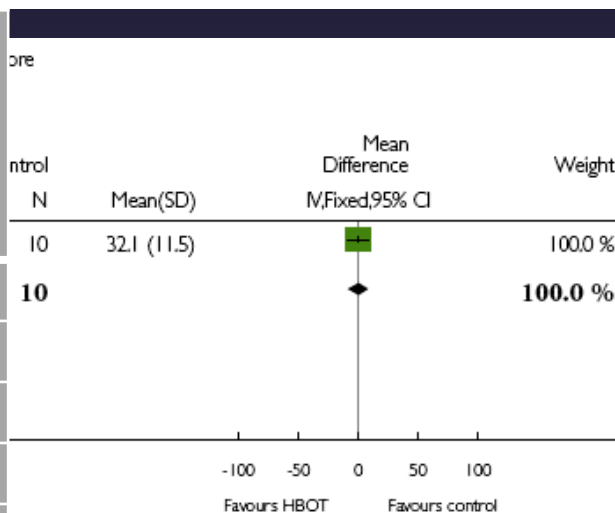
Quality of Life

PICO #1 (All DFU, HBOT +SC vs. SC)

Outcome: 22 Quality of life - SF-36 mental summary score



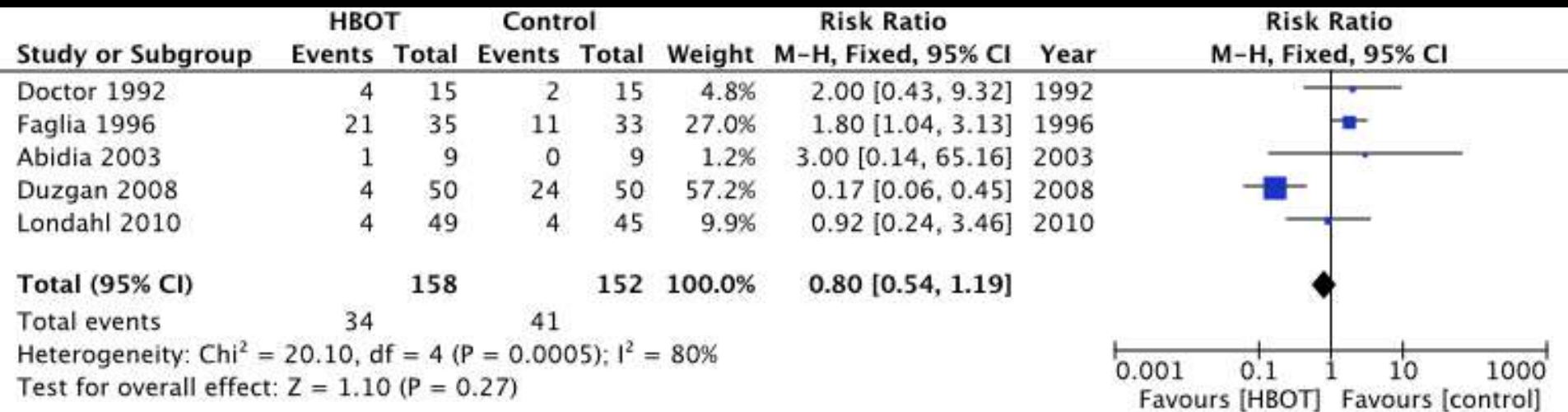
Randomized Controlled Trials	Risk of Bias					
	Randomized	Controlled	Trials	Risk of Bias	Randomized	Controlled
No Stopping Early for Benefit						
Strict Allocation Concealment						
None Lost to Follow-up						
Blinded Study						
Used Intention to Treat						



START	4
Risk of Bias	-1
Inconsistency	0
Indirectness	0
Imprecision	-2
Publication Bias	0
Large Effect	0
Dose Response	0
Confounders	0
FINAL	1

Minor Amputation

PICO #1 (All DFU, HBOT +SC vs. SC)



Randomized Controlled Trials	Doctor 1992	Faglia 1996	Abidia 2003	Vocel 2008	Duzgan 2008	Londahl 2010	Mean
Risk of Bias							
No Stopping Early for Benefit							
Strict Allocation Concealment							
None Lost to Follow-up							
Blinded Study							
Used Intention to Treat							





