METHODOLOGICAL APPROACHES TO EVIDENCE BASED GUIDELINES IN BURN INJURY

Ph.D. Thesis

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1. LIST OF PUBLICATIONS

Publications related to Ph.D. thesis

I. Kis E, Szegesdi I, Dobos E, Nagy E, Boda K, Kemény L, Horvath AR.: Quality assessment of clinical practice guidelines for adaptation in burn injury. Burns. 36 :606-15, 2010
IF: 1,718

II. Horváh AR, **Kis E**, Dobos É.: Guidelines for the use of biomarkers: Principles, processes and practical considerations. Scand J Clin Lab Invest Suppl.; 242:109-16, 2010
IF: 1,629

III. Kis E, Oláh J, Ócsai H, Baltás E, Gyulai R, Kemény L, Horváth AR. Electrochemotherapy of cutaneous metastases of Melanoma – a case series study and systematic review of the evidence. Dermatol Surg. 137: 816-24, 2011
IF: 2,264

IV. Kis E. Dobos É, Nagy É, Kemény L., Horváth AR: A bizonyítékokon alapuló orvoslás gyakorlata / The practice of evidence based medicine Bőrgyógy Vener Szle 86: 103-107. 2010

V. Kis E, Szegesdi I, Ócsai H, Gyulai R, Kemény L, Oláh J: Melanoma-bőráttétek elektrokemoterápiája. Orv Hetil 151: 105–110, 2010

2. ABBREVIATIONS

EBM: Evidence-based medicine

CPG: Clinical practice guidelines

WHO: World Health Organization

AGREE: Appraisal of Guidelines for Research & Evaluation

3. INTRODUCTION

Evidence-based medicine (EBM) is a scientific approach that supports the application of the best available research evidence to medical decision making. The five key steps of the practice of evidence based medicine are shown in Figure 1.

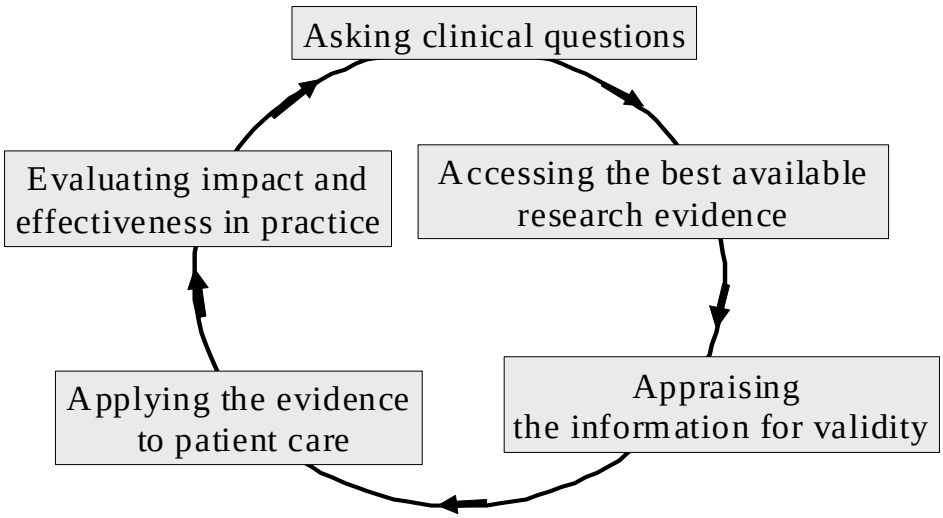

Figure 1. The practice of evidence based medicine

An understanding of EBM and how to implement it in practice is crucial for all professionals involved in the delivery of modern healthcare today. Guidelines are the most effective way of applying evidence into patient care. Potential increases in health costs and risks due to market-driven, uncontrolled use of novel clinical interventions also make guidelines increasingly important (1). Clinical practice guidelines (CPG) are aimed at bridging the gap between clinical research and everyday medical practice. Therefore CPGs are the end products of the research translation continuum (Figure 2.) (2)

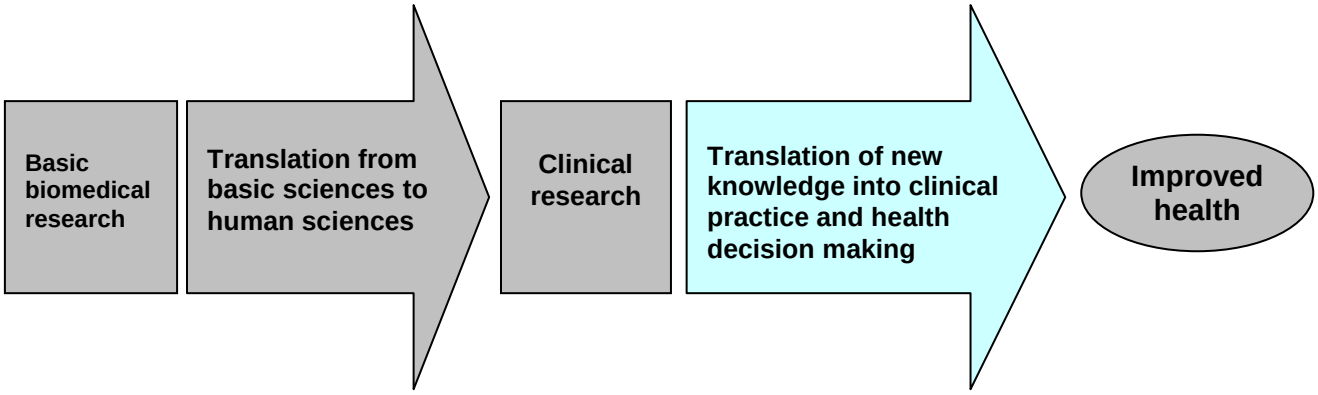

Figure 2. The role of guidelines in research translation

3. 1. The relevance of EBM in burn care

Evidence-based recommendations are particularly important in areas of health care, where costs and mortality rates are very high. Burn care is one such area and according to a WHO estimate for our region the death and mortality rates are at least ten-fold higher than in Western Europe (3). Burns are a serious public health problem globally, with over 300,000 deaths each year from fires alone. More deaths occur from scalds, electrical and other forms of burns, for which global data are not available. Fire-related deaths alone rank among the 15 leading causes of death of children and young adults aged 5-29 years. In addition to those who die, millions more are left with lifelong painful disabilities and disfigurements, often living with the resulting social/personal stigma and rejection.

High-income countries have made considerable progress in lowering rates of burn deaths through combination of proven prevention strategies and improvements in the care of burn victims. Most of these advances in prevention and care have been incompletely applied in low- and middle-income countries. Increased efforts to do so would likely lead to significant reductions in rates of burn-related death and disability (3). For these reasons we have identified burn care as a key topic in Hungary for guideline development with an evidence based methodological approach.

3. 2. Definition and characteristics of guidelines

Guidelines are systematically developed statements providing recommendations about the care of specific diseases. In addition, guidelines can play an important role in formulating health policy (4-6). CPGs potentially improve the quality and processes of care by putting research findings into clinical practice, provided the recommendations are rigorously developed and based on the best available research evidence. In the absence of such, a formal consensus from a multidisciplinary expert team on best clinical practices should be agreed upon. Many organizations produce CPGs on similar topics worldwide, but their quality is highly variable (7-13).

Good CPGs should be (14, 15):

- outcome oriented;
- internally valid – *i.e.* based on high quality research evidence or formal consensus when
- evidence is conflicting or lacking;

- reliable – *i.e.* developed in an explicit, transparent and reproducible manner free from commercial influence or bias;
- multidisciplinary;
- externally valid – *i.e.* clinically applicable;
- flexible – *i.e.* adaptable to various clinical circumstances and patient preferences;
- clear – *i.e.* specific and readily understood by users;
- regularly reviewed and updated;
- appropriately disseminated and implemented;
- cost-effective; and
- amenable to measurement of their impact in clinical practice.

3. 3. Different guideline building processes

Guidelines can be adopted, developed *de novo* or adapted. Adoption of guidelines means that recommendations are used in the same format as issued by the authority responsible for releasing the CPG. The flowchart of developing new CPGs is shown in Figure 3.

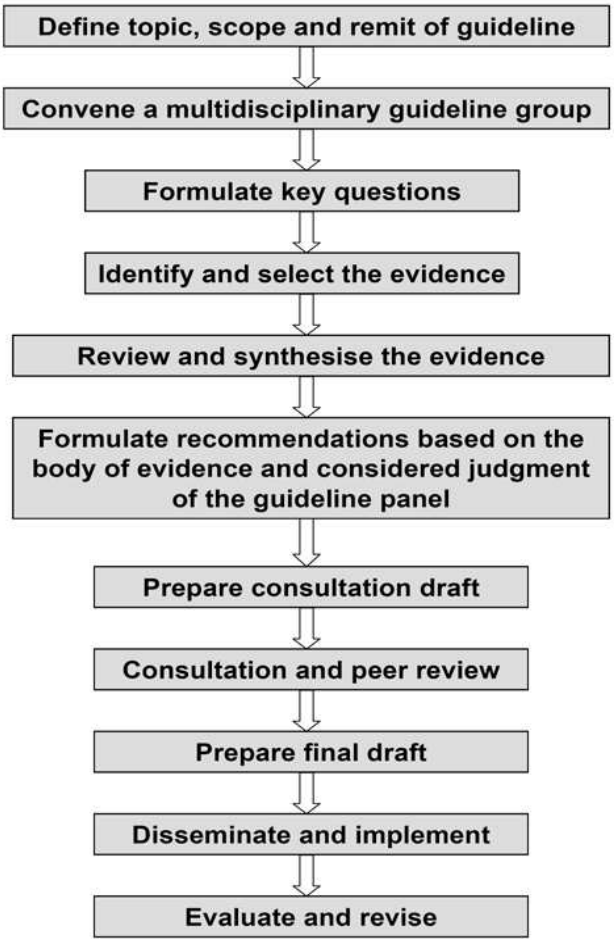

Figure 3. The process of *de novo* guideline development

Once the remit and clinical questions of the CPG are defined the critical steps in the process are how systematically the underlying research evidence is collected, selected, appraised and synthesized to give unbiased information which the CPG team can interpret further. This is probably the most time-consuming element of CPG development which needs special skills and training in systematic literature reviews and meta-analytic techniques. Often busy clinicians neither have the time, nor the necessary training to carry out such a thorough investigation.