START	4
Risk of Bias	-1
Inconsistency	-1
Indirectness	0
Imprecision	-1
Publication Bias	0
Large Effect	0
Dose Response	0
Confounders	0
FINAL	1

Rate Quality of Evidence

PICO #1 (All DFU, HBOT +SC vs. SC)

Outcome	Randomization	Blinding	Allocation	Measurement	Loss to Follow-up	Missing Data	Starting Score	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Large Effect	Dose Response	Confounders	Final Score
Major Amputation Rate							4	-1	-1	0	0	0	1	0	0	3
Complete Healing (1 year)							4	-1	-1	0	0	0	1	0	0	3
Resolution of Infection							4	-1	-2	-2	0	0	0	0	0	1
Quality of Life (SF36)							4	-1	0	0	-2	0	0	0	0	1
Minor Amputation Rate							4	-1	-1	0	0	0	0	0	0	2

Categories of Evidence

High	Further research is very unlikely to change our confidence in the estimate of effect	
Moderate	Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate	
Low	Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate	
Very low	Any estimate of effect is very uncertain	

Level of Evidence

PICO #1 (All DFU, HBOT +SC vs. SC)

Outcome	Final Score	GRADE Level of Evidence
Major Amputation Rate	3	Moderate
Complete Healing (1 year)	3	Moderate
Resolution of Infection	1	Very Low
Quality of Life (SF36)	1	Very Low
Minor Amputation Rate	2	Low

Formulate Recommendations

- For or Against an intervention
- Strong or Conditional Recommendation
- Considering the following
 - Quality of Evidence
 - Balance of Benefits / Harms
 - Values and Preferences
 - Resource Use (Cost)

Implications of a Strong recommendation

- **Population:** Most people in this situation would want the recommended course of action and only a small proportion would not
- **Health care workers:** Most people should receive the recommended course of action
- **Policy makers:** The recommendation can be adapted as a policy in most situations

Implications of a Conditional recommendation

- **Population:** The majority of people in this situation would want the recommended course of action, but many would not
- **Health care workers:** Be prepared to help people to make a decision that is consistent with their own values/decision aids and shared decision making
- **Policy makers:** There is a need for substantial debate and involvement of stakeholders

Level of Evidence

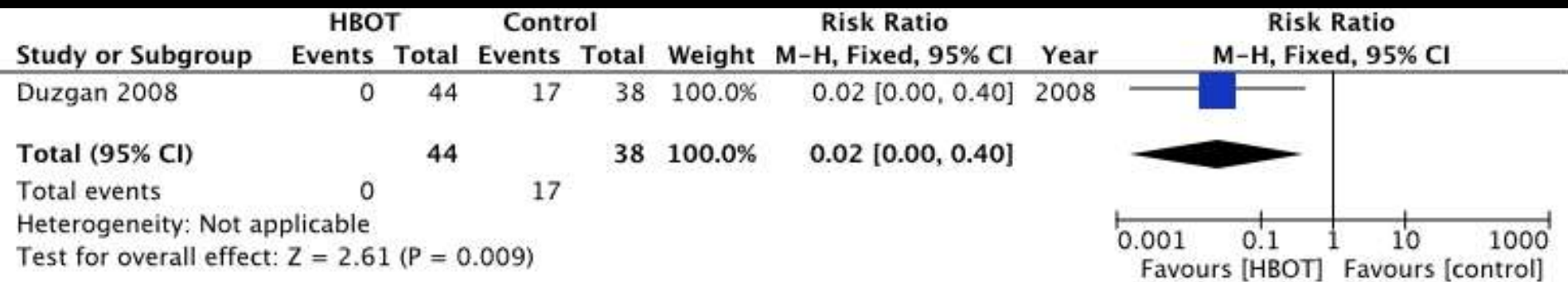
PICO #1 (All DFU, HBOT +SC vs. SC)

Outcome	Final Score	GRADE Level of Evidence	Strength of Recommendation
Major Amputation Rate	3	Moderate	Conditional
Complete Healing (1 year)	3	Moderate	Conditional
Resolution of Infection	1	Very Low	
Quality of Life (SF36)	1	Very Low	
Minor Amputation Rate	2	Low	

In patients with diabetic foot ulcers, we suggest adding Hyperbaric Oxygen Therapy to the Standard of Care with regard to preventing major amputation and promoting complete healing at 1 year (*moderate, conditional*).

Major Amputation

PICO #2 (DFU ≥ 30 days & Wagner ≥ 3 , HBOT +SC vs. SC)

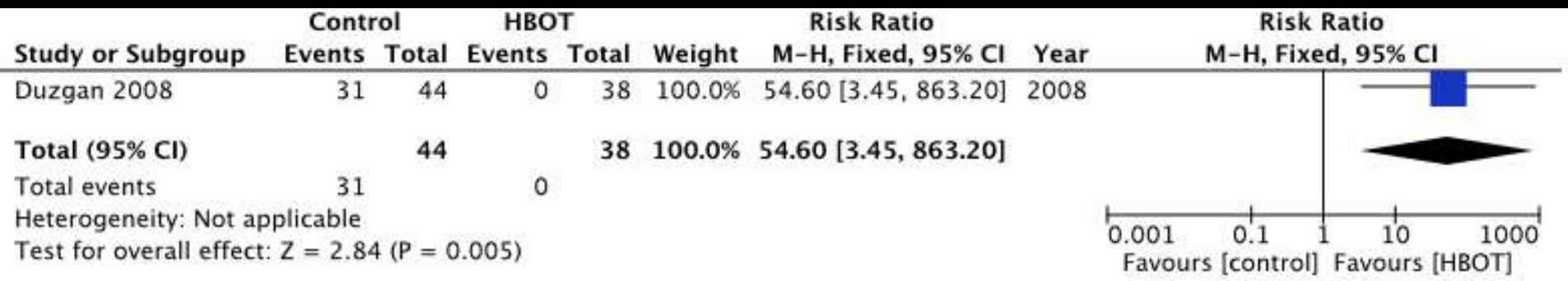


Randomized Controlled Trials	Risk of Bias						
	Duzgan 2008	Endlin 2006	Alkhalaf 2008	Vaccaro 2008	Duzgan 2008	Endlin 2006	Alkhalaf 2008
No Stopping Early for Benefit							
Strict Allocation Concealment							
None Lost to Follow-up							
Blinded Study							
Used Intention to Treat							

START	4
Risk of Bias	0
Inconsistency	0
Indirectness	0
Imprecision	-2
Publication Bias	0
Large Effect	0
Dose Response	0
Confounders	0
FINAL	2

Complete Healing at 1 Year

PICO #2 (DFU ≥ 30 days & Wagner ≥ 3 , HBOT +SC vs. SC)



Risk of Bias	Randomized Controlled Trials					
	Duzgan 2008	Endlin 2006	Ahidia 2008	Vocelero 2008	Duzgan 2008	Endlin 2006
No Stopping Early for Benefit						
Strict Allocation Concealment						
None Lost to Follow-up						
Blinded Study						
Used Intention to Treat						

START	4
Risk of Bias	0
Inconsistency	0
Indirectness	0
Imprecision	-2
Publication Bias	0
Large Effect	1
Dose Response	0
Confounders	0
FINAL	3

Minor Amputation

PICO #2 (DFU ≥ 30 days & Wagner ≥ 3, HBOT +SC vs. SC)



Randomized Controlled Trials	Duzgan 2008	Endlin 2006	Ahidia 2008	Vaccaro 2008	Duzgan 2008	Endlin 2006	Min 2008
Risk of Bias							
No Stopping Early for Benefit							
Strict Allocation Concealment							
None Lost to Follow-up							
Blinded Study							
Used Intention to Treat							

START	4
Risk of Bias	0
Inconsistency	0
Indirectness	0
Imprecision	0
Publication Bias	0
Large Effect	1
Dose Response	0
Confounders	0
FINAL	4

Rate Quality of Evidence

PICO #2 (DFU ≥ 30 days & Wagner ≥ 3 , HBOT +SC vs. SC)

Outcome	Randomization	Blinding	Allocation	Measurement	Follow-up	Loss to follow-up	Missing data	Starting Score	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Large Effect	Dose Response	Confounders	Final Score
Major Amputation Rate								4	0	0	0	-1	0	0	0	0	3
Complete Healing (1 year)								4	-1	-1	0	0	0	1	0	0	3
Resolution of Infection								0	0	0	0	0	0	0	0	0	0
Quality of Life (SF36)								0	0	0	0	0	0	0	0	0	0
Minor Amputation Rate								4	0	0	0	0	0	1	0	0	4