Guideline adaptation, according to the definition of the ADAPTE Working Group, refers to the modification of a CPG produced for use in one cultural and organizational context to be applied in a different setting (16). Adaptation can be used as an alternative to *de novo* guideline development or for customizing an existing guideline to suit the local context. Unnecessary duplication could be avoided if high quality existing CPGs were adapted rather than developed *de novo* (17). This approach could be particularly beneficial for countries and organizations with limited budgets and experience or skills in evidence-based CPG development (18).

According to the ADAPTE Working Group, CPG adaptation is carried out in the following phases(16):

- Step 1: Definition of key clinical topics and questions
- Step 2: Searching for and selection of source CPGs
- Step 3: Assessment of the clinical content of source CPGs
- Step 4: Evaluation of the quality and coherence of source CPGs
- Step 5: Adaptation of recommendations

4. AIMS AND OBJECTIVES

For the above reasons our main goal was to develop an evidence-based guideline adaptation methodology and pilot test key elements of that framework by adapting international CPGs to guide local practice of care in Hungary. For pilot testing the process we selected topics that are related to two high priority areas of dermatology such as burn care and melanoma treatment. Childs pointed out in 1998 that few rigorously conducted multicenter trials existed in burns literature (19). Therefore we studied whether the situation had improved over a decade later. Do evidence based recommendations exist for managing burn injury patients and

if so, how we can utilize published recommendations most efficiently during the adaptation process.

Our main objectives were:

- to identify and prioritize the key clinical questions to be addressed by evidence-based recommendations for national practice;
- to systematically search for existing guideline recommendations for key questions, or in the lack of those, for the best available evidence on the topic;
- to systematically assess the scope and the quality of evidence and that of CPGs;
- to systematically synthesize the available evidence in primary studies and CPGs; and
- to highlight potential shortcomings of current CPGs and gaps in our knowledge that may limit the effective delivery of care in practice.

For our aims we addressed the following key questions:

- Are prioritized topics and questions covered by existing guidelines for burn injury?
- Do existing burn injury guidelines meet methodological standards?
- What are the main shortcomings of existing burns injury guidelines and what explains those deficiencies?
- How does the methodological quality of guidelines for burn injury compare with those of other medical fields?
- Is there sufficient evidence for formulating recommendations in burn injury guidelines?
- What methods can be used to fill in evidence gaps when formulating recommendations?

5. METHODS

For the adaptation of international CPGs of burn injury for local settings in Hungary, we followed the first 5 steps of the ADAPTE Working Group's methodology (16). Steps 6 and 7 were beyond the scope of this study. We first established a multidisciplinary research team which included experts in CPG methodology, evidence based medicine, statistics, intensive care medicine, burn and plastic surgery.

5. 1. Definition of key clinical topics and questions

Key clinical topics for the CPG were primarily determined by mapping the usual care pathway of burn patients, and secondarily refined by collecting and comparing the scope of

source CPGs. Key clinical questions were formed for each topic area in consultation with experts of the Hungarian Burn Association.

5. 1. 1. Prioritization of clinical topics and questions

For prioritizing questions in each key CPG topic area we developed criteria which considered the potential impact of the intervention on important clinical, organizational or economic outcomes (Table 1). Priority scores were given from 1 (most important) to 4 (least important) by two independent assessors. Disagreements were resolved by consensus.

Table 1: Prioritization criteria for defining key clinical topics and questions of CPGs

Prioritization criteria	Explanatory notes
A: The intervention has high impact on clinical outcomes (e.g. morbidity, mortality, prognosis)	***A1*: The intervention or its characteristics are directly or indirectly linked to important clinical outcomes**
	***A2*: Major impact on clinical decisions**
	A3: There is current controversy on the use of the intervention in practice
	A4: There is high variation in practice with unfavourable outcomes
B: The intervention has high impact on organizational outcomes	***B1:*** Widely used intervention with uncertain impact
	B2: There is public/commercial/ professional/governmental pressure on the use of the intervention
C: The intervention has high impact on economic outcomes	***C:*** The intervention is associated with high costs

5. 2. Searching for and selection of source CPGs

5. 2. 1. Search strategy; databases

Literature search was carried out between January 1990 and December 2008 systematically, screening MEDLINE and SCOPUS, the websites of several general medical burns-related journals and various burn associations, electronic databases of major CPG development agencies (i.e. National Guidelines Clearinghouse, Guidelines International Network, EBM Guidelines) and by reviewing the reference lists of review articles including CPGs (list of

databases are shown in Table 2). Searching in Medline was carried out using the terms of ("Burns"[MeSH] OR "Eye Burns"[MeSH] OR "Burns, Inhalation"[MeSH] OR "Burns, Electric"[MeSH] OR "Burns, Chemical"[MeSH]) AND ("CPG"[Publication Type] OR "CPGs"[MeSH] OR "Practice CPG"[Publication Type]).

Table 2: Databases used in searching for CPGs

Professional associations •British Burn Association (http://www.britishburnassociation.co.uk) •Eastern Association for the Surgery of Trauma (EAST) (www.east.org) •American Burn Association (http://www.ameriburn.org) •Deutschen Gesellschaft fur Verbrennungsmedizin (www.verbrennungsmedizin.de) •European Burns Association (EBA): (www.euroburn.org/) •American Academy of Family Physicians (http://www.aafp.org) •Australian and New Zealand Burns Association (ANZBA) (http://www.anzba.org.au) •International Society for Burn Injuries (http://www.worldburn.org)
Electronic Guideline Databases •Clinical Practice Guidelines and Protocols in British Columbia (http://www.hlth.gov.bc.ca) •Scottish Intercollegiate Guidelines Network (http://www.sign.ac.uk) •Guidelines-International-Network (G.I.N) (http://www.g-i-n.net) •EBM Guidelines (http://ebmg.wiley.com) •SCHARR database (http://www.shef.ac.uk/~scharr/ir/guidelin.html) •US National Guideline Clearing House (http://guideline.gov) •US Agency for Healthcare Research and Quality (http://www.ahrq.com) •The Canadian Task Force on Preventive Health Care (http://www.ctfphc.org) •German Agency for Quality in Medicine (http://www.aezq.de) •Guidelines Information Service (http://www.leitlinien.de) •New Zealand Guidelines Group (http://www.nzgg.org.nz) •Australian National Health and Medical Research Council http://www.health.gov.au/nhmrc/publications) •National Institute for Clinical Excellence (http://www.nice.org.uk) Clinical Practice Guidelines (http://www.ogh.on.ca/library/cpg.htm)

5. 2. 2. Selection strategy; inclusion, exclusion criteria

CPGs published in English, German or French were selected by two independent reviewers according to the following inclusion criteria: 1/ the publications were clinically relevant to burn injuries and provided recommendations for clinical practice; 2/ the type of publication

fulfilled the definition of the Institute of Medicine for practice CPGs (6). We defined recommendations as any statements that promote or advocate a particular course of action in clinical care. Personal reviews, secondary/multiple publications, adoption of original practice CPGs, editorials and letters to the editor were excluded. If CPGs had updates, only the last version was selected for further evaluation. The selection process was thoroughly documented to make the process reproducible. Disagreements between reviewers were resolved by consensus.

5. 3. Assessment of the clinical content of source CPGs

Because the guidelines varied in their scope, reviewers coded the CPGs according to whether they had recommendations for the 12 key clinical topics covered: i.e. fluid resuscitation, initial assessment and management, nutritional support, referral, organization, delivery aspects of care, thromboprophylaxis, wound management, pain management, rehabilitation and reconstruction, electric injury, chemical burns, paediatric burn injuries and inhalation injuries. Two investigators working independently reviewed the guidelines for recommendations that covered the preset clinical topics. We resolved discrepancies through discussion within the study team.

5. 4. Evaluation of the quality and coherence of source CPGs

5. 4. 1. Appraisal of methodological quality

We assessed the methodological quality of source CPGs by the AGREE Instrument (Table 3) in order to select those that are suitable for further analysis of their content and coherence before adaptation (20). Prior to evaluating the methodological quality of burns CPGs, all four reviewers were trained in CPG appraisal and had substantial experience in using the AGREE Instrument. Four assessors scored each CPG independently and reached consensus when necessary.