Evidence and Recommendations

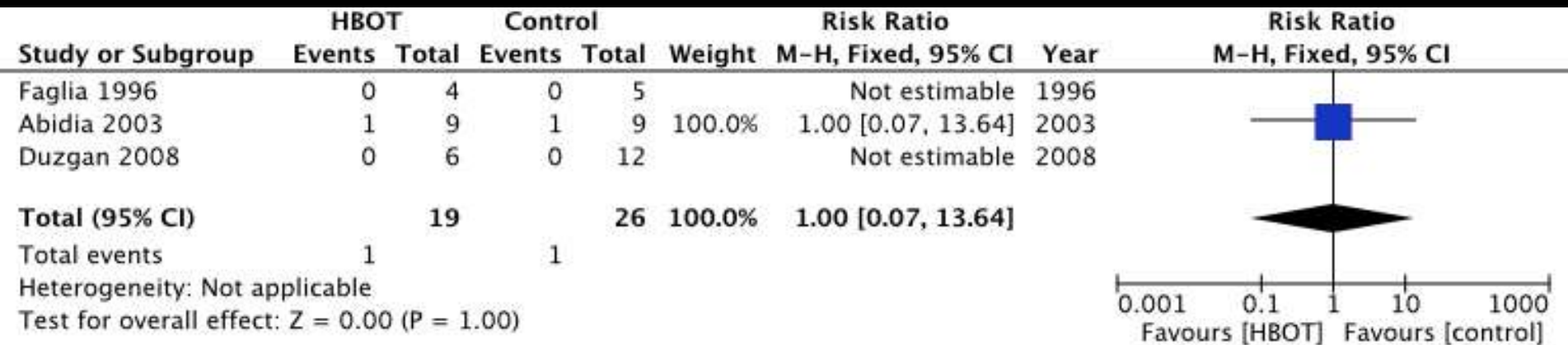
PICO #2 (DFU ≥ 30 days & Wagner ≥ 3 , HBOT +SC vs. SC)

Outcome	Final Score	GRADE Level of Evidence	Strength of Recommendation
Major Amputation Rate	3	Moderate	Conditional
Complete Healing (1 year)	3	Moderate	Conditional
Minor Amputation Rate	4	Low	

In patients with Wagner ≥ 3 diabetic foot ulcers, we suggest adding Hyperbaric Oxygen Therapy to the Standard of Care with regard to preventing major amputation and promoting complete healing at 1 year (*moderate, conditional*).

Major Amputation

PICO #3 (DFU ≥ 30 days & Wagner ≤ 2 , HBOT +SC vs. SC)

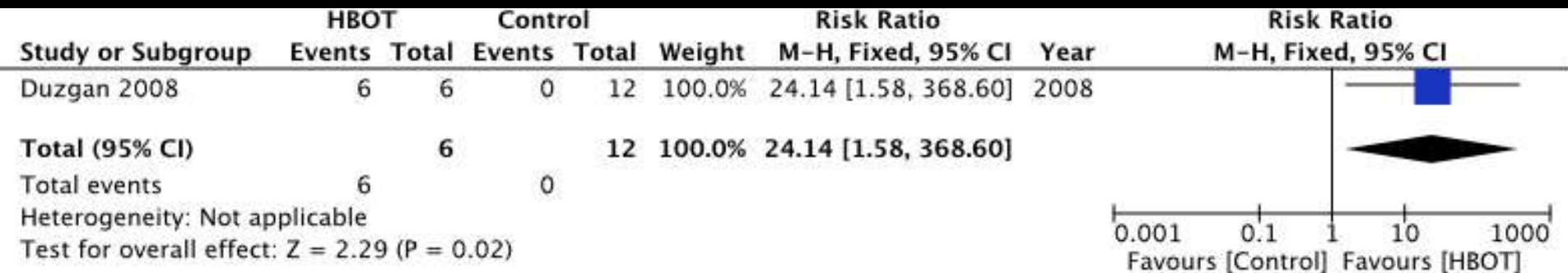


Randomized Controlled Trials	Duzgan 2008	Abidia 2003	Faglia 1996	Control	HBOT	Weight	Year
Risk of Bias							
No Stopping Early for Benefit							
Strict Allocation Concealment							
None Lost to Follow-up							
Blinded Study							
Used Intention to Treat							