5. 4. 2. Appraisal tool. The AGREE instrument

The AGREE Instrument (Table 3) critically evaluates the quality of reporting and the methodological quality of CPGs according to 23 criteria, grouped into six domains: 1/ scope and purpose; 2/ stakeholder involvement; 3/ rigor of development; 4/ clarity and presentation; 5/ applicability; and 6/ editorial independence (20). Each of the 23 items in the checklist were rated on a 4-point Likert scale ranging from 4 ‘Strongly agree’ to 1 ‘Strongly disagree’, with two mid points: 3 ‘Agree’ and 2 ‘Disagree’ The standardized percentage scores were calculated for each domain independently, as described in the manual of the AGREE

Instrument (20) Based on these scores, we made an overall assessment about the acceptability of the CPG. A CPG was „strongly recommended" or „not recommended" if most domain scores (i.e. at least 4 out of 6) were above 60% or below 30%, respectively. When most domain scores were between 30-60% CPGs were „recommended with provisos or alterations".

Table 3: The AGREE Instrument (20)

SCOPE AND PURPOSE
Item 1. The overall objective(s) of the guideline is (are) specifically described
Item 2. The clinical question(s) covered by the guideline is(are) specifically described
Item 3. The patients to whom the guideline is meant to apply are specifically described
STAKEHOLDER INVOLV E M E N T
Item 4. The guideline development group includes individuals from all relevant professional groups
Item 5. The patients' views and preferences have been sought
Item 6. The target users of the guideline are clearly defined.
Item 7. The guideline has been piloted among target users.
RIGOUR OF DEVELOPMENT
Item 8. Systematic methods were used to search for evidence
Item 9. The criteria for selecting the evidence are clearly described
Item 10. The methods used for formulating the recommendations are clearly described
Item 11. The health benefits, side effects, and risks have been considered in formulating the recommendations
Item 12. There is an explicit link between the recommendations and the supporting evidence
Item 13. The guideline has been externally reviewed by experts prior to its publication
Item 14. A procedure for updating the guideline is provided
CLARITY AND PRESENTAT I O N
Item 15. The recommendations are specific and unambiguous
Item 16. The different options for management of the condition are clearly presented
Item 17. The key recommendations are easily identifiable
Item 18. The guideline is supported with tools for application
A P P L I C A B I L T Y
Item 19. The potential organisational barriers in applying the recommendations have been discussed.
Item 20. The possible cost implications of applying the recommendations have been considered
Item 21. The guideline presents key review criteria for monitoring and/or audit purposes
EDITORIAL INDEPENDENCE
Item 22. The guideline is editorially independent from the funding body
Item 23. Conflicts of interest of guideline development members have been recorded

5. 4. 3. Data extraction and evaluation of CPGs

We used kappa statistics as a measure of the agreement among reviewers.We did not automatically calculate aggregated domain scores without comparing the item scores of assessors. If the difference in item scores between assessors was more than 2, the disagreements were resolved by discussion and consensus. The kappa statistics for multiple raters was then applied to each of the 23 items of the AGREE Instrument (20). The MAGREE macro of the SAS system for Windows, that can handle the case of multiple raters, was used for calculations (21).

We also determined whether the CPG was evidence- or consensus-based (i.e. EB or CB). Each CPG was classified as CB, when there was no reported literature retrieval strategy, consideration about the quality of evidence or no consistent evidence available and practice recommendations were based on expert consensus. A CPG was classified as EB, when there was a documented and reproducible literature search methodology and/or some form of assessment of the quality of evidence while developing the CPG.

5. 5. Methodological quality of guidelines in other medical fields of recommendations

We compared the methodological quality of burn injury guidelines with that of other medical fields for two reasons:

1. to see if the methodological scores found were specific to this particular field only or reflect a general quality of CPGs;
2. to explore how consistent our guideline appraisal methodology is with published studies using the same critical appraisal technique.

For this investigation we carried out a systematic search of the literature for any studies which used the AGREE Instrument for the critical appraisal of any guidelines. The following search terms were used to retrieve such studies and overviews: (“guidelines” AND “AGREE”). AGREE domain scores of the retrieved studies were listed and results synthesized and compared to domain scores found for burn injury guidelines.

5 .6. Adaptation of recommendations

For efficient use of all published recommendations, in the fifth step of the framework, we have modified the ADAPTE process. According to ADAPTE, each of the selected guidelines listed in a comparative table facilitate the selection of relevant high quality source guidelines and the identification of recommendations that can be adopted unchanged or that will require modification. The ADAPTE framework groups CPGs by similarity and uses separate tools for assessing guideline currency, consistency and applicability. As we have reviewed a large number of guidelines and wished to have each key question covered by a recommendation, we found it more practical to produce a comparative recommendation matrix for each key question with the relevant recommendations quoted from the actual source guidelines in chronological order, if available. This allowed us to assess the currency, consistency and adaptability as well as the quality and validity of similar recommendations. As a result of this process, for each clinical question adaptation could vary in intensity: i.e. from adoption as is (when recommendations were consistent and applicable), through translation, reformatting or reformulation with justifications, or literature update (when recommendations were outdated) to *de novo* development (when there were no relevant recommendations or these were poor quality or the evidence base was lacking or unclear). The applicability of each treatment option was considered in a new context whilst formulating the new recommendations for the Hungarian setting.

5. 7. Survey of the evidence based background of recommendations in burn injury

Because CB guidelines were more prevalent than expected, we were interested whether this could be explained by shortcomings of the burn literature. We performed a broad search in Medline between 1967 and 2010. The following search terms were used: ("burns"[MeSH Terms] OR "Eye Burns"[MeSH] OR "Burns, Inhalation"[MeSH] OR "Burns, Electric"[MeSH] OR "Burns, Chemical"[MeSH]) NOT "sunburn"[MeSH Terms]) NOT burns [Author]. Computerised search of Medline using the 'Type of Article' category enabled us to identify meta-analyses, randomised controlled trials, controlled clinical trials, comparative studies and case series/reports on the evidence hierarchy scale (Figure 4). All other publications including editorials, letters to the editor, review papers, personal reports, addenda, book reviews and supplements were excluded.

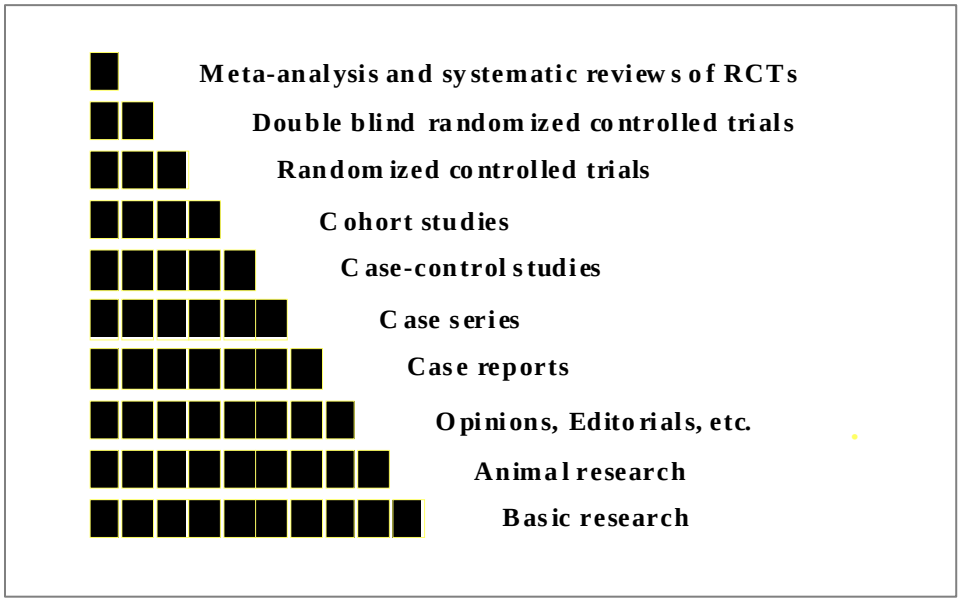

Figure 4: Evidence hierarchy

5. 8. Methods for formulating recommendations when there is an evidence gap

When recommendations are conflicting across several guidelines due to the heterogeneity of the evidence base, guideline teams need to investigate the quality and consistency of the best available evidence in a systematic manner or even carry out some local primary studies or clinical audits to provide some form of objective data the guideline team can consider when formulating recommendations. Systematic reviewing techniques are used to fill in such evidence gaps. To pilot test this element of the guideline adaptation process, we chose another topical and as yet unresolved problem in dermatology, i.e. electrotherapy of melanoma metastases. We conducted a primary study and a systematic search of the medical literature to identify relevant studies on the effectiveness of bleomycin-based electrotherapy on melanoma patients. In the context of this thesis we only focus on presenting the systematic reviewing techniques that can be utilized in any guideline adaptation process, irrespective of the topic. The bibliographic search was performed from January 1980 to January 2010 in the PubMed database, using the keywords [electrochemotherapy AND melanoma AND bleomycin].

6. RESULTS

6. 1. Definition of key clinical topics and questions

6. 1. 1. Prioritization order of topics and questions

Key topics were prioritized in order to investigate whether questions of high priority are addressed in source CPGs in a more rigorous (i.e. EB *versus* CB) fashion. Experts of the Hungarian Burn Association defined two main CPG areas (i.e., general management of burn injuries and special burn injuries) and 12 key topics with 55 key questions. Questions specifically related to intensive care units of burn centres are marked with asterisks. The rankings of clinical topics are presented in Table 4. Main reasons for prioritization, according to the criteria in Table 1, were if the intervention had a high impact on clinical outcomes (A1: 38 questions, 69%; A2: 23 questions, 42%; A3: 4 questions, 7%; A4: 14 questions, 25%). Questions, related to economic (C: 9 questions, 16%) and organizational outcomes (B1: 1 question, 2%; B2: 7 questions, 13%), were given gradually lower priority (Table 4).