START	4
Risk of Bias	-1
Inconsistency	0
Indirectness	0
Imprecision	-2
Publication Bias	0
Large Effect	0
Dose Response	0
Confounders	0
FINAL	1

Complete Healing (1 year)

PICO #3 (DFU ≥ 30 days & Wagner ≤2, HBOT +SC vs. SC)

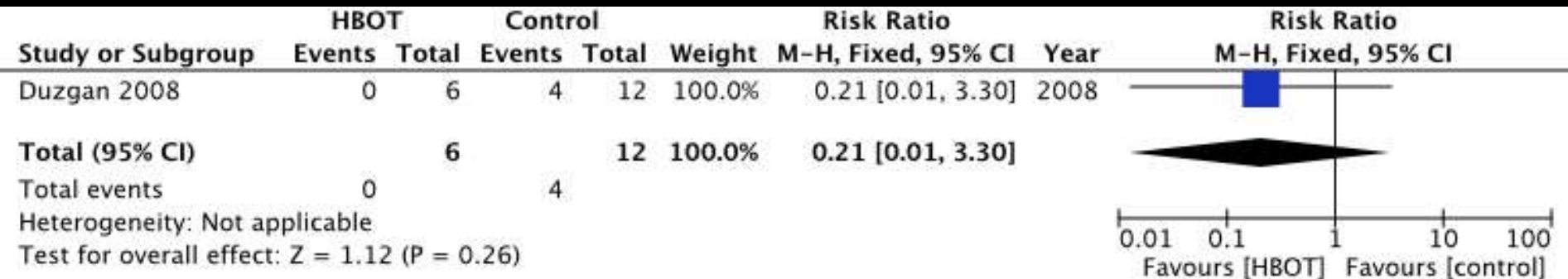


Randomized Controlled Trials	Risk of Bias						
	Duzgan 2008	Endlin 2006	Alkhalaf 2008	Vaccaro 2008	Duzgan 2008	Endlin 2006	Alkhalaf 2008
No Stopping Early for Benefit							
Strict Allocation Concealment							
None Lost to Follow-up							
Blinded Study							
Used Intention to Treat							

START	4
Risk of Bias	0
Inconsistency	0
Indirectness	0
Imprecision	-2
Publication Bias	0
Large Effect	0
Dose Response	0
Confounders	0
FINAL	2

Minor Amputation

PICO #3 (DFU ≥ 30 days & Wagner ≤ 2 , HBOT +SC vs. SC)



Randomized Controlled Trials	Duzgan 2008	Endlin 2006	Ahidia 2008	Vocler 2008	Duzgan 2008	Endlin 2006	Min 2008
Risk of Bias							
No Stopping Early for Benefit							
Strict Allocation Concealment							
None Lost to Follow-up							
Blinded Study							
Used Intention to Treat							

START	4
Risk of Bias	0
Inconsistency	0
Indirectness	0
Imprecision	-2
Publication Bias	0
Large Effect	1
Dose Response	0
Confounders	0
FINAL	3

Rate Quality of Evidence

PICO #3 (DFU ≥ 30 days & Wagner ≥ 3 , HBOT +SC vs. SC)

Outcome	Randomization	Blinding	Allocation	Measurement	Loss to Follow-up	Other	Starting Score	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Large Effect	Dose Response	Confounders	Final Score
Major Amputation Rate							4	-1	0	0	-2	0	0	0	0	1
Complete Healing (1 year)							4	0	0	0	-2	0	0	0	0	2
Resolution of Infection							0	0	0	0	0	0	0	0	0	0
Quality of Life (SF36)							0	0	0	0	0	0	0	0	0	0
Minor Amputation Rate							4	0	0	0	-2	0	1	0	0	3

Evidence and Recommendations

PICO #3 (DFU ≥ 30 days & Wagner ≤ 2 , HBOT +SC vs. SC)

Outcome	Final Score	GRADE Level of Evidence	Strength of Recommendation
Major Amputation Rate	1	Very Low	Conditional
Complete Healing (1 year)	2	Low	
Minor Amputation Rate	3	Low	

In patients with Wagner ≤ 2 diabetic foot ulcers, we suggest against adding Hyperbaric Oxygen Therapy to the Standard of Care with regard to preventing major amputation and promoting complete healing at 1 year (*very low, conditional*).

Major Amputation - RCT

PICO #4 (Surgical DFU, Immediate HBOT+SC vs. SC)

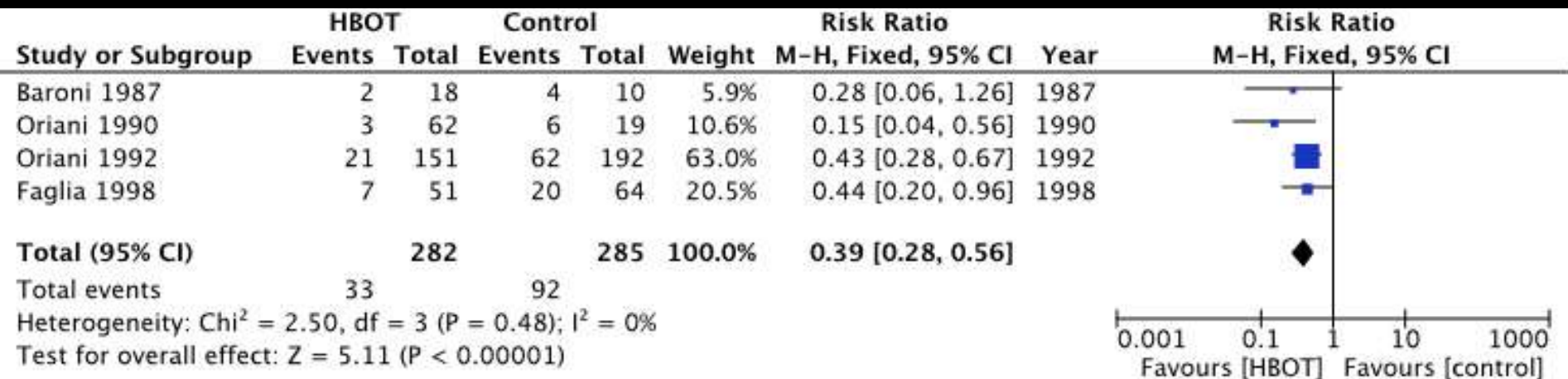


Randomized Controlled Trials	Risk of Bias						
	Doctor 1992	Faglia 1996	Ahidia 2000	Vocler 2000	Durston 2000	Lindahl 2000	M 2000
No Stopping Early for Benefit							
Strict Allocation Concealment							
None Lost to Follow-up							
Blinded Study							
Used Intention to Treat							

START	4
Risk of Bias	-1
Inconsistency	0
Indirectness	-1
Imprecision	0
Publication Bias	0
Large Effect	1
Dose Response	0
Confounders	0
FINAL	3

Major Amputation - OBS

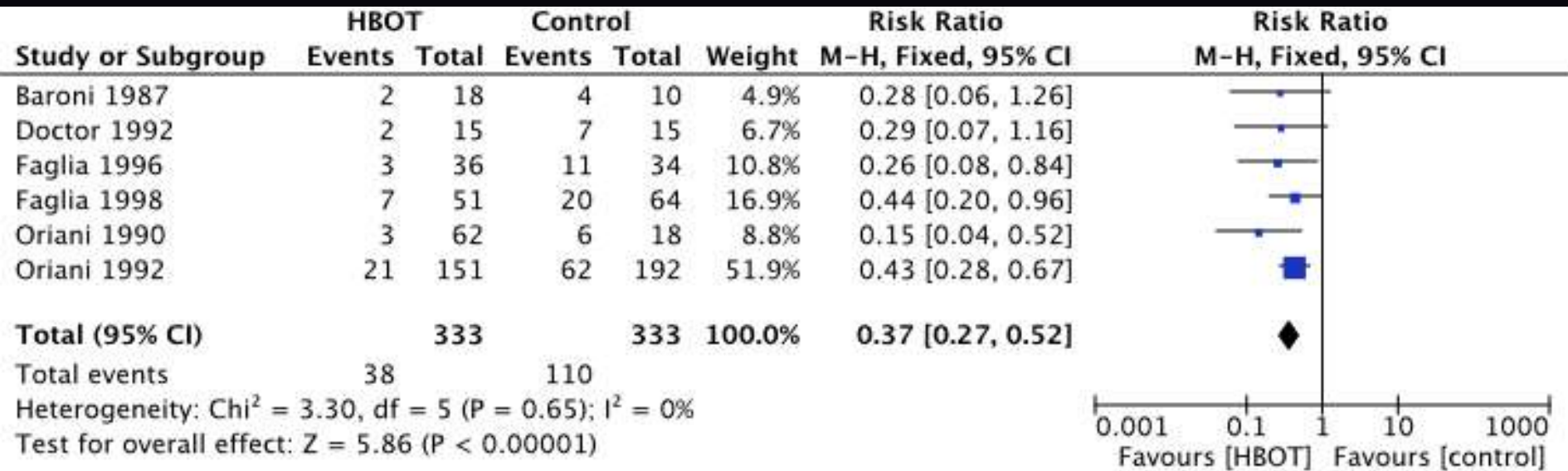
PICO #4 (Surgical DFU, Immediate HBOT+SC vs. SC)