Table 4: Definition and prioritization of key clinical topics and questions

KEY CLINICAL TOPICS AND QUESTIONS	Reasons for prioritization	Priority scores (1-4)
I. GENERAL MANAGEMENT OF BURN INJURIES		
Fluid resuscitation		**1.0**
How to calculate fluid requirement? Which formula is favourable?	A1, A4	1
Which patient groups require special fluid management?*	A1	1
How to monitor fluid resuscitation? (usable end-points)	A1, A2	1
How to manage complications of resuscitation therapy?	A1, A4	1
Initial assessment and management		**1.5**
When cooling should start, for how long, and with what?	A1, A3, A4	1
How to determine the severity of burn? (Which formula is the most precise and easy to use?)	A1, A2	1
Above what size of injured body surface area should immediate fluid resuscitation start?	A1	1
What are the key pieces of information to be recorded in burn injury? (e.g. exact mechanism and timing of injury)	A2	2
What is the ideal initial covering for burn wounds?	A1,A2, A4	2
Which tests should be used for evaluation of patient's progress?	A2	2
Nutritional support		**1.5**
How to estimate Macronutrient Formulation?*	A1, A2	1
When to start enteral feeding?*	A1, A2,	1
What is the preferred route of nutrition support?*	A4	2
Which factors can influence energy requirements?*	A2	2
How to monitor nutritional support?*	A2,	1
How to use specific nutrients?*	A1	2
Referral, organization, delivery of care		**1.6**
Who should be referred to a burn centre?	A1, A2, A3, A4, B2, C	1
What organizational structure and equipments a burn centre must have?*	A4, B2, C	2
What specialties should be included in the burn team?*	A3, C	2
How many burn centres are necessary for the care of burn patients in our region /country?	A4, B1, B2, C	1
Within what time-interval the burnt patient should be transferred to a burn centre, and under what circumstances?	A1, A2, C	2

KEY CLINICAL TOPICS AND QUESTIONS	Reasons for prioritization	Priority scores (1-4)
Thromboprophylaxis		**2.0**
What are the risks of venous thromboembolism in burn patients with different severity and type of burns?*	A1,A2	2
When thromboprophylaxis should start?*	A3, A4	1
For how long thromboprophylaxis should be given?*	A1, A3	1
How to monitor the efficacy of thromboprophylaxis treatment?*	A2	2
When to use mechanical prevention?	A1	4
Wound management		**2.0**
Which are the indications for escharotomies and fasciotomies?	A1	1
What indicates a surgical wound closure?*	A1	1
Which topical management is optimal for epidermal burns and scalds?	A4, A1,B2,C	2
Which topical management is optimal for superficial and mid-dermal burns or scalds?	A4, A1, B2, C	2
How to manage blisters?	A4	4
When do we need a skin bank?*	A1, C, B2	2
How to treat patients with burns of special areas?*	A1	2
What is the optimal time for necrectomy in severe burn patients?*	A1, A2	2
Pain management		**2.2**
What is the first choice for burn pain management?	A4	1
How to assess, document and monitor pain in burn injury?*	A2	2
How to manage background pain?*	A1	2
How to manage procedural pain?*	A1	2
What are the non-pharmacological interventions supplementing burn pain management?*	A2	4
Rehabilitation and reconstruction		**3.5**
What are the psychological responses to burn injury, and how they should be managed?	A1, A2	3
How to control hypertrophy of scar tissue? *	A1, B2, C	4

KEY CLINICAL TOPICS AND QUESTIONS	Reasons for prioritization	Priority scores (1-4)
II. MANAGEMENT OF SPECIAL BURN INJURIES		
Electric injury		**1.0**
How to assess electric injury?	A1, A2	1
When and how to perform fasciotomy to maintain peripheral circulation?	A1, A2	1
What are the key principles of the management of patients with electric injury?*	A1	1
Chemical burns		**1.3**
Which factors determine the severity of chemical injuries?	A2	2
How to treat injuries with specific substances?*	A1	1
What is the initial management of chemical burns?	A1	1
Paediatric burn injuries		**1.3**
How to assess burn size in children at different ages?	A1, A2	1
How to calculate fluid requirements in children?	A1	1
What are the best routes of fluid administration in paediatric patients?	A1	2
Inhalation injuries		**1.4**
How to determine the presence of inhalation injury?	A2,A4	1
What is the initial management of patients with suspected inhalation injury?	A1	1
When patients should be intubated?	A1,A4	1
How to ventilate patients with inhalation injury?*	A4	2
How to avoid and treat long-term complications of inhalation injury?*	A1, A2	2

***** Questions labelled with asterisks are specific for intensive care units of burn centres.
Reasons for prioritization: for explanation of codes see Table 1.
Average priority scores for key topics are printed in bold.
Priority scores: 1 – most important, i.e. top priority; 2 – important; 3 – moderately important; 4 – least important

6. 2. Search results, selection of guidelines

We screened 519 citations identified through computerized database searches (Figure 5). An additional 27 citations had been identified through hand searching in reference lists of papers, and web site searches of CPG resources. After screening for relevance and other preset inclusion and exclusion criteria, we retained 24 CPGs for further evaluation and critical appraisal (22-45). Reasons for exclusion are shown in Figure 5. Selected CPGs were of two types: 1/ specifically oriented to burns, and 2/ other clinical CPGs in which certain chapters dealt with the management of burn injury.

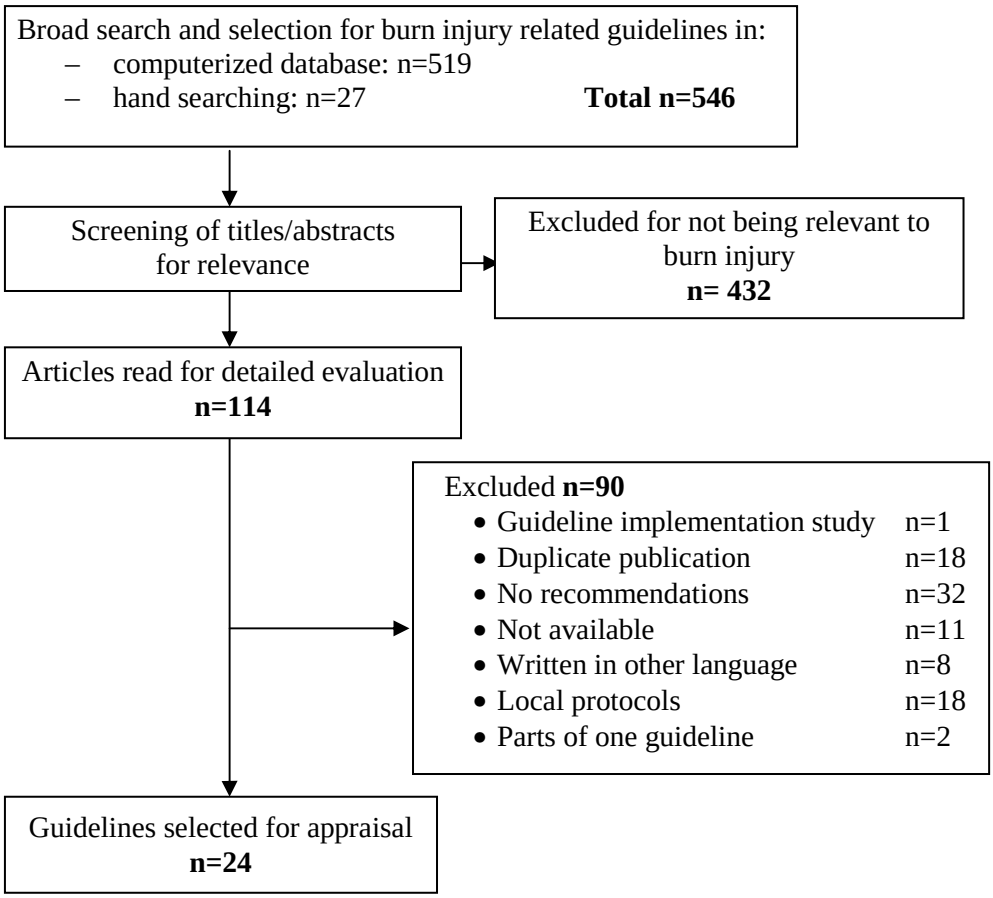

Figure 5: Searching and selecting burn injury guidelines

6. 3. Main characteristics of and clinical topics covered in selected guidelines

The main characteristics and clinical topics of selected CPGs are shown in Table 5. Of the 24 CPGs, 42% (n=10) were evidence-based (EB), and the rest consensus-based (CB). The distribution of EB *versus* CB CPGs for each key clinical topic is also shown in Table 5. For paediatric burn injuries and pain management we found only CB CPGs, while for thromboprophylaxis and nutritional support the majority of CPGs were EB. Sixty percent of CPGs for electric and inhalation injuries were also EB. All major burn injury topics were covered by at least one CPG, but no single CPG addressed all areas (Table 5). A number of CPGs addressed the topics which are most important in terms of patients' outcomes in the first 24-48 hours of burn injury. Due to the nature of burn disease most CPGs provided recommendations for initial assessment (n=15, 63%) and immediate fluid resuscitation (n=8, 29%) that are crucial for patient survival, but nearly two thirds of these were CB. In terms of outcomes it is essential that after initial assessment patients are triaged for referral to a burn centre. Six CPGs (25%) made recommendations on referral criteria, and other important organizational aspects of care, and only one third of these were EB (Table 5).

Table 5: Main characteristics of and clinical topics covered in source guidelines for burns

Guideline reference number Date	Type of CPG	Topics covered in guidelines (in order of priority)											
		I. General management of burn injuries								II. Management of special burn injuries			
	Evidence-based (EB) or Consensus based (CB)	Fluid resuscitation	Initial assessment and management	Nutritional support	Referral, organization, delivery	Thromboprophylaxis	Wound management	Pain management	Rehabilitation and reconstruction	Electric injury	Chemical burns	Paediatric burn injuries	Inhalation injuries
[22] 1995	CB	+	+		+		+			+	+		
[23] 2001, 2002, 2005	CB		+		+			+	+				
[24] 2002	EB				+								
[25] 2002	EB			+									
[26] 2002	CB				+								
[27] 2002	EB		+										
[28] 2003	EB	+	+						+	+			
[29] 2003	CB								+				
[30] 2003	EB			+									
[31] 2004	CB		+					+					
[32] 2004	CB		+					+	+				+
[33] 2004	EB		+				+		+	+			+
[34] 2005	EB		+				+		+	+			+
[35] 2005	CB	+	+				+		+	+	+		

Guideline reference number Date	Type of CPG	Topics covered in guidelines (in order of priority)											
		I. General management of burn injuries								II. Management of special burn injuries			
	Evidence-based (EB) or Consensus based (CB)	Fluid resuscitation	Initial assessment and management	Nutritional support	Referral, organization, delivery	Thromboprophylaxis	Wound management	Pain management	Rehabilitation and reconstruction	Electric injury	Chemical burns	Paediatric burn injuries	Inhalation injuries
[36] 2006	EB					+							
[37] 2006	EB	+	+	+	+	+							+
[38] 2006	CB		+				+		+				
[39] 2007	CB	+	+				+		+		+		
[40] 2007	EB	+	+				+		+	+	+		
[41] 2007	CB			+									
[42] 2007	CB												+
[43] 2007	CB						+		+				
[44] 2008	CB	+	+				+	+	+			+	
[45] 2008	CB	+	+		+		+	+					
Number of CPGs covering the topic		8	15	4	6	2	10	5	12	5	4	1	5
Percentage of CPGs covering the topic		33	63	16	25	8	42	20	50	20	16	4	20
Percentage of EB CPGs covering the topic		38	33	75	33	100	30	0	33	60	25	0	60

6. 4. Evaluation of the quality and coherence of source CPGs

6. 4. 1. Assessment of burns guidelines by the AGREE Instrument

Quality scores of burn CPGs by the AGREE Instrument are shown in Table 6.

Table 6: Assessment of burns guidelines by the AGREE Instrument

CPG Ref No	Type of CPG	*Domain scores (%)*						
		Scope and purpose	**Stake holder involvement**	**Rigor of development**	**Clarity and presentation**	**Applicability**	**Editorial independence**	***Overall assessment***
[22]	CB	50	25	21	83	22	0	*Would not recommend*
[23]	CB	47	23	17	63	0	0	*Would not recommend*
[24]	EB	89	44	60	90	56	8	*Recommend with provisos or alterations*
[25]	EB	78	44	60	71	11	8	*Recommend with provisos or alterations*
[26]	CB	67	42	25	75	31	0	*Recommend with provisos or alterations*
[27]	EB	94	10	68	85	11	0	*Recommend with provisos or alterations*
[28]	EB	28	8	11	63	28	0	*Would not recommend*
[29]	CB	78	69	42	81	39	8	*Recommend with provisos or alterations*
[30]	EB	94	10	60	79	8	0	*Recommend with provisos or alterations*
[31]	CB	58	38	23	56	14	0	*Recommend with provisos or alterations*
[32]	CB	89	29	19	92	11	92	*Recommend with provisos or alterations*
[33]	EB	78	56	57	77	11	100	*Recommend with provisos or alterations*
[34]	EB	36	31	50	56	11	0	*Recommend with provisos or alterations*
[35]	CB	83	17	17	96	17	0	*Would not recommend*
[36]	EB	92	48	79	92	33	63	*Strongly recommended*
[37]	EB	81	46	87	79	25	25	*Recommend with provisos or alterations*
[38]	CB	72	63	35	65	14	0	*Recommend with provisos or alterations*
[39]	CB	94	25	14	83	11	0	*Would not recommend*
[40]	EB	94	54	82	100	72	92	*Strongly recommended*
[41]	CB	64	15	13	73	6	0	*Would not recommend*
[42]	CB	89	25	19	65	11	0	*Would not recommend*
[43]	CB	92	40	26	79	33	0	*Recommend with provisos or alterations*
[44]	CB	69	35	14	88	22	8	*Recommend with provisos or alterations*
[45]	CB	69	35	19	94	17	0	*Would not recommend*
Mean		**74**	**35**	**38**	**79**	**21**	**17**	
Range		**28-94**	**8-69**	**11-87**	**56-100**	**0-72**	**0-100**	
Mean of CB CPGs		**73**	**34**	**22**	**78**	**18**	**8**	
Mean of EB CPGs		**76**	**35**	**61**	**79**	**27**	**30**	

6. 4. 1. 1. Scope and purpose

The score for this domain represents the degree to which the overall objectives of the CPG, the clinical questions and the patients to whom the CPG is applied to, were specifically described. Most CPGs performed well in this domain with a mean score of 74%, with only five CPGs (21%) scoring less than 60% (22,23,28,31,34). There was no difference between the mean scores of EB *versus* CB CPGs in this domain.

6. 4. 1. 2. Stakeholder involvement

This domain evaluates the degree to which the CPG represents the views of its intended users. Specifically it investigates whether all relevant professional and patient groups were represented, the target users of the CPG were well-defined and the CPG was piloted among end-users. The mean score for this domain was 35%, with only 2 CPGs (8%) scoring slightly above 60% (29,38) Only 5 CPGs (21%) included individuals from all relevant professional groups in the development stage (24,29,31,37,40), and none was piloted among end-users. The average scores of EB and CB CPGs did not differ.

6. 4. 1. 3. Rigor of development

This domain evaluates whether: systematic methods and specific criteria were used for searching and selecting the evidence and for formulating recommendations; there is an explicit link between the recommendations and the supporting evidence; and a procedure for updating is provided. The mean score for this domain was 38%, with 71% of CPGs scoring <60%. Only 5 CPGs (21%) described systematic methods for searching and selecting the evidence (27,30,36,37,40), 8 CPGs (33%) considered health benefits, side effects and risks when formulating the recommendations (25,27,30,32,35-37,40), and 7 CPGs (29%) described the methods used to formulate the recommendations (24-27,36,37,40). Seven CPGs (29%) were externally reviewed prior to publication (22,25,29,33,37,40). Eight CPGs (33%) provided any procedure for future (23-25,29,33,37-39). The mean score in this domain was much lower in CB (22%) than in EB CPGs (61%).

6. 4. 1. 4. Clarity and presentation

This domain describes whether the recommendations were specific and unambiguous; the different management options were clearly presented, key recommendations were easily identifiable; and the CPG was supported with tools for application. The mean score was 79%, and only two CPGs (8%) scored <60% for this domain (27,33). Three CPGs (13%) included tools for application (24,39,44). The average scores of EB and CB CPGs did not differ.

6. 4. 1. 5. Applicability

This domain evaluates issues that are pertinent to CPG implementation, such as organizational barriers, cost implications, and monitoring criteria. The mean score in this domain was 21% with only one CPG scoring >60% (40). Three CPGs provided review criteria for monitoring purposes (25,30,41), and also 3 discussed potential organizational barriers (28,37,40). No CPG discussed cost implications. Consensus-based CPGs scored somewhat lower (18%) than EB ones (27%).

6. 4. 1. 6. Editorial independence

This domain addresses whether the CPG was editorially independent from the funding body; and potential conflicts of interest were reported for the members of the CPG development group. The score in this domain was the lowest of all, with a mean of 17%. Four CPGs (17%) scored >60% (32,33,36,40). Potential conflicts of interests of CPG developers were recorded only in 3 CPGs (12%) (32,33,40). Evidence-based CPGs scored much better but still only about one third of them reported these issues as compared to 8% of CB CPGs.

6. 4. 1. 7. Overall recommendations

After assessing the quality of all CPGs reviewers recommended for adaptation those that were considered to influence outcomes in some form and that demonstrated acceptable quality on the AGREE Instrument. In total, we recommended 16 (67%) CPGs for adaptation of which 9 (56%) were EB, and 7 (44%) CB. Two EB CPGs (8%) were strongly recommended and 14 (58%) with provisos or alterations (Table 6).

6. 4. 2. Agreement among Reviewers

Table 7 demonstrates the degree of agreement beyond chance (kappa statistics) among the reviewers for the 23 items of the AGREE Instrument. The kappa values indicate that overall agreement was fair to moderate for 61% of the items and was substantial to excellent for 39% of the items. In the final rating where there were some disagreements assessors based their scores on consensus. The final scoring system of the AGREE Instrument may obscure disagreements between assessors. Therefore we investigated and discussed any disagreements between appraisers for each item when a difference in scores was greater than 2 in order to reach consensus on the final scores.