START	2
Risk of Bias	0
Inconsistency	0
Indirectness	0
Imprecision	0
Publication Bias	-1
Large Effect	1
Dose Response	0
Confounders	0
FINAL	2

Major Amputation – RCT+OBS

PICO #4 (Surgical DFU, Immediate HBOT+SC vs. SC)



RCT Grade 3

OBS Grade 2

Resolution of Infection

PICO #4 (Surgical DFU, Immediate HBOT+SC vs. SC)

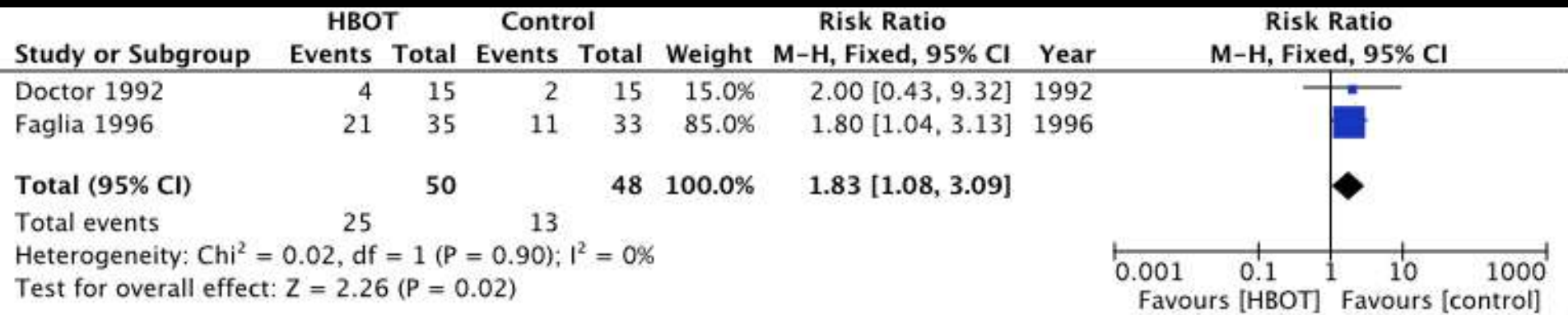


Randomized Controlled Trials	Risk of Bias					
	Doctor 1992	Faglia 1996	Ahidia 2000	Vaccaro 2000	Duggan 2000	Lindahl 2000
No Stopping Early for Benefit						
Strict Allocation Concealment						
None Lost to Follow-up						
Blinded Study						
Used Intention to Treat						

START	4
Risk of Bias	-1
Inconsistency	-2
Indirectness	0
Imprecision	0
Publication Bias	0
Large Effect	0
Dose Response	0
Confounders	0
FINAL	1

Minor Amputation

PICO #4 (Surgical DFU, Immediate HBOT+SC vs. SC)



Randomized Controlled Trials							
	Doctor 1992	Faglia 1996	Ahidia 2000	Vaccaro 2000	Durkin 2000	Lindahl 2000	Mazzuca 2000
Risk of Bias							
No Stopping Early for Benefit							
Strict Allocation Concealment							
None Lost to Follow-up							
Blinded Study							
Used Intention to Treat							

START	4
Risk of Bias	-1
Inconsistency	0
Indirectness	-1
Imprecision	0
Publication Bias	0
Large Effect	0
Dose Response	0
Confounders	0
FINAL	3

Rate Quality of Evidence

PICO #4 (Surgical DFU, Immediate HBOT+SC vs. SC)