Table 7: Agreement among Reviewers for AGREE Instrument Items

Strength of Agreement	Agreement	Items, No Kappa Statistic
Poor	< 0.00	0
Slight	0.00–0.20	0
Fair	0.21–0.40	4
Moderate	0.41–0.60	10
Substantial	0.61–0.80	6
Excellent	>0.80	3

6. 5. Comparison of the methodological quality of burn guidelines with guidelines in other medical fields

We compared the methodological quality of burn injury guidelines (Table 6) with that of other medical fields (46). Altogether 1338 CPGs were investigated with the AGREE Instrument in many medical fields, including results of our own systematic review of 712 CPGs (7) along with a more recent systematic review of 626 CPGs published between 2003 and 2008 (47) (Table 8). This overview revealed that in most guidelines the scope and purpose of recommendations (Domain 1) are clearly defined and guidance is given in a clear format (Domain 4). There are significant shortcomings, however, in the multidisciplinary composition of guideline teams and involvement of patients in formulating recommendations (Domain 2). The scores in these critical assessments were also low for the rigour (or reporting) of an evidence-based CPG methodology (Domain 3). Guidelines often fail the criteria of editorial independence, *i.e.* reporting on funding and potential conflicts of interest (Domain 6). Furthermore, all reviews in Table 8 found that most recommendations lack external validity, *i.e.* applicability in practice (Domain 5). The average domain scores in these reviews are very similar to what we have found in burns CPGs.

Table 8. Overview of publications investigating the quality of guidelines with the AGREE Instrument

Reference	Publication date of guidelines	Number of CPGs	D1	D2	D3	D4	D5	D6
Horvath *et al.*,2007 (7)	2003-2007	712*	65	34	34	63	26	30
Alonso-Coello *et al*., 2009 (47)	2003-2008	626	64	35	43	60	22	30
Kis *et al*., 2009(46)	1995-2008	24	74	35	38	79	21	17

D: Domain according to the AGREE Instrument (20)
* Figure includes unpublished assessment of 189 national guidelines and care pathway protocols retrieved from the "grey literature".

6. 6. Modification of the ADAPTE process

For a more effective guideline adaptation and for the efficient use of all published recommendations we modified the fifth step of the ADAPTE framework and developed the algorithm presented in Figure 6. This modification enables guideline teams to address all tailored *a priori* questions, and to objectively compare the underlying evidence with final recommendations in various guidelines.

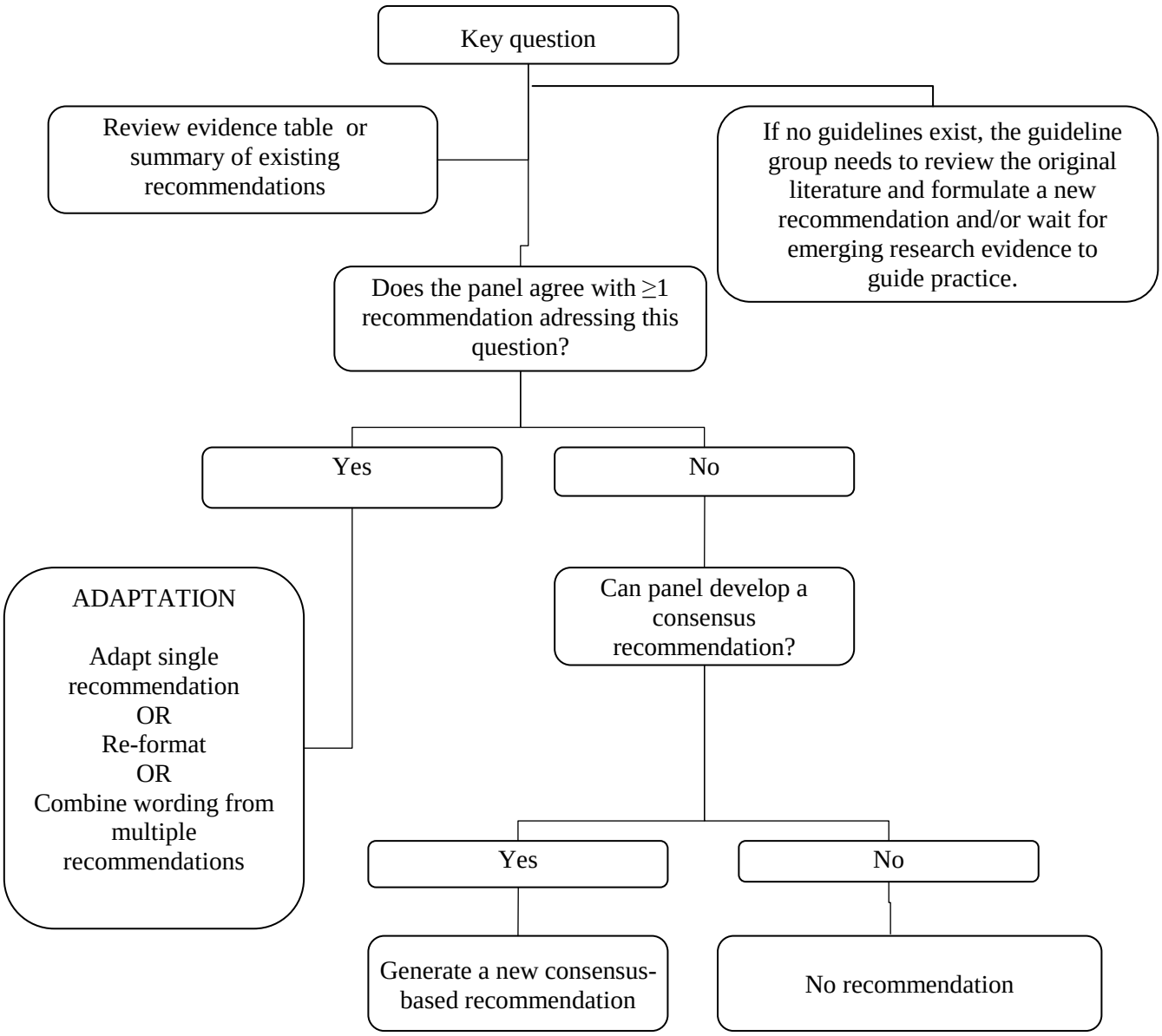

Figure 6: Algorithm of the modified ADAPTE process

6. 7. Literature review for high quality evidence in burn care

By searching MEDLINE for primary evidence in burn literature, a total number of 41.502 publications were evaluated, of which 10.830 (26%) could be classified according to the evidence hierarchy in Figure 4. Of these only 19 (0.04%) were meta-analyses, 606 (1.4%) randomized controlled trials, 904 (2.2%) controlled trials, 2745 (6.6%) comparative studies and 6556 (15 %) case series and case reports (Table 9).

Table 9: Literature review for evidence in burn care

Medline search	Meta-analyses	Randomised controlled trials	Controlled trials	Comparative studies	Case series and case reports
Number of articles	19	606	904	2745	6556
Percentage of all publications retrieved	0.04%	1.4%	2.2%	6.6%	15%
Percentage of all articles that could be classified according to the evidence hierarchy	0.17%	5.6%	8.34%	25.34%	60.53%

6. 8. Formulating recommendations when there is an evidence gap

Systematic overviews coupled with evidence from appropriately designed local studies can assist in making recommendations that can be applied to national practice even in areas where there is no international consensus or guidance to inform the guideline adaptation team. Electrochemotherapy, which is a novel method in the treatment of the cutaneous metastases of malignant melanoma, was chosen as an example where clear recommendations for practice are still lacking and there are conflicting views on its effectiveness. Therefore we performed a local primary study and compared our own findings to the results of a systematic literature review. Searches were performed from January 1980 to January 2010 in the PubMed database. We retrieved 27 papers of which, after checking titles and abstracts, 11 were identified as being relevant for inclusion. The characteristics and results of these studies, together with the results of our own primary study are summarized in Table 10. Due to the low sample size in each study, we did not carry out a meta-analysis, even though objective response rates to treatment showed fairly homogeneous results.

Table 10. Systematic review on electrochemotherapy treated melanoma metastases (48)

Author	Number of treated patients	Number of treated metastases	Administration of cytostatic drugs	Treated metastases per patient	Objective response (%)	Complete response (%)
Glass(1996)	5	23	Intratumoral	4.6	95	78
Heller(1998)	12	84	Intratumoral	7	98	89
Rols(2000)	4	55	Intravenous	13.7	90	9
Cuevas(2001)	2	13	Intratumoral	7.5	84.5	23
Byrne(2005)	19	53	Intratumoral	2.7	73	64
Kubota(2005)	1	8	Intratumoral	8	100	100
Gaudy(2006)	12	23	Intratumoral	1.9	66	37
Marty(2006)	20	98	Intratumoral/ intravenous	4.9	81	66
Snoj(2007)*	1	224	Intravenous	224	100	100
Quaglino(2008)	14	233	Intravenous	16.6	93	58
Campana(2009)	34	373	Intratumoral/ intravenous	10.9	96	50
Kaehler(2010)	1	6	Intratumoral	6	100	100
Kis (2011)	9	158	Intravenous	17.5	62	23
Total	**134**	**1351**	**Average**	**25**	**87.6**	**61.3**

7. DISCUSSION

The translation of research evidence into recommendations for clinical practice is not always straightforward (49). It is well known that different guideline teams often arrive at different conclusions even when using the same sources of evidence. This usually emanates from the fact that the evidence is often limited, ambiguous or controversial and resources differ among countries and regions. Considered judgment beyond the evidence is therefore always necessary, and should take into account the balance between benefits, harms, risks, patients' views, preferences and the potential organizational and financial barriers (50). Addressing these issues requires careful discussions within a working group that includes representatives from all relevant disciplines and stakeholders involved in the management of the given condition. In contrast to the development of systematic reviews, guidelines cannot be produced in an "ivory tower" by only a few academic experts. When the evidence is not strong or fully applicable to the patient population targeted in the guideline, the working group may depart from the evidence. Such diversions are often justifiable, provided the guideline team uses transparent methodology to explain their reasons for translating the evidence into local practice differently to other guideline groups (49).

Before adapting international CPGs to local practice the following questions need to be addressed: 1/ Are international guidelines of appropriate quality available? 2/ Are published recommendations based on the best available evidence, or in the lack of it on expert consensus conceived in a transparent and explicit process? 3/ Are recommendations transferable to our local settings? Our guideline adaptation study on burn care investigated all these issues and resulted in a pilot tested framework of methods that can be successfully used by guideline teams in various medical disciplines. We discuss our findings as they relate to the key questions listed in the "Aims and Objectives" section of this thesis.

7. 1. Are prioritized topics and questions covered by existing guidelines for burn injury?

Our guideline adaptation study on burn care demonstrated that nearly 60% of the internationally available CPGs were based on expert opinion or consensus. All key topics for burn care were covered by at least one guideline, but none of the guidelines covered all clinically important areas. Moreover, some topics and questions were covered by several guidelines. In areas such as thromboprophylaxis and nutritional support, which are more relevant to burn centres, more EB recommendations were found even though these aspects of

burn care were lower on our priority list. These findings may be explained by several factors, such as 1/ differences in the evaluation of the clinical importance and impact of various management steps in burn care; 2/ differences in the general scope and/or target users of our CPGs; or 3/ lack of international prioritization of research (51) and CPG questions in terms of the impact of certain interventions on patient-centred outcomes; 4/ more research (and money) goes into areas related to the approval and use of new medications than into traditional or practical clinical/organizational aspects of care (1). From the perspectives of patients, our findings also highlight the need for better definition of clinically important gaps and questions for future research(1), and that scientific and CPG teams develop concerted efforts to focus on fields which are more important for patient survival. Prioritization criteria, similar to what we developed and used for this study, could assist CPG developers and adapters in achieving these aims.

7. 2. Do existing burn injury guidelines meet methodological standards?

The assessment of guideline attributes by using the AGREE scores helped in deciding which guidelines could be trusted and used to base our local recommendations upon. The recommendation matrix proposed in this thesis helped us analysing the underlying evidence and comparing the homogeneity of the content of relevant recommendations. Evaluation of source CPGs with the AGREE Instrument revealed that the majority of burns CPGs defined their scope and purpose reasonably well and presented their recommendations clearly. In this respect we found no difference between EB and CB CPGs. Equally, no difference could be seen between CB and EB CPGs in terms of multidisciplinarity. Nevertheless, both types of CPGs often failed to involve related disciplines in the development process (Table 6), even though a European survey has shown that in intensive care mostly plastic and trauma surgeons and anaesthetists are responsible for the management of burn injuries (52).

In 88% of the CPGs in our study, potential conflicts of interest on the part of the CPG developers were not recorded. This does not imply of course that such conflicts of interest were present, but that we just do not know whether they were or not. There appears to be a high degree of interaction between authors of clinical practice CPGs and the pharmaceutical industry and therefore it is important to know to what extent these specific interactions might have influenced the recommendations (1,53). Readers of CPGs can evaluate the merit of CPGs only if they are duly informed of financial or other conflicts of interest with authors of CPGs(53). It is encouraging that EB CPGs more often made such declarations than CB ones, but it is less so that we could observe no improvement in this regard over the investigated

time scale (Table 6). In general, as EB CPG methods have been published in the last 5 years or so, we expected some improvement of methodological quality of CPGs over time. In fact, neither the number of EB *vs* CB CPGs, nor the actual AGREE domain scores showed any tendency of improvement (Table 6).

For CPG adaptation in a resource-constraint setting it is particularly important that recommendations are applied in a cost-effective manner. Optimal management of burn patients is vastly expensive and a long-term period of surgical, medical and psychological rehabilitation may be required after survival. A recent article has demonstrated that in every stage of burn care cost effective measures can be adapted without compromising the quality of care (54). As healthcare budgets are limited in all countries, evaluations of the availability of resources, cost-effectiveness and cost-benefit analyses are increasingly considered as part of the value judgment process of CPG development (55,56). However, our study revealed no CPGs that discussed cost implications of the care recommended.

The adequacy of CPGs for adaptation is best reflected by the rigor of development and clinical applicability of the recommendations. In both domains burns CPGs achieved rather low scores (i.e., 38% and 21%, respectively) (Table 6). The low scores in the former are explained by the fact that most of the reviewed CPGs referred to some underlying literature, but many did not report the methodology of literature retrieval and selection or how recommendations were finally arrived at. One may argue that the large difference we found between the scores of EB and CB CPGs in the "rigor of development" domain (i.e., 61% versus 22%; Table 6) is due to the fact that the AGREE Instrument is mostly applicable to evidence-based CPGs. In our assessment and according to the AGREE criteria, CB CPGs are also considered valid and may receive high scores, provided it is made explicit and transparent that authors searched for and appraised the literature, but due to the lack of suitable evidence a multidisciplinary expert team had to conceive its recommendations in a formal consensus process. For CPG adapters, thorough documentation and reporting of such processes in source CPGs is particularly important as consensus is often influenced by local value judgements related to societal, cultural, organizational and economic aspects of care which are not directly transferable from one setting to another.

7. 3. How does the methodological quality of guidelines for burn injury compare with those of other medical fields?

Critical appraisal of the methodology of CPGs by the AGREE Instrument (20) has shown that "all that glitters is not gold" and CPGs, often issued by prestigious authorities, lack the desirable attributes in many medical fields (7, 10, 47, 57). We compared our findings on the quality of burn CPGs to that of 1338 CPGs also assessed by the AGREE Instrument (7) (Table 8). This comparison revealed that the majority of CPGs lack multidisciplinary teams and involvement of patients in formulating recommendations. It has been shown that the composition of a guideline panel could grossly influence the focus of guidelines and could enlarge the interests of certain specialties, governmental agencies or industry (51). If patient representatives are not involved in the CPG committee, guidelines are often too narrowly focused on single diseases and do not sufficiently represent the interests and preferences of patients in decisions about their care (47). It is generally found that most CPGs fail the criteria of the rigour (or reporting) of an evidence-based methodology and editorial independence. The Institute of Medicine has also identified "significant risk of undue industry influence" in CPGs and has therefore recently issued a set of recommendations about handling conflict of interest related matters in medicine (58). Furthermore, we found that most recommendations lack external validity, *i.e.* applicability in practice, have a one-size-fits-all mentality and rarely build flexibility or contextualization into the recommendations or allow for individualization of care (59).

Our comparative analysis thus demonstrates that burns CPGs are no better or worse than other CPGs in the medical literature. However, the fact that most CPGs on burns scored rather low on the "stakeholder, rigor of development, applicability and editorial independence" domains, suggests that adaptation of international CPGs to use in another country will need a lot of additional work in terms of retrieving the evidence, reaching consensus amongst experts and reformatting recommendations so that they can be applied to local practice. Coherence and content analyses of selected CPGs, using a recommendation matrix for all key questions, are under way to identify whether there are any areas of conflicting recommendations that need to be covered by more systematic reviewing of the literature or a wider consensus.

7. 4. What are the main shortcomings of existing burns injury guidelines and what explains those deficiencies?

CPG validity depends not only on the rigor of its development but also on the quality of the underlying evidence base(7). As pointed out by Childs(19), few rigorously conducted multicenter trials existed in burns literature in 1998, which may explain why 58% of the CPGs in our review were still consensus based over a decade later. However, we expected that at least in some key topic areas, such as fluid resuscitation and initial assessment and management, which are crucial in determining patient outcomes, more evidence-based recommendations will be found. In contrast, nearly two thirds of CPGs that covered these topics were consensus-based (Table 5).

Therefore we were interested whether this finding could be explained by shortcomings of the burn literature. Our findings presented in Table 9 confirmed the results of a recent study, that evaluated the quantity and quality of research evidence in peer-reviewed burn care journals (60). The main observations of this study are extracted in Table 11 for comparison.

Table 11: Research evidence in burn care journals (60)

Journal	Meta-analyses (%)	Randomised controlled trials (%)	Controlled trials (%)	Comparative studies (%)	Case series and case reports (%)	Total
Burns	1 (0.0%)	92(6.2%)	34(2.3%)	413(27.9%)	943(63.6%)	1483
JBCR	2 (0.0%)	87(11.9%)	22(3.0%)	302(41.4%)	319(43.7%)	732
Total	3 (0.0%)	179 (8.1%)	56 (2.5%)	715 (32.3%)	1262 (57.1%)	2215

Another systematic review aimed at checking the methodological quality of randomised controlled trials in burns care (61). This study revealed that the quality of the existing limited number of trials is highly variable and the trials do not fulfil appropriate, evidence-based standards (61). Therefore it is not surprising that in the Cochrane Database of Systematic Reviews just less than 1% of the completed reviews or protocols have some relevance to burns care and management (62).