Outcome	Randomization	Blinding	Allocation	Measurement	Dropouts	Intention to Treat	Missing	Starting Score	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Large Effect	Dose Response	Confounders	Final Score
Major Amputation Rate								4	-1	0	-1	0	0	1	0	0	3
Healing % (1 year)								0	0	0	0	0	0	0	0	0	0
Resolution of Infection								4	-1	0	-2	0	0	0	0	0	1
Quality of Life (SF36)								0	0	0	0	0	0	0	0	0	0
Minor Amputation Rate								4	-1	-1	0	0	0	0	0	0	2

Rate Quality of Evidence

PICO #4 (Surgical DFU, Immediate HBOT+SC vs. SC)

[illegible]

Evidence and Recommendations

PICO #4 (Surgical DFU, Immediate HBOT+SC vs. SC)

Outcome	Final Score	GRADE Level of Evidence	Strength of Recommendation
Major Amputation Rate	3	Moderate	Strong

In patients with Wagner ≥ 3 diabetic foot ulcers that require immediate surgery, we recommend adding immediate, inpatient Hyperbaric Oxygen Therapy to the Standard of Care with regard to preventing major amputation and promoting complete healing at 1 year (*moderate, strong*).

Formulate question

Select outcomes

Rate importance

Outcomes across studies

Create evidence profile with GRADEpro

Rate quality of evidence for each outcome

RCT start high, obs. data start low

P
I
C
O

Outcome Critical

Outcome Critical

Outcome Important

Outcome Less important

important



Summary of findings & estimate of effect for each outcome

High
Moderate
Low
Very low

Grade down

1. Risk of bias
2. Inconsistency
3. Indirectness
4. Imprecision
5. Publication bias

Grade up

1. Large effect
2. Dose response
3. Confounders

Systematic review



Guideline development

Formulate recommendations:

- For or against (direction)
- Strong or weak (strength)

By considering:

- ☐ Quality of evidence
- ☐ Balance benefits/harms
- ☐ Values and preferences

Revise if necessary by considering:

- ☐ Resource use (cost)



Rate overall quality of evidence across outcomes based on lowest quality of **critical** outcomes

- "We recommend using..."
- "We suggest using..."
- "We recommend against using..."
- "We suggest against using..."

Courtesy of Dr. Yngve Falck-Ytter

Recommendations

- In patients with diabetic foot ulcers, we suggest adding Hyperbaric Oxygen Therapy to the Standard of Care with regard to preventing major amputation and promoting complete healing at 1 year (*moderate, conditional*).
- In patients with Wagner ≥ 3 diabetic foot ulcers, we suggest adding Hyperbaric Oxygen Therapy to the Standard of Care with regard to preventing major amputation and promoting complete healing at 1 year (*moderate, conditional*).

Recommendations

- In patients with Wagner ≤ 2 diabetic foot ulcers, we suggest against adding Hyperbaric Oxygen Therapy to the Standard of Care with regard to preventing major amputation and promoting complete healing at 1 year (*very low, conditional*).
- In patients with Wagner ≥ 3 diabetic foot ulcers that require immediate surgery, we recommend adding immediate, inpatient Hyperbaric Oxygen Therapy to the Standard of Care with regard to preventing major amputation and promoting complete healing at 1 year (*moderate, strong*).

Generate CPG

- List Recommendations
- Add Technical Comments and Discussion

Directions for Future Research

- Methodology
 - CONSORT compliant
 - Reduce Risk of Bias
- PICO
 - Subgroups with no data
 - Better DFU Classification System
 - Outcomes of interest
 - Time to Heal
 - Cost Effectiveness
 - Healing Durability
 - Quality of Life
 - Resolution of Infection
 - Interventions
 - Standardize
 - Interventions

Final Steps

- External Review
 - Transparency via Public Presentation
 - Pre-course at next ASM?
 - UHMS Publications Committee
 - Public Comment Period
- Publish on www.guidelines.gov

Goals and Objectives

- By the end of this lecture, attendees should be able to:
 - Develop an understanding of how to use GRADE methodology to evaluate the existing HBOT literature
 - Evaluate the preliminary recommendations from the DFU CPG Review Committee
 - Understand where future research needs to be directed

Announcement

- CPG Reviewers meeting at Noon today
- Mills 3

Questions?

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jalmans400c@gmail.com