There are many explanations for the lack of appropriately designed and executed trials in burn literature: e.g. the patient population is not homogenous and may grossly differ by age, comorbidities, the extent of the injury, etc. Therefore recruiting the number of treated patients needed for a randomised controlled trial either takes a long period of time or needs a wide-scale international collaboration amongst burn centres that would deliver comparable care to patients (60). Because of the irreversibility of surgical treatments, randomisation can also cause ethical problems for surgeons when utilising new treatments which they have less knowledge of and/or trust in their efficacy. For the same reasons it is difficult to get patients' consent for taking part in a randomised trial. These problems do not only affect burn surgery, but in general the whole surgical field. In surgical trials these factors explain mostly the dominance of expertise-based randomised controlled trials(63-66). Furthermore, it is difficult to find sponsors who would provide the financial background to large-scale international trials aiming at practical clinical questions or comparing the effectiveness of routine clinical practices when such interventions involve no particular marketable products. In addition, burn surgeons generally have no time and scientific incentives for engaging in research beside their labourious clinical duties (1,60,67). Nevertheless, evidence-based trials are still required to ensure that recommendations for best practice are based on solid scientific data (63).

We therefore conclude that burn care literature suffers from a shortage of high-quality evidence which explains why consensus based guidelines are in the majority. Nevertheless, well conducted CB guidelines proved to be valuable, especially in a field, where we are lacking a solid underlying evidence base. Good quality consensus based guidelines, which were developed with a rigorous methodology and by formal consensus techniques are worthy for adaptation. For topics where we cannot find existing evidence, due to the nature of the question or it is not feasible, it is useful to compare the opinions of different expert groups and check whether their recommendations regarding the same clinical question are conflicting or harmonizing. With this method one can also broaden the external expertise behind guideline recommendations.

7. 5. What methods can be used to fill in evidence gaps when formulating recommendations?

Our study demonstrated that especially in areas where the evidence base is not particularly strong, guideline adaptation could be made more effective and explicit by following the modified ADAPTE process (Figure 6). The biggest advantage of this modification is that it maximizes the potential to address all tailored *a priori* questions and facilitates the objective appraisal, synthesis and comparison of the validity and consistency of the underlying evidence across various guidelines (Table 12). This modified framework also assists in grading or re-grading the adapted recommendations. The strength of this process lies in its transparency and reproducibility. This allows guideline users to easily review the underlying evidence and recommendation matrices which can inform their decisions of how the evidence can be used in practice and applied to managing individual patients.

Table 12: Comparison of ADAPTE *versus* the Modified ADAPTE framework

Guideline phase	ADAPTE	Modified ADAPTE framework	Advantage of modification
Critical appraisal and synthesis of the evidence	**Table format:** Recommendations grouped by guidelines OR Recommendations grouped by similarity Separate tools to assess guideline currency, consistency and applicability	**Table format:** Create separate table for each key question and group recommendations by similarity according to publication date. Apply simplified grading system across all guidelines.	Maximizes potential to address all tailored a priori questions. More feasible when reviewing a large volume of guidelines. Facilitates comparisons of evidence across guidelines. Currency, consistency and quality of evidence are all presented in one table.
Adaptation	**Unit for adaptation**: Whole guideline	**Unit for adaptation** Individual recommendation	Efficient use of all published recommendations Contextualizes recommendations.

With the explosion of evidence based guidelines there have been a large number of ways to describe the quality of evidence behind the recommendations. Due to the current multiplication, a guideline user may be faced with the same recommendation being classified as ‘‘II-2, B’’, ‘‘C+, 1’’, or ‘‘strong evidence, strongly recommended’’, depending on which grading system is used. This certainly adds to the confusion of the physician and deters health professionals from using any recommendations. In our modified framework, for all adapted

guidelines we propose the application of the simplified grading system of the New Zealand Guidelines Group (Table 13; (40)).

Table 13: Proposed grading system for recommendations following the modified ADAPTE process

Definition	Grade
The recommendation is supported by good evidence (where there are a number of studies that are valid, consistent, applicable and clinically relevant).	A
The recommendation is supported by fair evidence (based on studies that are valid, but there are some concerns about the volume, consistency, applicability and clinical relevance of the evidence that may cause some uncertainty but are not likely to be overturned by other evidence).	B
The recommendation is supported by international expert opinion.	C
Grades indicate the strength of the supporting evidence, rather than the importance of the recommendations	

Developed by New Zealand guidelines Group (40)

7. 6. Is there sufficient evidence for formulating recommendations in burn injury guidelines?

Our findings that a large proportion of recommendations in burn injury guidelines are based on lower levels of evidence or expert opinion highlight deficiencies in the sources of definitive data available for the generation of recommendations. To remedy this problem, the medical research community needs to streamline clinical trials, focus on areas of deficient evidence, and expand funding for clinical research. In addition, the process of guideline development needs to take into account the impact that recommendations, based on lower levels of evidence, have on clinical practice. Clinicians need to exercise caution when considering recommendations not supported by solid evidence(1). Most importantly the basis of the guideline-development group's recommendations should be transparent to enable guideline users to judge the appropriateness of each recommendation for individual patients' circumstances.

One of the principal aims of EBM is to translate new knowledge into clinical practice and health decision making. Our pilot systematic review of electrochemotherapy treatment of melanoma metastases, coupled with our own primary investigation (Table 10), was meant to demonstrate, how EBM methodologies can help such decisions, especially when the evidence

base is conflicting or lacking. Such systematic reviews compared to local experience on limited number of cases also help guideline teams to make informed and graded recommendations in a more objective and evidence-based fashion (48). The underlying evidence synthesized in Table 10, due to its homogeneity and consistency across various small studies, would qualify for a grade A recommendation, in spite of the small sample size in each individual study that investigated the effectiveness of this treatment modality. Considered judgment of various factors, such as the non-invasive nature of treatment, ease of use, need for minimal investment into equipment, significantly reduced side effects as compared to radiotherapy, patient preferences, low costs of treatment, etc. would all be part of this process, in addition to the evidence on clinical effectiveness.

Organizations deciding to adapt existing CPGs could avoid duplication of effort but this approach implies that CPG teams have access to high-quality and internally and externally valid source CPGs or recommendations which are based on the best available evidence and/or expert consensus. The European Society of Medical Oncology's initiative facilitates this approach in Europe by providing 'Minimum Clinical Recommendations', which are a set of statements for a basic standard of care considered necessary in all European countries (68,69). Similar initiatives would be welcome in other medical fields as well, particularly when there are relatively huge variations in practice of a relatively rare condition, such as severe burn injury.

8. SUMMARY

- We have developed and pilot tested a contemporary, evidence-based guideline adaptation framework that meets international methodological standards and can be universally used in any medical field when international CPGs are adapted to local use in Hungary.
- We have developed prioritization criteria for defining key clinical topics and questions for guidelines. These criteria are primarily based on patient relevant clinical, organisational and economic outcome considerations, and help guideline teams in addressing high priority topics in guidelines with more rigorous and transparent evidence-based methodologies.
- We have modified the ADAPTE process to make guideline adaptation more effective and explicit. The modification maximizes the potential to address all tailored key questions and enables the objective comparison and efficient use of all published

recommendations. It also provides a tool for a more transparent (re)grading of recommendations based on the quality of evidence and other pragmatic, value-based considerations.

- We have proposed and pilot tested systematic reviewing techniques coupled with local primary studies and clinical audits to help formulating recommendations when evidence is lacking or controversial.
- Using burn injury as a high-cost, high-mortality condition for our guideline adaptation pilot, we have mapped that all high priority burn injury topics were covered by at least one CPG, but no single CPG addressed all areas. This highlights the need that guideline adaptation must be a systematic process and should not simply rely on adoption of any one preselected international CPG.
- We have shown that the majority of burn injury guidelines are consensus based and a large proportion of recommendations are based on lower levels of evidence or expert opinion. As an explanation we have found that burn care literature suffers from a shortage of high-quality evidence which is partly due to organisational and ethical barriers of performing large-scale randomised controlled trials.
- Whilst existing international CPGs for the management of burn injury may accurately reflect agreed clinical practice, most performed poorly when evaluated for methodological quality by the AGREE Instrument.
- The methodological shortcomings of burn injury CPGs are very similar to those in other medical fields.
- Critical appraisal of international burns CPGs revealed that the majority defined their scope and purpose well, but there were serious shortcomings in involving all relevant stakeholders in the guideline development process and in the rigour and editorial independence of the development of recommendations. Burn injury CPGs also failed the majority of the clinical applicability criteria. These methodological shortcomings raise concerns about both the internal and the external validity of recommendations and therefore guideline adaptation teams must investigate the evidence or reasoning behind key recommendations before formulating and releasing local guidelines.

In conclusions, we make the following recommendations for the future:

- To improve the quality and validity of current guidelines systematic and explicit methods, based on the state-of-the art of guideline development and adaptation, are needed in burn care and any other medical fields.
- In Hungary guideline adaptation is a more pragmatic and cost-efficient approach and should adhere to a standardized framework, such as the one pilot tested in this study.
- All external CPGs should be critically evaluated for methodology and content before recommendations are adopted/adapted and endorsed for use in clinical practice.
- Guideline adaptation needs special skills and basic knowledge in evidence-based medicine and critical appraisal techniques, therefore training of guideline adapting teams should precede any such endeavours.
- Guideline adaptation should involve a close collaboration between all relevant stakeholders caring for the condition targeted by the recommendations.
- Guideline teams must disclose any potential conflicts of interest that might bias their judgment while formulating recommendations.
- Beyond the evidence the guideline adaptation team should consider the practical aspects and applicability of international recommendations, and diversions form the evidence or any other reasoning behind local recommendations should be documented explicitly and transparently.
- A standardised grading/re-grading system should be developed for adapting international recommendations in Hungary.

Future CPG efforts addressing these issues would add substantially to the improved management of burn injury and any other medical conditions in Hungary.

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11. APPENDIX